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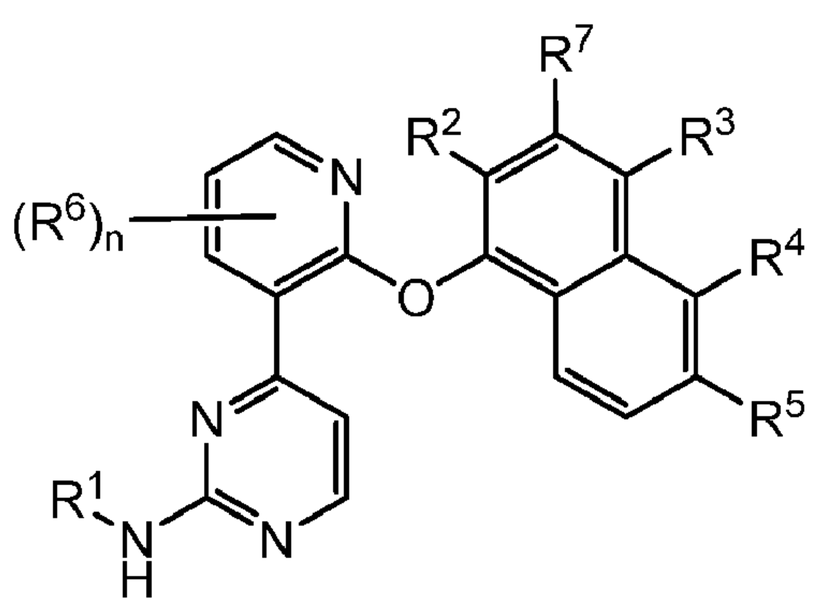
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(54) Titre : COMPOSES PYRIMIDINYL-PYRIDYLOXY-NAPHTYLE ET PROCEDES DE TRAITEMENT DE MALADIES ET DE TROUBLES LIES A IRE1

(54) Title: PYRIMIDINYL-PYRIDYLOXY-NAPHTHYL COMPOUNDS AND METHODS OF TREATING IRE1-RELATED DISEASES AND DISORDERS



I

(57) Abrégé/Abstract:
Described herein are pyrimidinyl-pyridyloxy-naphthyl compounds with inositol requiring enzyme 1 (IRE1) modulation activity or function having the Formula (I) or (I') structure : or stereoisomers, tautomers, or pharmaceutically acceptable salts thereof, and with the substituents and structural features described herein. Also described are pharmaceutical compositions and medicaments that include the Formula (I) or (I') compounds, as well as methods of using such IRE1 modulators, alone and in combination with other therapeutic agents, for treating diseases or conditions that are mediated or dependent upon estrogen receptors.

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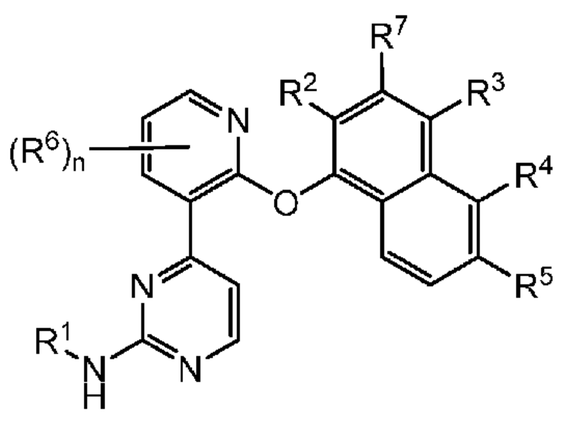
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(54) **Title:** PYRIMIDINYL-PYRIDYLOXY-NAPHTHYL COMPOUNDS AND METHODS OF TREATING IRE1-RELATED DISEASES AND DISORDERS



I

(57) **Abstract:** Described herein are pyrimidinyl-pyridyloxy-naphthyl compounds with inositol requiring enzyme 1 (IRE1) modulation activity or function having the Formula (I) or (I') structure : or stereoisomers, tautomers, or pharmaceutically acceptable salts thereof, and with the substituents and structural features described herein. Also described are pharmaceutical compositions and medicaments that include the Formula (I) or (I') compounds, as well as methods of using such IRE1 modulators, alone and in combination with other therapeutic agents, for treating diseases or conditions that are mediated or dependent upon estrogen receptors.

DEMANDE OU BREVET VOLUMINEUX

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

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 364

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JUMBO APPLICATIONS/PATENTS

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

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 364

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PYRIMIDINYL-PYRIDYLOXY-NAPHTHYL COMPOUNDS AND METHODS OF TREATING IRE1-RELATED DISEASES AND DISORDERS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to International Patent Application No. PCT/CN2017/077059 filed 17 March 2017, the contents of which application are hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] Described herein are compounds that target inositol requiring enzyme 1 (IRE1 alpha,α), including pharmaceutically acceptable salts, solvates, metabolites, prodrugs thereof, pharmaceutical compositions comprising such compounds, and methods of using such compounds to treat, prevent or diagnose diseases.

BACKGROUND OF THE INVENTION

[0003] The kinase/endoribonuclease inositol requiring enzyme 1 (IRE1 a, alpha,α), one of the key sensors of misfolded protein accumulation in the endoplasmic reticulum that triggers the unfolded protein response (UPR), is a potential therapeutic target for diverse diseases including cancer for inhibitors that bind to the ATP-binding site on the kinase moiety of IRE1α and block its endoribonuclease activity. IRE1α is a transmembrane, bifunctional protein with a luminal domain that binds to misfolded proteins, a transmembrane segment, and a cytoplasmic portion consisting of a kinase moiety and a tandem endoribonuclease domain. Structure-activity relationship (SAR) studies led to compounds selective in recombinant IRE1α kinase screens and potent against endoribonuclease activity of recombinant IRE1α as well as cellular IRE1α. IRE1α activity mediates certain cytoprotective and pro-survival functions of the UPR, increases viability and growth in certain tumor cell lines, and may be an effective therapeutic target for specific small molecule inhibitors that block malignant tumor growth, contrary to an earlier report (Harrington, P.E. et al (2015) ACS Med. Chem. Lett. 6:68-72). In addition, inhibitors of IRE1α may be therapeutically useful for other types of diseases besides cancer including certain autoimmune, neurodegenerative, fibrotic and metabolic disorders (Wang M. and Kaufman, R.J. (2016) Nature 529:326-335).

[0004] Homeostatic regulation of protein folding in the endoplasmic reticulum (ER) is under the control of three key intracellular signaling pathways: IRE1α, PERK, and ATF6, which together orchestrate the unfolded protein response (UPR) (Schroder, et al (2005) Mutat Res-

Fund Mol Mech Metagenesis 569:29 – 63). An increase in demand for protein folding in the ER or certain types of cellular injury or stress lead to the accumulation of unfolded proteins in the ER – a condition called ER stress. Cells respond to ER stress by activating the UPR to help adjust or maintain their high-fidelity protein synthetic capacity (Walter, P. and Ron, D. (2011) Science, 334:1081-1086). IRE1α is the most evolutionarily conserved of the three branches of the UPR. Importantly, the UPR makes life/ death decisions for the cell, depending on the severity and duration of ER stress, and the final outcome is either cell survival and recovery or programmed cell death (apoptosis) (Sovolyova et al, (2014) Biol Chem 395: 1-13). All three pathways of the UPR form a coordinated reaction to the accumulation of unfolded proteins; and several studies have demonstrated that there is cross talk between the different pathways (Yamamoto et al, J. Biochem. (2004) 136:343-350); Arai et al, FEBS Letts. (2006) 580:184-190; Adachi et al, Cell Struct. Func. (2008) 33:75-89). ER stress and activation of the UPR can be caused by mechanical injury, inflammation, genetic mutations, infections, oxidative stress, metabolic stress, and other types of cellular stress associated with malignancy. ER stress has also been implicated in diseases that result in fibrotic remodeling of internal organs, such as chronic liver diseases (Galligan et al, J. Toxicol. (2012) Vol. 2012, Article ID 207594, 12 pgs.; Shin et al, Cell Reports (2013) 5:654-665; Ji, Int. J. Hepatol. (2014) Vol. 2014, Article ID 513787, 11 pages), pulmonary fibrosis (Baek et al, Am. J. Resp. Cell Mol. Bio. (2012) 46:731-739); Tanjore et al, Biochim Biophys Acta (2012, online), (2013) 1832:940-947), kidney fibrosis (Chiang et al, Mol. Med. (2011) 17:1295-1305), cardiovascular disease (Spitler & Webb, Hypertension (2014) 63:e40-e45), and inflammatory bowel disease (Bogaert et al, PLoS One (2011) 6(10) e25589; Cao et al, Gastroent (2013) 144:989-1000).

[0005] IRE1α (alpha) is a transmembrane, bifunctional protein with cytoplasmic kinase and endoribonuclease activity. The N-terminal domain of IRE1α is proposed to sense the presence of unfolded proteins in the ER lumen, triggering activation of the cytoplasmic kinase domain, which, in turn, activates the C-terminal endoribonuclease. IRE1α transmits information across the ER lipid bilayer (Tirasophon et al, Genes & Develop. (2000) 14:2725-2736). Increased ER protein load and presence of unfolded proteins leads to the dissociation of the ER chaperone GRP78/BiP from IRE1α molecules, which bind to misfolded proteins and then undergo dimerization and trans-autophosphorylation in the cytoplasmic kinase domain. This leads to activation of the IRE1α endoribonuclease moiety in the cytosol. The IRE1α endoribonuclease has the ability to cleave the mRNA that encodes unspliced X box protein 1 (XBP1u); this excises a 26-nucleotide intron and leads to formation of spliced XBP1 (XBP1s) mRNA, which

encodes a potent transcription factor. After transport into the nucleus, the XBP1s protein binds to UPR promoter elements to initiate transcription of genes that enhance the ability of the ER to cope with unfolded proteins, for example, through enhanced ER-associated degradation of misfolded proteins, and through elevated levels of chaperones and disulfide isomerases that support protein folding in the ER. IRE1α activation is also associated with enlargement of the ER volume, which has been interpreted as an adaptive mechanism to increase protein folding capacity (Sriburi et al, J. Cell. Bio. (2004) 167:35-41); (Chen, Y. (2013) Trends Cell Biol., 23,547−555). In addition, the IRE1α endoribonuclease cleaves various mRNAs in a process called regulated IRE1α -dependent decay of mRNA (RIDD), which reduces both protein translation and import of proteins into the ER to help reestablish homeostasis (Hollien & Weissman, Science (2006) 313:104-107). In cancer cells, IRE1α suppresses ER-stress-induced apoptosis by reducing the mRNA levels of death receptor 5 (DR5) through RIDD (Lu et al., Science (2014) 345:98-101).

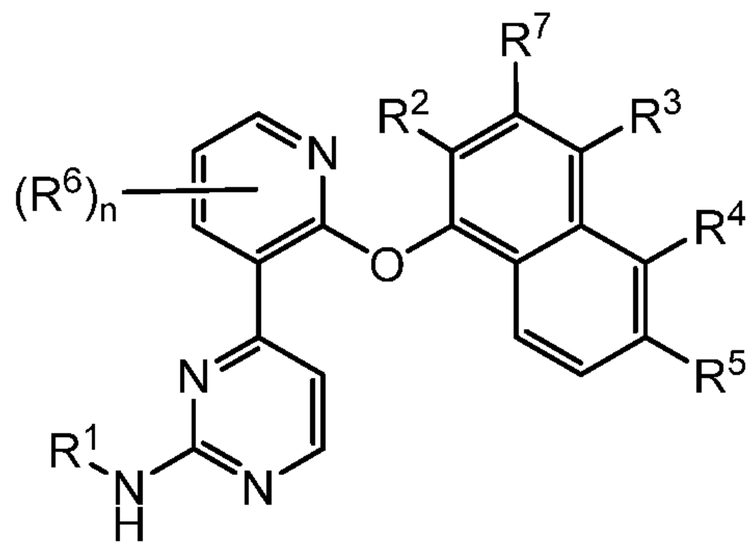
[0006] Besides degrading mRNA (Binet et al, Cell Metabol. (2013) 17:353-371), it was recently shown that IRE1α also has the ability to degrade microRNAs (miRs) (Upton et al, Science (2012) 338:818-822). miRs are short noncoding RNA oligonucleotides consisting of 17–25 nucleotides that generally act to inhibit gene expression by binding to complementary sequences in the 30-untranslated region of target mRNAs, either to repress mRNA translation or to induce mRNA cleavage. A number of cellular functions such as proliferation, differentiation, and apoptosis are regulated by miRs, and aberrant miR expression is observed in a variety of human diseases including fibrosis (Bowen et al, J. Pathol (2013) 229:274-285). Inhibitors that specifically target individual components of the UPR have recently been described. The inhibitor 4μ8C that stably binds to lysine 907 in the IRE1a endoribonuclease domain has been shown to inhibit both RIDD activity and XBP-1 splicing (Cross et al, Proc Natl. Acad. Sci. (2012) 109:E869-E878). High levels of 4μ8C cause no measurable toxicity in cells and concentrations ranging from 80 to 128 lM of 4μ8C completely block XBP1 splicing without affecting IRE1α (alpha) kinase activity (Cross et al, 2012). The inhibitor 4μ8C thus represents an important tool to delineate the functions of IRE1α in vivo as IRE1α-knockout mice die during embryonic development. Inhibition of IRE1α prevents activation of myofibroblasts and reduces fibrosis in animal models of liver and skin fibrosis. Pharmacological inhibition of IRE1α could revert the profibrotic phenotype of activated myofibroblasts isolated from patients with scleroderma and indicates that ER stress inhibitors

should be taken into consideration when developing new strategies for the treatment of fibrotic diseases (Heindryckx, F. et al (2016) EMBO Molecular Medicine Vol 8(7):729-744).

[0007] Activation of the UPR has been shown to be an important survival pathway for tumors of secretory cell origin like multiple myeloma that have a very high protein synthesis burden. Therefore, efforts to disrupt the UPR by blocking the IRE1α endoribonuclease cleavage and activation of XBP1 have been an active area of cancer research. As a specific IRE1α RNase product, XBP1s is a direct indicator of functional IRE1 inhibition. A potent and selective IRE1α inhibitor would serve as an important tool to test the hypothesis that, without full UPR activation, tumor cells would be driven to apoptosis. IRE1α inhibitors and activating compounds have been reported (Harrington, P.E. et al (2015) ACS Med. Chem. Lett. 6:68-72; Volkmann, K., et al (2011) J. Biol. Chem., 286:12743−12755; Cross, B.C.S., et al (2012) Proc. Natl. Acad. Sci. U.S.A., 109:E869−E878; Wang, L., et al (2012) Nat. Chem. Biol., 8:982−989; Ghosh, R., et al (2014) Cell, 158:534−548; Ranatunga, S., et al (2014) J. Med. Chem., 57, 4289−4301; US 9382230; US 8815885).

SUMMARY OF THE INVENTION

[0008] The invention relates generally to heteroaryl compounds with IRE1 modulation activity or function having the Formula I structure:



I

or stereoisomers, tautomers, or pharmaceutically acceptable salts thereof, and with the substituents and structural features described herein.

[0009] An aspect of the invention is a pharmaceutical composition of a Formula I compound and a pharmaceutically acceptable carrier, glidant, diluent, or excipient.

[0010] An aspect of the invention is a process for making a Formula I compound or a pharmaceutical composition comprising a Formula I compound.

[0011] An aspect of the invention is a method of treating an IRE1-related disease or disorder in a patient comprising administering a therapeutically effective amount of the pharmaceutical composition to a patient with an IRE1-related disease or disorder.

[0012] An aspect of the invention is a kit for treating a condition mediated by an IRE1 receptor, comprising:

a) a pharmaceutical composition comprising a Formula I compound; and

b) instructions for use.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

[0013] Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents which may be included within the scope of the present invention as defined by the claims. One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. The present invention is in no way limited to the methods and materials described. In the event that one or more of the incorporated literature, patents, and similar materials differs from or contradicts this application, including but not limited to defined terms, term usage, described techniques, or the like, this application controls. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. The nomenclature used in this Application is based on IUPAC systematic nomenclature, unless indicated otherwise.

Definitions

[0014] The term "substituent" denotes an atom or a group of atoms replacing a hydrogen atom on the parent molecule. The term "substituted" denotes that a specified group bears one or more substituents. Where any group may carry multiple substituents and a variety of possible substituents is provided, the substituents are independently selected and need not to be

the same. The term "unsubstituted" means that the specified group bears no substituents. The term "optionally substituted" means that the specified group is unsubstituted or substituted by one or more substituents, independently chosen from the group of possible substituents. When indicating the number of substituents, the term "one or more" means from one substituent to the highest possible number of substitution, i.e. replacement of one hydrogen up to replacement of all hydrogens by substituents.

[0015] The term "alkyl" as used herein refers to a saturated linear or branched-chain monovalent hydrocarbon radical of one to twelve carbon atoms (C_1–C_{12}), wherein the alkyl radical may be optionally substituted independently with one or more substituents described below. In another embodiment, an alkyl radical is one to eight carbon atoms (C_1–C_8), or one to six carbon atoms (C_1–C_6). Examples of alkyl groups include, but are not limited to, methyl (Me, -CH_3), ethyl (Et, -CH_2CH_3), 1-propyl (n-Pr, n-propyl, -$CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, -$CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, -$CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, -$CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, -$CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, -$C(CH_3)_3$), 1-pentyl (n-pentyl, -$CH_2CH_2CH_2CH_2CH_3$), 2-pentyl (-$CH(CH_3)CH_2CH_2CH_3$), 3-pentyl (-$CH(CH_2CH_3)_2$), 2-methyl-2-butyl (-$C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl (-$CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl (-$CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl (-$CH_2CH(CH_3)CH_2CH_3$), 1-hexyl (-$CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl (-$CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl (-$CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl (-$C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl (-$CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl (-$CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl (-$C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl (-$CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl (-$C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl (-$CH(CH_3)C(CH_3)_3$, 1-heptyl, 1-octyl, and the like.

[0016] The term "alkyldiyl" as used herein refers to a saturated linear or branched-chain divalent hydrocarbon radical of about one to twelve carbon atoms (C_1–C_{12}), wherein the alkyldiyl radical may be optionally substituted independently with one or more substituents described below. In another embodiment, an alkyldiyl radical is one to eight carbon atoms (C_1–C_8), or one to six carbon atoms (C_1–C_6). Examples of alkyldiyl groups include, but are not limited to, methylene (-CH_2-), ethylene (-CH_2CH_2-), propylene (-$CH_2CH_2CH_2$-), and the like. An alkyldiyl group may also be referred to as an "alkylene" group.

[0017] The term "alkenyl" refers to linear or branched-chain monovalent hydrocarbon radical of two to eight carbon atoms (C_2–C_8) with at least one site of unsaturation, i.e., a carbon-carbon, sp^2 double bond, wherein the alkenyl radical may be optionally substituted

independently with one or more substituents described herein, and includes radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. Examples include, but are not limited to, ethenyl or vinyl (-CH=CH_2), allyl (-CH_2CH=CH_2), and the like.

[0018] The terms "alkenylene" or "alkenyldiyl" refer to a linear or branched-chain divalent hydrocarbon radical of two to eight carbon atoms (C_2–C_8) with at least one site of unsaturation, i.e., a carbon-carbon, sp^2 double bond, wherein the alkenylene radical may be optionally substituted independently with one or more substituents described herein, and includes radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. Examples include, but are not limited to, ethenylene or vinylene (-CH=CH-), allyl (-CH_2CH=CH-), and the like.

[0019] The term "alkynyl" refers to a linear or branched monovalent hydrocarbon radical of two to eight carbon atoms (C_2–C_8) with at least one site of unsaturation, i.e., a carbon-carbon, sp triple bond, wherein the alkynyl radical may be optionally substituted independently with one or more substituents described herein. Examples include, but are not limited to, ethynyl (-C≡CH), 1-propynyl (-C≡CCH_3), propargyl (-CH_2C≡CH), and the like.

[0020] The term "alkynylene" or "alkynyldiyl" refer to a linear or branched divalent hydrocarbon radical of two to eight carbon atoms (C_2–C_8) with at least one site of unsaturation, i.e., a carbon-carbon, sp triple bond, wherein the alkynylene radical may be optionally substituted independently with one or more substituents described herein. Examples include, but are not limited to, ethynylene (-C≡C-), propynylene (propargylene, -CH_2C≡C-), and the like.

[0021] The terms "carbocycle", "carbocyclyl", "carbocyclic ring" and "cycloalkyl" refer to a monovalent non-aromatic, saturated or partially unsaturated ring having 3 to 12 carbon atoms (C_3–C_{12}) as a monocyclic ring or 7 to 12 carbon atoms as a bicyclic ring. Bicyclic carbocycles having 7 to 12 atoms can be arranged, for example, as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, and bicyclic carbocycles having 9 or 10 ring atoms can be arranged as a bicyclo [5,6] or [6,6] system, or as bridged systems such as bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane and bicyclo[3.2.2]nonane. Spiro carbocyclyl moieties are also included within the scope of this definition. Examples of spiro carbocyclyl moieties include [2.2]pentanyl, [2.3]hexanyl, and [2.4]heptanyl. Examples of monocyclic carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, cyclododecyl, and the like.

Carbocyclyl groups are optionally substituted independently with one or more substituents described herein.

[0022] The term "carbocyclyldiyl" refers to a divalent non-aromatic, saturated or partially unsaturated ring having 3 to 12 carbon atoms (C_3–C_{12}) as a monocyclic ring or 7 to 12 carbon atoms as a bicyclic ring.

[0023] "Aryl" means a monovalent aromatic hydrocarbon radical of 6-20 carbon atoms (C_6–C_{20}) derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Some aryl groups are represented in the exemplary structures as "Ar". Aryl includes bicyclic radicals comprising an aromatic ring fused to a saturated, partially unsaturated ring, or aromatic carbocyclic ring. Typical aryl groups include, but are not limited to, radicals derived from benzene (phenyl), substituted benzenes, naphthalene, anthracene, biphenyl, indenyl, indanyl, 1,2-dihydronaphthalene, 1,2,3,4-tetrahydronaphthyl, and the like. Aryl groups are optionally substituted independently with one or more substituents described herein.

[0024] The terms "arylene" or "aryldiyl" mean a divalent aromatic hydrocarbon radical of 6-20 carbon atoms (C_6–C_{20}) derived by the removal of two hydrogen atom from a two carbon atoms of a parent aromatic ring system. Some aryldiyl groups are represented in the exemplary structures as "Ar". Aryldiyl includes bicyclic radicals comprising an aromatic ring fused to a saturated, partially unsaturated ring, or aromatic carbocyclic ring. Typical aryldiyl groups include, but are not limited to, radicals derived from benzene (phenyldiyl), substituted benzenes, naphthalene, anthracene, biphenylene, indenylene, indanylene, 1,2-dihydronaphthalene, 1,2,3,4-tetrahydronaphthyl, and the like. Aryldiyl groups are also referred to as "arylene", and are optionally substituted with one or more substituents described herein.

[0025] The terms "heterocycle," "heterocyclyl" and "heterocyclic ring" are used interchangeably herein and refer to a saturated or a partially unsaturated (i.e., having one or more double and/or triple bonds within the ring) carbocyclic radical of 3 to about 20 ring atoms in which at least one ring atom is a heteroatom selected from nitrogen, oxygen, phosphorus and sulfur, the remaining ring atoms being C, where one or more ring atoms is optionally substituted independently with one or more substituents described below. A heterocycle may be a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 4 heteroatoms selected from N, O, P, and S) or a bicycle having 7 to 10 ring members (4 to 9 carbon atoms and 1 to 6 heteroatoms selected from N, O, P, and S), for example: a bicyclo [4,5], [5,5], [5,6], or [6,6] system. Heterocycles are described in Paquette, Leo A.; "Principles of Modern

Heterocyclic Chemistry" (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and J. Am. Chem. Soc. (1960) 82:5566. "Heterocyclyl" also includes radicals where heterocycle radicals are fused with a saturated, partially unsaturated ring, or aromatic carbocyclic or heterocyclic ring. Examples of heterocyclic rings include, but are not limited to, morpholin-4-yl, piperidin-1-yl, piperazinyl, piperazin-4-yl-2-one, piperazin-4-yl-3-one, pyrrolidin-1-yl, thiomorpholin-4-yl, S-dioxothiomorpholin-4-yl, azocan-1-yl, azetidin-1-yl, octahydropyrido[1,2-a]pyrazin-2-yl, [1,4]diazepan-1-yl, pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, homopiperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinylimidazolinyl, imidazolidinyl, 3-azabicyco[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, azabicyclo[2.2.2]hexanyl, 3H-indolyl quinolizinyl and N-pyridyl ureas. Spiro heterocyclyl moieties are also included within the scope of this definition. Examples of spiro heterocyclyl moieties include azaspiro[2.5]octanyl and azaspiro[2.4]heptanyl. Examples of a heterocyclic group wherein 2 ring atoms are substituted with oxo (=O) moieties are pyrimidinonyl and 1,1-dioxo-thiomorpholinyl. The heterocycle groups herein are optionally substituted independently with one or more substituents described herein.

[0026] The term "heterocyclyldiyl" refers to a divalent, saturated or a partially unsaturated (i.e., having one or more double and/or triple bonds within the ring) carbocyclic radical of 3 to about 20 ring atoms in which at least one ring atom is a heteroatom selected from nitrogen, oxygen, phosphorus and sulfur, the remaining ring atoms being C, where one or more ring atoms is optionally substituted independently with one or more substituents as described.

[0027] The term "heteroaryl" refers to a monovalent aromatic radical of 5-, 6-, or 7-membered rings, and includes fused ring systems (at least one of which is aromatic) of 5-20 atoms, containing one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur. Examples of heteroaryl groups are pyridinyl (including, for example, 2-hydroxypyridinyl), imidazolyl, imidazopyridinyl, pyrimidinyl (including, for example, 4-hydroxypyrimidinyl), pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxadiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl,

tetrahydroisoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, triazolyl, thiadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. Heteroaryl groups are optionally substituted independently with one or more substituents described herein.

[0028] The term "heteroaryldiyl" refers to a divalent aromatic radical of 5-, 6-, or 7-membered rings, and includes fused ring systems (at least one of which is aromatic) of 5-20 atoms, containing one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0029] The heterocycle or heteroaryl groups may be carbon (carbon-linked), or nitrogen (nitrogen-linked) bonded where such is possible. By way of example and not limitation, carbon bonded heterocycles or heteroaryls are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline.

[0030] By way of example and not limitation, nitrogen bonded heterocycles or heteroaryls are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline.

[0031] The terms "treat" and "treatment" refer to therapeutic treatment, wherein the object is to slow down (lessen) an undesired physiological change or disorder, such as the development or spread of arthritis or cancer. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as

compared to expected survival if not receiving treatment. Those in need of treatment include those with the condition or disorder.

[0032] The phrase "therapeutically effective amount" means an amount of a compound of the present invention that (i) treats the particular disease, condition, or disorder, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition, or disorder described herein. In the case of cancer, the therapeutically effective amount of the drug may reduce the number of cancer cells; reduce the tumor size; inhibit (i.e., slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; and/or relieve to some extent one or more of the symptoms associated with the cancer. To the extent the drug may prevent growth and/or kill existing cancer cells, it may be cytostatic and/or cytotoxic. For cancer therapy, efficacy can be measured, for example, by assessing the time to disease progression (TTP) and/or determining the response rate (RR).

[0033] The terms "cancer" refers to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. A "tumor" comprises one or more cancerous cells. Examples of cancer include, but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia or lymphoid malignancies. More particular examples of such cancers include squamous cell cancer (*e.g.,* epithelial squamous cell cancer), lung cancer including small- cell lung cancer, non-small cell lung cancer ("NSCLC"), adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, as well as head and neck cancer.

[0034] "Hematological malignancies" (British spelling "Haematological" malignancies) are the types of cancer that affect blood, bone marrow, and lymph nodes. As the three are intimately connected through the immune system, a disease affecting one of the three will often affect the others as well: although lymphoma is a disease of the lymph nodes, it often spreads to the bone marrow, affecting the blood. Hematological malignancies are malignant neoplasms ("cancer"), and they are generally treated by specialists in hematology and/or oncology. In some centers "Hematology/oncology" is a single subspecialty of internal

medicine while in others they are considered separate divisions (there are also surgical and radiation oncologists). Not all hematological disorders are malignant ("cancerous"); these other blood conditions may also be managed by a hematologist. Hematological malignancies may derive from either of the two major blood cell lineages: myeloid and lymphoid cell lines. The myeloid cell line normally produces granulocytes, erythrocytes, thrombocytes, macrophages and mast cells; the lymphoid cell line produces B, T, NK and plasma cells. Lymphomas, lymphocytic leukemias, and myeloma are from the lymphoid line, while acute and chronic myelogenous leukemia, myelodysplastic syndromes and myeloproliferative diseases are myeloid in origin. Leukemias include Acute lymphoblastic leukemia (ALL), Acute myelogenous leukemia (AML), Chronic lymphocytic leukemia (CLL), Chronic myelogenous leukemia (CML), Acute monocytic leukemia (AMOL) and small lymphocytic lymphoma (SLL). Lymphomas include Hodgkin's lymphomas (all four subtypes) and Non-Hodgkin's lymphomas (NHL, all subtypes).

[0035] A “chemotherapeutic agent” is a chemical compound useful in the treatment of cancer, regardless of mechanism of action. Classes of chemotherapeutic agents include, but are not limited to: alkylating agents, antimetabolites, spindle poison plant alkaloids, cytotoxic/antitumor antibiotics, topoisomerase inhibitors, antibodies, photosensitizers, and kinase inhibitors. Chemotherapeutic agents include compounds used in “targeted therapy” and conventional chemotherapy. Examples of chemotherapeutic agents include proteasome inhibitors such as bortezomib (VELCADE®, Millennium Pharm., CAS Reg. No. 179324-69-7), carfilzomib (KYPROLIS®, Amgen, CAS Reg. No. 868540-17-4) and ixazomib (NINLARO®, Takeda, CAS Reg. No. 1072833-77-2); lenalidomide (REVLIMID®, Celgene, CAS Reg. No. 191732-72-6); pomalidomide (POMALYST®, Celgene, CAS Reg. No. 19171-19-8); venetoclax (VENCLEXTA®, GDC-0199, ABT-199, AbbVie/Genentech, CAS Reg. No. 1257044-40-8); ibrutinib (IMBRUVICA™, APCI-32765, Pharmacyclics Inc./Janssen Biotech Inc.; CAS Reg. No. 936563-96-1, US 7514444), idelalisib (ZYDELIG®, CAL-101, GS 1101, GS-1101, Gilead Sciences Inc.; CAS Reg. No. 1146702-54-6), erlotinib (TARCEVA®, Genentech/OSI Pharm.), docetaxel (TAXOTERE®, Sanofi-Aventis), 5-FU (fluorouracil, 5-fluorouracil, CAS Reg. No. 51-21-8), gemcitabine (GEMZAR®, Lilly), PD-0325901 (CAS No. 391210-10-9, Pfizer), cisplatin (Platinol®, (*SP*-4-2)-diamminedichloroplatinum(II), cis-diamine, dichloroplatinum(II), CAS No. 15663-27-1), carboplatin (CAS No. 41575-94-4), paclitaxel (TAXOL®, Bristol-Myers Squibb Oncology, Princeton, N.J.), trastuzumab (HERCEPTIN®, Genentech), temozolomide (4-methyl-5-oxo- 2,3,4,6,8-pentazabicyclo [4.3.0]

nona-2,7,9-triene- 9-carboxamide, CAS No. 85622-93-1, TEMODAR®, TEMODAL®, Schering Plough), tamoxifen ((*Z*)-2-[4-(1,2-diphenylbut-1-enyl)phenoxy]-*N*,*N*-dimethylethanamine, NOLVADEX®, ISTUBAL®, VALODEX®), and doxorubicin (ADRIAMYCIN®, CAS No. 23214-92-8), Akti-1/2, HPPD, and rapamycin.

[0036] Chemotherapeutic agents include inhibitors of B-cell receptor targets such as BTK, Bcl-2 and JAK inhibitors.

[0037] More examples of chemotherapeutic agents include: oxaliplatin (ELOXATIN®, Sanofi), sutent (SUNITINIB®, SU11248, Pfizer), letrozole (FEMARA®, Novartis), palbociclib, (IBRANCE®, Pfizer), imatinib mesylate (GLEEVEC®, Novartis), cobimetinib (COTELLIC™, GDC-0973, XL-518, Exelixis, WO 2007/044515, CAS Reg. No. 934660-93-2), ARRY-886 (Mek inhibitor, AZD6244, Array BioPharma, Astra Zeneca), SF-1126 (PI3K inhibitor, Semafore Pharmaceuticals), BEZ-235 (PI3K inhibitor, Novartis), XL-147 (PI3K inhibitor, Exelixis), PTK787/ZK 222584 (Novartis), fulvestrant (FASLODEX®, AstraZeneca), leucovorin (folinic acid), rapamycin (sirolimus, RAPAMUNE®, Wyeth), lapatinib (TYKERB®, GSK572016, Glaxo Smith Kline), lonafarnib (SARASAR™, SCH 66336, Schering Plough), sorafenib (NEXAVAR®, BAY43-9006, Bayer Labs), gefitinib (IRESSA®, AstraZeneca), irinotecan (CAMPTOSAR®, CPT-11, Pfizer), tipifarnib (ZARNESTRA™, Johnson & Johnson), ABRAXANE™ (Cremophor-free), albumin-engineered nanoparticle formulations of paclitaxel (American Pharmaceutical Partners, Schaumberg, Il), vandetanib (rINN, ZD6474, ZACTIMA®, AstraZeneca), chlorambucil, AG1478, AG1571 (SU 5271; Sugen), temsirolimus (TORISEL®, Wyeth), pazopanib (GlaxoSmithKline), canfosfamide (TELCYTA®, Telik), thiotepa and cyclosphosphamide (CYTOXAN®, NEOSAR®); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analog topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogs); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogs, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, chlorophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosoureas such as carmustine,

chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, calicheamicin gamma1I, calicheamicin omegaI1 (Angew Chem. Intl. Ed. Engl. (1994) 33:183-186); dynemicin, dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, carminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, nemorubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogs such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfornithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, OR); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; vinorelbine (NAVELBINE®); novantrone; teniposide; edatrexate; daunomycin; aminopterin; capecitabine (XELODA®, Roche); ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; and pharmaceutically acceptable salts, acids and derivatives of any of the above.

[0038] Also included in the definition of "chemotherapeutic agent" are: (i) anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including NOLVADEX®; tamoxifen citrate), raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, ketoxifene, LY117018, onapristone, and FARESTON® (toremifine citrate) and selective estrogen receptor modulators (SERDs) such as brilanestrant (GDC-0810, AR810, Genentech, Seragon), GDC-0927 (Genentech, Seragon), fulvestrant (FASLODEX®, Astra Zeneca); (ii) aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, MEGASE® (megestrol acetate), AROMASIN® (exemestane; Pfizer), formestanie, fadrozole, RIVISOR® (vorozole), FEMARA® (letrozole; Novartis), and ARIMIDEX® (anastrozole; AstraZeneca); (iii) anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; as well as troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); (iv) protein kinase inhibitors such as MEK inhibitors, such as cobimetinib (WO 2007/044515); (v) lipid kinase inhibitors, such as taselisib (GDC-0032, Genentech Inc.); (vi) antisense oligonucleotides, particularly those which inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation, for example, PKC-alpha, Raf and H-Ras, such as oblimersen (GENASENSE®, Genta Inc.); (vii) ribozymes such as VEGF expression inhibitors (e.g., ANGIOZYME®) and HER2 expression inhibitors; (viii) vaccines such as gene therapy vaccines, for example, ALLOVECTIN®, LEUVECTIN®, and VAXID®; PROLEUKIN® rIL-2; topoisomerase 1 inhibitors such as LURTOTECAN®; ABARELIX® rmRH; (ix) anti-angiogenic agents such as bevacizumab (AVASTIN®, Genentech); and pharmaceutically acceptable salts, acids and derivatives of any of the above.

[0039] Also included in the definition of "chemotherapeutic agent" are therapeutic antibodies such as atezolizumab (TECENTRIQ®, anti-PDL-1, Genentech, CAS Reg. No. 1380723-44-3), nivolumab (OPDIVO®, Bristol-Myers Squib, CAS Reg. No. 946414-94-4), daratumumab (DARZALEX®, anti-CD38, Janssen Biotech, CAS Reg. No. 945721-28-8), pembrolizumab (KEYTRUDA®, MK-3475, lambrolizumab, Merck, anti-PD1, CAS Reg. No. 1374853-91-4), alemtuzumab (Campath), bevacizumab (AVASTIN®, Genentech); cetuximab (ERBITUX®, Imclone); panitumumab (VECTIBIX®, Amgen), rituximab (RITUXAN®, Genentech/Biogen Idec), pertuzumab (PERJETA™, 2C4, Genentech), trastuzumab (HERCEPTIN®, Genentech), trastuzumab emtansine (KADCYLA®, Genentech Inc.), and tositumomab (BEXXAR, Corixia).

[0040] A "metabolite" is a product produced through metabolism in the body of a specified compound or salt thereof. Metabolites of a compound may be identified using routine techniques known in the art and their activities determined using tests such as those described herein. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, deamidation, esterification, deesterification, enzymatic cleavage, and the like, of the administered compound. Accordingly, the invention includes metabolites of compounds of the invention, including compounds produced by a process comprising contacting a Formula I compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof.

[0041] The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products.

[0042] The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

[0043] The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

[0044] "Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

[0045] "Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

[0046] Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., *McGraw-Hill Dictionary of Chemical Terms* (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., New York, 1994. The compounds of the invention may contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the invention, including but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present invention. Many organic compounds exist in optically active

forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or *R* and *S,* are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity. Enantiomers may be separated from a racemic mixture by a chiral separation method, such as supercritical fluid chromatography (SFC). Assignment of configuration at chiral centers in separated stereoisomers may be tentative, and depicted in Table 1 structures for illustrative purposes, before stereochemistry is definitively established, such as from x-ray crystallographic data.

[0047] The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

[0048] The term "pharmaceutically acceptable salts" denotes salts which are not biologically or otherwise undesirable. Pharmaceutically acceptable salts include both acid and base addition salts. The phrase "pharmaceutically acceptable" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

[0049] The term "pharmaceutically acceptable acid addition salt" denotes those pharmaceutically acceptable salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, carbonic acid, phosphoric acid, and organic acids selected from aliphatic, cycloaliphatic, aromatic, aryl-aliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, gluconic acid, lactic acid, pyruvic acid, oxalic acid, malic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, aspartic acid, ascorbic acid, glutamic acid,

anthranilic acid, benzoic acid, cinnamic acid, mandelic acid, embonic acid, phenylacetic acid, methanesulfonic acid "mesylate", ethanesulfonic acid, p-toluenesulfonic acid, and salicyclic acid.

[0050] The term "pharmaceutically acceptable base addition salt" denotes those pharmaceutically acceptable salts formed with an organic or inorganic base. Examples of acceptable inorganic bases include sodium, potassium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, and aluminum salts. Salts derived from pharmaceutically acceptable organic nontoxic bases includes salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, and polyamine resins.

[0051] A "solvate" refers to an association or complex of one or more solvent molecules and a compound of the invention. Examples of solvents that form solvates include, but are not limited to, water (i.e., "hydrate"), isopropanol, ethanol, methanol, DMSO, ethylacetate (EtOAc), acetic acid (AcOH), and ethanolamine.

[0052] The term "EC_{50}" is the half maximal effective concentration" and denotes the plasma concentration of a particular compound required for obtaining 50% of the maximum of a particular effect in vivo.

[0053] The term "Ki" is the inhibition constant and denotes the absolute binding affinity of a particular inhibitor to a receptor. It is measured using competition binding assays and is equal to the concentration where the particular inhibitor would occupy 50% of the receptors if no competing ligand (e.g. a radioligand) was present. Ki values can be converted logarithmically to pKi values (-log Ki), in which higher values indicate exponentially greater potency.

[0054] The term "IC_{50}" is the half maximal inhibitory concentration and denotes the concentration of a particular compound required for obtaining 50% inhibition of a biological process in vitro. IC_{50} values can be converted logarithmically to pIC_{50} values (-log IC_{50}), in which higher values indicate exponentially greater potency. The IC_{50} value is not an absolute value but depends on experimental conditions e.g. concentrations employed, and can be converted to an absolute inhibition constant (Ki) using the Cheng-Prusoff equation (Biochem.

Pharmacol. (1973) 22:3099). Other percent inhibition parameters, such as IC_{70}, IC_{90}, etc., may be calculated.

[0055] The terms "compound of this invention," and "compounds of the present invention" and "compounds of Formula I" include compounds of Formula I, and stereoisomers, geometric isomers, tautomers, solvates, metabolites, and pharmaceutically acceptable salts and prodrugs thereof.

[0056] Any formula or structure given herein, including Formula I compounds, is also intended to represent hydrates, solvates, and polymorphs of such compounds, and mixtures thereof.

[0057] Any formula or structure given herein, including Formula I compounds, is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as, but not limited to ^{2}H (deuterium, D), ^{3}H (tritium), ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F, ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, and ^{125}I. Various isotopically labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated. Such isotopically labeled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. Deuterium labeled or substituted therapeutic compounds of the invention may have improved DMPK (drug metabolism and pharmacokinetics) properties, relating to distribution, metabolism, and excretion (ADME). Substitution with heavier isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements. An 18F labeled compound may be useful for PET or SPECT studies. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent. Further, substitution with heavier isotopes, particularly deuterium (i.e., ^{2}H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is

understood that deuterium in this context is regarded as a substituent in the compound of the formula (I). The concentration of such a heavier isotope, specifically deuterium, may be defined by an isotopic enrichment factor. In the compounds of this invention any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Accordingly, in the compounds of this invention any atom specifically designated as a deuterium (D) is meant to represent deuterium.

IRE1 Assays

[0058] Inhibition of IRE1α RNase activity was determined in an enzyme assay that measured cleavage of the XBP1 stem loop by autophosphorylated IRE1α. This assay format was chosen to ensure that inhibitors of either the IRE1α kinase or the RNase domains would be identified. Binding to the ATP pocket and inhibition of IRE1α kinase activity are not necessarily required to inhibit the RNase activity. Compounds were also profiled in cellular assays by direct measurement of XBP1s (B-DNA assay) or by quantification of the luciferase signal in HT1080 XBP1-Luc, which carries a luciferase fusion that is only in frame and expressed from the spliced XBP1 transcript. In the IRE1α enzyme and XPB1-Luc assays, pyrimidinyl-pyridyloxy-naphthyl compounds described herein (e.g., compounds in Tables 1 and 2) demonstrated activity.

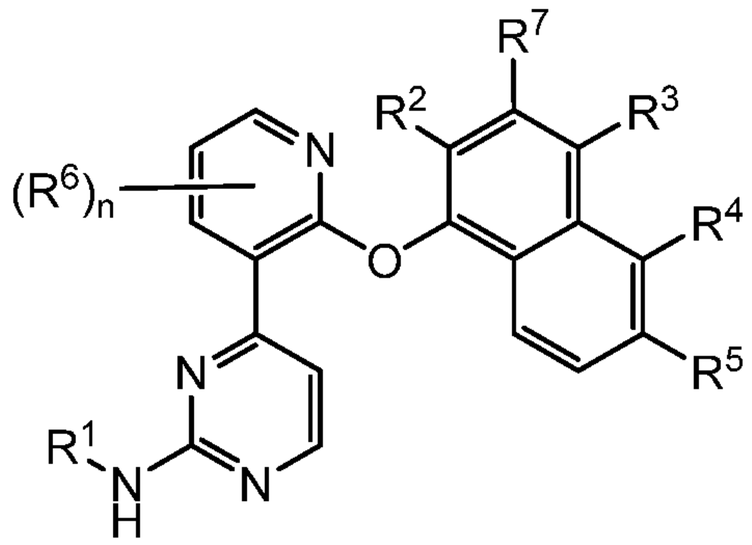
Pyrimidinyl-pyridyloxy-naphthyl Compounds

[0059] The present invention provides pyrimidinyl-pyridyloxy-naphthyl compounds of Formula I including subgeneric formulas and pharmaceutical formulations thereof, which are potentially useful in the treatment of diseases, conditions and/or disorders modulated by inositol requiring enzyme 1 (IRE1).

[0060] Compounds of the invention include salt forms of Formula I compounds.

[0061] In an effort to probe this pathway and identify suitable therapeutic compounds, IRE1α inhibitors were designed and prepared.

[0062] Formula I compounds have the structure:



I

or stereoisomers, tautomers, or pharmaceutically acceptable salts thereof, wherein:

R^1 is selected from C_3–C_{12} cycloalkyl, C_3-C_{12} heterocyclyl, C_1–C_{12} heteroaryl, C_6–C_{20} aryl, –(C_1–C_6 alkyldiyl)–(C_3–C_{12} cycloalkyl), and –(C_1–C_6 alkyldiyl)–(C_3-C_{12} heterocyclyl);

R^2 is selected from H, F, Cl, –CN, $-OCH_3$, $-OCH_2CH_3$, and C_1–C_6 alkyl;

R^3 and R^4 are independently selected from H, –CN, C_3-C_{12} cycloalkyl, C_3-C_{12} heterocyclyl, C_1–C_{12} heteroaryl, C_6–C_{20} aryl, –O–(C_1–C_{12} heteroaryl), –O–(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl), $-NR^8R^9$, $-NR^8C(O)R^9$, $-NR^8C(O)OR^9$, $-NR^8C(O)NHR^9$, $-NR^8SO_2$–(C_1–C_6 alkyl), $-NR^8SO_2$–(C_1–C_6 alkenyl), $-NR^8SO_2$–(C_1–C_{12} heteroaryl), $-NR^8SO_2$–(C_1–C_6 alkyldiyl)–(C_3–C_{12} cycloalkyl), $-NR^8SO_2$–(C_1–C_6 alkyldiyl)–(C_3-C_{12} heterocyclyl), $-NR^8SO_2$–(C_1–C_6 alkyldiyl)–(C_1–C_{12} heteroaryl), $-NR^8SO_2$–(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl), $-NR^8SO_2NR^8R^9$, and $-SO_2NR^8R^9$;

R^5 and R^7 are independently selected from H, F, Cl, –CN, $-CH_2OH$, $-C(O)NH_2$, –OH, $-OCH_3$, $-OCH_2CH_3$, and C_1–C_6 alkyl;

R^6 are independently selected from H, F, Cl, Br, I, –CN, $-NO_2$, and C_1–C_6 alkyl;

R^8 is independently selected from H, and C_1–C_6 alkyl;

R^9 is independently selected from C_1–C_6 alkyl, C_2–C_6 alkenyl, C_3–C_{12} cycloalkyl, C_3-C_{12} heterocyclyl, C_1–C_{12} heteroaryl, C_6–C_{20} aryl; –(C_1–C_6 alkyldiyl)–(C_3–C_{12} cycloalkyl), –(C_1–C_6 alkyldiyl)–(C_3-C_{12} heterocyclyl), –(C_1–C_6 alkyldiyl)–(C_1–C_6 heteroaryl), –(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl), and –(C_1–C_6 alkyldiyl)–O–(C_6–C_{20} aryl); and

n is 0, 1, 2, or 3;

wherein cycloalkyl, heterocyclyl, heteroaryl, aryl, alkyl, alkyldiyl, and alkenyl are optionally and independently substituted with one or more groups selected from F, Cl, Br, I, -CN, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2C(CH_3)_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OH$, $-C(CH_3)_2OH$, $-CH(OH)CH(CH_3)_2$,

-$C(CH_3)_2CH_2OH$, $–CH_2CH_2CH_2OH$, $–CH_2CH_2C(CH_3)_2OH$, $–CH_2CH_2OCH_3$, -$CH_2CH(CH_3)OCH_3$, $–CH_2CH_2CH_2OCH_3$, $–CH_2CH_2C(CH_3)_2OCH_3$, $–CH_2CH_2SO_2CH_3$, -$CH_2OP(O)(OH)_2$, $–CH_2F$, $–CHF_2$, $–CH_2NH_2$, $–CH_2NHSO_2CH_3$, $–CH_2NHCH_3$, –$CH_2N(CH_3)_2$, -CF_3, $–CH_2CF_3$, $–CH_2CHF_2$, $–CH_2CH_2CHF_2$, $–CH_2CH_2CF_3$,–$CH(CH_3)CN$, –$C(CH_3)_2CN$, -CH_2CN, $–CO_2H$, $–COCH_3$, $–CO_2CH_3$, $–CO_2C(CH_3)_3$, $–COCH(OH)CH_3$, –$CONH_2$, -$CONHCH_3$, $–CONHCH_2CH_3$, $–CONHCH(CH_3)_2$, $–CON(CH_3)_2$, $–C(CH_3)_2CONH_2$, $–NH_2$, -$NHCH_3$, -$N(CH_3)_2$, $–N(CH_3)CH_2CH_3$, $–NHCOCH_3$, $–N(CH_3)COCH_3$, $–NHS(O)_2CH_3$, -$N(CH_3)C(CH_3)_2CONH_2$, $–N(CH_3)CH_2CH_2S(O)_2CH_3$, $–NO_2$, =O, –OH, $–OCH_3$, $–OCH_2CH_3$, -$OCH_2CH_2OCH_3$, $–OCH_2CH_2OH$, $–OCH_2CH_2N(CH_3)_2$, $–OP(O)(OH)_2$, $–S(O)_2N(CH_3)_2$, -SCH_3, -$S(O)_2CH_3$, $–S(O)_3H$, cyclopropyl, cyclopropylamide, cyclobutyl, oxetanyl, azetidinyl, 1-methylazetidin-3-yl)oxy, *N*-methyl-N-oxetan-3-ylamino, azetidin-1-ylmethyl, benzyloxyphenyl, pyrrolidin-1-yl, pyrrolidin-1-yl-methanone, phenyl, piperazin-1-yl, piperidin-1-yl, morpholinomethyl, morpholino-methanone, and morpholino.

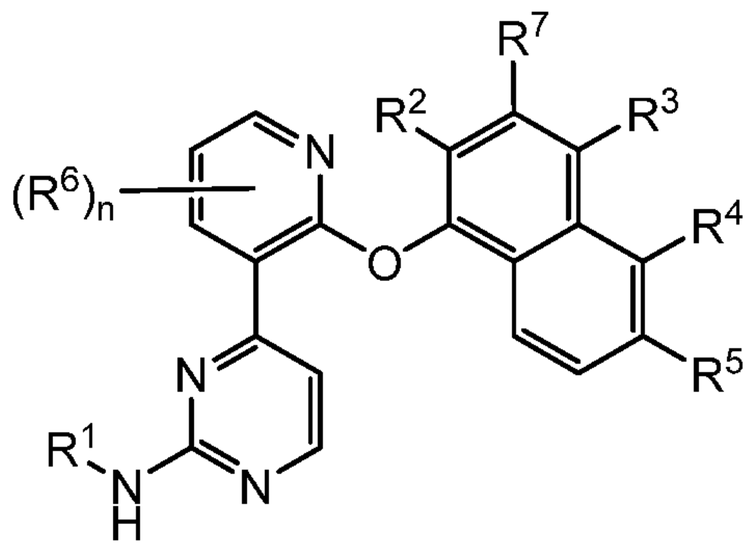
[0063] In some embodiments of the compound of the Formula I, or stereoisomers, tautomers, or pharmaceutically acceptable salts thereof, the compound is other than Compound Nos. 1x-17x of Table 1X. In some embodiments of the Formula I, or stereoisomers, tautomers, or pharmaceutically acceptable salts thereof, wherein R^3 is other than –NH-(heteroaryl).

Table 1X

No.	Name
1x	1,4-Cyclohexanediamine, N1-[4-[2-[[4-(2-benzoxazolylamino)-2-methyl-1-naphthalenyl]oxy]-3-pyridinyl]-2-pyrimidinyl]-, trans-
2x	1H-Benzimidazol-2-amine, N-[3-methyl-4-[[3-[2-[(3S)-3-piperidinylamino]-4-pyrimidinyl]-2-pyridinyl]oxy]-1-naphthalenyl]-
3x	1,4-Cyclohexanediamine, N1-[4-[2-[[4-(1H-benzimidazol-2-ylamino)-2-methyl-1-naphthalenyl]oxy]-3-pyridinyl]-2-pyrimidinyl]-, trans-
4x	1,4-Cyclohexanediamine, N1-[4-[2-[[4-(1H-benzimidazol-2-ylamino)-1-naphthalenyl]oxy]-3-pyridinyl]-2-pyrimidinyl]-, cis-
5x	1,4-Cyclohexanediamine, N1-[4-[2-[[4-(1H-benzimidazol-2-ylamino)-1-naphthalenyl]oxy]-3-pyridinyl]-2-pyrimidinyl]-, trans-
6x	1H-Benzimidazol-2-amine, N-[4-[[3-[2-[(3S)-3-piperidinylamino]-4-pyrimidinyl]-2-pyridinyl]oxy]-1-naphthalenyl]-
7x	1H-Benzimidazol-2-amine, N-[4-[[3-[2-[(3R)-3-piperidinylamino]-4-pyrimidinyl]-2-pyridinyl]oxy]-1-naphthalenyl]-
8x	1H-Benzimidazol-2-amine, N-[4-[[3-[2-[(1-methyl-3-piperidinyl)amino]-4-pyrimidinyl]-2-pyridinyl]oxy]-1-naphthalenyl]-

9x	Ethanol, 2-[[4-[2-[[4-(1H-benzimidazol-2-ylamino)-1-naphthalenyl]oxy]-3-pyridinyl]-2-pyrimidinyl]amino]-
10x	1H-Benzimidazol-2-amine, N-[4-[[3-[2-[(3-methylbutyl)amino]-4-pyrimidinyl]-2-pyridinyl]oxy]-1-naphthalenyl]-
11x	1,2-Ethanediamine, N2-[4-[2-[[4-(1H-benzimidazol-2-ylamino)-2-methyl-1-naphthalenyl]oxy]-3-pyridinyl]-2-pyrimidinyl]-N1,N1-dimethyl-
12x	1H-Benzimidazol-2-amine, N-[4-[[3-[2-[[3-(1-piperidinyl)propyl]amino]-4-pyrimidinyl]-2-pyridinyl]oxy]-1-naphthalenyl]-
13x	1H-Benzimidazol-2-amine, N-[4-[[3-[2-[(1-methyl-4-piperidinyl)amino]-4-pyrimidinyl]-2-pyridinyl]oxy]-1-naphthalenyl]-
14x	1H-Benzimidazol-2-amine, N-[4-[[3-[2-[[(1-ethyl-4-piperidinyl)methyl]amino]-4-pyrimidinyl]-2-pyridinyl]oxy]-1-naphthalenyl]-
15x	1H-Benzimidazol-2-amine, N-[4-[[3-[2-[[2-(1-methyl-2-pyrrolidinyl)ethyl]amino]-4-pyrimidinyl]-2-pyridinyl]oxy]-1-naphthalenyl]-
16x	1H-Benzimidazol-2-amine, N-[4-[[3-[2-[[3-(1-pyrrolidinyl)propyl]amino]-4-pyrimidinyl]-2-pyridinyl]oxy]-1-naphthalenyl]-
17x	1H-Benzimidazol-2-amine, N-[4-[[3-[2-[[2-(4-morpholinyl)ethyl]amino]-4-pyrimidinyl]-2-pyridinyl]oxy]-1-naphthalenyl]-

[0064] In some embodiments, provided is a compound of the Formula I′:



I′

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein:

R^1 is C_3–C_{12} cycloalkyl, C_3-C_{12} heterocyclyl, C_1–C_{12} heteroaryl, C_6–C_{20} aryl, -(C_1–C_6 alkyldiyl)–(C_3–C_{12} cycloalkyl), or –(C_1–C_6 alkyldiyl)–(C_3-C_{12} heterocyclyl);

R^2 is H, F, Cl, –CN, $–OCH_3$, $–OCH_2CH_3$, or C_1–C_6 alkyl;

R^3 is H, –CN, C_3-C_{12} cycloalkyl, C_3-C_{12} heterocyclyl, C_1–C_{12} heteroaryl, C_6–C_{20} aryl, -O–(C_1–C_{12} heteroaryl), -O–(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl), -N(R^8)(C_1–C_6 alkyl), $-NR^8C(O)R^9$, $-NR^8C(O)OR^9$, $-NR^8C(O)NHR^9$, $-NR^8SO_2$–(C_1–C_6 alkyl), $-NR^8SO_2$–(C_1–C_6 alkenyl), $-NR^8SO_2$–(C_3–C_{12} cycloalkyl), $-NR^8SO_2$–(C_1–C_{12} heteroaryl), $-NR^8SO_2$–(C_1–C_6 alkyldiyl)–(C_3–C_{12} cycloalkyl), $-NR^8SO_2$–(C_1–C_6 alkyldiyl)–(C_3-C_{12} heterocyclyl), $-NR^8SO_2$–

(C_1–C_6 alkyldiyl)–(C_1–C_{12} heteroaryl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl), -$NR^8SO_2NR^8R^9$, or -$SO_2NR^8R^9$;

R^4 is H, –CN, C_3-C_{12} cycloalkyl, C_3-C_{12} heterocyclyl, C_1–C_{12} heteroaryl, C_6–C_{20} aryl, -O–(C_1–C_{12} heteroaryl), -O–(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl), -NR^8R^9, -$NR^8C(O)R^9$, -$NR^8C(O)OR^9$, -$NR^8C(O)NHR^9$, -NR^8SO_2–(C_1–C_6 alkyl), -NR^8SO_2–(C_1–C_6 alkenyl), -NR^8SO_2–(C_1–C_{12} heteroaryl), -NR^8SO_2–(C_3–C_{12} cycloalkyl), -NR^8SO_2–(C_3-C_{12} heterocyclyl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_3–C_{12} cycloalkyl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_3-C_{12} heterocyclyl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_1–C_{12} heteroaryl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl), -$NR^8SO_2NR^8R^9$, or -$SO_2NR^8R^9$;

each R^5 and R^7 are independently H, F, Cl, –CN, –CH_2OH, –$C(O)NH_2$, –OH, -OCH_3, -OCH_2CH_3, or C_1–C_6 alkyl;

n is 0, 1, 2, or 3;

each R^6 is independently H, F, Cl, Br, I, –CN, –NO_2, -O-(C_1–C_6 alkyl) or C_1–C_6 alkyl;

each R^8 is independently H, or C_1–C_6 alkyl;

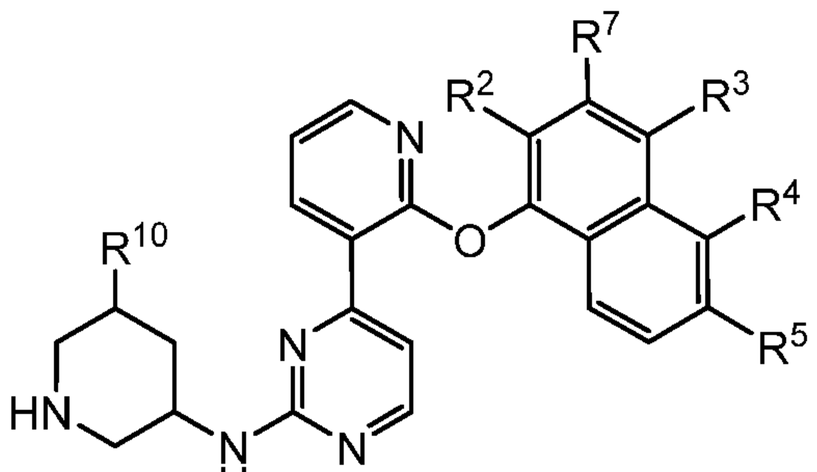
each R^9 is independently C_1–C_6 alkyl, C_2–C_6 alkenyl, C_3–C_{12} cycloalkyl, C_3-C_{12} heterocyclyl, C_1–C_{12} heteroaryl, C_6–C_{20} aryl; –(C_1–C_6 alkyldiyl)–(C_3–C_{12} cycloalkyl), –(C_1–C_6 alkyldiyl)–(C_3-C_{12} heterocyclyl), –(C_1–C_6 alkyldiyl)–(C_1–C_6 heteroaryl), –(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl), or –(C_1–C_6 alkyldiyl)–O–(C_6–C_{20} aryl); and

wherein cycloalkyl, heterocyclyl, heteroaryl, aryl, alkyl, alkyldiyl, and alkenyl are optionally and independently substituted with one or more (e.g., 1 to 2, 1 to 3, 1 to 4, or 1 to 5) substituents selected from the group consisting of F, Cl, Br, I, –CN, –CH_3, –CH_2CH_3, -$CH_2CH_2CH_3$, –$CH(CH_3)_2$, –$CH_2CH(CH_3)_2$, -$CH(CH_3)CH_2CH_3$, –$CH_2C(CH_3)_3$, –CH_2OH, -CH_2OCH_3, –CH_2CH_2OH, –$C(CH_3)_2OH$, -$CH(OH)CH(CH_3)_2$, –$C(CH_3)_2CH_2OH$, -$CH_2CH_2CH_2OH$, –$CH_2CH_2C(CH_3)_2OH$, -$CH_2CH_2OCH_3$, –$CH_2CH(CH_3)OCH_3$, -$CH_2CH_2CH_2OCH_3$, –$CH_2CH_2C(CH_3)_2OCH_3$, -$CH_2CH_2SO_2CH_3$, –$CH_2OP(O)(OH)_2$, -CH_2F, -CHF_2, –CH_2NH_2, –$CH_2NHSO_2CH_3$, -CH_2NHCH_3, –$CH_2N(CH_3)_2$, –CF_3, –CH_2CF_3, -CH_2CHF_2, –$CH_2CH_2CHF_2$, –$CH_2CH_2CF_3$, -$CH(CH_3)CN$, –$C(CH_3)_2CN$, –CH_2CN, –CO_2H, -$COCH_3$, -CO_2CH_3, –$CO_2C(CH_3)_3$, -$COCH(OH)CH_3$, –$CONH_2$, –$CONHCH_3$, -$CONHCH_2CH_3$, -$CONHCH(CH_3)_2$, –$CON(CH_3)_2$, -$C(CH_3)_2CONH_2$, –NH_2, –$NHCH_3$, -$N(CH_3)_2$, -$N(CH_3)CH_2CH_3$, -$NHCOCH_3$, -$N(CH_3)COCH_3$, -$NHS(O)_2CH_3$, -$N(CH_3)C(CH_3)_2CONH_2$, -$N(CH_3)CH_2CH_2S(O)_2CH_3$, –$NO_2$, =O, –OH, -$OCH_3$, -$OCH_2CH_3$,

-$OCH_2CH_2OCH_3$, -OCH_2CH_2OH, –$OCH_2CH_2N(CH_3)_2$, –$OP(O)(OH)_2$, -$S(O)_2N(CH_3)_2$, -SCH_3, –$S(O)_2CH_3$, -$S(O)_3H$, cyclopropyl, cyclopropylamide, cyclobutyl, oxetanyl, azetidinyl, 1-methylazetidin-3-yl)oxy, *N*-methyl-N-oxetan-3-ylamino, azetidin-1-ylmethyl, benzyloxyphenyl, pyrrolidin-1-yl, pyrrolidin-1-yl-methanone, phenyl, piperazin-1-yl, piperidin-1-yl, morpholinomethyl, morpholino-methanone, and morpholino.

[0065] In some embodiments of the compound of Formula I′, or stereoisomers, tautomers, or pharmaceutically acceptable salts thereof, wherein R^1 is optionally substituted C_3–C_{12} cycloalkyl or optionally substituted C_3-C_{12} heterocyclyl. In some embodiments, R^1 is cyclohexyl or piperidinyl, optionally substituted with one or more (e.g., 1 to 2, 1 to3, 1 to 4, or 1 to 5) substituents selected from the group consisting of F, –CH_3, and –NH_2. In some embodiments, R^1 is piperidinyl (e,g, 3-piperidinyl) optionally substituted with one or more substituents selected from the group consisting of F, -CH_3 and -OCH_3. In some embodiments, R^1 is piperidinyl (e,g, 3-piperidinyl) optionally substituted with one to four substituents selected from the group consisting of F, –CH_3 and –OCH_3. In some embodiments, R^1 is selected from the group consisting of piperidin-3-yl, 5-fluoropiperidin-3-yl, 5-methylpiperidin-3-yl and 5-fluro-5-methylpiperidin-3-yl. In some embodiments, R^2 is H, F, Cl or C_1–C_6 alkyl. In some embodiments, R^2 is C_1–C_6 alkyl (e.g., methyl). In some embodiments, R^3 is H, C_3-C_{12} heterocyclyl, -$N(R^8)(C_1$–C_6 alkyl), -$NR^8C(O)R^9$, -NR^8SO_2–(C_1–C_6 alkyl), -NR^8SO_2–(C_1–C_6 alkenyl), -NR^8SO_2–(C_3–C_{12} cycloalkyl), -NR^8SO_2–(C_1–C_{12} heteroaryl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_3–C_{12} cycloalkyl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_3-C_{12} heterocyclyl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_1–C_{12} heteroaryl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl), -$NR^8SO_2NR^8R^9$, or -$SO_2NR^8R^9$. In some embodiments, R^3 is H, and R^4 is C_3-C_{12} cycloalkyl, C_3-C_{12} heterocyclyl, C_1–C_{12} heteroaryl, C_6–C_{20} aryl, -O–(C_1–C_{12} heteroaryl), -O–(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl), -NR^8R^9, -$NR^8C(O)R^9$, -$NR^8C(O)OR^9$, -$NR^8C(O)NHR^9$, -NR^8SO_2–(C_1–C_6 alkyl), -NR^8SO_2–(C_1–C_6 alkenyl), -NR^8SO_2–(C_1–C_{12} heteroaryl), -NR^8SO_2–(C_3–C_{12} cycloalkyl), -NR^8SO_2–(C_3-C_{12} heterocyclyl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_3–C_{12} cycloalkyl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_3-C_{12} heterocyclyl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_1–C_{12} heteroaryl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl), -$NR^8SO_2NR^8R^9$, or -$SO_2NR^8R^9$. In some embodiments, R^5 is H, F, Cl or CH_3. In some embodiments, R^5 is H. In some embodiments, R^7 is hydrogen or fluoro. In some embodiments, R^5 and R^7 are hydrogen. In any of these embodiments, cycloalkyl, heterocyclyl, heteroaryl, aryl, alkyl, alkyldiyl, and alkenyl are optionally and independently substituted as defined for Formula I′.

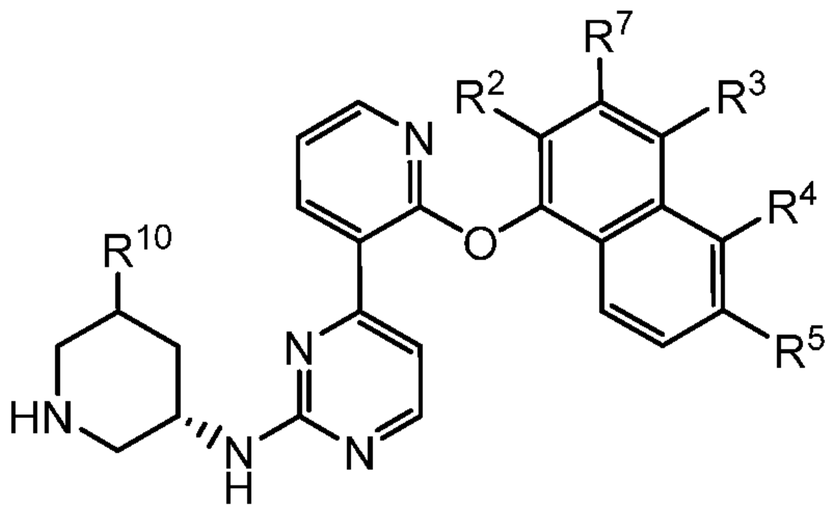
[0066] Exemplary embodiments of Formula I or I′ compounds include Formula Ia:



Ia

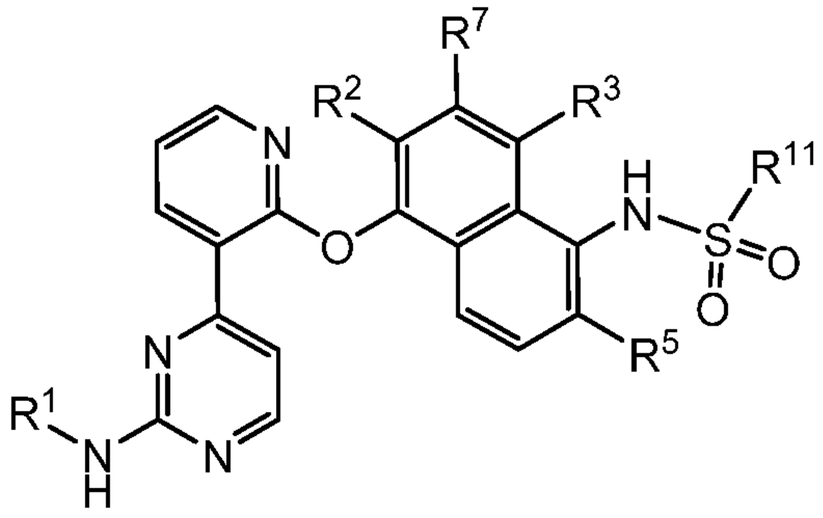
wherein R^{10} is selected from H, F, $-CH_3$, and $-NH_2$.

[0067] Exemplary embodiments of Formula Ia compounds include Formula Ib:



Ib

[0068] Exemplary embodiments of Formula I or I′ compounds include Formula Ic:



Ic

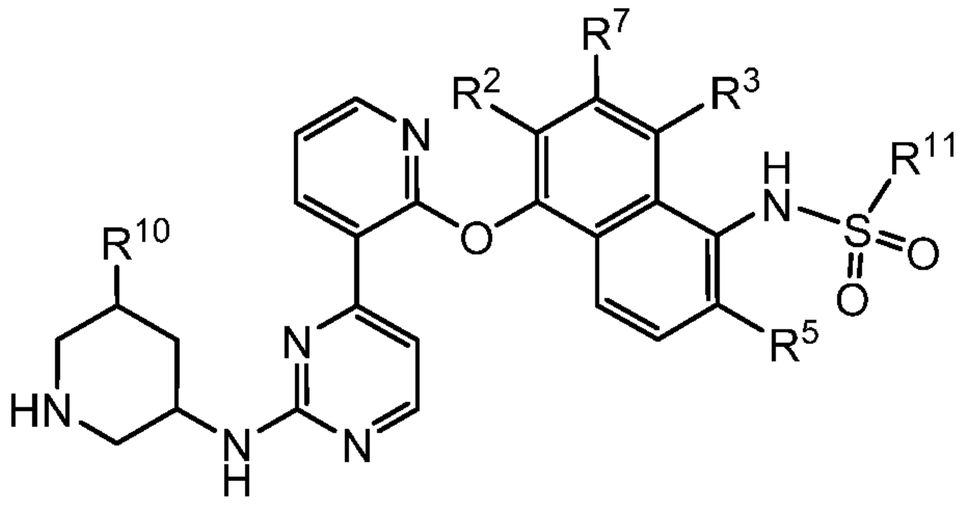
wherein R^{11} is selected from C_1–C_6 alkyl, C_1–C_6 alkenyl, C_1–C_{12} heteroaryl, (C_1–C_6 alkyldiyl)–(C_3-C_{12} heterocyclyl), (C_1–C_6 alkyldiyl)–(C_1–C_{12} heteroaryl), (C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl), (C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl), NR^7–(C_1–C_{12} heteroaryl), NR^7–(C_1–C_6 alkyl), and NR^7–(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl).

[0069] Formula Ic compounds include wherein R^{11} is selected from benzyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentanyl, cyclopentanylmethyl, cyclohexyl, cyclohexylmethyl, pyrrolidin-1-yl, piperidin-1-yl, pyridyl, pyridylmethyl, tetrahydrofuranyl, tetrahydrofuranylmethyl, and tetrahydropyranyl, tetrahydropyranylmethyl,

thiazolyl, and thiazolylmethyl, optionally and independently substituted with one groups selected from fluoro, chloro, bromo, $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, and $-CN$.

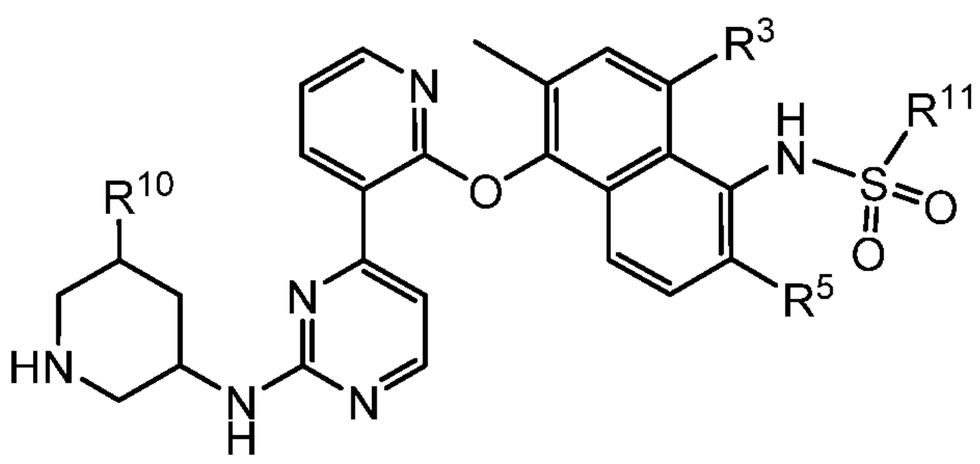
[0070] Formula Ic compounds include wherein R^{11} is selected from $-CH_3$, $-CH_2CH_3$, $-CH{=}CH_2$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2C(CH_3)_3$, $-CH_2CHF_2$, $-CH_2CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2CH_2OCH_3$, $-CH_2CH(CH_3)OCH_3$, $-CH_2F$, $-CH_2Cl$, $-CH_2Br$, $-CH_2CN$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, and $-N(CH_3)CH_2CH_3$.

[0071] Exemplary embodiments of Formula Ic compounds have Formula Id:



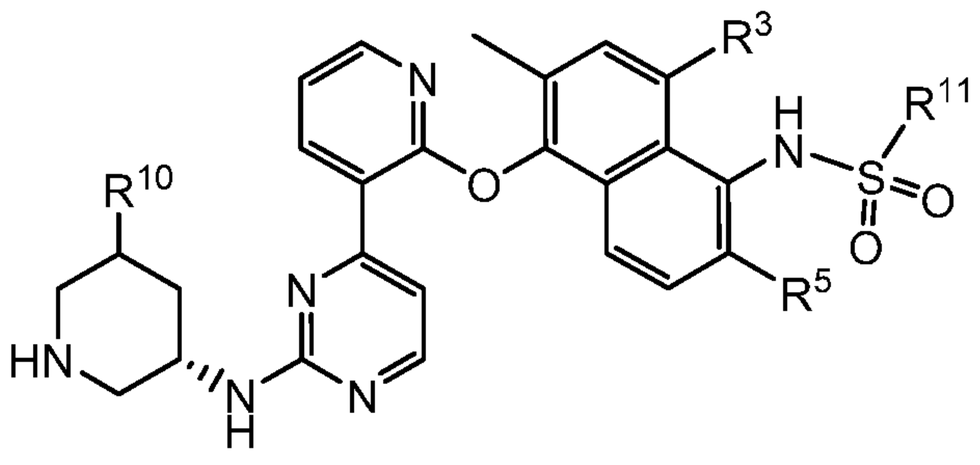
Id .

[0072] Exemplary embodiments of Formula Id compounds have Formula Ie:



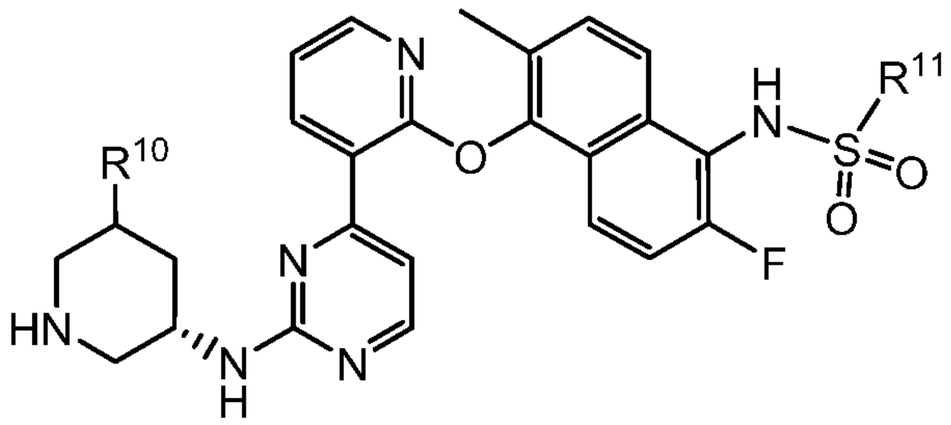
Ie .

[0073] Exemplary embodiments of Formula Ie compounds have Formula If:



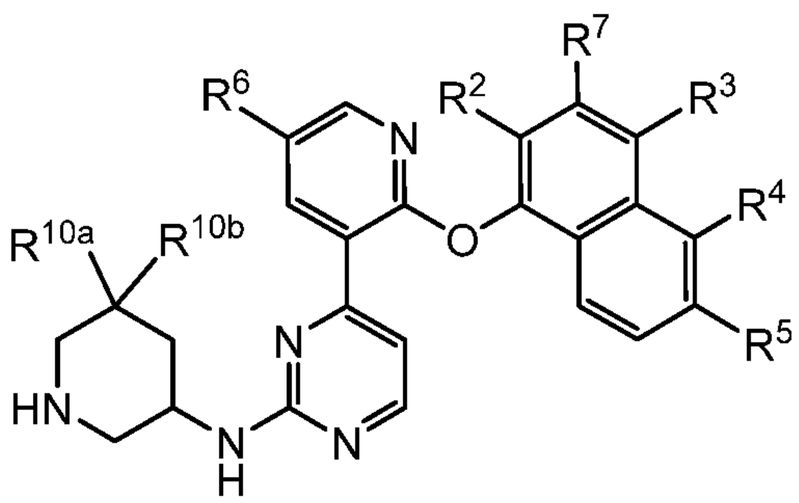
If .

[0074] Formula If compounds include wherein R^5 is F, having Formula Ig:



Ig .

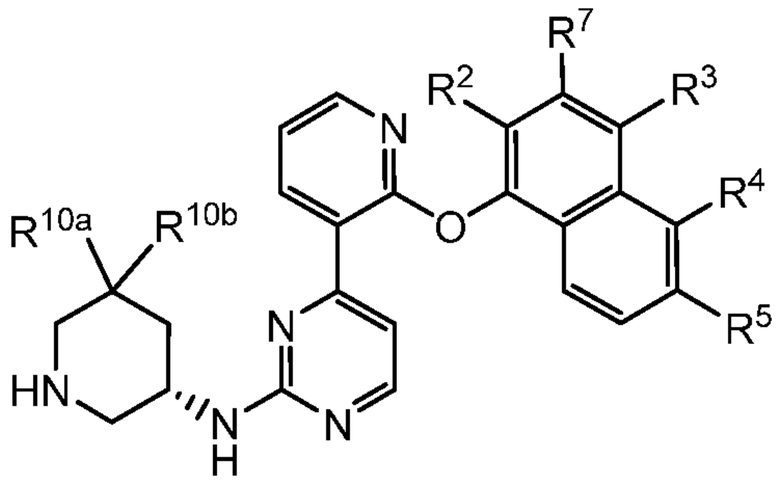
[0075] In some embodiments of the compound of Formula I or I′, or stereoisomers, tautomers, or pharmaceutically acceptable salts thereof, wherein R^1 is optionally substituted piperidin-3-yl. In some embodiments, the compound is of Formula Ih:



Ih ,

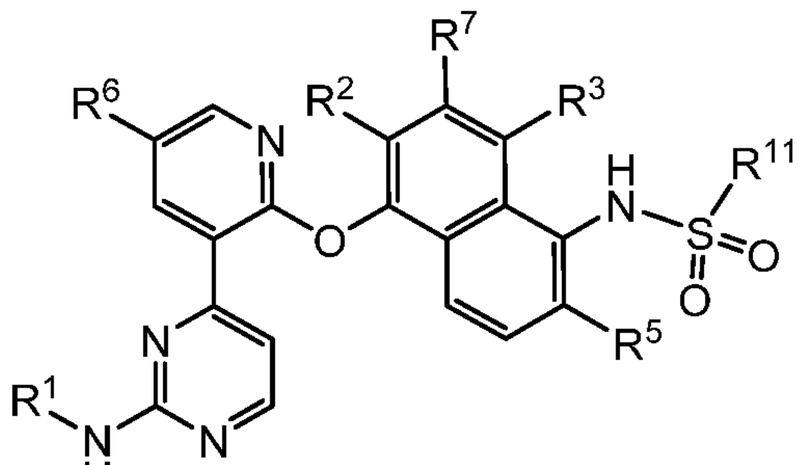
wherein R^{10a} and R^{10b} are independently H, F, $-CH_3$ or $-NH_2$; and R^2, R^3, R^4, R^5, R^6 and R^7 are as described for Formula I or I′. In some embodiments, R^2 is H, F, Cl or C_1–C_6 alkyl. In some embodiments, R^2 is C_1–C_6 alkyl (e.g., methyl). In some embodiments, R^5 is H, F, Cl or CH_3. In some embodiments, R^7 is hydrogen or fluoro. In some embodiments, R^5 and R^7 are hydrogen. In some embodiments, R^6 is H, F, Cl, Br, -OCH_3, or C_1–C_6 alkyl (e.g., methyl and ethyl). In some embodiments, R^6 is H. In some embodiments, R^{10a} and R^{10b} are independently H, F or -CH_3.

[0076] In some embodiments of the compound of Formula Ih, or a variation thereof, the compound is of the Formula Ii:



Ii .

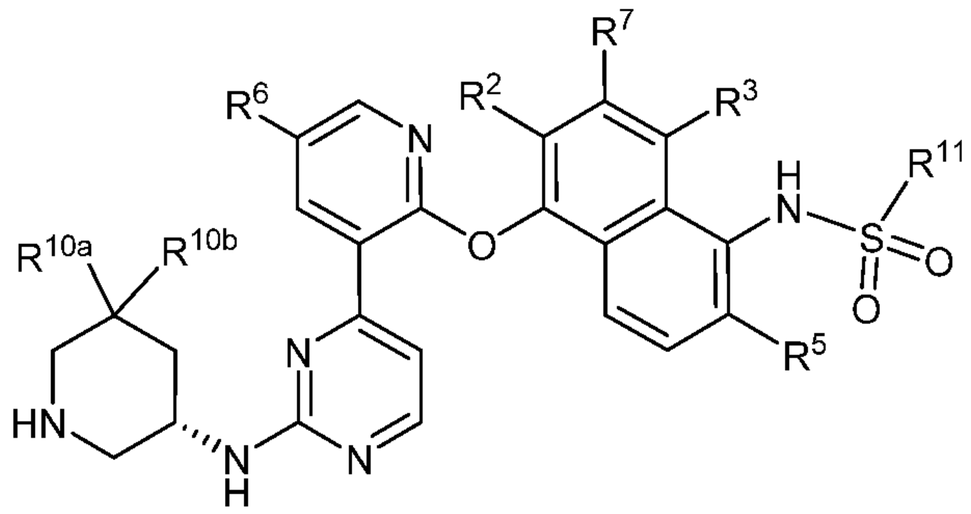
[0077] In some embodiments of the compound of Formula I′, or stereoisomers, tautomers, or pharmaceutically acceptable salts thereof, n is 0 and the compound is of Formula Ij:



Ij ,

wherein R^{11} is C_1–C_6 alkyl, C_1–C_6 alkenyl, C_1–C_{12} heteroaryl, C_3-C_{12} cycloalkyl, C_3-C_{12} heterocyclyl, -(C_1–C_6 alkyldiyl)–(C_3–C_{12} cycloalkyl), -(C_1–C_6 alkyldiyl)–(C_3-C_{12} heterocyclyl), -(C_1–C_6 alkyldiyl)–(C_1–C_{12} heteroaryl), -(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl), -NR^8–(C_1–C_{12} heteroaryl), -NR^8–(C_1–C_6 alkyl), or -NR^8–(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl); and R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are as described for Formula I′. In some embodiments, R^{11} is C_1–C_6 alkyl, C_1–C_6 alkenyl, C_1–C_{12} heteroaryl, C_3-C_{12} cycloalkyl, C_3-C_{12} heterocyclyl, -(C_1–C_6 alkyldiyl)–(C_3–C_{12} cycloalkyl), -(C_1–C_6 alkyldiyl)–(C_3-C_{12} heterocyclyl), -(C_1–C_6 alkyldiyl)–(C_1–C_{12} heteroaryl), or -(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl). In some embodiments, R^{11} is -NR^8–(C_1–C_{12} heteroaryl), -NR^8–(C_1–C_6 alkyl), or -NR^8–(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl); and R^8 is H or –CH_3. In some embodiments, R^{11} is selected from the group consisting of benzyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentanyl, cyclopentanylmethyl, cyclohexyl, cyclohexylmethyl, pyrrolidin-1-yl, piperidin-1-yl, pyridyl, pyridylmethyl, tetrahydrofuranyl, tetrahydrofuranylmethyl, and tetrahydropyranyl, tetrahydropyranylmethyl, thiazolyl, and thiazolylmethyl; each of which is optionally and independently substituted with one or more (e.g., 1 to 2, 1 to 3, 1 to 4, or 1 to 5) substituents selected from fluoro, chloro, bromo, –CH_3, –CH_2CH_3, –CH_2OH, and –CN. In some embodiments, R^{11} is selected from the group consisting of –CH_3, –CH_2CH_3, –CH=CH_2, –$CH_2CH_2CH_3$, –$CH(CH_3)_2$, –$CH_2CH(CH_3)_2$, –$CH(CH_3)CH_2CH_3$, –$CH_2C(CH_3)_3$, –CH_2CHF_2, –$CH_2CH_2CHF_2$, –CH_2CF_3, –$CH_2CH_2CF_3$, –$CH_2CH_2OCH_3$, –$CH_2CH_2CH_2OCH_3$, –$CH_2CH_(CH_3)OCH_3$, –CH_2F, –CH_2Cl, –CH_2Br, –CH_2CN, –NH_2, –$NHCH_3$, –$N(CH_3)_2$, and –$N(CH_3)CH_2CH_3$. In some embodiments, R^2 is H, F, Cl or C_1–C_6 alkyl. In some embodiments, R^2 is C_1–C_6 alkyl (e.g., methyl). In some embodiments, R^3 is H. In some embodiments, R^5 is H, F, Cl or CH_3. In some embodiments, R^7 is hydrogen or fluoro. In some embodiments, R^5 and R^7 are hydrogen. In some embodiments, R^6 is H, F, Cl, Br, -OCH_3, or C_1–C_6 alkyl (e.g., methyl and ethyl). In some embodiments, R^6 is H.

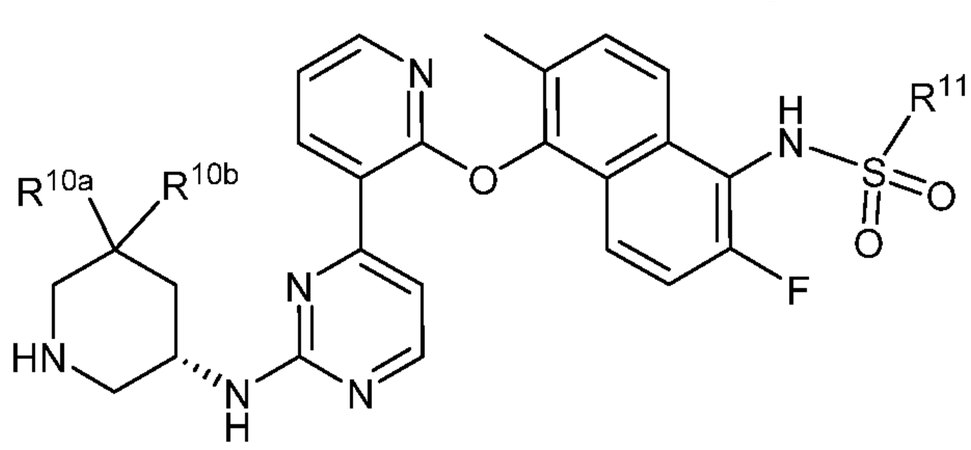
[0078] In some embodiments of the compound of Formula Ij, or a variation thereof, the compound is of the Formula Ik:



Ik ,

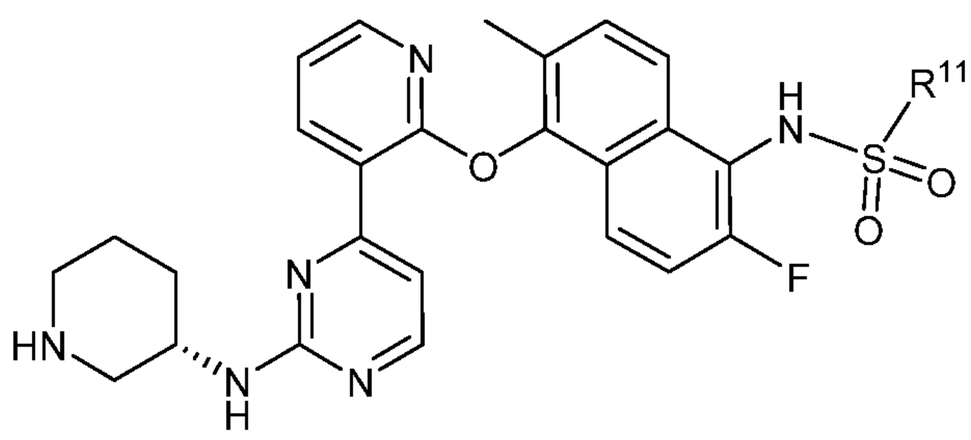
wherein R^{10a} and R^{10b} are independently H, F or $-CH_3$. In some embodiments, R^{10a} and R^{10b} are H. In some embodiments, one of R^{10a} and R^{10b} is F and the other one of R^{10a} and R^{10b} is H. In some embodiments, one of R^{10a} and R^{10b} is H and the other one of R^{10a} and R^{10b} is $-CH_3$. In some embodiments, one of R^{10a} and R^{10b} is F and the other one of R^{10a} and R^{10b} is $-CH_3$.

[0079] In some embodiments of the compound of Formula Ik, or a variation thereof, R^2 is $-CH_3$, R^3, R^6 and R^7 are H, R^5 is F; and the compound is of the Formula Il:



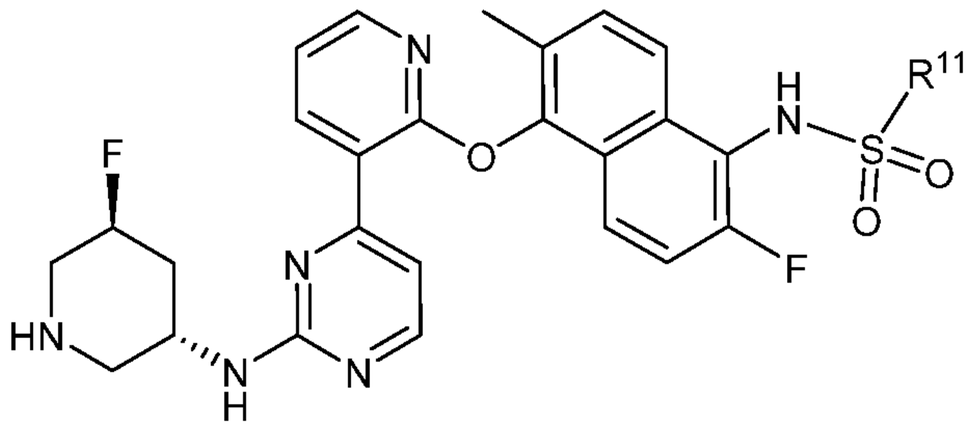
Il .

[0080] In some embodiments of the compound of Formula Il, or a variation thereof, R^{10a} and R^{10b} are H; and the compound is of the Formula Im:



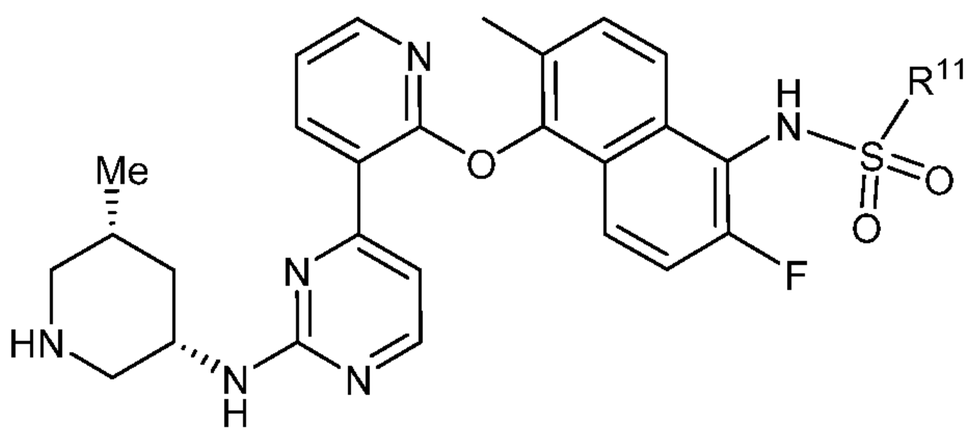
Im .

[0081] In some embodiments of the compound of Formula Il, or a variation thereof, R^{10a} is F and R^{10b} is H; and the compound is of the Formula In:



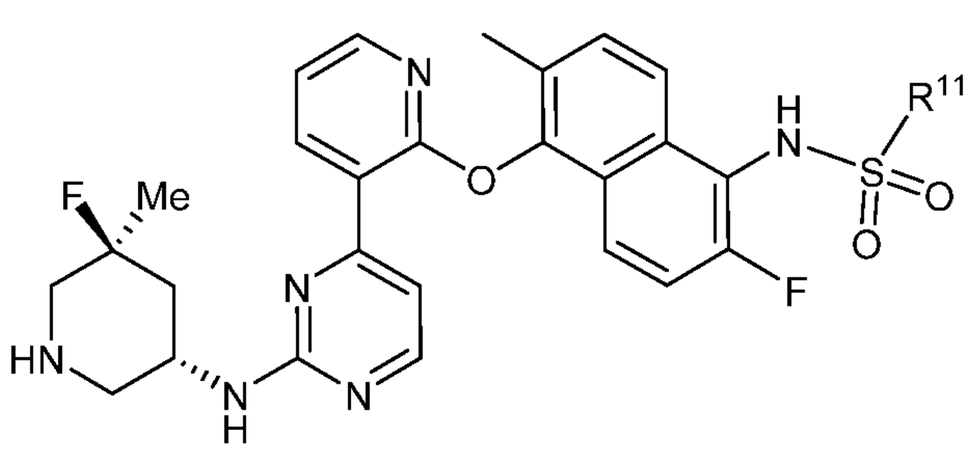
In .

[0082] In some embodiments of the compound of Formula II, or a variation thereof, R^{10a} is H and R^{10b} is -CH_3; and the compound is of the Formula Io:



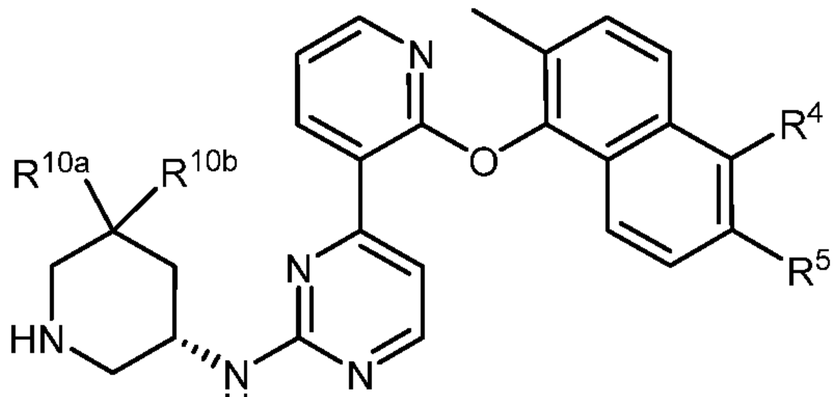
Io .

[0083] In some embodiments of the compound of Formula II, or a variation thereof, R^{10a} is F and R^{10b} is -CH_3; and the compound is of the Formula Ip:



Ip .

[0084] In some embodiments of the compound of Formula I or I′, or stereoisomers, tautomers, or pharmaceutically acceptable salts thereof, wherein n is 0, R^2 is -CH_3, R^3 and R^7 are H, R^1 is optionally substituted piperidin-3-yl, and the compound is of Formula Iq:

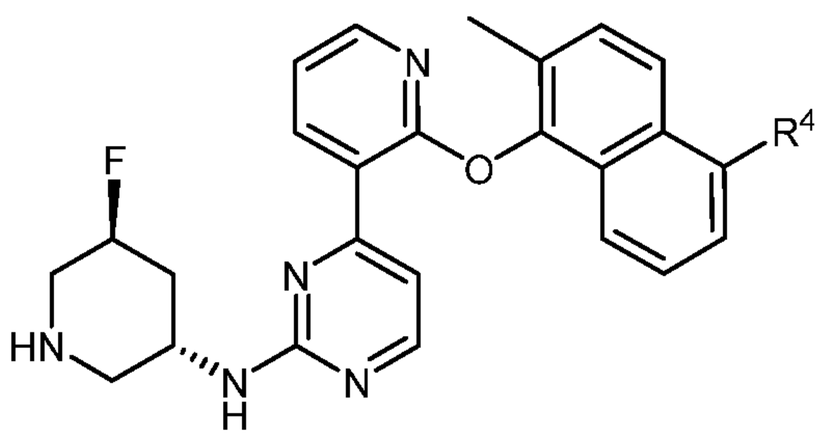


Iq ,

wherein R^{10a} and R^{10b} are independently H, F or CH_3; and R^4 and R^5 are as described for Formula I or I′. In some embodiments, R^4 is –CN, C_3-C_{12} cycloalkyl, C_3-C_{12} heterocyclyl, C_1–C_{12} heteroaryl, C_6–C_{20} aryl, -O–(C_1–C_{12} heteroaryl), -O–(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl),

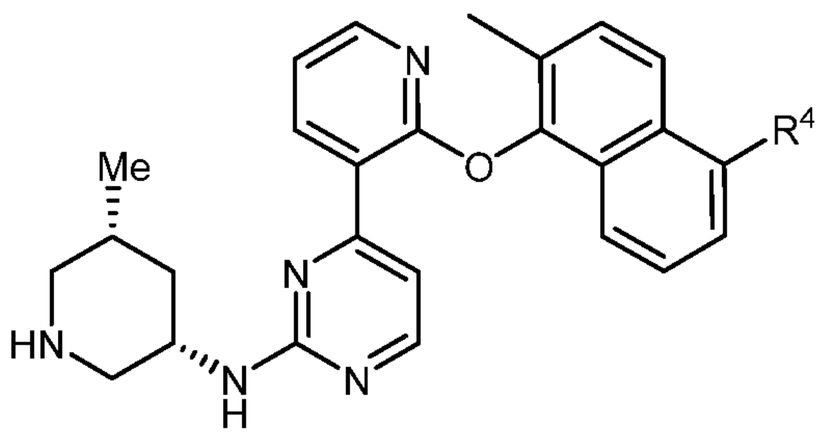
-NR^8R^9, -$NR^8C(O)R^9$, -$NR^8C(O)OR^9$, -$NR^8C(O)NHR^9$, or -$SO_2NR^8R^9$. In some embodiments, R^4 is C_3-C_{12} heterocyclyl, C_1–C_{12} heteroaryl, -NR^8R^9, -$NR^8C(O)R^9$, -$NR^8C(O)OR^9$, -$NR^8C(O)NHR^9$ or -$SO_2NR^8R^9$. In some embodiments, R^4 is C_3-C_{12} heterocyclyl, C_1–C_{12} heteroaryl, -NR^8R^9 or -$NR^8C(O)R^9$. In some embodiments, R^5 is H, F, Cl or CH_3. In some embodiments, R^5 is H or F. In one variation, R^5 is H. In another variation, R^5 is F. In some of these embodiments, R^{10a} and R^{10b} are H. In some of these embodiments, one of R^{10a} and R^{10b} is F and the other one of R^{10a} and R^{10b} are H. In some of these embodiments, one of R^{10a} and R^{10b} is H and the other one of R^{10a} and R^{10b} is -CH_3. In some of these embodiments, one of R^{10a} and R^{10b} is F and the other one of R^{10a} and R^{10b} is -CH_3.

[0085] In some embodiments of the compound of Formula Iq, or a variation thereof, the compound is of the Formula Ir:



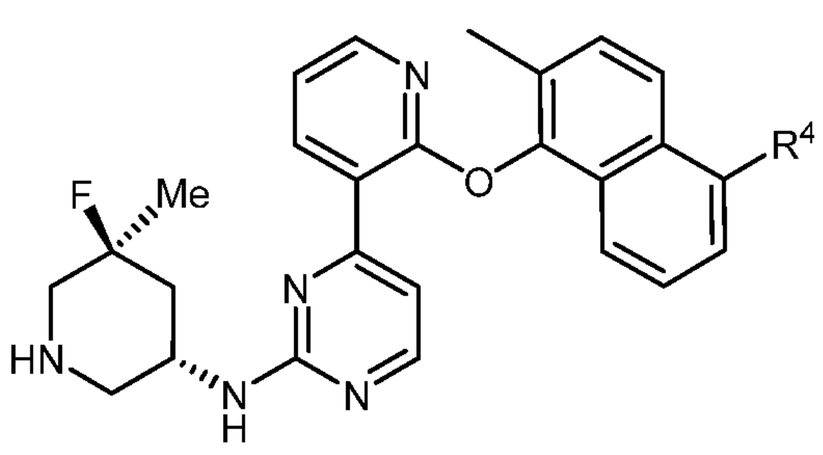
Ir .

[0086] In some embodiments of the compound of Formula Iq, or a variation thereof, the compound is of the Formula Is:



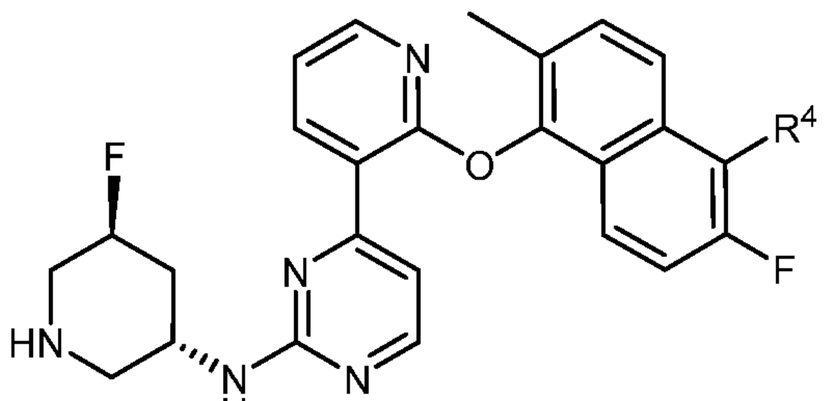
Is .

[0087] In some embodiments of the compound of Formula Iq, or a variation thereof, the compound is of the Formula It:



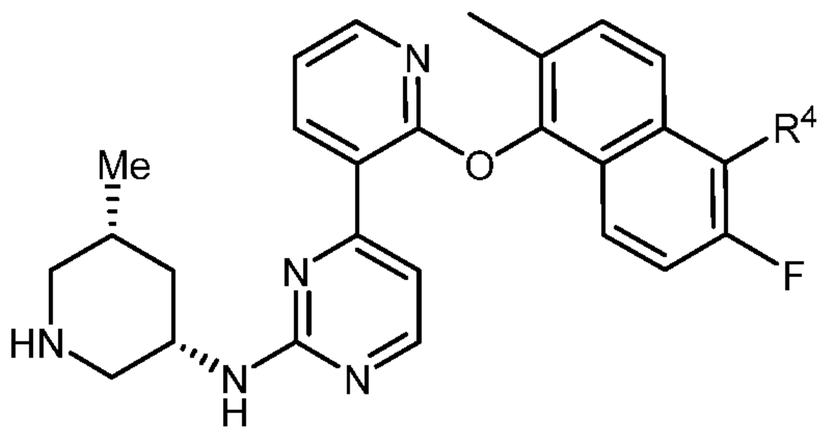
It .

[0088] In some embodiments of the compound of Formula Iq, or a variation thereof, the compound is of the Formula Iu:



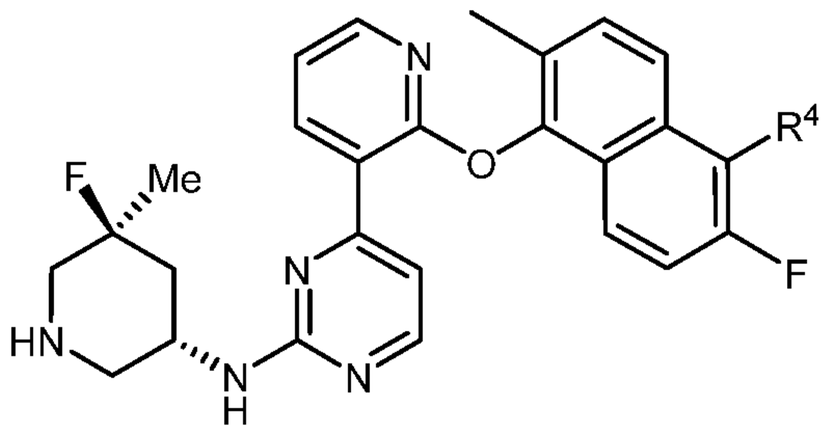
Iu .

[0089] In some embodiments of the compound of Formula Iq, or a variation thereof, the compound is of the Formula Iv:



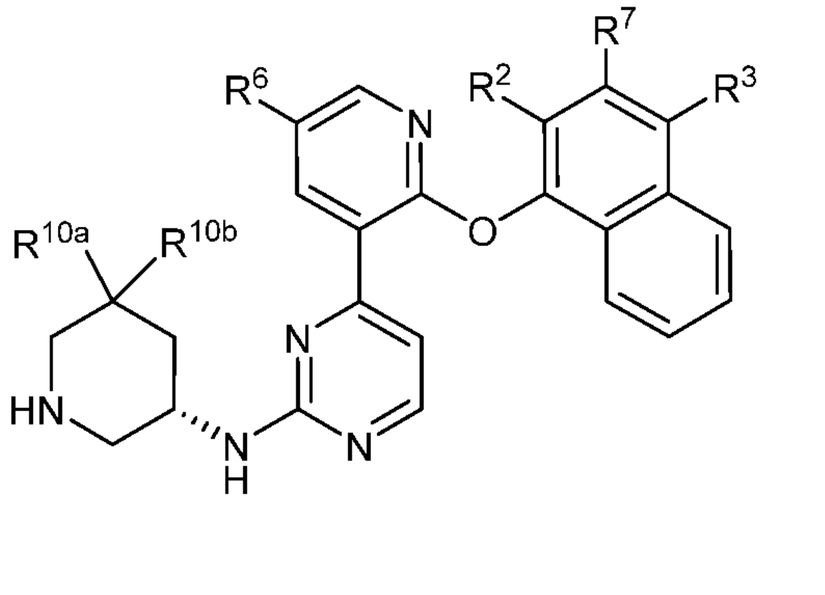
Iv .

[0090] In some embodiments of the compound of Formula Iq, or a variation thereof, the compound is of the Formula Iw:



Iw .

[0091] In some embodiments of the compound of Formula I or I′, or stereoisomers, tautomers, or pharmaceutically acceptable salts thereof, wherein R^4 and R^5 are H, R^1 is optionally substituted piperidin-3-yl, and the compound is of Formula Ix:

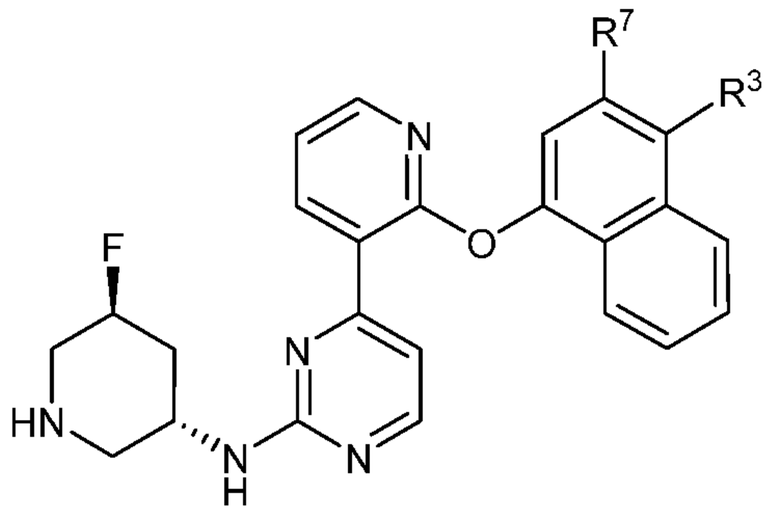


Ix ,

wherein R^{10a} and R^{10b} are independently H, F or CH_3; and R^2, R^3, R^6 and R^7 are as described for Formula I or I′. In some embodiments, R^2 is H, F, Cl or C_1–C_6 alkyl. In some embodiments, R^2 is C_1–C_6 alkyl (e.g., methyl). In some embodiments, R^6 is H, F, Cl, Br, -OCH_3, or C_1–C_6 alkyl (e.g., methyl and ethyl). In some embodiments, R^6 is H. In some embodiments, R^7 is hydrogen or fluoro. In some embodiments, R^7 is hydrogen. In some embodiments, R^3 is –CN, C_3-C_{12} cycloalkyl, C_3-C_{12} heterocyclyl, C_1–C_{12} heteroaryl, C_6–C_{20} aryl, -O–(C_1–C_{12} heteroaryl), -O–(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl), -N(R^8)(C_1–C_6 alkyl), -$NR^8C(O)R^9$, -$NR^8C(O)OR^9$, -$NR^8C(O)NHR^9$, -NR^8SO_2–(C_1–C_6 alkyl), -NR^8SO_2–(C_1–C_6 alkenyl), -NR^8SO_2–(C_3–C_{12} cycloalkyl), -NR^8SO_2–(C_1–C_{12} heteroaryl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_3–C_{12} cycloalkyl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_3-C_{12} heterocyclyl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_1–C_{12} heteroaryl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl), -$NR^8SO_2NR^8R^9$, or -$SO_2NR^8R^9$. In some embodiments, R^3 is C_3-C_{12} heterocyclyl, -N(R^8)(C_1–C_6 alkyl) or -$NR^8C(O)R^9$. In some embodiments, R^3 is -NR^8SO_2–(C_1–C_6 alkyl), -NR^8SO_2–(C_1–C_6 alkenyl), -NR^8SO_2–(C_3–C_{12} cycloalkyl), -NR^8SO_2–(C_1–C_{12} heteroaryl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_3–C_{12} cycloalkyl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_3-C_{12} heterocyclyl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_1–C_{12} heteroaryl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl) or -$NR^8SO_2NR^8R^9$. In some embodiments, R^3 is -NR^8SO_2–(C_1–C_6 alkyl). In some of these embodiments, R^{10a} and R^{10b} are H. In some of these embodiments, one of R^{10a} and R^{10b} is F and the other one of R^{10a} and R^{10b} are H. In some of these embodiments, one of R^{10a} and R^{10b} is H and the other one of R^{10a} and R^{10b} is -CH_3. In some of these embodiments, one of R^{10a} and R^{10b} is F and the other one of R^{10a} and R^{10b} is -CH_3.

[0092] In some embodiments of the compound of Formula Ix, R^2 is C_1–C_6 alkyl (e.g., methyl), R^3 is C_3-C_{12} heterocyclyl, -N(R^8)(C_1–C_6 alkyl) or -$NR^8C(O)R^9$ and R^7 is hydrogen. In some embodiments of the compound of Formula Ix, R^2 is C_1–C_6 alkyl (e.g., methyl), R^3 is -NR^8SO_2–(C_1–C_6 alkyl) and R^7 is fluoro.

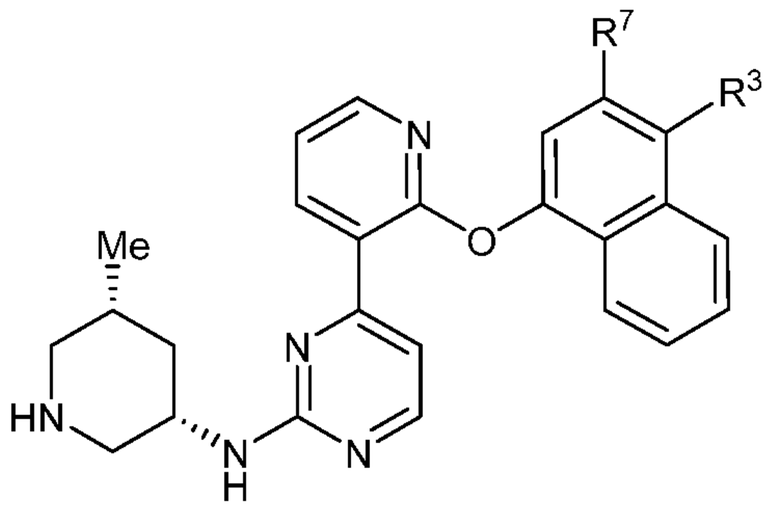
[0093] In some embodiments of the compound of Formula Ix, or a variation thereof, where R^2 and R^6 are hydrogen, and the compound is of the Formula Iy:



Iy .

In some embodiments, R^7 is hydrogen or fluoro. In some embodiments, R^7 is hydrogen. In some embodiments, R^7 is fluoro.

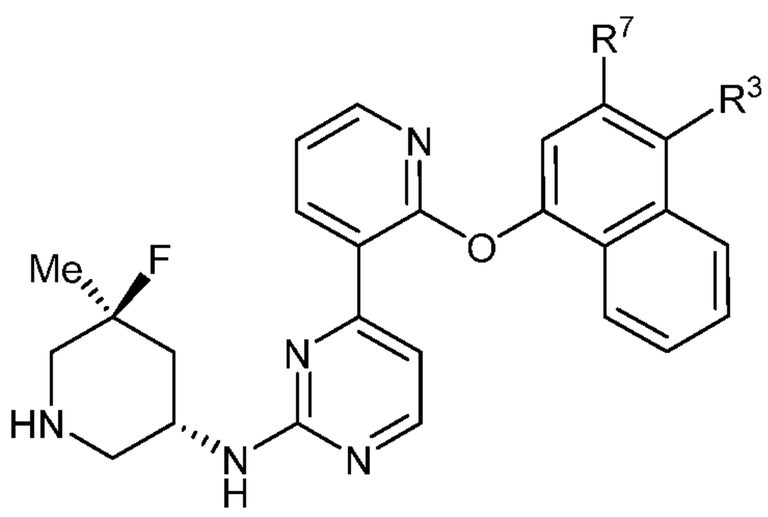
[0094] In some embodiments of the compound of Formula Ix, or a variation thereof, where R^2 and R^6 are hydrogen, and the compound is of the Formula Iz:



Iz .

In some embodiments, R^7 is hydrogen or fluoro. In some embodiments, R^7 is hydrogen. In some embodiments, R^7 is fluoro.

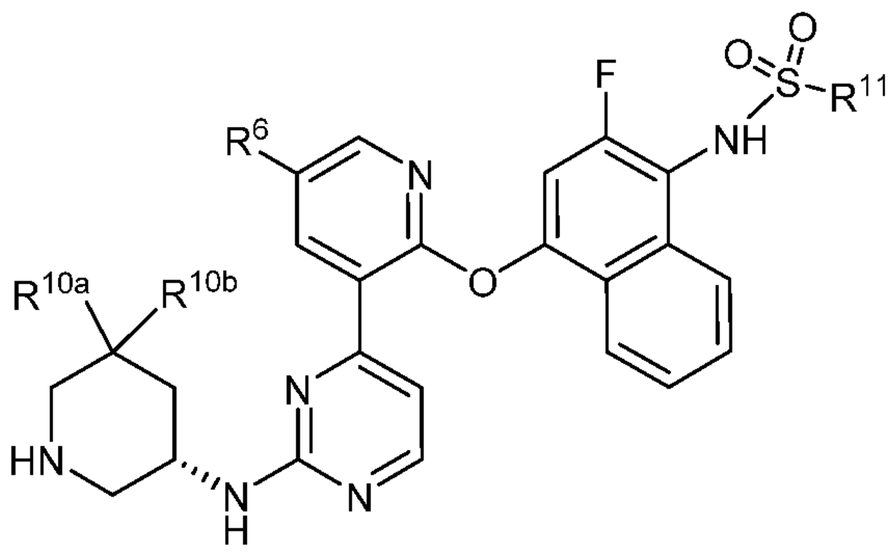
[0095] In some embodiments of the compound of Formula Ix, or a variation thereof, where R^2 and R^6 are hydrogen, and the compound is of the Formula Iaa:



Iaa .

In some embodiments, R^7 is hydrogen or fluoro. In some embodiments, R^7 is hydrogen. In some embodiments, R^7 is fluoro.

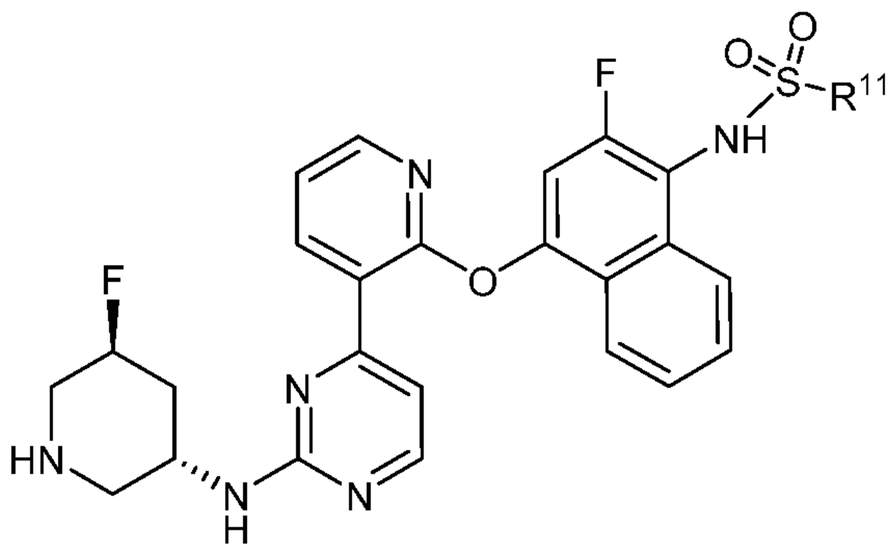
[0096] In some embodiments of the compound of Formula Ix, or a variation thereof, where R^2 is hydrogen and R^7 is fluoro, and the compound is of the Formula Iab:



Iab ,

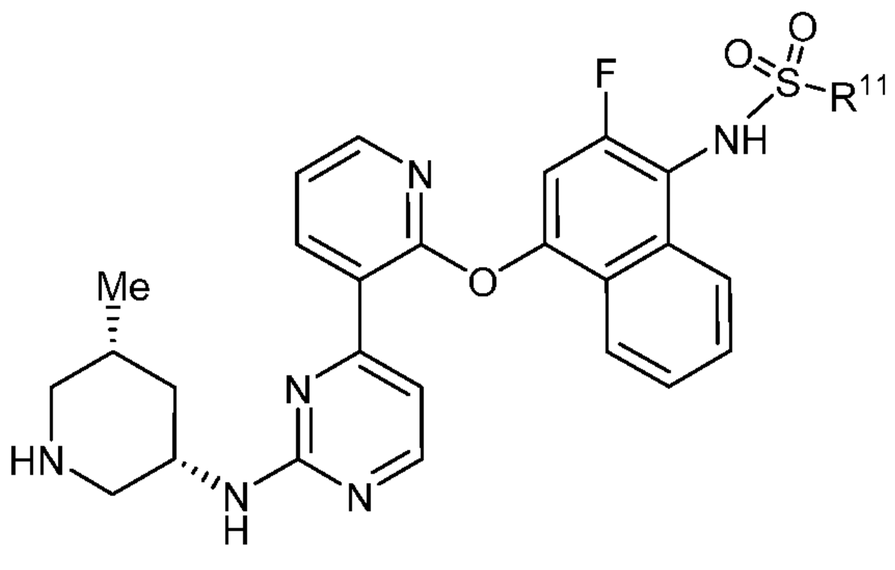
wherein R^{11} is as described for the Formula Ij or a variation thereof.

[0097] In some embodiments of the compound of Formula Iab, or a variation thereof, wherein R^6 is hydrogen, and the compound is of the Formula Iac:



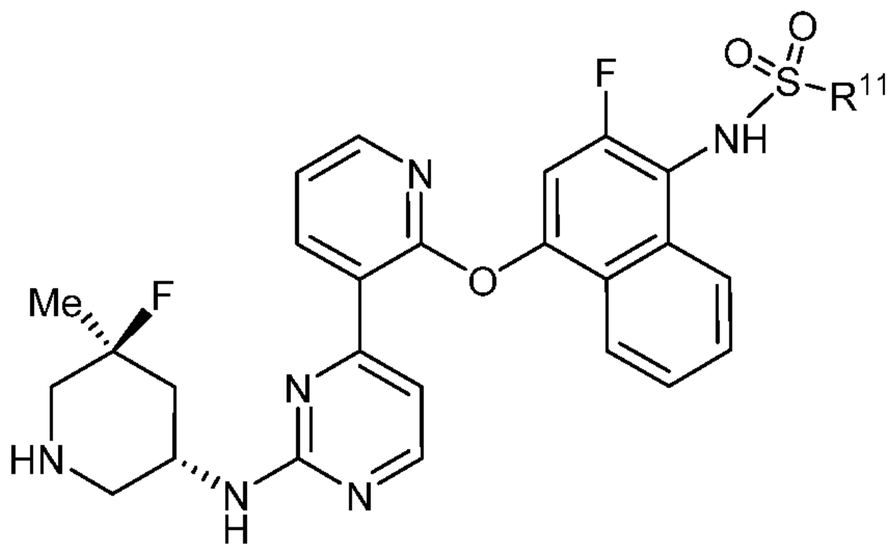
Iac .

[0098] In some embodiments of the compound of Formula Iab, or a variation thereof, wherein R^6 is hydrogen, and the compound is of the Formula Iad:



Iad .

[0099] In some embodiments of the compound of Formula Iab, or a variation thereof, wherein R^6 is hydrogen, and the compound is of the Formula Iae:



Iae .

[0100] Formula I or I′ compounds include wherein R^1 is C_3–C_{12} cycloalkyl or C_3-C_{12} heterocyclyl.

[0101] Formula I or I′ compounds include wherein R^1 is cyclohexyl or piperidinyl, optionally substituted with one or more groups selected from F, $–CH_3$, and $–NH_2$.

[0102] Formula I or I′ compounds include wherein R^2 is $–CH_3$.

[0103] Formula I compounds include wherein R^3 is selected from $–NR^6R^7$, $–NR^6C(O)R^7$, $–NR^6C(O)R^7$, $–NR^6C(O)OR^7$, $–NR^6C(O)NR^6$, $–NR^6SO_2–(C_1–C_6$ alkyl), $–NR^6SO_2–(C_1–C_6$ alkenyl), $–NR^6SO_2–(C_1–C_{12}$ heteroaryl), $–NR^6SO_2–(C_1–C_6$ alkyldiyl)–(C_3-C_{12} heterocyclyl), $–NR^6SO_2–(C_1–C_6$ alkyldiyl)–($C_1–C_{12}$ heteroaryl), $–NR^6SO_2–(C_1–C_6$ alkyldiyl)–($C_6–C_{20}$ aryl), $–NR^6SO_2NR^6–(C_1–C_{12}$ heteroaryl), $–NR^6SO_2NR^6–(C_1–C_6$ alkyl), and $–NR^6SO_2NR^6–(C_1–C_6$ alkyldiyl)–($C_6–C_{20}$ aryl).

[0104] Formula I compounds include wherein each of the three R^6 is H.

[0105] Formula I compounds include wherein R^4 is selected from $–NR^6R^7$, $–NR^6C(O)R^7$, $–NR^6C(O)R^7$, $–NR^6C(O)OR^7$, $–NR^6C(O)NR^6$, $–NR^6SO_2–(C_1–C_6$ alkyl), $–NR^6SO_2–(C_1–C_6$ alkenyl), $–NR^6SO_2–(C_1–C_{12}$ heteroaryl), $–NR^6SO_2–(C_1–C_6$ alkyldiyl)–(C_3-C_{12} heterocyclyl), $–NR^6SO_2–(C_1–C_6$ alkyldiyl)–($C_1–C_{12}$ heteroaryl), $–NR^6SO_2–(C_1–C_6$ alkyldiyl)–($C_6–C_{20}$ aryl), $–NR^6SO_2NR^6–(C_1–C_{12}$ heteroaryl), $–NR^6SO_2NR^6–(C_1–C_6$ alkyl), and $–NR^6SO_2NR^6–(C_1–C_6$ alkyldiyl)–($C_6–C_{20}$ aryl).

[0106] In any of the embodiments described for the Formulae Ia – Iad, or variations thereof, where applicable, cycloalkyl, heterocyclyl, heteroaryl, aryl, alkyl, alkyldiyl, and alkenyl are optionally and independently substituted as defined for Formula I or I′.

[0107] Exemplary embodiments of Formula I or I′ compounds include the compounds of Tables 1, 2 and 3.

[0108] In some embodiments, provided is a compound of Formula I or I′, or pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of one or more of Compound Nos. 101-392 of Table 1, Compound Nos. 393-500 of Table 2, and Compound Nos. 501-545 of Table 3. In some embodiments, the compound is selected from the group consisting of Compound Nos. 101-392 in Table 1. In some embodiments, the compound is selected from the group consisting of Compound Nos. 393-500 of Table 2. In some embodiments, the compound is selected from the group consisting of Compound Nos. 501-545 of Table 3.

Biological Evaluation

[0109] The relative efficacies of Formula I or I′ compounds as inhibitors of an enzyme activity (or other biological activity) can be established by determining the concentrations at which each compound inhibits the activity to a predefined extent and then comparing the results. Typically, the preferred determination is the concentration that inhibits 50% of the activity in a biochemical assay, i.e., the 50% inhibitory concentration or "IC_{50}". Determination of IC_{50} values can be accomplished using conventional techniques known in the art. In general, an IC_{50} can be determined by measuring the activity of a given enzyme in the presence of a range of concentrations of the inhibitor under study. The experimentally obtained values of enzyme activity then are plotted against the inhibitor concentrations used. The concentration of the inhibitor that shows 50% enzyme activity (as compared to the activity in the absence of any inhibitor) is taken as the IC_{50} value. Analogously, other inhibitory concentrations can be defined through appropriate determinations of activity. For example, in some settings it can be desirable to establish a 90% inhibitory concentration, i.e., IC_{90}, etc.

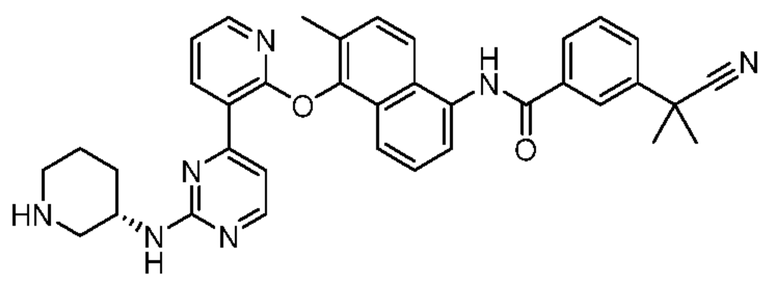
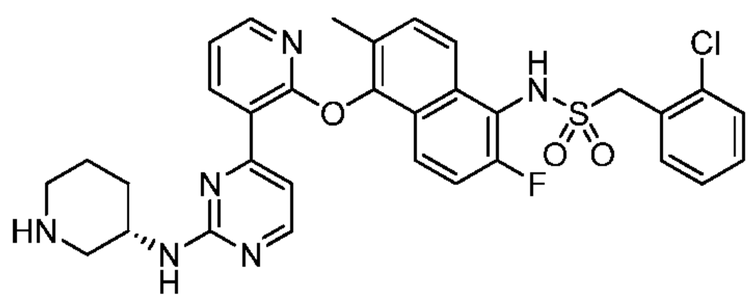
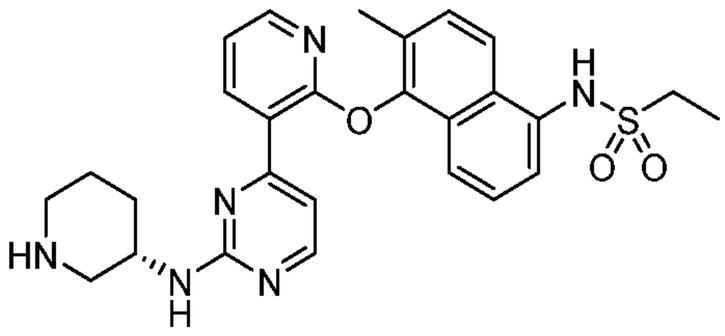
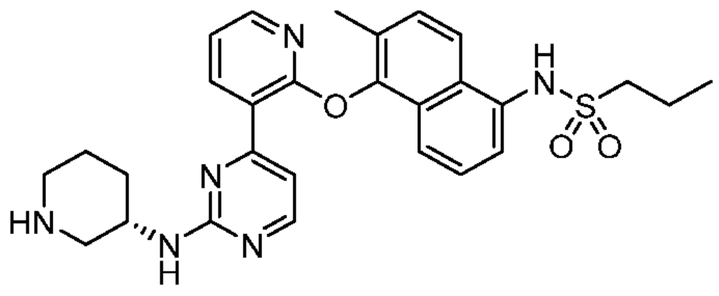
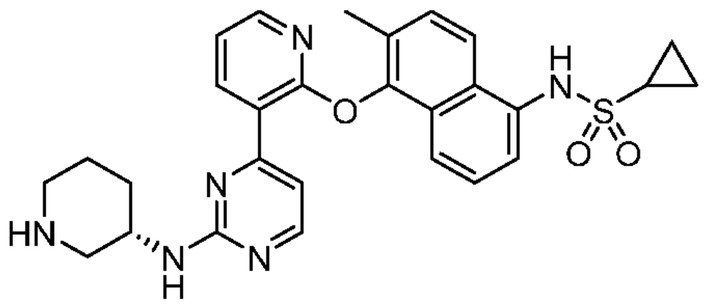
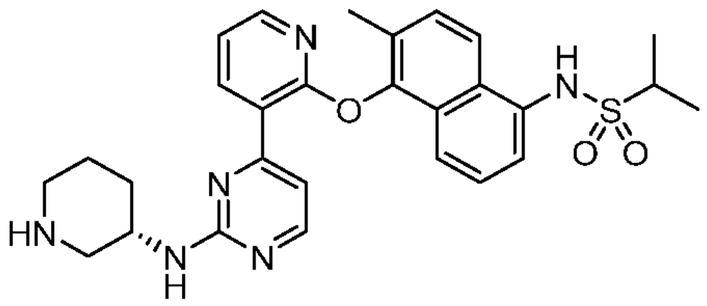
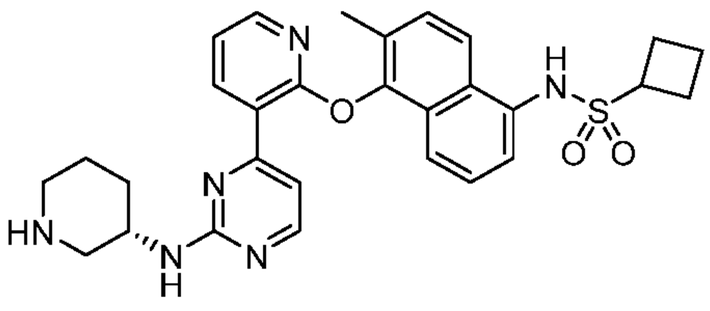
[0110] Cell proliferation, cytotoxicity, and cell viability of the Formula I or I′ compounds can be measured by the CellTiter-Glo® Luminescent Cell Viability Assay (Promega Corp.). The CellTiter-Glo® Luminescent Cell Viability Assay is a homogeneous method of determining the number of viable cells in culture based on quantitation of the ATP present, an indicator of metabolically active cells. The CellTiter-Glo® Assay is designed for use with multiwell formats, making it ideal for automated high-throughput screening (HTS), cell proliferation and cytotoxicity assays. The homogeneous assay procedure involves adding the single reagent (CellTiter-Glo® Reagent) directly to cells cultured in serum-supplemented medium. Cell washing, removal of medium and multiple pipetting steps are not required. The system detects as few as 15 cells/well in a 384-well format in 10 minutes after adding reagent and mixing.

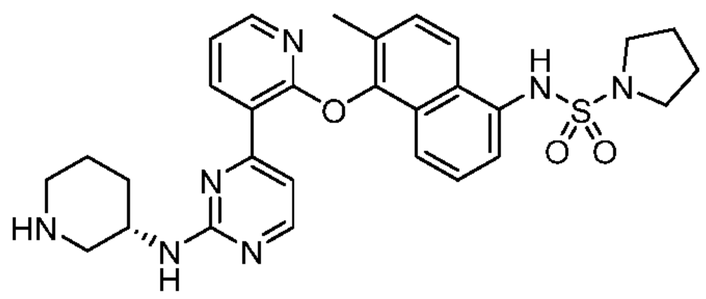
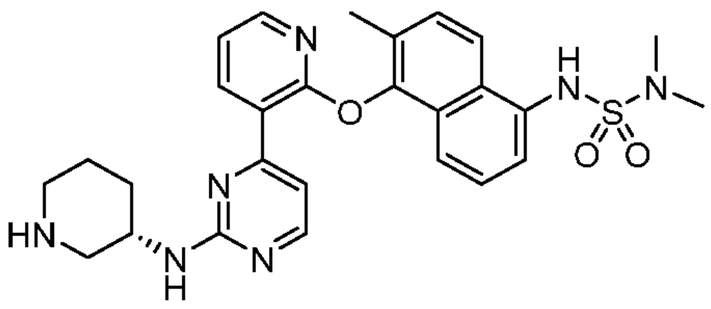
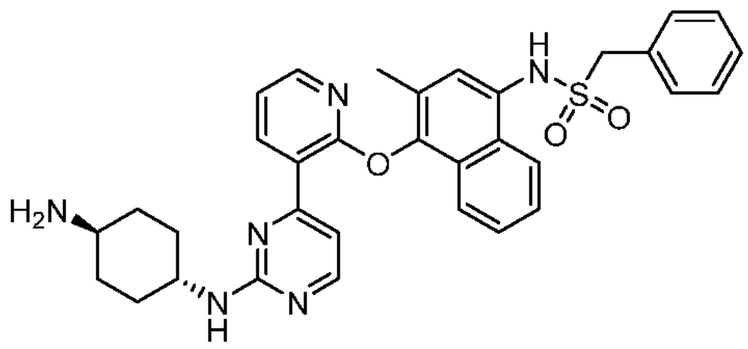
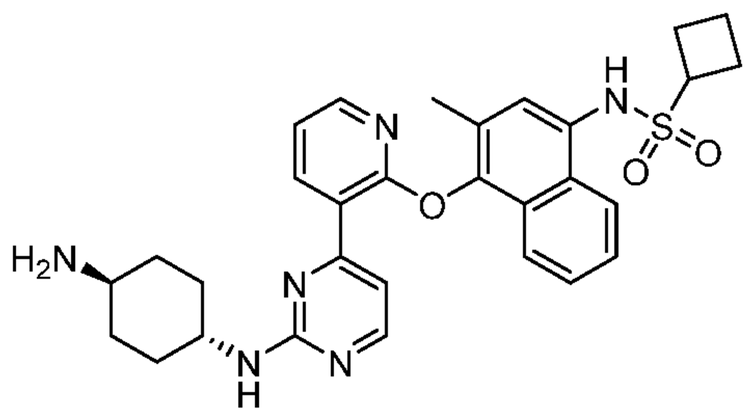
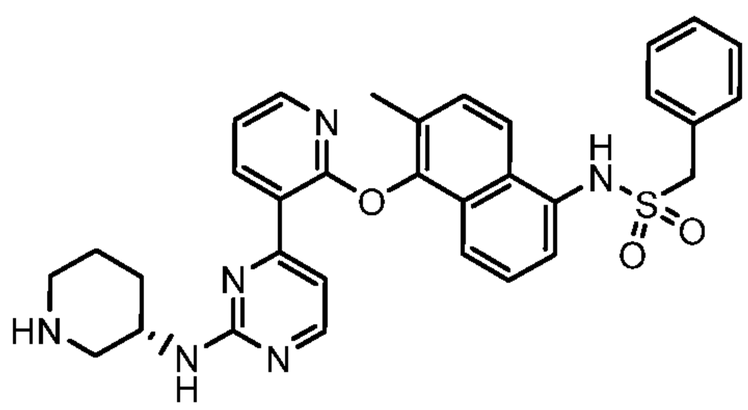
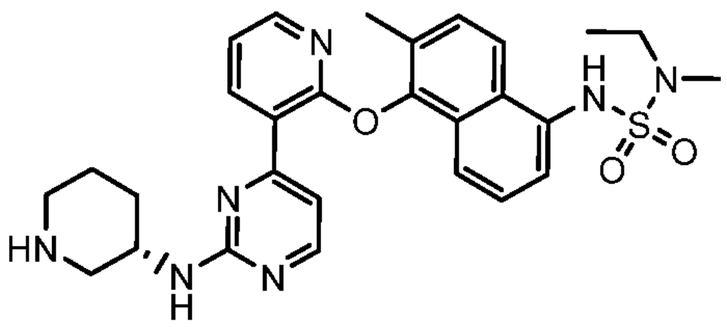
[0111] Biological activity of Formula I or I′ compounds was measured by an IRE1 biochemical binding assay (Example 901), a biochemical RNase assay (Example 902), a cellular PD assay, XBP1s-LUC reporter (Example 903), and an IRE1α-based inhibition of multiple myeloma (MM) cell proliferation assay.

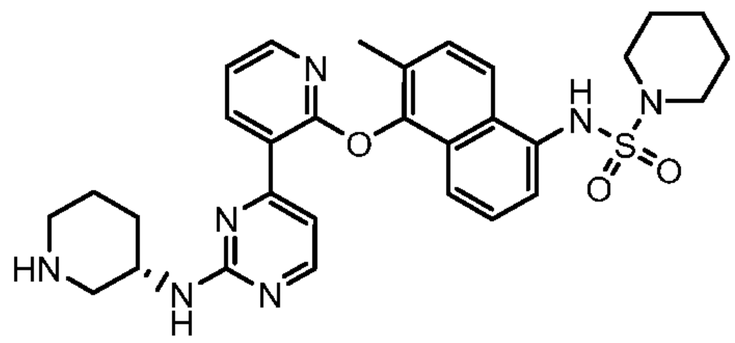
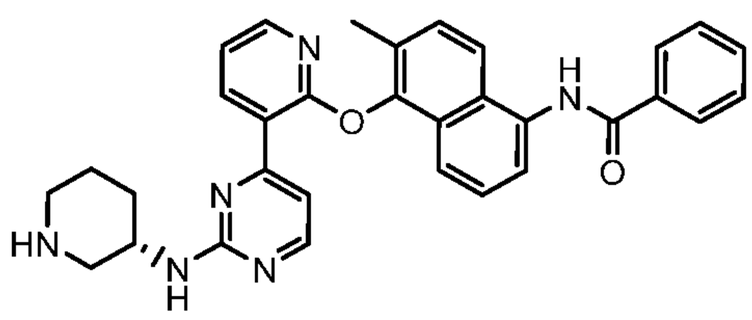
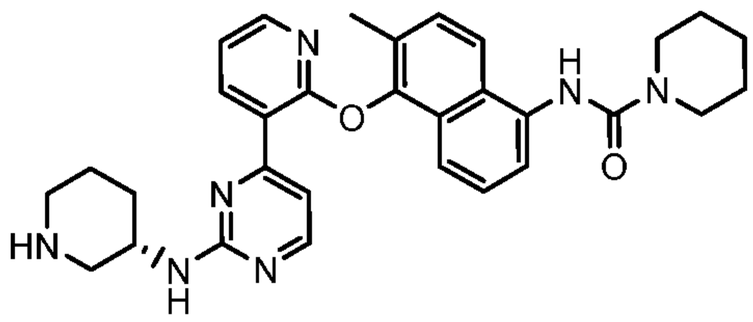
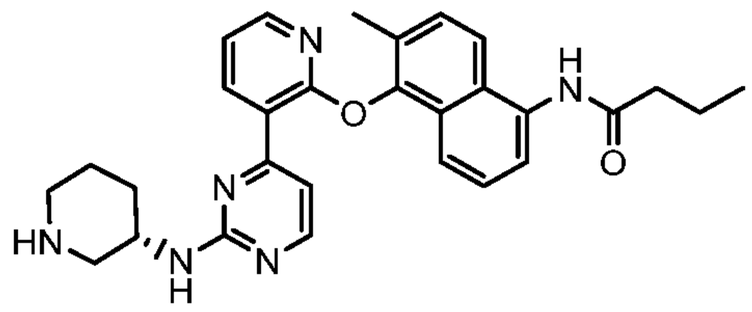
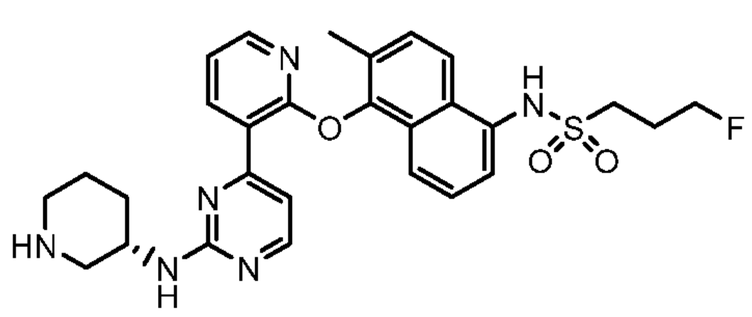
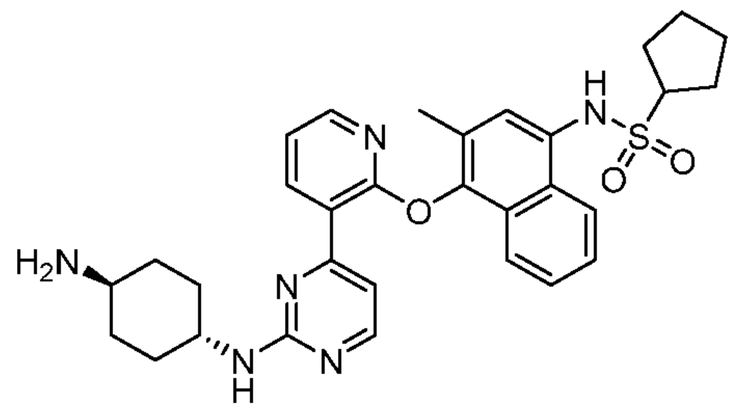
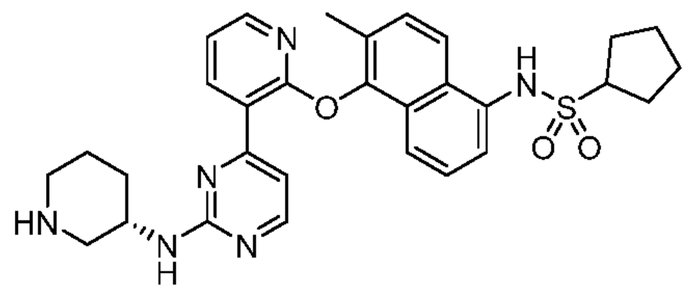
[0112] All of the exemplary Formula I or I′ compounds in Tables 1 and 2 were made and characterized by LCMS $[M+H]^+$ (liquid chromatography mass spectroscopy) with detection of parent ion. All of the exemplary Formula I compounds in Tables 1 and 2 were prepared according to the procedures of the Schemes, General Procedures, and Examples. All of the exemplary Formula I or I′ compounds in Tables 1 and 2 were tested for binding to IRE1 (inositol requiring enzyme 1 alpha) and biological activity according to the assays and protocols of Example 901-903. Exemplary Formula I or I′ compounds in Tables 1 and 2 have the following structures, corresponding IUPAC names (ChemBioDraw, Version 12.0.2, CambridgeSoft Corp., Cambridge MA), and biological activity. Where more than one name is associated with a Formula I or I′ compound or intermediate in Tables 1 and 2 and the Experimental Procedures, the chemical structure shall define the compound. Assignment of configuration at chiral centers in separated stereoisomers may be tentative, and depicted in Tables 1 and 2 structures for illustrative purposes, before stereochemistry is definitively established, such as from x-ray crystallographic data. In some cases, stereoisomers are separated and tested for biological activity before the stereochemistry of the separated stereoisomers is determined; and stereochemistry in some instances was inferred based on structure-activity relationship (SAR) knowledge from previous compounds. In some cases, the compounds are tested as racemic or diastereomeric mixtures. Where more than one potency value is entered on a row, separated stereoisomers represented by the structure and name on that row were tested. Exemplary compounds of Formula I or I′ in Table 3 can be prepared using methods known in the art or according to procedures similar to those described in the Schemes, General Procedures, and Examples 101-500. Biological activities of compounds in Table 3 can be tested in biological assays, for example, those in Examples 901, 902 and 903 described herein.

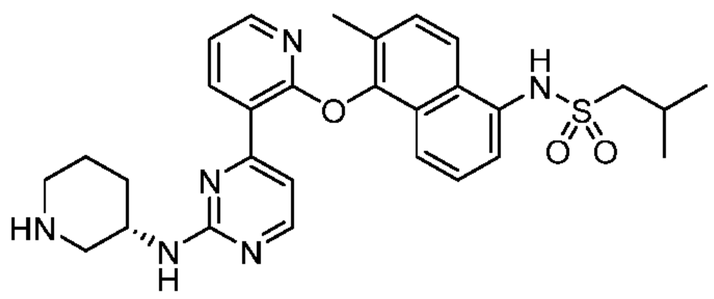
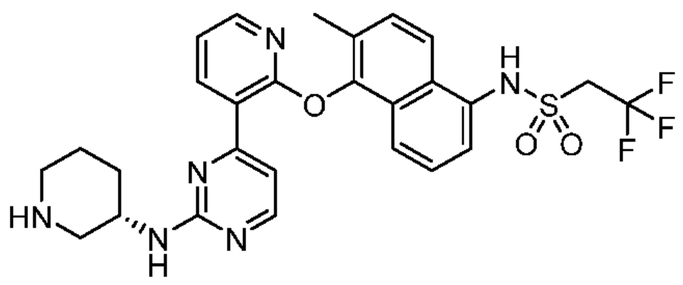
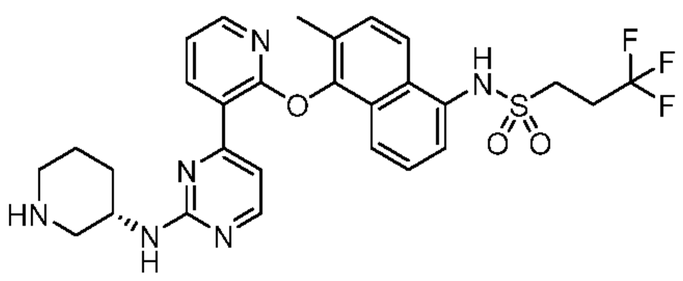
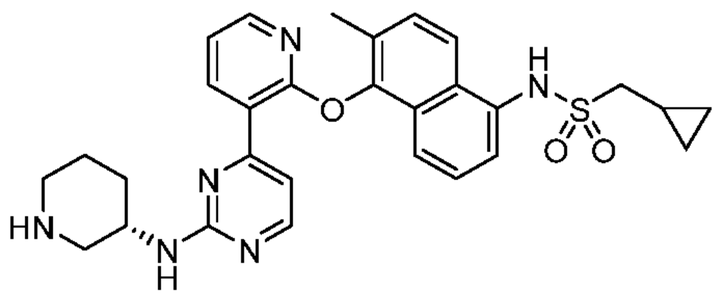
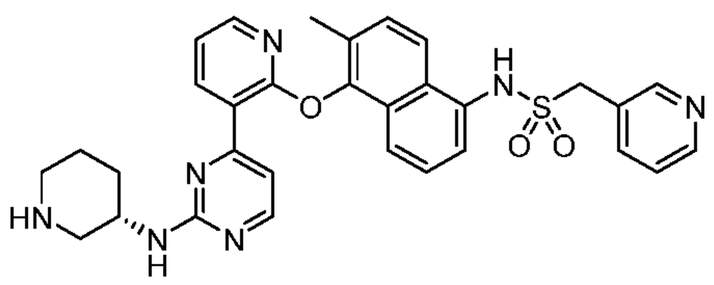
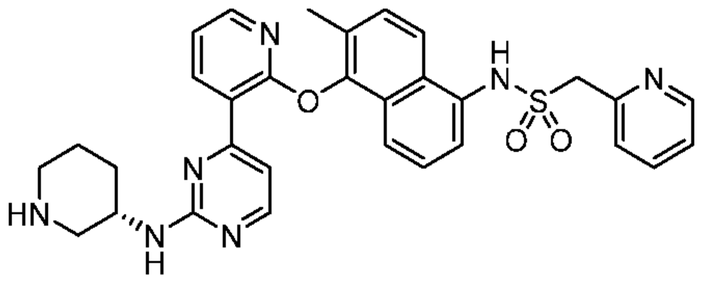
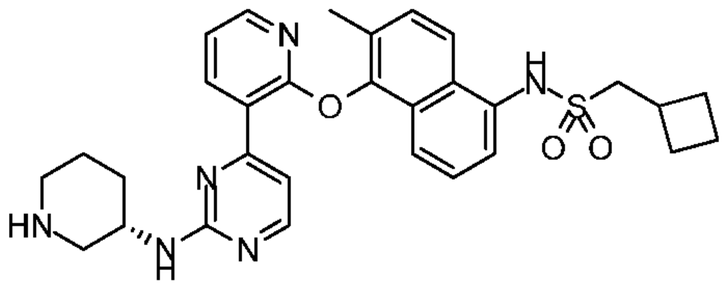
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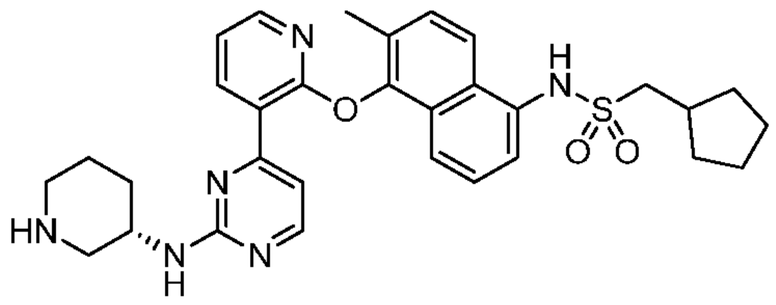
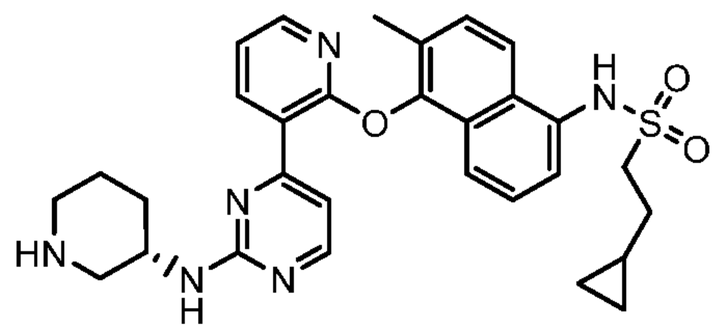
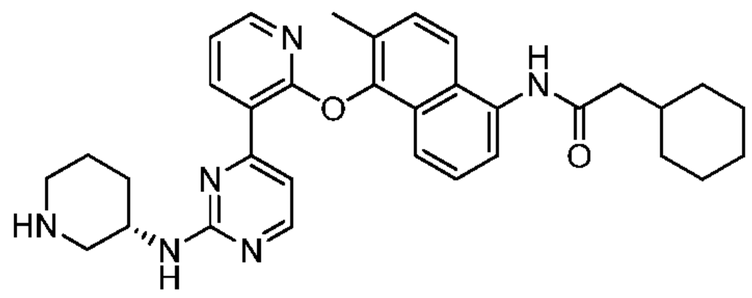
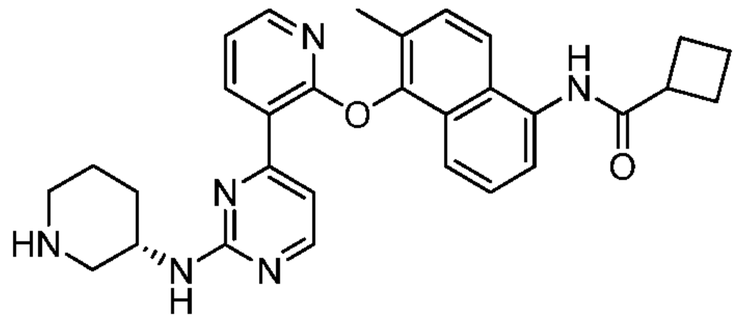
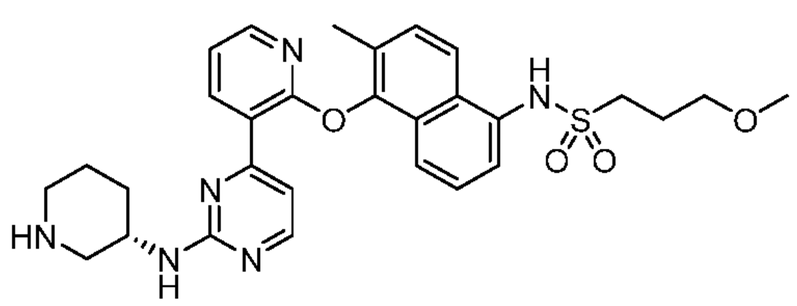
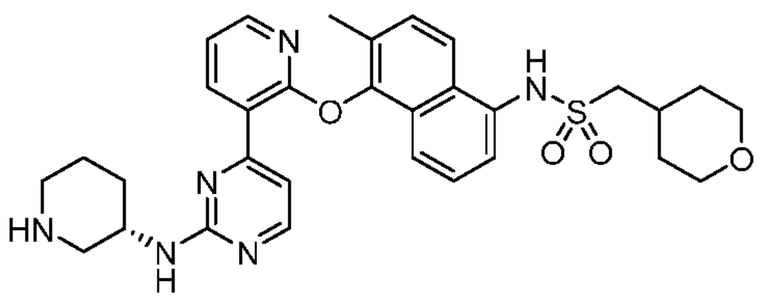
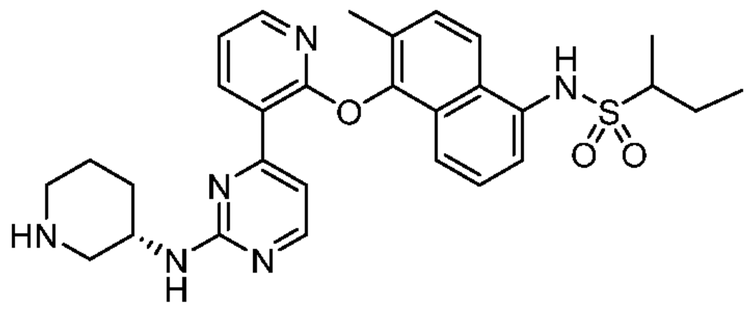
No.	Structure	Name	XBP1s-luc 293 LUC (IC_{50}) (μmol)

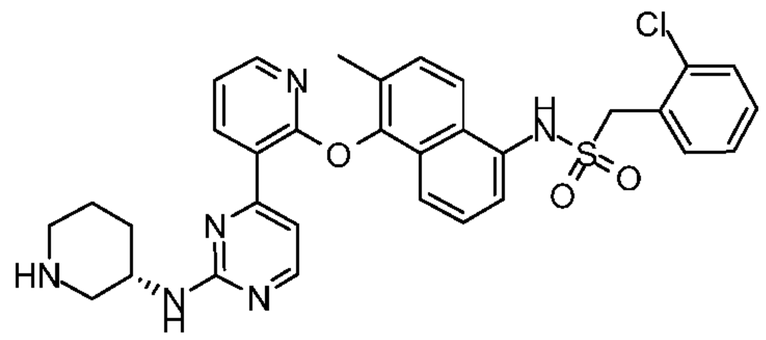
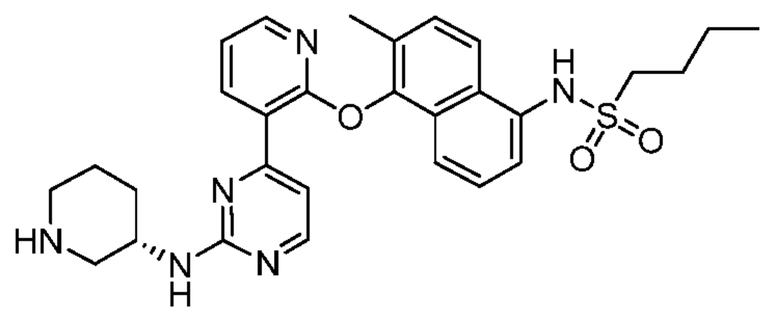
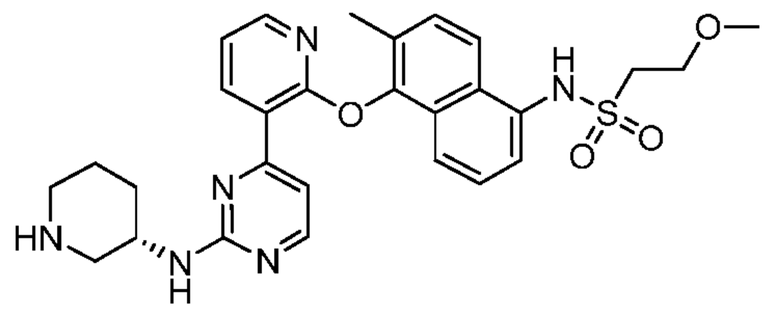
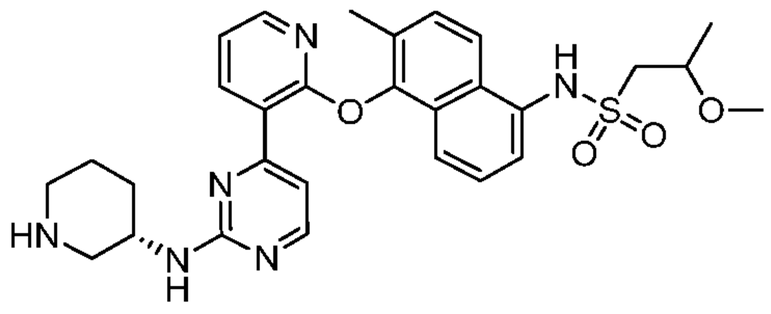
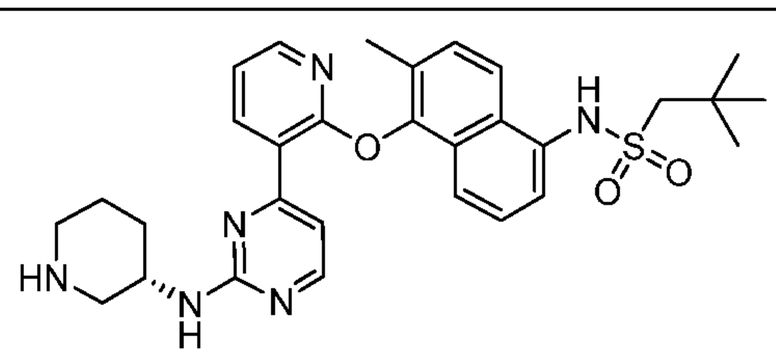
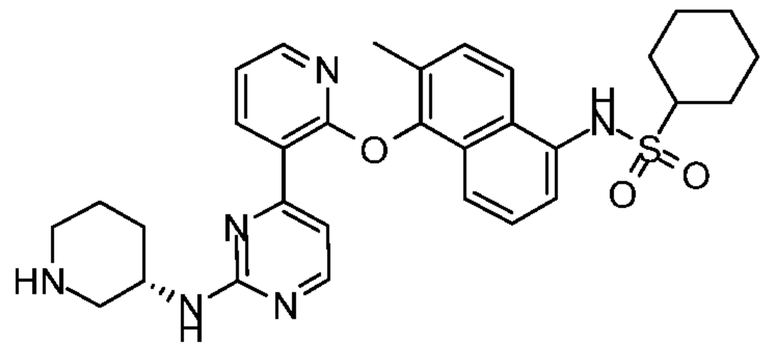
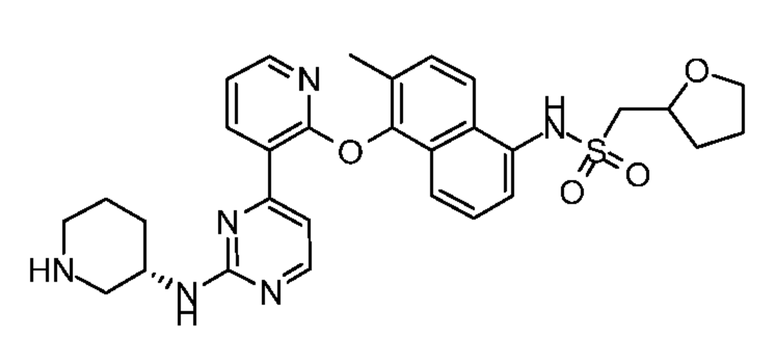
101		(*S*)-3-(2-Cyanopropan-2-yl)-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)benzamide	0.102
102		(*S*)-1-(2-Chlorophenyl)-*N*-(2-fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide	0.0046
103		(*S*)-*N*-(6-Methyl-5-(3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yloxy)naphthalen-1-yl)ethanesulfonamide	0.255
104		(*S*)-*N*-(6-Methyl-5-(3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yloxy)naphthalen-1-yl)propane-1-sulfonamide	0.131
105		(*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropanesulfonamide	0.493
106		(*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl) methylethylsulfonamide	0.349
107		(*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclobutanesulfonamide	0.252

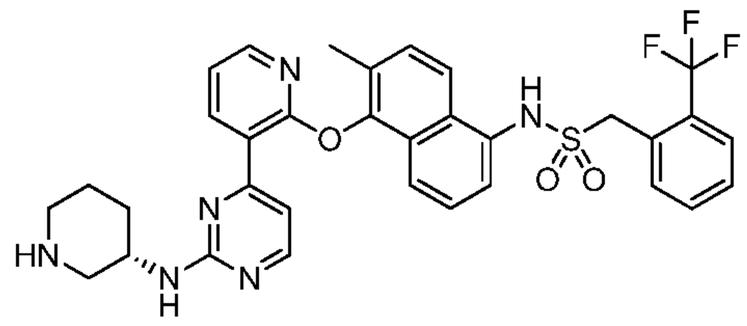
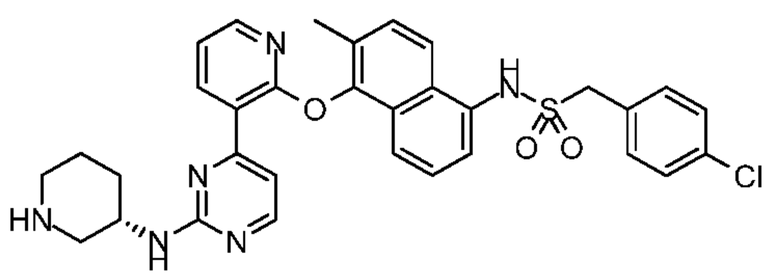
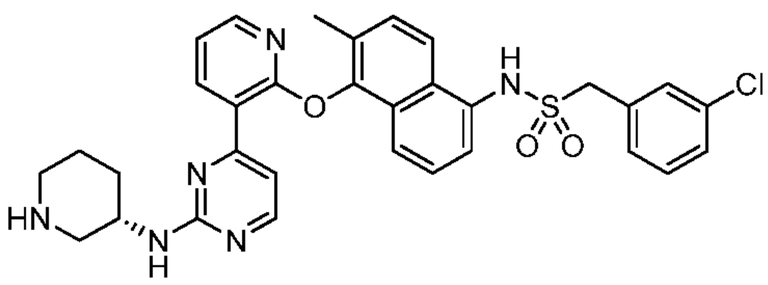
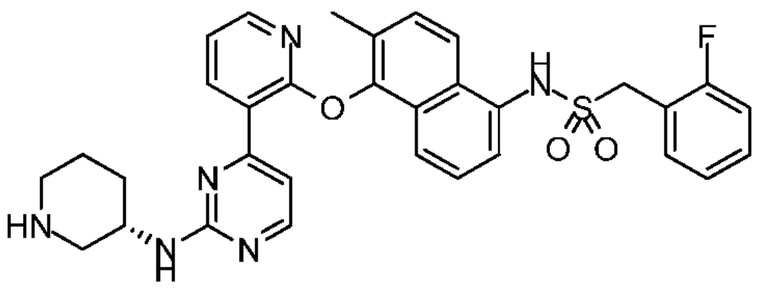
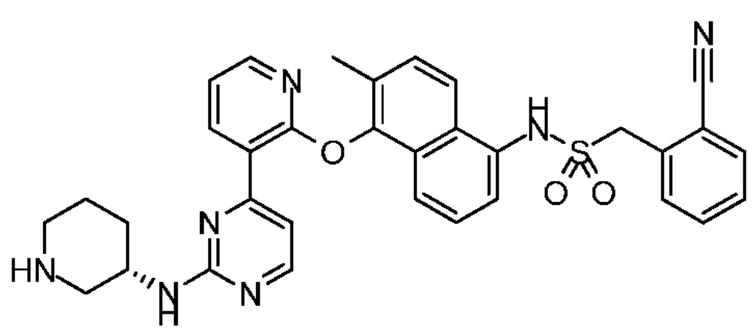
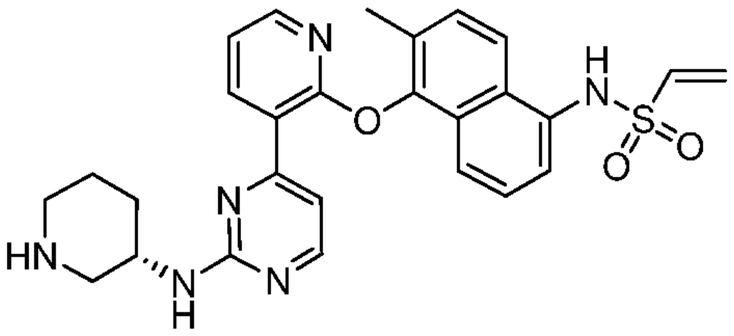
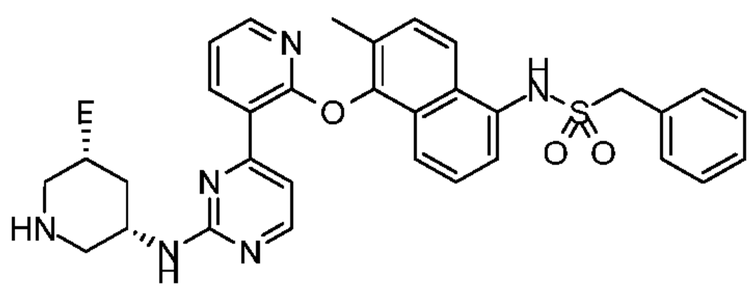
108		(*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidine-1-sulfonamide	0.298
109		4-[2-[[5-(Dimethylsulfamoylamino)-2-methyl-1-naphthyl]oxy]-3-pyridyl]-2-[[(3*S*)-3-piperidyl]amino]pyrimidine	0.222
110		*N*-(4-((3-(2-(((1*R*,4*R*)-4-Aminocyclohexyl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)-1-phenylmethanesulfonamide	0.119
111		*N*-(4-((3-(2-(((1*R*,4*R*)-4-Aminocyclohexyl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)cyclobutanesulfonamide	0.447
112		*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-Piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]-1-phenyl-methanesulfonamide	0.021
113		4-[2-[[5-[[Ethyl(methyl)sulfamoyl]amino]-2-methyl-1-naphthyl]oxy]-3-pyridyl]-2-[[(3*S*)-3-piperidyl]amino]pyrimidine	0.343

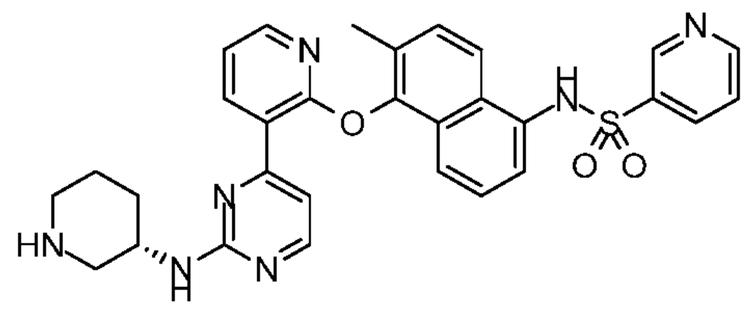
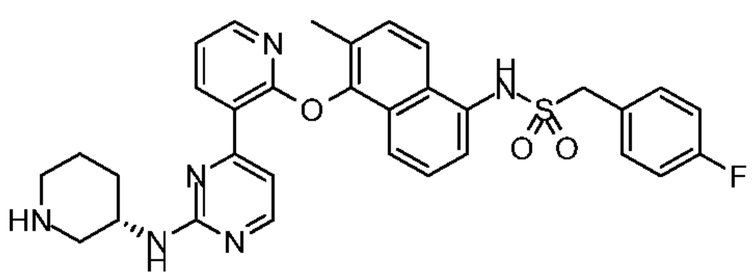
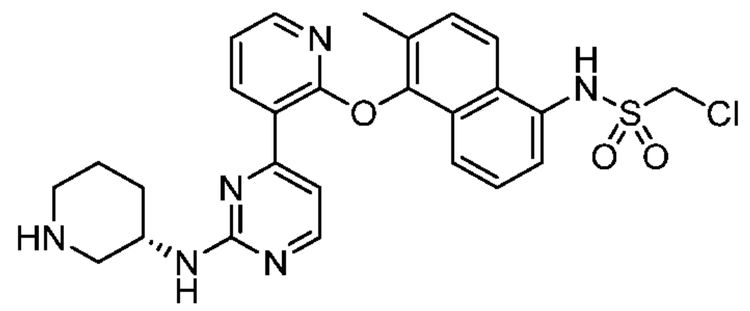
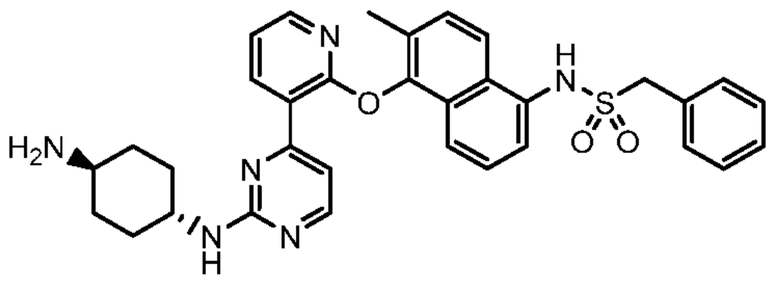
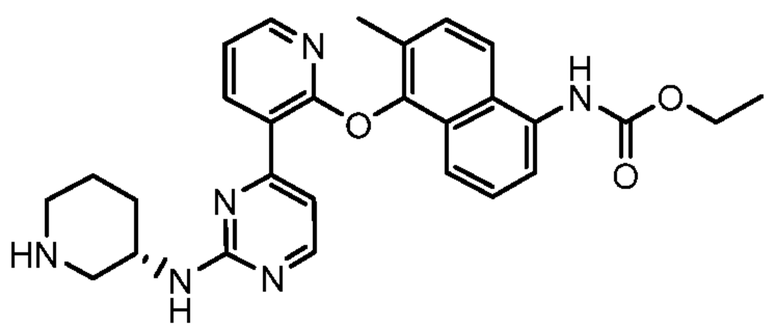
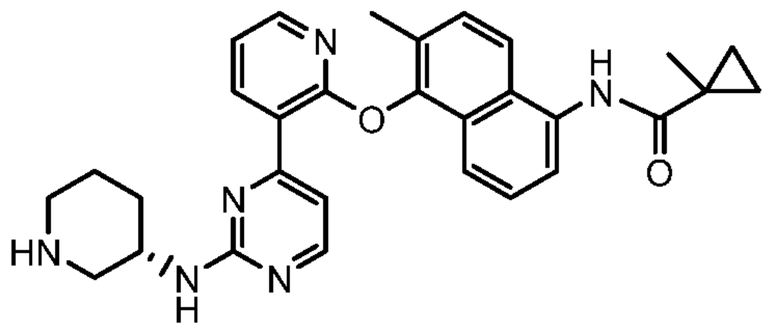
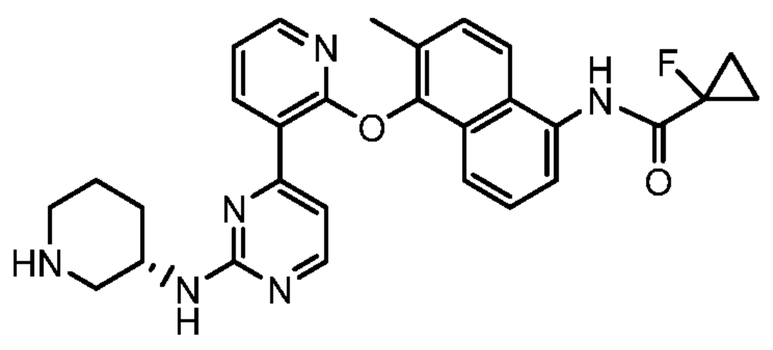
114		(*S*)-*N*-(6-methyl-5-((3-(2-(Piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)piperidine-1-sulfonamide	0.382
115		*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-Piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]benzamide	0.262
116		*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-Piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]piperidine-1-carboxamide	0.43
117		*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-Piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]butanamide	0.145
118		3-Fluoro-N-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]propane-1-sulfonamide	0.323
119		*N*-(4-((3-(2-(((*trans*)-4-Aminocyclohexyl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)cyclopentanesulfonamide	0.312
120		(*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentanesulfonamide	0.18

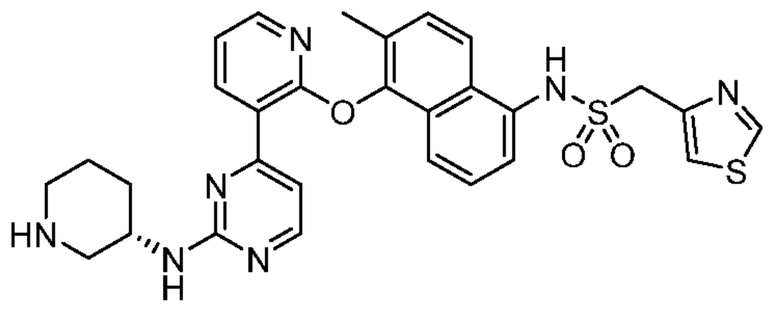
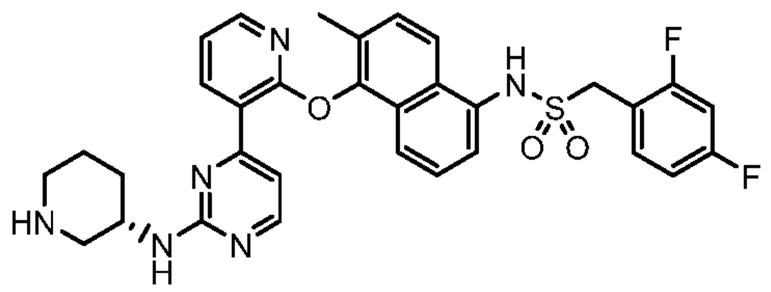
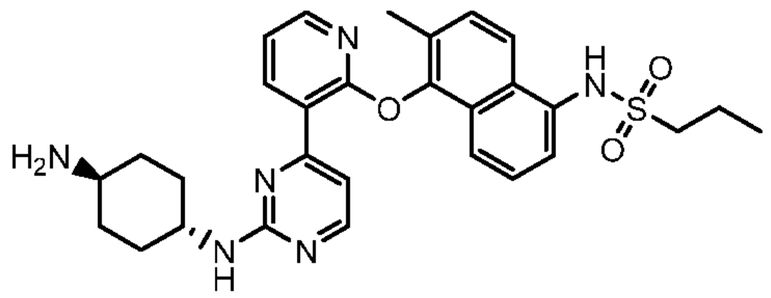
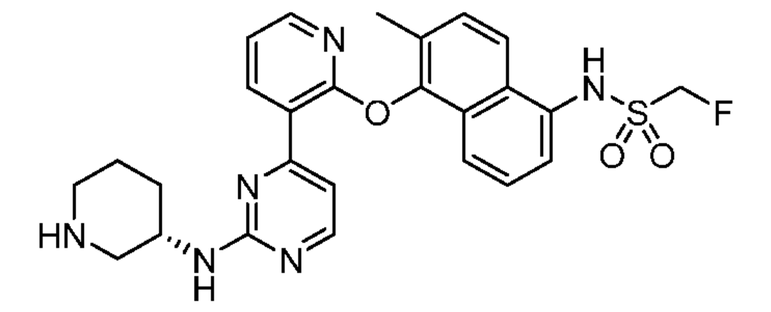
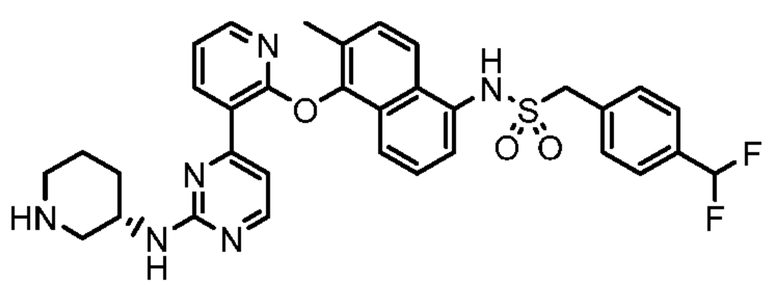
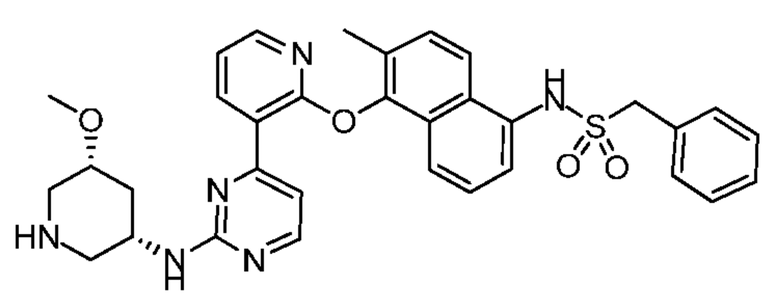
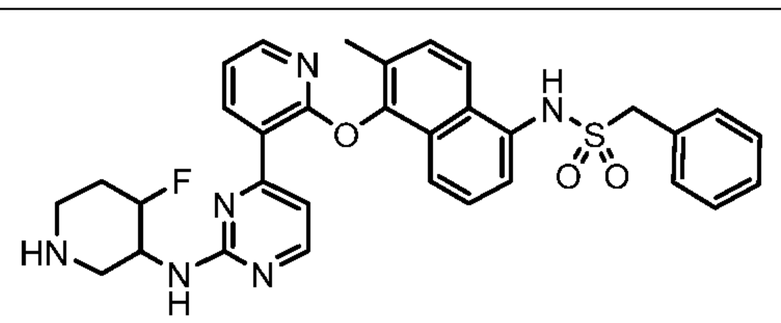
121		(*S*)-2-Methyl-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide	0.103
122		(*S*)-2,2,2-Trifluoro-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)ethane-1-sulfonamide	0.105
123		(*S*)-3,3,3-Trifluoro-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide	0.084
124		(*S*)-1-Cyclopropyl-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide	0.105
125		(*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-(pyridin-3-yl)methanesulfonamide	0.318
126		(*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-(pyridin-2-yl)methanesulfonamide	0.054
127		1-Cyclobutyl-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]methanesulfonamide	0.233

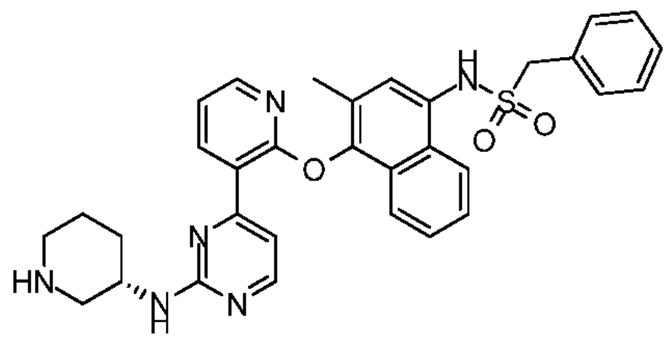
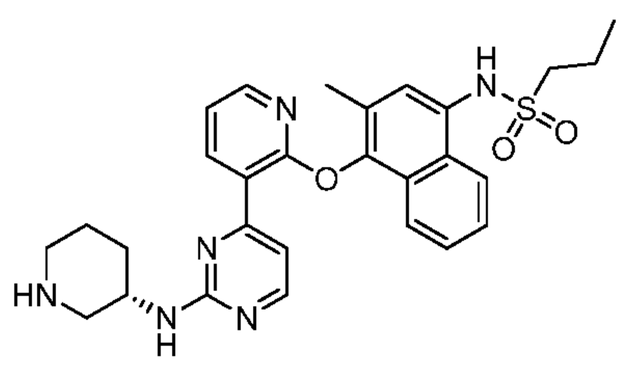
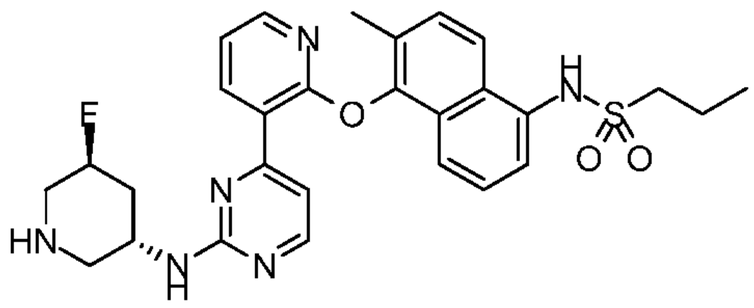
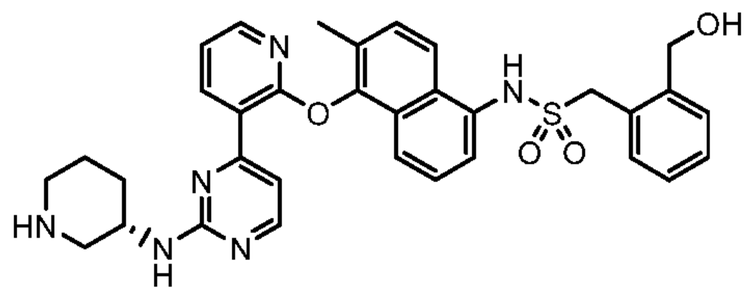
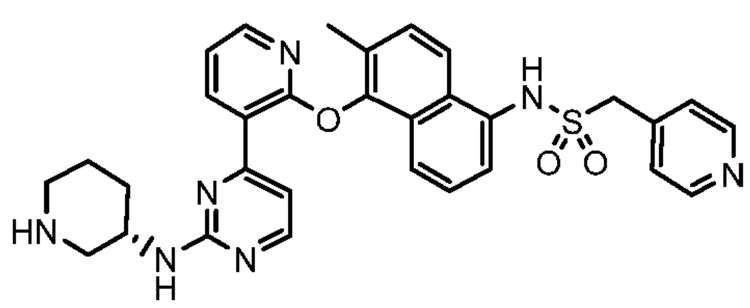
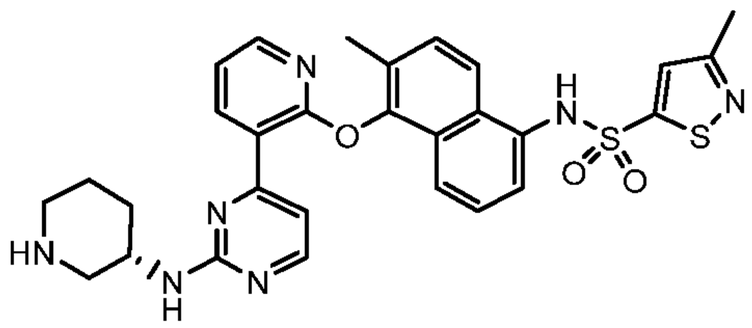
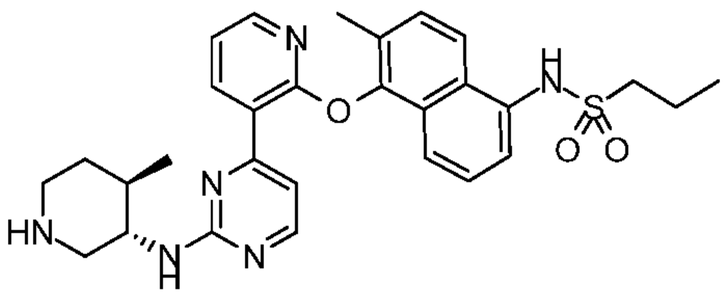
128		1-Cyclopentyl-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]methanesulfonamide	0.317
129		2-Cyclopropyl-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]ethanesulfonamide	0.301
130		2-Cyclohexyl-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]acetamide	0.228
131		(*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclobutanecarboxamide	0.153
132		(*S*)-3-Methoxy-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide	0.365
133		(*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-(tetrahydro-2H-pyran-4-yl)methanesulfonamide	0.158
134		*N*-(6-Methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)butane-2-sulfonamide	0.26

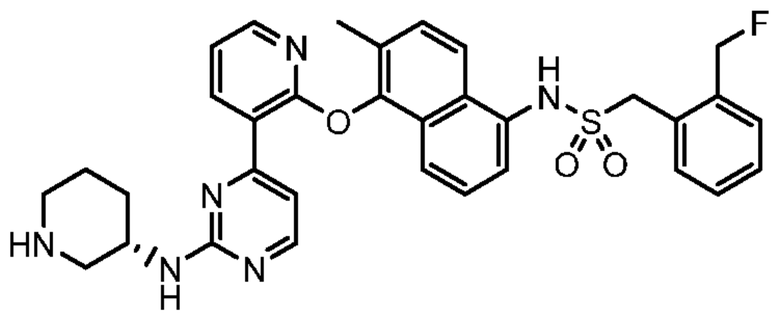
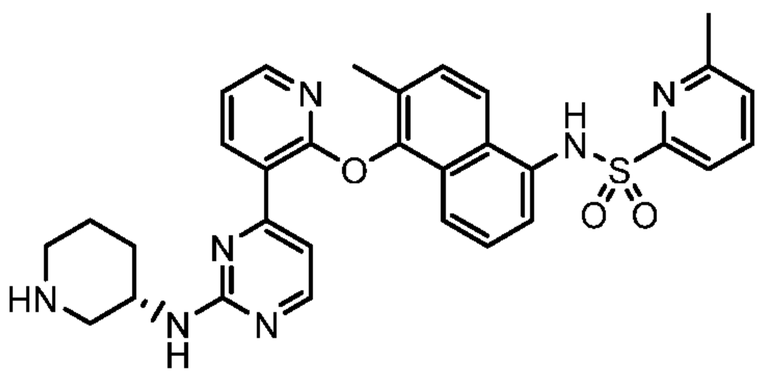
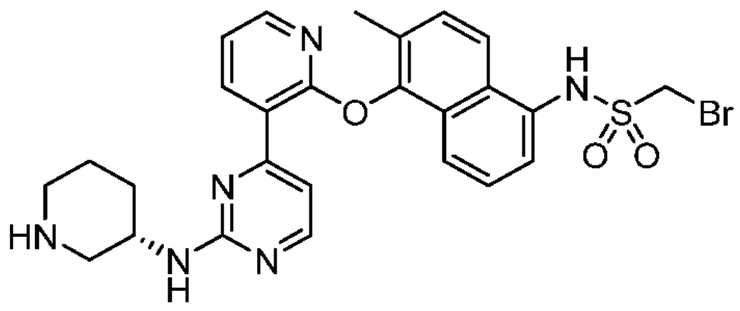
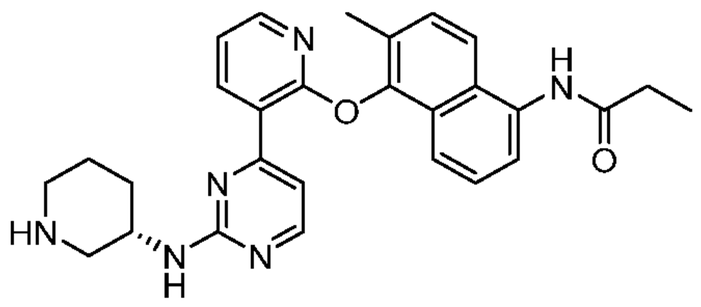
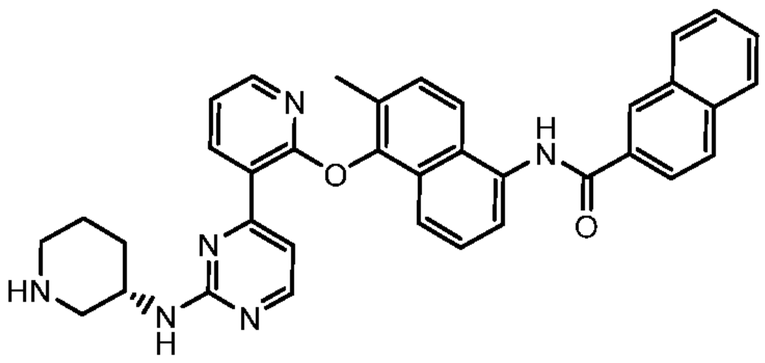
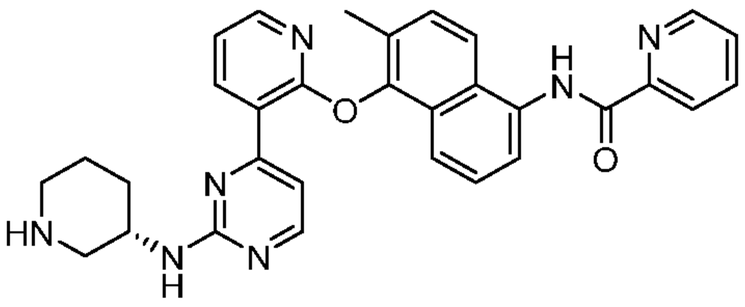
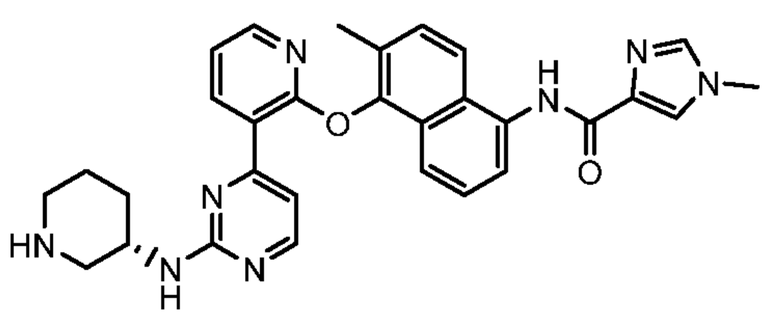
135		(*S*)-1-(2-Chlorophenyl)-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide	0.01
136		(*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalene-1-yl)butane-1-sulfonamide	0.297
137		(*S*)-2-Methoxy-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)ethanesulfonamide	0.477
138		2-Methoxy-*N*-(6-methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide	0.388
139		((*S*)-2,2-Dimethyl-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide	0.241
140		(*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclohexanesulfonamide	0.177
141		*N*-(6-Methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-(tetrahydrofuran-2-yl)methanesulfonamide	0.457

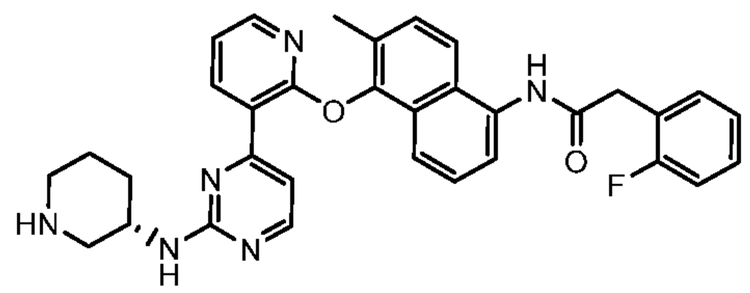
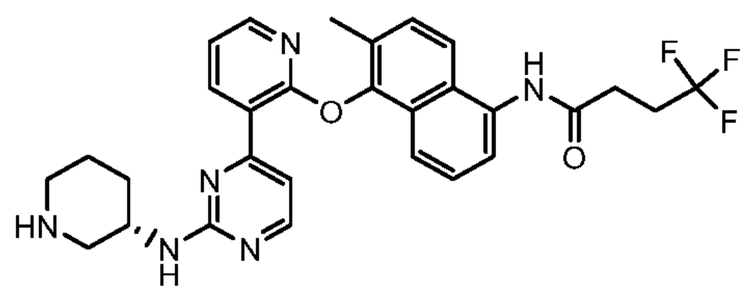
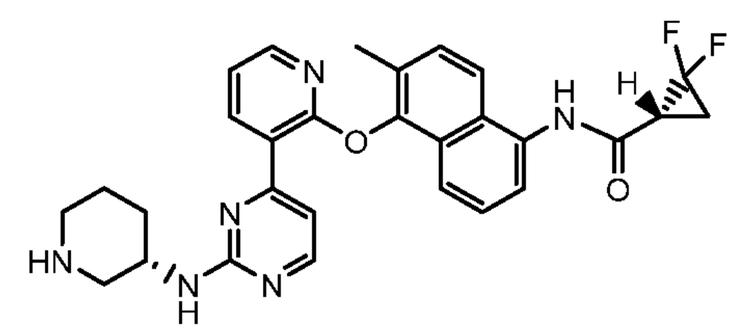
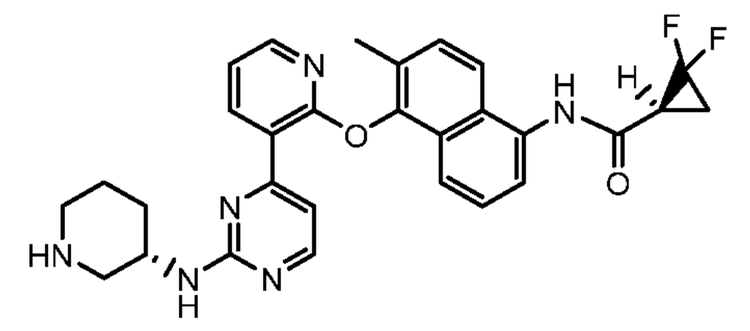
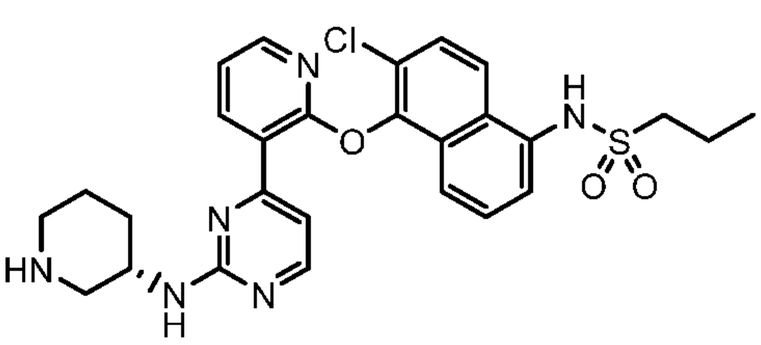
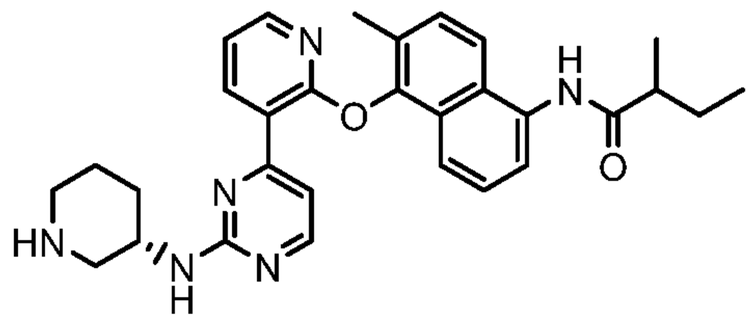
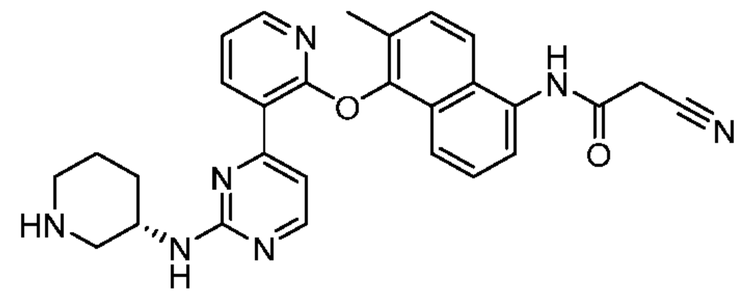
142		(*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-(2-(trifluoromethyl)phenyl)methanesulfonamide	0.008
143		(*S*)-1-(4-Chlorophenyl)-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide	0.017
144		(*S*)-1-(3-Chlorophenyl)-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide	0.025
145		(*S*)-1-(2-Fluorophenyl)-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide	0.015
146		(*S*)-1-(2-Cyanophenyl)-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide	0.018
147		(*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)ethenesulfonamide	0.139
148		*N*-(5-((3-(2-(((3*S*,5*R*)-5-Fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)-1-phenylmethanesulfonamide	0.211

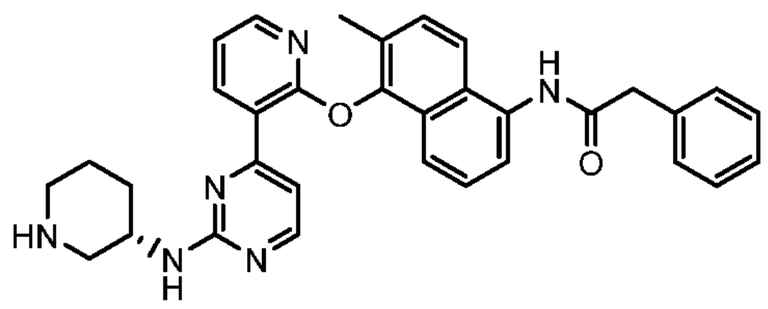
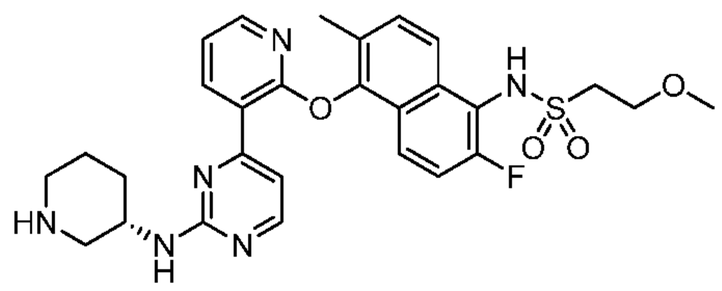
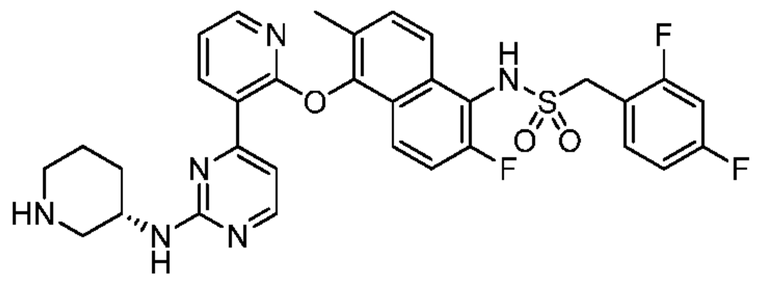
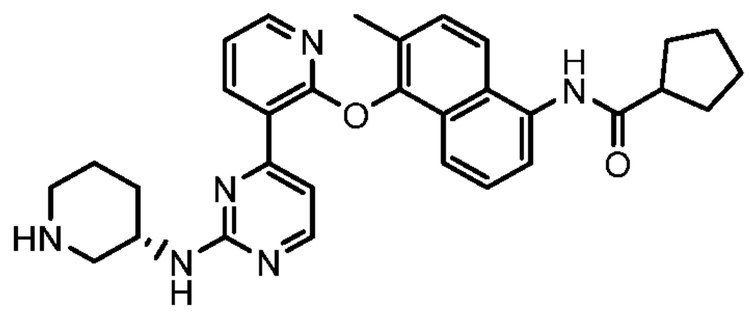
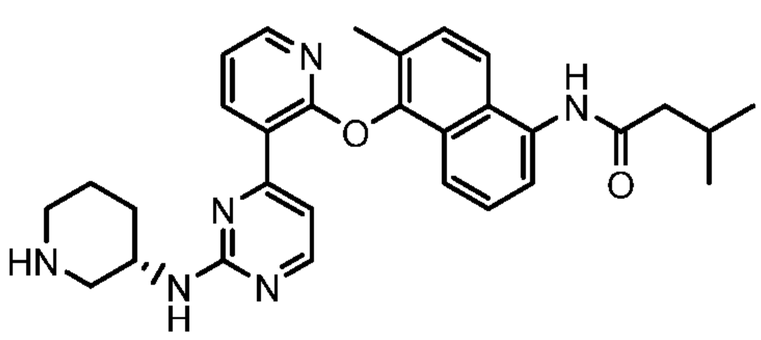
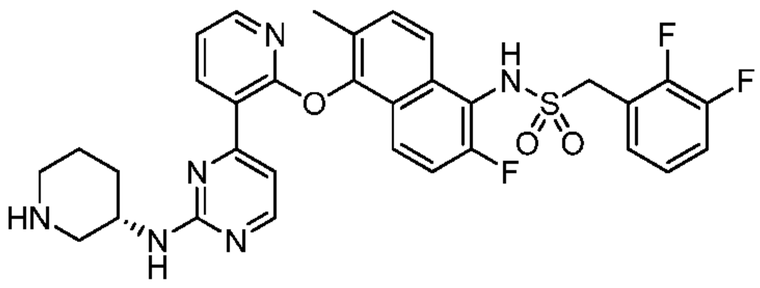
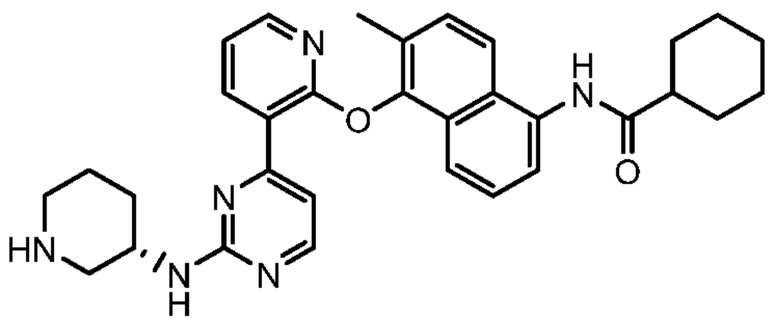
149		(*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyridine-3-sulfonamide	0.494
150		(*S*)-1-(4-Fluorophenyl)-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide	0.025
151		(*S*)-1-Chloro-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide	0.14
152		*N*-(5-((3-(2-(((*trans*)-4-Aminocyclohexyl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)-1-phenylmethanesulfonamide	0.241
153		Ethyl *N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]carbamate	0.143
154		1-Methyl-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]cyclopropanecarboxamide	0.239
155		1-Fluoro-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]cyclopropanecarboxamide	0.38

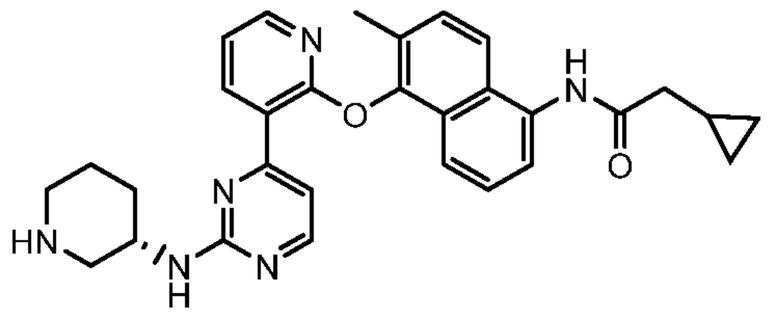
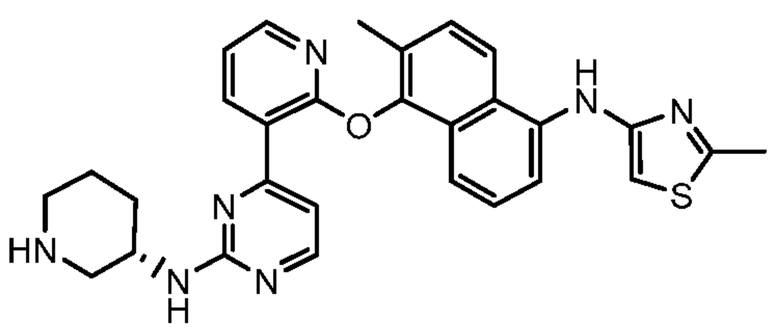
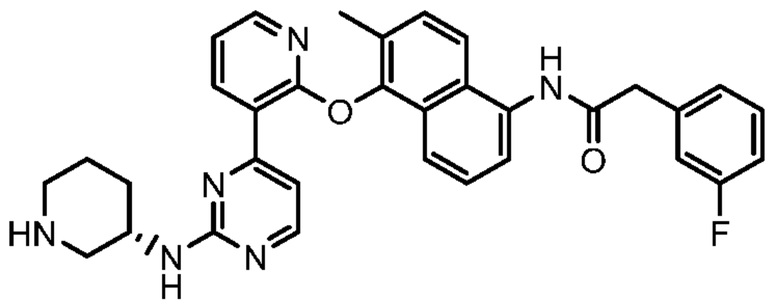
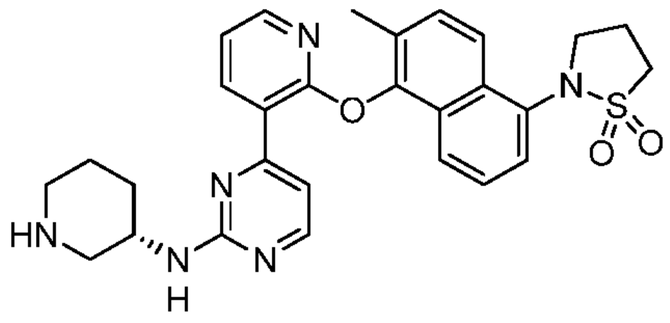
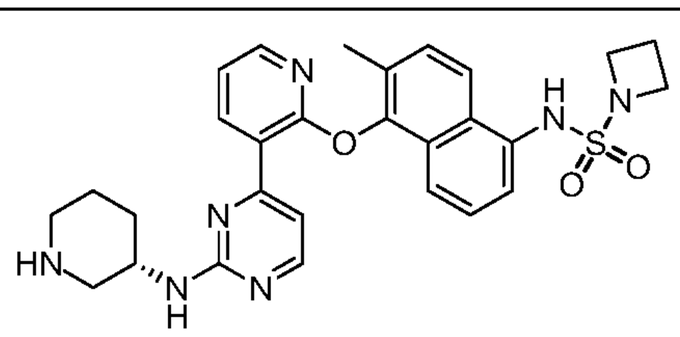
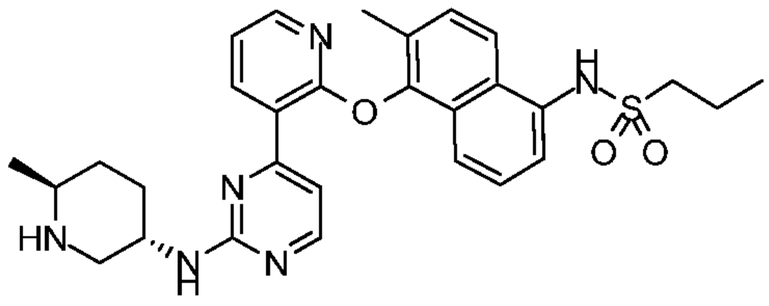
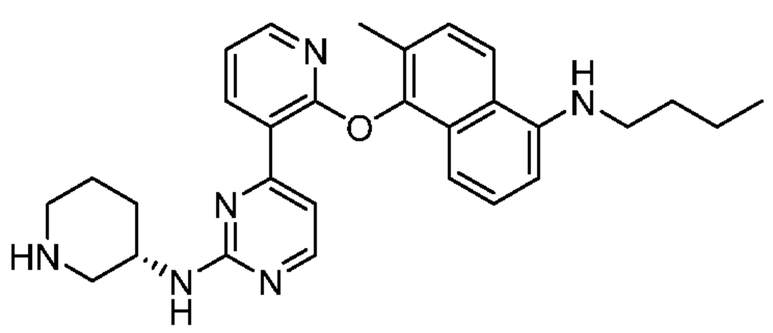
156		(*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-(thiazol-4-yl)methanesulfonamide	0.157
157		1-(2,4-Difluorophenyl)-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]methanesulfonamide	0.008
158		*N*-(5-((3-(2-(((*trans*)-4-Aminocyclohexyl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)propane-1-sulfonamide	0.471
159		(*S*)-1-Fluoro-*N*-(6-methyl-5-(3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yloxy)naphthalen-1-yl)methanesulfonamide	0.174
160		1-[4-(Difluoromethyl)phenyl]-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]methanesulfonamide	0.013
161		*N*-(5-((3-(2-(((3*S*,5*R*)-5-Methoxypiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)-1-phenylmethanesulfonamide	0.046
162		*N*-[5-[[3-[2-[(4-Fluoro-3-piperidyl)amino]pyrimidin-4-yl]-2-pyridyl]oxy]-6-methyl-1-naphthyl]-1-phenyl-methanesulfonamide	0.067

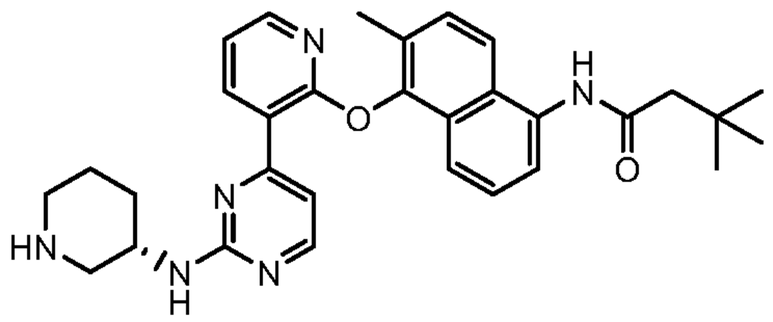
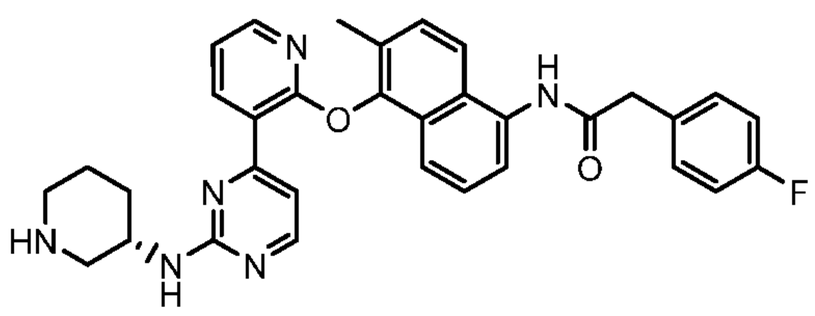
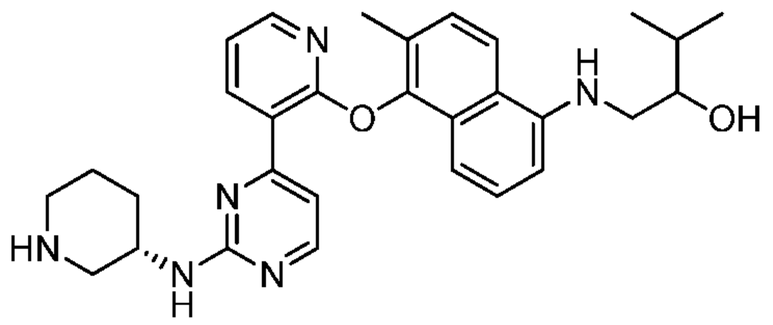
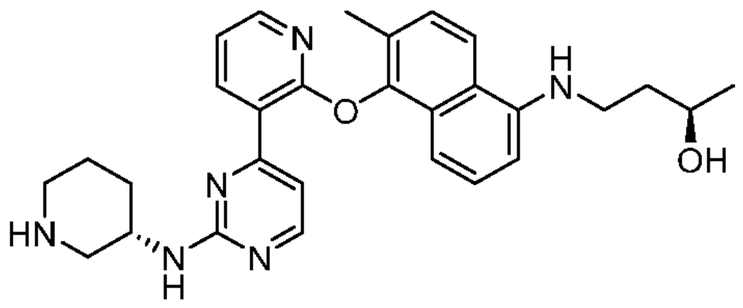
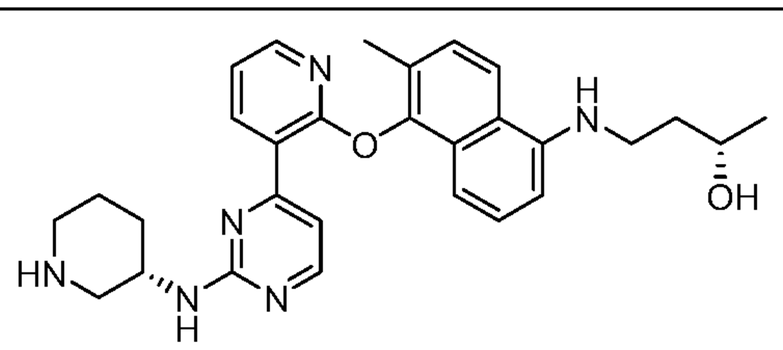
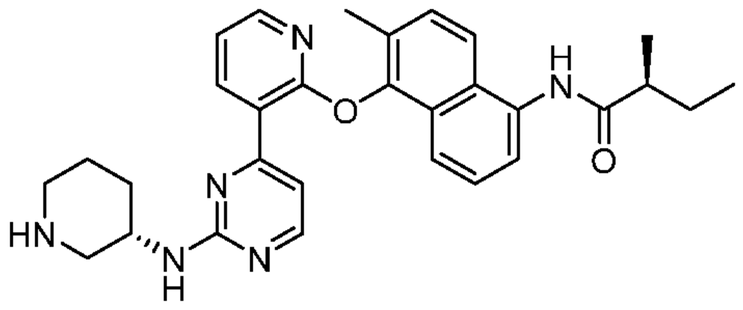
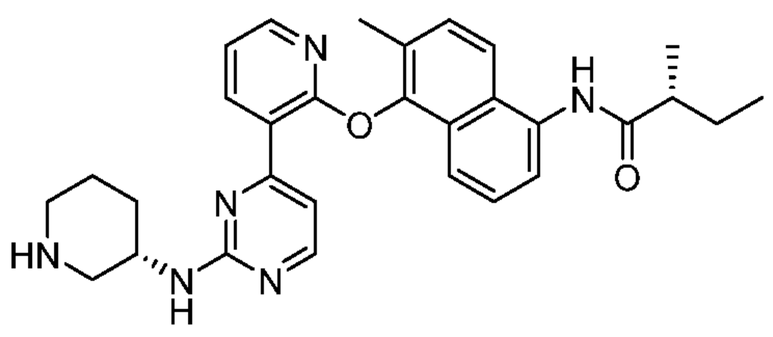
163		*N*-[3-Methyl-4-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]-1-phenyl-methanesulfonamide	0.047
164		*N*-[3-Methyl-4-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]propane-1-sulfonamide	0.147
165		*N*-[5-[[3-[2-[[(3*S*,5*S*)-5-Fluoro-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-6-methyl-1-naphthyl]propane-1-sulfonamide	0.164
166		1-[2-(Hydroxymethyl)phenyl]-*N*-[6-methyl-5-[[3-[2-[[(3S)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]methanesulfonamide	0.118
167		*N*-[6-Methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]-1-(4-pyridyl)methanesulfonamide	0.019
168		3-Methyl-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]isothiazole-5-sulfonamide	0.172
169		*N*-(6-Methyl-5-((3-(2-(((3*S*,4*R*)-4-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide	0.121

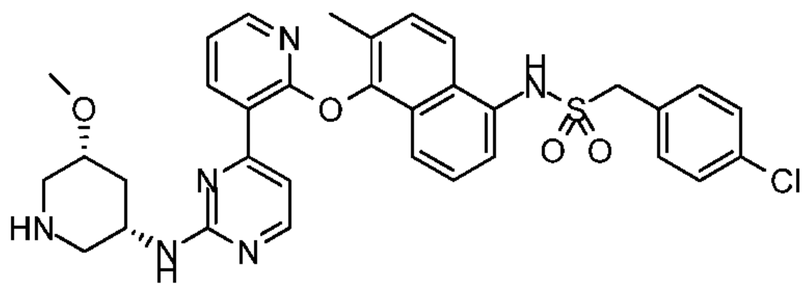
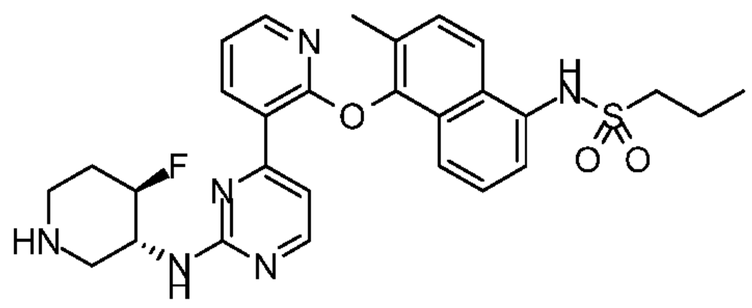
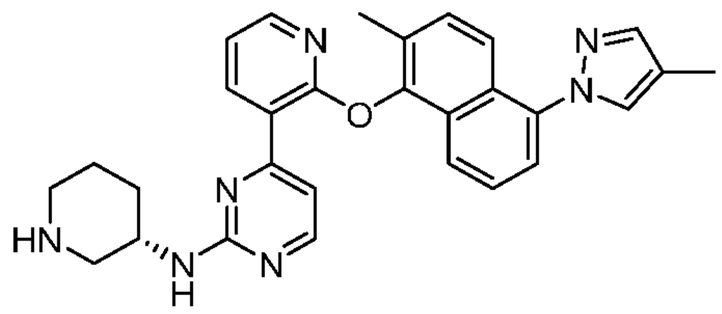
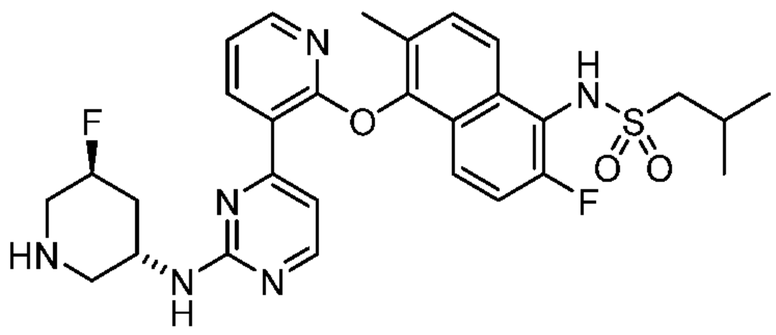
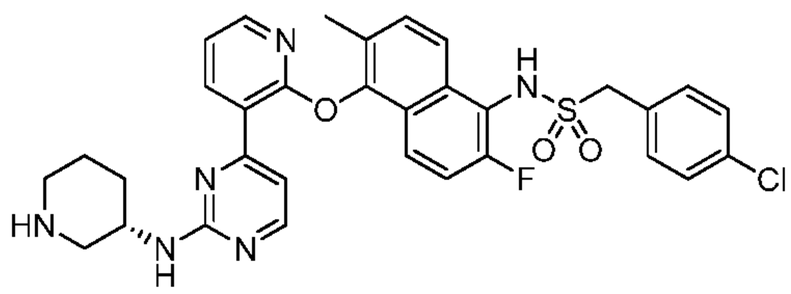
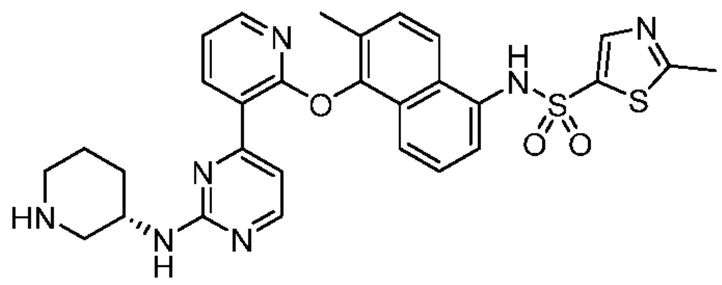
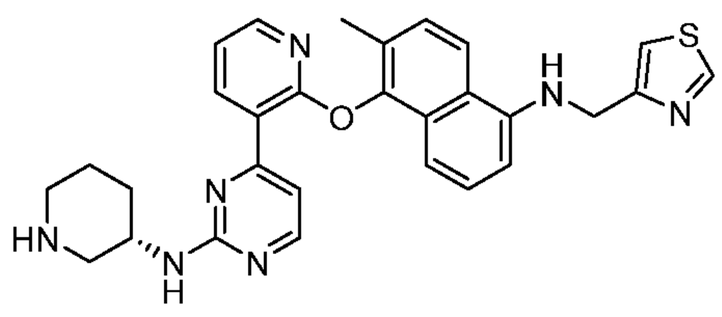
170		1-[2-(Fluoromethyl)phenyl]-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]methanesulfonamide	0.015
171		6-Methyl-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]pyridine-2-sulfonamide	0.309
172		(*S*)-1-Bromo-*N*-(6-methyl-5-(3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yloxy)naphthalen-1-yl)methanesulfonamide	0.393
173		*N*-[6-Methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]propanamide	0.226
174		*N*-[6-Methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]naphthalene-2-carboxamide	0.278
175		*N*-[6-Methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]pyridine-2-carboxamide	0.333
176		(*S*)-1-Methyl-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1H-imidazole-4-carboxamide	0.368

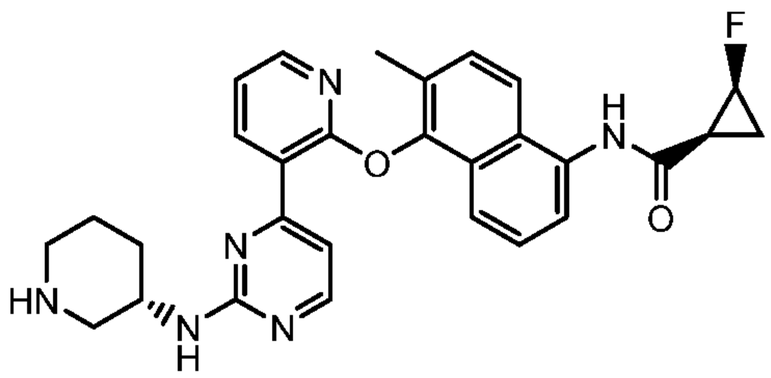
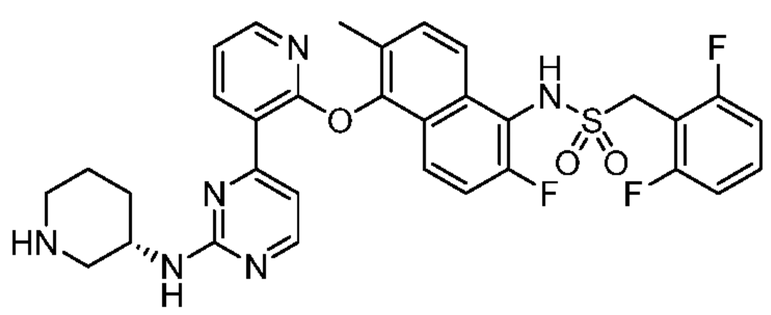
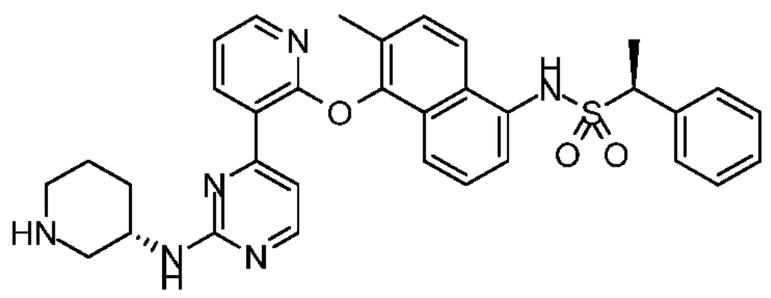
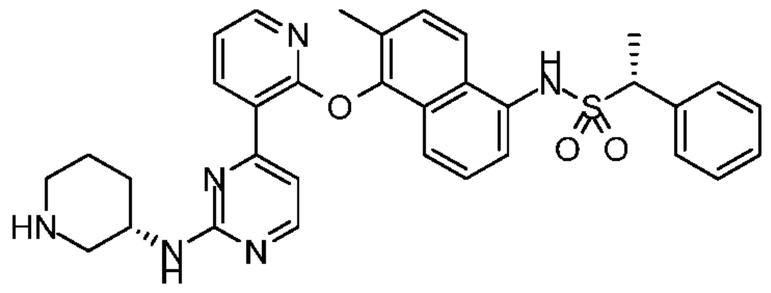
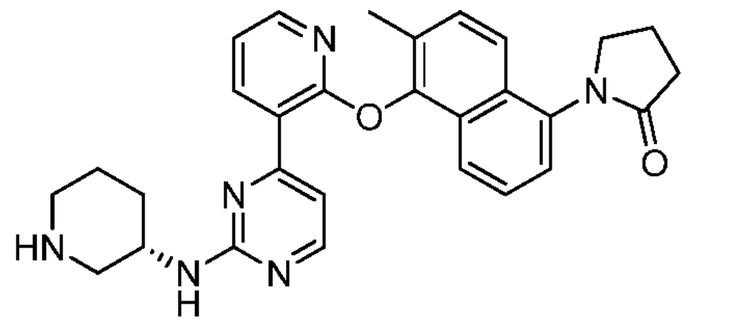
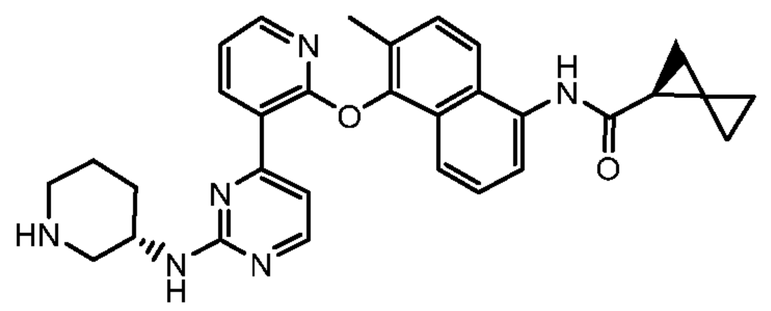
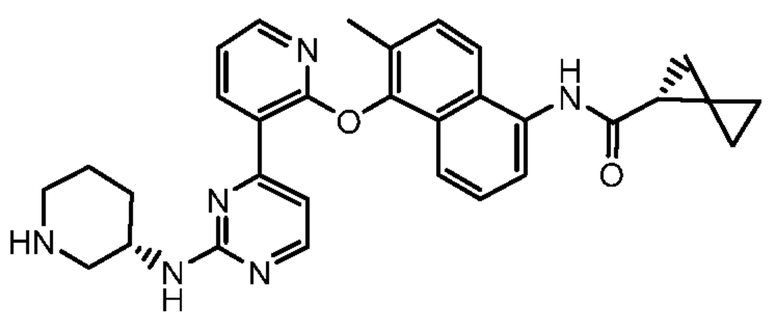
177		2-(2-Fluorophenyl)-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]acetamide	0.108
178		4,4,4-Trifluoro-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]butanamide	0.125
179		(*R*)-2,2-Difluoro-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide	0.076
180		(*S*)-2,2-Difluoro-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide	0.213
181		*N*-[6-Chloro-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]propane-1-sulfonamide	0.185
182		2-Methyl-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)butanamide	0.154
183		2-Cyano-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]acetamide	0.26

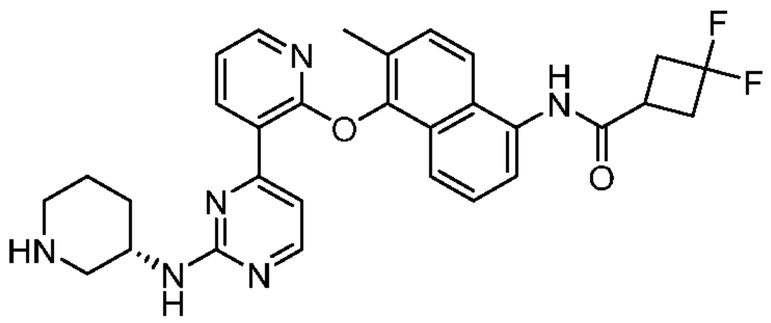
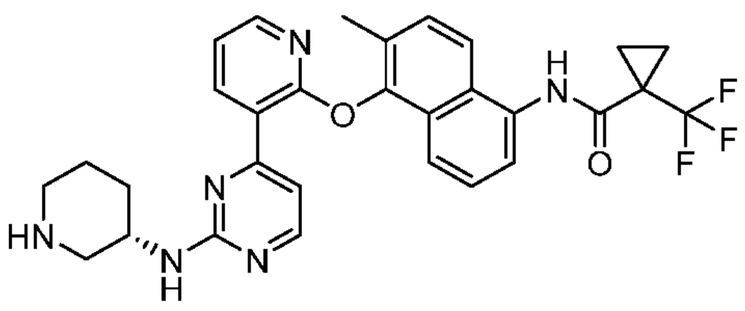
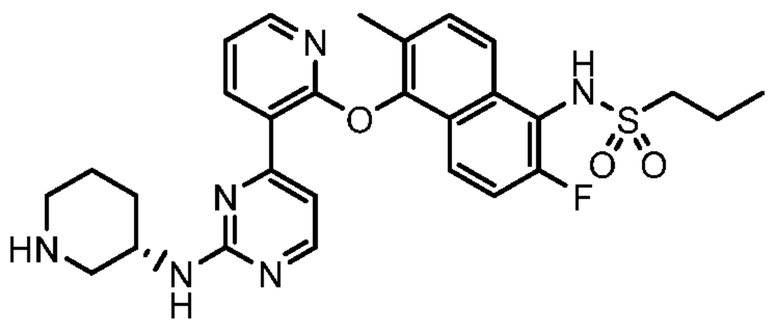
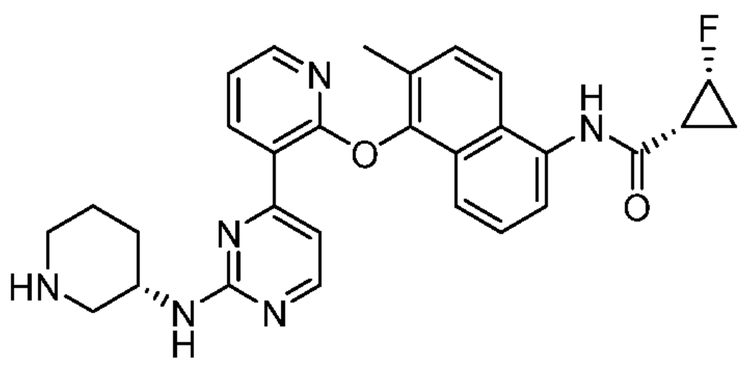
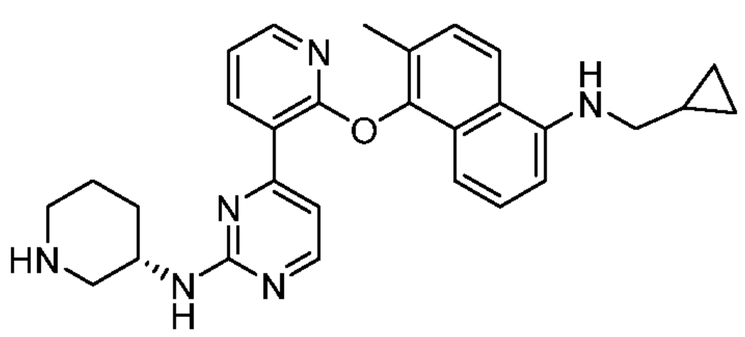
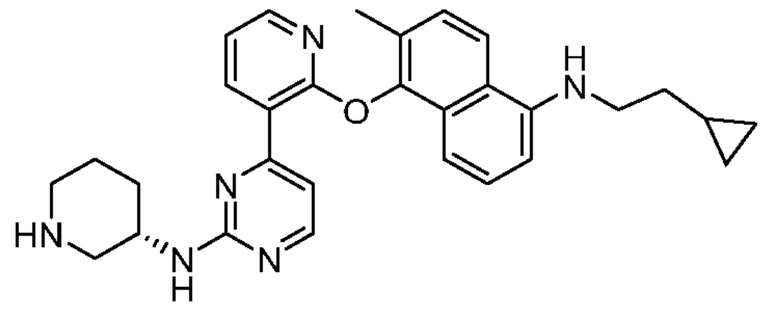
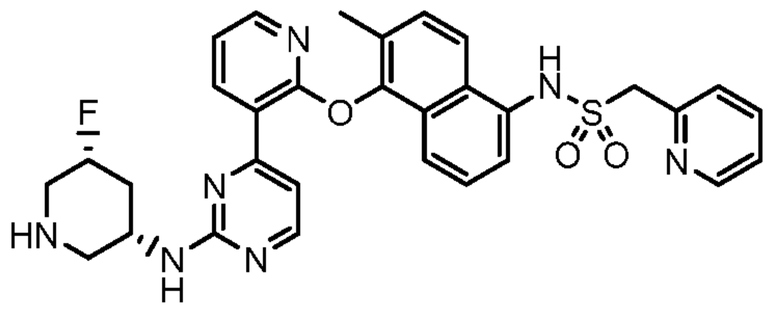
184		*N*-[6-Methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]-2-phenyl-acetamide	0.1
185		(*S*)-*N*-(2-Fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-methoxyethanesulfonamid	0.0735
186		(*S*)-1-(2,4-Difluorophenyl)-*N*-(2-fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide	0.00489
187		*N*-[6-Methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]cyclopentanecarboxamide	0.157
188		3-Methyl-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]butanamide	0.141
189		(*S*)-1-(2,3-Difluorophenyl)-*N*-(2-fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide	0.00507
190		*N*-[6-Methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]cyclohexanecarboxamide	0.273

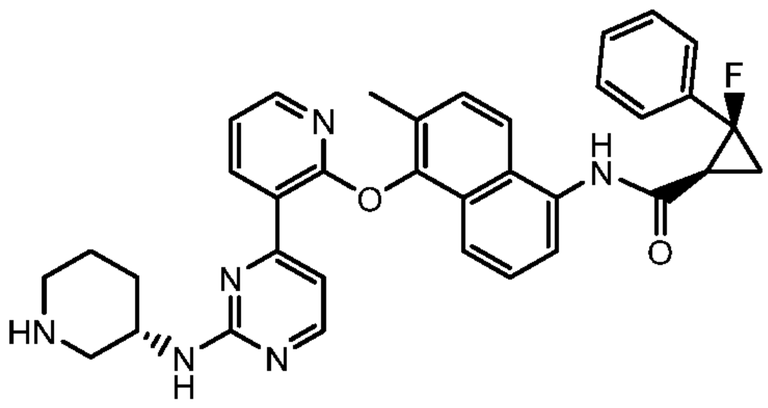
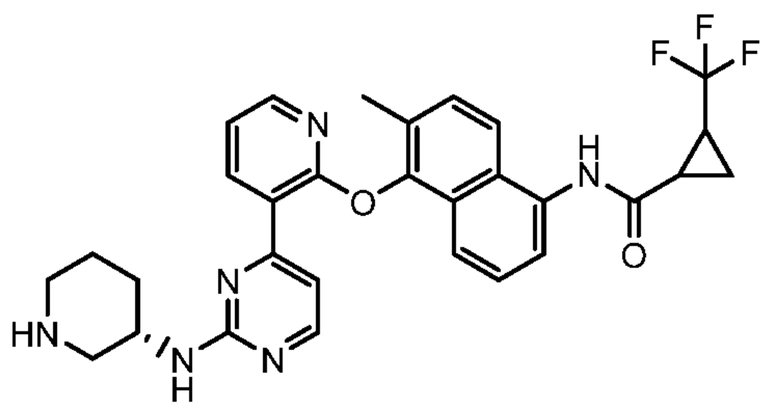
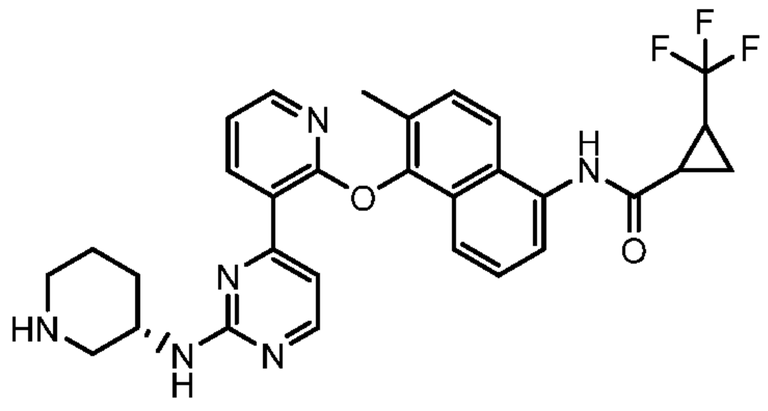
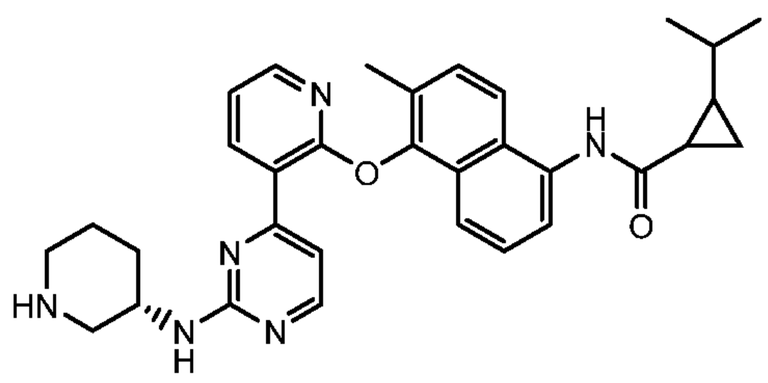
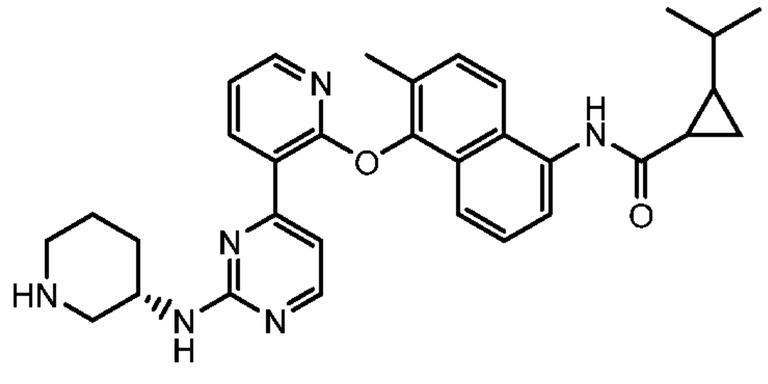
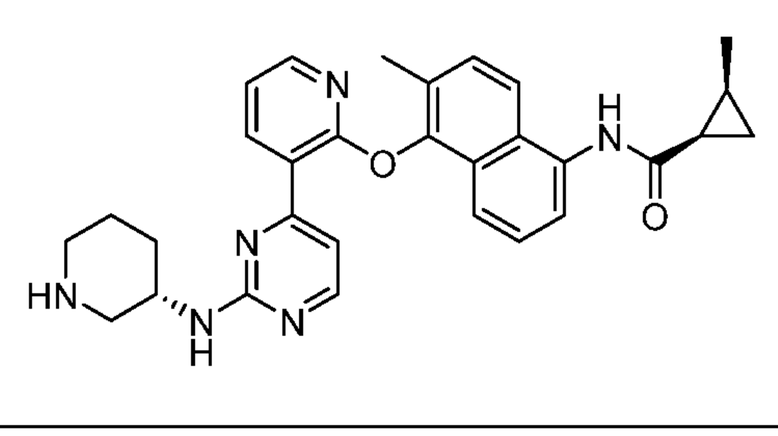
191		2-Cyclopropyl-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]acetamide	0.234
192		2-Methyl-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]thiazol-4-amine	0.444
193		2-(3-Fluorophenyl)-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]acetamide	0.086
194		4-[2-[[5-(1,1-Dioxo-1,2-thiazolidin-2-yl)-2-methyl-1-naphthyl]oxy]-3-pyridyl]-N-[(3*S*)-3-piperidyl]pyrimidin-2-amine	0.313
195		*N*-[6-Methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]azetidine-1-sulfonamide	0.202
196		*N*-(6-Methyl-5-((3-(2-(((3*S*,6*S*)-6-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide	0.162
197		4-[2-[[5-(Butylamino)-2-methyl-1-naphthyl]oxy]-3-pyridyl]-*N*-[(3*S*)-3-piperidyl]pyrimidin-2-amine	0.228

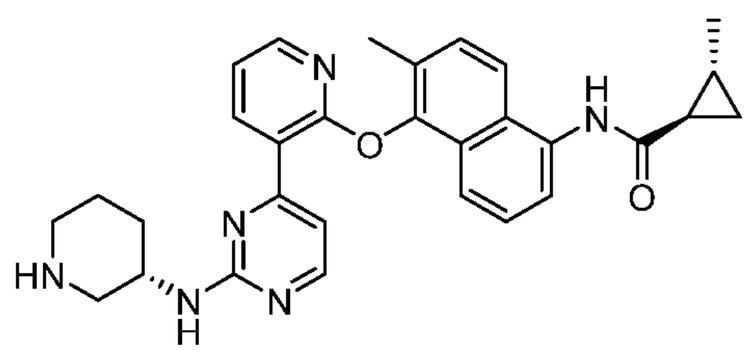
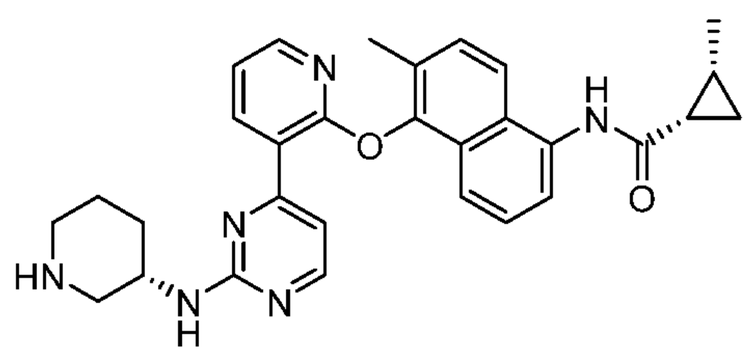
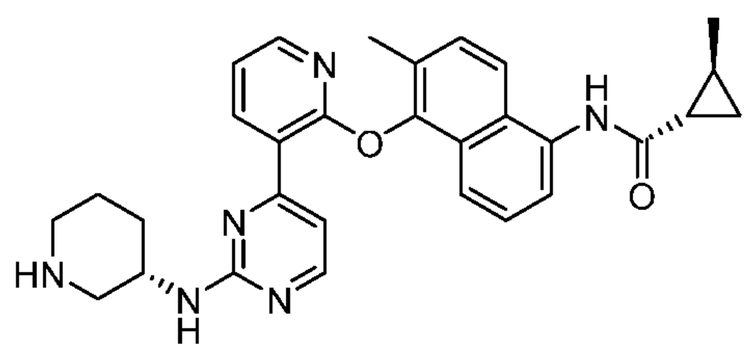
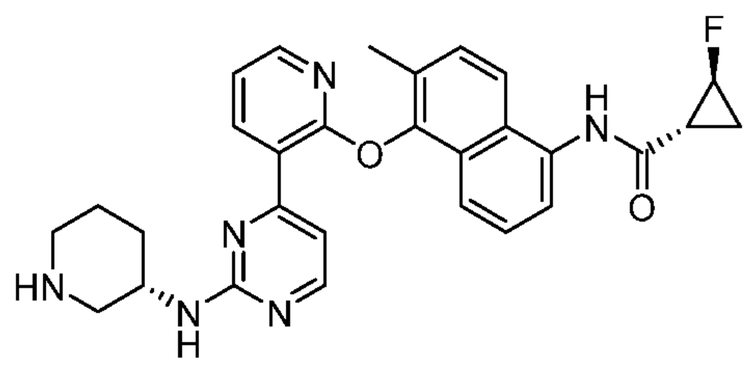
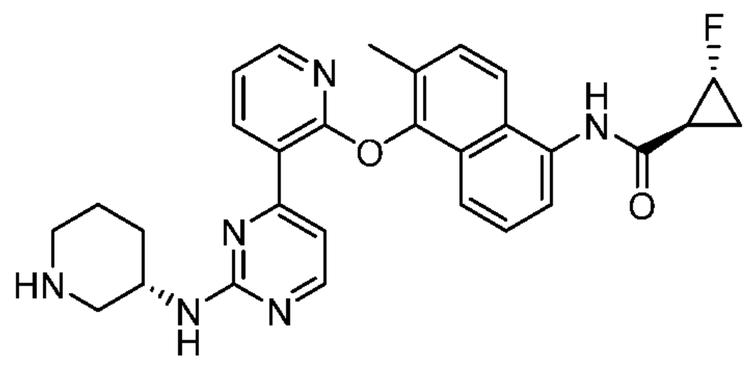
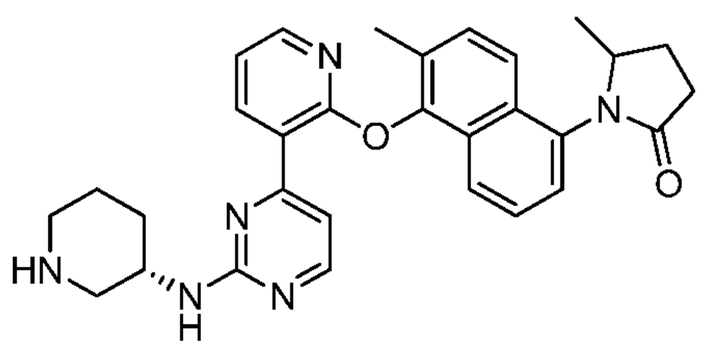
198		3,3-Dimethyl-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]butanamide	0.161
199		2-(4-Fluorophenyl)-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]acetamide	0.155
200		3-Methyl-1-((6-methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)butan-2-ol	0.077
201		(*R*)-4-((6-Methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)butan-2-ol	0.133
202		(*S*)-4-((6-Methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)butan-2-ol	0.123
203		(*S*)-2-Methyl-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)butanamide	0.161
204		(*R*)-2-methyl-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)butanamide	0.449

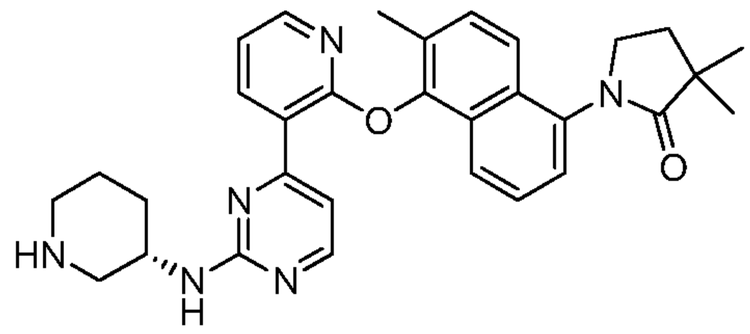
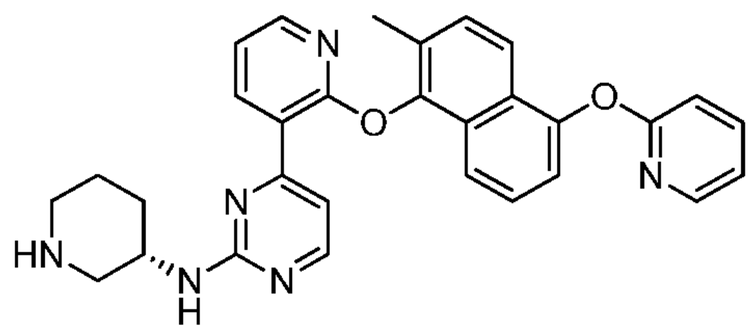
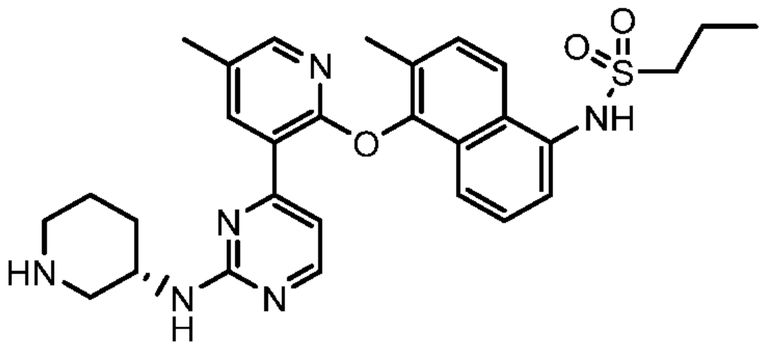
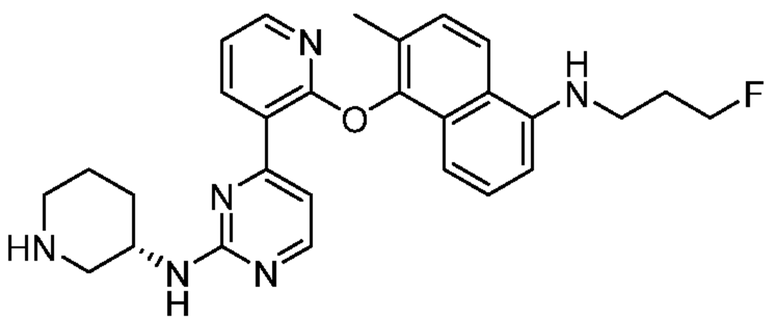
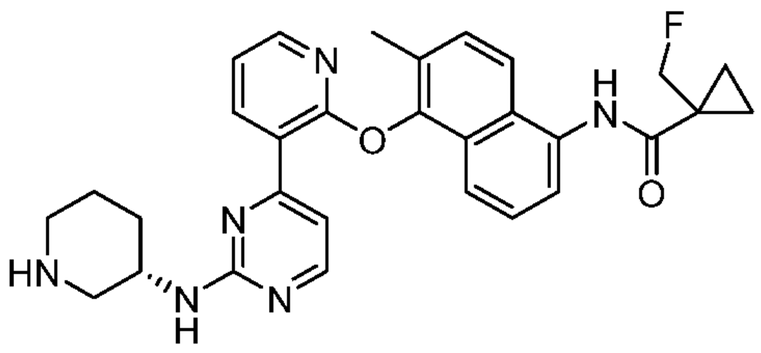
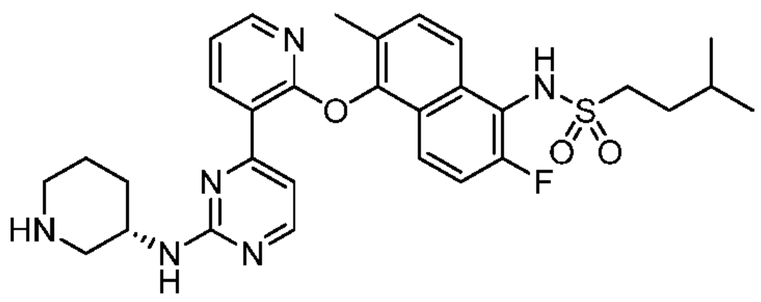
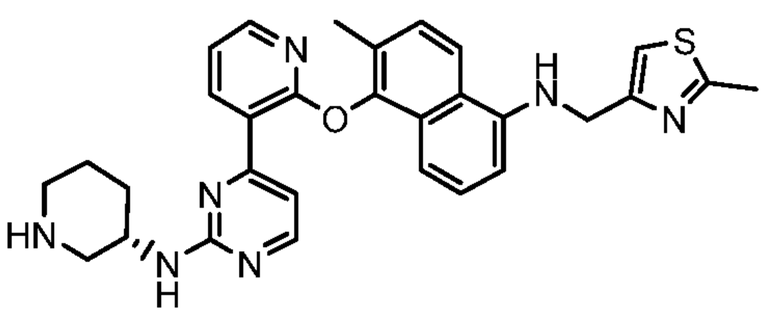
205		1-(4-Chlorophenyl)-*N*-(5-((3-(2-(((3*S*,5*R*)-5-methoxypiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)methanesulfonamide	0.13
206		*N*-(5-((3-(2-(((3*R*,4*R*)-4-Fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)propane-1-sulfonamide	0.487
207		4-[2-[[2-Methyl-5-(4-methylpyrazol-1-yl)-1-naphthyl]oxy]-3-pyridyl]-*N*-[(3*S*)-3-piperidyl]pyrimidin-2-amine	0.251
208		*N*-(2-Fluoro-5-((3-(2-(((3*S*,5*S*)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)-2-methylpropane-1-sulfonamide	0.0182
209		(*S*)-1-(4-Chlorophenyl)-*N*-(2-fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide	0.00804
210		2-Methyl-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]thiazole-5-sulfonamide	0.459
211		4-[2-[[2-Methyl-5-(thiazol-4-ylmethylamino)-1-naphthyl]oxy]-3-pyridyl]-*N*-[(3*S*)-3-piperidyl]pyrimidin-2-amine	0.07

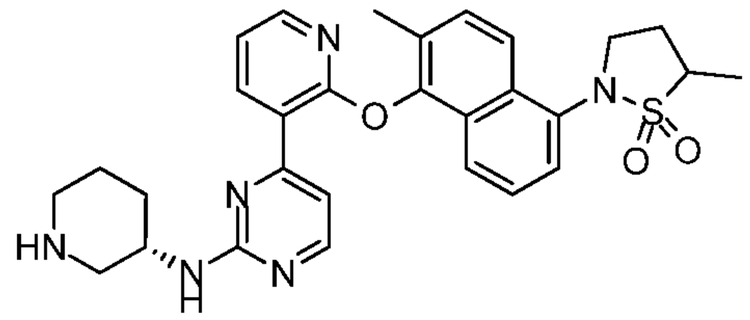
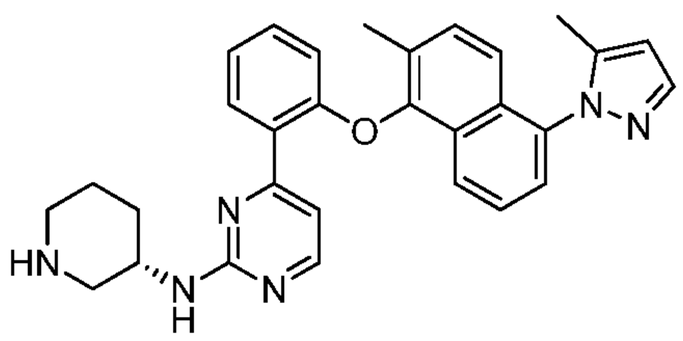
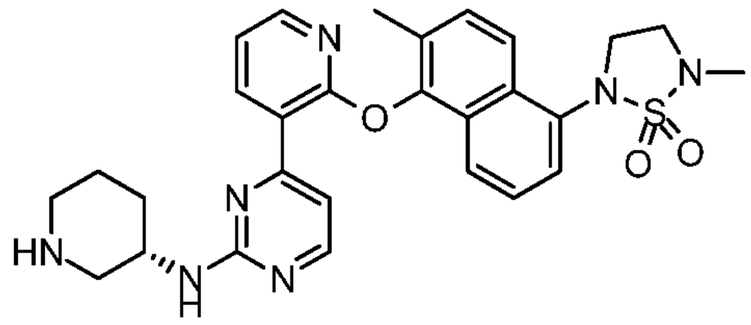
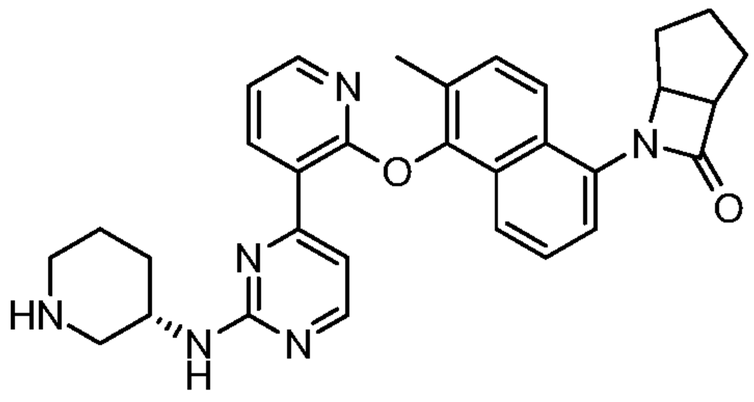
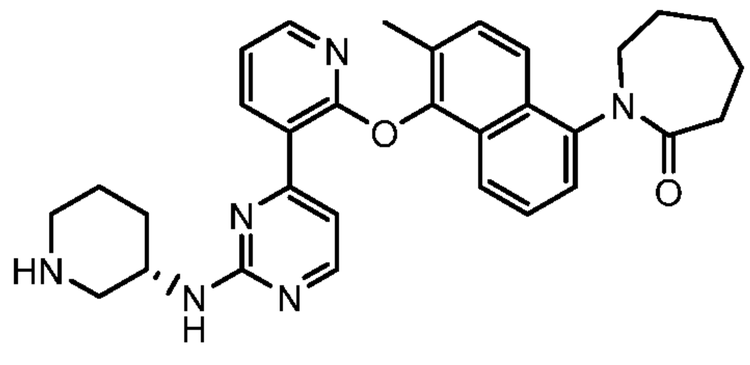
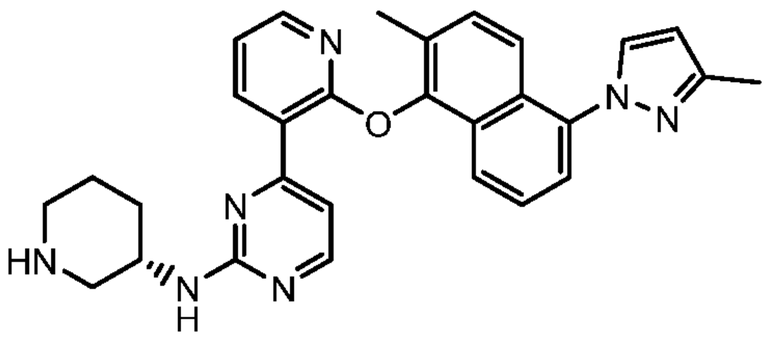
212		(1*S*,2*S*)-2-Fluoro-*N*-[6-methyl-5-[[3-[2-[[(3S)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]cyclopropanecarboxamide	0.122
213		(*S*)-1-(2,6-Difluorophenyl)-*N*-(2-fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide	0.00457
214		(*S*)-*N*-(6-Methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-phenylethanesulfonamide	0.076
215		*(R)*-*N*-(6-Methyl-5-((3-(2-((S)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-phenylethanesulfonamide	0.211
216		1-[6-Methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]pyrrolidin-2-one	0.26
217		(*S*)-*N*-(6-Methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)spiro[2.2]pentane-1-carboxamide	0.055
218		(*R*)-*N*-(6-Methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)spiro[2.2]pentane-1-carboxamide	0.174

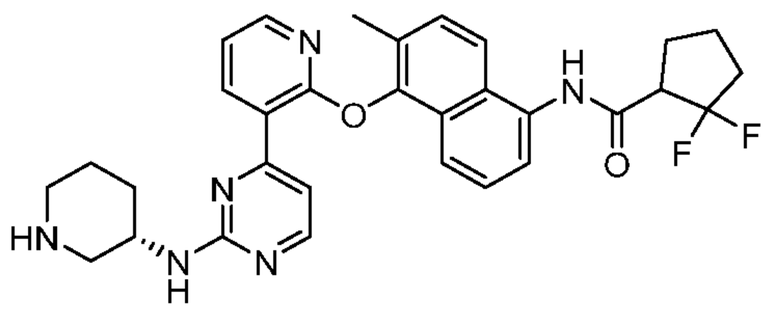
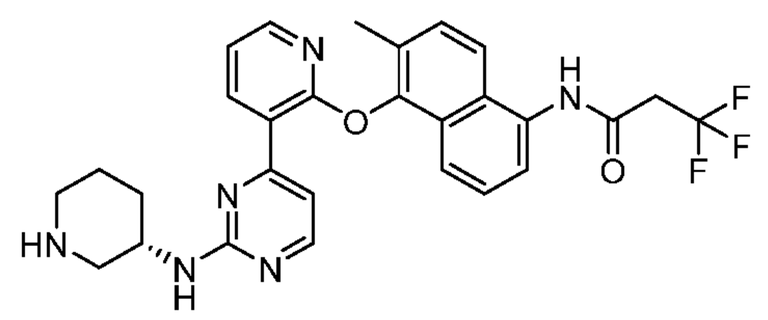
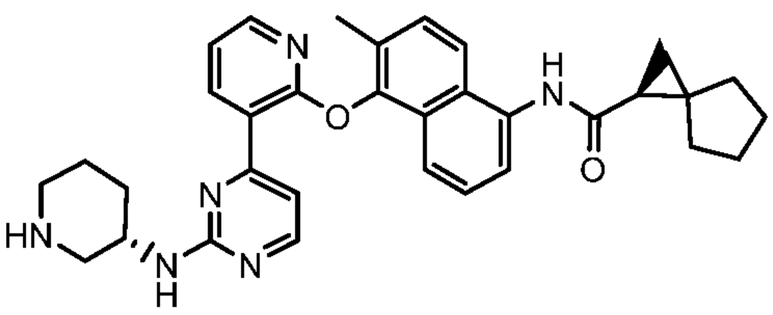
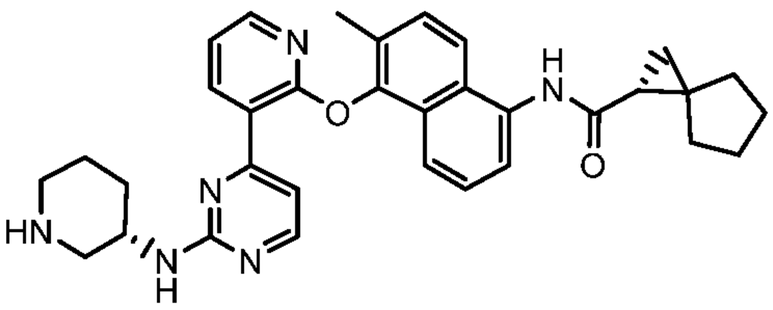
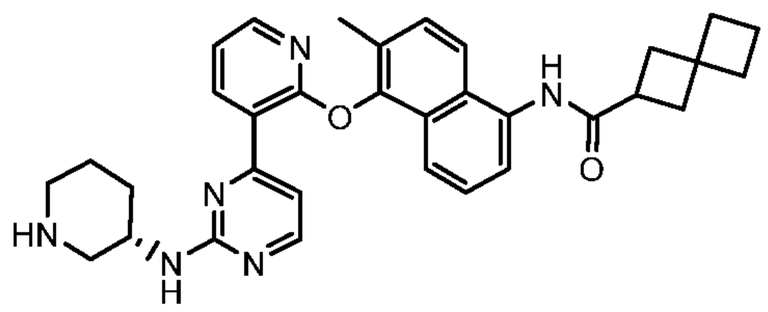
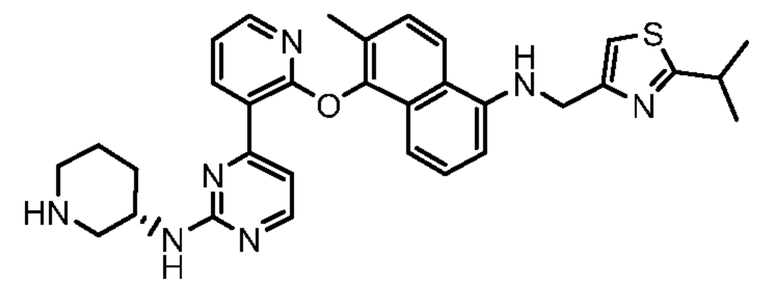
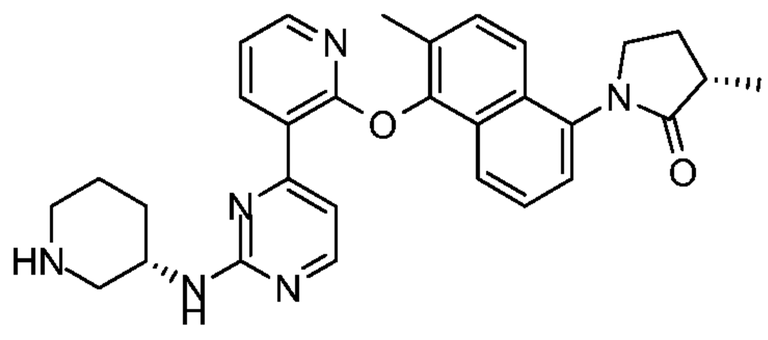
219		(*S*)-3,3-Difluoro-*N*-(6-methyl-5-(3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yloxy)naphthalen-1-yl)cyclobutanecarboxamide	0.119
220		(*S*)-*N*-(6-Methyl-5-(3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yloxy)naphthalen-1-yl)-1-(trifluoromethyl)cyclopropane carboxamide	0.309
221		*N*-[2-Fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]propane-1-sulfonamide	0.037
222		(1*R*,2*R*)-2-Fluoro-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]cyclopropanecarboxamide	0.093
223		4-[2-[[5-(Cyclopropylmethylamino)-2-methyl-1-naphthyl]oxy]-3-pyridyl]-*N*-[(3*S*)-3-piperidyl]pyrimidin-2-amine	0.212
224		4-[2-[[5-(2-Cyclopropylethylamino)-2-methyl-1-naphthyl]oxy]-3-pyridyl]-*N*-[(3*S*)-3-piperidyl]pyrimidin-2-amine	0.177
225		*N*-[5-[[3-[2-[[(3*S*,5*R*)-5-Fluoro-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-6-methyl-1-naphthyl]-1-(2-pyridyl)methanesulfonamide	0.467

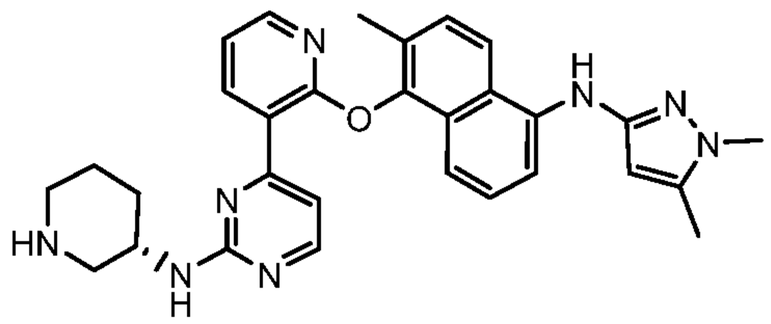
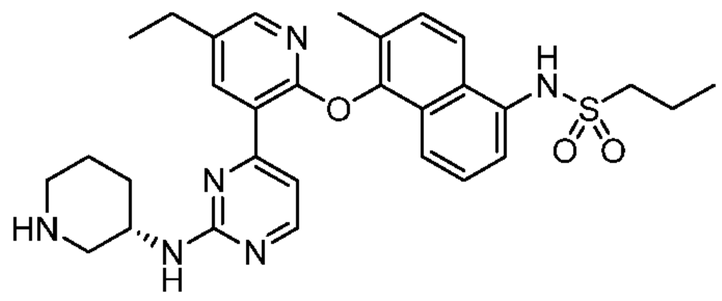
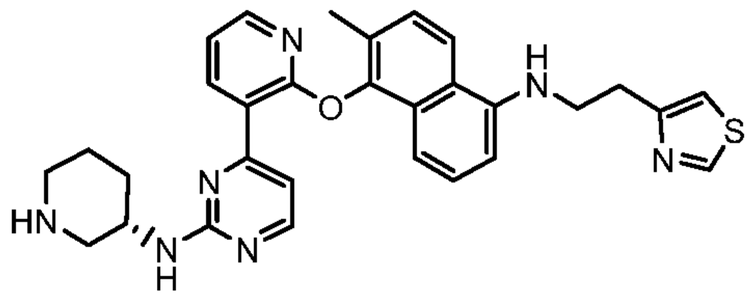
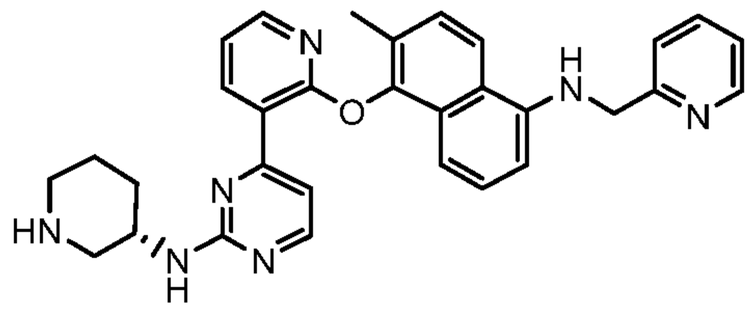
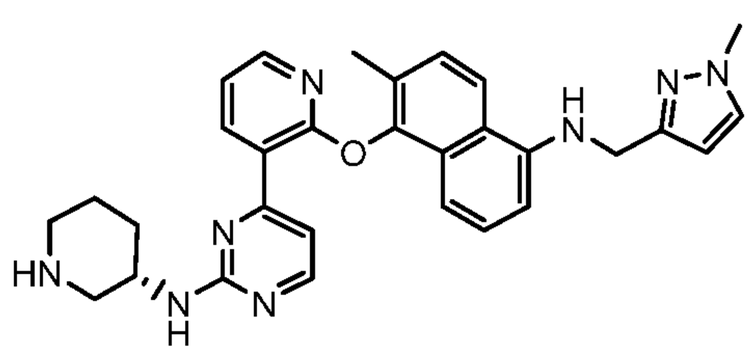
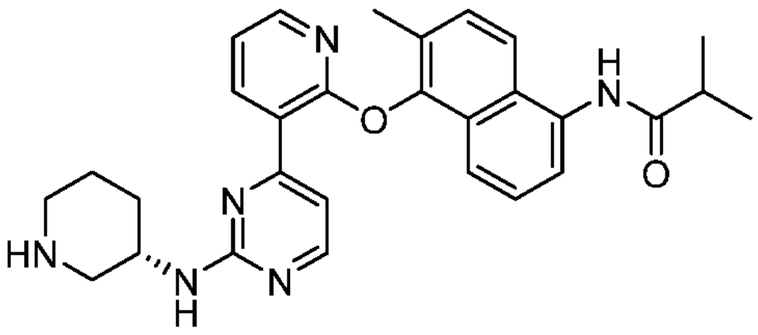
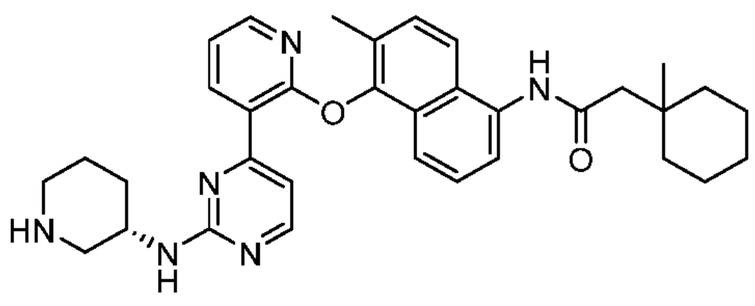
226		2-Fluoro-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-phenylcyclopropane-1-carboxamide	0.223
227		*N*-(6-Methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-(trifluoromethyl)cyclopropane-1-carboxamide	0.493
228		*N*-(6-Methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-(trifluoromethyl)cyclopropane-1-carboxamide	0.088
229		2-Isopropyl-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide	0.454
230		2-Isopropyl-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide	0.08
231		(1*R*,2*S*)-2-Methyl-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide	0.053 0.0333

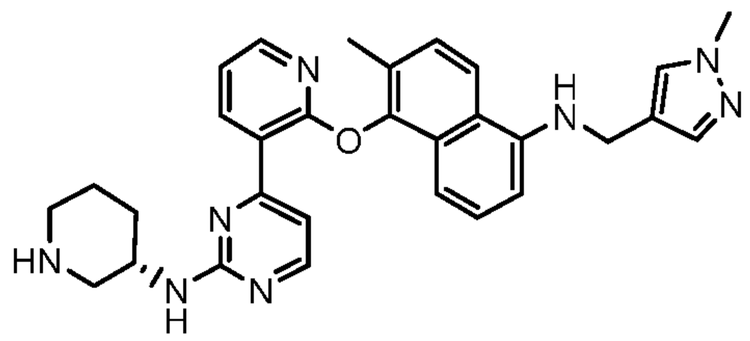
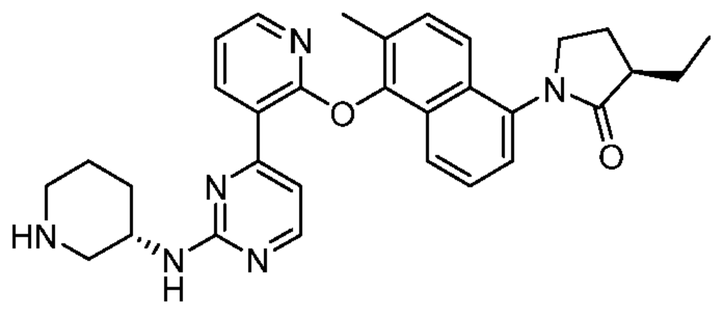
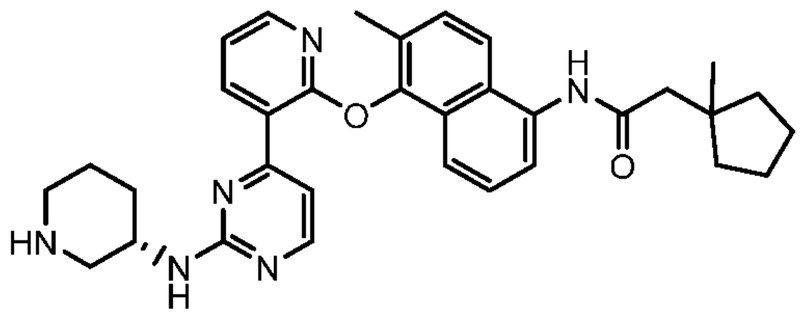
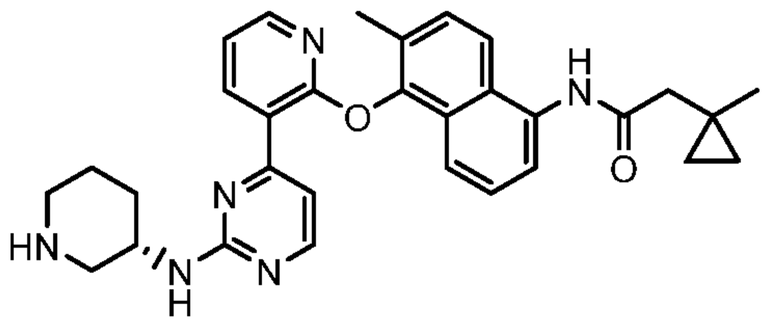
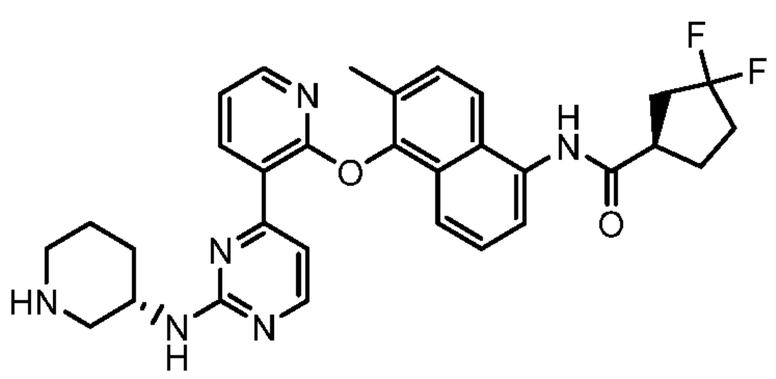
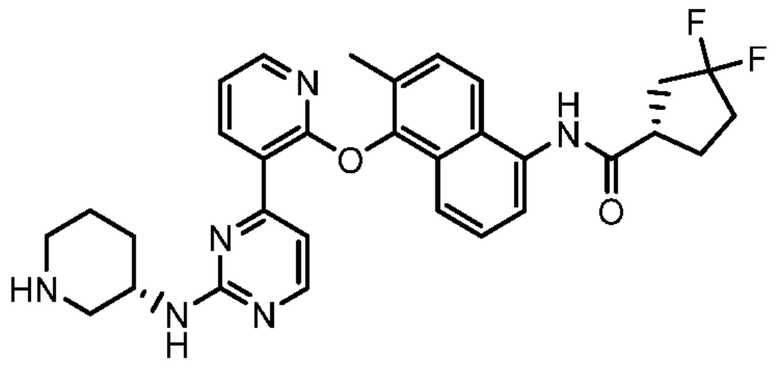
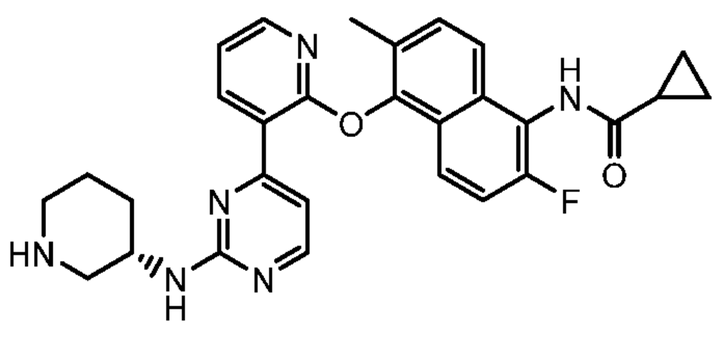
232		(1*R*,2*R*)-2-Methyl-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide	0.136
233		(1*S*,2*R*)-2-Methyl-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide	0.332 0.11
234		(1*S*,2*S*)-2-Methyl-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide	0.111
235		(1*R*,2*S*)-2-Fluoro-*N*-(6-methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide	0.145
236		(1*S*,2*R*)-2-Fluoro-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide	0.174
237		5-Methyl-1-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidin-2-one	0.472

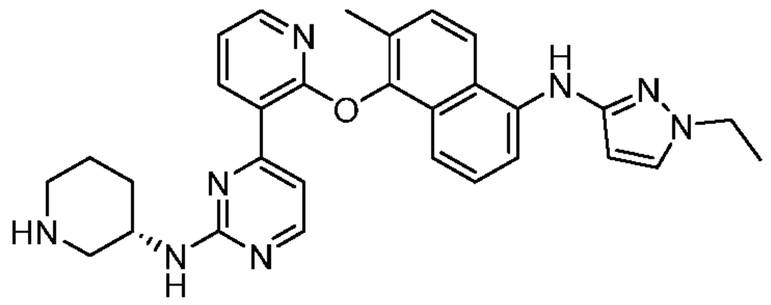
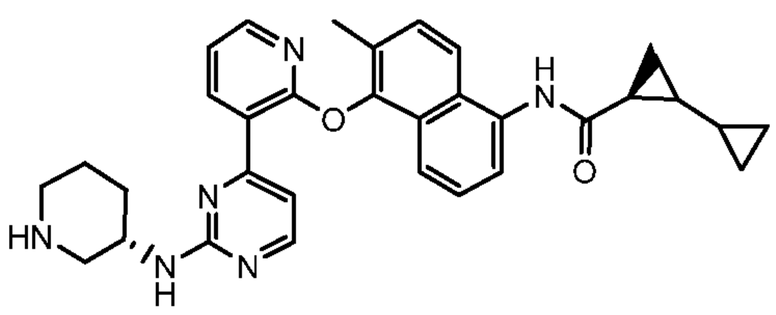
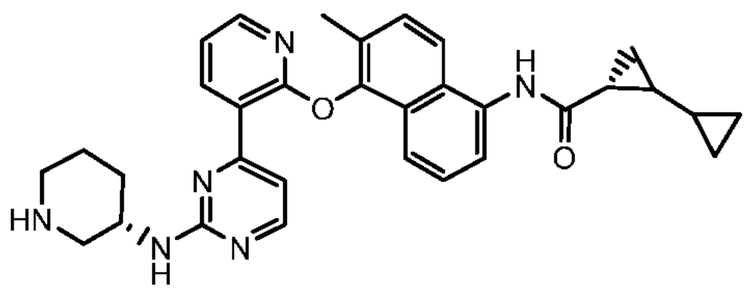
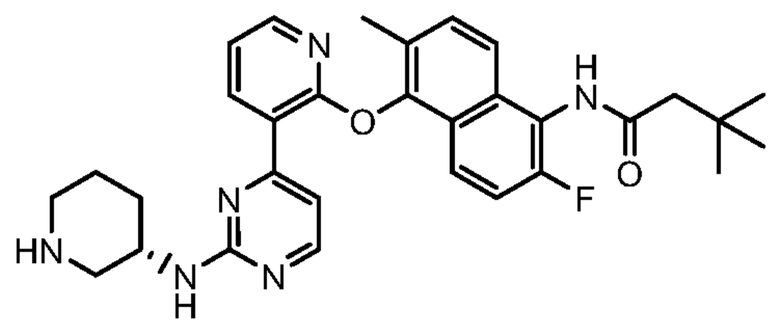
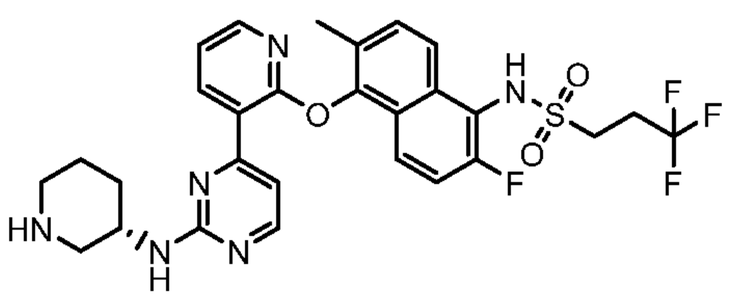
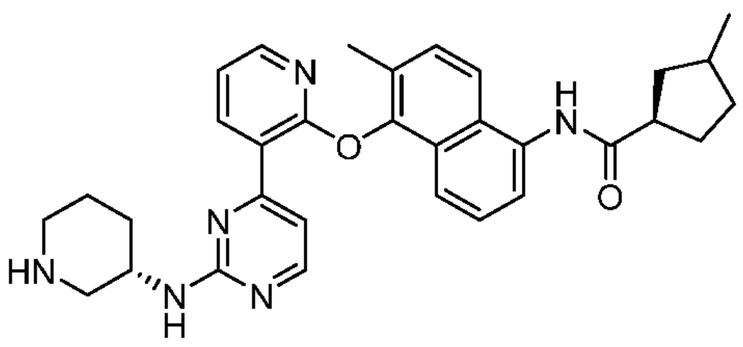
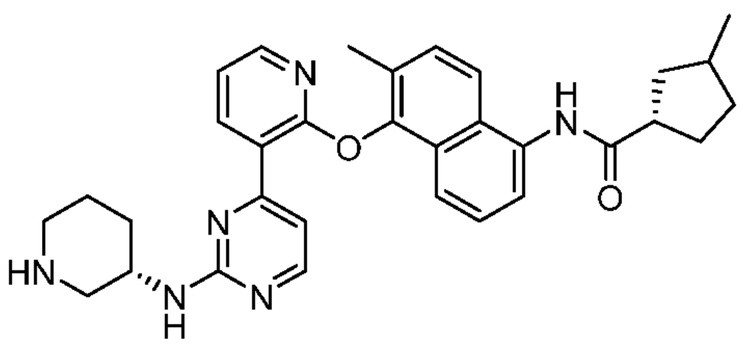
238		3,3-Dimethyl-1-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]pyrrolidin-2-one	0.275
239		4-[2-[[2-Methyl-5-(2-pyridyloxy)-1-naphthyl]oxy]-3-pyridyl]-*N*-[(3*S*)-3-piperidyl]pyrimidin-2-amine	0.245
240		*N*-[6-Methyl-5-[[5-methyl-3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]propane-1-sulfonamide	0.167
241		4-[2-[[5-(3-Fluoropropylamino)-2-methyl-1-naphthyl]oxy]-3-pyridyl]-*N*-[(3*S*)-3-piperidyl]pyrimidin-2-amine	0.141
242		1-(Fluoromethyl)-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]cyclopropanecarboxamide	0.361
243		(*S*)-*N*-(2-Fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-3-methylbutane-1-sulfonamide	0.068
244		4-[2-[[2-Methyl-5-[(2-methylthiazol-4-yl)methylamino]-1-naphthyl]oxy]-3-pyridyl]-*N*-[(3*S*)-3-piperidyl]pyrimidin-2-amine	0.012

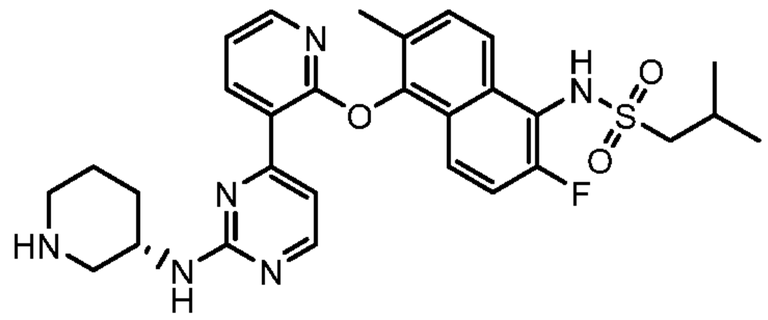
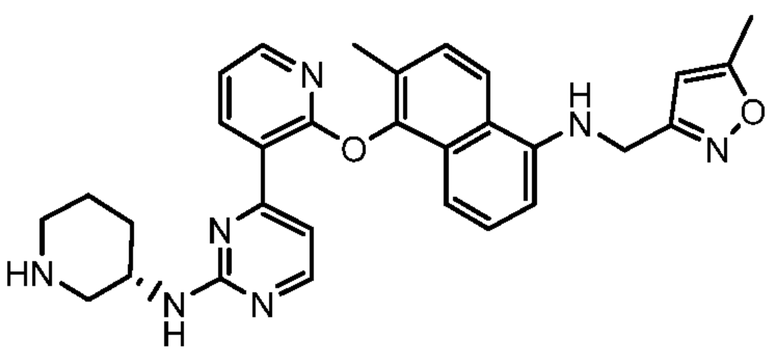
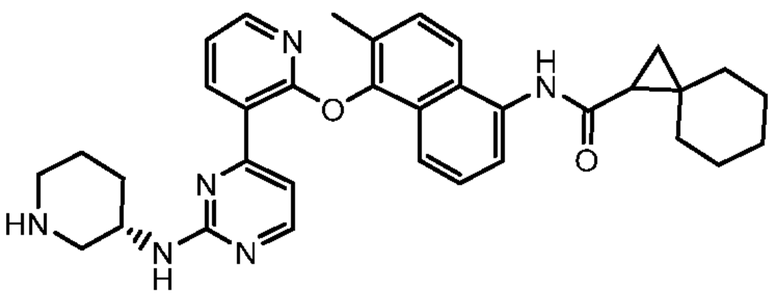
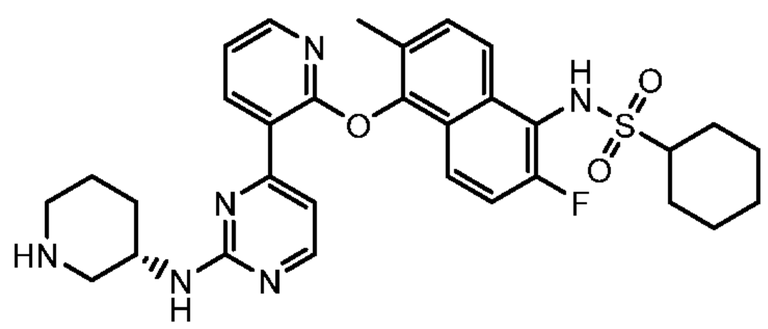
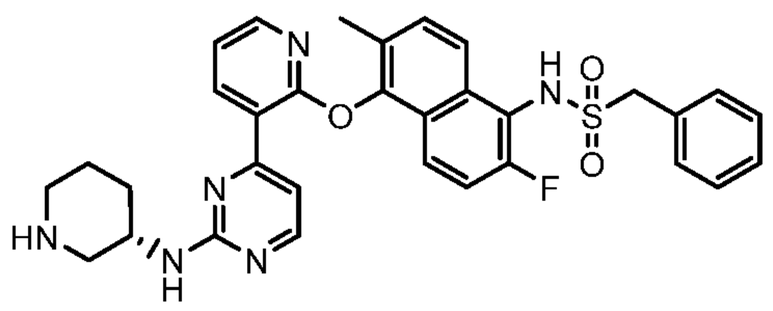
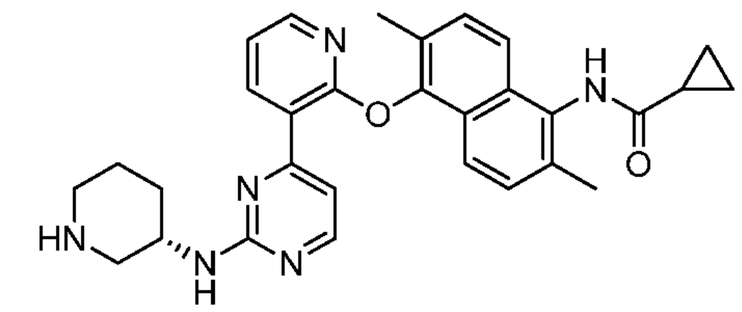
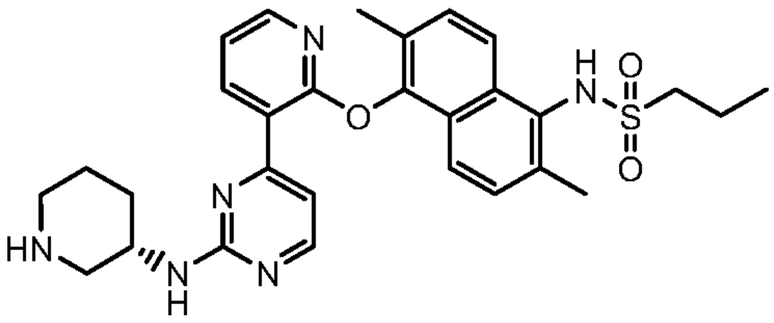
245		5-Methyl-2-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)isothiazolidine 1,1-dioxide	0.294
246		4-[2-[[2-Methyl-5-(5-methylpyrazol-1-yl)-1-naphthyl]oxy]-3-pyridyl]-*N*-[(3*S*)-3-piperidyl]pyrimidin-2-amine	0.235
247		4-[2-[[2-Methyl-5-(5-methyl-1,1-dioxo-1,2,5-thiadiazolidin-2-yl)-1-naphthyl]oxy]-3-pyridyl]-*N*-[(3*S*)-3-piperidyl]pyrimidin-2-amine	0.36
248		6-(6-Methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-6-azabicyclo[3.2.0]heptan-7-one	0.457
249		1-[6-Methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]azepan-2-one	0.309
250		4-[2-[[2-Methyl-5-(3-methylpyrazol-1-yl)-1-naphthyl]oxy]-3-pyridyl]-*N*-[(3*S*)-3-piperidyl]pyrimidin-2-amine	0.258

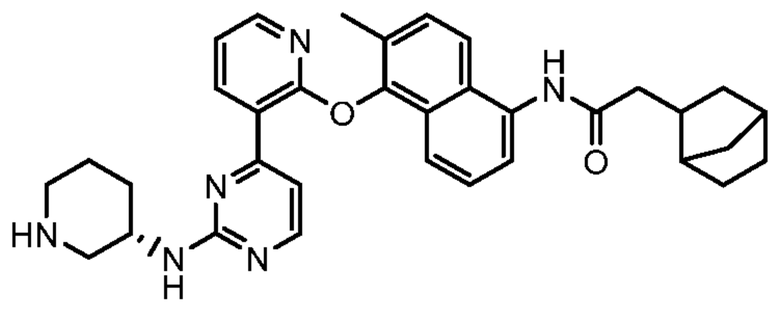
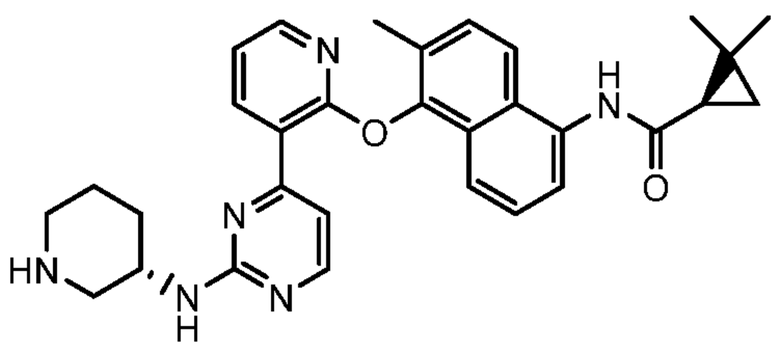
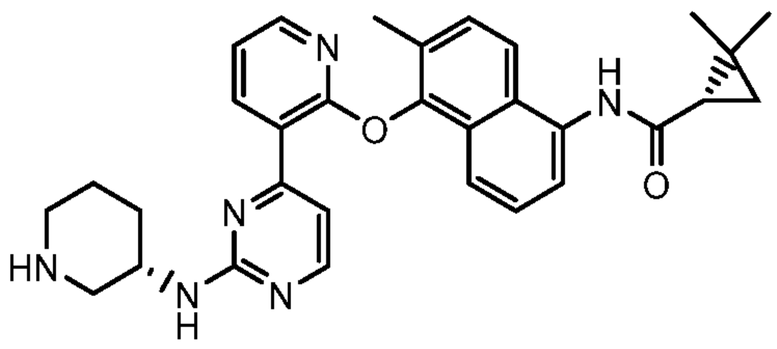
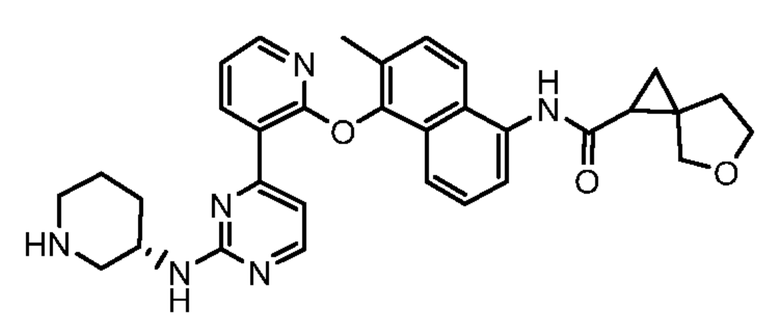
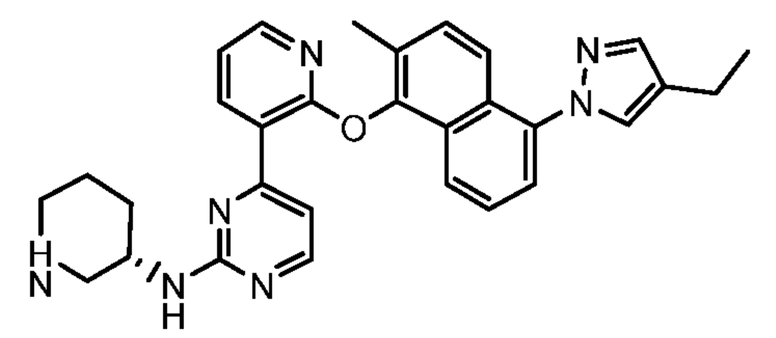
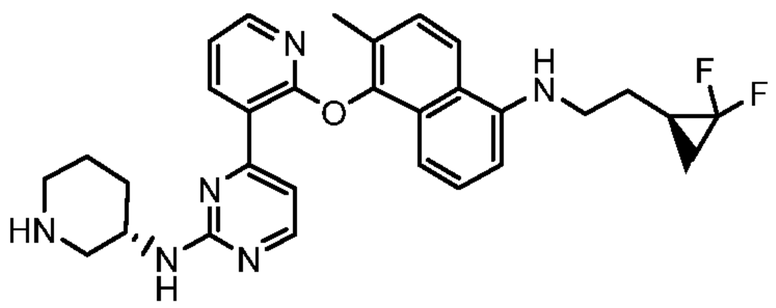
251		2,2-Difluoro-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentane-1-carboxamide	0.145
252		3,3,3-Trifluoro-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]propanamide	0.134
253		(*S*)-*N*-(6-Methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)spiro[2.4]heptane-1-carboxamide	0.352
254		(*R*)-*N*-(6-Methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)spiro[2.4]heptane-1-carboxamide	0.069
255		*N*-[6-Methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]spiro[3.3]heptane-2-carboxamide	0.182
256		4-[2-[[5-[(2-Isopropylthiazol-4-yl)methylamino]-2-methyl-1-naphthyl]oxy]-3-pyridyl]-*N*-[(3*S*)-3-piperidyl]pyrimidin-2-amine	0.21
257		(*S*)-3-Methyl-1-(6-methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidin-2-one	0.264

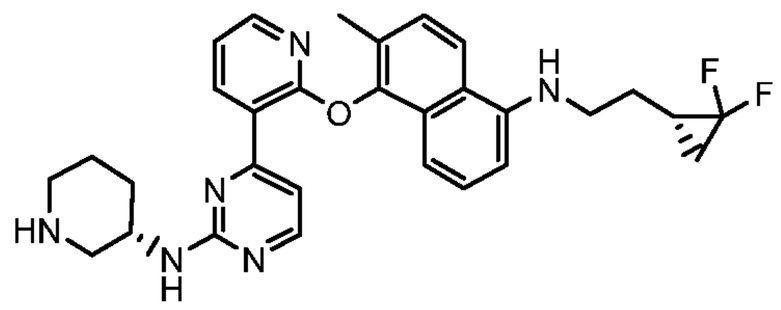
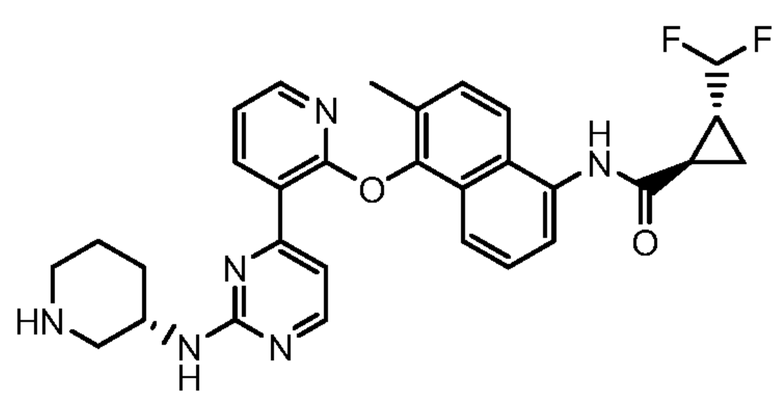
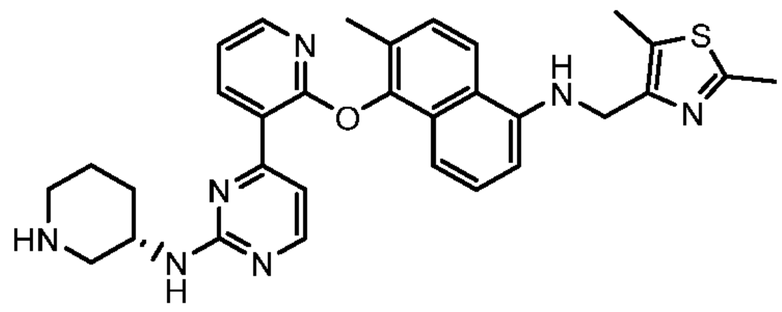
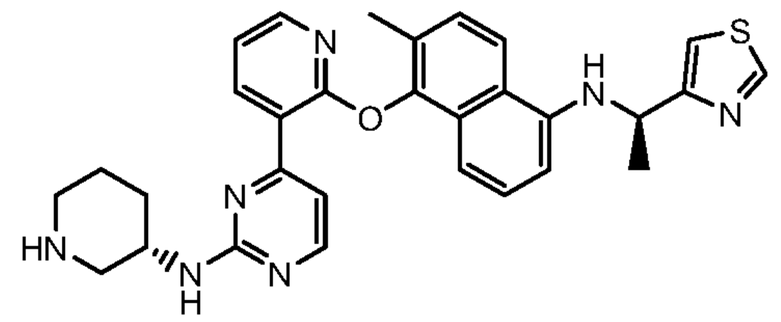
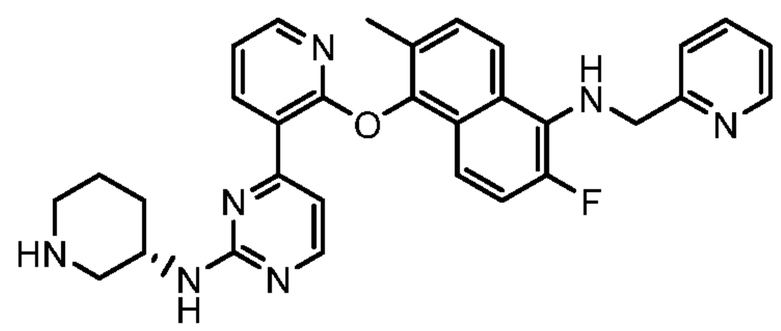
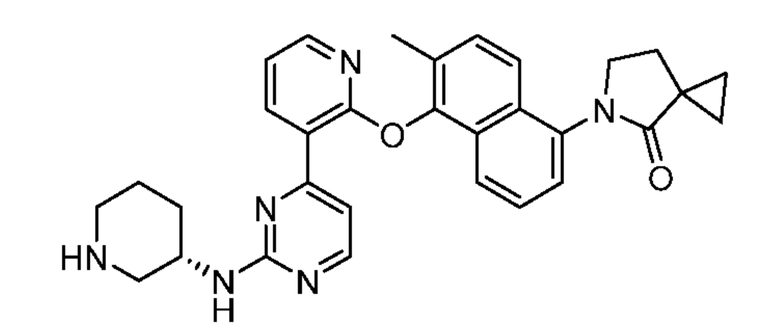
258		4-[2-[[5-[(1,5-Dimethylpyrazol-3-yl)amino]-2-methyl-1-naphthyl]oxy]-3-pyridyl]-*N*-[(3*S*)-3-piperidyl]pyrimidin-2-amine	0.419
259		(*S*)-*N*-(5-((5-Ethyl-3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)propane-1-sulfonamide	0.361
260		4-[2-[[2-Methyl-5-(2-thiazol-4-ylethylamino)-1-naphthyl]oxy]-3-pyridyl]-*N*-[(3*S*)-3-piperidyl]pyrimidin-2-amine	0.103
261		4-[2-[[2-Methyl-5-(2-pyridylmethylamino)-1-naphthyl]oxy]-3-pyridyl]-*N*-[(3*S*)-3-piperidyl]pyrimidin-2-amine	0.22
262		4-[2-[[2-Methyl-5-[(1-methylpyrazol-3-yl)methylamino]-1-naphthyl]oxy]-3-pyridyl]-*N*-[(3*S*)-3-piperidyl]pyrimidin-2-amine	0.171
263		(*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)isobutyramide	0.362
264		(*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-(1-methylcyclohexyl)acetamide	0.350

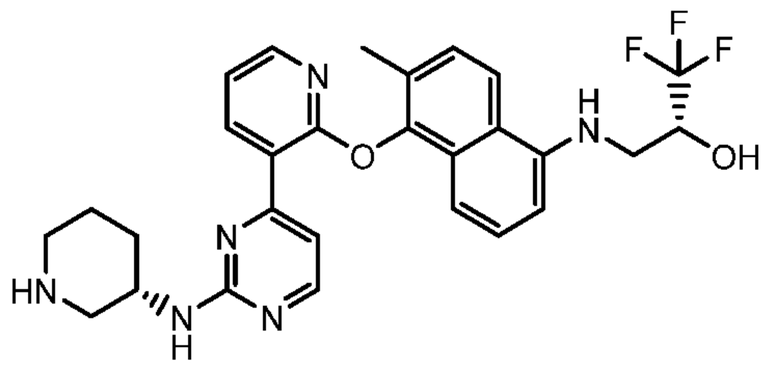
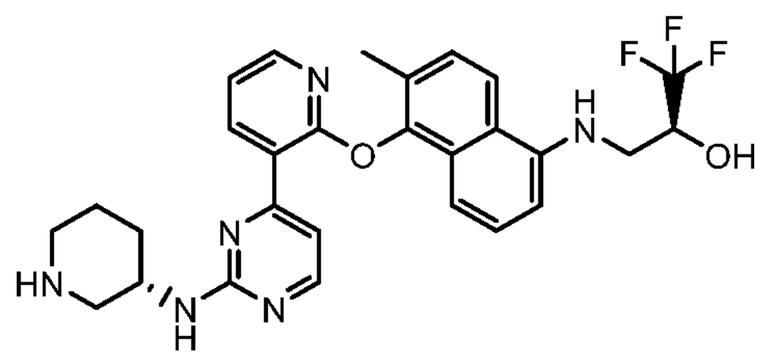
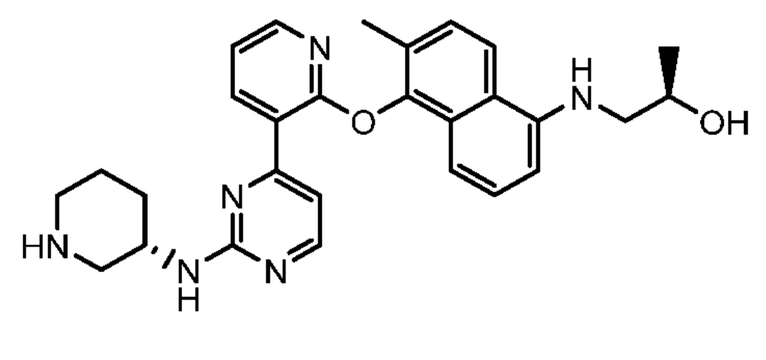
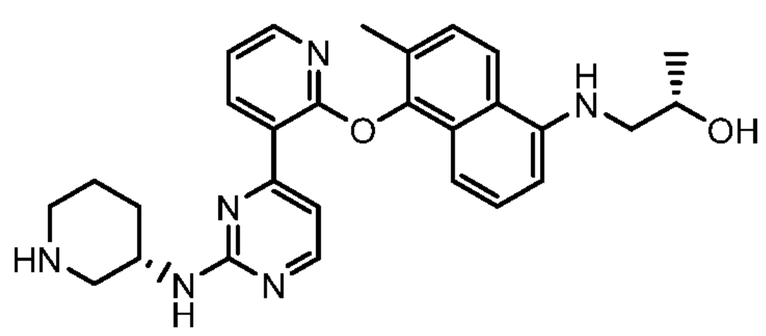
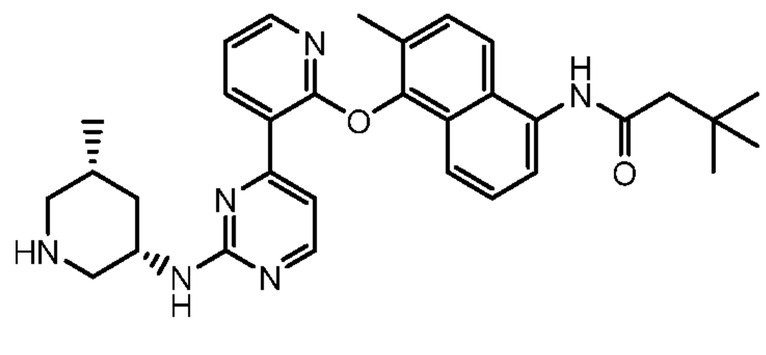
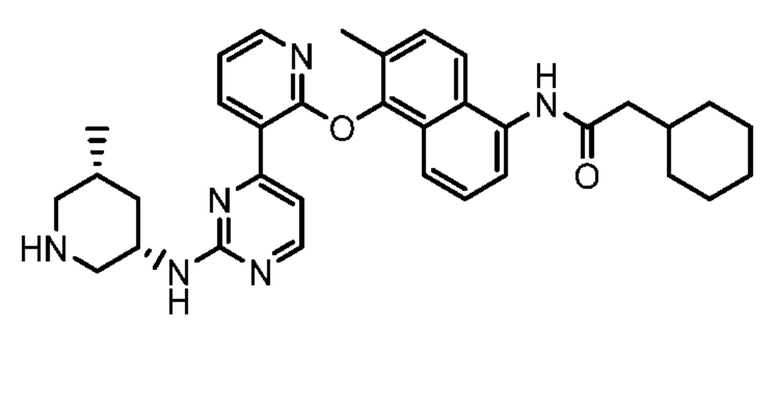
265		4-[2-[[2-Methyl-5-[(1-methylpyrazol-4-yl)methylamino]-1-naphthyl]oxy]-3-pyridyl]-*N*-[(3*S*)-3-piperidyl]pyrimidin-2-amine	0.393
266		(*R*)-3-Ethyl-1-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidin-2-one	0.121
267		2-(1-Methylcyclopentyl)-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]acetamide	0.162
268		2-(1-Methylcyclopropyl)-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]acetamide	0.257
269		(*R*)-3,3-Difluoro-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentane-1-carboxamide	0.336
270		(*S*)-3,3-Difluoro-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentane-1-carboxamide	0.189
271		*N*-[2-Fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]cyclopropanecarboxamide	0.271

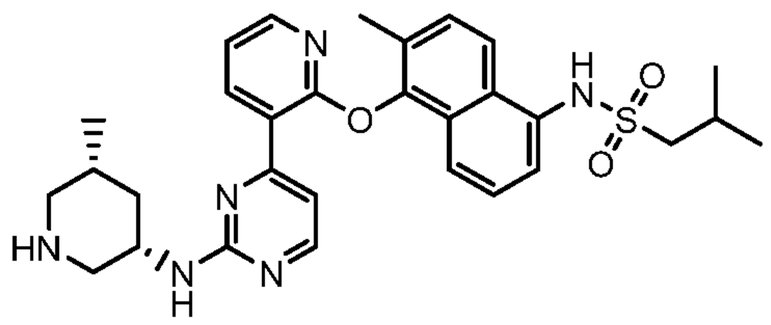
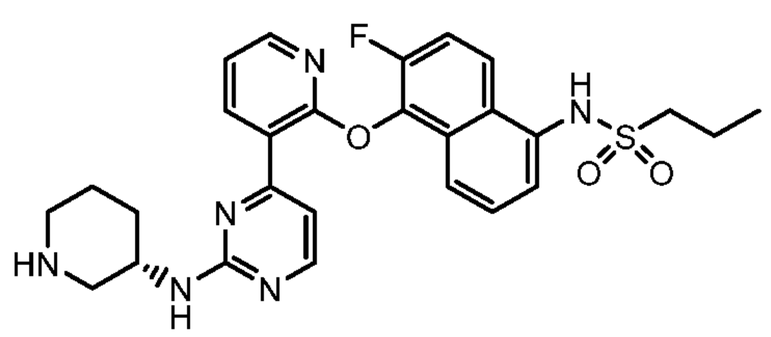
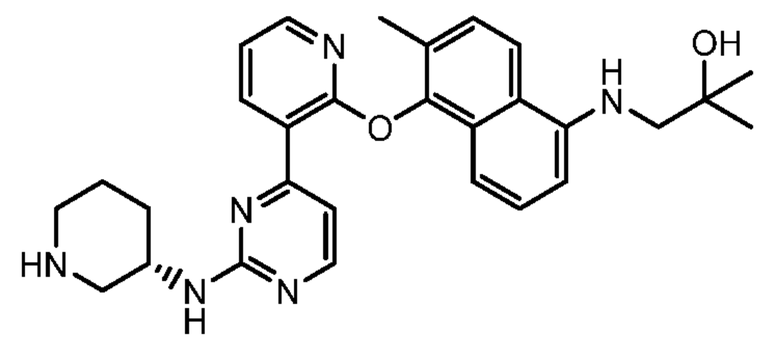
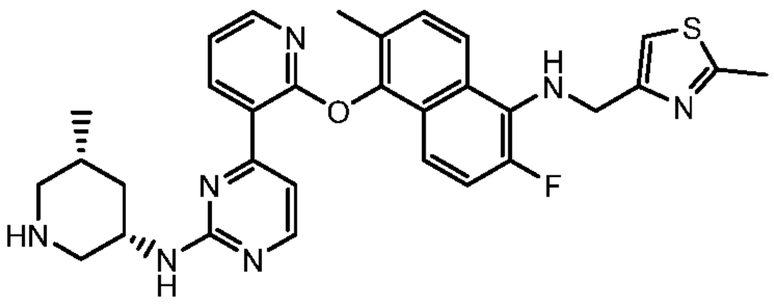
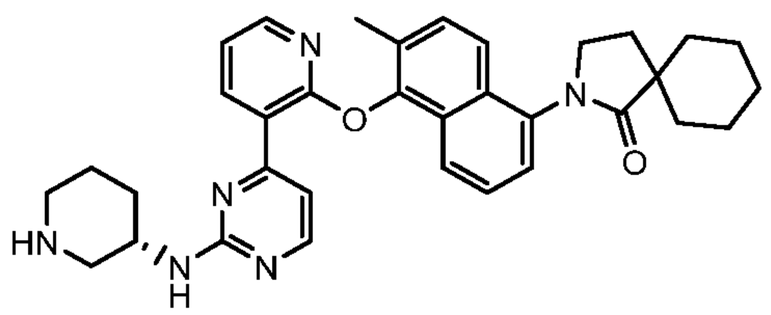
272		4-[2-[[5-[(1-Ethylpyrazol-3-yl)amino]-2-methyl-1-naphthyl]oxy]-3-pyridyl]-*N*-[(3*S*)-3-piperidyl]pyrimidin-2-amine	0.463
273		(2*S*)-*N*-(6-Methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-[1,1'-bi(cyclopropane)]-2-carboxamide	0.305
274		(2*R*)-*N*-(6-Methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-[1,1'-bi(cyclopropane)]-2-carboxamide	0.10
275		*N*-[2-Fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]-3,3-dimethyl-butanamide	0.075
276		3,3,3-Trifluoro-*N*-[2-fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]propane-1-sulfonamide	0.0441
277		(1*R*)-3-Methyl-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentane-1-carboxamide	0.171
278		(1*S*)-3-Methyl-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentane-1-carboxamide	0.313

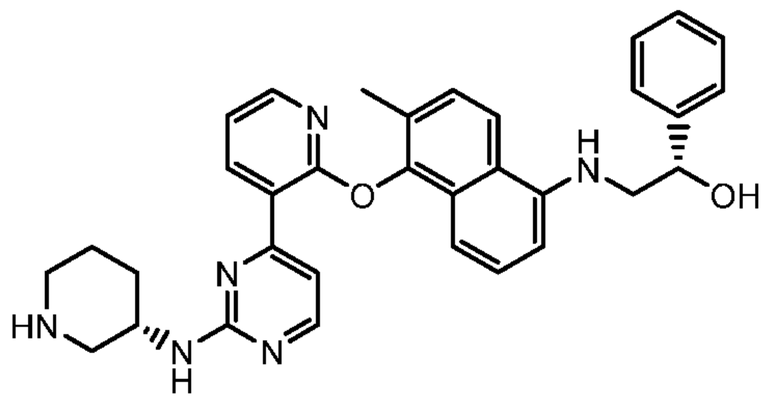
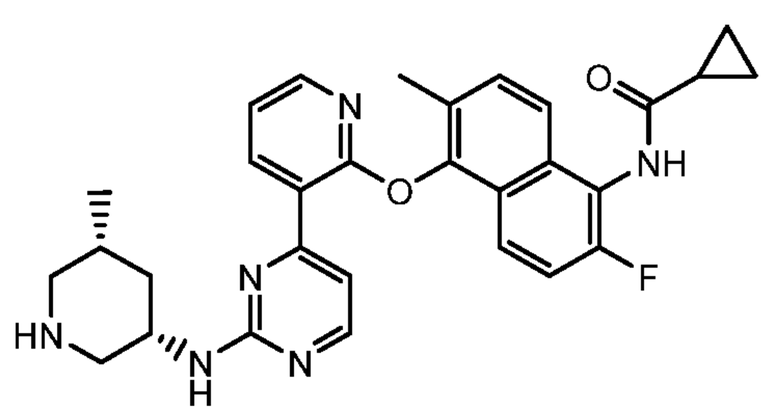
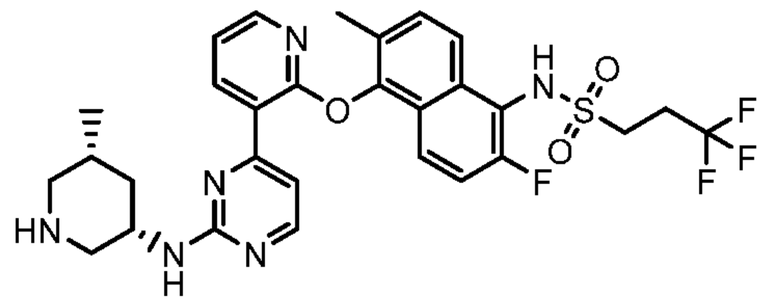
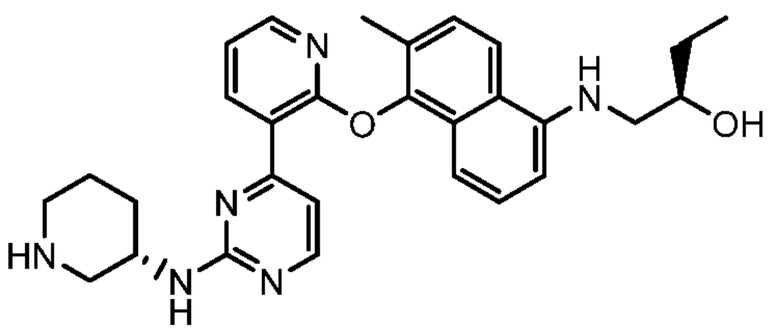
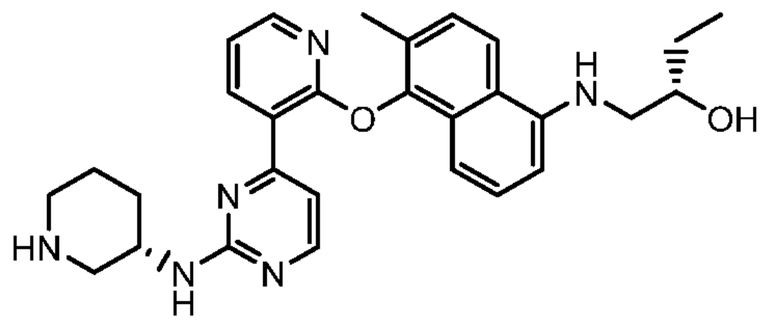
279		*N*-[2-Fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]-2-methyl-propane-1-sulfonamide	0.0247
280		4-[2-[[2-Methyl-5-[(5-methylisoxazol-3-yl)methylamino]-1-naphthyl]oxy]-3-pyridyl]-*N*-[(3*S*)-3-piperidyl]pyrimidin-2-amine	0.134
281		*N*-(6-Methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)spiro[2.5]octane-1-carboxamide	0.089
282		*N*-[2-Fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]cyclohexanesulfonamide	0.0248
283		*N*-[2-Fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]-1-phenyl-methanesulfonamide	0.00296
284		*N*-[2,6-Dimethyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]cyclopropanecarboxamide	0.0982
285		*N*-[2,6-Dimethyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]propane-1-sulfonamide	0.071

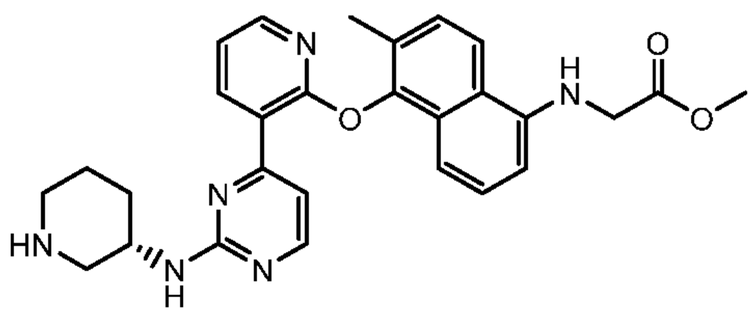
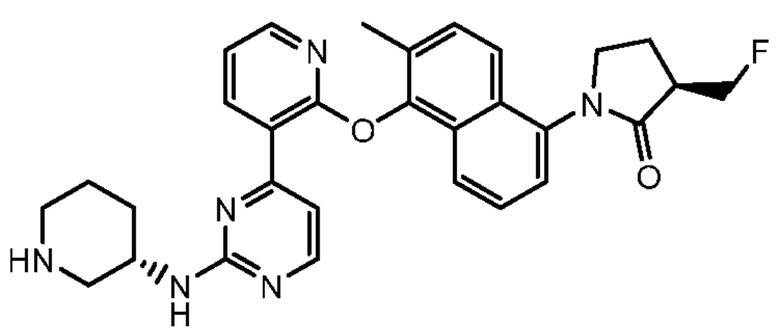
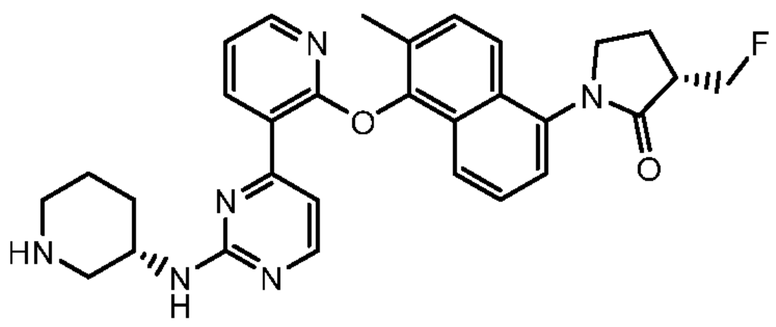
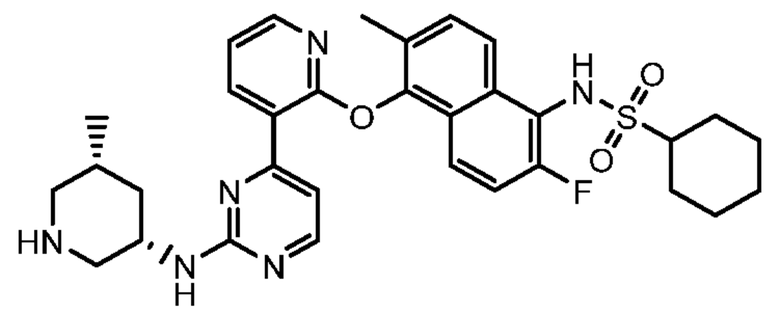
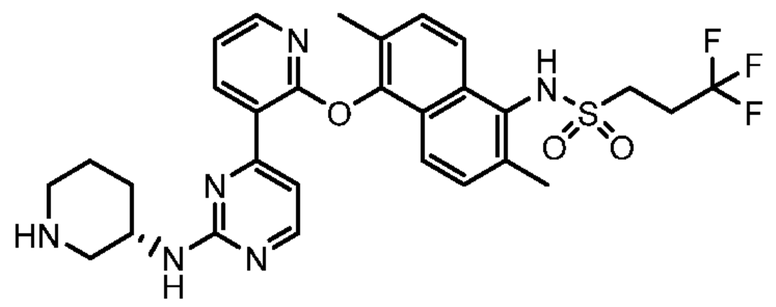
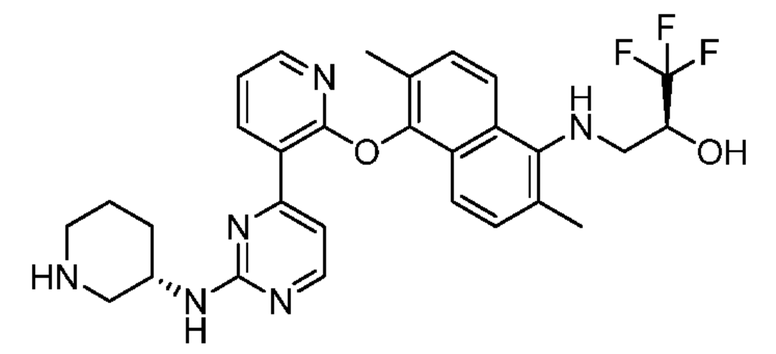
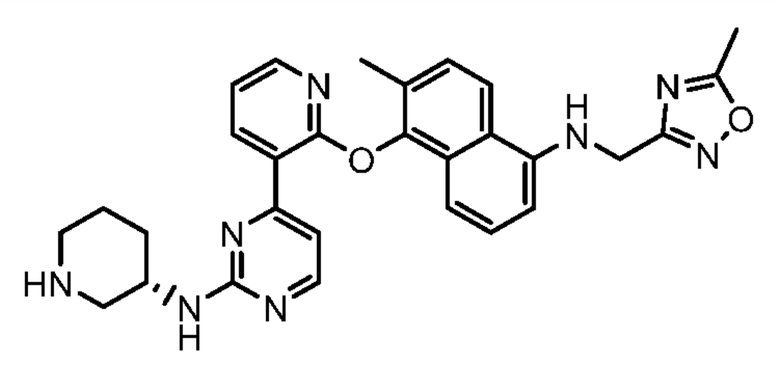
286		2-(Bicyclo[2.2.1]heptan-2-yl)-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)acetamide	0.174
287		(*R*)-2,2-Dimethyl-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide	0.0394
288		(*S*)-2,2-Dimethyl-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide	0.185
289		*N*-(6-Methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-5-oxaspiro[2.4]heptane-1-carboxamide	0.431
290		4-[2-[[5-(4-Ethylpyrazol-1-yl)-2-methyl-1-naphthyl]oxy]-3-pyridyl]-*N*-[(3*S*)-3-piperidyl]pyrimidin-2-amine	0.409
291		4-(2-((5-((2-((R)-2,2-difluorocyclopropyl)ethyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-N-((S)-piperidin-3-yl)pyrimidin-2-amine	0.361

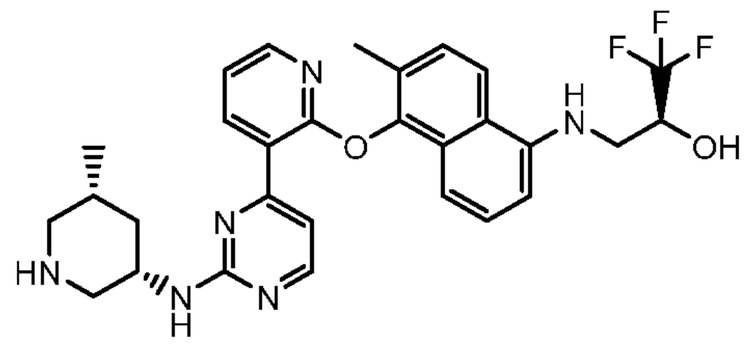
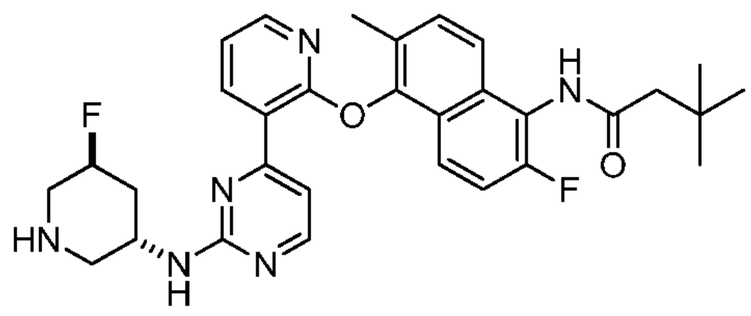
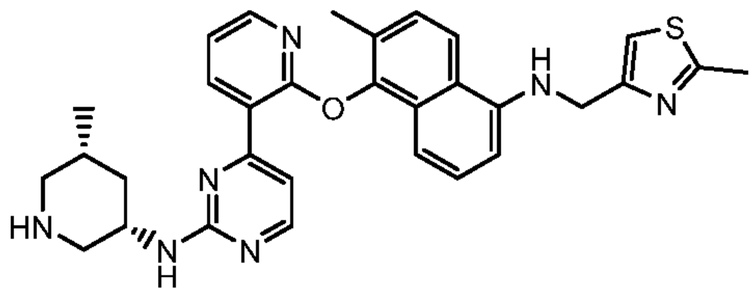
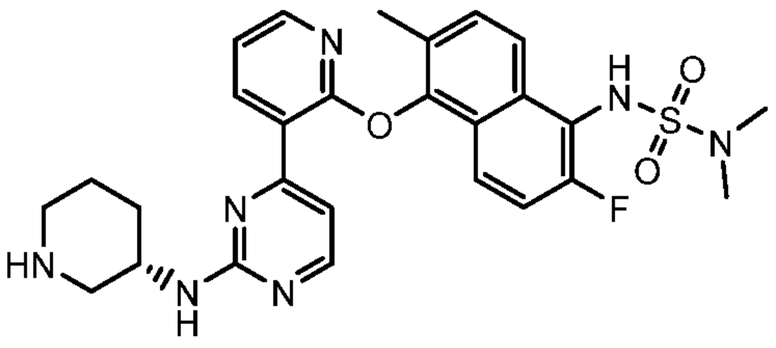
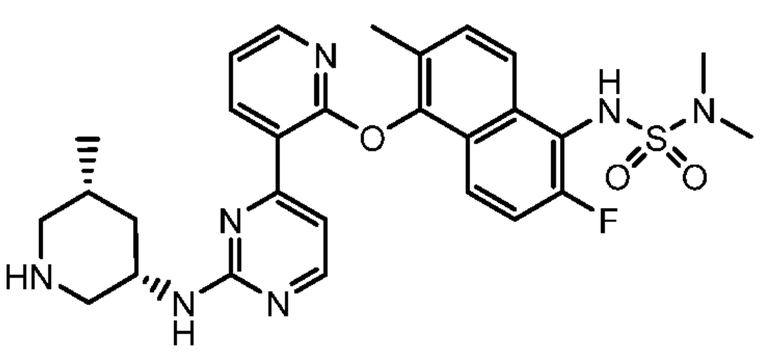
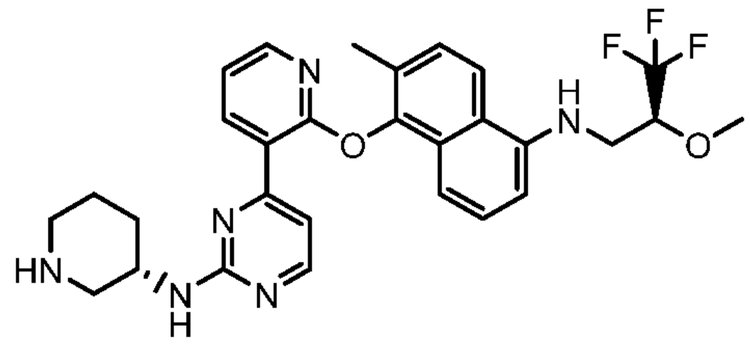
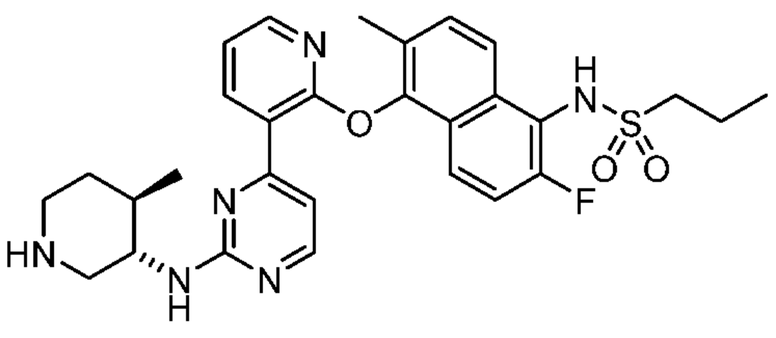
292		4-(2-((5-((2-((*S*)-2,2-Difluorocyclopropyl)ethyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-*N*-((*S*)-piperidin-3-yl)pyrimidin-2-amine	0.294
293		(1*R*,2*R*)-2-(Difluoromethyl)-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide	0.0905
294		4-[2-[[5-[(2,5-Dimethylthiazol-4-yl)methylamino]-2-methyl-1-naphthyl]oxy]-3-pyridyl]-*N*-[(3*S*)-3-piperidyl]pyrimidin-2-amine	0.241
295		4-(2-((2-Methyl-5-((1-(thiazol-4-yl)ethyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)-*N*-((*S*)-piperidin-3-yl)pyrimidin-2-amine	0.209
296		4-[2-[[6-Fluoro-2-methyl-5-(2-pyridylmethylamino)-1-naphthyl]oxy]-3-pyridyl]-*N*-[(3*S*)-3-piperidyl]pyrimidin-2-amine	0.22
297		5-[6-Methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]-5-azaspiro[2.4]heptan-4-one	0.173

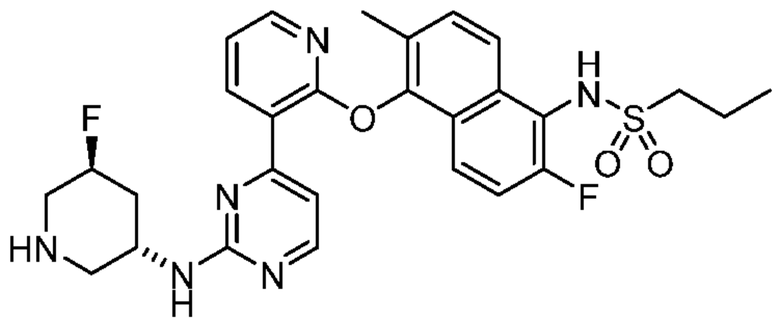
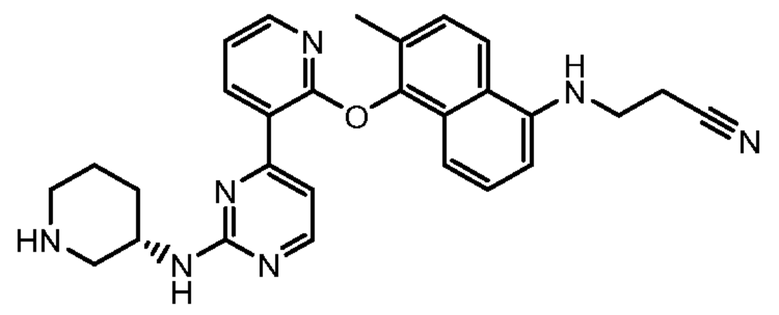
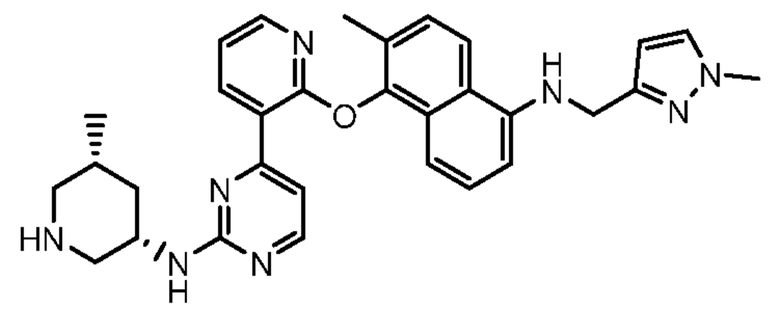
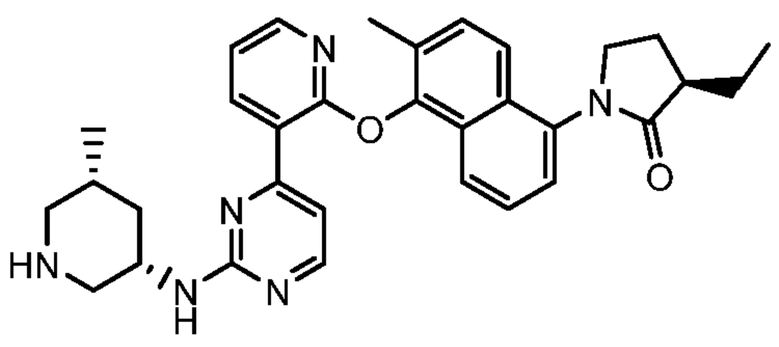
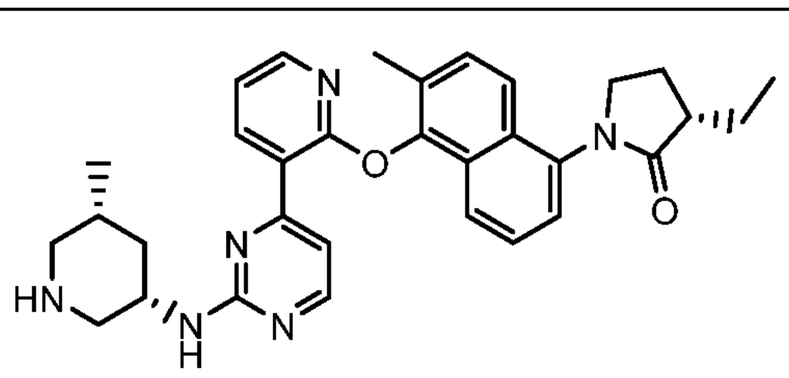
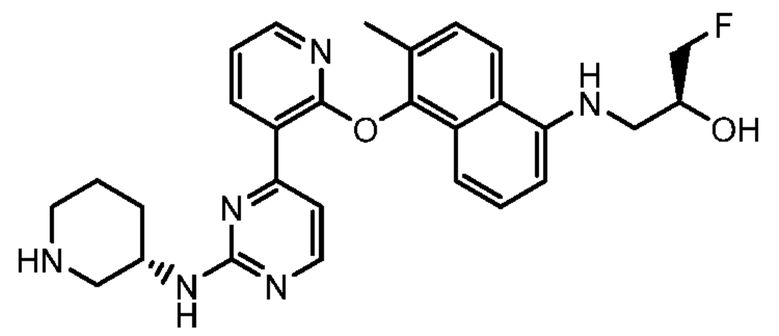
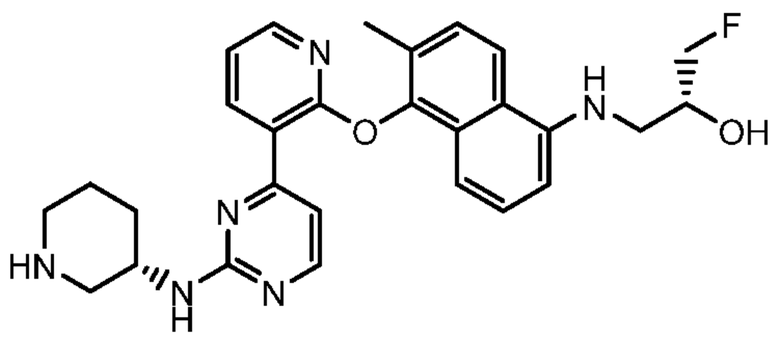
298		(2*R*)-1,1,1-Trifluoro-3-[[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]amino]propan-2-ol	0.0672
299		(2*S*)-1,1,1-Trifluoro-3-[[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]amino]propan-2-ol	0.00858
300		(2*R*)-1-[[6-Methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]amino]propan-2-ol	0.0554
301		(2*S*)-1-[[6-Methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]amino]propan-2-ol	0.424
302		3,3-Dimethyl-*N*-[6-methyl-5-[[3-[2-[[(3*S*,5*R*)-5-methyl-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]butanamide	0.0935
303		2-Cyclohexyl-*N*-[6-methyl-5-[[3-[2-[[(3*S*,5*R*)-5-methyl-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]acetamide	0.126

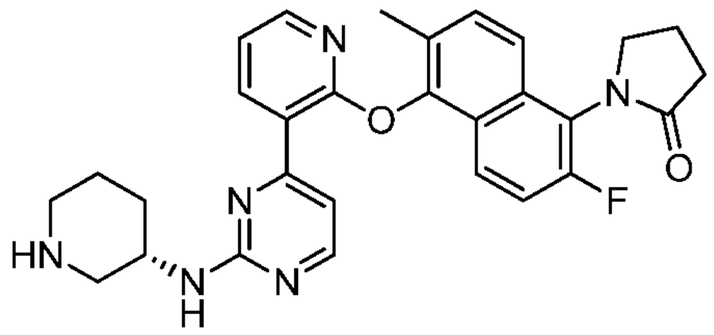
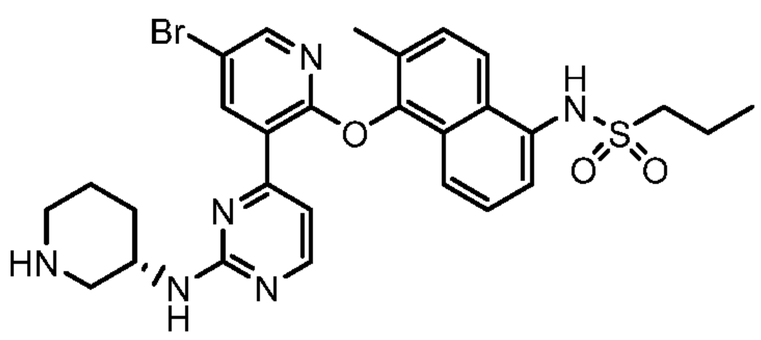
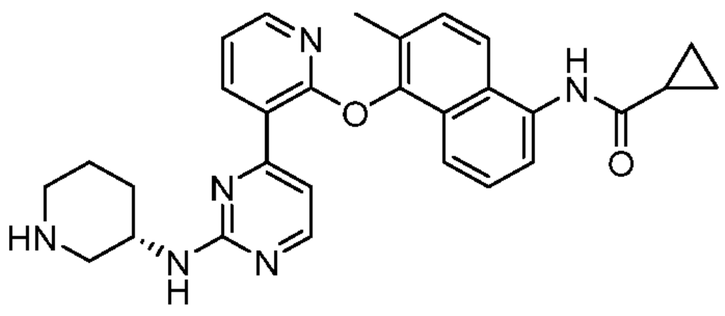
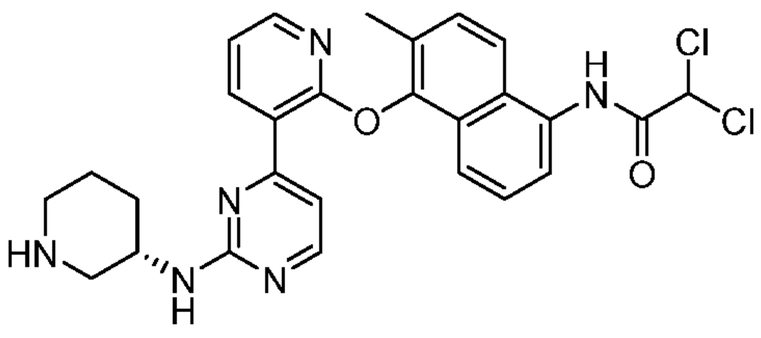
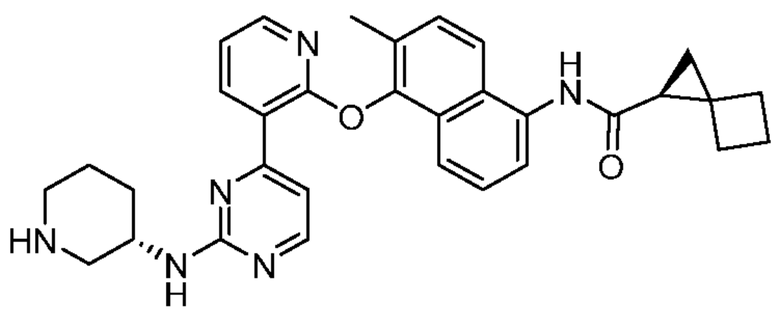
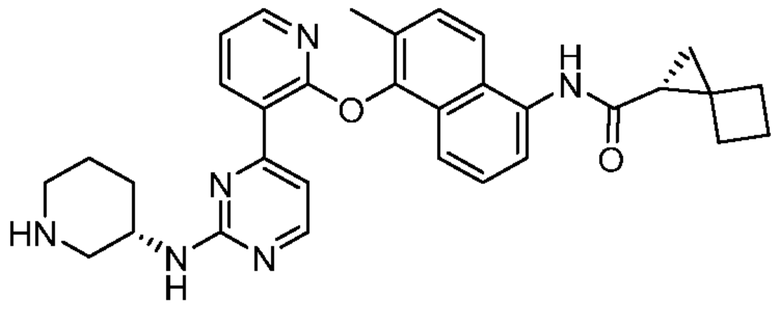
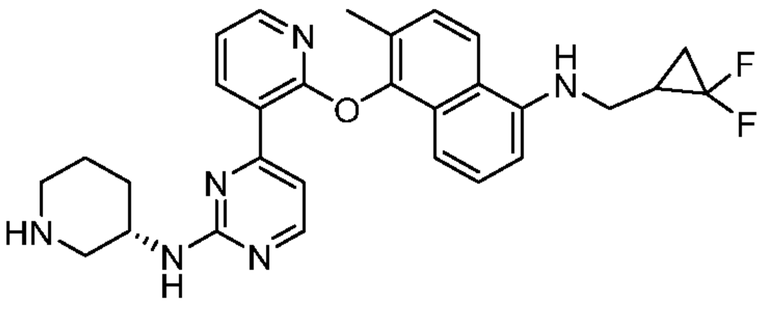
304		2-Methyl-*N*-[6-methyl-5-[[3-[2-[[(3*S*,5*R*)-5-methyl-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]propane-1-sulfonamide	0.105
305		*N*-[6-Fluoro-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]propane-1-sulfonamide	0.481
306		2-Methyl-1-[[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]amino]propan-2-ol	0.24
307		4-[2-[[6-Fluoro-2-methyl-5-[(2-methylthiazol-4-yl)methylamino]-1-naphthyl]oxy]-3-pyridyl]-*N*-[(3*S*,5*R*)-5-methyl-3-piperidyl]pyrimidin-2-amine	0.36
308		2-[6-Methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]-2-azaspiro[4.5]decan-1-one	0.211

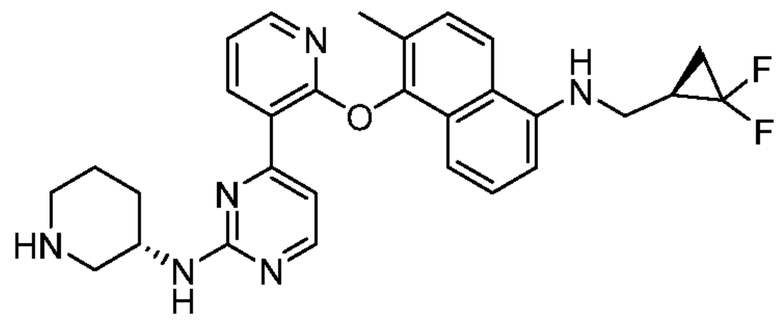
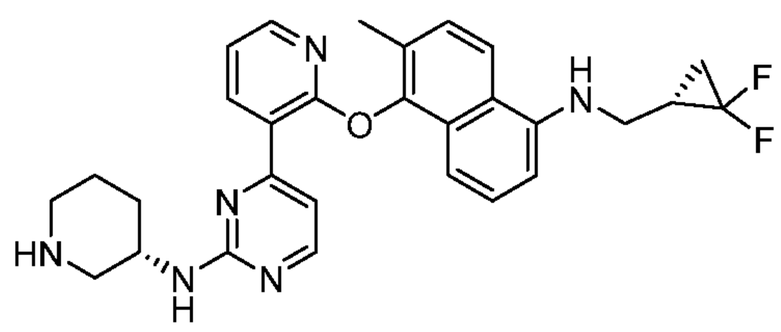
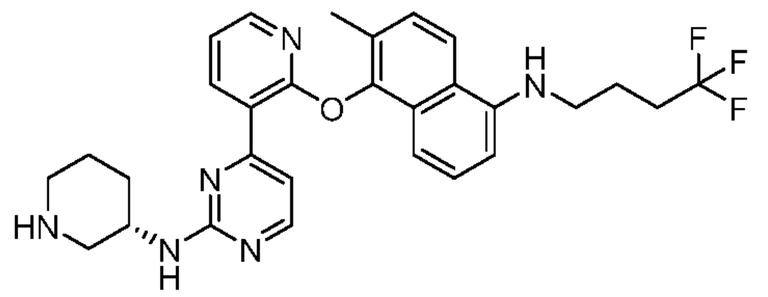
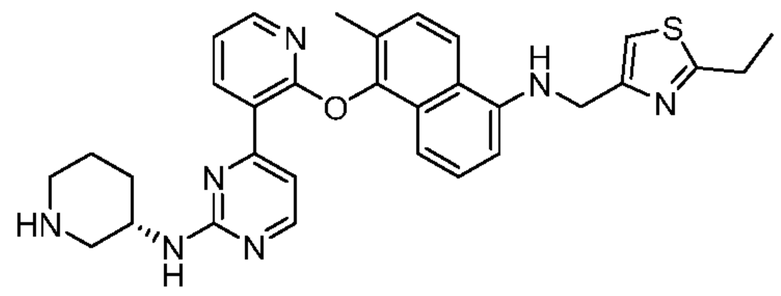
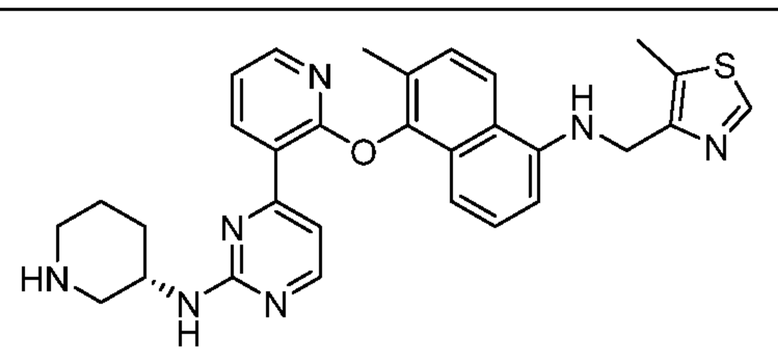
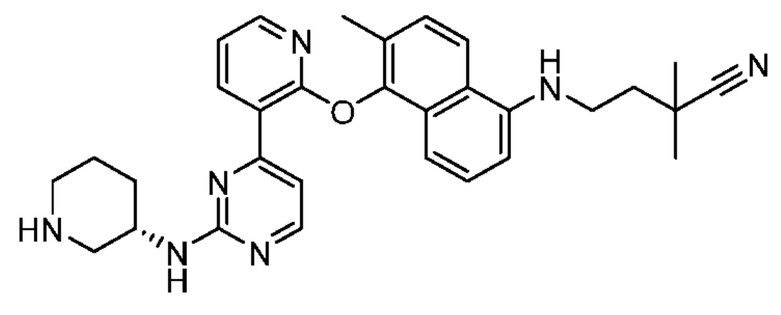
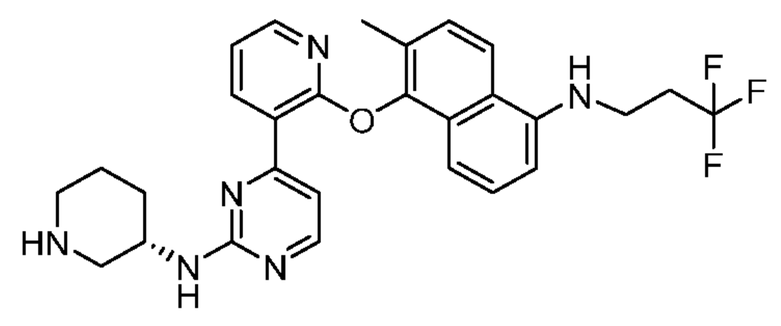
309		(1*S*)-2-[[6-Methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]amino]-1-phenyl-ethanol	0.433
310		*N*-[2-Fluoro-6-methyl-5-[[3-[2-[[(3*S*,5*R*)-5-methyl-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]cyclopropanecarboxamide	0.135
311		3,3,3-Trifluoro-*N*-[2-fluoro-6-methyl-5-[[3-[2-[[(3*S*,5*R*)-5-methyl-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]propane-1-sulfonamide	0.00616
312		(2*R*)-1-[[6-Methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]amino]butan-2-ol	0.0274
313		(2*S*)-1-[[6-Methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]amino]butan-2-ol	0.148

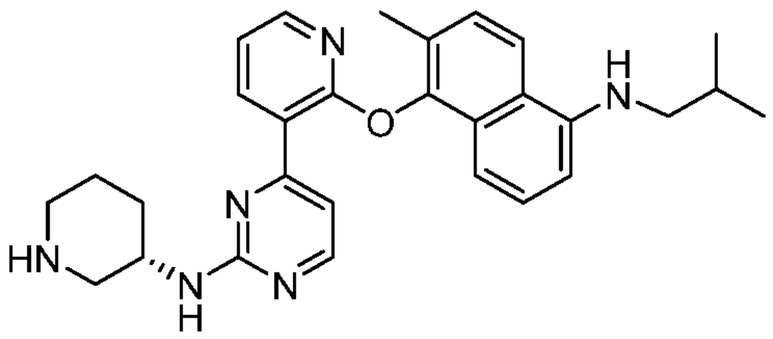
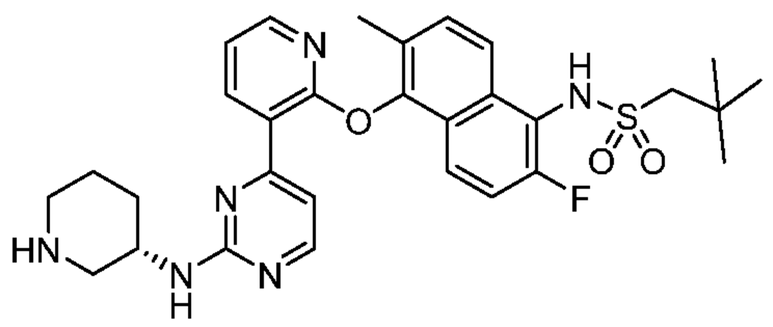
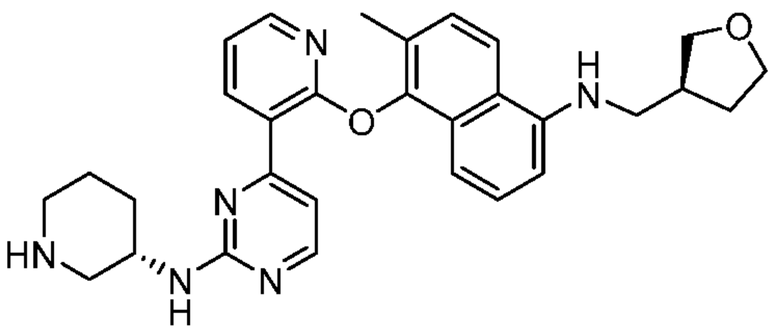
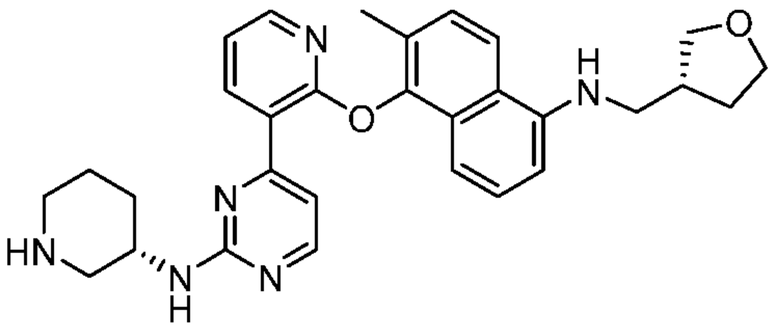
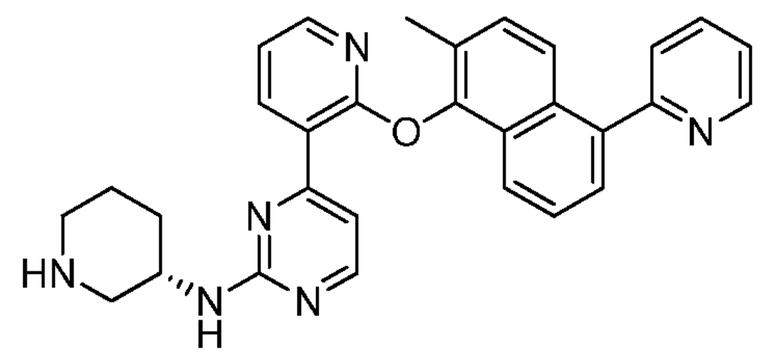
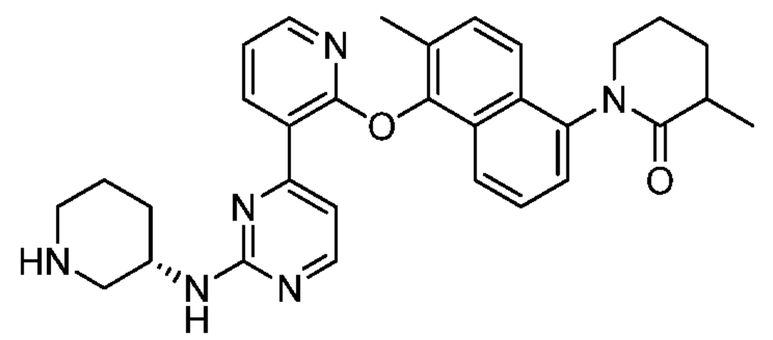
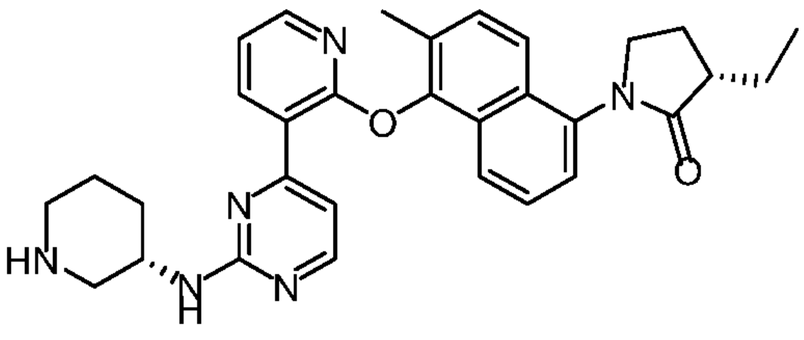
314		Methyl 2-[[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]amino]acetate	0.208
315		(*R*)-3-(Fluoromethyl)-1-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidin-2-one	0.471
316		(*S*)-3-(Fluoromethyl)-1-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidin-2-one	0.213
317		*N*-[2-Fluoro-6-methyl-5-[[3-[2-[[(3*S*,5*R*)-5-methyl-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]cyclohexanesulfonamide	0.0176
318		*N*-[2,6-Dimethyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]-3,3,3-trifluoro-propane-1-sulfonamide	0.0417
319		(2*S*)-3-[[2,6-Dimethyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]amino]-1,1,1-trifluoro-propan-2-ol	0.0482
320		4-[2-[[2-Methyl-5-[(5-methyl-1,2,4-oxadiazol-3-yl)methylamino]-1-naphthyl]oxy]-3-pyridyl]-*N*-[(3*S*)-3-piperidyl]pyrimidin-2-amine	0.74

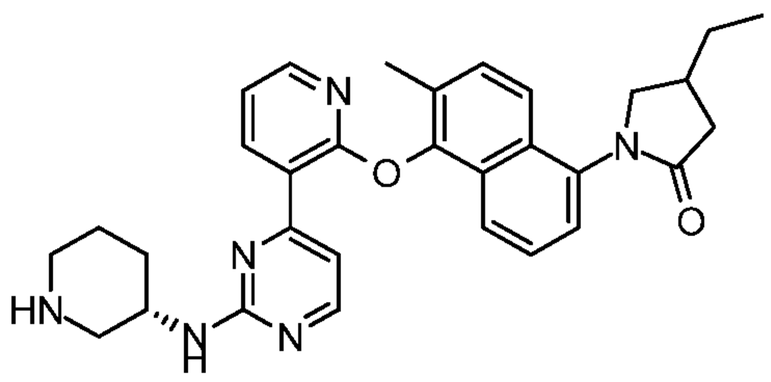
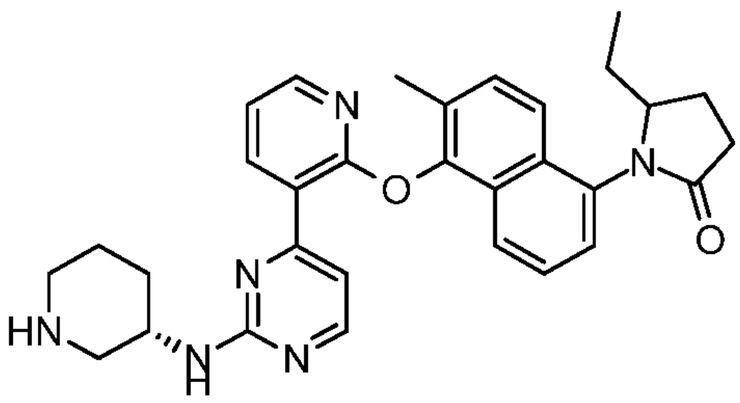
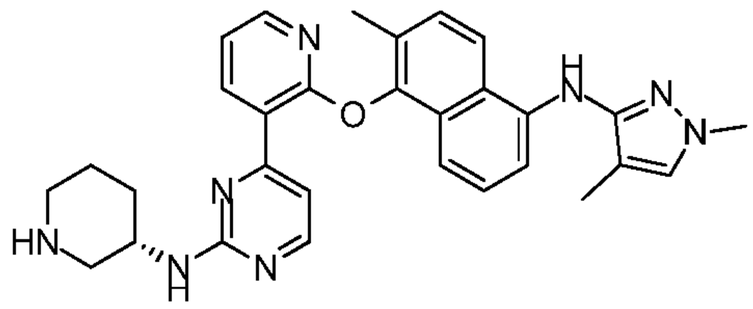
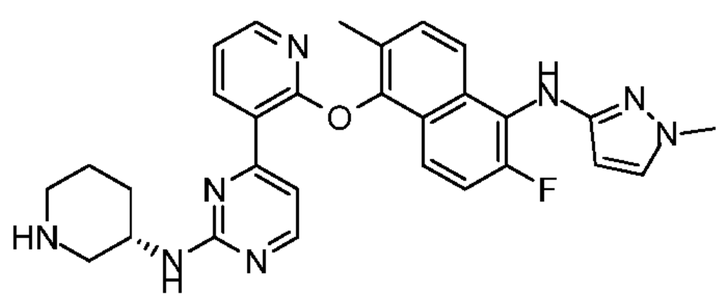
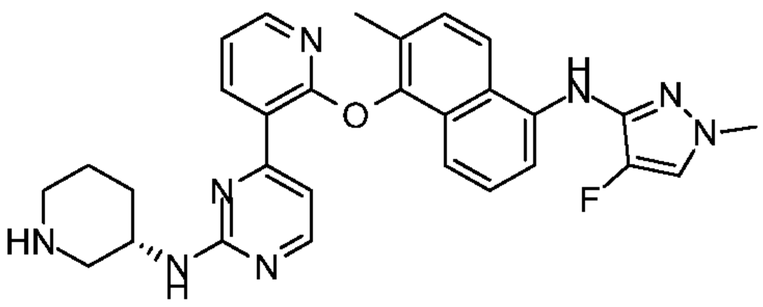
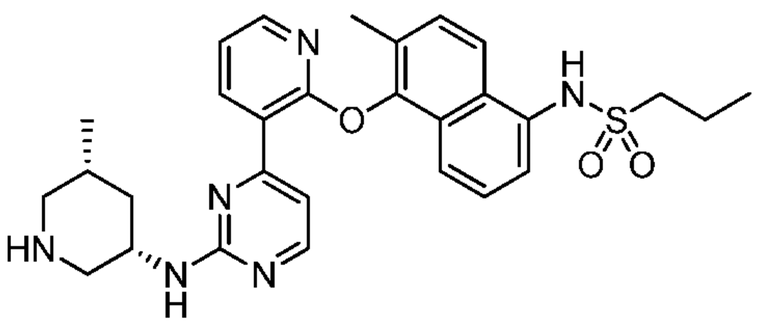
321		(2*S*)-1,1,1-Trifluoro-3-[[6-methyl-5-[[3-[2-[[(3*S*,5*R*)-5-methyl-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]amino]propan-2-ol	0.00736
322		*N*-(2-Fluoro-5-((3-(2-(((3*S*,5*S*)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)-3,3-dimethylbutanamide	0.0407
323		4-(2-((2-Methyl-5-(((2-methylthiazol-4-yl)methyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)-*N*-((3*S*,5*R*)-5-methylpiperidin-3-yl)pyrimidin-2-amine	0.0889
324		4-[2-[[5-(Dimethylsulfamoylamino)-6-fluoro-2-methyl-1-naphthyl]oxy]-3-pyridyl]-2-[[(3*S*)-3-piperidyl]amino]pyrimidine	0.0455
325		4-[2-[[5-(Dimethylsulfamoylamino)-6-fluoro-2-methyl-1-naphthyl]oxy]-3-pyridyl]-2-[[(3*S*,5*R*)-5-methyl-3-piperidyl]amino]pyrimidine	0.035
326		4-[2-[[2-Methyl-5-[[(2*S*)-3,3,3-trifluoro-2-methoxy-propyl]amino]-1-naphthyl]oxy]-3-pyridyl]-N-[(3S)-3-piperidyl]pyrimidin-2-amine	0.0284
327		*N*-(2-Fluoro-6-methyl-5-((3-(2-(((3*S*,4*R*)-4-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide	0.254

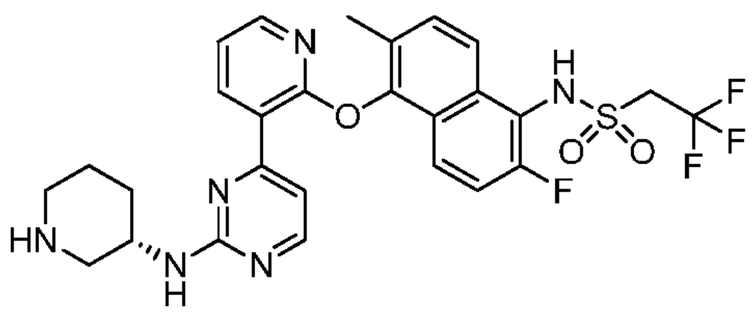
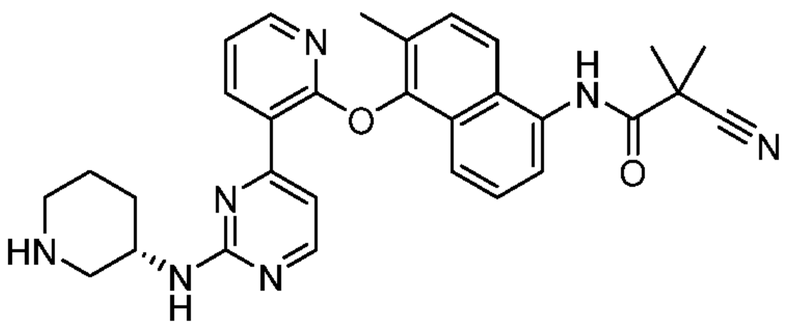
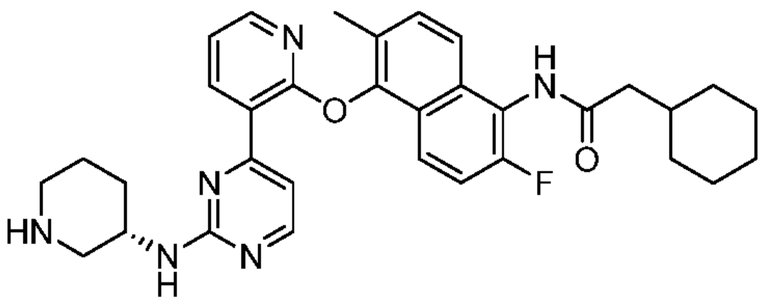
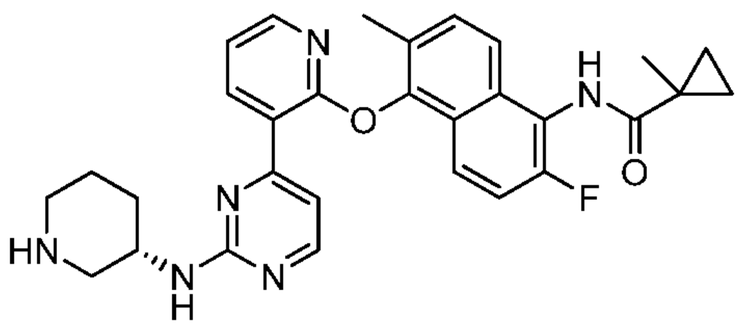
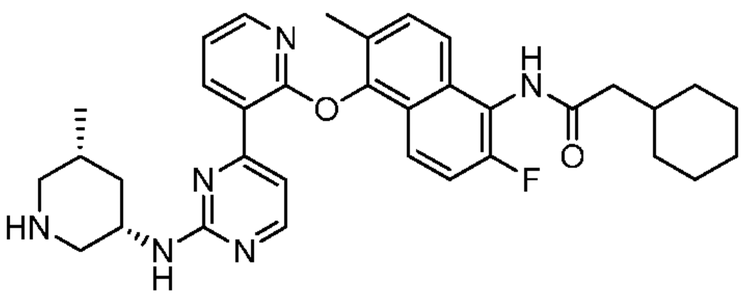
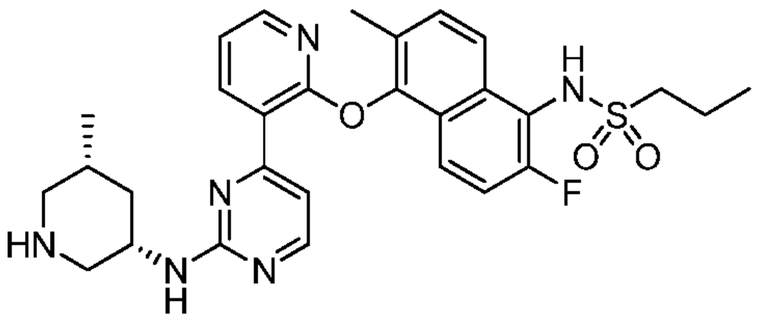
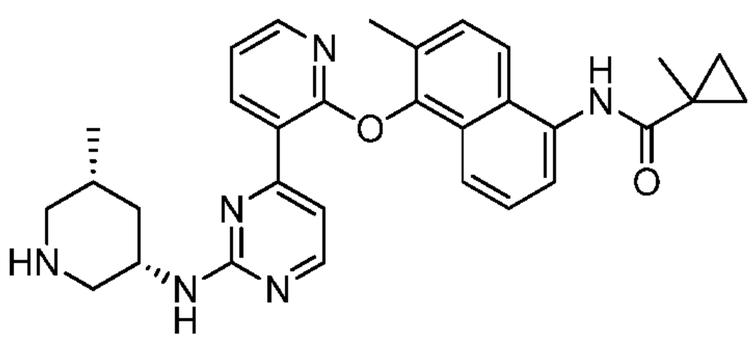
328		*N*-(2-Fluoro-5-((3-(2-(((3*S*,5*S*)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)propane-1-sulfonamide	0.0152
329		(*S*)-3-((6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)propanenitrile	0.123
330		4-[2-[[2-Methyl-5-[(1-methylpyrazol-3-yl)methylamino]-1-naphthyl]oxy]-3-pyridyl]-*N*-[(3*S*,5*R*)-5-methyl-3-piperidyl]pyrimidin-2-amine	0.197
331		(*R*)-3-Ethyl-1-(6-methyl-5-((3-(2-(((3*S*,5*R*)-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidin-2-one	0.0579
332		(*S*)-3-Ethyl-1-(6-methyl-5-((3-(2-(((3*S*,5*R*)-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidin-2-one	0.194
333		(*S*)-1-Fluoro-3-((6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)propan-2-ol	0.0446
334		(*R*)-1-Fluoro-3-((6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)propan-2-ol	0.0897

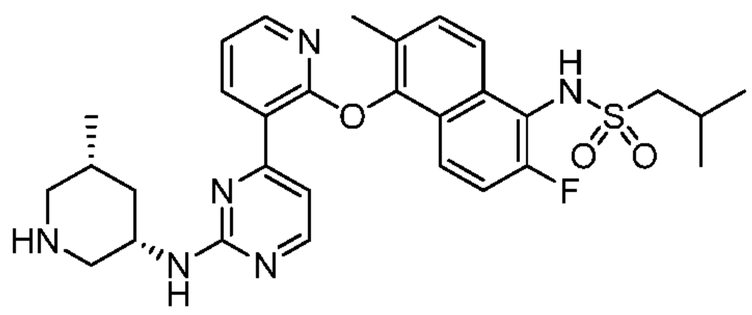
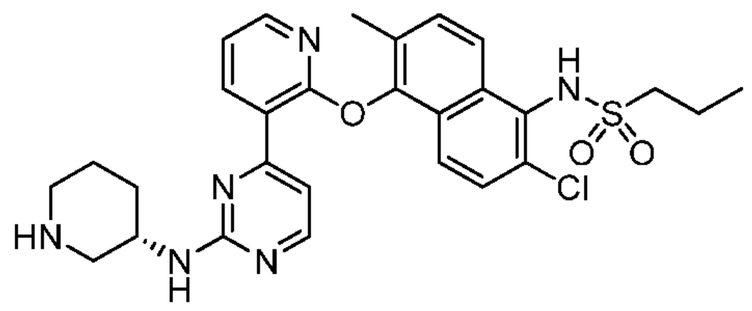
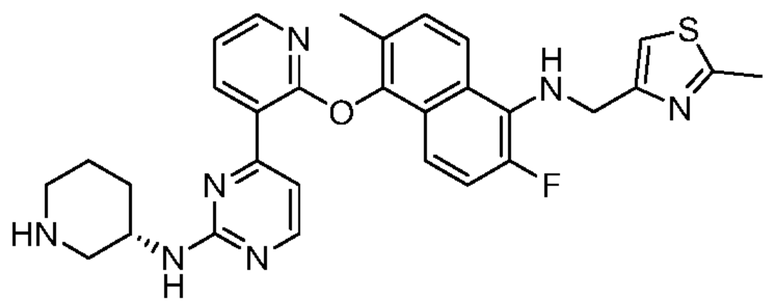
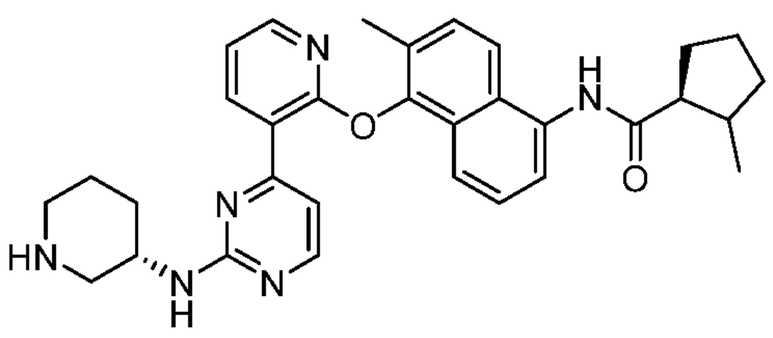
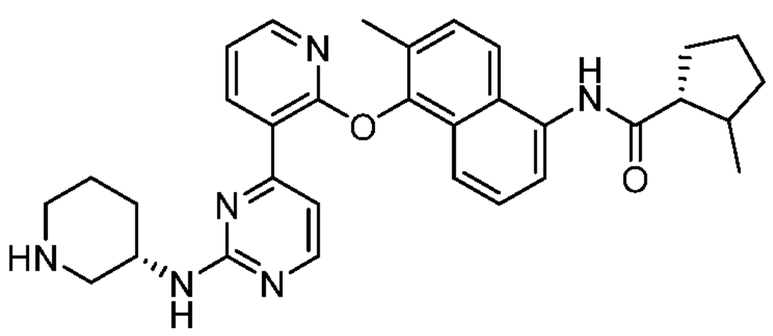
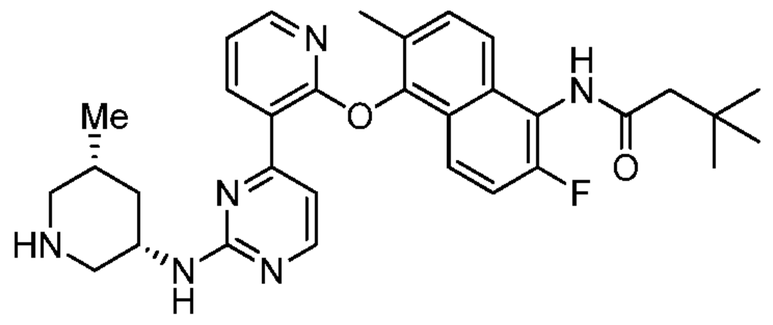
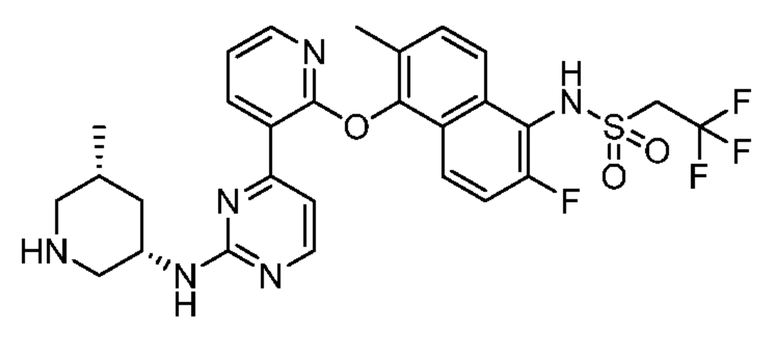
335		(*S*)-1-(2-Fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidin-2-one	0.384
336		(*S*)-*N*-(5-((5-Bromo-3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)propane-1-sulfonamide	0.54
337		(*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropanecarboxamide	0.0842
338		(*S*)-2,2-Dichloro-*N*-(6-methyl-5-(3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yloxy)naphthalen-1-yl)acetamide	0.161
339		(*S*)-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)spiro[2.3]hexane-1-carboxamide	0.137
340		(*R*)-*N*-(6-Methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)spiro[2.3]hexane-1-carboxamide	0.0177
341		4-(2-((5-(((2,2-Difluorocyclopropyl)methyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-*N*-((*S*)-piperidin-3-yl)pyrimidin-2-amine	0.118

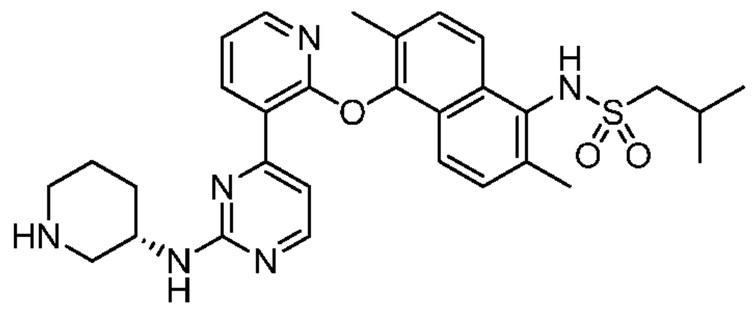
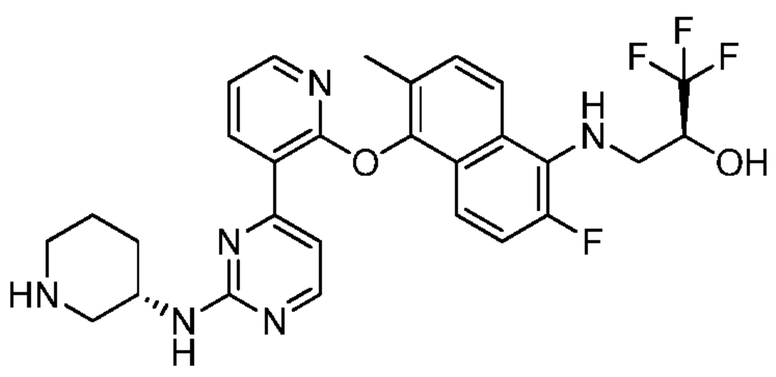
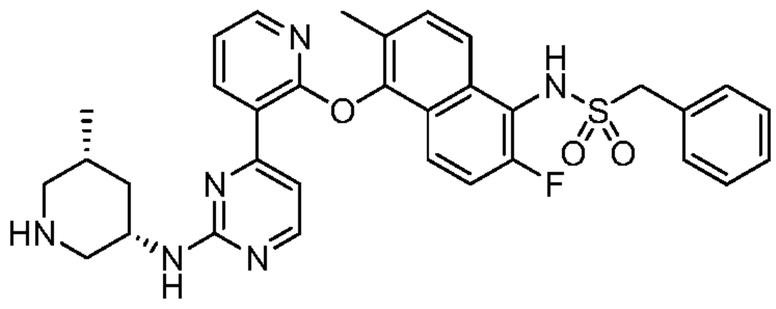
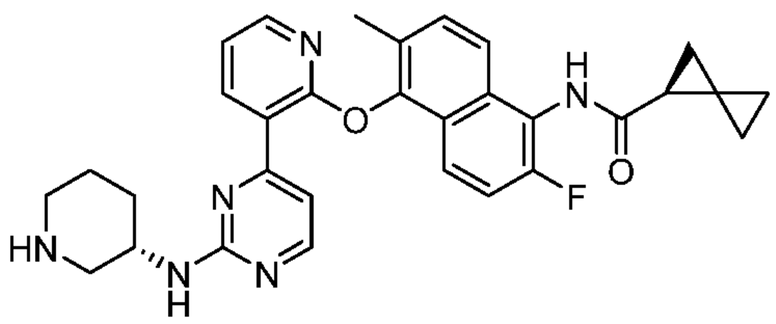
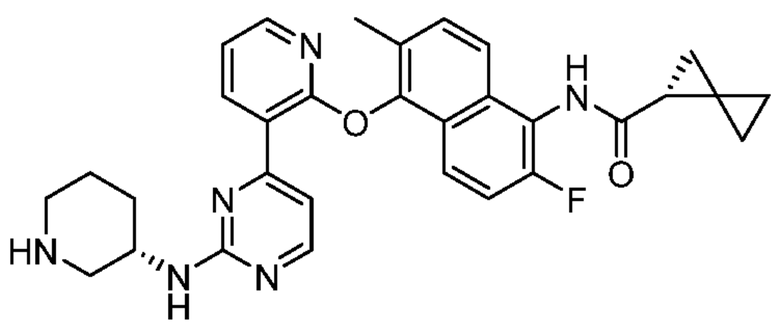
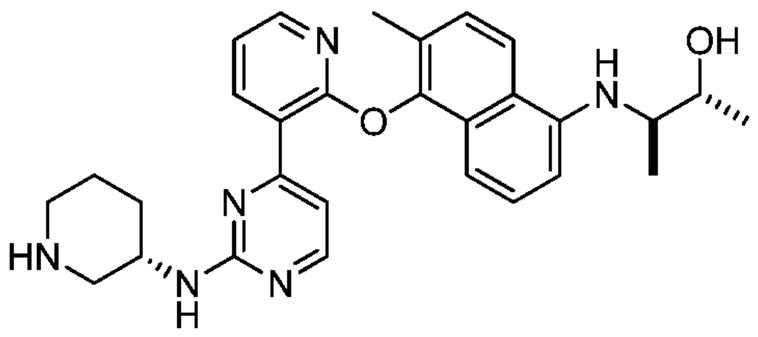
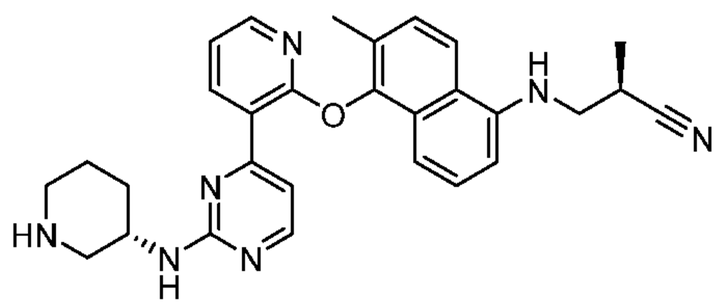
342		4-(2-((5-((((*R*)-2,2-Difluorocyclopropyl)methyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-*N*-((*S*)-piperidin-3-yl)pyrimidin-2-amine	0.121
343		4-(2-((5-((((*S*)-2,2-Difluorocyclopropyl)methyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-*N*-((*S*)-piperidin-3-yl)pyrimidin-2-amine	0.181
344		(*S*)-4-(2-((2-Methyl-5-((4,4,4-trifluorobutyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-2-amine	0.35
345		(*S*)-4-(2-((5-(((2-Ethylthiazol-4-yl)methyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-2-amine	0.171
346		(*S*)-4-(2-((2-Methyl-5-(((5-methylthiazol-4-yl)methyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-2-amine	0.136
347		(*S*)-2,2-Dimethyl-4-((6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)butanenitrile	0.048
348		(*S*)-4-(2-((2-Methyl-5-((3,3,3-trifluoropropyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-2-amine	0.079

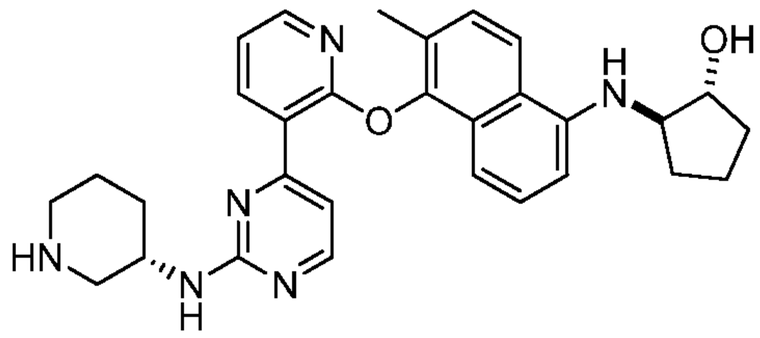
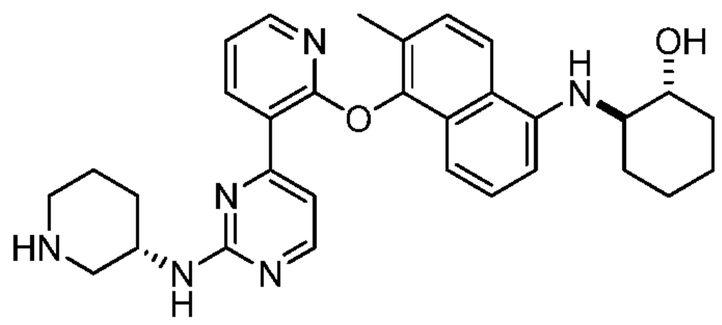
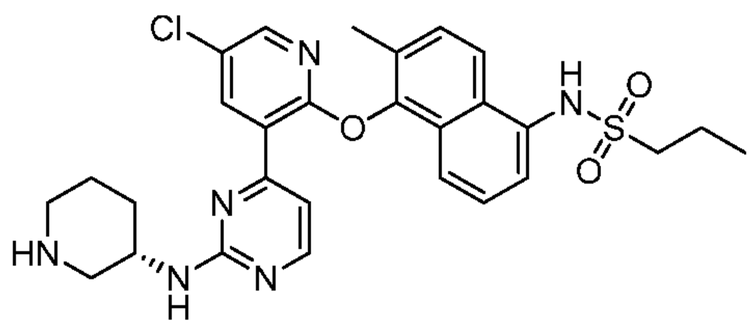
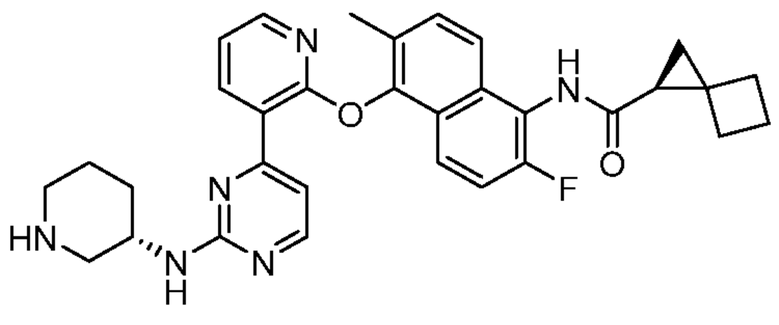
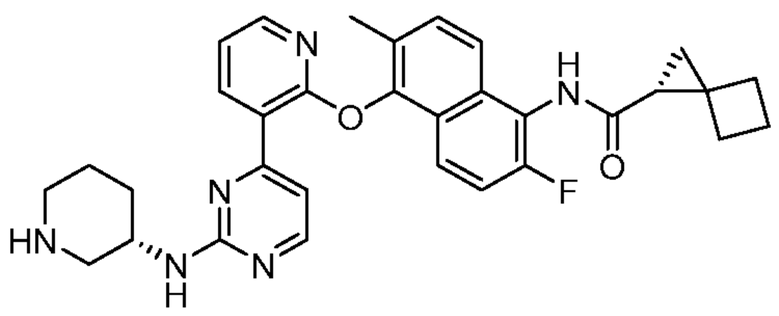
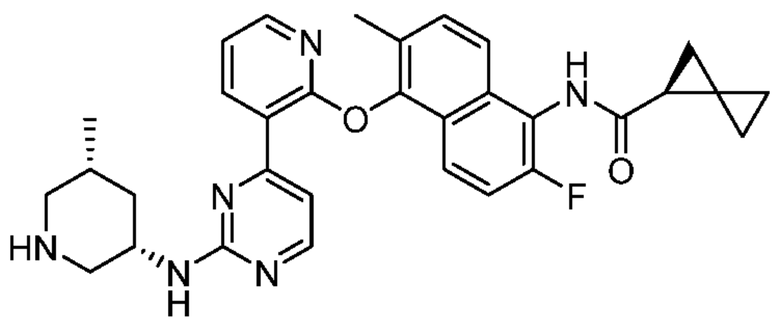
349		(*S*)-4-(2-((5-(Isobutylamino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-2-amine	0.432
350		(*S*)-*N*-(2-Fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2,2-dimethylpropane-1-sulfonamide	0.0374
351		4-(2-((2-Methyl-5-((((*S*)-tetrahydrofuran-3-yl)methyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)-*N*-((*S*)-piperidin-3-yl)pyrimidin-2-amine	0.50
352		4-(2-((2-Methyl-5-((((*R*)-tetrahydrofuran-3-yl)methyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)-N-((*S*)-piperidin-3-yl)pyrimidin-2-amine	0.499
353		(*S*)-4-(2-((2-Methyl-5-(pyridin-2-yl)naphthalen-1-yl)oxy)pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-2-amine	0.133
354		3-Methyl-1-(6-methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)piperidin-2-one	0.318
355		(*S*)-3-Ethyl-1-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidin-2-one	0.365

356		4-Ethyl-1-(6-methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidin-2-one	0.279
357		5-Ethyl-1-(6-methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidin-2-one	0.26
358		(*S*)-4-(2-((5-((1,4-Dimethyl-1*H*-pyrazol-3-yl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-2-amine	0.266
359		(*S*)-4-(2-((6-Fluoro-2-methyl-5-((1-methyl-1*H*-pyrazol-3-yl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-2-amine	0.438
360		(*S*)-4-(2-((5-((4-Fluoro-1-methyl-1*H*-pyrazol-3-yl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-2-amine	0.455
361		*N*-(6-Methyl-5-((3-(2-(((3*S*,5*R*)-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide	0.0851

362		(*S*)-2,2,2-Trifluoro-*N*-(2-fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)ethanesulfonamide	0.0234
363		(*S*)-2-Cyano-2-methyl-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalene-1-yl)propanamide	0.408
364		(*S*)-2-Cyclohexyl-*N*-(2-fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)acetamide	0.216
365		(*S*)-*N*-(2-Fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-methylcyclopropanecarboxamide	0.438
366		2-Cyclohexyl-*N*-(2-fluoro-6-methyl-5-((3-(2-(((3*S*,5*R*)-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)acetamide	0.101
367		*N*-(2-Fluoro-6-methyl-5-((3-(2-(((3*S*,5*R*)-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide	0.0145
368		1-Methyl-*N*-(6-methyl-5-((3-(2-(((3*S*,5*R*)-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropanecarboxamide	0.214

369		*N*-(2-Fluoro-6-methyl-5-((3-(2-(((3*S*,5*R*)-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-methylpropane-1-sulfonamide	0.0194
370		(*S*)-*N*-(2-Chloro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide	0.0276
371		(*S*)-4-(2-((6-Fluoro-2-methyl-5-(((2-methylthiazol-4-yl)methyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-2-amine	0.381
372		(1*S*)-2-Methyl-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentane-1-carboxamide	0.47
373		(1*R*)-2-Methyl-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentane-1-carboxamide	0.193
374		*N*-(2-Fluoro-6-methyl-5-((3-(2-(((3*S*,5*R*)-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-3,3-dimethylbutanamide	0.0394
375		2,2,2-Trifluoro-*N*-(2-fluoro-6-methyl-5-((3-(2-(((3*S*,5*R*)-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)ethanesulfonamide	0.0132

376		(*S*)-*N*-(2,6-Dimethyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-methylpropane-1-sulfonamide	0.0735
377		(*S*)-1,1,1-Trifluoro-3-((2-fluoro-6-methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)propan-2-ol	0.0102
378		*N*-(2-Fluoro-6-methyl-5-((3-(2-(((3*S*,5*R*)-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-phenylmethanesulfonamide	0.00141
379		(*S*)-*N*-(2-Fluoro-6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)spiro[2.2]pentane-1-carboxamide	0.279
380		(*R*)-*N*-(2-Fluoro-6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)spiro[2.2]pentane-1-carboxamide	0.0566
381		*anti*-3-((6-Methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)butan-2-ol	0.403
382		(*R*)-2-Methyl-3-((6-methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)propanenitrile	0.0623

383		*anti*-2-((6-Methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)cyclopentanol	0.231
384		*trans*-2-((6-Methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)cyclohexanol	0.146
385		(*S*)-*N*-(5-((5-Chloro-3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)propane-1-sulfonamide	0.366
386		(*S*)-*N*-(2-Fluoro-6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)spiro[2.3]hexane-1-carboxamide	0.28
387		(*R*)-*N*-(2-Fluoro-6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)spiro[2.3]hexane-1-carboxamide	0.0283
388		(*S*)-*N*-(2-Fluoro-6-methyl-5-((3-(2-(((3*S*,5*R*)-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)spiro[2.2]pentane-1-carboxamide	0.136

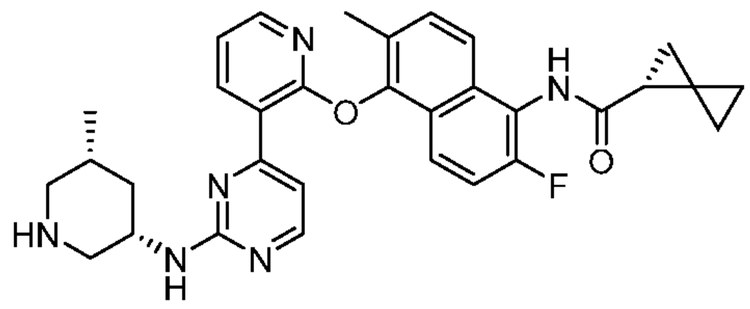
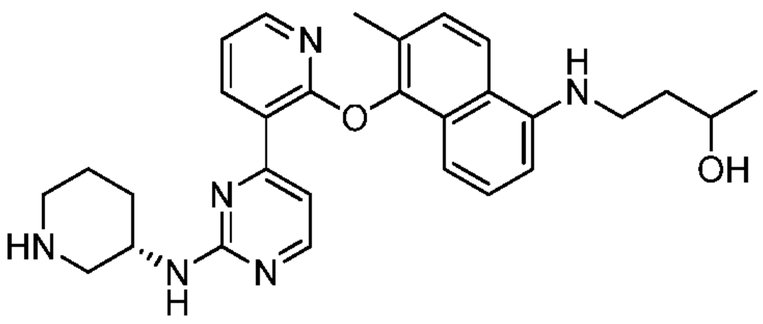
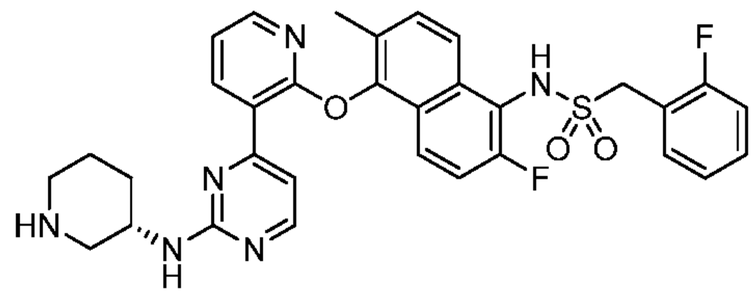
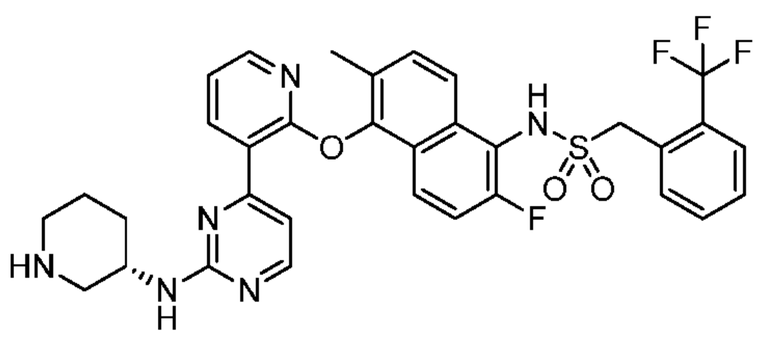
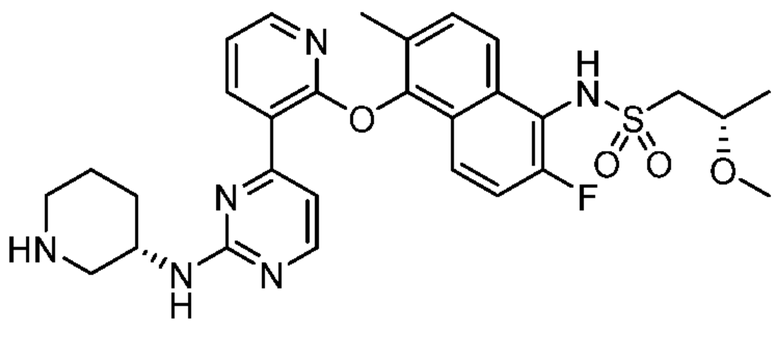
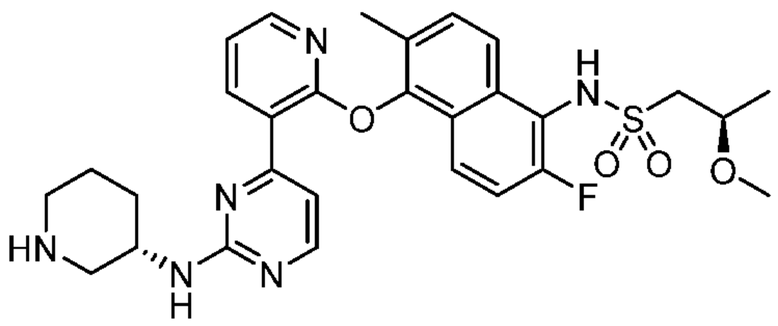
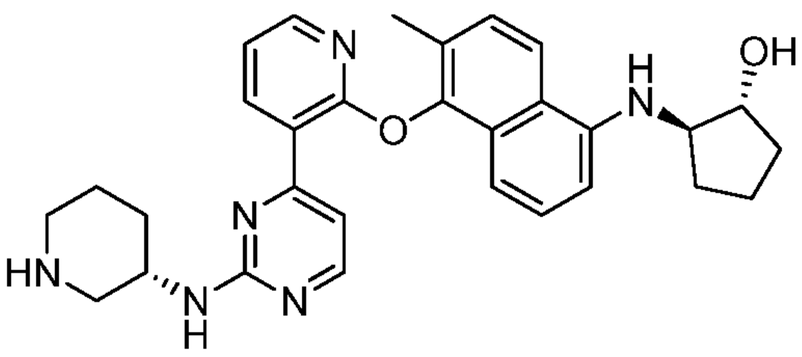
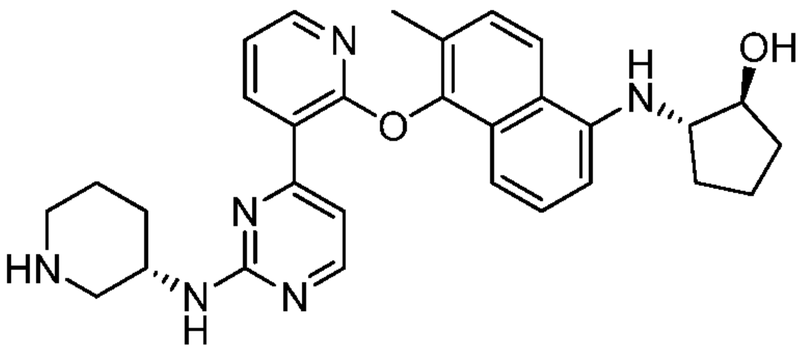
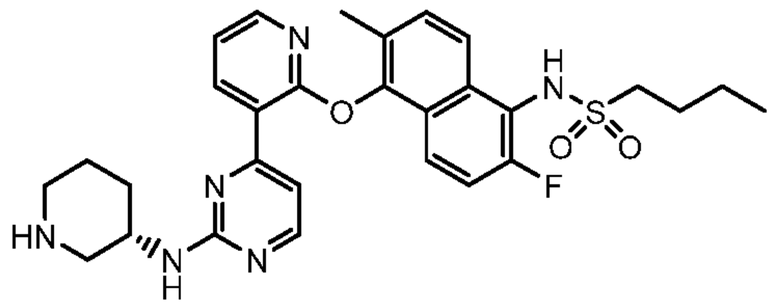
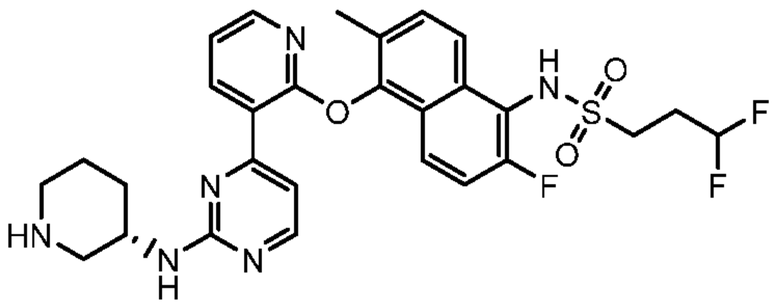
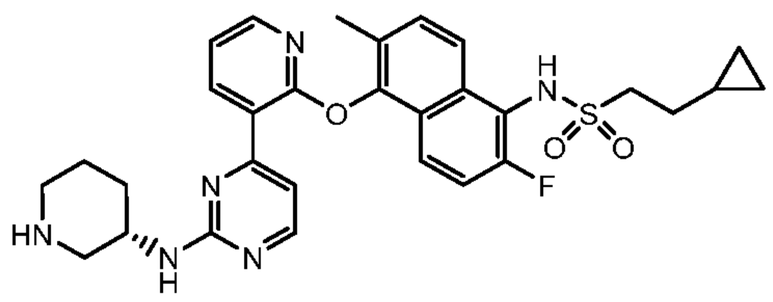
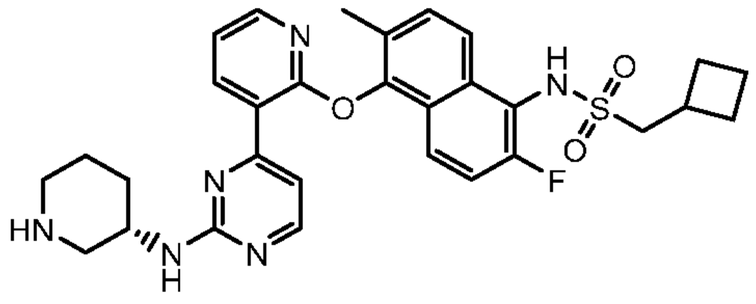
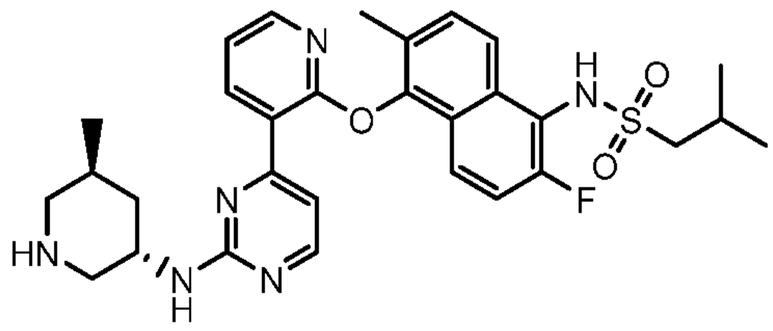
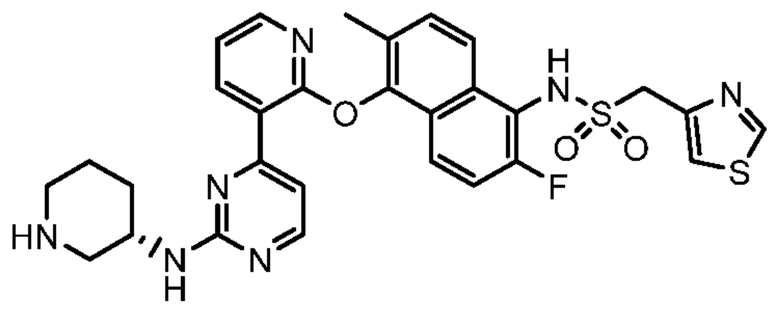
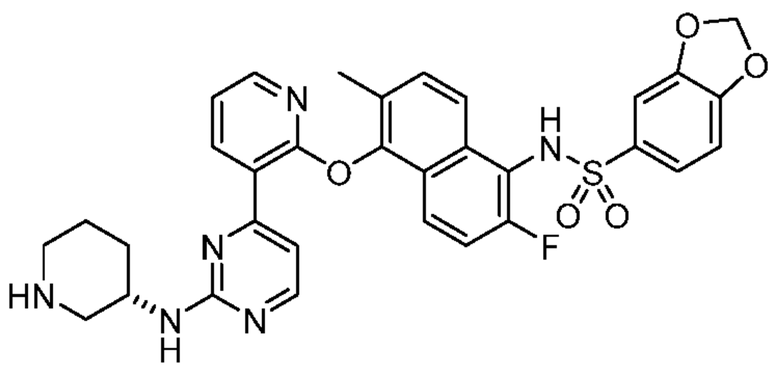
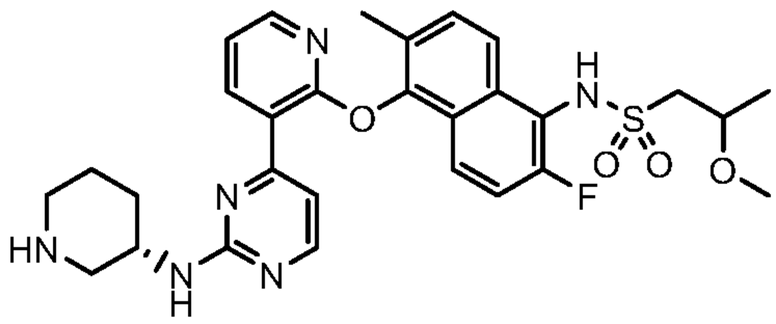
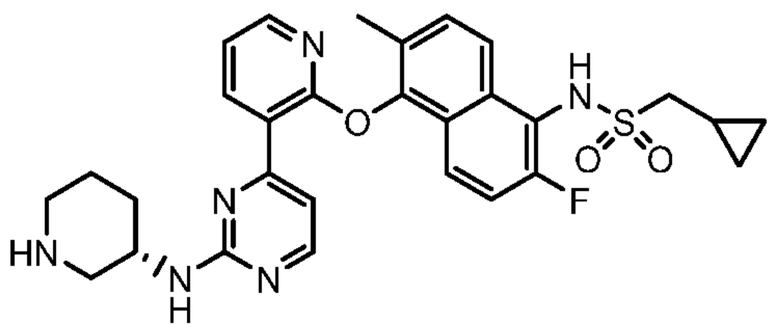
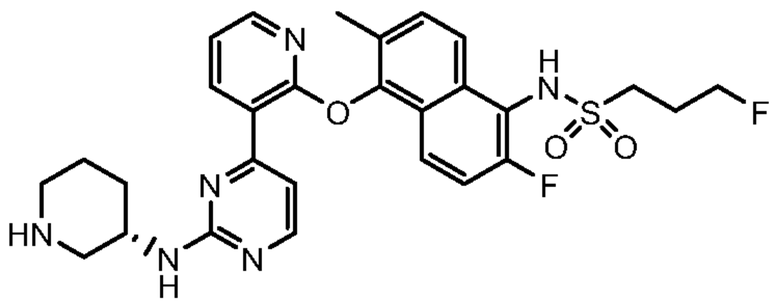
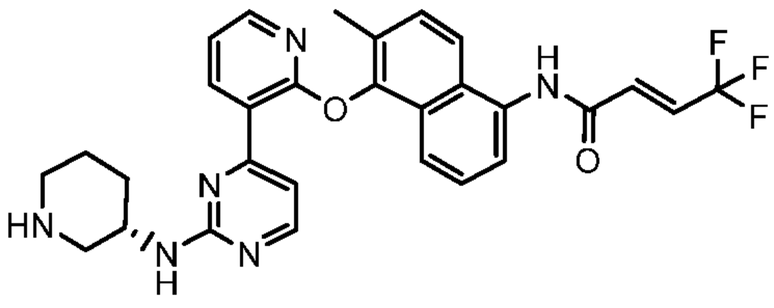
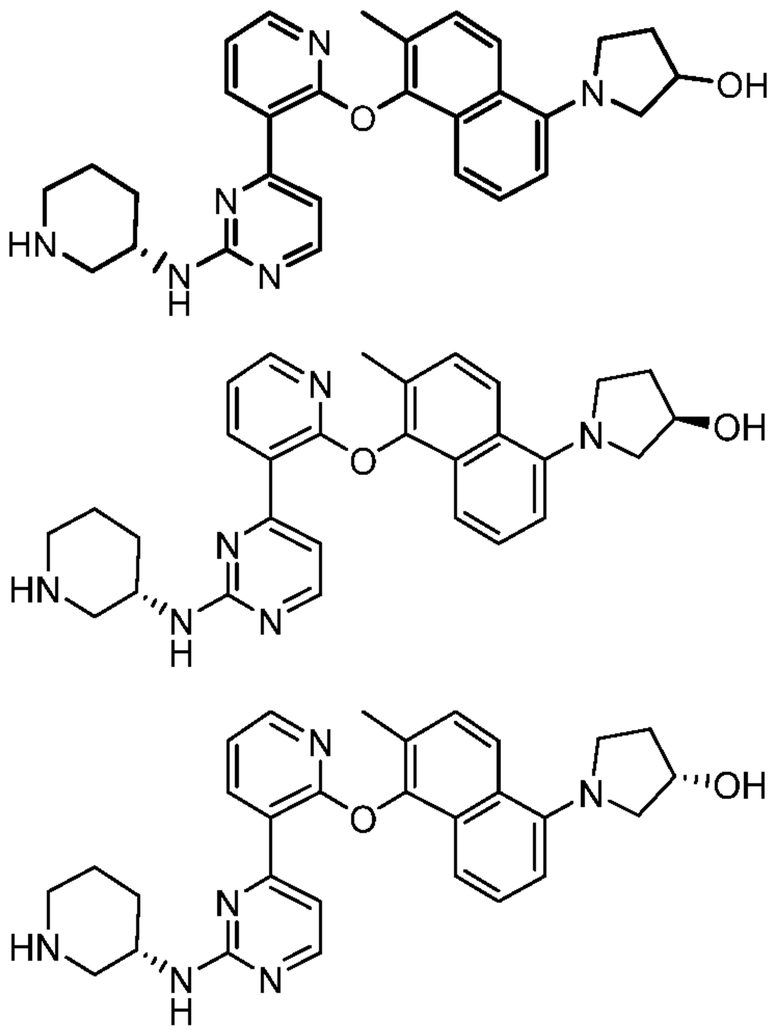
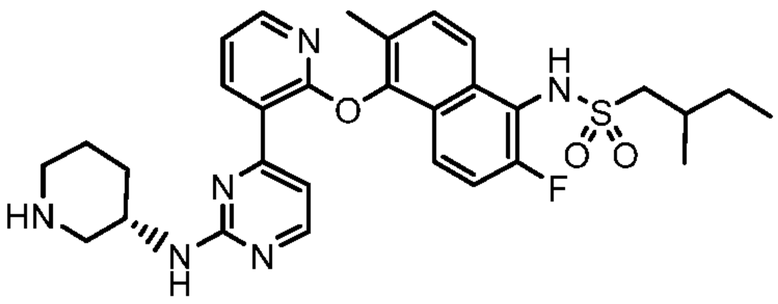
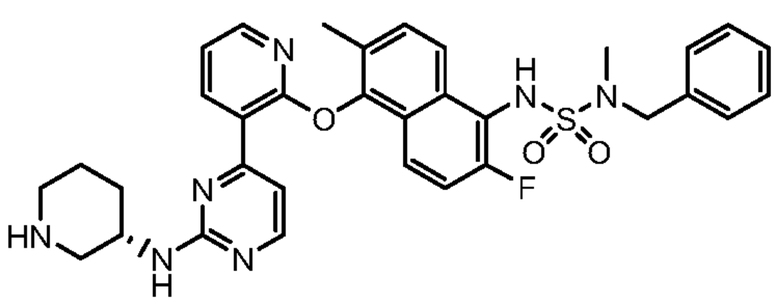
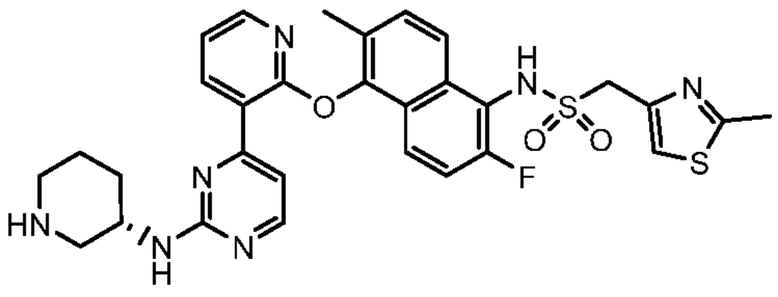
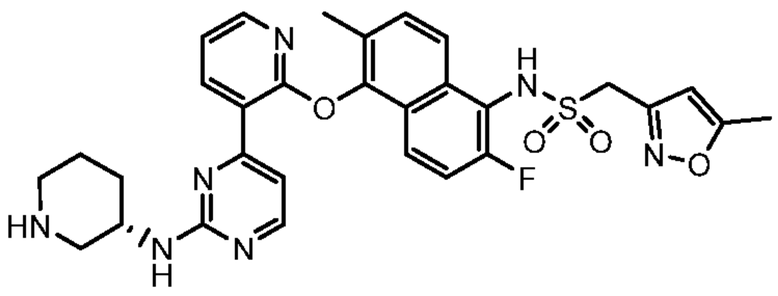
389		(*R*)-*N*-(2-Fluoro-6-methyl-5-((3-(2-(((3*S*,5*R*)-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)spiro[2.2]pentane-1-carboxamide	0.0417
390		4-((6-Methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)butan-2-ol	0.143
391		(*S*)-*N*-(2-Fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-(2-fluorophenyl)methanesulfonamide	0.00277
392		(*S*)-*N*-(2-Fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-(2-(trifluoromethyl)phenyl)methanesulfonamide	0.00632

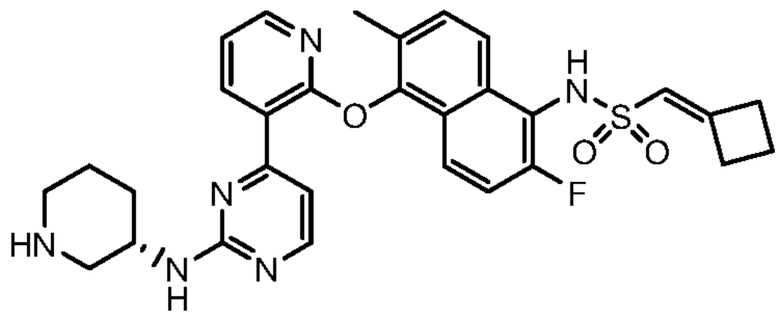
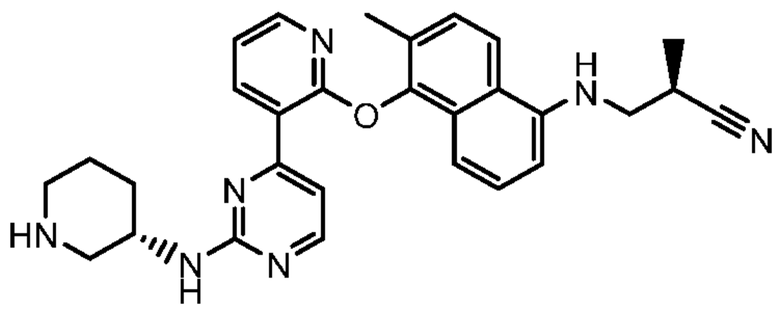
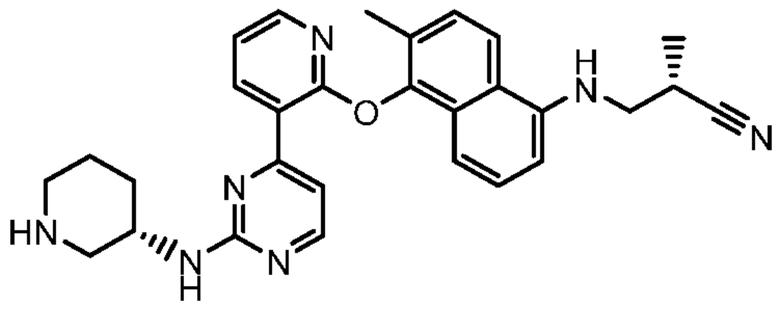
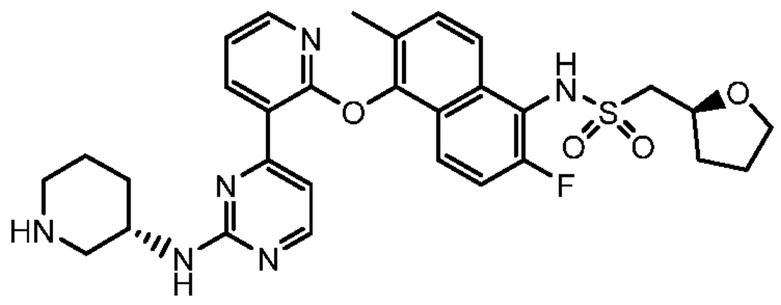
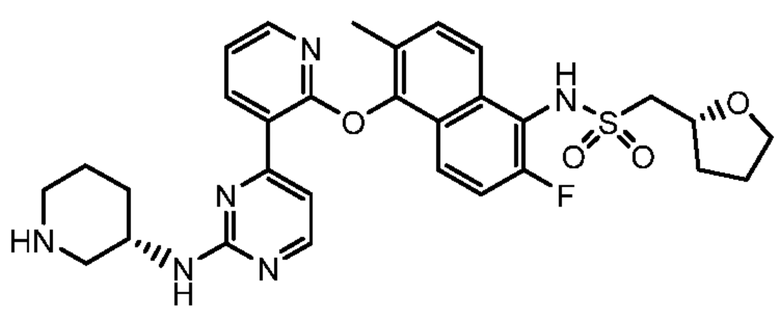
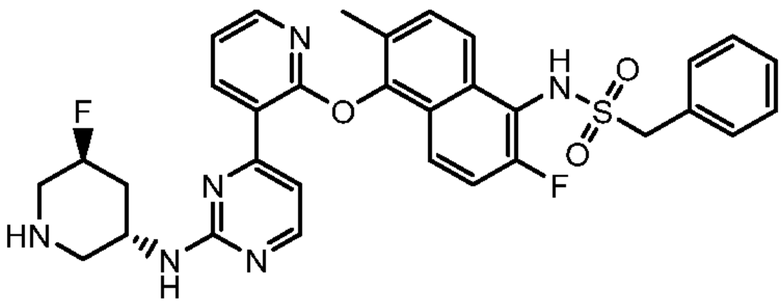
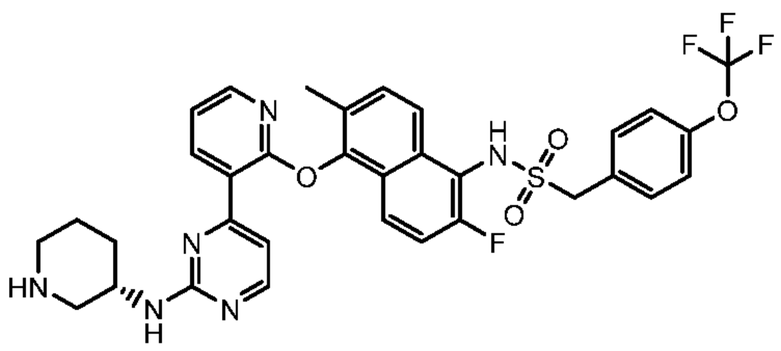
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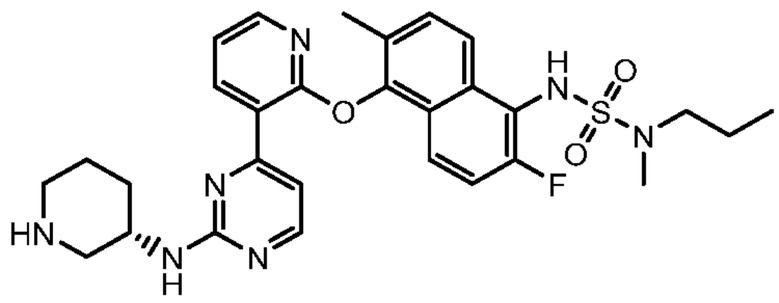
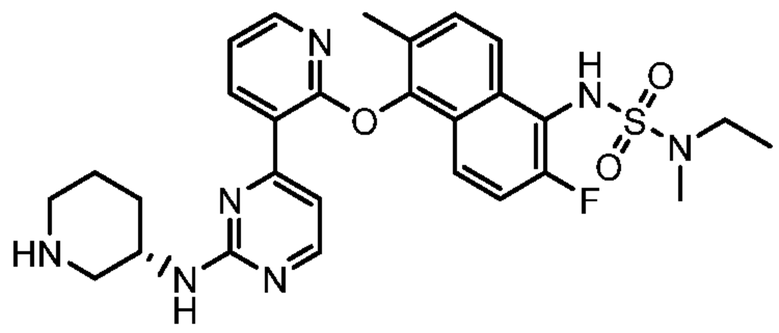
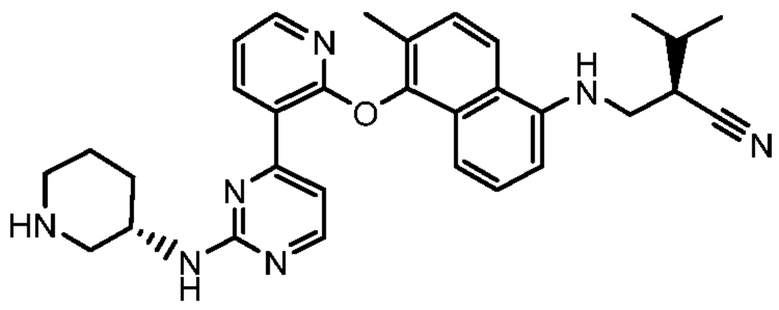
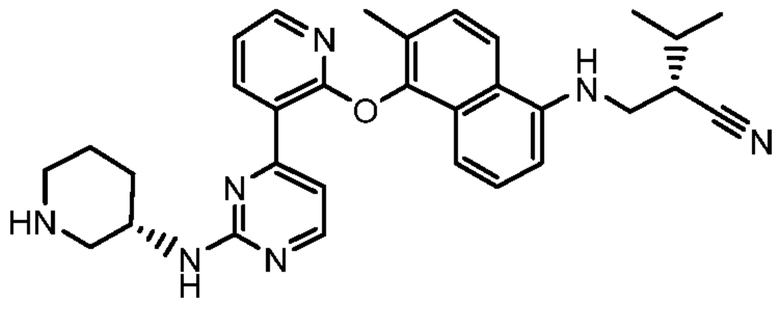
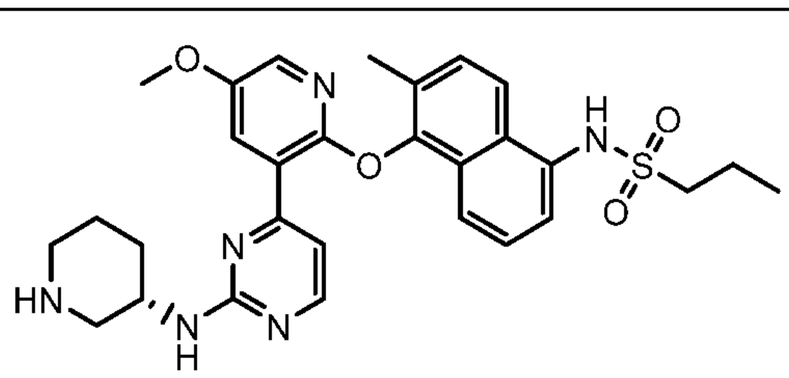
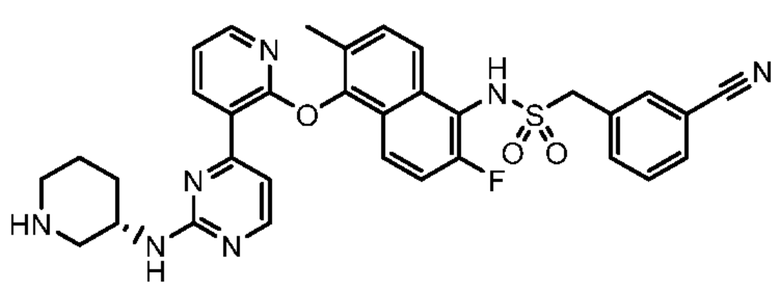
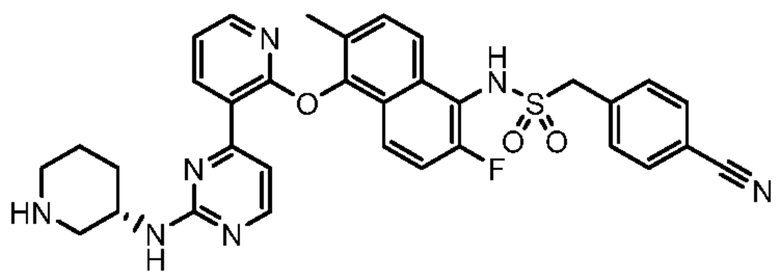
No.	Structure	Name	XBP1s-luc 293 LUC (IC_{50}) (μmol)
393		*(S)*-*N*-(2-Fluoro-6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-methoxypropane-1-sulfonamide	0.076

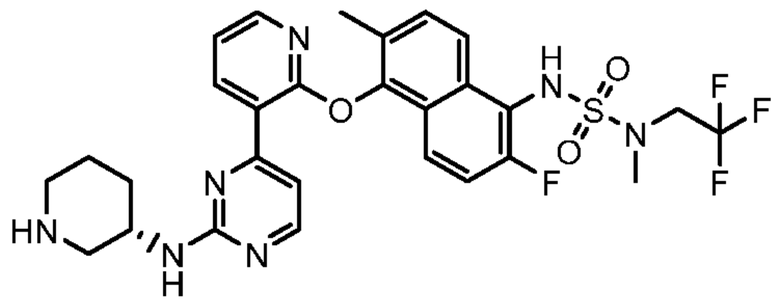
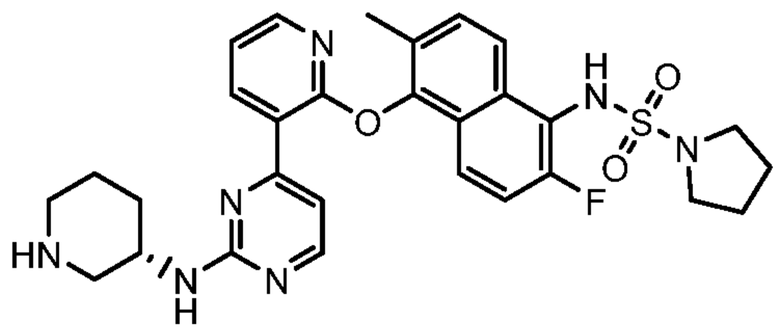
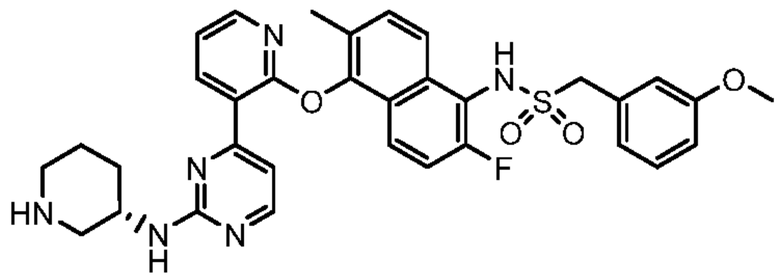
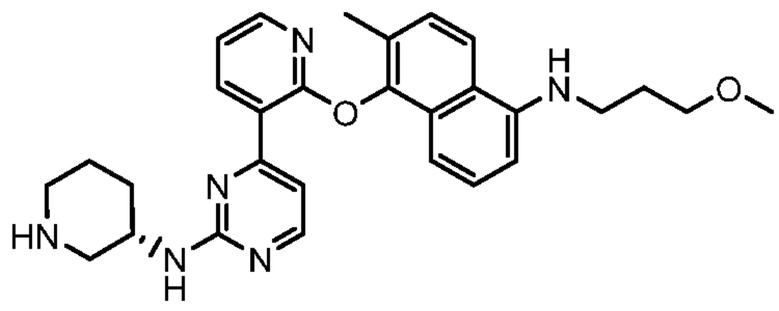
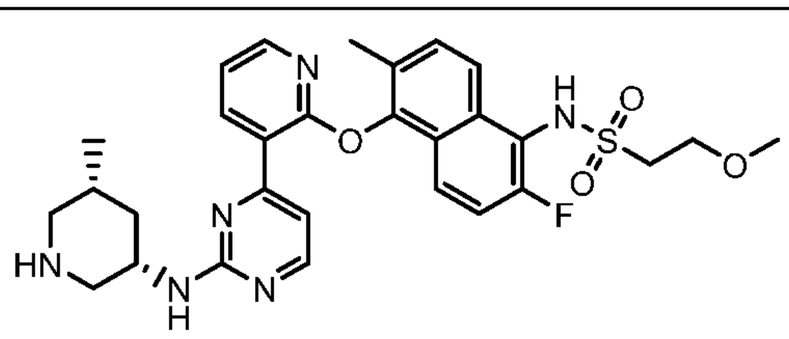
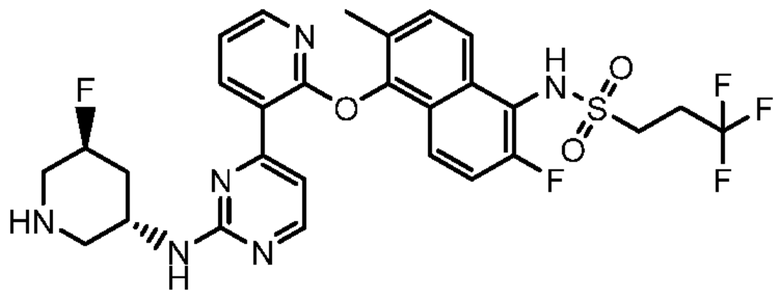
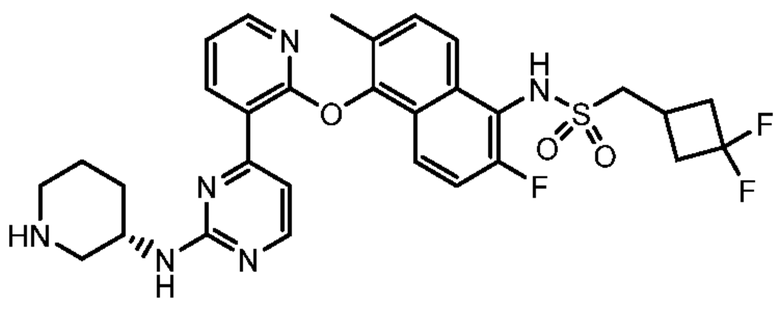
394		*(R)*-*N*-(2-Fluoro-6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-methoxypropane-1-sulfonamide	0.028
395		(1*R*,2*R*)-2-((6-Methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)cyclopentanol	0.109
396		(1*S*,2*S*)-2-((6-Methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)cyclopentanol	0.27
397		*N*-[2-Fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]butane-1-sulfonamide	0.034
398		3,3-Difluoro-*N*-[2-fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]propane-1-sulfonamide	0.022
399		2-Cyclopropyl-*N*-[2-fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]ethanesulfonamide	0.072
400		1-Cyclobutyl-*N*-[2-fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]methanesulfonamide	0.026

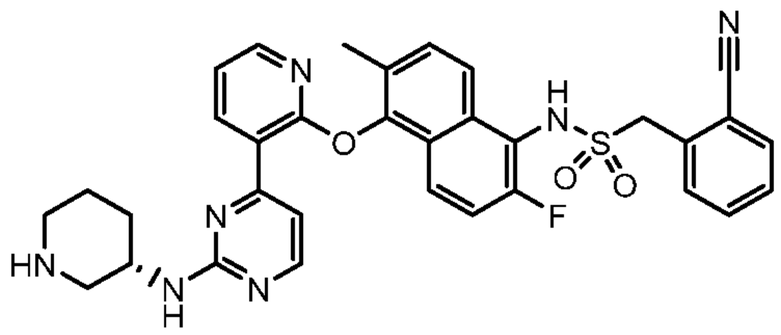
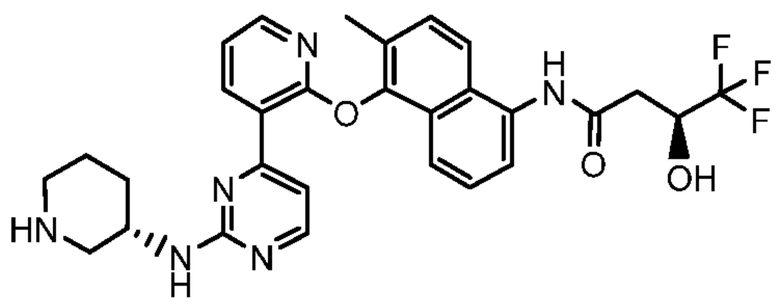
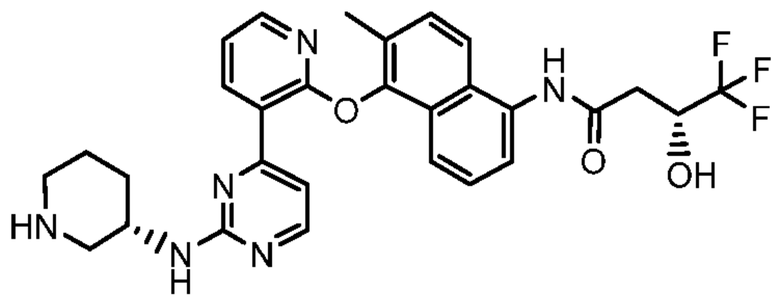
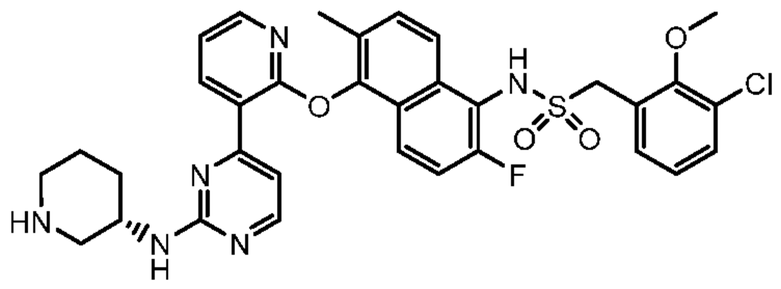
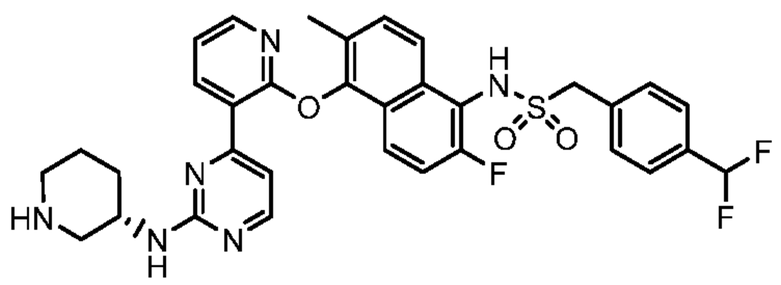
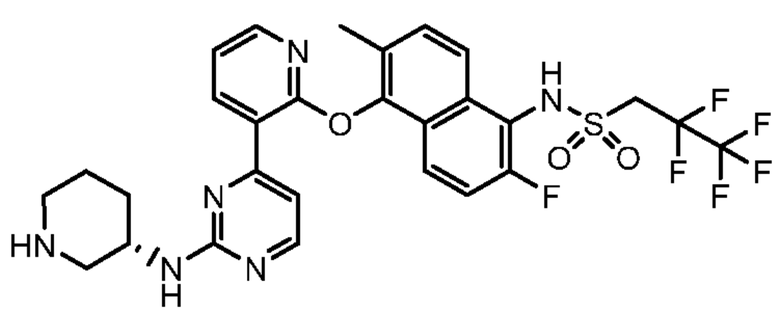
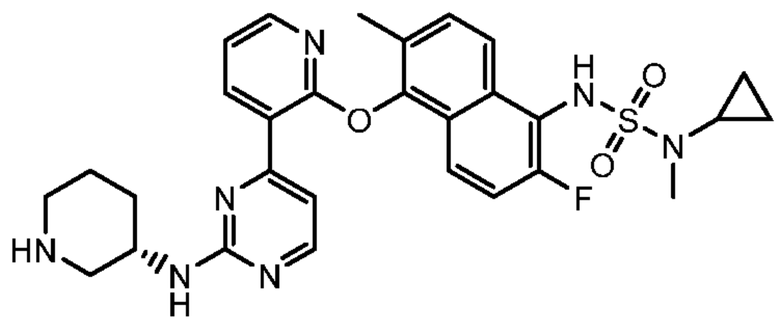
401		*N*-[2-Fluoro-6-methyl-5-[[3-[2-[[(3*S*,5*S*)-5-methyl-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]-2-methyl-propane-1-sulfonamide	0.067
402		*N*-[2-Fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]-1-thiazol-4-yl-methanesulfonamide	0.051
403		*N-[2-Fluoro-6-methyl-5-[[3-[2-[[(3S)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]-1,3-benzodioxole-5-sulfonamide*	0.044
404		*N*-(2-Fluoro-6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-methoxypropane-1-sulfonamide	0.034
405		1-Cyclopropyl-*N*-[2-fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]methanesulfonamide	0.025
406		3-Fluoro-*N*-[2-fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]propane-1-sulfonamide	0.031
407		(*E*)-4,4,4-Trifluoro-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]but-2-enamide	0.221

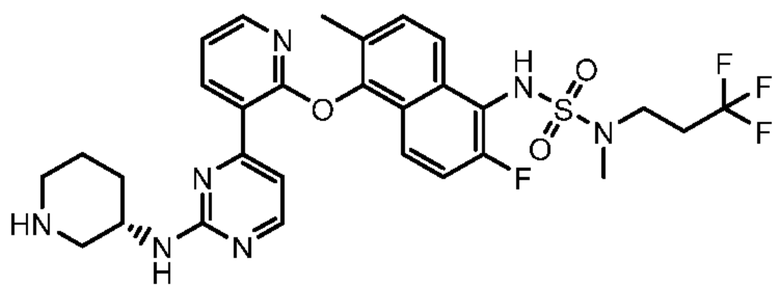
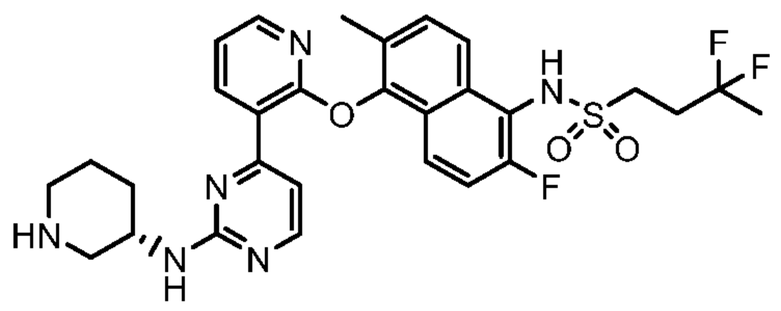
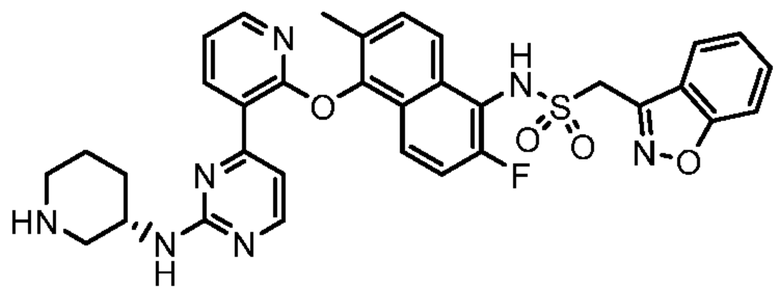
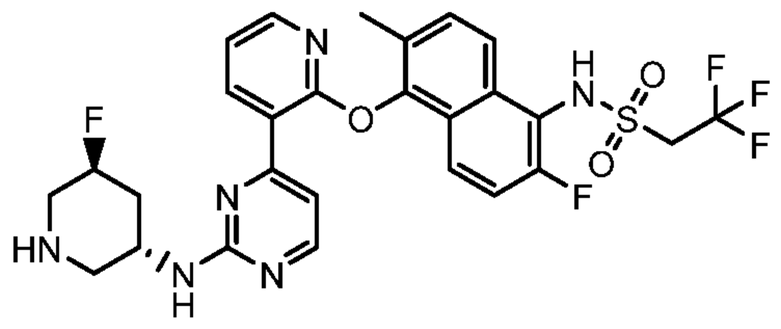
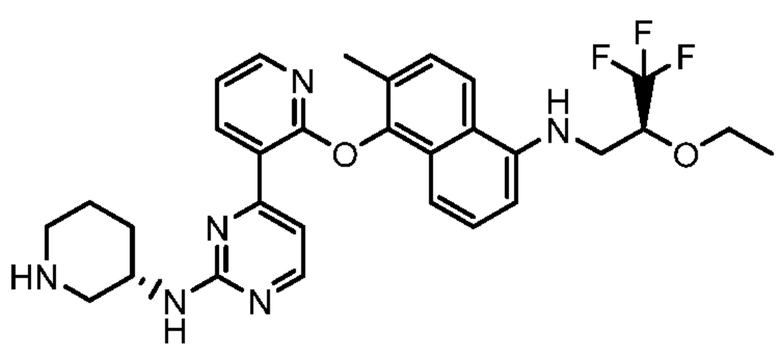
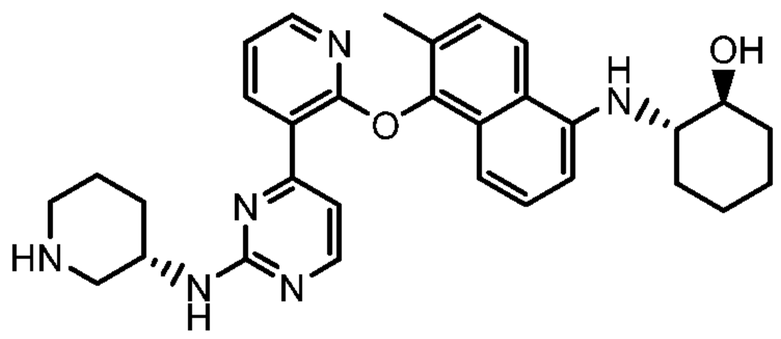
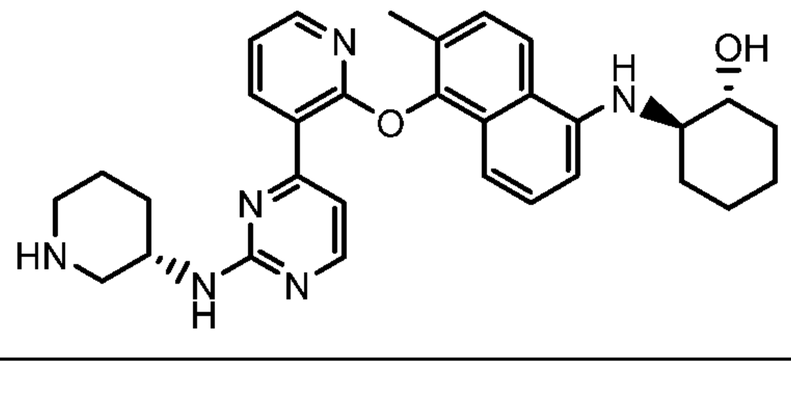
408		1-(6-Methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidin-3-ol	0.47 (Isomer 1)
409		*N*-(2-Fluoro-6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-methylbutane-1-sulfonamide	0.025
410		4-[2-[[5-[[Benzyl(methyl)sulfamoyl]amino]-6-fluoro-2-methyl-1-naphthyl]oxy]-3-pyridyl]-2-[[(3*S*)-3-piperidyl]amino]pyrimidine	0.087
411		*N*-[2-Fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]-1-(2-methylthiazol-4-yl)methanesulfonamide	0.012
412		*N*-[2-Fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]-1-(5-methylisoxazol-3-yl)methanesulfonamide	0.007

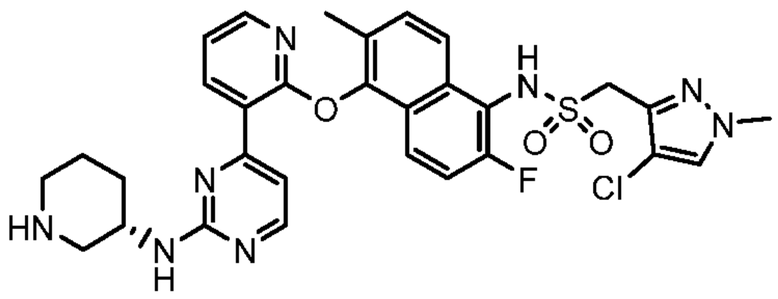
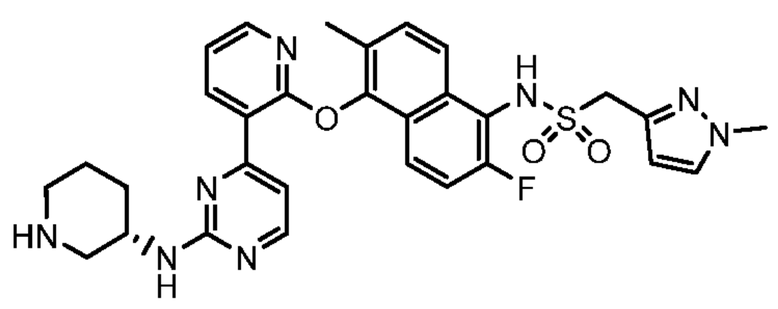
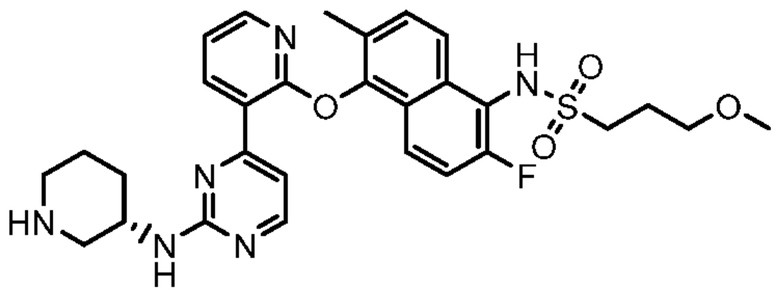
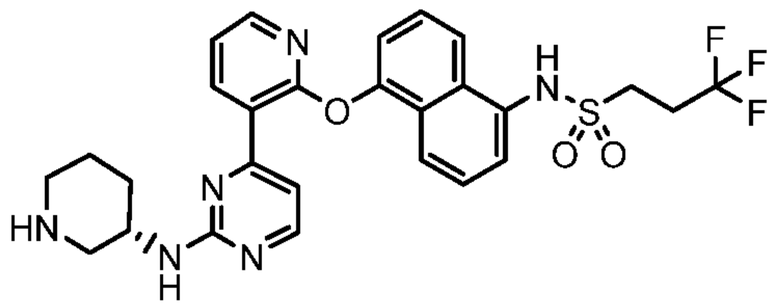
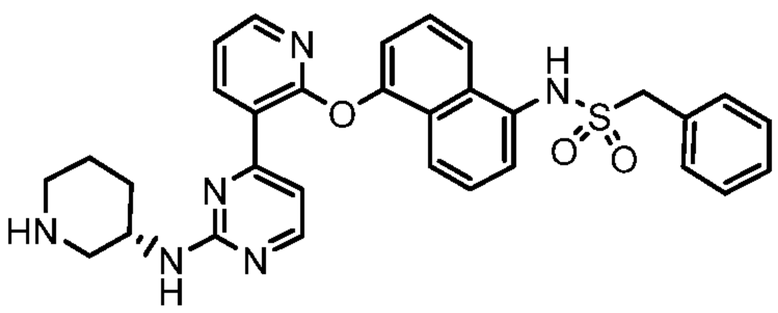
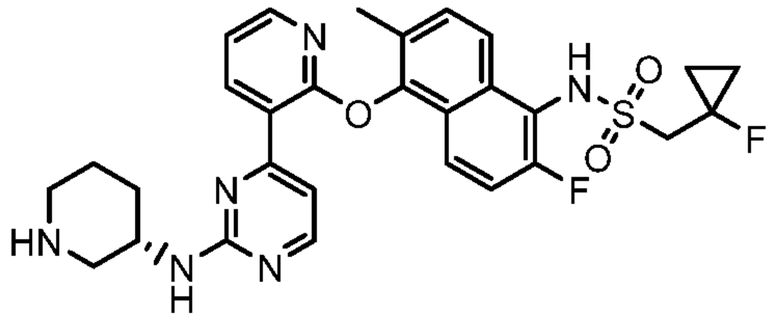
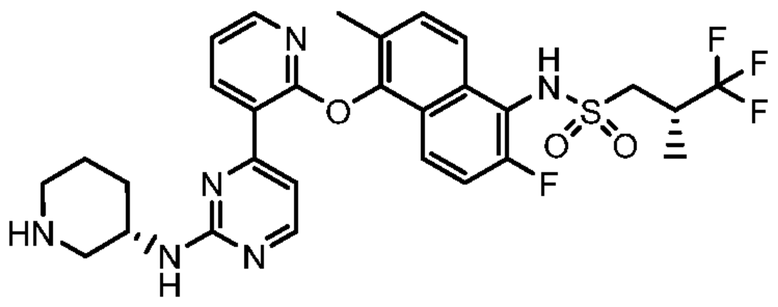
413		1-Cyclobutylidene-*N*-[2-fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]methanesulfonamide	0.05
414		(*R*)-2-Methyl-3-((6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)propanenitrile	0.059
415		(*S*)-2-Methyl-3-((6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)propanenitrile	0.269
416		*N*-(2-Fluoro-6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-((*S*)-tetrahydrofuran-2-yl)methanesulfonamide	0.105
417		*N*-(2-Fluoro-6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-((*R*)-tetrahydrofuran-2-yl)methanesulfonamide	0.074
418		*N*-[2-Fluoro-5-[[3-[2-[[(3*S*,5*S*)-5-fluoro-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-6-methyl-1-naphthyl]-1-phenyl-methanesulfonamide	0.002
419		*N*-[2-Fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]-1-[4-(trifluoromethoxy)phenyl]methanesulfonamide	0.129

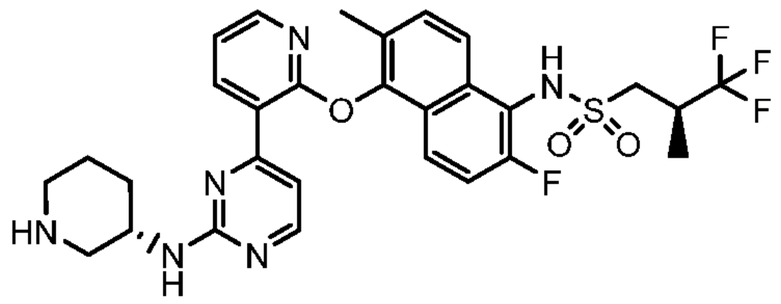
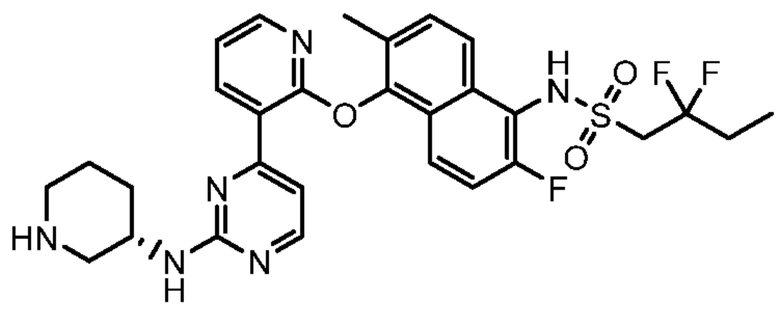
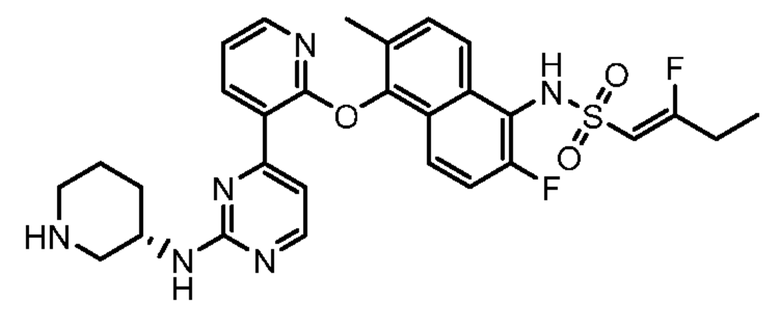
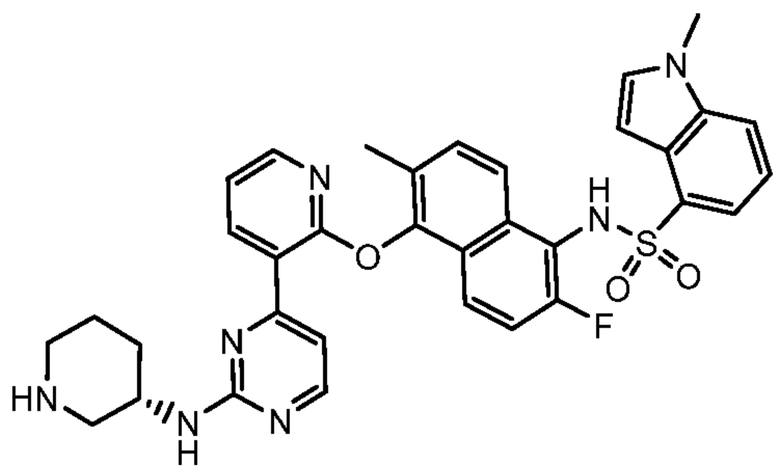
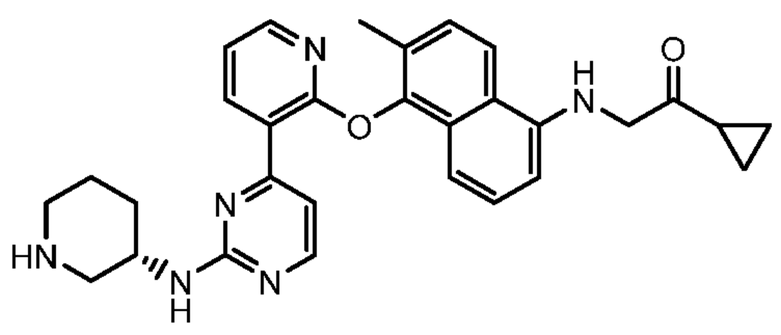
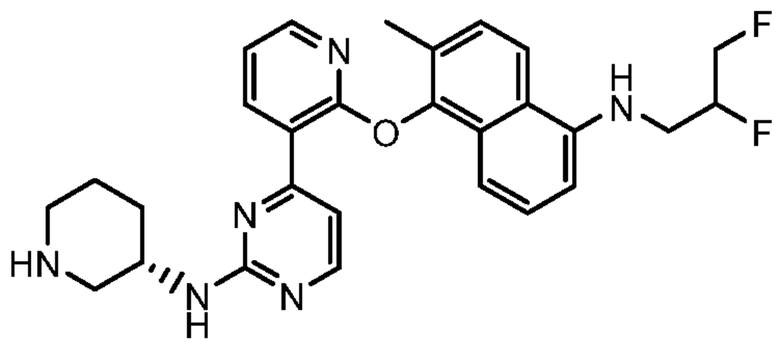
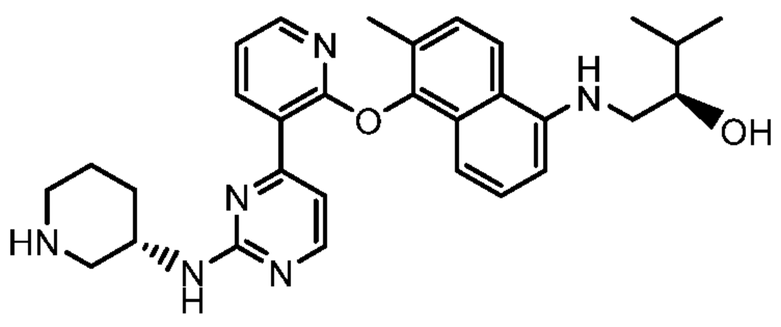
420		4-[2-[[6-Fluoro-2-methyl-5-[[methyl(propyl)sulfamoyl]amino]-1-naphthyl]oxy]-3-pyridyl]-2-[[(3*S*)-3-piperidyl]amino]pyrimidine	0.041
421		4-[2-[[5-[[Ethyl(methyl)sulfamoyl]amino]-6-fluoro-2-methyl-1-naphthyl]oxy]-3-pyridyl]-2-[[(3*S*)-3-piperidyl]amino]pyrimidine	0.044
422		(*R*)-3-Methyl-2-(((6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)methyl)butanenitrile	0.083
423		(*S*)-3-Methyl-2-(((6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)methyl)butanenitrile	0.207
424		*N*-[5-[[5-Methoxy-3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-6-methyl-1-naphthyl]propane-1-sulfonamide	0.392
425		1-(3-Cyanophenyl)-*N*-[2-fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]methanesulfonamide	0.016
426		1-(4-Cyanophenyl)-*N*-[2-fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]methanesulfonamide	0.005

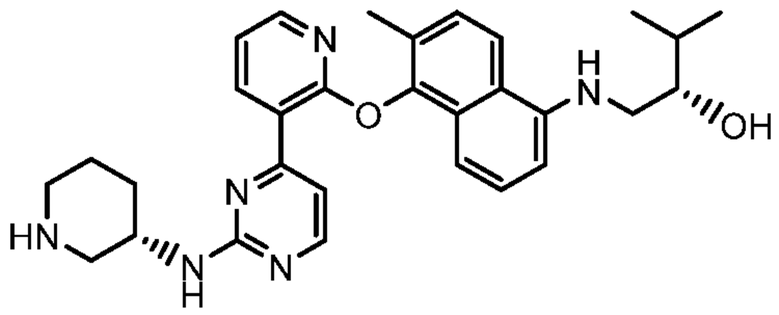
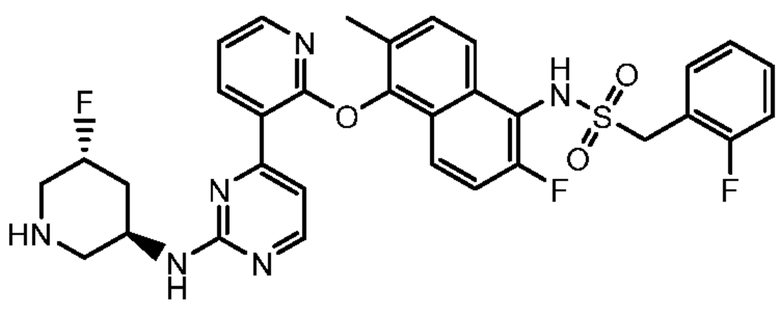
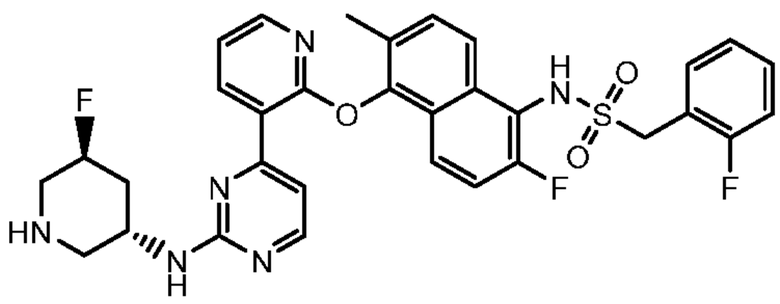
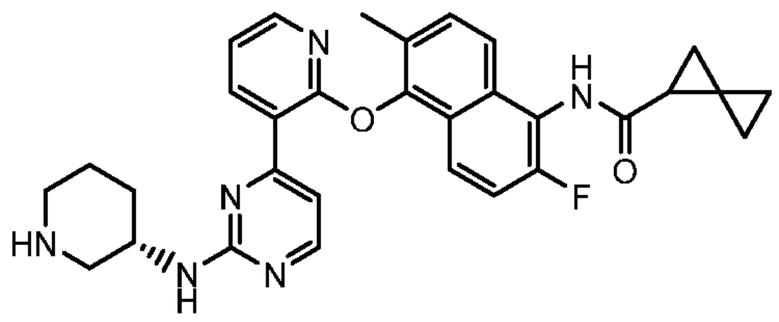
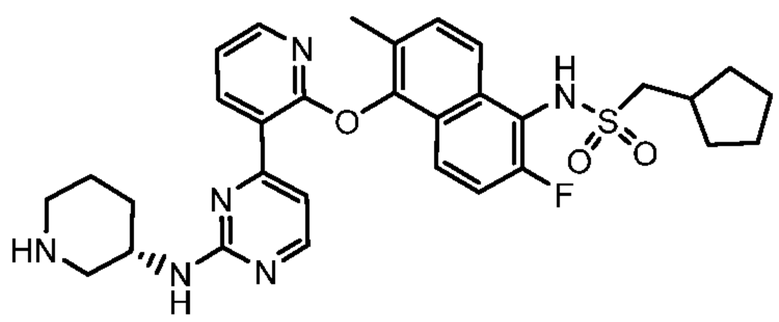
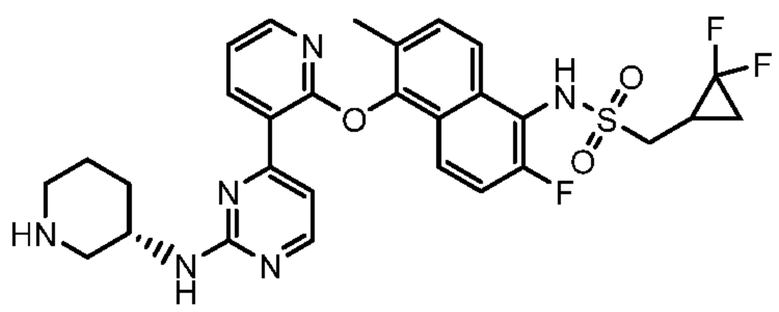
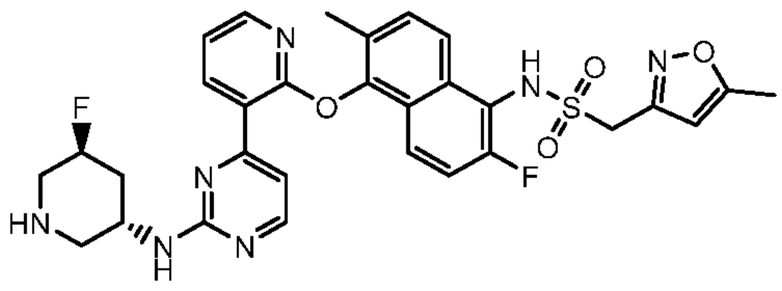
427		4-[2-[[6-Fluoro-2-methyl-5-[[methyl(2,2,2-trifluoroethyl)sulfamoyl]amino]-1-naphthyl]oxy]-3-pyridyl]-2-[[(3*S*)-3-piperidyl]amino]pyrimidine	0.006
428		*N*-[2-Fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]pyrrolidine-1-sulfonamide	0.028
429		*N*-[2-Fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]-1-(3-methoxyphenyl)methanesulfonamide	0.005
430		4-[2-[[5-(3-Methoxypropylamino)-2-methyl-1-naphthyl]oxy]-3-pyridyl]-*N*-[(3*S*)-3-piperidyl]pyrimidin-2-amine	0.275
431		*N*-[2-Fluoro-6-methyl-5-[[3-[2-[[(3*S*,5*R*)-5-methyl-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]-2-methoxy-ethanesulfonamide	0.034
432		3,3,3-Trifluoro-*N*-(2-fluoro-5-((3-(2-(((3*S*,5*S*)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)propane-1-sulfonamide	0.028
433		1-(3,3-Difluorocyclobutyl)-*N*-[2-fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]methanesulfonamide	0.076

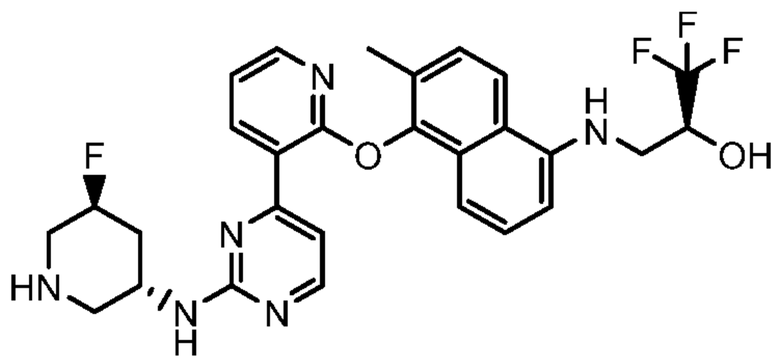
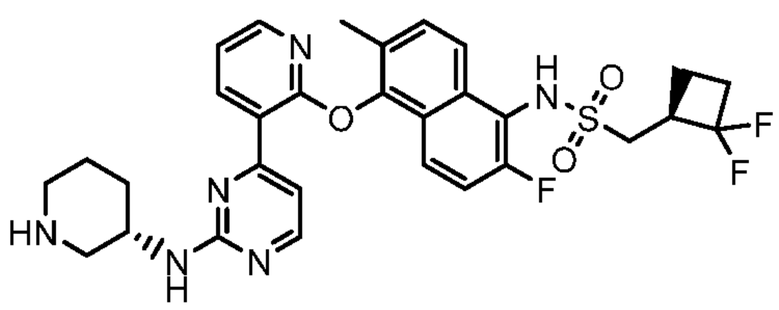
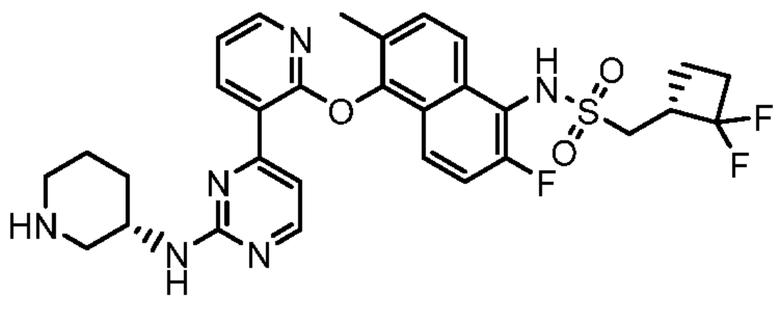
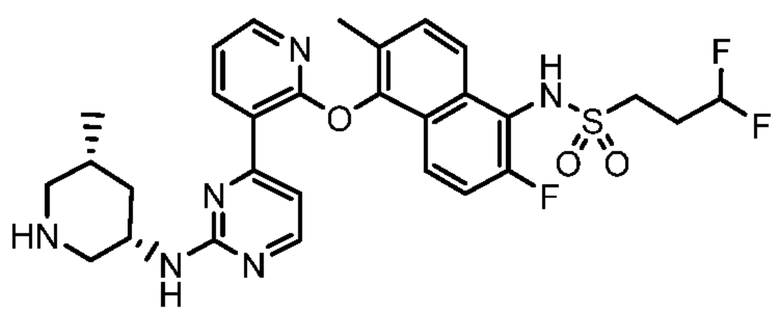
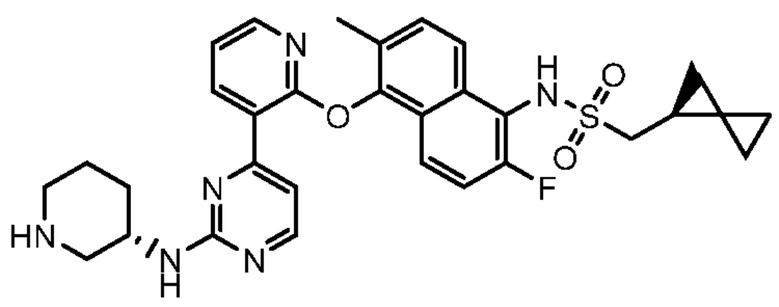
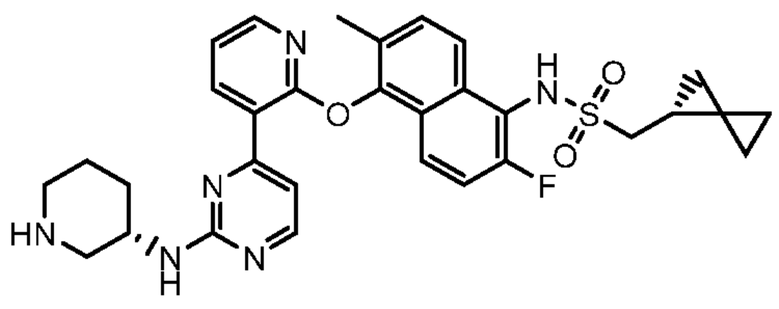
434		1-(2-Cyanophenyl)-*N*-[2-fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]methanesulfonamide	0.006
435		(*S*)-4,4,4-Trifluoro-3-hydroxy-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)butanamide	0.338
436		(*R*)-4,4,4-Trifluoro-3-hydroxy-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)butanamide	0.075
437		1-(3-Chloro-2-methoxy-phenyl)-*N*-[2-fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]methanesulfonamide	0.018
438		1-[4-(Difluoromethyl)phenyl]-*N*-[2-fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]methanesulfonamide	0.005
439		2,2,3,3,3-Pentafluoro-*N*-[2-fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]propane-1-sulfonamide	0.155
440		4-[2-[[5-[[Cyclopropyl(methyl)sulfamoyl]amino]-6-fluoro-2-methyl-1-naphthyl]oxy]-3-pyridyl]-2-[[(3*S*)-3-piperidyl]amino]pyrimidine	0.026

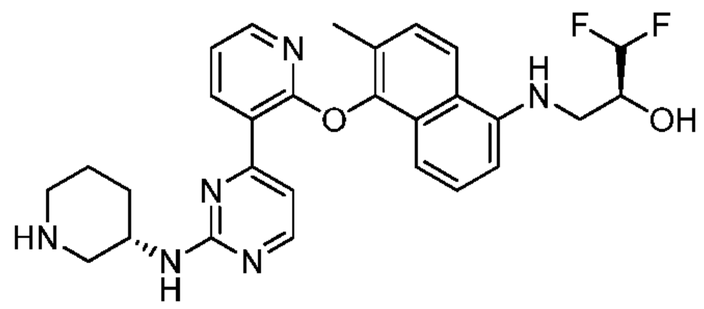
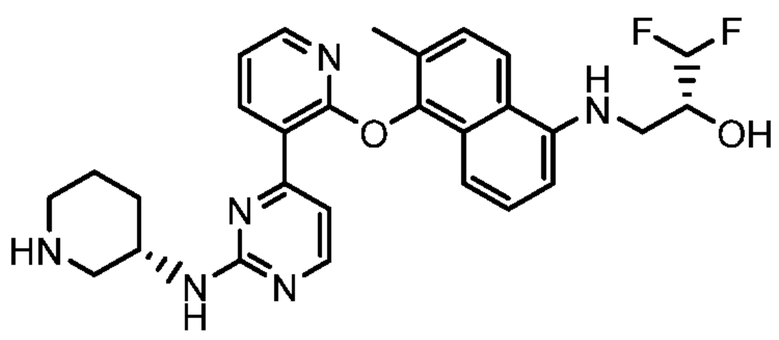
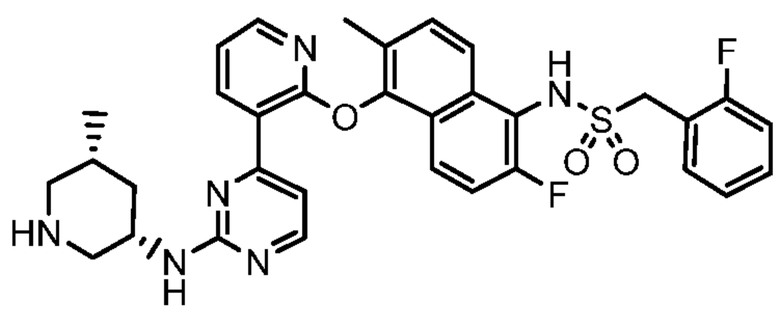
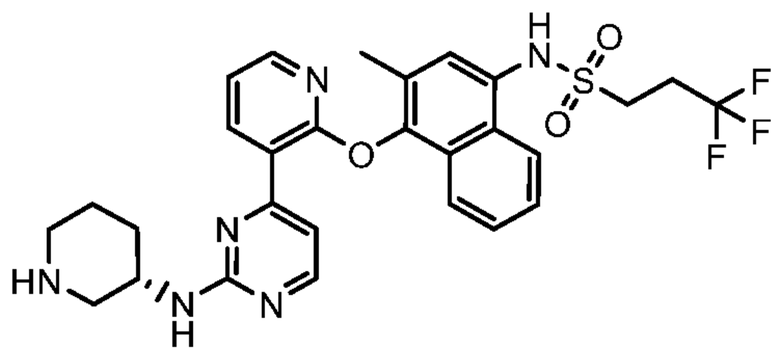
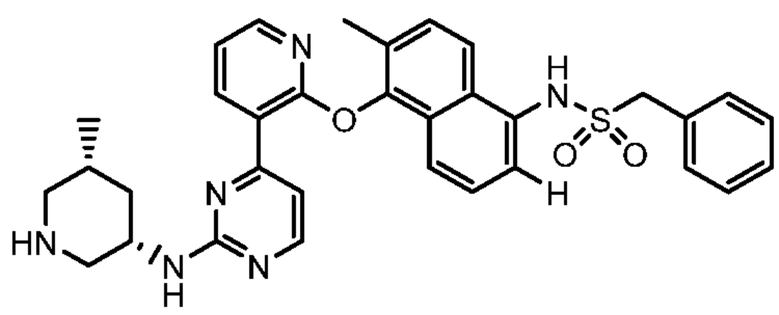
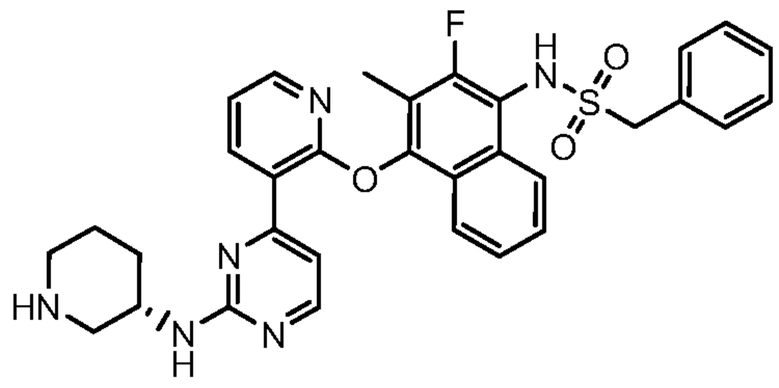
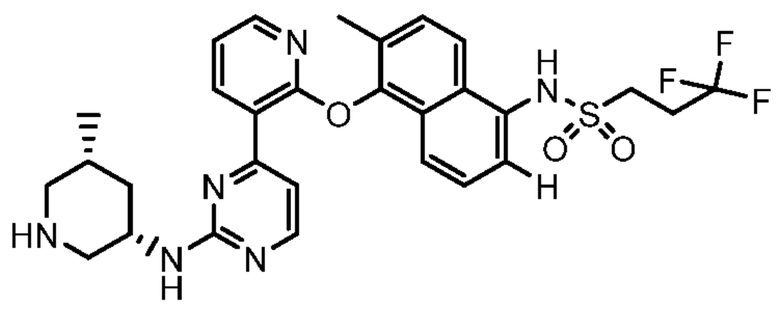
441		4-[2-[[6-Fluoro-2-methyl-5-[[methyl(3,3,3-trifluoropropyl)sulfamoyl]amino]-1-naphthyl]oxy]-3-pyridyl]-2-[[(3*S*)-3-piperidyl]amino]pyrimidine	0.048
442		3,3-Difluoro-*N*-[2-fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]butane-1-sulfonamide	0.04
443		1-(1,2-Benzoxazol-3-yl)-*N*-[2-fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]methanesulfonamide	0.008
444		2,2,2-Trifluoro-*N*-(2-fluoro-5-((3-(2-(((3*S*,5*S*)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)ethane-1-sulfonamide	0.019
445		4-[2-[[5-[[(2*S*)-2-Ethoxy-3,3,3-trifluoro-propyl]amino]-2-methyl-1-naphthyl]oxy]-3-pyridyl]-*N*-[(3S)-3-piperidyl]pyrimidin-2-amine	0.078
446		(1*S*,2*S*)-2-((6-Methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)cyclohexan-1-ol	0.067
447		(1*R*,2*R*)-2-((6-Methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)cyclohexan-1-ol	0.146

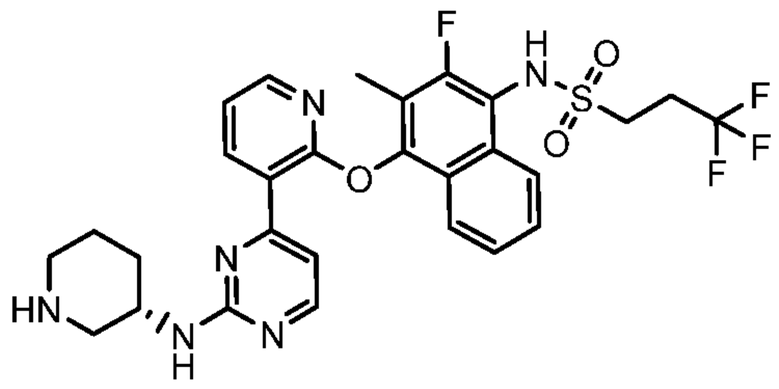
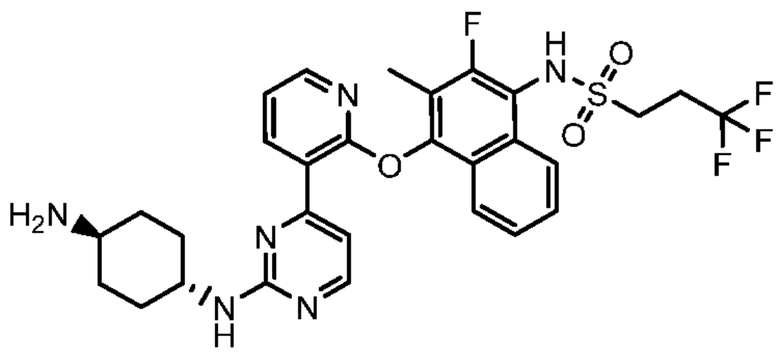
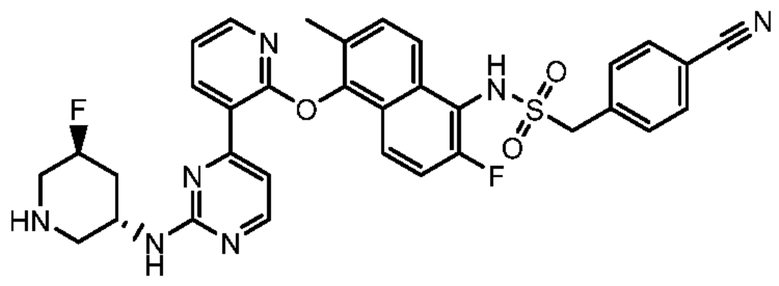
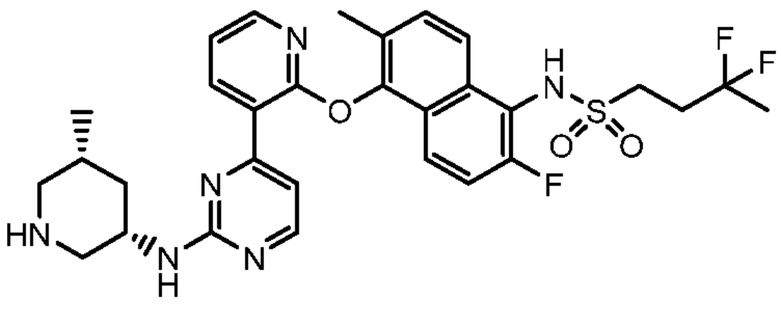
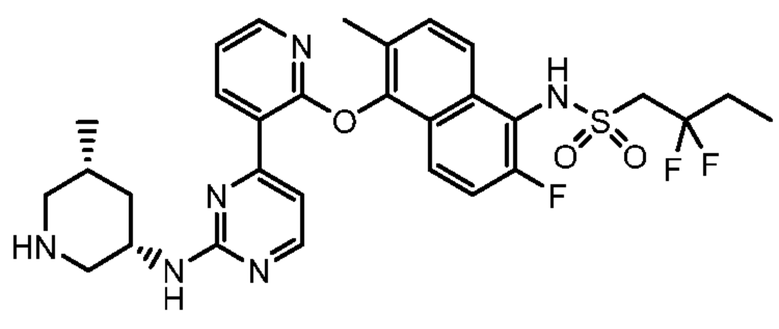
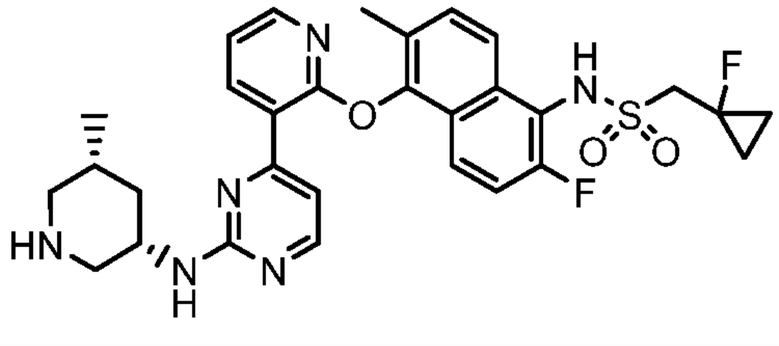
448		1-(4-Chloro-1-methyl-pyrazol-3-yl)-*N*-[2-fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]methanesulfonamide	0.019
449		*N*-[2-Fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]-1-(1-methylpyrazol-3-yl)methanesulfonamide	0.025
450		N-[2-Fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]-3-methoxy-propane-1-sulfonamide	0.104
451		3,3,3-Trifluoro-*N*-[5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]propane-1-sulfonamide	0.345
452		1-Phenyl-*N*-[5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]methanesulfonamide	0.019
453		1-(1-Fluorocyclopropyl)-*N*-[2-fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]methanesulfonamide	0.018
454		(*S*)-3,3,3-Trifluoro-*N*-(2-fluoro-6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-methylpropane-1-sulfonamide	0.024

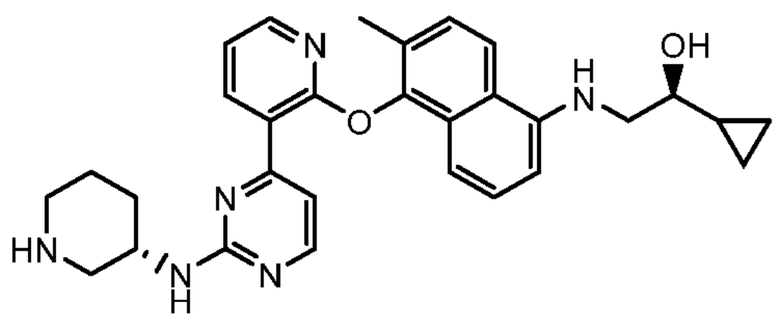
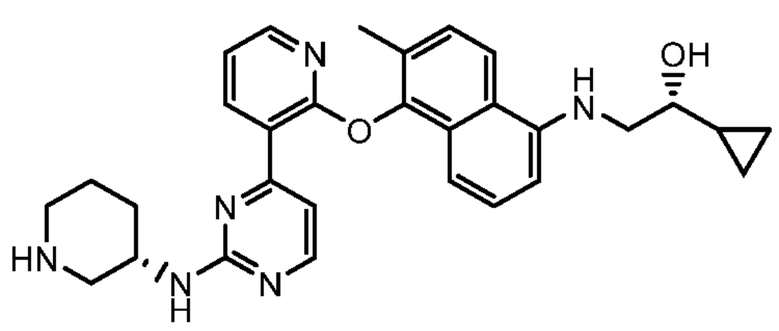
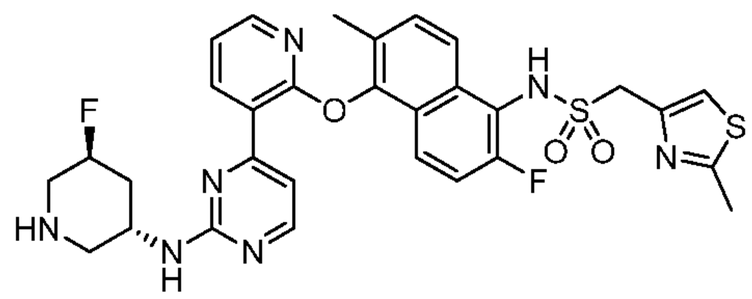
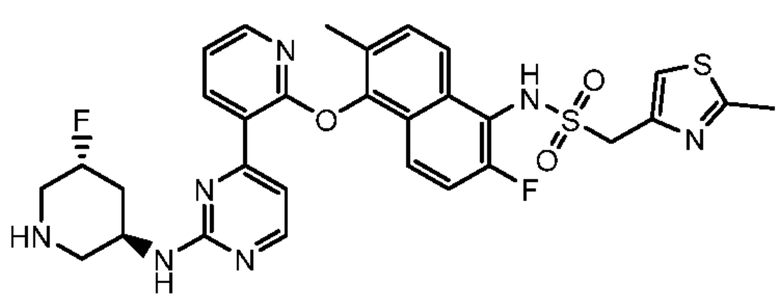
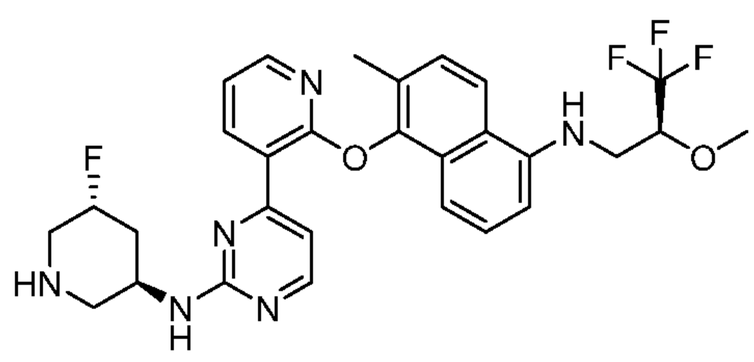
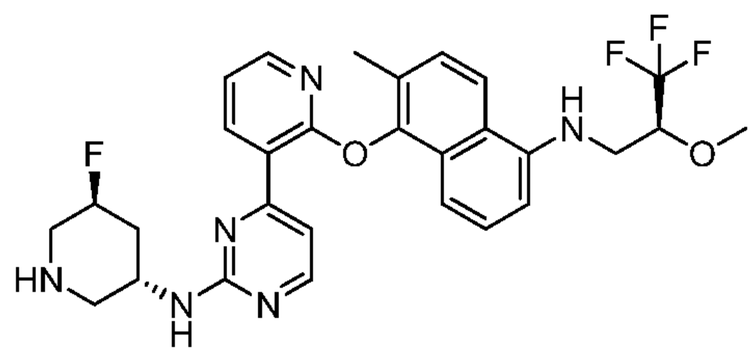
455		(*R*)-3,3,3-Trifluoro-*N*-(2-fluoro-6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-methylpropane-1-sulfonamide	0.018
456		2,2-Difluoro-*N*-[2-fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]butane-1-sulfonamide	0.011
457		(*Z*)-2-Fluoro-*N*-[2-fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]but-1-ene-1-sulfonamide	0.105
458		*N*-[2-Fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]-1-methyl-indole-4-sulfonamide	0.019
459		1-Cyclopropyl-2-[[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]amino]ethanone	0.312
460		4-(2-((5-((2,3-Difluoropropyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-*N*-((*S*)-piperidin-3-yl)pyrimidin-2-amine	0.092
461		(*R*)-3-Methyl-1-((6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)butan-2-ol	0.042

462		(*S*)-3-Methyl-1-((6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)butan-2-ol	0.11
463		*N*-(2-Fluoro-5-((3-(2-(((3*R*,5*R*)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)-1-(2-fluorophenyl)methanesulfonamide	0.268
464		*N*-(2-Fluoro-5-((3-(2-(((3*S*,5*S*)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)-1-(2-fluorophenyl)methanesulfonamide	0.004
465		*N*-(2-Fluoro-6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)spiro[2.2]pentane-1-carboxamide	0.057
466		1-Cyclopentyl-*N*-[2-fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]methanesulfonamide	0.057
467		1-(2,2-Difluorocyclopropyl)-*N*-(2-fluoro-6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide	0.042
468		*N*-(2-Fluoro-5-((3-(2-(((3*S*,5*S*)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)-1-(5-methylisoxazol-3-yl)methanesulfonamide	0.01

469		(*S*)-1,1,1-Trifluoro-3-((5-((3-(2-(((3*S*,5*S*)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)amino)propan-2-ol	0.005
470		1-((*S*)-2,2-Difluorocyclobutyl)-*N*-(2-fluoro-6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide	0.024
471		1-((*R*)-2,2-Difluorocyclobutyl)-*N*-(2-fluoro-6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide	0.017
472		3,3-Difluoro-*N*-[2-fluoro-6-methyl-5-[[3-[2-[[(3*S*,5*R*)-5-methyl-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]propane-1-sulfonamide	0.008
473		N-(2-Fluoro-6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-((*S*)-spiro[2.2]pentan-1-yl)methanesulfonamide	0.076
474		N-(2-Fluoro-6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-((*R*)-spiro[2.2]pentan-1-yl)methanesulfonamide	0.052

475		(*S*)-1,1-Difluoro-3-((6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)propan-2-ol	0.019
476		(*R*)-1,1-Difluoro-3-((6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)propan-2-ol	0.129
477		*N*-[2-Fluoro-6-methyl-5-[[3-[2-[[(3*S*,5*R*)-5-methyl-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]-1-(2-fluorophenyl)methanesulfonamide	0.007
478		3,3,3-Trifluoro-*N*-[3-methyl-4-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]propane-1-sulfonamide	0.118
479		*N*-[6-Methyl-5-[[3-[2-[[(3*S*,5*R*)-5-methyl-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]-1-phenyl-methanesulfonamide	0.012
480		*N*-[2-Fluoro-3-methyl-4-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]-1-phenyl-methanesulfonamide	0.007
481		3,3,3-Trifluoro-*N*-[6-methyl-5-[[3-[2-[[(3*S*,5*R*)-5-methyl-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]propane-1-sulfonamide	0.07

482		3,3,3-Trifluoro-*N*-[2-fluoro-3-methyl-4-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]propane-1-sulfonamide	0.065
483		*N*-(4-((3-(2-(((*trans*)-4-Aminocyclohexyl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-2-fluoro-3-methylnaphthalen-1-yl)-3,3,3-trifluoropropane-1-sulfonamide	0.146
484		1-(4-Cyanophenyl)-*N*-(2-fluoro-5-((3-(2-(((3*S*,5*S*)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)methanesulfonamide	0.005
485		3,3-Difluoro-*N*-[2-fluoro-6-methyl-5-[[3-[2-[[(3*S*,5*R*)-5-methyl-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]butane-1-sulfonamide	0.006
486		2,2-Difluoro-*N*-[2-fluoro-6-methyl-5-[[3-[2-[[(3*S*,5*R*)-5-methyl-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]butane-1-sulfonamide	0.003
487		1-(1-Fluorocyclopropyl)-*N*-[2-fluoro-6-methyl-5-[[3-[2-[[(3*S*,5*R*)-5-methyl-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]methanesulfonamide	0.009

488		(*S*)-1-Cyclopropyl-2-((6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)ethan-1-ol	0.03
489		(*R*)-1-Cyclopropyl-2-((6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)ethan-1-ol	0.132
490		*N*-(2-Fluoro-5-((3-(2-(((3*S*,5*S*)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)-1-(2-methylthiazol-4-yl)methanesulfonamide	0.004
491		*N*-(2-Fluoro-5-((3-(2-(((3*R*,5*R*)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)-1-(2-methylthiazol-4-yl)methanesulfonamide	0.117
492		*N*-((3*R*,5*R*)-5-Fluoropiperidin-3-yl)-4-(2-((2-methyl-5-(((*S*)-3,3,3-trifluoro-2-methoxypropyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-amine	
493		*N*-((3*S*,5*S*)-5-Fluoropiperidin-3-yl)-4-(2-((2-methyl-5-(((*S*)-3,3,3-trifluoro-2-methoxypropyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-amine	0.021

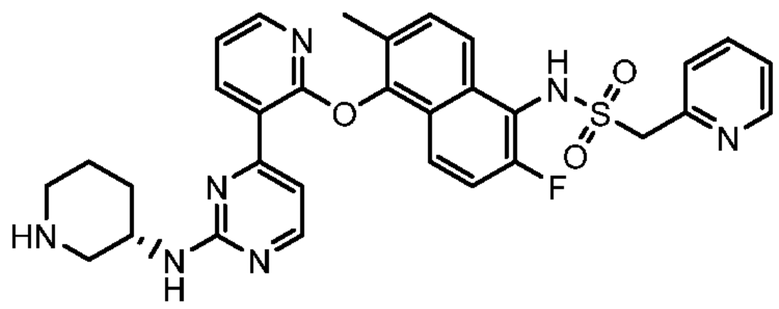
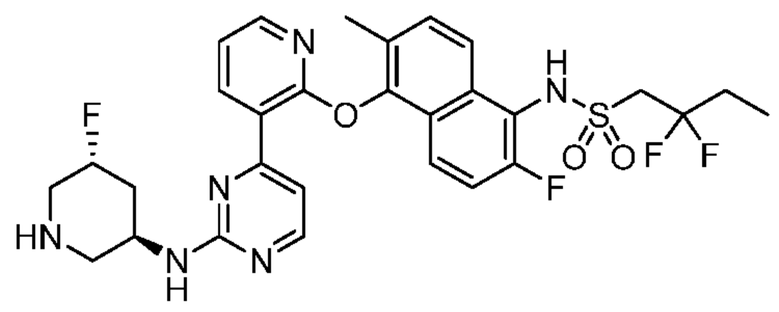
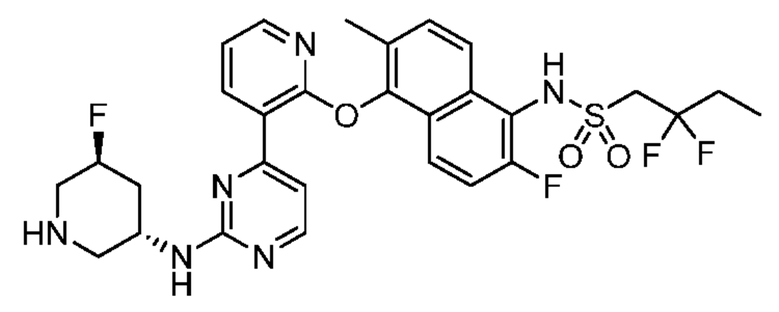
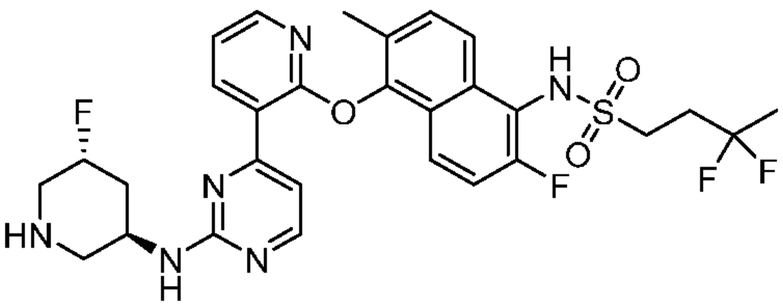
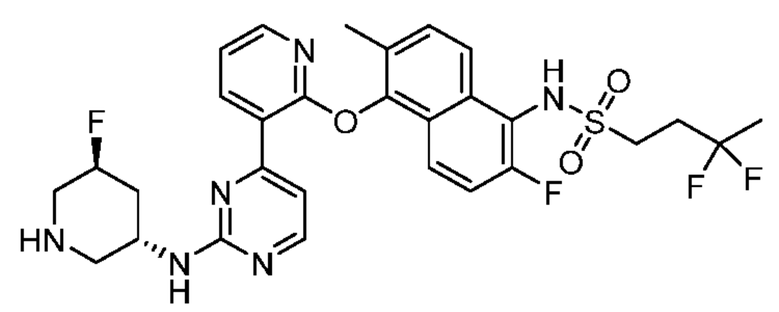
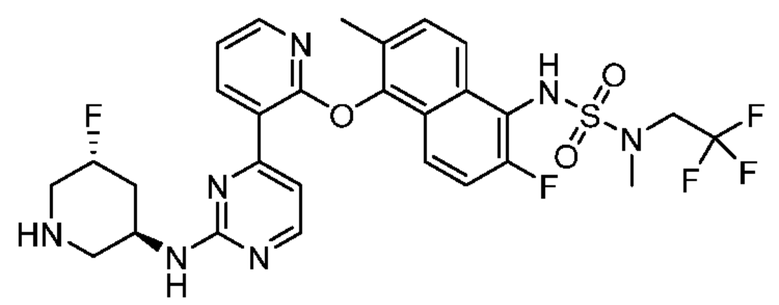
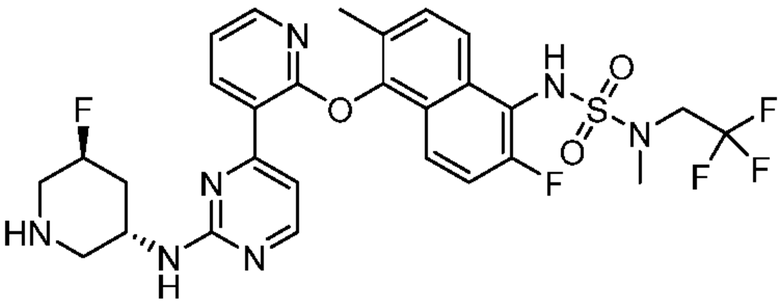
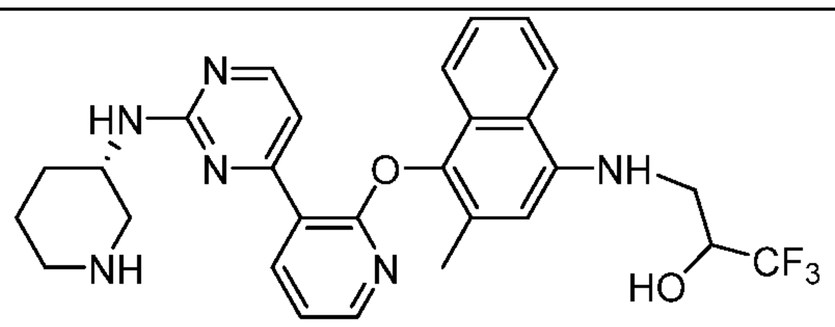
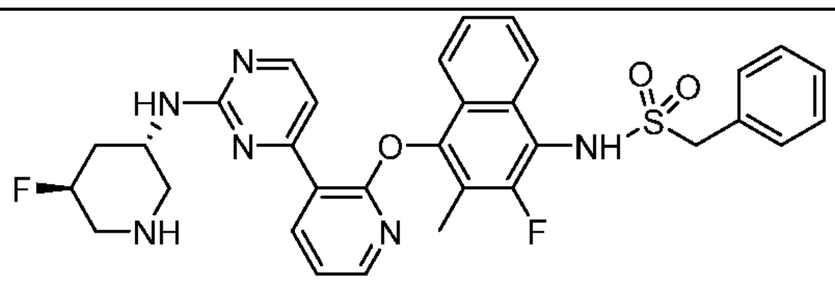
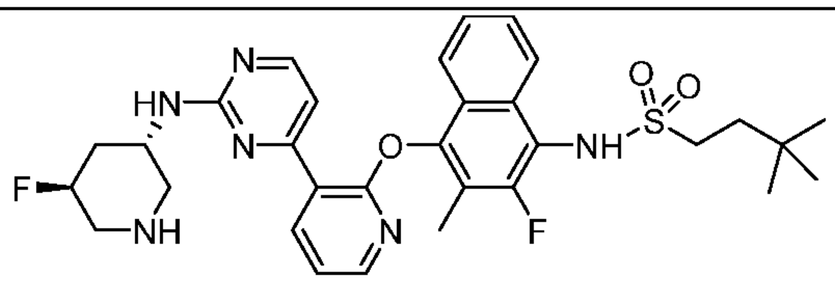
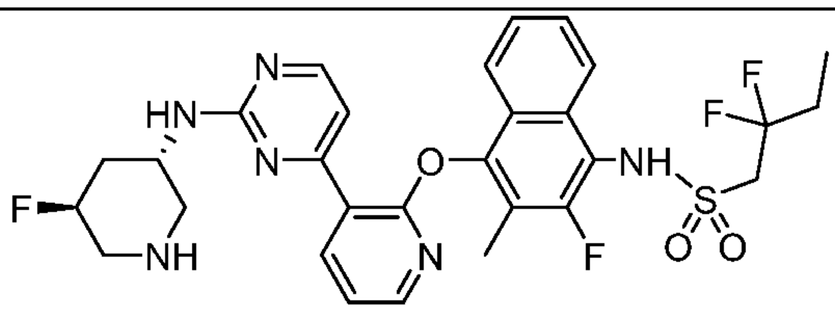
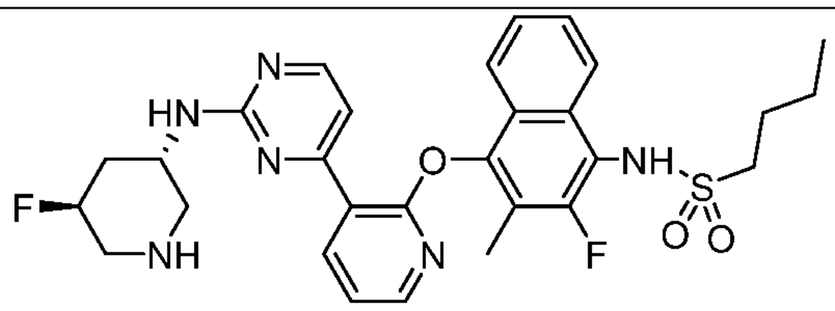
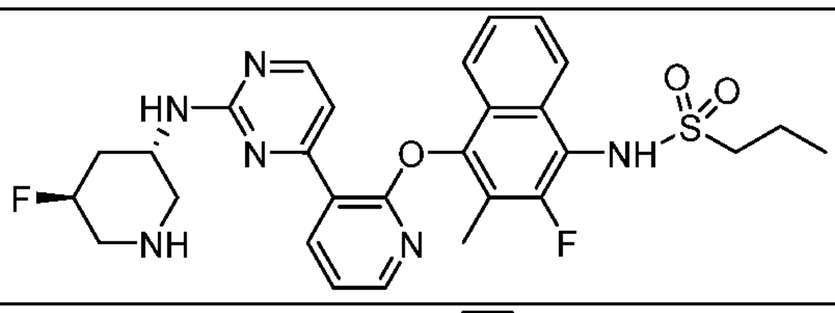
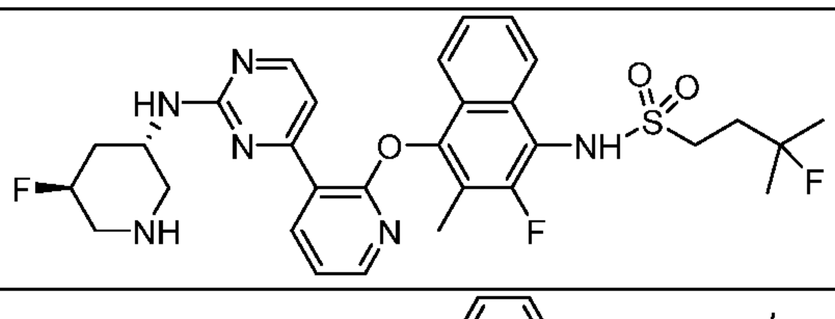
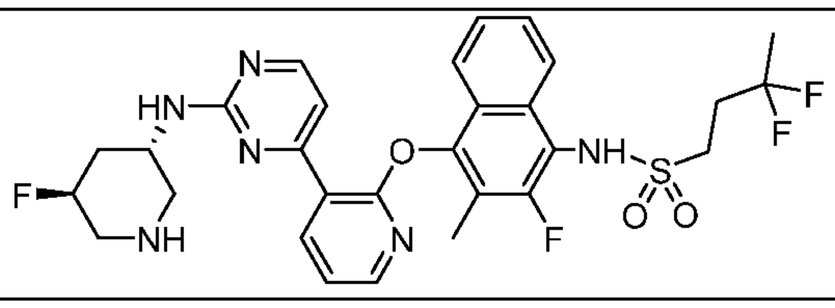
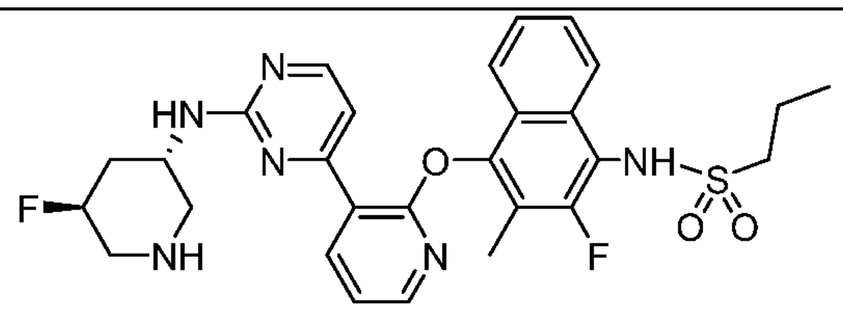
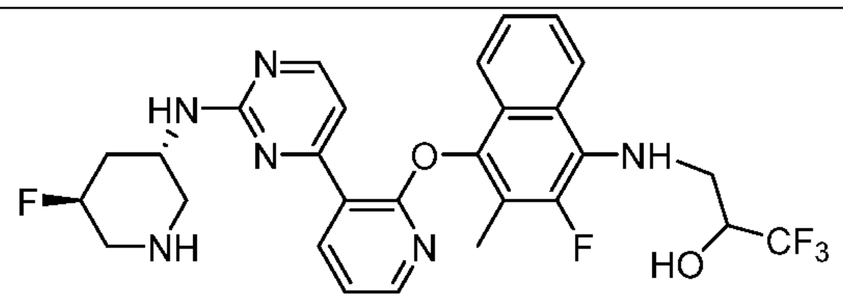
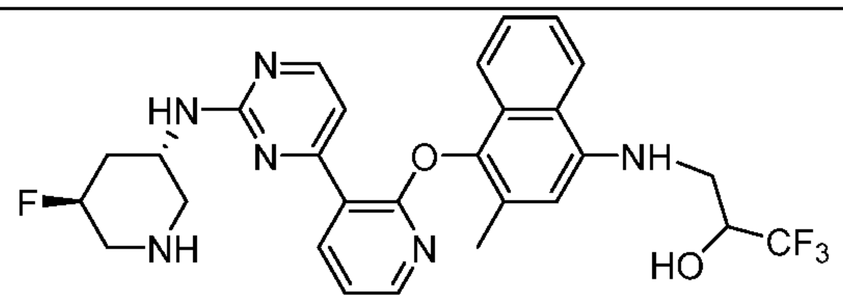
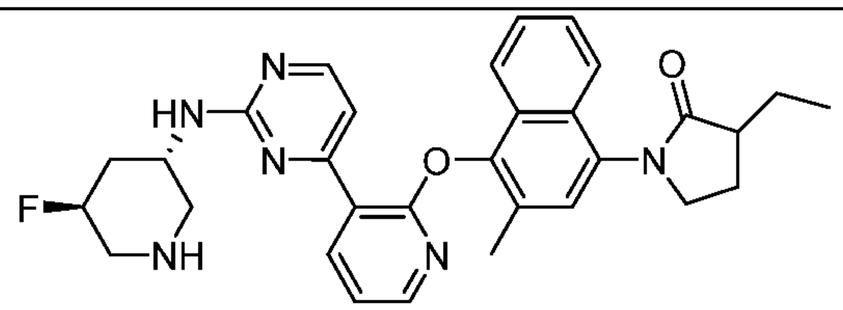
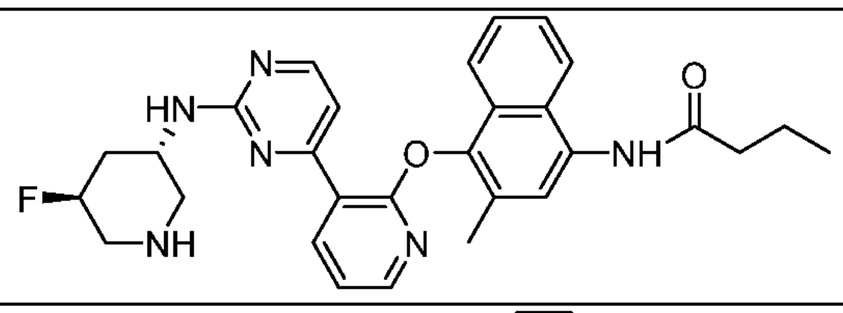
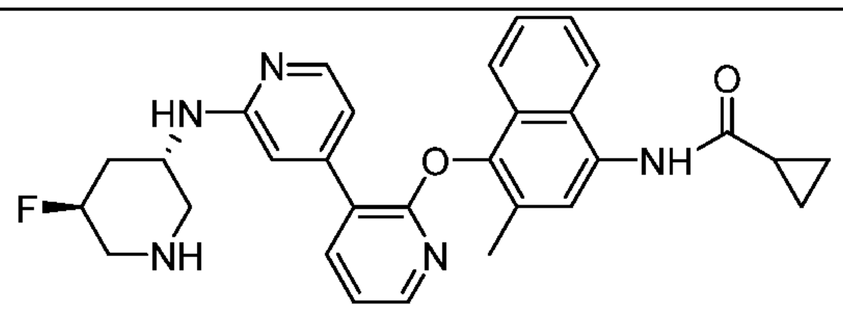
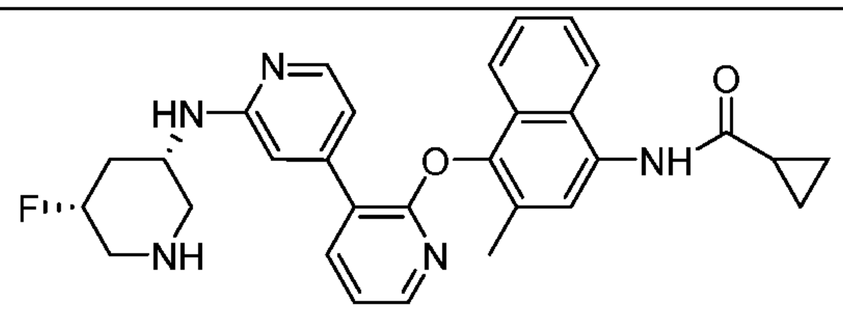
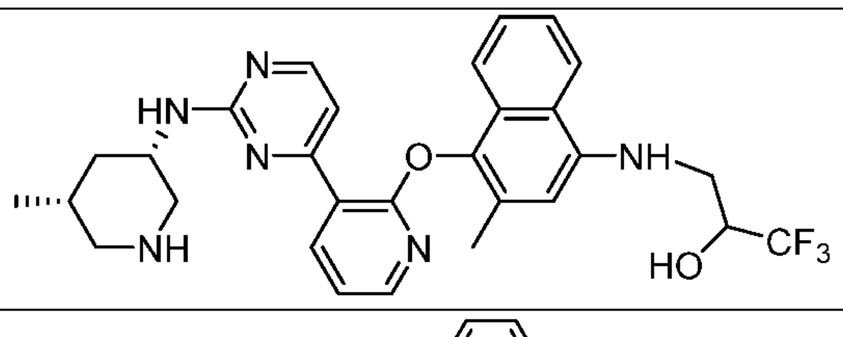
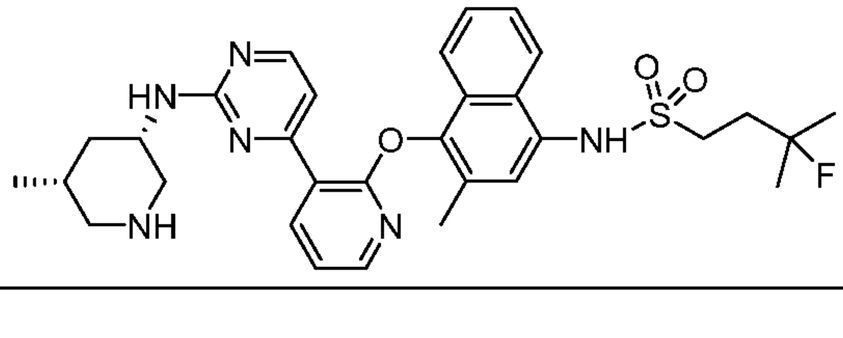
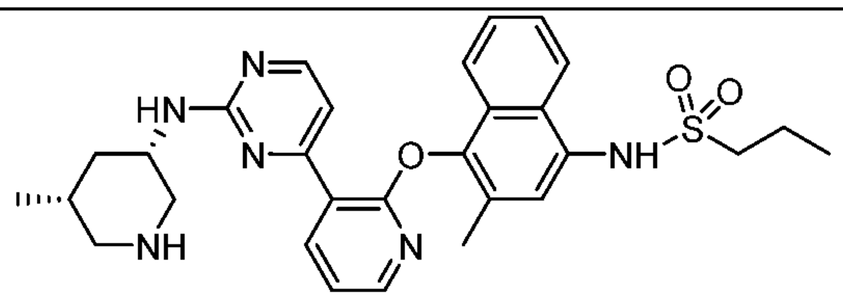
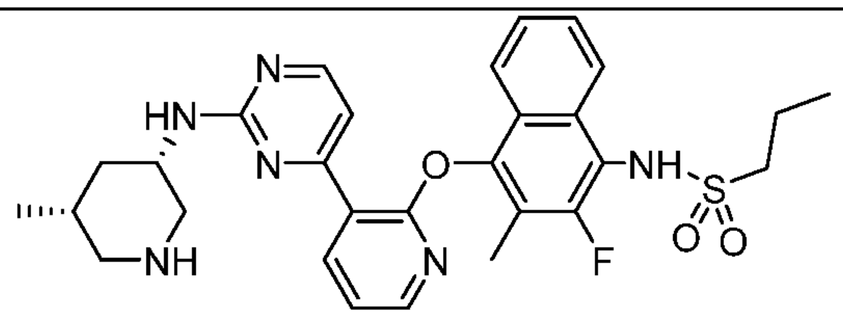
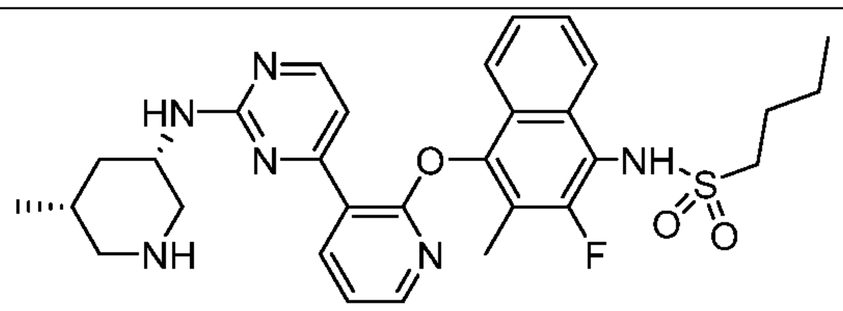
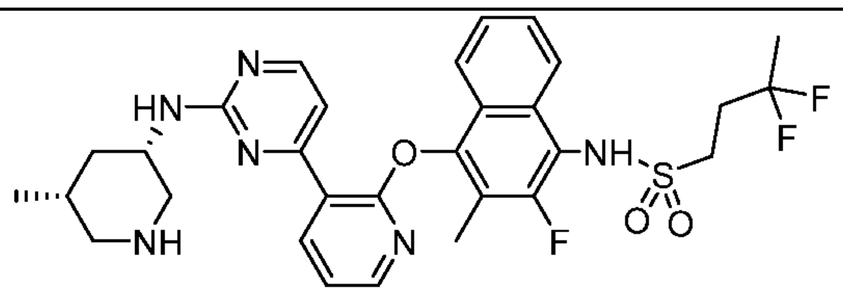
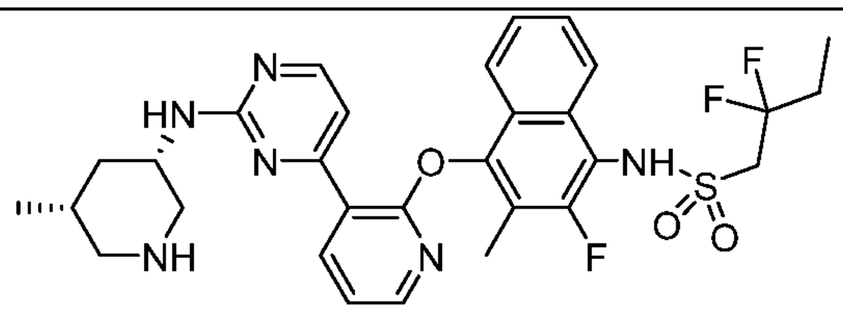
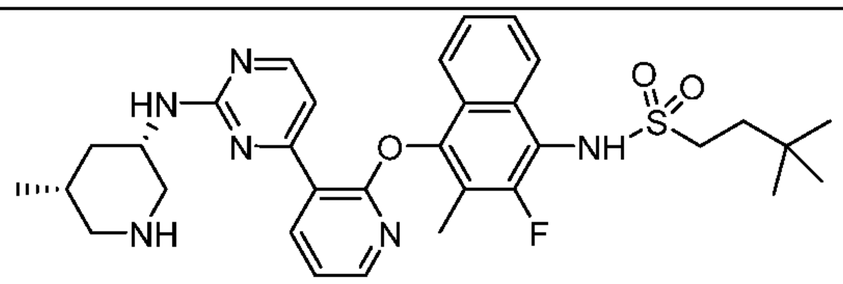
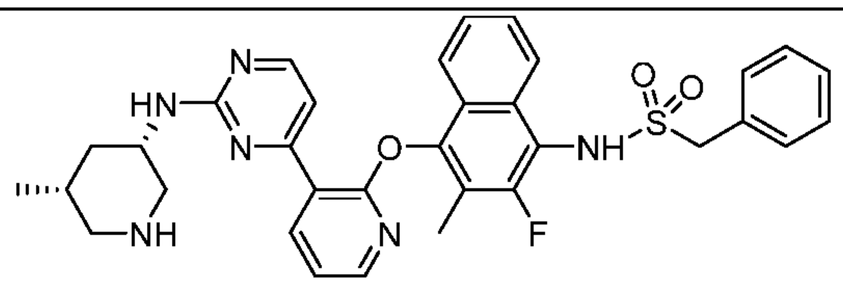
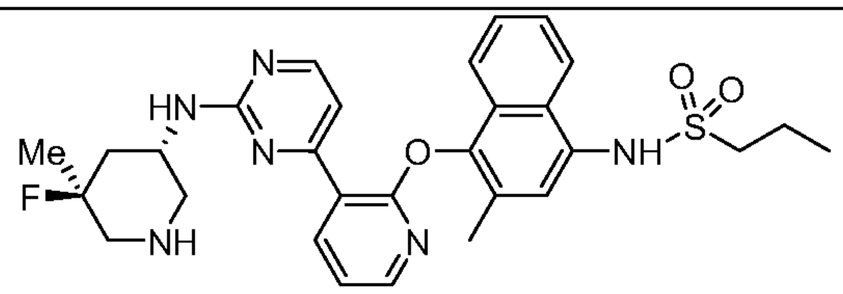
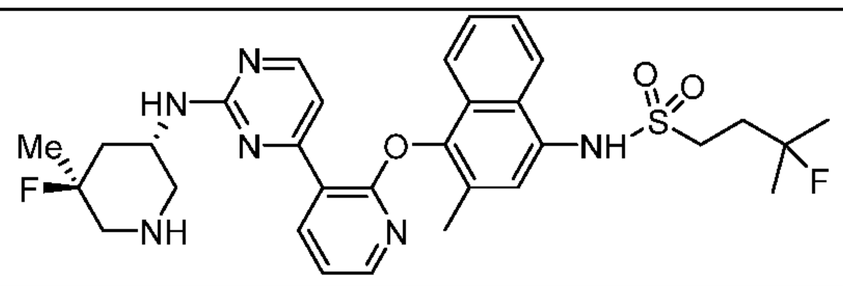
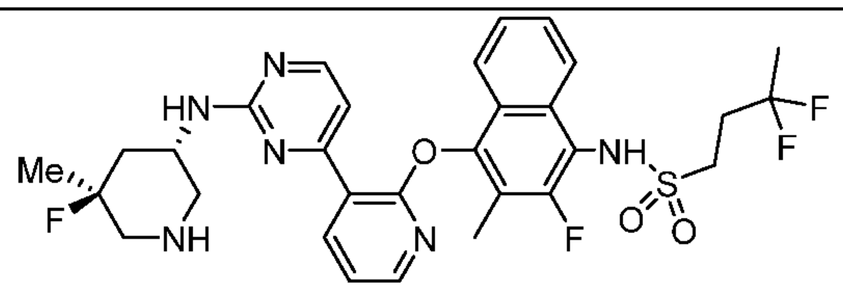
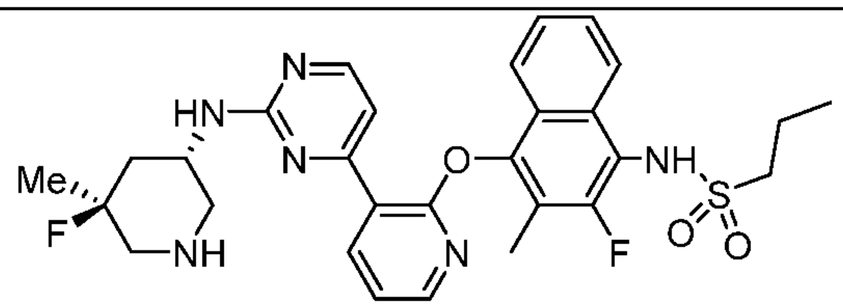
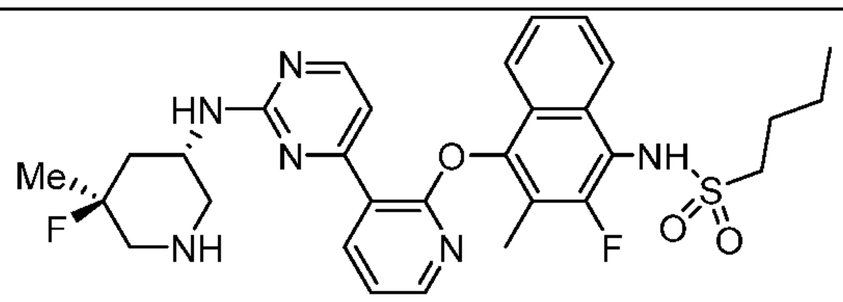
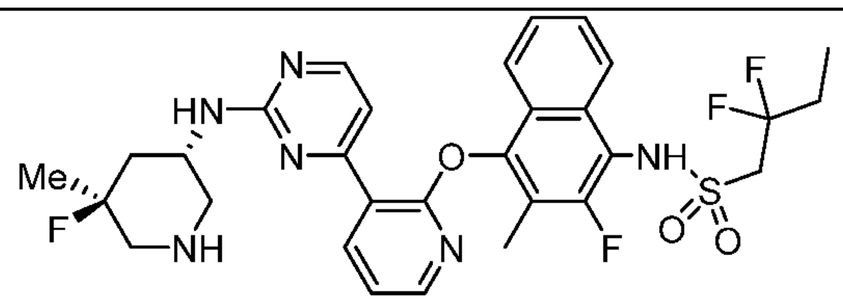
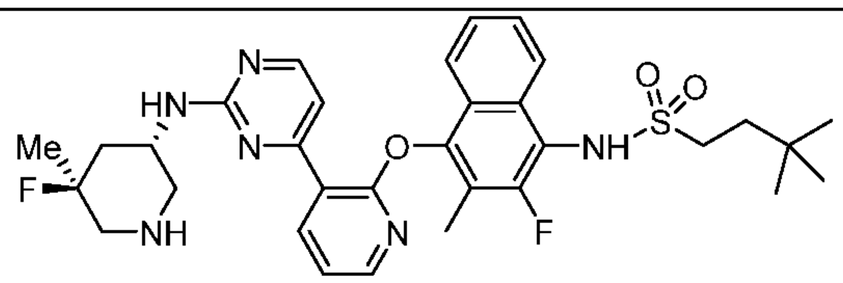
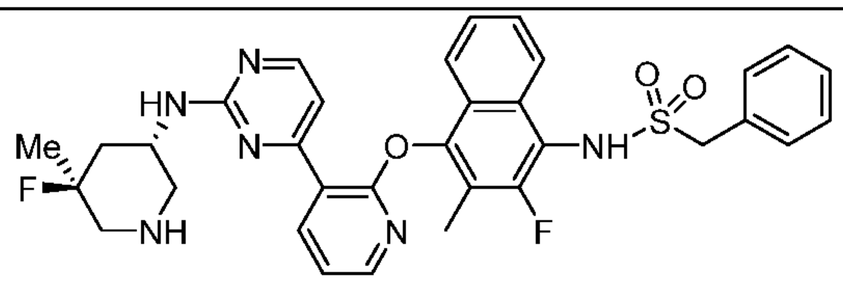
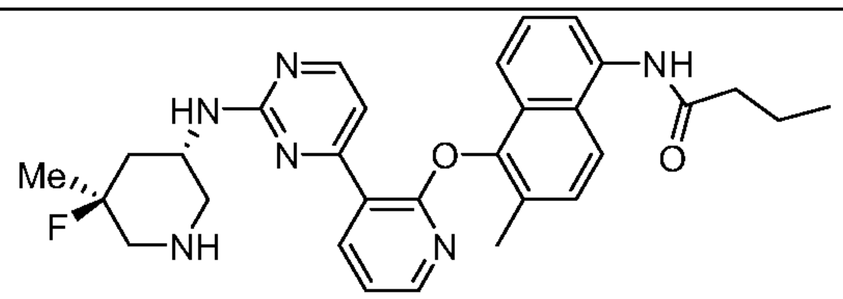
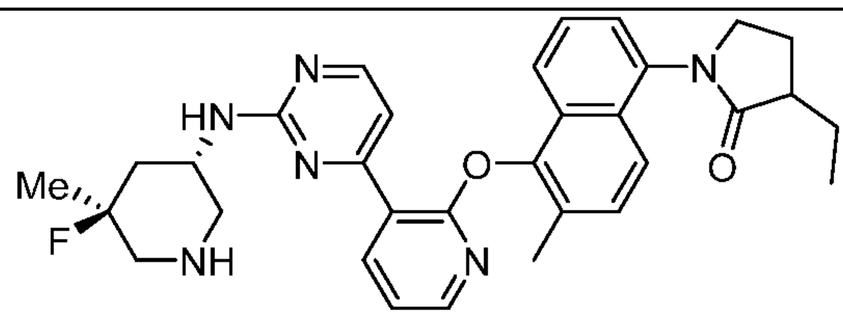
494		*N*-[2-Fluoro-6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]-1-(2-pyridyl)methanesulfonamide	0.0125
495		2,2-Difluoro-*N*-(2-fluoro-5-((3-(2-(((3*R*,5*R*)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)butane-1-sulfonamide	0.469
496		2,2-Difluoro-*N*-(2-fluoro-5-((3-(2-(((3*S*,5*S*)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)butane-1-sulfonamide	0.0179
497		3,3-Difluoro-*N*-(2-fluoro-5-((3-(2-(((3*R*,5*R*)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)butane-1-sulfonamide	5.1
498		3,3-Difluoro-*N*-(2-fluoro-5-((3-(2-(((3*S*,5*S*)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)butane-1-sulfonamide	0.033
499		4-[2-[[6-Fluoro-2-methyl-5-[[methyl(2,2,2-trifluoroethyl)sulfamoyl]amino]-1-naphthyl]oxy]-3-pyridyl]-2-[[(3*R*,5*R*)-5-fluoro-3-piperidyl]amino]pyrimidine	0.68
500		4-[2-[[6-Fluoro-2-methyl-5-[[methyl(2,2,2-trifluoroethyl)sulfamoyl]amino]-1-naphthyl]oxy]-3-pyridyl]-2-[[(3*S*,5*S*)-5-fluoro-3-piperidyl]amino]pyrimidine	0.0087

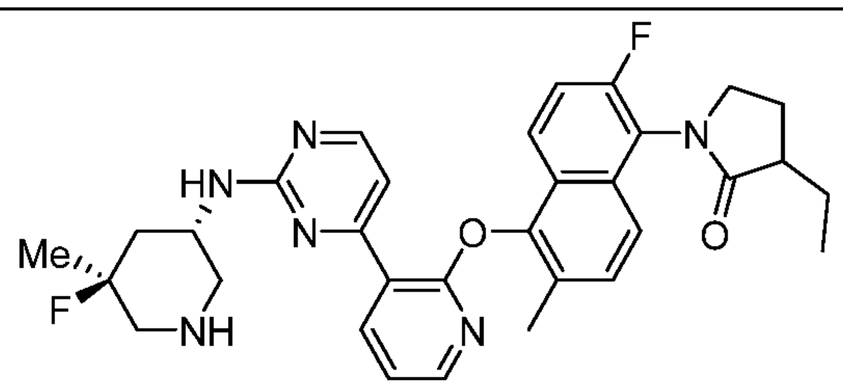
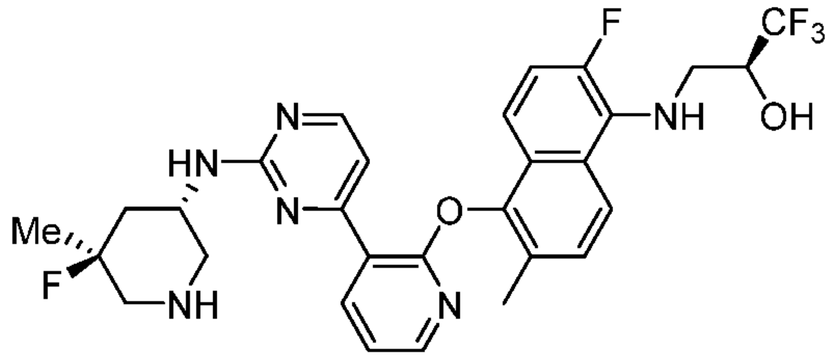
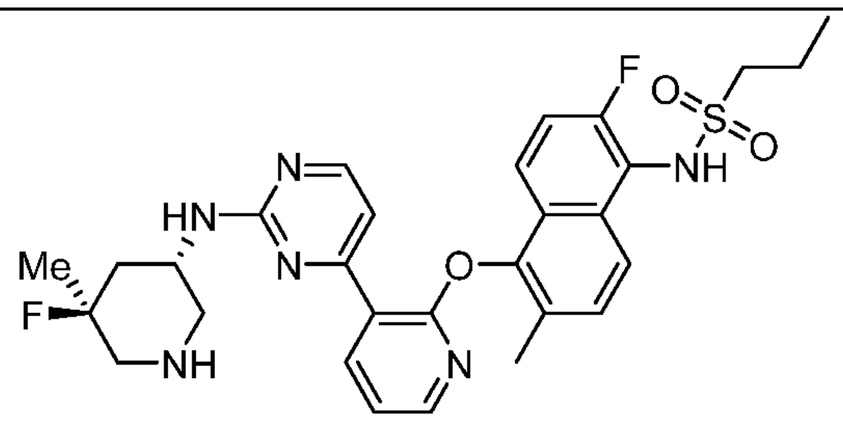
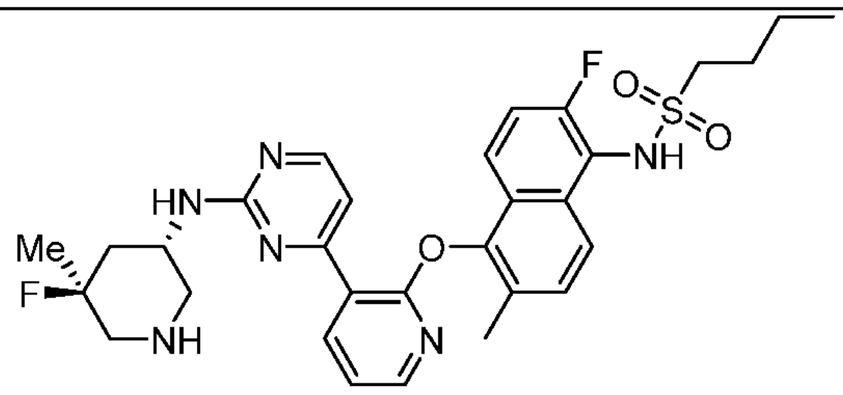
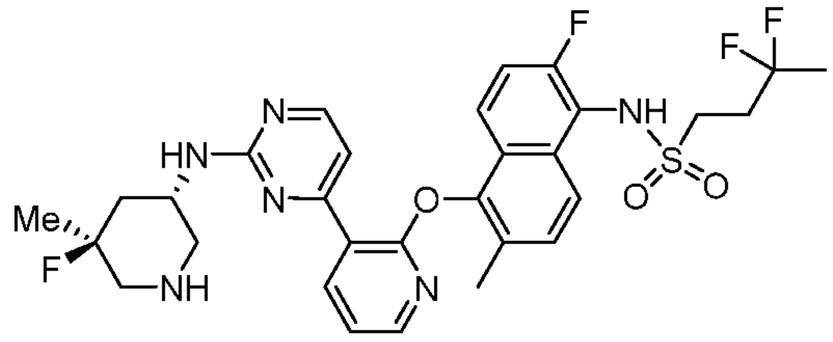
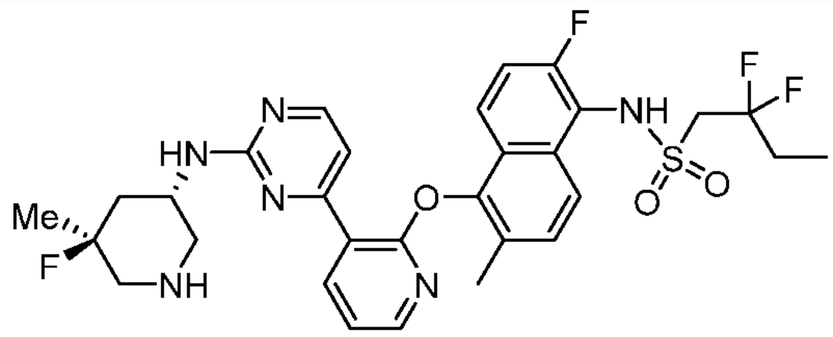
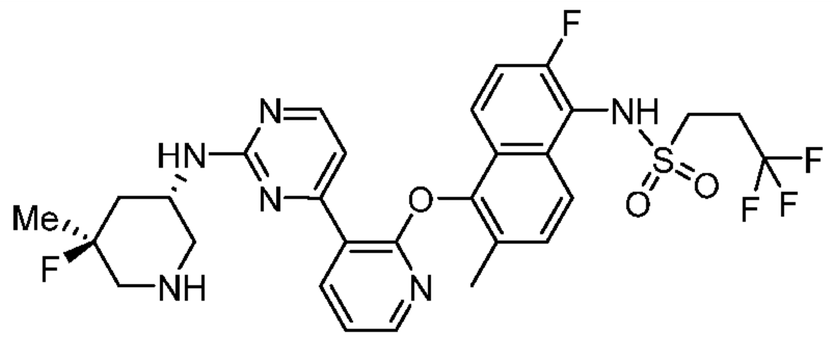
***Table* 3**

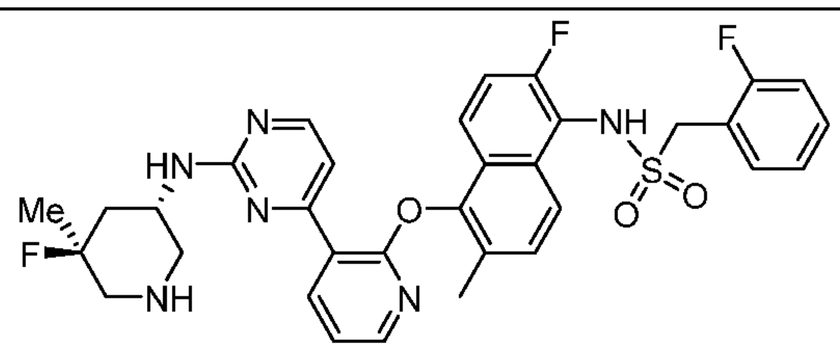
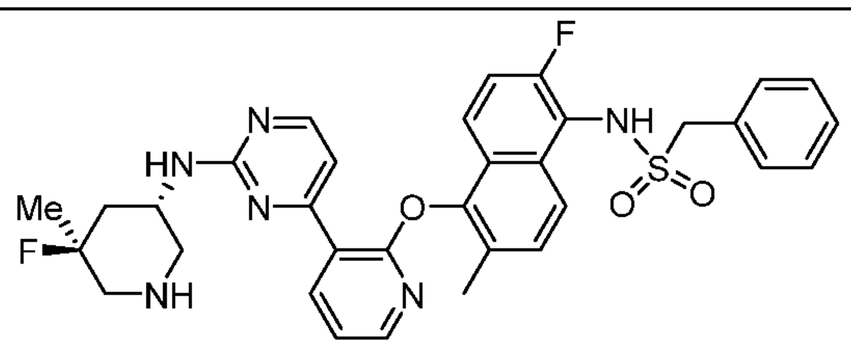
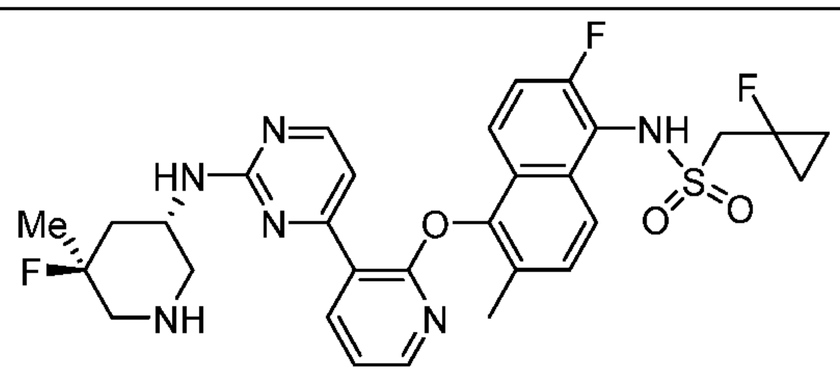
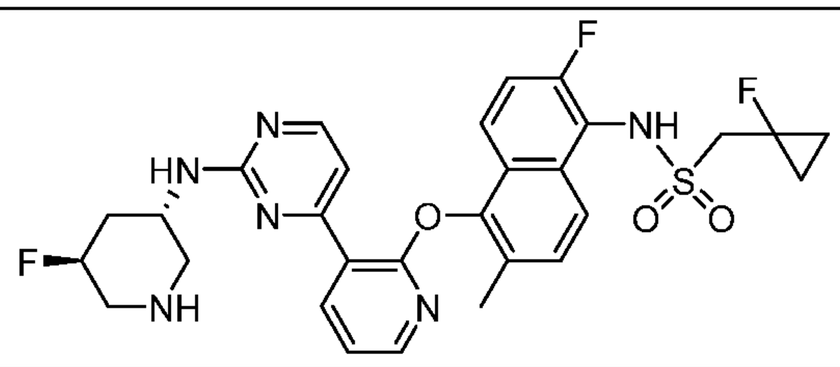
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502		*N*-(2-Fluoro-4-((3-(2-(((3*S*,5*S*)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)-1-phenylmethanesulfonamide
503		N-(2-Fluoro-4-((3-(2-(((3*S*,5*S*)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)-3,3-dimethylbutane-1-sulfonamide
504		2,2-D -*N*-(2-fluoro-4-((3-(2-(((3S,5S)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)butane-1-sulfonamide
505		*N*-(2-Fluoro-4-((3-(2-(((3*S*,5*S*)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)butane-1-sulfonamide
506		*N*-(2-Fluoro-4-((3-(2-(((3*S*,5*S*)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)propane-1-sulfonamide
507		3-Fluoro-*N*-(2-fluoro-4-((3-(2-(((3*S*,5*S*)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)-3-methylbutane-1-sulfonamide
508		3,3-Difluoro-*N*-(2-fluoro-4-((3-(2-(((3*S*,5*S*)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)butane-1-sulfonamide

509		*N*-(2-Fluoro-4-((3-(2-(((3*S*,5*S*)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)propane-1-sulfonamide
510		1,1,1-Trifluoro-3-((2-fluoro-4-((3-(2-(((3*S*,5*S*)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)amino)propan-2-ol
511		1,1,1-Trifluoro-3-((4-((3-(2-(((3*S*,5*S*)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)amino)propan-2-ol
512		3-Ethyl-1-(4-((3-(2-(((3*S*,5*S*)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)pyrrolidin-2-one
513		*N*-(4-((3-(2-(((3*S*,5*S*)-5-Fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)butyramide
514		*N*-(4-((2'-(((3*S*,5*S*)-5-fluoropiperidin-3-yl)amino)-[3,4'-bipyridin]-2-yl)oxy)-3-methylnaphthalen-1-yl)cyclopropanecarboxamide
515		*N*-(4-((2'-(((3*S*,5*R*)-5-Fluoropiperidin-3-yl)amino)-[3,4'-bipyridin]-2-yl)oxy)-3-methylnaphthalen-1-yl)cyclopropanecarboxamide
516		1,1,1-Trifluoro-3-((3-methyl-4-((3-(2-(((3*S*,5*R*)-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)propan-2-ol
517		3-Fluoro-3-methyl-*N*-(3-methyl-4-((3-(2-(((3*S*,5*R*)-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)butane-1-sulfonamide

518		*N*-(3-Methyl-4-((3-(2-(((3*S*,5*R*)-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide
519		*N*-(2-Fuoro-3-methyl-4-((3-(2-(((3*S*,5*R*)-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide
520		*N*-(2-Fluoro-3-methyl-4-((3-(2-(((3*S*,5*R*)-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)butane-1-sulfonamide
521		3,3-Difluoro-*N*-(2-fluoro-3-methyl-4-((3-(2-(((3*S*,5*R*)-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)butane-1-sulfonamide
522		2,2-Difluoro-*N*-(2-fluoro-3-methyl-4-((3-(2-(((3*S*,5*R*)-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)butane-1-sulfonamide
523		*N*-(2-Fluoro-3-methyl-4-((3-(2-(((3*S*,5*R*)-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-3,3-dimethylbutane-1-sulfonamide
524		*N*-(2-Fluoro-3-methyl-4-((3-(2-(((3*S*,5*R*)-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-phenylmethanesulfonamide
525		*N*-(4-((3-(2-(((3*S*,5*S*)-5-Fluoro-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)propane-1-sulfonamide
526		3-fFuoro-*N*-(4-((3-(2-(((3*S*,5*S*)-5-fluoro-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)-3-methylbutane-1-sulfonamide

527		3,3-Difluoro-*N*-(2-fluoro-4-((3-(2-(((3*S*,5*S*)-5-fluoro-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)butane-1-sulfonamide
528		*N*-(2-Fluoro-4-((3-(2-(((3*S*,5*S*)-5-fluoro-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)propane-1-sulfonamide
529		*N*-(2-Fluoro-4-((3-(2-(((3*S*,5*S*)-5-fluoro-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)butane-1-sulfonamide
530		2,2-Difluoro-*N*-(2-fluoro-4-((3-(2-(((3*S*,5*S*)-5-fluoro-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)butane-1-sulfonamide
531		*N*-(2-Fluoro-4-((3-(2-(((3*S*,5*S*)-5-fluoro-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)-3,3-dimethylbutane-1-sulfonamide
532		*N*-(2-fFuoro-4-((3-(2-(((3*S*,5*S*)-5-fluoro-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)-1-phenylmethanesulfonamide
533		N-(5-((3-(2-(((3*S*,5*S*)-5-Fluoro-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)butyramide
534		3-Ethyl-1-(5-((3-(2-(((3*S*,5*S*)-5-fluoro-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)pyrrolidin-2-one

535		3-Ethyl-1-(2-fluoro-5-((3-(2-(((3*S*,5*S*)-5-fluoro-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)pyrrolidin-2-one
536		(*S*)-1,1,1-Trifluoro-3-((2-fluoro-5-((3-(2-(((3*S*,5*S*)-5-fluoro-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)amino)propan-2-ol
537		*N*-(2-Fluoro-5-((3-(2-(((3S,5S)-5-fluoro-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)propane-1-sulfonamide
538		*N*-(2-Fluoro-5-((3-(2-(((3*S*,5*S*)-5-fluoro-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)butane-1-sulfonamide
539		3,3-Difluoro-*N*-(2-fluoro-5-((3-(2-(((3*S*,5*S*)-5-fluoro-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)butane-1-sulfonamide
540		2,2-Difluoro-*N*-(2-fluoro-5-((3-(2-(((3*S*,5*S*)-5-fluoro-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)butane-1-sulfonamide
541		3,3,3-Trifluoro-*N*-(2-fluoro-5-((3-(2-(((3*S*,5*S*)-5-fluoro-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)propane-1-sulfonamide

542		*N*-(2-Fluoro-5-((3-(2-(((3*S*,5*S*)-5-fluoro-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)-1-(2-fluorophenyl)methanesulfonamide
543		*N*-(2-Fluoro-5-((3-(2-(((3*S*,5*S*)-5-fluoro-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)-1-phenylmethanesulfonamide
544		*N*-(2-Fluoro-5-((3-(2-(((3*S*,5*S*)-5-fluoro-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)-1-(1-fluorocyclopropyl)methanesulfonamide
545		*N*-(2-Fluoro-5-((3-(2-(((3*S*,5*S*)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)-1-(1-fluorocyclopropyl)methanesulfonamide

Administration of Compounds

[0113] The compounds of the invention may be administered by any route appropriate to the condition to be treated. Suitable routes include oral, parenteral (including subcutaneous, intramuscular, intravenous, intraarterial, intradermal, intrathecal and epidural), transdermal, rectal, nasal, topical (including buccal and sublingual), vaginal, intraperitoneal, intrapulmonary and intranasal. For local immunosuppressive treatment, the compounds may be administered by intralesional administration, including perfusing or otherwise contacting the graft with the inhibitor before transplantation. It will be appreciated that the preferred route may vary with for example the condition of the recipient. Where the compound is administered orally, it may be formulated as a pill, capsule, tablet, etc. with a pharmaceutically acceptable carrier or excipient. Where the compound is administered parenterally, it may be formulated with a pharmaceutically acceptable parenteral vehicle and in a unit dosage injectable form, as detailed below.

[0114] A dose to treat human patients may range from about 10 mg to about 1000 mg of Formula I or I′ compound. A typical dose may be about 100 mg to about 300 mg of the compound. A dose may be administered once a day (QID), twice per day (BID), or more frequently, depending on the pharmacokinetic and pharmacodynamic properties, including absorption, distribution, metabolism, and excretion of the particular compound. In addition, toxicity factors may influence the dosage and administration regimen. When administered orally, the pill, capsule, or tablet may be ingested daily or less frequently for a specified period of time. The regimen may be repeated for a number of cycles of therapy.

Methods of Treatment

[0115] Formula I or I′ compounds of the present invention are useful for treating a human or animal patient suffering from a disease or disorder arising from abnormal cell growth, function or behavior associated with the UPR pathway such as cancer, an immune disorder, cardiovascular disease, viral infection, inflammation, a metabolism/endocrine disorder or a neurological disorder, may thus be treated by a method comprising the administration thereto of a compound of the present invention as defined above. A human or animal patient suffering from cancer may also be treated by a method comprising the administration thereto of a compound of the present invention as defined above. The condition of the patient may thereby be improved or ameliorated.

[0116] Methods of the invention also include treating cancer selected from breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach, skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, non-small cell lung carcinoma (NSCLC), small cell carcinoma, lung adenocarcinoma, bone, colon, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, pancreatic, myeloid disorders, lymphoma, hairy cells, buccal cavity, naso-pharyngeal, pharynx, lip, tongue, mouth, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, Hodgkin's, leukemia, bronchus, thyroid, liver and intrahepatic bile duct, hepatocellular, gastric, glioma/glioblastoma, endometrial, melanoma, kidney and renal pelvis, urinary bladder, uterine corpus, uterine cervix, multiple myeloma, acute myelogenous leukemia, chronic myelogenous leukemia, lymphocytic leukemia, chronic lymphoid leukemia (CLL), myeloid leukemia, oral cavity and pharynx, non-Hodgkin lymphoma, melanoma, and villous colon adenoma.

[0117] In one aspect, provided is a method of treating an IRE1-related disease or disorder in a patient comprising administering a therapeutically effective amount of a compound of Formula I or I′, or any variations detailed herein, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, to a patient with an IRE1-related disease or condition. In another aspect, the method comprises administering to a patient with an IRE1-related disease or condition an effective amount of a pharmaceutical composition comprising a compound of Formula I or I′, or any variations detailed herein, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, glidant, diluent, or excipient. In some embodiments, the compound is of the Formula I excluding compounds of Table 1X. In other embodiments, the compound is of the Formula I including compounds of Table 1X. In some embodiments, the compound is of the Formula I′ or variations thereof. In some embodiments, the compound is selected from Tables 1, 2 and 3, or a pharmaceutically acceptable salt thereof. In some embodiments, the patient is a human patient.

[0118] In one aspect, provided is a compound of Formula I or I′, or any variations detailed herein, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, for use in a method for treating an IRE1-related disease or disorder. In one aspect, provided is a use of a compound of Formula I or I′, or any variations detailed herein, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of an IRE1-related disease or disorder.

[0119] In some embodiments, the IRE1-related disease or disorder is cancer selected from the group consisting of squamous cell cancer, small-cell lung cancer, non-small cell lung cancer ("NSCLC"), adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, stomach cancer, gastrointestinal cancer, esophageal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, and head and neck cancer.

[0120] In some embodiments, the IRE1-related disease or disorder is a hematological malignancy selected from the group consisting of lymphomas, lymphocytic leukemia, myeloma, acute and chronic myelogenous leukemia, myelodysplastic syndrome and myeloproliferative disease.

[0121] In some embodiments, the IRE1-related disease or disorder is multiple myeloma. In some embodiments, wherein the IRE1-related disease or disorder is a breast cancer (e.g., a triple-negative breast cancer ("TNBC")).

[0122] In some embodiments of the method of treating an IRE1-related disease or disorder in a patient comprising administering a therapeutically effective amount of a compound of Formula I or I′, or any variations detailed herein, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, to a patient with an IRE1-related disease or condition, the method further comprising administering one or more additional therapeutic agent(s) selected from the group consisting of an anti-inflammatory agent, a corticosteroid, an immunomodulatory agent, chemotherapeutic agent, an apoptosis-enhancer, a neurotropic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, an agent for treating metabolic disorders, an agent for treating autoimmune disorders, an agent for treating immunodeficiency disorders, and combinations thereof. In some embodiments, the additional therapeutic agent is a corticosteroid, a proteasome inhibitor, an IMiD, an antibody, or a combination thereof. In some embodiments, the additional therapeutic agent is a proteasome inhibitor (e.g. carfilzomib, bortezomib, or ixazomib). In some embodiments, the additional therapeutic agent is an IMiD (e.g. lenalidomide or pomalidomide). In some embodiments, the additional therapeutic agent is an antibody (e.g., an anti-CD38 antibody, an anti-VEGF-A antibody, an anti-PD-1 antibody, an anti-PD-L1 antibody or an anti-interleukin-6 antibody). In some embodiments, the additional therapeutic agent is a corticosteroid (e.g., dexamethasone). In some embodiments, the method further comprises radiotherapy.

[0123] Also provided herein is a method of treating a disease caused by abnormal levels of Ire1 activity in a human or animal patient in need of such treatment with a Formula I or I′ compound. The disease may be caused by an amount of Ire1 activity that is too low or too high. For example, the disease may be caused by a deficiency in Ire1 activity or by abnormally high Ire1 activity (e.g., hyperactivity of Ire1). The method includes administering to the patient a therapeutically effective amount of an Ire1 modulator Formula I or I′ compound.

[0124] Ire1 deficiency is a decreased amount of Ire1 activity compared to normal levels of Ire1 activity in a particular subject or a population of healthy subjects. The decreased amount of Ire1 activity results in excessive amounts of misfolded protein accumulation thereby causing the disease state.

[0125] Ire1 hyperactivity is an increased amount of Ire1 activity compared to normal levels of Ire1 activity in a particular subject or a population of healthy subjects. The increased amount of Ire1 activity may result in, for example, excessive amounts of cell proliferation thereby causing the disease state.

[0126] In some embodiments, the disease is associated with Ire1 deficiency. Such diseases include, but are not limited to, cystic fibrosis, retinitis pigmentosa, diabetes, or a neurodegenerative disease. The neurodegenerative disease may include Alexander's disease, Alper's disease, Alzheimer's disease, Amyotrophic lateral sclerosis, Ataxia telangiectasia, Batten disease (also known as Spielmeyer-Vogt-Sjogren-Batten disease). Bovine spongiform encephalopathy (BSF), Canavan disease, Cockayne syndrome, Corticobasal degeneration, Creutzfeldt-Jakob disease, Huntington's disease, HIV-associated dementia, Kennedy's disease, Krabbe's disease, Lewy body dementia, Machado-Joseph disease (Spinocerebellar ataxia type 3), Multiple sclerosis, Multiple System Atrophy, Narcolepsy, Neuroborreliosis, Parkinson's disease, Pelizaeus-Merzbacher Disease, Pick's disease, Primary lateral sclerosis, Prion diseases, Refsum's disease, Sandhoff's disease, Schilder's disease, Subacute combined degeneration of spinal cord secondary to Pernicious Anaemia, Schizophrenia, Spinocerebellar ataxia (multiple types with varying characteristics), Spinal muscular atrophy, Steele-Richardson-Olszewski disease, or Tabes dorsalis.

[0127] In other embodiments, the disease is associated with abnormally high Ire1. Such diseases include, but are not limited, to cancers, inflammatory diseases, and autoimmune diseases. Exemplary cancers include, but am not limited to, breast cancer and multiple myeloma. In one embodiment, the disease is multiple myeloma. In one embodiment, the disease is a triple-negative breast cancer. Exemplary inflammatory diseases include, but are not limited to, asthma, chronic inflammation, chronic prostatitis, glomerulonephritis, hypersensitivities, inflammatory bowel diseases, pelvic inflammatory disease; reperfusion injury, rheumatoid arthritis, transplant rejection, and vasculitis. Exemplary autoimmune diseases include, but are not limited to, XBP1-linked Crohn's disease, Coeliac disease, diabetes mellitus type 1 (IDDM), systemic lupus erythematosus (SLE), Sjogren's syndrome, Churg-Strauss Syndrome, Hashimoto's thyroiditis, Graves' disease, idiopathic thrombocytopenic purpura, and rheumatoid arthritis. In one embodiment, the disease is XBP1-linked. Crohn's disease.

Pharmaceutical Formulations

[0128] In order to use a Formula I or I′ compound for the therapeutic treatment of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. According to this aspect of the invention there is provided a pharmaceutical composition comprising a compound of this invention in association with a pharmaceutically acceptable diluent or carrier.

[0129] A typical formulation is prepared by mixing a compound of the present invention and a carrier, diluent or excipient. Suitable carriers, diluents and excipients are well known to those skilled in the art and include materials such as carbohydrates, waxes, water soluble and/or swellable polymers, hydrophilic or hydrophobic materials, gelatin, oils, solvents, water and the like. The particular carrier, diluent or excipient used will depend upon the means and purpose for which the compound of the present invention is being applied. Solvents are generally selected based on solvents recognized by persons skilled in the art as safe (GRAS) to be administered to a mammal. In general, safe solvents are non-toxic aqueous solvents such as water and other non-toxic solvents that are soluble or miscible in water. Suitable aqueous solvents include water, ethanol, propylene glycol, polyethylene glycols (e.g., PEG 400, PEG 300), etc. and mixtures thereof. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

[0130] The formulations may be prepared using conventional dissolution and mixing procedures. For example, the bulk drug substance (i.e., compound of the present invention or stabilized form of the compound (e.g., complex with a cyclodextrin derivative or other known complexation agent) is dissolved in a suitable solvent in the presence of one or more of the excipients described above. The compound of the present invention is typically formulated into pharmaceutical dosage forms to provide an easily controllable dosage of the drug and to enable patient compliance with the prescribed regimen.

[0131] The pharmaceutical composition (or formulation) for application may be packaged in a variety of ways depending upon the method used for administering the drug. Generally, an article for distribution includes a container having deposited therein the pharmaceutical

formulation in an appropriate form. Suitable containers are well known to those skilled in the art and include materials such as bottles (plastic and glass), sachets, ampoules, plastic bags, metal cylinders, and the like. The container may also include a tamper-proof assemblage to prevent indiscreet access to the contents of the package. In addition, the container has deposited thereon a label that describes the contents of the container. The label may also include appropriate warnings.

[0132] Pharmaceutical formulations of the compounds of the present invention may be prepared for various routes and types of administration. For example, a compound of Formula I or I′ having the desired degree of purity may optionally be mixed with pharmaceutically acceptable diluents, carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences (1980) 16th edition, Osol, A. Ed.), in the form of a lyophilized formulation, milled powder, or an aqueous solution. Formulation may be conducted by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed. The pH of the formulation depends mainly on the particular use and the concentration of compound, but may range from about 3 to about 8. Formulation in an acetate buffer at pH 5 is a suitable embodiment.

[0133] The compound ordinarily can be stored as a solid composition, a lyophilized formulation or as an aqueous solution.

[0134] The pharmaceutical compositions of the invention will be formulated, dosed and administered in a fashion, i.e., amounts, concentrations, schedules, course, vehicles and route of administration, consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The "therapeutically effective amount" of the compound to be administered will be governed by such considerations, and is the minimum amount necessary to ameliorate, or treat the hyperproliferative disorder.

[0135] As a general proposition, the initial pharmaceutically effective amount of the inhibitor administered parenterally per dose will be in the range of about 0.01-100 mg/kg, namely about 0.1 to 20 mg/kg of patient body weight per day, with the typical initial range of compound used being 0.3 to 15 mg/kg/day.

[0136] Acceptable diluents, carriers, excipients and stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG). The active pharmaceutical ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980).

[0137] Sustained-release preparations of compounds of Formula I or I′ may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing a compound of Formula I or I′, which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinyl alcohol)), polylactides (US 3773919), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate) and poly-D-(-)-3-hydroxybutyric acid.

[0138] The formulations include those suitable for the administration routes detailed herein. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in *Remington's Pharmaceutical Sciences* (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active ingredient with the carrier

which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

[0139] Formulations of a compound of Formula I or I′ suitable for oral administration may be prepared as discrete units such as pills, capsules, cachets or tablets each containing a predetermined amount of a compound of Formula I or I′. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom. Tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, e.g., gelatin capsules, syrups or elixirs may be prepared for oral use. Formulations of compounds of Formula I or I′ intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

[0140] For treatment of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include a polyhydric

alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulfoxide and related analogs. The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

[0141] Aqueous suspensions of Formula I or I′ compounds contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, croscarmellose, povidone, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

[0142] The pharmaceutical compositions of compounds of Formula I or I′ may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butanediol or

prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

[0143] The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

[0144] Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

[0145] Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of about 0.5 to 20% w/w, for example about 0.5 to 10% w/w, for example about 1.5% w/w.

[0146] Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

[0147] Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

[0148] Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns (including particle sizes in a range between 0.1 and 500 microns in increments microns such as 0.5, 1, 30 microns, 35 microns, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis disorders as described below.

[0149] Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

[0150] The formulations may be packaged in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water, for injection immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

[0151] The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefore. Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered parenterally, orally or by any other desired route.

Combination Therapy

[0152] The compounds of Formula I or I′ may be employed alone or in combination with additional therapeutic agents for the treatment of a disease or disorder described herein, such as inflammation or a hyperproliferative disorder (e.g., cancer). In certain embodiments, a compound of Formula I or I′ is combined in a pharmaceutical combination formulation, or dosing regimen as combination therapy, with an additional, second therapeutic compound that has anti-inflammatory or anti-hyperproliferative properties or that is useful for treating an inflammation, immune-response disorder, or hyperproliferative disorder (e.g., cancer). The

additional therapeutic may be a Bcl-2 inhibitor, a JAK inhibitor, a PI3K inhibitor, an mTOR inhibitor, an anti-inflammatory agent, an immunomodulatory agent, chemotherapeutic agent, an apoptosis-enhancer, a neurotropic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, and an agent for treating immunodeficiency disorders. The second therapeutic agent may be an NSAID anti-inflammatory agent. The second therapeutic agent may be a chemotherapeutic agent. The second compound of the pharmaceutical combination formulation or dosing regimen preferably has complementary activities to the compound of Formula I or I′ such that they do not adversely affect each other. Such compounds are suitably present in combination in amounts that are effective for the purpose intended. In one embodiment, a composition of this invention comprises a compound of Formula I or I′, or a stereoisomer, tautomer, solvate, metabolite, or pharmaceutically acceptable salt or prodrug thereof, in combination with a therapeutic agent such as an NSAID.

[0153] The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations. The combined administration includes coadministration, using separate formulations or a single pharmaceutical formulation, and consecutive administration in either order, wherein preferably there is a time period while both (or all) active agents simultaneously exert their biological activities.

[0154] Suitable dosages for any of the above coadministered agents are those presently used and may be lowered due to the combined action (synergy) of the newly identified agent and other therapeutic agents or treatments.

[0155] The combination therapy may provide "synergy" and prove "synergistic", i.e., the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined, unit dosage formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, e.g., by different injections in separate syringes, separate pills or capsules, or separate infusions. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, i.e., serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together.

[0156] In a particular embodiment of therapy, a compound of Formula I or I′, or a stereoisomer, tautomer, solvate, metabolite, or pharmaceutically acceptable salt or prodrug thereof, may be combined with other therapeutic, hormonal or antibody agents such as those described herein, as well as combined with surgical therapy and radiotherapy. Combination therapies according to the present invention thus comprise the administration of at least one compound of Formula I or I′, or a stereoisomer, tautomer, solvate, metabolite, or pharmaceutically acceptable salt or prodrug thereof, and the use of at least one other cancer treatment method. The amounts of the compound(s) of Formula I or I′, and the other pharmaceutically active therapeutic agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

[0157] In some embodiments, a compound of Formula I or I′, or a pharmaceutically acceptable salt thereof, is used in combination with an aromatase inhibitor, a phosphoinositide 3-kinase (PI3K)/mTOR pathway inhibitor, a CDK 4/6 inhibitor, a HER-2 inhibitor, an EGFR inhibitor, a PD-1 inhibitor, poly ADP-ribose polymerase (PARP) inhibitor, a histone deacetylase (HDAC) inhibitor, an HSP90 inhibitor, a VEGFR inhibitor, an AKT inhibitor, chemotherapy, or any combination thereof.

[0158] In some embodiments, a pharmaceutical composition comprising a compound of Formula I or I′, or a pharmaceutically acceptable salt thereof, is administered in combination with a therapeutic agent selected from paclitaxel, anastrozole, exemestane, cyclophosphamide, epirubicin, fulvestrant, letrozole, palbociclib, gemcitabine, trastuzumab (HERCEPTIN®, Genentech), trastuzumab emtansine (KADCYLA®, Genentech), pegfilgrastim, filgrastim, tamoxifen, docetaxel, toremifene, vinorelbine, capecitabine, and ixabepilone.

[0159] In some embodiments, a compound of Formula I or I′, or a pharmaceutically acceptable salt thereof, is used in combination with hormone blocking therapy, chemotherapy, radiation therapy, monoclonal antibodies, or combinations thereof.

Metabolites of Compounds of Formula I or I'

[0160] Also falling within the scope of this invention are the *in vivo* metabolic products of Formula I or I′ described herein. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, deamidation, esterification, deesterification, enzymatic cleavage, and the like, of the administered compound. Accordingly, the invention includes metabolites of compounds of Formula I or I′, including compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof.

[0161] Metabolite products typically are identified by preparing a radiolabelled (e.g., ^{14}C or ^{3}H) isotope of a compound of the invention, administering it parenterally in a detectable dose (e.g., greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g., by MS, LC/MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well known to those skilled in the art. The metabolite products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention.

Articles of Manufacture

[0162] In another embodiment of the invention, an article of manufacture, or "kit", containing materials useful for the treatment of the diseases and disorders described above is provided. In one embodiment, the kit comprises a container comprising a compound of Formula I or I′, or a stereoisomer, tautomer, solvate, metabolite, or pharmaceutically acceptable salt or prodrug thereof. The kit may further comprise a label or package insert on or associated with the container. The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products. Suitable containers include, for example, bottles, vials, syringes, blister pack, etc. The container may be formed from a variety of materials such as glass or plastic. The container may hold a compound of Formula I or I′ or a formulation thereof which is effective for treating the condition and may have a sterile access port (for example, the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is a compound of Formula I or I′. The label or package insert indicates that the composition is used for treating the condition of choice, such as cancer. In addition, the label or package insert may indicate that the patient to be treated is one having a disorder such as a hyperproliferative disorder, neurodegeneration, cardiac hypertrophy, pain, migraine or a neurotraumatic disease or event. In one embodiment, the label or package inserts indicates that the composition comprising a compound of Formula I or I′ can be used to treat a disorder resulting from

abnormal cell growth. The label or package insert may also indicate that the composition can be used to treat other disorders. Alternatively, or additionally, the article of manufacture may further comprise a second container comprising a pharmaceutically acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

[0163] The kit may further comprise directions for the administration of the compound of Formula I or I′ and, if present, the second pharmaceutical formulation. For example, if the kit comprises a first composition comprising a compound of Formula I or I′ and a second pharmaceutical formulation, the kit may further comprise directions for the simultaneous, sequential or separate administration of the first and second pharmaceutical compositions to a patient in need thereof.

[0164] In another embodiment, the kits are suitable for the delivery of solid oral forms of a compound of Formula I or I′, such as tablets or capsules. Such a kit preferably includes a number of unit dosages. Such kits can include a card having the dosages oriented in the order of their intended use. An example of such a kit is a "blister pack". Blister packs are well known in the packaging industry and are widely used for packaging pharmaceutical unit dosage forms. If desired, a memory aid can be provided, for example in the form of numbers, letters, or other markings or with a calendar insert, designating the days in the treatment schedule in which the dosages can be administered.

[0165] According to one embodiment, a kit may comprise (a) a first container with a compound of Formula I or I′ contained therein; and optionally (b) a second container with a second pharmaceutical formulation contained therein, wherein the second pharmaceutical formulation comprises a second compound with anti-hyperproliferative activity. Alternatively, or additionally, the kit may further comprise a third container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

[0166] In certain other embodiments wherein the kit comprises a composition of Formula I or I′ and a second therapeutic agent, the kit may comprise a container for containing the separate compositions such as a divided bottle or a divided foil packet, however, the separate compositions may also be contained within a single, undivided container. Typically, the kit comprises directions for the administration of the separate components. The kit form is

particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

Preparation of Formula I or I' Compounds

[0167] Formula I or I′ compounds may be synthesized by synthetic routes that include processes analogous to those well-known in the chemical arts, particularly in light of the description contained herein, and those for other heterocycles described in: Comprehensive Heterocyclic Chemistry II, Editors Katritzky and Rees, Elsevier, 1997, e.g. Volume 3; Liebigs Annalen der Chemie, (9):1910-16, (1985); Helvetica Chimica Acta, 41:1052-60, (1958); Arzneimittel-Forschung, 40(12):1328-31, (1990), each of which are expressly incorporated by reference. Starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, WI) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, *Reagents for Organic Synthesis*, v. 1-23, Wiley, N.Y. (1967-2006 ed.), or *Beilsteins Handbuch der organischen Chemie*, 4, Aufl. ed. Springer-Verlag, Berlin, including supplements (also available via the Beilstein online database). Formula I or I′ compounds may also be made following the procedures found in US 8476434, US 7880000, WO 2005/113494, US 7868177, and WO 2007/100646.

[0168] Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing Formula I or I′ compounds and necessary reagents and intermediates are known in the art and include, for example, those described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley and Sons (1999); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995) and subsequent editions thereof.

[0169] Compounds of Formula I or I′ may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, or 10 to 100 compounds. Libraries of compounds of Formula I or I′ may be prepared by a combinatorial 'split and mix' approach or by multiple parallel syntheses using either solution phase or solid phase chemistry, by procedures known to those skilled in the art. Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds, or pharmaceutically acceptable salts thereof.

[0170] The Examples provide exemplary methods for preparing Formula I or I′ compounds. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the Formula I or I′ compounds. Although specific starting materials and reagents are depicted and discussed in the Examples, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the exemplary compounds prepared by the described methods can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

[0171] In preparing compounds of Formula I or I′, protection of remote functionality (e.g., primary or secondary amine) of intermediates may be necessary. The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. Suitable amino-protecting groups include acetyl, trifluoroacetyl, t-butoxycarbonyl (BOC), benzyloxycarbonyl (CBz) and 9-fluorenylmethyleneoxycarbonyl (Fmoc). The need for such protection is readily determined by one skilled in the art. For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

[0172] In the methods of preparing Formula I or I′ compounds, it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed (SMB) and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

[0173] Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like. Selection of appropriate methods of separation depends on the nature of the materials involved, such as, boiling point and

molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like.

[0174] Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Also, some of the compounds of the present invention may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of a chiral HPLC column.

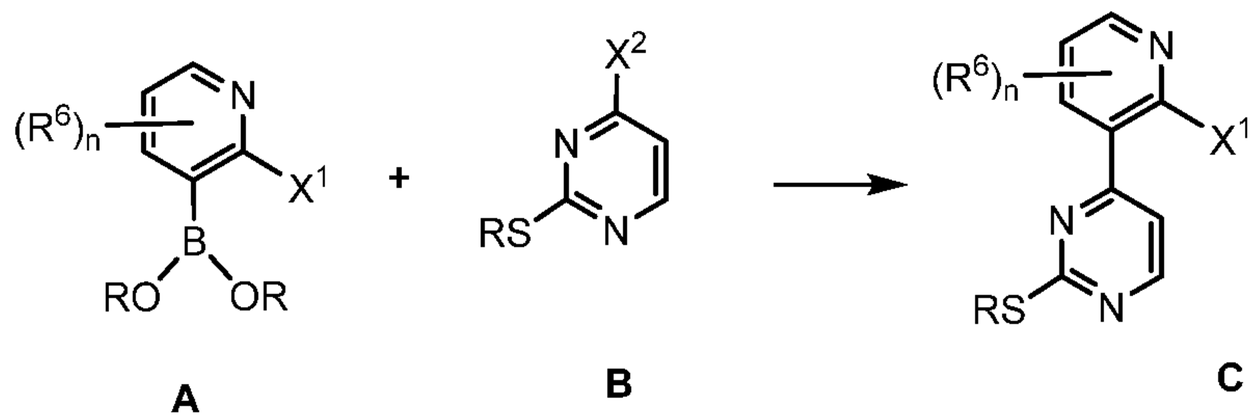
[0175] A single stereoisomer, e.g., an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents (Eliel, E. and Wilen, S. "Stereochemistry of Organic Compounds," John Wiley & Sons, Inc., New York, 1994; Lochmuller, C. H., (1975) J. Chromatogr., 113(3):283-302). Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions. See: "Drug Stereochemistry, Analytical Methods and Pharmacology," Irving W. Wainer, Ed., Marcel Dekker, Inc., New York (1993).

[0176] Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, α-methyl-β-phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts.

[0177] Alternatively, by method (2), the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (E. and Wilen, S. "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., 1994, p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the pure or enriched enantiomer. A method of determining optical purity involves making chiral esters, such as a menthyl ester, e.g., (-) menthyl chloroformate in the presence of base, or Mosher ester, α-methoxy-α-(trifluoromethyl)phenyl acetate (Jacob III. J. Org. Chem. (1982) 47:4165), of the racemic mixture, and analyzing the ^{1}H NMR spectrum for the presence of the two atropisomeric enantiomers or diastereomers. Stable diastereomers of atropisomeric compounds can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (WO 96/15111). By method (3), a racemic mixture of two enantiomers can be separated by chromatography using a chiral stationary phase ("Chiral Liquid Chromatography" (1989) W. J. Lough, Ed., Chapman and Hall, New York; Okamoto, J. Chromatogr., (1990) 513:375-378). Enriched or purified enantiomers can be distinguished by methods used to distinguish other chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism.

[0178] Formula I or I′ compounds can be prepared by procedures in the Examples, the General Procedures, and generally by Schemes 1-4, where R groups are as described in Formula I or I′ compounds, or precursors thereof.

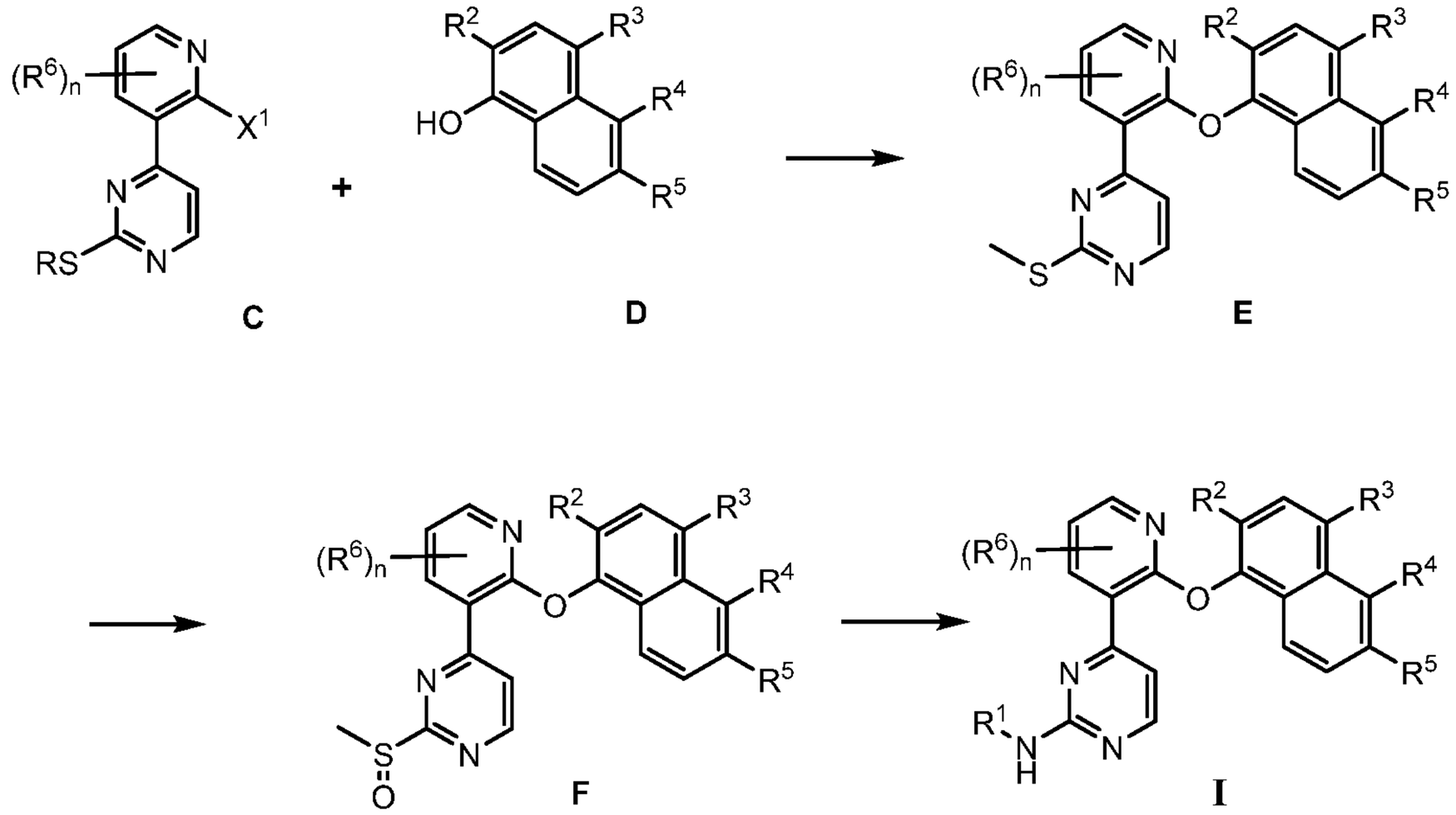
Scheme 1



A B C

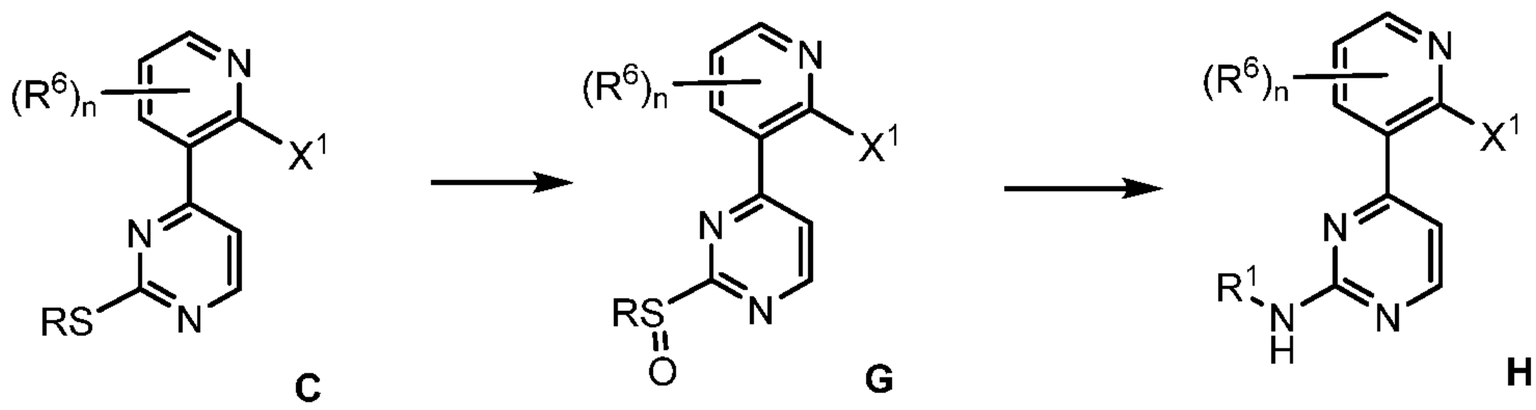
[0179] Scheme 1 shows coupling of a (2-halopyridin-3-yl)boronic acid or ester compound **A** (R = H, C_1–C_6 alkyl, pinacol; X^1 = halogen) with a 4-chloro-2-(methylthio)pyrimidine compound **B** (R = C_1–C_6 alkyl, X^2 = halogen) under palladium catalysis to form 4-(2-halopyridin-3-yl)-2-(alkylthio)pyrimidine compound **C**.

Scheme 2



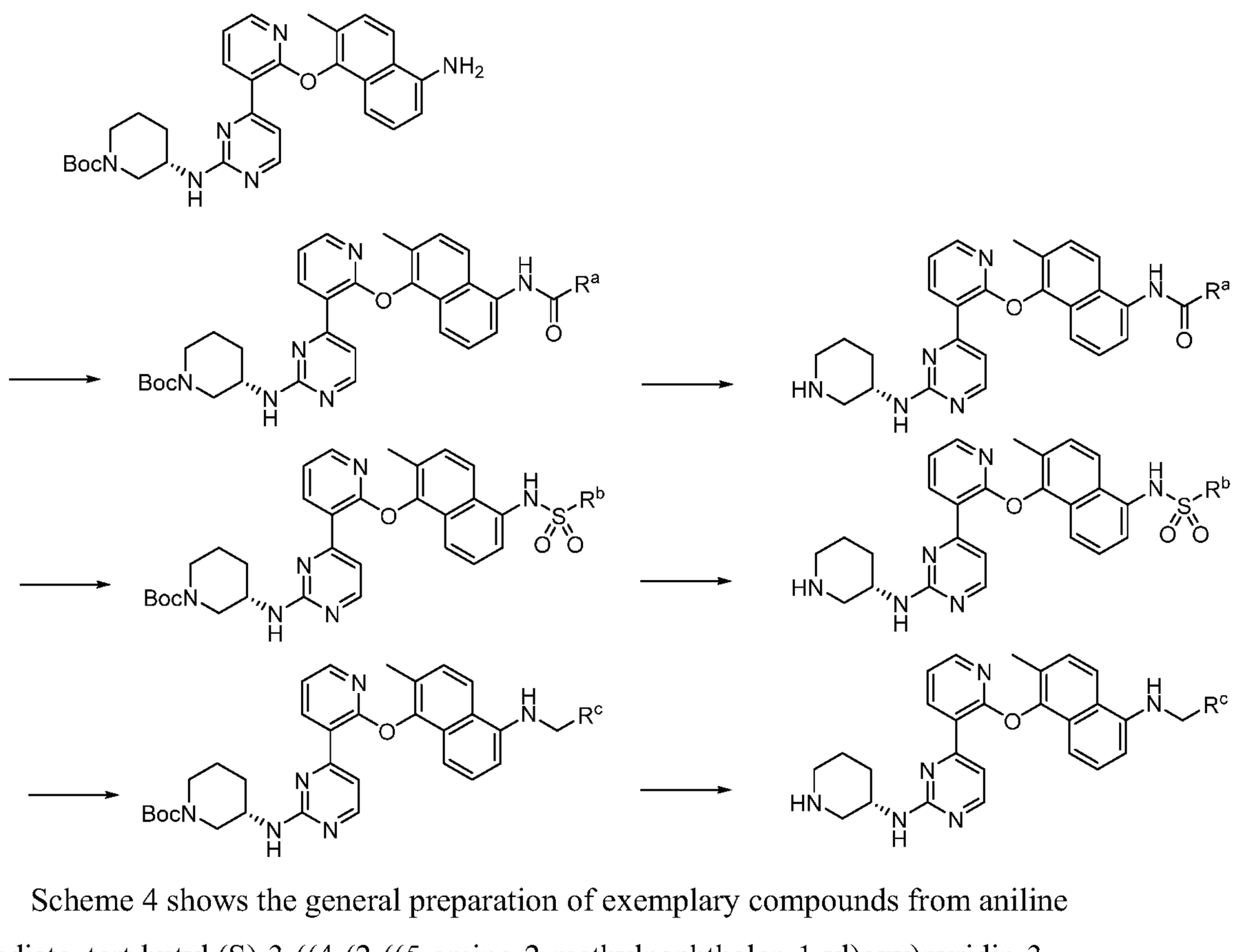
[0180] Scheme 2 shows coupling of a naphthalen-1-ol compound **D** with a 4-(2-halopyridin-3-yl)-2-(alkylthio)pyrimidine compound **C** to form a 4-(2-(naphthalen-1-yloxy)pyridin-3-yl)pyrimidine-2-alkylthiol **E** compound. Oxidation of the sulfur atom forms 2-(alkylsulfinyl)-4-(2-(naphthalen-1-yloxy)pyridin-3-yl)pyrimidine compound **F**. The sulfoxide is displaced with a primary amine (R^1–NH_2) to form a Formula I or I′ compound, or an intermediate to be converted to a Formula I or I′ compound.

Scheme 3



[0181] Scheme 3 shows an alternative route to Formula I or I′ compounds where a 4-(2-halopyridin-3-yl)-2-(alkylthio)pyrimidine compound **C** is oxidized to a 4-(2-halopyridin-3-yl)-2-(alkylsulfinyl)pyrimidine compound **G**. The sulfoxide is displaced with a primary amine (R^1–NH_2) to form a 4-(2-halopyridin-3-yl)-N-alkylpyrimidin-2-amine compound **H**. Coupling of compound **H** with a naphthalen-1-ol compound **D** forms a Formula I or I′ compound, or an intermediate to be converted to a Formula I or I′ compound.

Scheme 4



[0182] Scheme 4 shows the general preparation of exemplary compounds from aniline intermediate, tert-butyl (S)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (see, Example 101). The aniline intermediate is treated with a carboxlic acid (R^aCOOH) and a coupling reagent, such as 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU) as in General Procedure C, or alternatively with an acid chloride (R^aCOCl) and an amine base such as diisopropylethylamine (DIPEA) or pyridine, to form Boc-protected, amide intermediates (top). The aniline intermediate is treated with a sulfonyl chloride (R^bSO_2Cl) and an amine base to form Boc-protected, sulfonamide intermediates (middle) as in General Procedure A. The aniline intermediate is treated with an alkylating agent as in General Procedure G, or by reductive amination (R^cCHO) to form Boc-protected, amine intermediates (bottom) as in General Procedure E. The Boc-protected intermediates are deprotected with acid, such as hydrochloric acid as in General Procedure B, to form exemplary compounds, such as those in Tables 1 and 2 and the following Examples.

[0183] The following General Procedures illustrate synthetic reactions and operations useful to prepare certain Example compounds (Tables 1 and 2). The reagents, solvents, amounts, equivalents, and conditions are illustrative and exemplary, and not meant to be limiting.

General Procedure A - sulfonamide synthesis:

[0184] To a solution of the aniline (1.0 equiv) in pyridine (5 mL/mmol) and a solvent such as dichloromethane (DCM) at 0 °C or room temperature (rt) was added the corresponding sulfonyl chloride (1.2 equiv typically otherwise noted). After the addition was completed, the reaction solution was stirred at rt for about 16 h. Water (10 mL) was added. The mixture was extracted with DCM. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*.

General Procedure B - Boc deprotection

[0185] To a mixture of the t-butyl-carbamate (Boc) intermediate (100 mg, 0.16 mmol) in DCM (25 mL/mmol) or EtOAc was added hydrochloric acid (4 M in dioxane, 10 mL/mmol). The mixture was then stirred at rt for 1 h and concentrated *in vacuo* or the resulting HCl salt was isolated by filtration.

General Procedure C - amide coupling using carboxylic acids:

[0186] To a solution of the aniline intermediate (1.05 equiv otherwise indicated) and DIPEA (3.0 equiv otherwise indicated) in DCM (16 mL/ mmol otherwise indicated) was added HATU (2.0 equiv otherwise indicated). The mixture was stirred at rt for 0.5 h. The acid (1.0 equiv otherwise indicated) was added and the resulting mixture was refluxed overnight. The mixture was diluted in DCM, washed with water and brine, dried on anhydrous sodium sulfate, and concentrated *in vacuo*. Alternatively, to a solution of the aniline in CH_2Cl_2 was added the acid chloride followed by addition of $(iPr)_2NEt$ or Et_3N or pyridine and stirring at rt. Alternatively, to a solution of the aniline in DMF was added the carboxylic acid and HATU followed by addition of $(iPr)_2NEt$ or Et_3N and stirring at rt. Other coupling reagents may be used in General Procedure C. The crude product was isolated and purified using methods known in the art or as described in the Examples.

General Procedure E - reductive amination:

[0187] To a mixture of aniline and aldehyde in CH_2Cl_2 was added sodium triacetoxyborohydride and HOAc (caution bubbling - vent vessel) and the mixture stirred at rt. The crude product was isolated and purified using methods known in the art or as described in the Examples.

General Procedure F - epoxide ring opening:

[0188] A mixture of aniline and epoxide in HOAc was stirred at rt unless otherwise noted. When complete, the mixture was concentrated *in vacuo*. The crude product was isolated and purified using methods known in the art or as described in the Examples.

General Procedure G - aniline alkylation with alkyl halides:

[0189] A mixture of aniline, alkyl-halide, cesium carbonate, Cs_2CO_3 and tetrabutylammonium iodide in DMF was heated at 50 °C. The crude product was isolated and purified using methods known in the art or as described in the Examples.

General Procedure H - Cbz deprotection:

[0190] A mixture of benzyl-carbamate, palladium on carbon (Pd/C) and ammonium formate in iPrOH was heated at 60 °C. When complete, the mixture was filtered through celite using MeOH/CH_2Cl_2 and concentrated *in vacuo*.

Analytical Methods:

[0191] LCMS (Liquid Chromatography Mass Spectrometry) methods to separate and characterize the exemplary compounds were performed on the following:

[0192] SHIMADZU LC-MS 2010EV coupled with SHIMADZU LC20AB using ESI as ionization source. The LC separation was using Column: MERCK, RP-18e 25-2 mm; Detector: PDA, ELSD; Wavelength: UV 220 nm; Column temperature: 50 °C; mobile Phase: 1.5 mL/4 LTFA in water (solvent A) and 0.75 mL/4 L TFA in acetonitrile (solvent B), using the elution gradient 5%-95% (solvent B) over 0.7 minutes and holding at 95% for 0.4 minutes at a flow rate of 1.5 mL/min;

[0193] SHIMADZU LC-MS 2010EV coupled with SHIMADZU LC20AB using ESI as ionization source. The LC separation was using Column: MERCK, RP-18e 25-2 mm; Detector: PDA, ELSD; Wavelength: UV 220 nm; Column temperature: 50°C; mobile Phase: 1.5 mL/4 L TFA in water (solvent A) and 0.75 mL/4 L TFA in acetonitrile (solvent B),using the elution gradient 5%-95% (solvent B) over 0.7 minutes and holding at 95% for 0.4 minutes at a flow rate of 1.5 mL/min;

[0194] Agilent 1200 Series coupled with 6110 Quadrupole mass spectrometer, using ESI as ionization source. The LC separation was using Column: Xtimate C18 2.1 x 30mm, 3 μm; Wavelength: UV 220 nm; Column temperature: 50 °C; Detector: PDA&ELSD. mobile Phase: 1.5 mL/4 L TFA in water (solvent A) and 0.75 mL/4 LTFA in acetonitrile (solvent B), using

the elution gradient 10%-80% (solvent B) over 0.9 minutes and holding at 80% for 0.6 minutes at a flow rate of 1.2 mL/min.

[0195] SHIMADZU 2020 HPLC coupled with SHIMADZU MSD mass spectrometer using ESI as ionization source. The LC separation was using an Shim-Pack XR-ODS-C18, 50 x 3.0 mm column with a 1 ml / minute flow rate. Solvent A is water with 0.05% TFA and solvent B is acetonitrile with 0.05% TFA. The gradient consisted with 5 - 100% solvent B over 2.2 minutes and hold 100% B for 1 minute. LC column temperature is 40 °C. UV absorbance was collected from 190 nm to 400 nm and mass spec full scan was applied to all experiments.

[0196] SHIMADZU 2020 HPLC coupled with SHIMADZU MSD mass spectrometer using ESI as ionization source. The LC separation was using an Gemini-NX 3μ C18 110A, 50 x 3.0 mm column with a 1.2 ml / minute flow rate. Solvent A is water with 0.4% NH_4HCO3 and solvent B is acetonitrile. The gradient consisted with 10 - 50% solvent B over 4 minutes and hold 50% B for 1.2 minutes. LC column temperature is 40 °C. UV absorbance was collected from 190 nm to 400 nm and mass spec full scan was applied to all experiments.

[0197] SHIMADZU UFLC-MS 2010EV coupled with SHIMADZU MSD mass spectrometer using ESI as ionization source. The LC separation was using a Shim-pack XR-ODS-C18, 50 x 3.0 mm column with a 1 ml / minute flow rate. Solvent A is water with 0.05% TFA and solvent B is acetonitrile with 0.05% TFA. The gradient consisted with 5 - 100% solvent B over 2.2 minutes and hold 100% B for 1 minute. LC column temperature is 40 °C. UV absorbance was collected from 190 nm to 400 nm and mass spec full scan was applied to all experiments.

[0198] Waters Alliance 2695 HPLC with column heater coupled with Waters ZQ 2000 mass spectrometer using ESI as ionization source (ES+, 100-1200 amu). The LC separation was using an XBridge C18, 3.5μm, 4.6 x 30mm column at 25°C with a 3.0 mL / minute flow rate. Solvent A is Milli-Q H2O + 10mM Ammonium Formate pH: 3.8, and solvent B is acetonitrile. The gradient consisted of isocratic 5% solvent B for 0.2 min, 5% to 100% B in 1.8 minutes; hold 100% B for 1 minute. LC column temperature is 25 °C. UV absorbance was collected from 195 – 320 nm using a Waters PDA 996 UV detector and mass spec full scan was applied to all experiments.

[0199] Waters Alliance 2695 HPLC with column heater coupled with Waters ZQ 2000 mass spectrometer using ESI as ionization source (ES+, 100-1200 amu). The LC separation was using an XBridge C18, 3.5μm, 4.6 x 30mm column at 25°C with a 3.0 mL / minute flow rate. Solvent A is Milli-Q H2O + 10mM Ammonium Bicarbonate pH: 10, and solvent B is

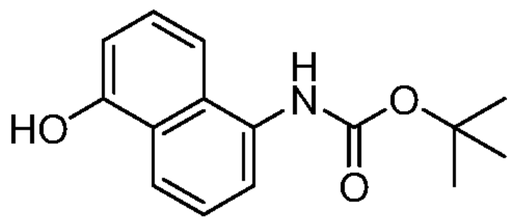
acetonitrile. The gradient consisted of isocratic 5% solvent B for 0.2 min, 5% to 100% B in 1.8 minutes; hold 100% B for 1 minute. LC column temperature is 25 °C. UV absorbance was collected from 195 – 320 nm using a Waters PDA 996 UV detector and mass spec full scan was applied to all experiments.

EXAMPLES

Synthetic Examples

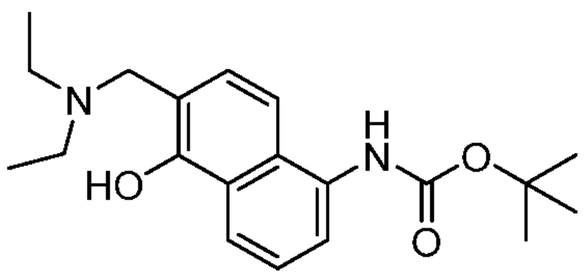
Example 101 *(S)-3-(2-Cyanopropan-2-yl)-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)benzamide* ***101***

[0200] Step 1: *tert*-Butyl 5-hydroxynaphthalen-1-ylcarbamate



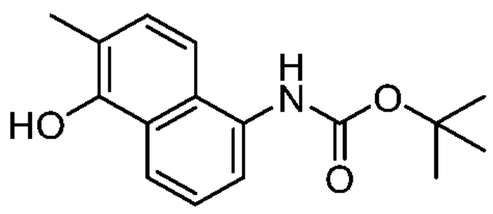
[0201] To a 5 L 4-necked round-bottom flask was placed 5-aminonaphthalen-1-ol (400 g, 2.51 mol, 1.00 equiv.), di-*tert*-butyl dicarbonate, Boc_2O (660 g, 3.01 mol, 1.20 equiv.) and 1,4-dioxane (2.5 L). The resulting solution was stirred at rt for 30 min and then heated under reflux for 3 h. The reaction mixture was then cooled to rt and concentrated *in vacuo*. The product was re-crystallized from ethyl acetate: petroleum ether (1:5) to yield 500 g (77%) of the title compound as a gray solid. LCMS (ESI) $[M+H-56]^+ = 204$.

[0202] Step 2: *tert*-Butyl 6-((diethylamino)methyl)-5-hydroxynaphthalen-1-ylcarbamate



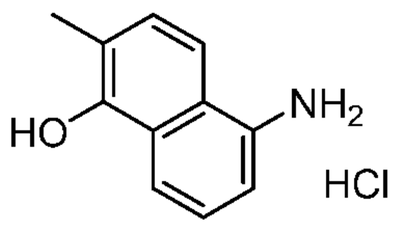
[0203] To a 2000-mL 4-necked round-bottom flask was placed *tert*-butyl *N*-(5-hydroxynaphthalen-1-yl)carbamate (100 g, 386 mmol), methanol (800 mL), diethylamine (31.4 g, 424 mmol, 1.10 equiv.) and formaldehyde (35 g, 424 mmol, 37% solution in water). The resulting solution was stirred at rt for 1 h and concentrated *in vacuo*. The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether (1:5-1:3) to yield 100 g (75%) of the title compound as a reddish oil. LCMS (ESI) $[M+H]^+ = 345$.

[0204] Step 3: *tert*-Butyl 5-hydroxy-6-methylnaphthalen-1-ylcarbamate



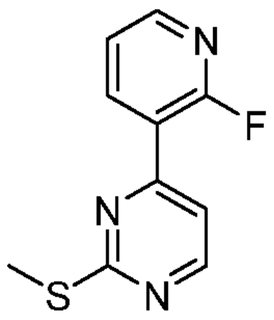
[0205] To a 3 L 4-necked round-bottom flask was placed *tert*-butyl *N*-[6-[(diethylamino)methyl]-5-hydroxynaphthalen-1-yl]carbamate (200 g, 581 mmol), ethanol (1.5 L) and palladium on carbon (30 g). Hydrogen, H_2 (gas) was introduced *via* a hydrogen balloon) to the above system. The resulting suspension was stirred at rt (room temperature) overnight and filtered. The filtrate was concentrated *in vacuo* to yield 200 g of the crude title compound as a brown oil. LCMS (ESI) $[M+H-56]^+ = 218$.

[0206] Step 4: 5-Amino-2-methylnaphthalen-1-ol hydrochloride



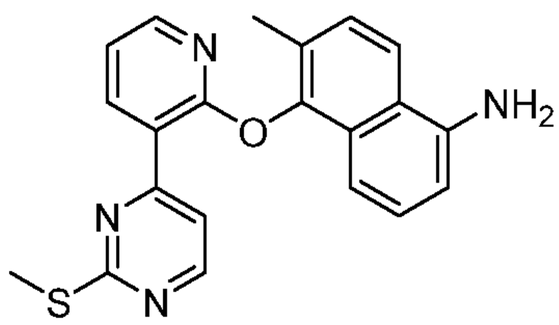
[0207] To a 5 L 4-necked round-bottom flask was placed a solution of *tert*-butyl *N*-(5-hydroxy-6-methylnaphthalen-1-yl)carbamate (100 g, 366 mmol) in dichloromethane, DCM (3 L) followed by bubbling hydrogen chloride, HCl (gas). The resulting solution was stirred at rt for 2 h and concentrated *in vacuo*. The crude product was purified by re-crystallization from DCM. The solids were collected by filtration and dried *in vacuo* to yield 73 g (95%) of the title compound as a white solid. LCMS (ESI) $[M+H]^+ = 174$.

[0208] Step 5: 4-(2-Fluoropyridin-3-yl)-2-(methylthio)pyrimidine



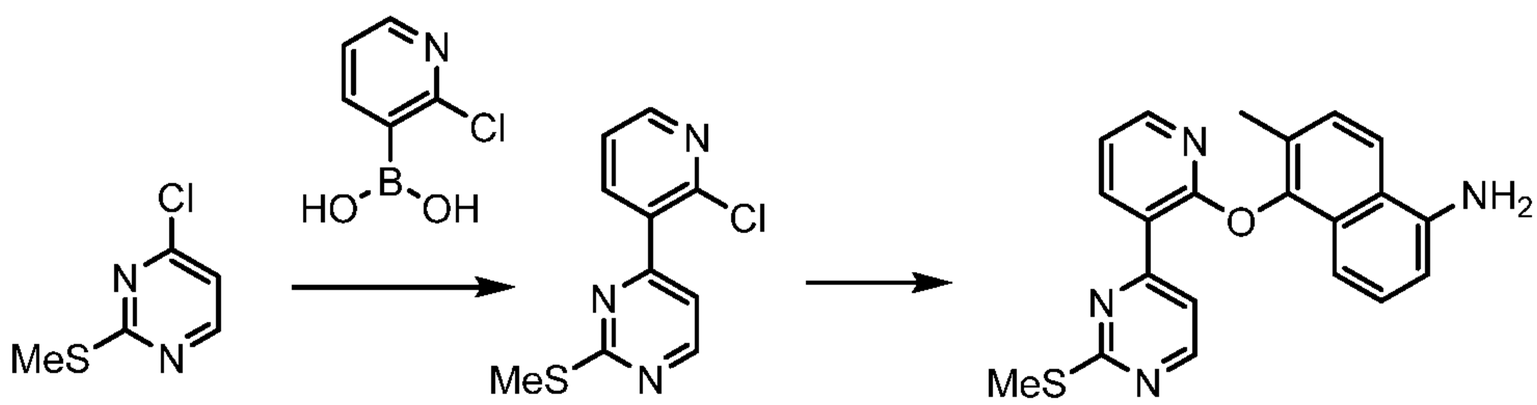
[0209] To a 3 L 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 4-chloro-2-(methylsulfanyl)pyrimidine (80 g, 498 mmol), (2-fluoropyridin-3-yl)boronic acid (98.7 g, 697 mmol), sodium carbonate (117 g, 1.10 mol), tetrakis(triphenylphosphine)palladium(0) (29 g, 24.9 mmol), water (160 mL) and 1,4-dioxane (1.6 L). The resulting solution was stirred at 100 ºC in an oil bath overnight, cooled to rt, and filtered. The filtrate was diluted with brine and was then extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified *via* flash silica chromatography (solvent gradient: 10-50% ethyl acetate in petroleum ether) to yield 80 g (73%) of the title compound as a yellow solid. LCMS (ESI) $[M+H]^+ = 222$.

[0210] Step 6: 6-Methyl-5-(3-(2-(methylthio)pyrimidin-4-yl)pyridin-2-yloxy)naphthalen-1-amine

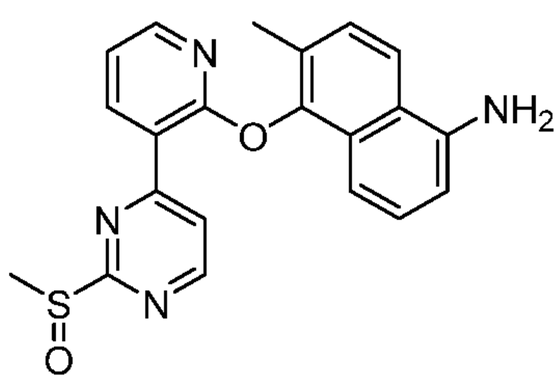


[0211] To a 2 L 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 5-amino-2-methylnaphthalen-1-ol hydrochloride (100 g, 477 mmol), N-methyl-2-pyrrolidone, NMP (1 L), 4-(2-fluoropyridin-3-yl)-2-(methylsulfanyl)pyrimidine (105 g, 477 mmol), and caesium carbonate (328 g, 1.00 mol). The resulting solution was stirred at 120 °C in an oil bath overnight, cooled to room temperature, and diluted with 1 L of brine. The resulting solution was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified *via* flash silica chromatography (solvent gradient: 20-50% ethyl acetate in petroleum ether) to yield 80 g (45%) of the title compound as a brown solid. LCMS (ESI) $[M+H]^+ = 375$.

[0212] Alternatively, the title compound can be prepared by the following scheme where 4-chloro-2-(methylthio)pyrimidine and (2-chloropyridin-3-yl)boronic acid are coupled as in Step 5 to form 4-(2-chloropyridin-3-yl)-2-(methylthio)pyrimidine which is reacted with 5-amino-2-methylnaphthalen-1-ol hydrochloride:



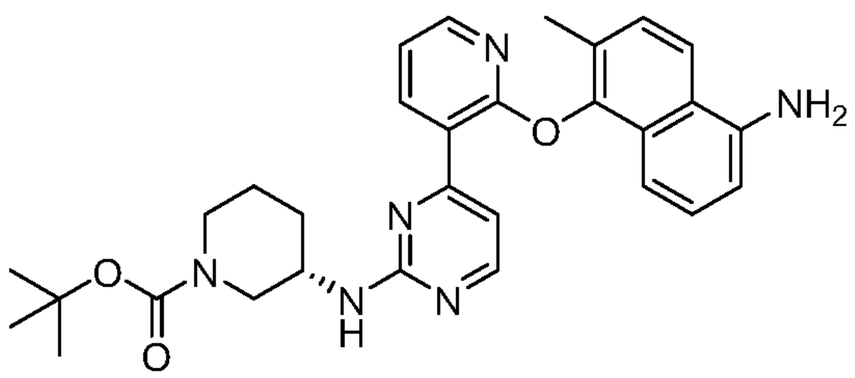
[0213] Step 7: 6-Methyl-5-((3-(2-(methylsulfinyl)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-amine



[0214] To a 3 L 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 6-methyl-5-([3-[2-(methylsulfanyl)pyrimidin-4-yl]pyridin-2-yl]oxy)naphthalen-1-amine (100 g, 267 mmol), DCM (2 L) and 3-chlorobenzene-1-

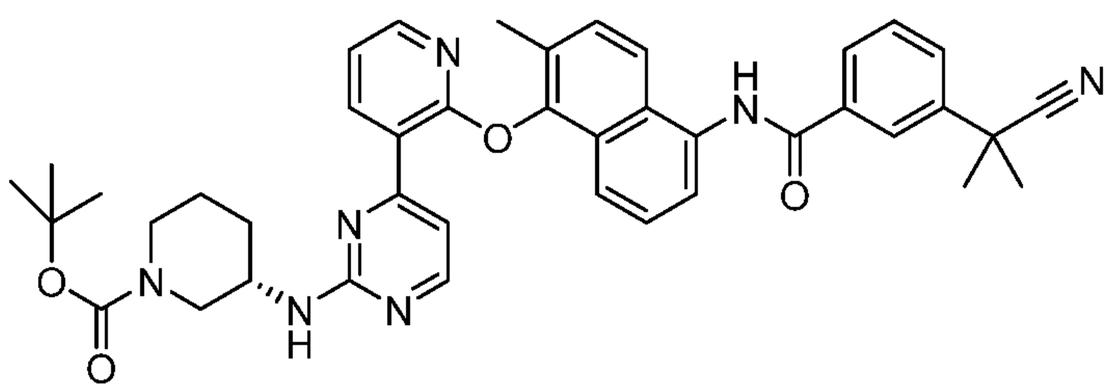
carboperoxoic acid (56 g, 321 mmol). The resulting solution was stirred at rt for 4 h and quenched with the addition of 1 L of a saturated solution of sodium hydrogenocarbonate. The organic phase was separated, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified *via* flash silica chromatography (solvent gradient: 20% ethyl acetate in petroleum ether and then 2% methanol in DCM) to yield 65 g (62%) of the title compound as a yellow solid.

[0215] Step 8: *tert*-Butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0216] To a 2 L 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 5-[[3-(2-methanesulfinylpyrimidin-4-yl)pyridin-2-yl]oxy]-6-methylnaphthalen-1-amine (75 g, 192 mmol), *tert*-butyl (3*S*)-3-aminopiperidine-1-carboxylate (152 g, 768 mmol), 1,4-dioxane (1 L) and DIPEA (98 g, 768 mmol). The resulting solution was stirred at 110 °C in an oil bath overnight, cooled to rt and concentrated *in vacuo*. The residue was purified *via* flash silica chromatography (solvent gradient: 20% ethyl acetate in petroleum ether and then 2% methanol in DCM) to yield 50.5 g (50%) of the title compound as a yellow solid. LCMS: (ES, m/z): $[M+H]^+ = 527$.

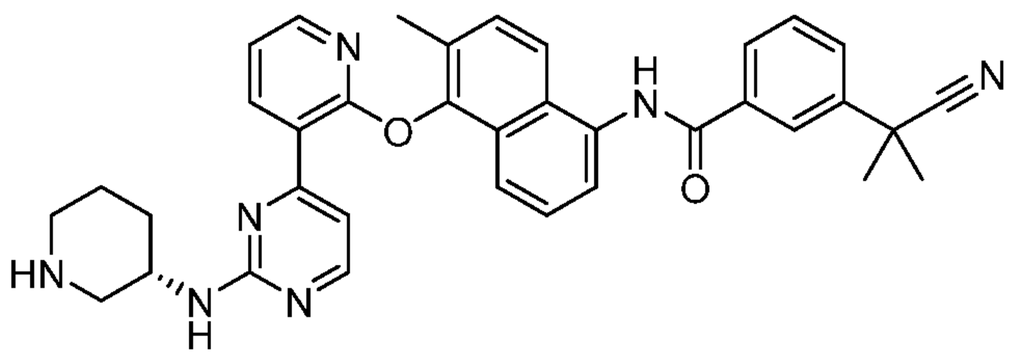
[0217] Step 9: (*S*)-*tert*-Butyl 3-(4-(2-(4-(3-(2-cyanopropan-2-yl)benzamido)-2-methylnaphthalen-1-yloxy)pyridin-3-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate



[0218] A solution of *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (275 mg, 0.52 mmol**),** 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate**,** HATU, CAS Reg. No. 148893-10-1, (218 mg, 0.57 mmol), DIPEA (134 mg, 1.04 mmol), and 3-(2-cyanopropan-2-yl)benzoic acid (108 mg, 0.57 mmol) in dry *N,N*-

dimethylformamide (10 mL) was stirred at room temperature for 12 h. The reaction mixture was poured into water and then extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (petroleum / EtOAc = 2:1 to 1:1) to yield 200 mg (55% yield) of the title compound as a white solid. LCMS (ESI) $[M+H]^+$ = 698.8.

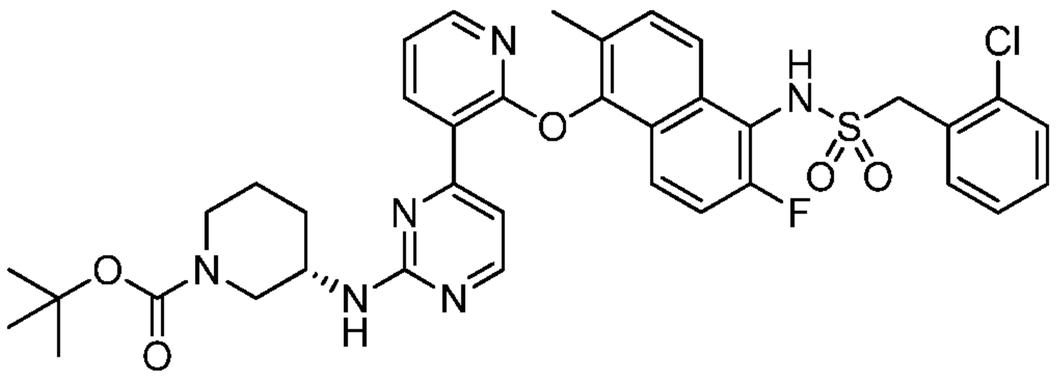
[0219] Step 10: (*S*)-3-(2-Cyanopropan-2-yl)-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)benzamide



[0220] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-(4-(2-(4-(3-(2-cyanopropan-2-yl)benzamido)-2-methylnaphthalen-1-yloxy)pyridin-3-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate (200 mg, 0.31 mmol), ethylacetate (3 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). The residue was purified by Prep-HPLC to yield 100 mg (65%) of **101** as a white solid. LCMS (ESI): $[M+H]^+$ = 598.3; NMR (400 MHz, DMSO-d_6) δ 10.57 (s, 1H), 8.51 (d, J = 7.7 Hz, 1H), 8.42 (d, J = 5.1 Hz, 1H), 8.20 (t, J = 1.9 Hz, 1H), 8.13 – 8.08 (m, 1H), 8.06 (dd, J = 5.0, 1.9 Hz, 1H), 7.85 (d, J = 8.7 Hz, 1H), 7.83 – 7.78 (m, 1H), 7.65 (t, J = 7.8 Hz, 2H), 7.55 (dd, J = 7.4, 1.3 Hz, 1H), 7.50 (dd, J = 8.4, 5.7 Hz, 2H), 7.46 (d, J = 5.2 Hz, 1H), 7.27 (dd, J = 7.6, 4.8 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 4.09 (q, J = 5.2 Hz, 1H), 3.89 (s, 1H), 3.10 (d, J = 11.7 Hz, 1H), 2.78 (m, 1H), 2.47 – 2.37 (m, 2H), 2.23 (s, 3H), 1.93 (d, J = 11.6 Hz, 1H), 1.78 (s, 6H), 1.64 (m, 1H), 1.56 – 1.36 (m, 2H).

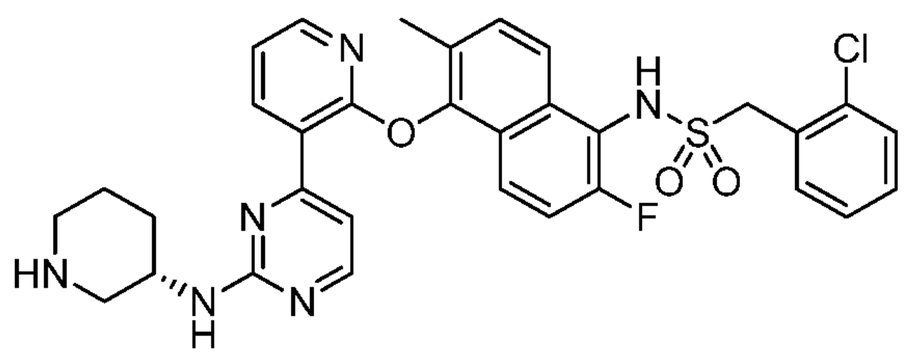
Example 102 *(S)-1-(2-Chlorophenyl)-N-(2-fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide* ***102***

[0221] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-((2-chlorophenyl)methylsulfonamido)-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0222] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 275 (65 mg, 0.12 mmol), pyridine (0.14 mL, 1.79 mmol), DMAP (1.5 mg, 0.01 mmol), DCM (0.9 mL), and (2-chlorophenyl)methanesulfonyl chloride (54 mg, 0.24 mmol). After stirring 1 h at rt, the reaction was diluted with DCM and washed with 1N $KHSO_4$(aq) (10 mL), dried (Na_2SO_4), filtered and evaporated. The crude product was purified by flash chromatography through silica gel (0 - 50% EtOAc/DCM) to provide 58 mg (88% yield) of the title compound as a solid. LCMS (ESI) $[M+H]^+$ = 733.5, rt = 2.04 min.

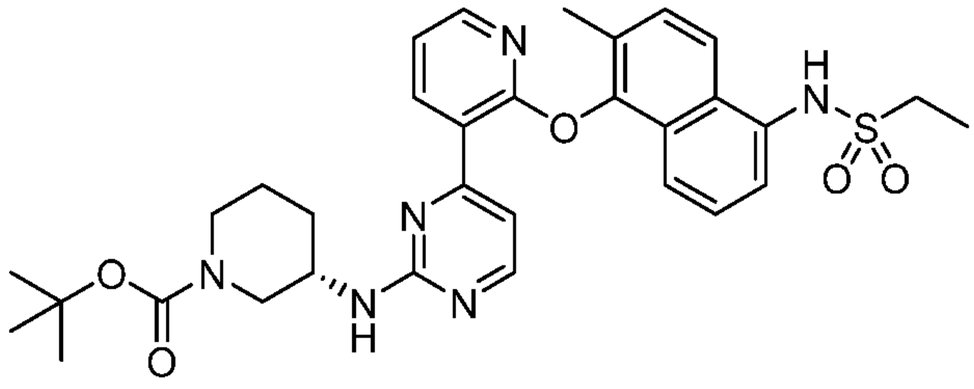
[0223] Step 2: (*S*)-1-(2-Chlorophenyl)-*N*-(2-fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide



[0224] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-((2-chlorophenyl)methylsulfonamido)-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (58 mg, 0.08 mmol), 1,4-dioxane (0.5 mL) and hydrochloric acid (4 M in dioxane, 0.73 mL, 2.92 mmol). After 60 min, the suspension was diluted with Et_2O (15 mL) and the precipitate was filtered and washed with Et_2O. The precipitate was dissolved in MeCN and water and lyophilized to provide 46 mg (88% yield) of **102** as a fluffy light yellow solid. LCMS (ESI) $[M+H]^+$ = 633.5, rt = 1.53 min; ^1H NMR (400 MHz, d6-dmso) δ 10.04 (s, 1H), 8.84 (bs, 2H), 8.66 (s, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.09 (dd, J = 4.8, 2.0 Hz, 1H), 8.02 (d, J = 8.8 Hz, 1H), 7.74 (dd, J = 9.2, 5.1 Hz, 1H), 7.66 - 7.46 (m, 6H), 7.46 - 7.36 (m, 2H), 7.29 (dd, J = 7.6, 4.8 Hz, 1H), 4.77 (s, 2H), 4.27 (s, 1H), 3.50 - 3.37 (m, 1H), 3.21 (d, J = 12.0 Hz, 1H), 2.96 - 2.74 (m, 2H), 2.19 (s, 3H), 2.07 - 1.97 (m, 1H), 1.97 - 1.87 (m, 1H), 1.82 - 1.55 (m, 2H).

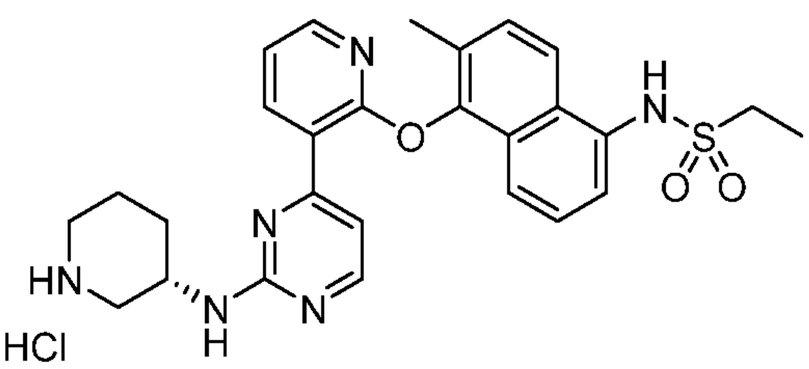
Example 103 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)ethanesulfonamide* ***103***

[0225] Step 1: *tert*-Butyl (*S*)-3-(4-(2-(5-(ethylsulfonamido)-2-methylnaphthalen-1-yloxy)pyridin-3-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate



[0226] The General Procedure A was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (100 mg, 0.19 mmol), pyridine (2 mL) and ethanesulfonyl chloride (29 mg, 0.23 mmol). The residue was purified by Prep-TLC (normal phase, petroleum ether/ethyl acetate = 2 / 1) to yield 110 mg (93%) of the title compound as a white solid. LCMS (ESI) $[M+H]^+$ = 619.

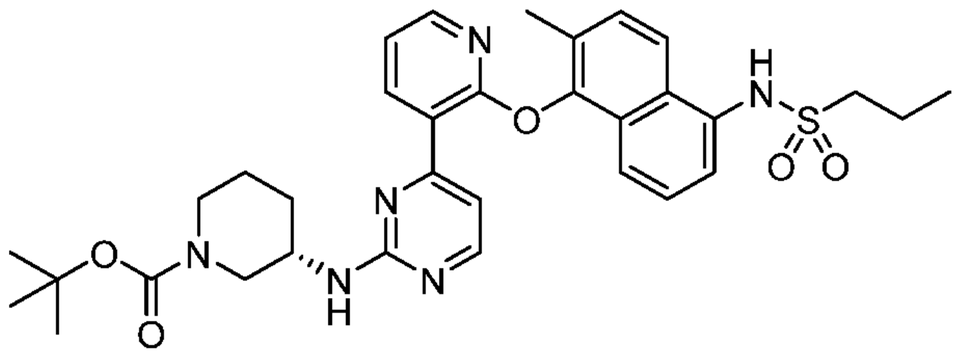
[0227] Step 2: (*S*)-*N*-(6-Methyl-5-(3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yloxy)naphthalen-1-yl)ethanesulfonamide hydrochloride



[0228] The General Procedure B was followed, using *tert*-butyl (*S*)-3-(4-(2-(5-(ethylsulfonamido)-2-methylnaphthalen-1-yloxy)pyridin-3-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate (110 mg, 0.18 mmol), DCM (5 mL) and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% TFA) B: ACN) to yield 40 mg (40%) of hydrochloride **103** as a white solid. LCMS (ESI): $[M+H]^+$ = 519.7; ^{1}H NMR (400 MHz, CD_3OD) δ 8.67 (m, 1H), 8.46 (d, J = 5.6 Hz, 1H), 8.16 (d, J = 8.8 Hz, 1H), 8.01 (m, 1H), 7.71 (d, J = 5.6 Hz, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.57 (s, 1H), 7.54 (s, 1H), 7.39 (t, *J* = 8 Hz, 15.6 Hz, 1H), 7.26-7.22 (m, 1H), 4.37-4.36 (m, 1H), 3.66-3.61 (m, 1H), 3.37-3.32 (m, 1H), 3.21-3.15 (m, 2H), 3.11-3.04 (m, 2H), 2.29 (s, 3H), 2.23-2.11 (m, 2H), 1.93-1.83 (m, 2H), 1.41-1.31 (m, 3H).

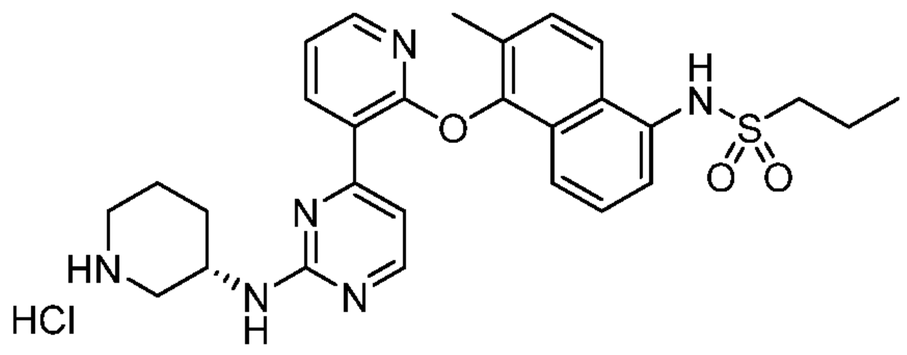
Example 104 *(S)-N-(6-Methyl-5-(3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yloxy)naphthalen-1-yl)propane-1-sulfonamide hydrochloride* ***104***

[0229] Step 1: *tert*-Butyl (*S*)-3-(4-(2-(2-methyl-5-(propylsulfonamido)naphthalen-1-yloxy)pyridin-3-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate



[0230] The General Procedure A was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol), pyridine (2 mL) and 1-propanesulfonyl chloride (200 mg, 1.4 mmol). The crude was then purified by Prep-TLC (petroleum ether/ethyl acetate = 1 / 1) to yield 100 mg (82% yield) of the title compound as a brown solid. LCMS (ESI) $[M+H]^+$ = 633.

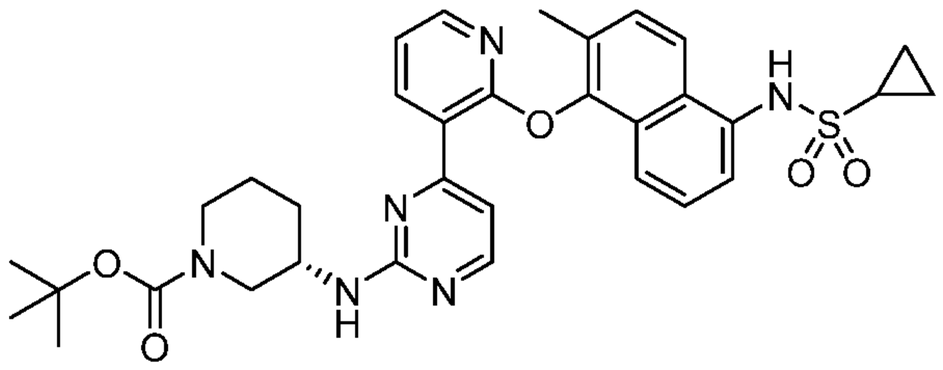
[0231] Step 2: (*S*)-*N*-(6-Methyl-5-(3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yloxy)naphthalen-1-yl)propane-1-sulfonamide hydrochloride



[0232] The General Procedure B was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[[2-methyl-5-(propylsulfonylamino)-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.16 mmol), DCM (5 mL) and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). The residue was purified by Prep-HPLC to yield 52 mg (62%) of **104** as a white solid. LCMS (ESI): $[M+H]^+$ = 533; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.54 (s, 1H), 8.43 (d, J = 5.1 Hz, 1H), 8.33 (s, 1H), 8.13 (d, J = 8.7 Hz, 1H), 8.04 (dd, J = 4.8, 1.9 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.49 (d, J = 5.1 Hz, 1H), 7.46 – 7.37 (m, 2H), 7.32 – 7.24 (m, 2H), 4.06 (s, 1H), 3.24 (d, J = 10.5 Hz, 1H), 3.16 – 3.08 (m, 2H), 2.97 (d, J = 12.3 Hz, 1H), 2.71 – 2.54 (m, 2H), 2.21 (s, 3H), 1.96 (s, 1H), 1.83 – 1.69 (m, 3H), 1.56 (s, 2H), 0.96 (t, J = 7.4 Hz).

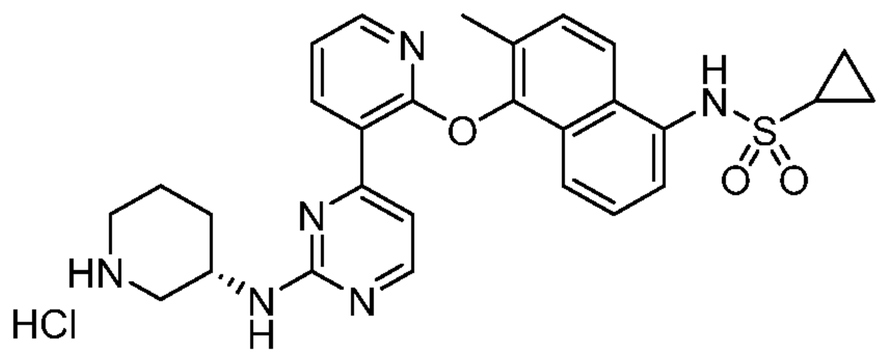
Example 105 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropanesulfonamide hydrochloride* ***105***

[0233] Step 1: *tert*-Butyl (*S*)-3-(4-(2-(2-methyl-5-(cyclopropanesulfonamido)naphthalen-1-yloxy)pyridin-3-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate



[0234] The General Procedure A was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (100 mg, 0.19 mmol), pyridine (2 mL) and cyclopropanesulfonyl chloride (200 mg, 1.4 mmol). The crude was then purified by Prep-TLC (petroleum ether/ethyl acetate = 1 / 1) to yield 37 mg (29% yield) of the title compound as a white solid. LCMS (ESI) $[M+H]^+$ = 631.

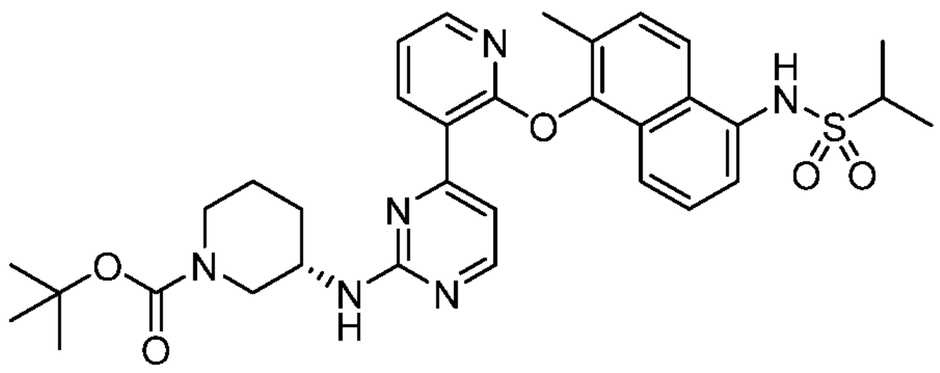
[0235] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropanesulfonamide hydrochloride



[0236] The General Procedure B was followed, using *tert*-butyl (*S*)-3-(4-(2-(2-methyl-5-(cyclopropanesulfonamido)naphthalen-1-yloxy)pyridin-3-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate (37 mg, 0.16 mmol), DCM (5 mL) and hydrochloric acid (4 M in dioxane, 1 mL, 4 mmol). The residue was purified by Prep-HPLC to yield 16 mg (52%) of hydrochloride **105** as a white solid. LCMS (ESI): $[M+H]^+$ = 531; 1H NMR (400 MHz, CD3OD) δ 8.67 (d, J = 6.8 Hz, 1H), 8.58 (s, 1H), 8.44 (d, J = 5.2 Hz, 1H), 8.21 (d, J = 8.7 Hz, 1H), 8.07 – 7.95 (m, 1H), 7.76 – 7.65 (m, 2H), 7.56 (dd, J = 12.2, 8.1 Hz, 2H), 7.39 (t, J = 7.9 Hz, 15.8 Hz, 1H), 7.23 (dd, J = 7.5, 4.9 Hz, 1H), 4.33 (s, 1H), 3.58 (d, J = 9.8 Hz, 1H), 3.27 (s, 1H), 2.98 (t, J = 10.8 Hz, 21.6 Hz, 2H), 2.73 – 2.56 (m, 1H), 2.28 (s, 3H), 2.19 (d, J = 11.1 Hz, 1H), 2.07 (d, J = 14.1 Hz, 1H), 1.96 – 1.68 (m, 2H), 1.03 (d, J = 3.2 Hz, 2H), 0.95 (d, J = 7.5 Hz, 2H).

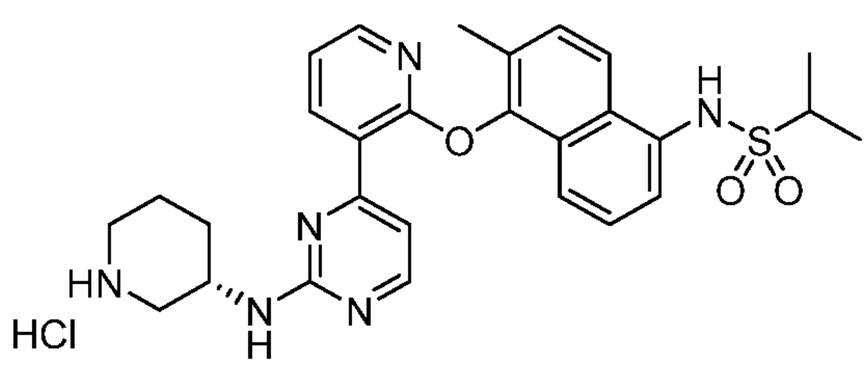
Example 106 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl) methylethylsulfonamide hydrochloride* ***106***

[0237] Step 1: *tert*-Butyl (*S*)-3-(4-(2-(2-methyl-5-(methylethylpropanesulfonamido)naphthalen-1-yloxy)pyridin-3-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate



[0238] The General Procedure A was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (100 mg, 0.19 mmol), pyridine (2 mL) and isopropylsulfonyl chloride (32 mg, 0.23 mmol). The crude was then purified by Prep-TLC (petroleum ether/ethyl acetate = 2 / 1) to yield (50 mg, 0.08 mmol, 40% yield) as a white solid.

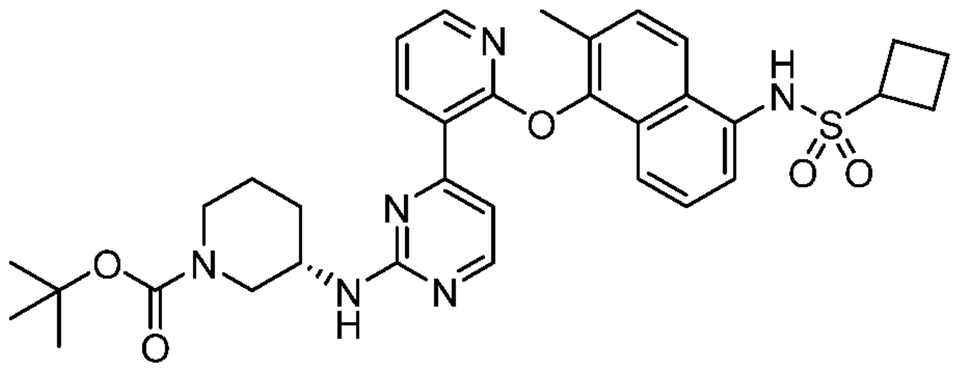
[0239] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl) methylethylsulfonamide hydrochloride



[0240] The General Procedure B was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[[2-methyl-5-(propylsulfonylamino)-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (50 mg, 0.08 mmol), DCM (5 mL) and hydrochloric acid (4 M in dioxane, 1 mL, 4 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% TFA) B: ACN) to yield 30 mg (60%) of hydrochloride **106** as a white solid. LCMS (ESI): $[M+H]^+$ = 533.7; ^1H NMR (400 MHz, CD_3OD) δ 8.66 (d, J = 6.8Hz, 1H), 8.46 (d, J = 5.2Hz, 1H), 8.17(d, J = 8.8Hz, 1H), 8.01 (m, 1H), 7.71 (d, J = 5.2Hz, 1H), 7.63-7.54 (m, 3H), 7.38 (t, J = 8 Hz, 16.4 Hz, 1H), 7.26-7.22 (m, 1H), 4.37 (s, 1H), 3.66-3.62 (m, 1H), 3.41-3.28 (m, 2H), 3.11-3.04 (m, 2H), 2.28 (s, 3H), 2.23-2.11 (m, 2H), 1.92-1.80 (m, 2H), 1.42 (s, 3H), 1.40 (s, 3H).

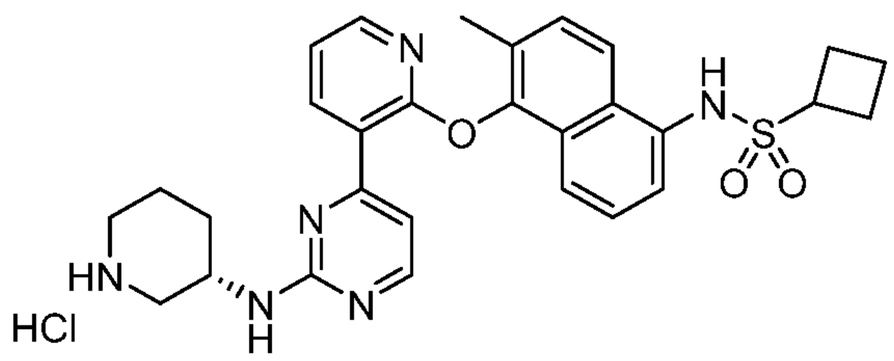
Example 107 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclobutanesulfonamide hydrochloride* ***107***

[0241] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((5-(Cyclobutanesulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0242] The General Procedure A was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (100 mg, 0.19 mmol), pyridine (2 mL) and cyclobutanesulfonyl chloride (35 mg, 0.23 mmol). The crude was then purified by Prep-TLC (petroleum ether/ethyl acetate = 1 / 1) to yield 120 mg (95% yield) of the title compound as a brown solid. LCMS (ESI) $[M+H]^+$ = 645.

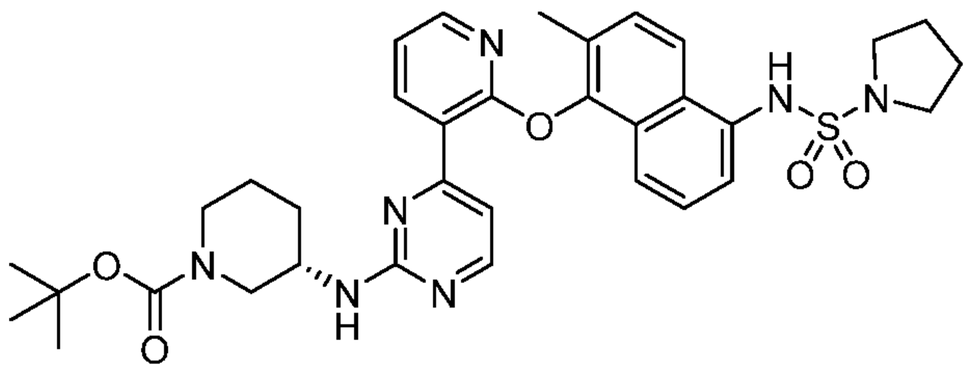
[0243] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclobutanesulfonamide hydrochloride



[0244] The General Procedure B was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[[2-methyl-5-(propylsulfonylamino)-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (120 mg, 0.19 mmol), DCM (5 mL) and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). The residue was purified by Prep-HPLC to yield 90 mg (88% yield) of **107** as a white solid. LCMS (ESI): $[M+H]^+$ = 560; ^1H NMR (400 MHz, CD_3OD) δ 8.68 (d, J = 7.2 Hz, 1H), 8.45 (d, J = 5.6 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 8.01 (m, 1H), 7.74 (s, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.53 (t, J = 8.8 Hz, 16.4 Hz, 2H), 7.38 (t, J = 8.4 Hz, 16.8 Hz, 1H), 7.26-7.23 (m, 1H), 4.39 (s, 1H), 3.97-3.88 (m, 1H), 3.66-3.62 (m, 1H), 3.37-3.32 (m, 1H), 3.11-3.03 (m, 2H), 2.56-2.46 (m, 2H), 2.28-2.21 (m, 7H), 2.12-1.88 (m, 4H).

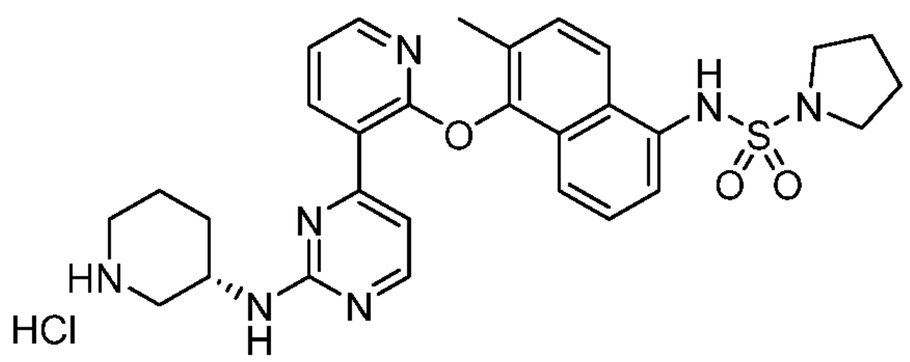
Example 108 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidine-1-sulfonamide hydrochloride* ***108***

[0245] Step 1: *tert*-Butyl (S)-3-((4-(2-((2-methyl-5-(pyrrolidine-1-sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0246] The General Procedure A was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (100 mg, 0.19 mmol), pyridine (2 mL) and pyrrolidine-1-sulfonyl chloride (200 mg, 1.18 mmol). The crude was then purified by Prep-TLC (petroleum ether/ethyl acetate = 1 / 1) to yield 100 mg (73% yield) of the title compound as a white solid. LCMS (ESI) $[M+H]^+$ = 660.

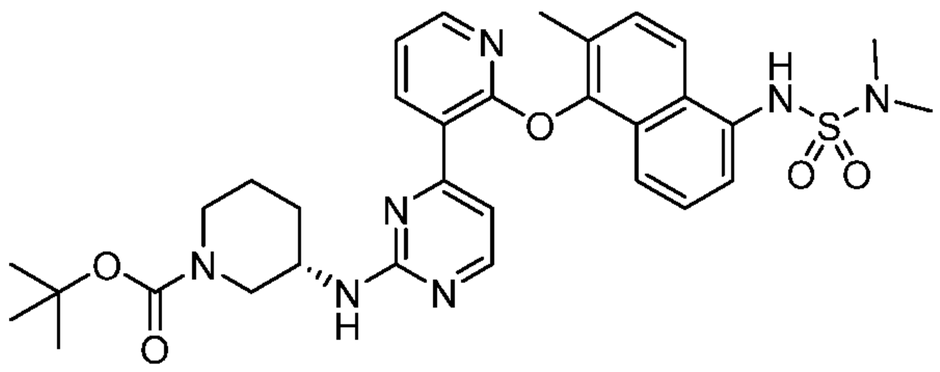
[0247] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidine-1-sulfonamide hydrochloride



[0248] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-(pyrrolidine-1-sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.15 mmol), DCM (5 mL) and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). The residue was purified by Prep-HPLC to yield 36 mg (42% yield) of hydrochloride **108** as a white solid. LCMS (ESI): $[M+H]^+$ = 560; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.43 (d, J = 5.1 Hz, 1H), 8.35 (s, 1H), 8.15 (d, *J* = 8.7 Hz, 1H), 8.04 (dd, J = 4.7, 1.8 Hz, 1H), 7.51 (dd, J = 13.4, 7.2 Hz, 4H), 7.39 (t, J = 7.9 Hz, 15.8 Hz, 1H), 7.34 – 7.21 (m, 2H), 4.05 (s, 1H), 3.19 (s, 5H), 2.96 (d, J = 11.2 Hz, 1H), 2.73 – 2.53 (m, 2H), 2.21 (s, 3H), 1.96 (s, 1H), 1.78 – 1.73 (m, 5H), 1.56 (d, J = 8.6 Hz, 2H).

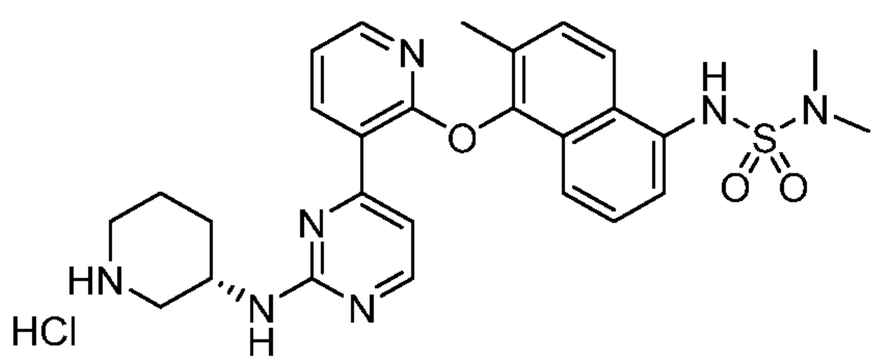
Example 109 *4-[2-[[5-(Dimethylsulfamoylamino)-2-methyl-1-naphthyl]oxy]-3-pyridyl]-2-[[(3S)-3-piperidyl]amino]pyrimidine hydrochloride* ***109***

[0249] Step 1: *tert*-Butyl 3-(4-(2-(5-(*N,N*-dimethylsulfamoylamino)-2-methylnaphthalen-1-yloxy)pyridin-3-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate



[0250] The General Procedure A was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (100 mg, 0.19 mmol), pyridine (2 mL) and dimethylsulfamoyl chloride (200 mg, 1.39 mmol). The crude was then purified by Prep-TLC (petroleum ether/ethyl acetate = 1 / 1) to yield 90 mg (70% yield) of the title compound as a white solid. LCMS (ESI) [M+H]+ = 634.

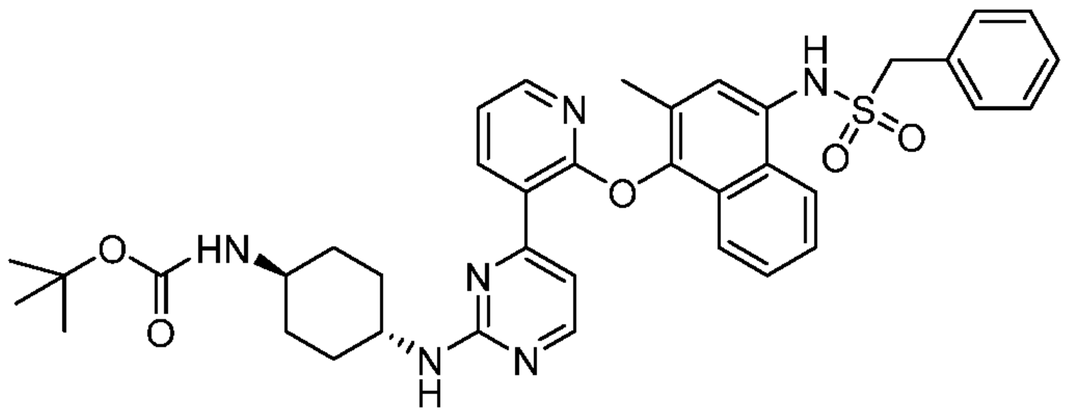
[0251] Step 2: 4-[2-[[5-(Dimethylsulfamoylamino)-2-methyl-1-naphthyl]oxy]-3-pyridyl]-2-[[(3*S*)-3-piperidyl]amino]pyrimidine hydrochloride



[0252] The General Procedure B was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[[5-(dimethylsulfamoylamino)-2-methyl-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (90 mg, 0.14 mmol), DCM (5 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). The residue was purified by Prep-HPLC to yield 42 mg (55% yield) of hydrochloride **109** as a white solid. LCMS (ESI): $[M+H]^+$ = 534; ^1H NMR (400 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.43 (d, J = 5.1 Hz, 1H), 8.34 (s, 1H), 8.17 (d, J = 8.7 Hz, 1H), 8.04 (dd, J = 4.8, 1.8 Hz, 1H), 7.49 (dd, J = 16.7, 8.1 Hz, 4H), 7.40 – 7.33 (m, 1H), 7.33 – 7.22 (m, 2H), 4.06 (s, 1H), 3.23 (s, 1H), 2.95 (s, 1H), 2.72 (s, 6H), 2.62 (s, 2H), 2.21 (s, 3H), 1.97 (s, 1H), 1.76 (s, 1H), 1.56 (s, 2H).

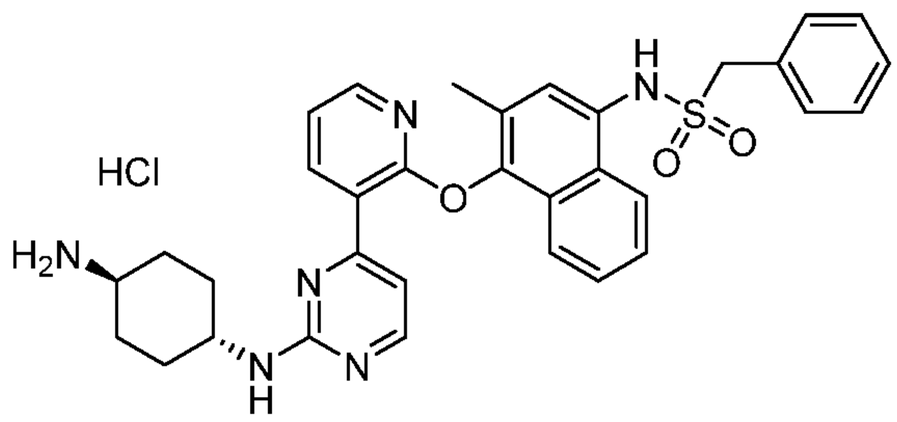
Example 110 *N-(4-((3-(2-(((1r,4r)-4-aminocyclohexyl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)-1-phenylmethanesulfonamide hydrochloride* ***110***

[0253] Step 1: *tert*-Butyl ((*trans*)-4-((4-(2-((2-methyl-4-((phenylmethyl)sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)cyclohexyl)carbamate



[0254] The General Procedure A was followed, using *tert*-butyl *N*-[4-[[4-[2-[(4-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]cyclohexyl]carbamate (90 mg, 0.17 mmol), pyridine (2 mL) and alpha-toluenesulfonylchloride (222 mg, 1.17 mmol). The crude was then purified by Prep-TLC (petroleum ether/ethyl acetate = 1 / 1) to yield 100 mg (86% yield) of the title compound as a yellow solid. LCMS (ESI) [M+H]+ = 695.

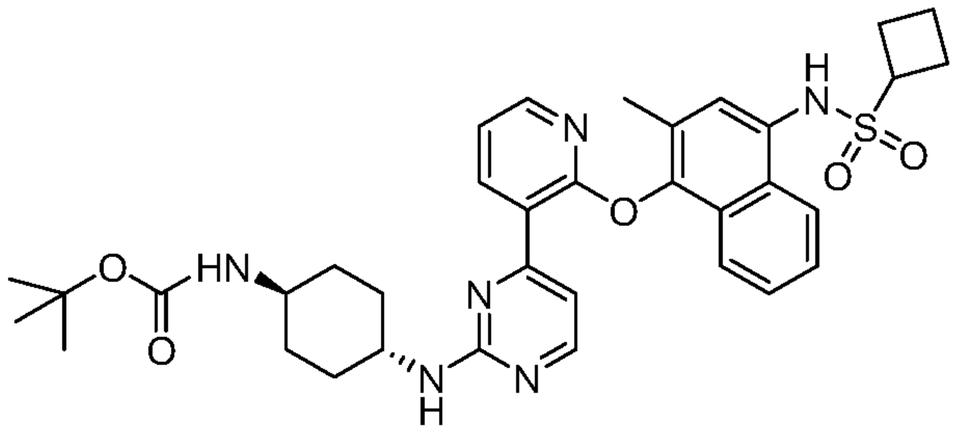
[0255] Step 2: *N*-(4-((3-(2-(((*trans*)-4-aminocyclohexyl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)-1-phenylmethanesulfonamide



[0256] The General Procedure B was followed, using *tert*-butyl ((1*r*,4*r*)-4-((4-(2-((2-methyl-4-((phenylmethyl)sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)cyclohexyl)carbamate (100 mg, 0.14 mmol), DCM (5 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). The residue was purified by Prep-HPLC to yield 39 mg (42% yield) of the title compound as a yellow solid.

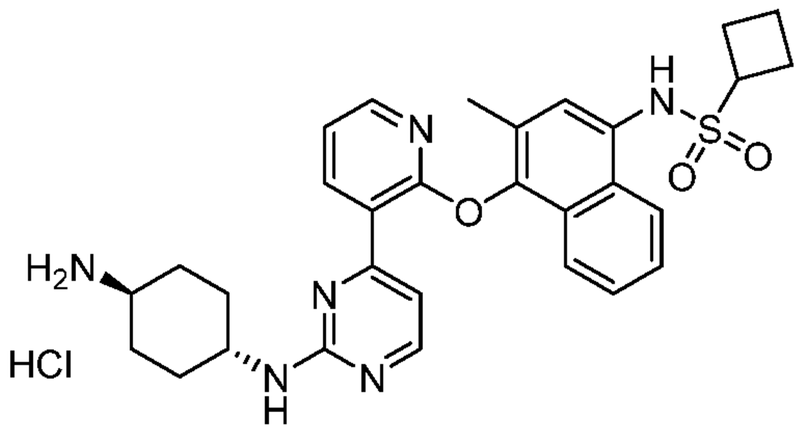
Example 111 *N-(4-((3-(2-(((trans)-4-Aminocyclohexyl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)cyclobutanesulfonamide hydrochloride* ***111***

[0257] Step 1: *tert*-Butyl ((*trans*)-4-((4-(2-((4-(Cyclobutanesulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)cyclohexyl)carbamate



[0258] The General Procedure A was followed, using *tert*-butyl *N*-[4-[[4-[2-[(4-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]cyclohexyl]carbamate (100 mg, 0.19 mmol), pyridine (2 mL) and cyclobutanesulfonyl chloride (43 mg, 0.28 mmol). The crude was then purified by Prep-TLC (petroleum ether/ethyl acetate = 1 / 1) to yield 60 mg (50% yield) of the title compound as a white solid. LCMS (ESI) [M+H]+ = 660.

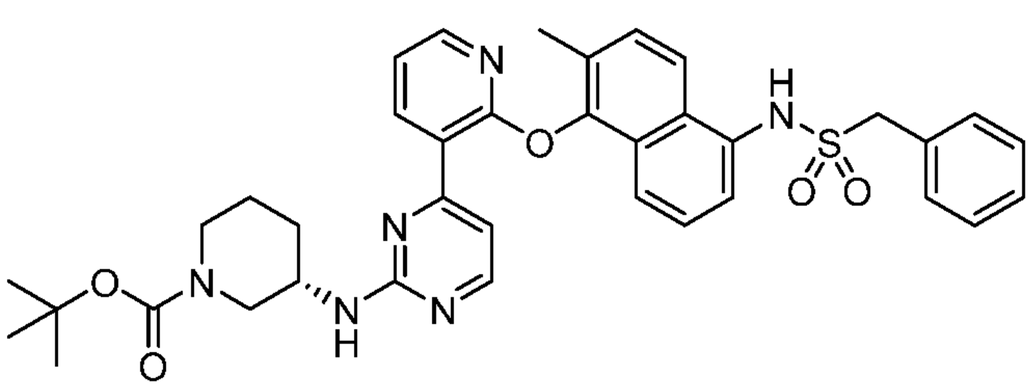
[0259] Step 2: *N*-(4-((3-(2-(((*trans*)-4-Aminocyclohexyl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)cyclobutanesulfonamide hydrochloride



[0260] The General Procedure B was followed, using *tert*-butyl ((1*r*,4*r*)-4-((4-(2-((4-(cyclobutanesulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)cyclohexyl)carbamate (60 mg, 0.09 mmol), DCM (5 mL) and hydrochloric acid (4 M in dioxane, 1 mL, 4.1 mmol). The residue was purified by Prep-HPLC to yield 42 mg (55% yield) of **111** as a yellow solid. LCMS (ESI): $[M+H]^+$ = 560; ^1H NMR (400 MHz, CD_3OD) δ 8.61 (d, J = 7.6 Hz, 1H), 8.40 (d, J = 5.6 Hz, 1H), 8.23 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 4.4 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.76-7.68 (m, 1H), 7.56 (d, J = 7.2 Hz, 1H), 7.53 (s, 1H), 7.46 (t, J = 15.2, 8 Hz, Hz, 1H), 7.27-7.25 (m, 1H), 3.94-4.02 (m, 2H), 3.20-3.14 (m, 1H), 2.56-2.48 (m, 2H), 2.33-2.28 (m, 7H), 2.14-2.11 (m, 2H), 2.05-1.96 (m, 2H), 1.51-1.72 (m, 4H).

Example 112 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-phenylmethanesulfonamide hydrochloride* ***112***

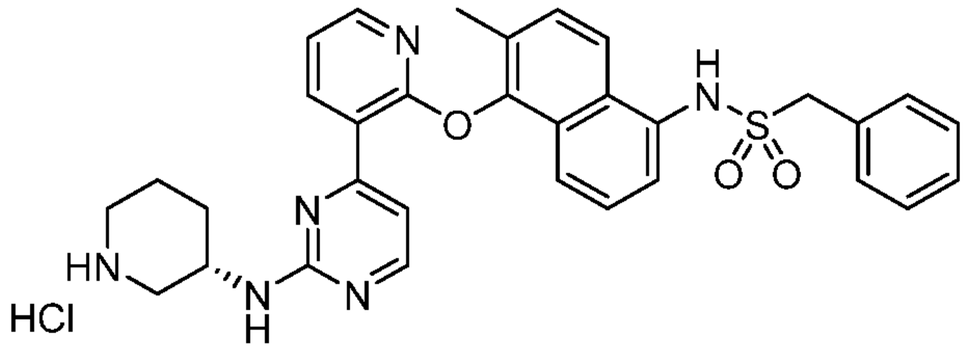
[0261] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-((phenylmethyl)sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0262] The General Procedure A was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (90 mg, 0.17 mmol), pyridine (2 mL) and alpha-toluenesulfonylchloride (162

mg, 0.85 mmol). The crude was then purified by Prep-TLC (petroleum ether/ethyl acetate = 1 / 1) to yield 130 mg (72% yield) of the title compound as a white solid. LCMS (ESI) [M+H]+ = 681.

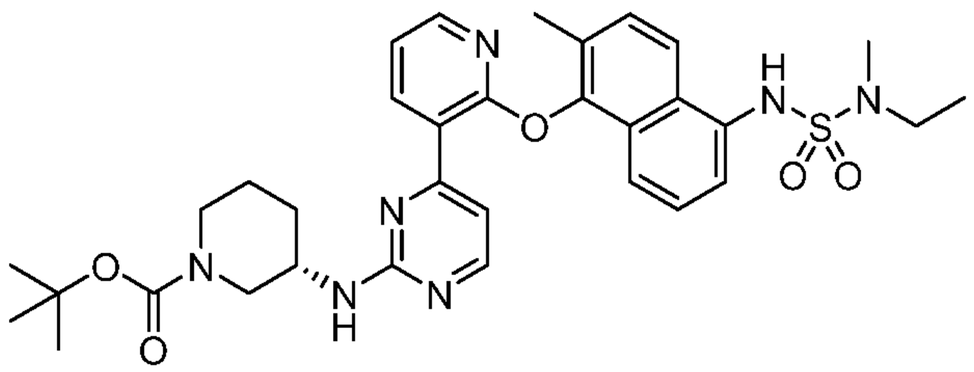
[0263] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-phenylmethanesulfonamide hydrochloride



[0264] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-((phenylmethyl)sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (130 mg, 0.19 mmol), DCM (5 mL) and hydrochloric acid (4 M in dioxane, 4 mL, 16 mmol). The residue was purified by Prep-HPLC to yield 60 mg (50% yield) of **112** as a white solid. LCMS (ESI): $[M+H]^+$ = 581; ^1H NMR (400 MHz, CD_3OD) δ 8.68 (d, J = 6.4 Hz, 1H), 8.46 (d, J = 5.2 Hz, 1H), 8.02-8.00 (m, 2H), 7.74 (d, J = 5.2 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.51-7.48 (m, 2H), 7.38-7.33 (m, 6H), 7.26-7.23 (m, 1H), 4.48 (s, 2H), 4.41-4.36 (m, 1H), 3.64 (dd, J = 12.4, 3.2 Hz, 1H), 3.32-3.42 (m, 1H), 3.11-3.03 (m, 2H), 2.33 (s, 3H), 2.28-2.11 (m, 2H), 1.93-1.80 (m, 2H).

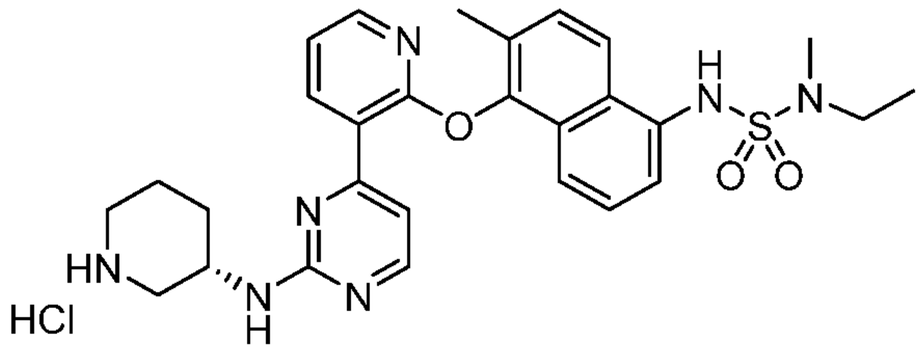
<u>Example 113</u> 4-[2-[[5-[[Ethyl(methyl)sulfamoyl]amino]-2-methyl-1-naphthyl]oxy]-3-pyridyl]-2-[[(3S)-3-piperidyl]amino]pyrimidine hydrochloride ***113***

[0265] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((5-((*N*-ethyl-*N*-methylsulfamoyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0266] The General Procedure A was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (90 mg, 0.17 mmol), pyridine (2 mL) and *N*-ethyl-*N*-methyl-sulfamoyl chloride (269 mg, 1.71 mmol). The crude was then purified by Prep-TLC (petroleum ether/ethyl acetate = 1 / 1) to yield 80 mg (72% yield) of the title compound as a yellow solid. LCMS (ESI) [M+H]+ = 648.

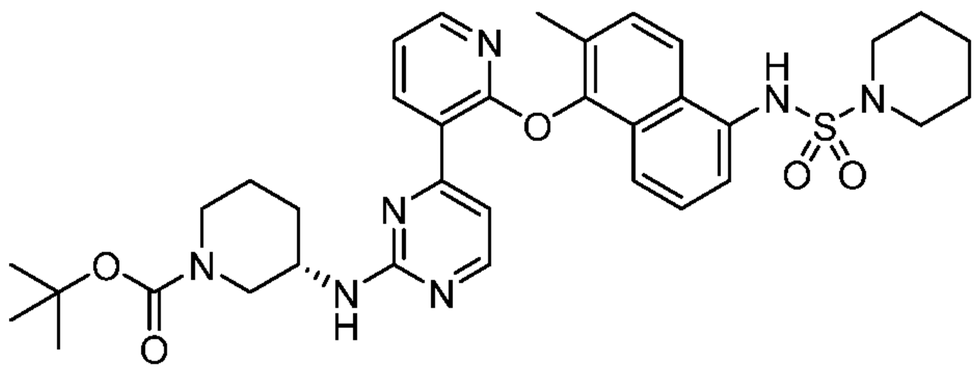
[0267] Step 2: 4-[2-[[5-[[Ethyl(methyl)sulfamoyl]amino]-2-methyl-1-naphthyl]oxy]-3-pyridyl]-2-[[(3S)-3-piperidyl]amino]pyrimidine hydrochloride



[0268] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-((*N*-ethyl-*N*-methylsulfamoyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (80 mg, 0.12 mmol), DCM (8 mL) and hydrochloric acid (4 M in dioxane, 4 mL, 16 mmol). The residue was purified by Prep-HPLC to yield 18 mg (25% yield) of **113** as a white solid. LCMS (ESI): $[M+H]^+$ = 548; ^1H NMR (400 MHz, CD_3OD) δ 8.66 (d, J = 6.8 Hz, 1H), 8.46 (d, J = 5.2 Hz, 1H), 8.16 (d, J = 8.8 Hz, 1H), 8.01 (dd, J = 1.6, 4.8 Hz, 1H), 7.71 (d, J = 5.2 Hz, 1H), 7.60-7.52 (m, 3H), 7.39-7.35 (m, 1H), 7.25-7.22 (m, 1H), 4.40-4.33 (m, 1H), 3.63 (dd, J = 3.2, 12.4 Hz, 1H), 3.38-3.32 (m, 1H), 3.25-3.18 (m, 2H), 3.08-3.02 (m, 2H), 2.83 (s, 3H), 2.28 (s, 3H), 2.24-2.09 (m, 2H), 1.95-1.77 (m, 2H), 1.09-1.05 (m, 3H).

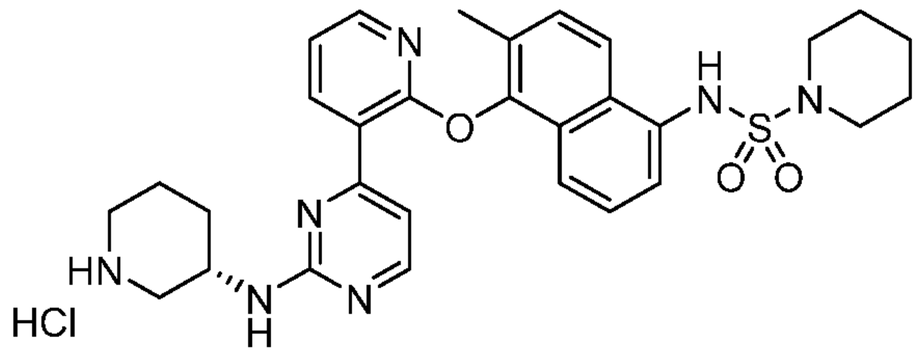
Example 114 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)piperidine-1-sulfonamide hydrochloride* ***114***

[0269] Step1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-(piperidine-1-sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0270] The General Procedure A was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (100 mg, 0.19 mmol), pyridine (2 mL) and piperidine-1-sulfonylchloride (200 mg, 1.09 mmol). The crude was then purified by Prep-TLC (petroleum ether/ethyl acetate = 1 / 1) to yield 100 mg (78% yield) of the title compound as a white solid. LCMS (ESI) [M+H]+ = 674.

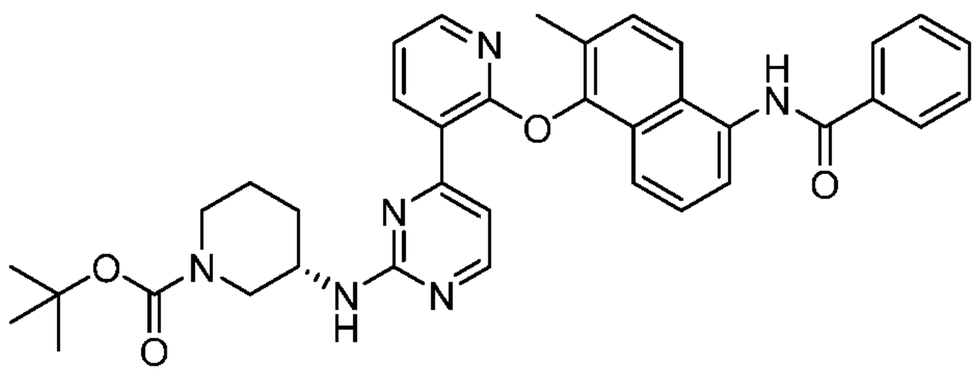
[0271] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)piperidine-1-sulfonamide hydrochloride



[0272] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-(piperidine-1-sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.15 mmol), DCM (5 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). The residue was purified by Prep-HPLC to yield 42 mg (55% yield) of **114** as a white solid. LCMS (ESI): $[M+H]^+$ = 574; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.77 (s, 1H), 8.71 (s, 2H), 8.58 (s, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.15 (d, J = 8.7 Hz, 1H), 8.06 (dd, J = 4.7, 1.8 Hz, 1H), 7.65 – 7.48 (m, 5H), 7.41 (t, *J* = 7.9 Hz, 15.8 Hz, 1H), 7.27 (dd, J = 7.5, 4.9 Hz, 1H), 4.25 (s, 1H), 3.45 (s, 1H), 3.23 (d, J = 12.8 Hz, 1H), 3.13 (s, 4H), 2.86 (s, 2H), 2.21 (s, 3H), 2.02 (d, J = 10.0 Hz, 1H), 1.93 (d, J = 13.9 Hz, 1H), 1.81 – 1.57 (m, 2H), 1.52 – 1.40 (m, 6H).

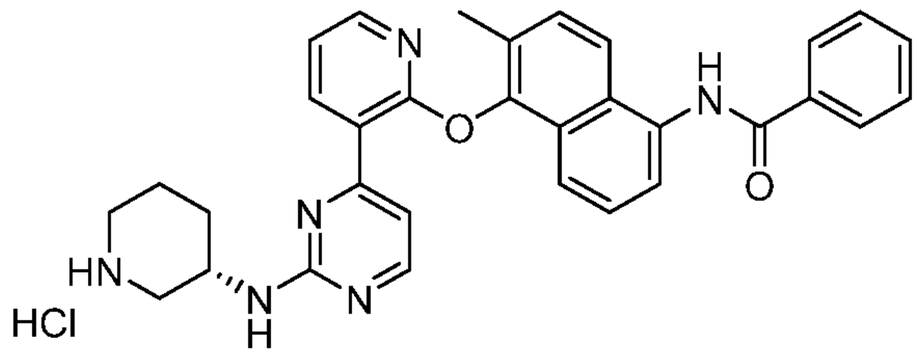
Example 115 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)benzamide hydrochloride* ***115***

[0273] Step1: *tert*-Butyl (*S*)-3-((4-(2-((5-benzamido-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0274] To an ice-cooled solution of *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol) and pyridine (1 mL) in dichloromethane (5 mL) was added benzoyl chloride (29 mg, 0.21 mmol). After being stirred at room temperature for 1 h, the mixture was concentrated to give crude tert-butyl (3*S*)-3-[[4-[2-[(5-benzamido-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (120 mg, 94% yield) as a yellow solid, which was used in the next step without further purification. LCMS (ESI) [M+H]+ = 631.3.

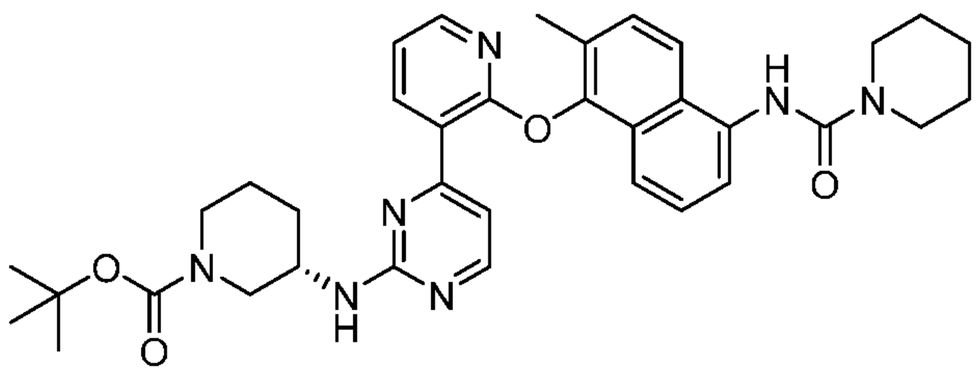
[0275] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)benzamide hydrochloride



[0276] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-(piperidine-1-sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (120 mg, 0.19 mmol), DCM (5 mL) and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). The residue was purified by Prep-HPLC to yield 99 mg (91% yield) of **115** as a white solid. LCMS (ESI): R_T (min) = 1.562, $[M+H]^+$ = 531.3, method = A; ^1H NMR (400 MHz, CD_3OD) δ 8.68 (d, J = 6.8 Hz, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.11-8.09 (m, 2H), 8.03-8.02 (m, 1H), 7.92-7.91 (m, 1H), 7.77-7.76 (m, 1H), 7.72-7.64 (m, 2H), 7.61-7.57 (m, 3H), 7.53-7.45 (m, 2H), 7.25 (dd, J = 4.8, 7.6 Hz, 1H), 4.42-4.40 (m, 1H), 3.65-3.62 (m, 1H), 3.36-3.33 (m, 1H), 3.12-3.03 (m, 2H), 2.29 (s, 3H), 2.23-2.11 (m, 2H), 1.95-1.81 (m, 2H).

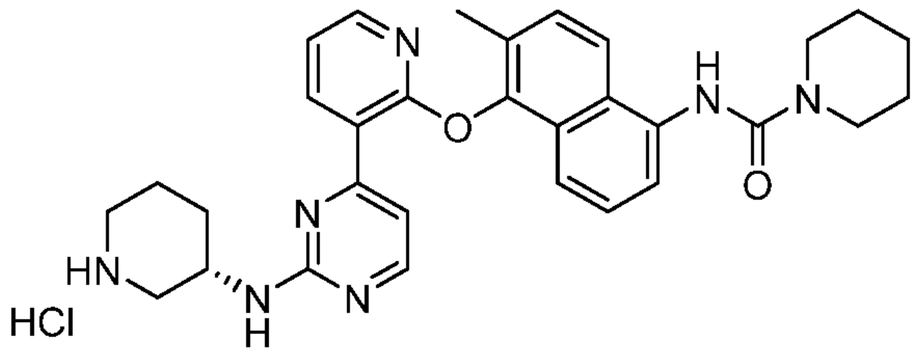
Example 116 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)piperidine-1-carboxamide hydrochloride* ***116***

[0277] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-(piperidine-1-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0278] To a solution of *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol) and triethylamine (38 mg, 0.38 mmol) in dry tetrahydrofuran (5 mL) was added triphosgene (33 mg, 0.11 mmol) at 0 °C. After addition, the reaction mixture was stirred at rt for 1 h. Then piperidine (16 mg, 0.19 mmol) was added to the reaction and continued to stir at rt for 2 h. The reaction was concentrated to dryness and the residue was taken up in ethyl acetate (20 mL). The organics were washed with water and brine. The organics were then separated and dried (magnesium sulphate) before concentration to dryness. The crude was then purified by Prep-TLC (petroleum ether/ethyl acetate = 1 / 1) to yield 100 mg (56% yield) of the title compound as a white solid. LCMS (ESI) [M+H]+ = 638.

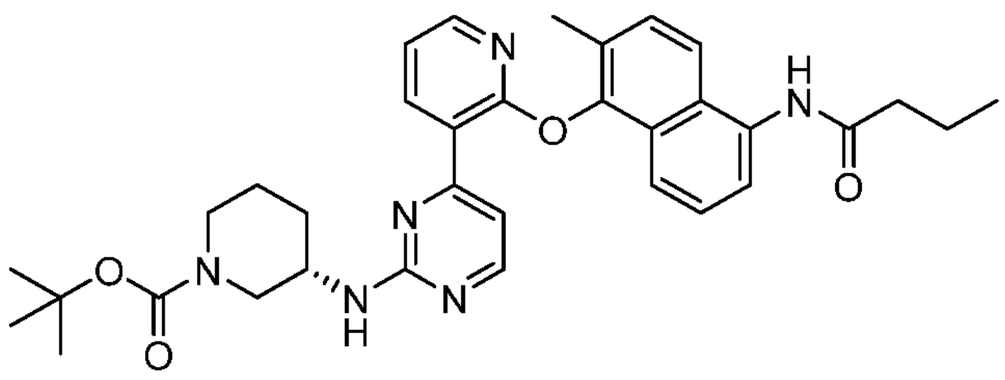
[0279] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)piperidine-1-carboxamide hydrochloride



[0280] To a mixture of *tert*-butyl (S)-3-((4-(2-((2-methyl-5-(piperidine-1-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.16 mmol) in DCM (5 mL) was added hydrochloric acid (4 M in dioxane, 3 mL, 12.48 mmol). Then the mixture was stirred at rt for 1 h. The mixture was concentrated to dryness. The residue was purified by Prep-HPLC to yield 34 mg (40% yield) of **116** as a white solid. LCMS (ESI): M+H]$^+$ = 538; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 1H), 8.44 (d, J = 5.2 Hz, 1H), 8.35 (s, 1H), 8.10 – 8.03 (m, 1H), 7.76 (d, J = 8.7 Hz, 1H), 7.52 (d, J = 5.1 Hz, 1H), 7.45 (d, J = 8.7 Hz, 2H), 7.41 – 7.30 (m, 3H), 7.26 (dd, J = 7.6, 4.7 Hz, 1H), 4.08 (s, 2H), 3.51 (d, J = 5.6 Hz, 4H), 3.25 (s, 1H), 2.99 (d, *J* = 11.0 Hz, 1H), 2.70 – 2.57 (m, 2H), 2.21 (s, 3H), 1.98 (s, 1H), 1.77 (s, 1H), 1.62 (s, 2H), 1.56 (s, 6H).

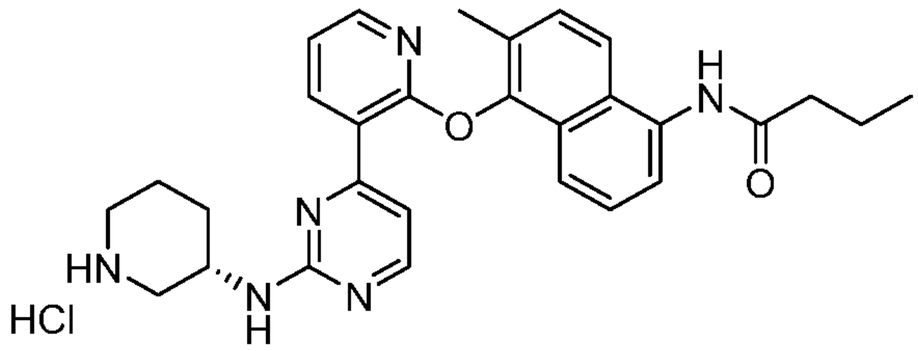
Example 117 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)butyramide hydrochloride* ***117***

[0281] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((5-butyramido-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0282] To a solution of *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol) and pyridine (0.05 mL, 0.57 mmol) in dry dichloromethane (10 mL) was added butyryl chloride (24 mg, 0.23 mmol) at 0 °C. After addition completed, the mixture was stirred at 25 °C for 2 h. Methanol was added and the mixture was concentrated to yield 113 mg (99% yield) of the title compound as a yellow solid. LC-MS (ESI): [M+H]$^+$ = 597.4.

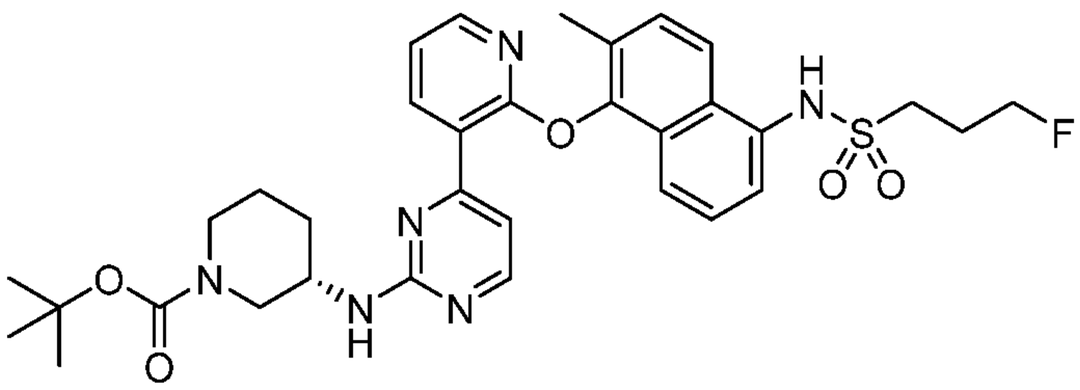
[0283] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)butyramide hydrochloride



[0284] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-(piperidine-1-sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (113 mg, 0.19 mmol), DCM (3 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). The residue was purified by Prep-HPLC to yield 50 mg (50% yield) of **117** as a white solid. LCMS (ESI): $[M+H]^+$ = 497.3; ^1H NMR (400 MHz, CD_3OD) δ 8.69 (d, J = 7.6 Hz, 1H), 8.47 (d, J = 5.2 Hz, 1H), 8.02 (d, J = 2.4 Hz, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 5.6 Hz, 1H), 7.63-7.51 (m, 3H), 7.40 (t, J = 8.0 Hz, 1H), 7.27-7.23 (m, 1H), 4.41 (m, 1H), 3.63 (dd, J = 12.4, 3.2 Hz, 1H), 3.12-3.03 (m, 2H), 2.56 (t, J = 7.2 Hz, 2H), 2.29 (s, 3H), 2.16-2.11 (m, 2H), 1.93-1.81 (m, 4H), 1.12 (t, J = 6.8 Hz, 3H).

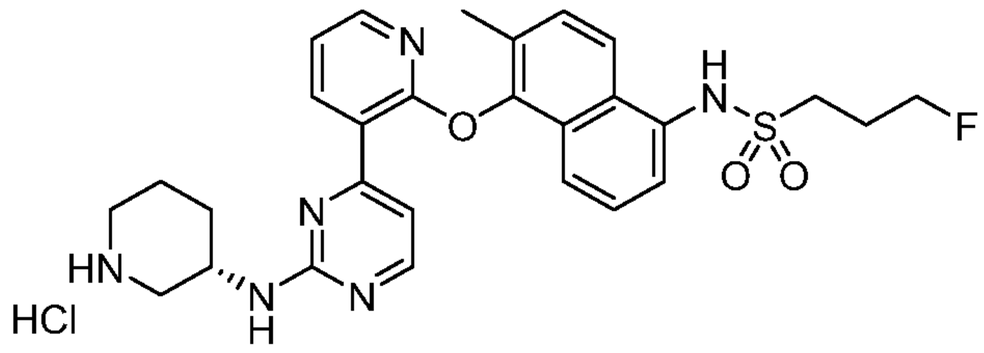
Example 118 *(S)-3-Fluoro-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide hydrochloride* ***118***

[0285] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((5-((3-fluoropropyl)sulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0286] The General Procedure A was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (100 mg, 0.19 mmol), pyridine (2 mL) and 3-fluoropropane-1-sulfonyl chloride (30 mg, 0.19 mmol). The crude was then purified by Prep-TLC (petroleum ether/ethyl acetate = 1 / 1) to yield 100 mg (81% yield) of the title compound as a white solid. LCMS (ESI) [M+H]+ = 651.

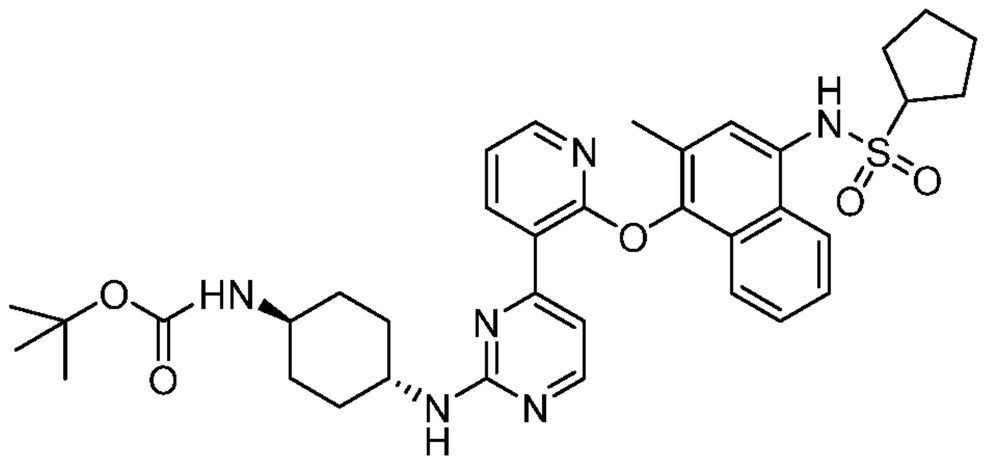
[0287] Step 2: (*S*)-3-Fluoro-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide hydrochloride



[0288] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-((3-fluoropropyl)sulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.15 mmol), DCM (5 mL) and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). The residue was purified by Prep-HPLC to yield 65 mg (75% yield) of **118** as a red solid. LCMS (ESI): $[M+H]^+$ = 551; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.56 (s, 1H), 8.44 (d, J = 5.1 Hz, 1H), 8.32 (s, 1H), 8.14 (d, J = 8.6 Hz, 1H), 8.05 (d, J = 4.6 Hz, 1H), 7.49 (t, J = 10.1 Hz, 3H), 7.40 (t, J = 8.5 Hz, 2H), 7.34 (d, J = 7.3 Hz, 1H), 7.30 – 7.22 (m, 1H), 4.60 (t, J = 5.9 Hz, 1H), 4.48 (t, J = 5.8 Hz, 1H), 4.07 (s, 1H), 3.25 (s, 1H), 3.23 – 3.18 (m, 2H), 3.00 (d, J = 12.0 Hz, 1H), 2.71 – 2.56 (m, 2H), 2.21 (s, 3H), 2.12 (d, J = 24.7 Hz, 2H), 1.97 (s, 1H), 1.77 (s, 1H), 1.56 (s, 2H).

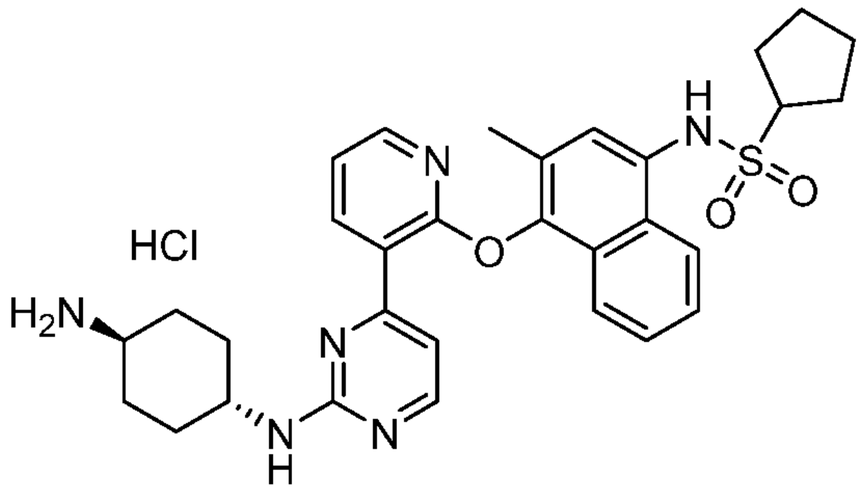
Example 119 *N-(4-((3-(2-(((trans)-4-aminocyclohexyl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)cyclopentanesulfonamide hydrochloride* ***119***

[0289] Step1 : *tert*-Butyl ((*trans*)-4-((4-(2-((4-(cyclopentanesulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)cyclohexyl)carbamate



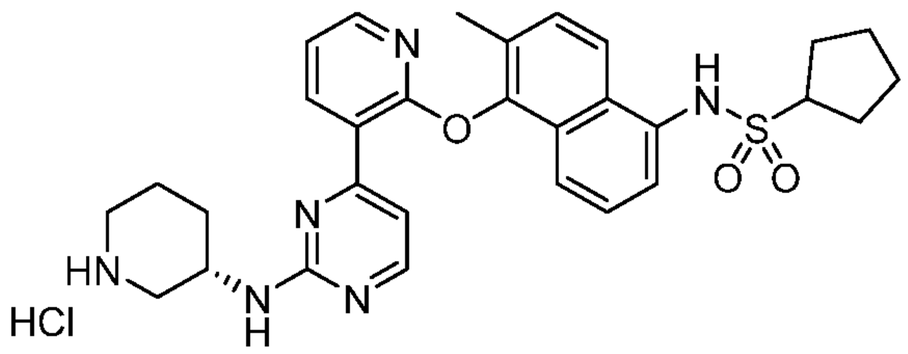
[0290] The General Procedure A was followed, using *tert*-butyl *N*-[4-[[4-[2-[(4-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]cyclohexyl]carbamate (100 mg, 0.18 mmol), pyridine (2 mL) and cyclopentanesulfonylchloride (31 mg, 0.18 mmol). The crude was then purified by Prep-TLC (petroleum ether/ethyl acetate = 1 / 1) to yield 30 mg (24% yield) of the title compound as a yellowsolid. LCMS (ESI) [M+H]+ = 573.

[0291] Step 2: *N*-(4-((3-(2-(((*trans*)-4-aminocyclohexyl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-3-methylnaphthalen-1-yl)cyclopentanesulfonamide hydrochloride



[0292] The General Procedure B was followed, using *tert*-Butyl ((*trans*)-4-((4-(2-((4-(cyclopentanesulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)cyclohexyl)carbamate (30 mg, 0.04 mmol), DCM (2 mL) and hydrochloric acid (4 M in dioxane, 1 mL, 4 mmol). The residue was purified by Prep-HPLC to yield 17 mg (62% yield) of **119** as a white solid. LCMS (ESI): $[M+H]^+$ = 573; ^{1}H NMR (400 MHz, CD_3OD) δ 8.60 (d, J = 6.4 Hz, 1H), 8.40 (d, J = 5.6 Hz, 1H), 8.29 (d, J = 8.4 Hz, 1H), 8.04-8.03 (m, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 6.4 Hz, 1H), 7.60-7.45 (m, 3H), 7.25 (dd, J = 4.8, 7.6 Hz, 1H), 4.06-3.92 (m, 1H), 3.71-3.63 (m, 1H), 3.18-3.14 (m, 1H), 2.31-2.23 (m, 5H), 2.17-2.11 (m, 4H), 2.02-1.96 (m, 2H), 1.68-1.60 (m, 2H), 1.56-1.48 (m, 6H).

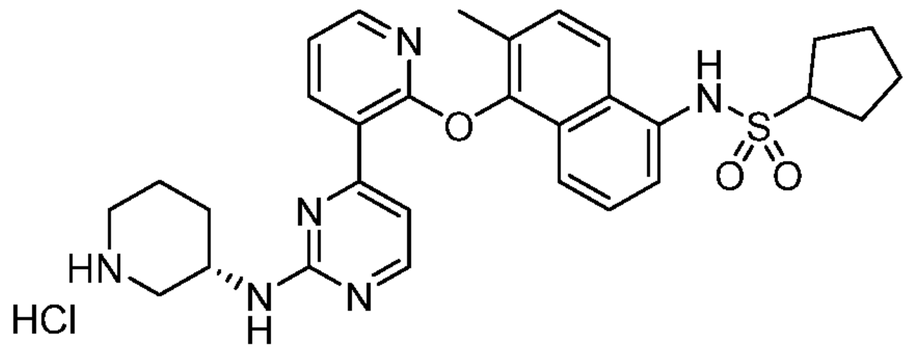
Example 120 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentanesulfonamide hydrochloride* ***120***



[0293] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((5-(cyclopentanesulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate

[0294] The General Procedure A was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (100 mg, 0.19 mmol), pyridine (2 mL) and cyclopentanesulfonylchloride (32 mg, 0.19 mmol). The crude was then purified by Prep-TLC (petroleum ether/ethyl acetate = 1 / 1) to yield 90 mg (72% yield) of the title compound as a white solid. LCMS (ESI) [M+H]+ = 659.

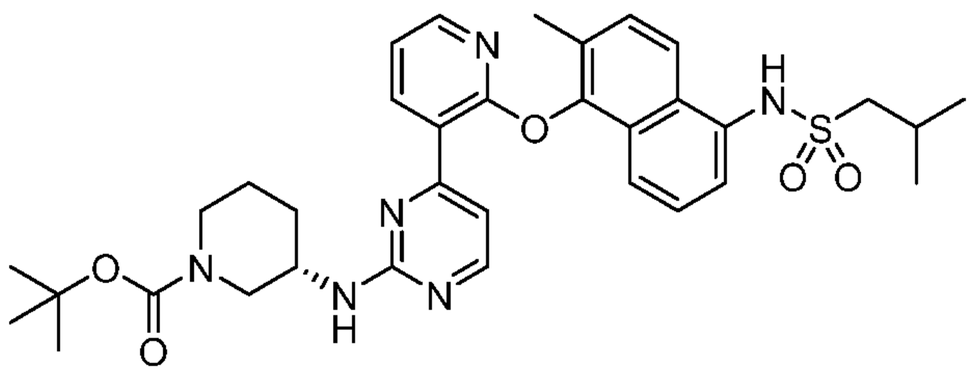
[0295] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentanesulfonamide hydrochloride



[0296] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-(cyclopentanesulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (140 mg, 0.22 mmol), DCM (4 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). The residue was purified by Prep-HPLC to yield 15 mg (18% yield) of **120** as a yellowsolid. LCMS (ESI): $[M+H]^+$ = 559; ^{1}H-NMR(400 MHz, CD_3OD) δ 8.68 (d, J = 7.6 Hz, 1H), 8.46 (d, J = 5.6 Hz, 1H), 8.16 (d, J = 8.8 Hz, 1H), 8.01 (d, J = 4.8 Hz, 1H), 7.73 (d, J = 5.6 Hz, 1H), 7.64-7.54 (m, 3H), 7.40-7.36 (m, 1H), 7.26-7.23 (m, 1H), 4.43-4.34 (m, 1H), 3.65-3.60 (m, 2H), 3.39-3.32 (m, 1H), 3.10-3.03 (m, 2H), 2.28 (s, 3H), 2.22-1.76 (m, 10H), 1.67-1.57 (m, 2H).

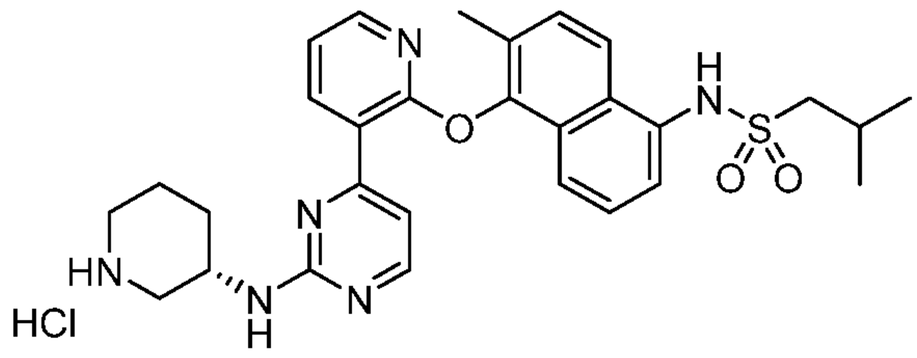
Example 121 *(S)-2-Methyl-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide hydrochloride* ***121***

[0297] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-((2-methylpropyl)sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0298] The General Procedure A was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (100 mg, 0.19 mmol), pyridine (3 mL) and isobutanesulfonylchloride (0.15 mL, 1.15 mmol). The crude was then purified by Prep-TLC (petroleum ether/ethyl acetate = 1 / 1) to yield 120 mg (95% yield) of the title compound as a white solid. LCMS (ESI) [M+H]+ = 647.

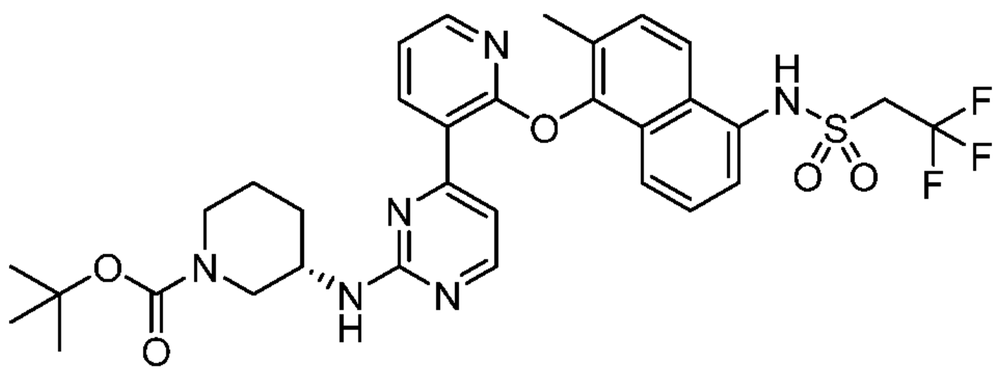
[0299] Step 2: (*S*)-2-Methyl-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide hydrochloride



[0300] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-((2-methylpropyl)sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (140 mg, 0.22 mmol), DCM (3 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). The residue was purified by Prep-HPLC to yield 37 mg (29% yield) of **121** as a white solid. LCMS (ESI): $[M+H]^+$ = 547; ^{1}H-NMR(400 MHz, CD_3OD) δ : 8.69 (d, J = 7.3 Hz, 1H), 8.57-8.56 (m, 1H), 8.45-8.44 (m, 1H), 8.14 (d, J = 4.6 Hz, 1H), 7.69-7.63 (m, 2H), 7.56 (s, 1H), 7.55 (s, 1H), 7.40 (t, J = 8.1 Hz, 1H), 7.24 (q, J = 5.0 Hz, 1H), 4.31-4.29 (m, 1H), 3.55 (d, J = 7.2 Hz, 1H), 3.30-3.26 (m, 1H), 3.06 (s, 1H), 3.04 (s, 1H), 3.00-2.94 (m, 2H), 2.32-2.25 (m, 4H), 2.20-2.17 (m, 1H), 2.09-2.05 (m, 1H), 1.90-1.72 (m, 2H), 1.08 (d, J = 7.8 Hz, 6H).

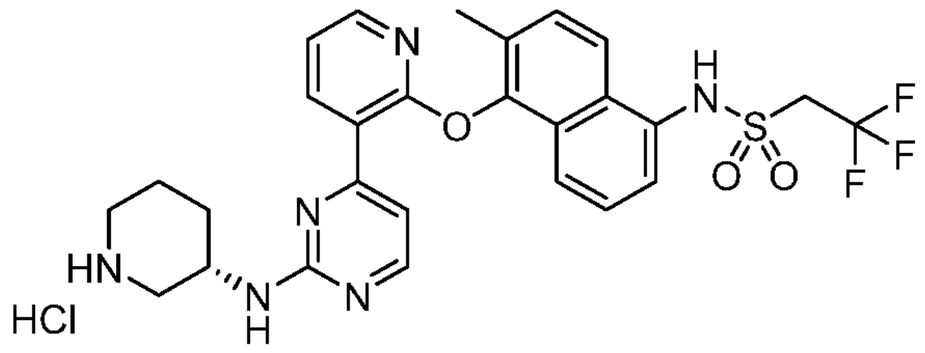
Example 122 *(S)-2,2,2-Trifluoro-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)ethane-1-sulfonamide hydrochloride* ***122***

[0301] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-((2,2,2-trifluoroethyl)sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0302] The General Procedure A was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (150 mg, 0.28 mmol), pyridine (2 mL) and 2,2,2-trifluoroethanesulfonyl chloride (52 mg, 0.28 mmol). The crude was then purified by Prep-TLC (petroleum ether/ethyl acetate = 1 / 1) to yield 170 mg (89% yield) of the title compound as a colorless oil. LCMS (ESI) [M+H]+ = 673.

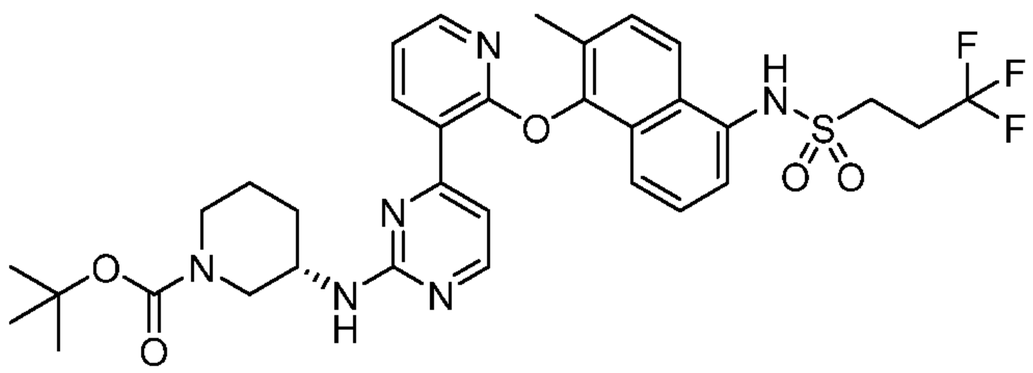
[0303] Step 2: (*S*)-2,2,2-Trifluoro-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)ethane-1-sulfonamide hydrochloride



[0304] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-((2,2,2-trifluoroethyl)sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (170 mg, 0.25 mmol), DCM (4 mL) and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). The residue was purified by Prep-HPLC to yield 100 mg (65% yield) of **122** as a white solid. LCMS (ESI): $[M+H]^+$ = 592; ^{1}H-NMR(400 MHz, CD_3OD) δ 8.68 (d, J = 6.8 Hz, 1H), 8.46 (d, J = 5.2 Hz, 1H), 8.13 (d, J = 8.8 Hz, 1H), 8.01 (d, J = 2.8 Hz, 1H), 7.74-7.70 (m, 2H), 7.60-7.57 (m, 2H), 7.43 (t, J = 8.0 Hz, 16 Hz, 1H), 7.25 (dd, J = 4.8, 7.6 Hz, 1H), 4.40-4.38 (m,1H), 4.24-4.18 (m, 2H), 3.65-3.62 (m, 1H), 3.10-3.03 (m, 2H), 2.29 (s, 3H), 2.23-2.11 (m, 2H), 1.92-1.81 (m, 2H).

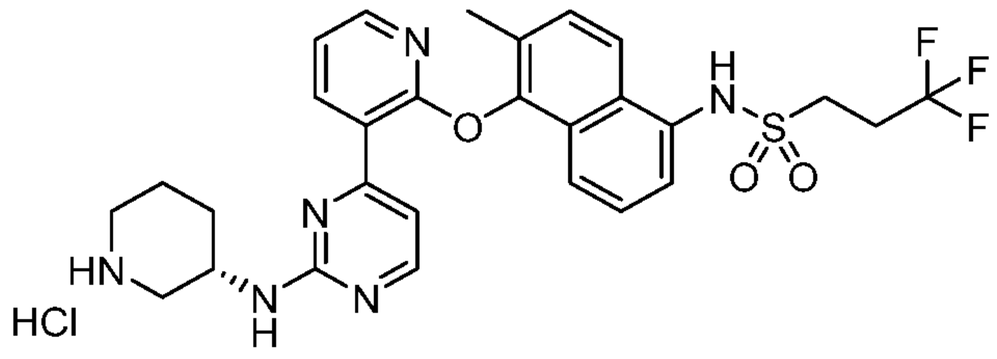
Example 123 *(S)-3,3,3-Trifluoro-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide hydrochloride* ***123***

[0305] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-((3,3,3-trifluoropropyl)sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0306] The General Procedure A was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (100 mg, 0.19 mmol), pyridine (3 mL) and 3,3,3-trifluoropropane-1-sulfonylchloride (300 mg, 1.53 mmol). The crude was then purified by Prep-TLC (petroleum ether/ethyl acetate = 1 / 2) to yield 70 mg (54% yield) of the title compound as a white solid. LCMS (ESI) [M+H]+ = 587.

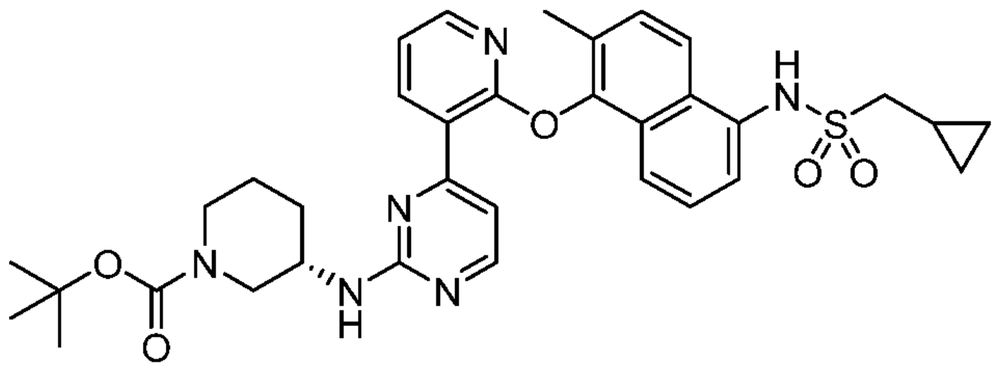
[0307] Step 2: (*S*)-3,3,3-Trifluoro-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide hydrochloride



[0308] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-((3,3,3-trifluoropropyl)sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (70 mg, 0.10 mmol), DCM (3 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). The residue was purified by Prep-HPLC to yield 51 mg (80% yield) of **123** as a yellow solid. LCMS (ESI): $[M+H]^+$ = 587.2; ^{1}H-NMR(400 Hz, CD_3OD) δ 8.70 (d, J = 7.2 Hz, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.14 (d, J = 8.7 Hz, 1H), 8.02 (dd, J = 4.9, 1.6 Hz, 1H), 7.76 (d, J =4.9 Hz, 1H), 7.69 (d, J = 8.5 Hz, 1H), 7.60-7.55 (m, 2H), 7.42 (t, J = 2.0 Hz, 1H), 7.27-7.24(m, 1H), 4.40 (s, 1H), 3.64 (dd, J = 12.2, 8.6 Hz, 1H), 3.43-3.39 (m, 3H), 3.11-3.03 (m, 2H), 2.83-2.71 (m, 2H), 2.30 (s, 3H), 2.29-2.11 (m, 2H), 1.93-1.79 (m, 2H).

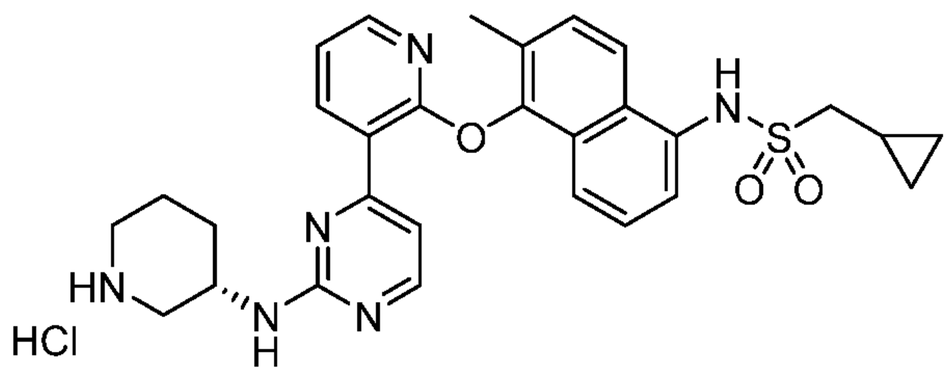
Example 124 *(S)-1-Cyclopropyl-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide hydrochloride* ***124***

[0309] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((5-((cyclopropylmethyl)sulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0310] The General Procedure A was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (100 mg, 0.19 mmol), pyridine (2 mL) and cyclopropylmethanesulfonyl chloride (100 mg, 0.65 mmol). The crude was then purified by Prep-TLC (petroleum ether/ethyl acetate = 1 / 1) to yield 120 mg (98% yield) of the title compound as a white solid. LCMS (ESI) [M+H]+ = 645.

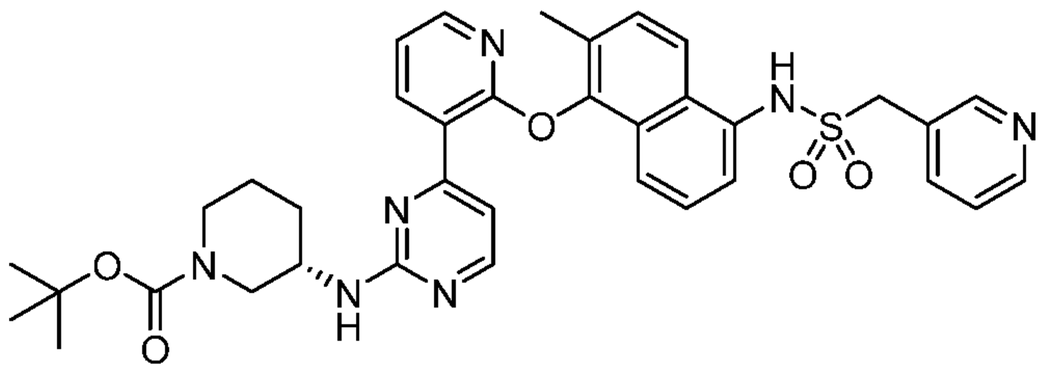
[0311] Step 2: (*S*)-1-Cyclopropyl-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide hydrochloride



[0312] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-((cyclopropylmethyl)sulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (120 mg, 0.19 mmol), DCM (4 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). The residue was purified by Prep-HPLC to yield 97 mg (89% yield) of **124** as a yellow solid. LCMS (ESI): $[M+H]^+$ = 545; ^{1}H-NMR : (400 MHz, CD_3OD) δ 8.68 (d, J = 6.8 Hz, 1H), 8.46 (d, J = 5.2 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 3.6 Hz, 1H), 7.74 (d, J = 5.6 Hz, 1H), 7.63-7.54 (m, 3H), 7.41-7.37 (m, 1H), 7.24 (dd, J = 4.8, 7.2 Hz, 1H), 4.43-4.32 (m, 1H), 3.66-3.62 (m, 1H), 3.39-3.36 (m, 1H), 3.13-3.03 (m, 4H), 2.29-2.11 (m, 5H), 1.92-1.80 (m, 2H), 1.21-1.12 (m, 1H), 0.66-0.61 (m, 2H), 0.37-0.33 (m, 2H).

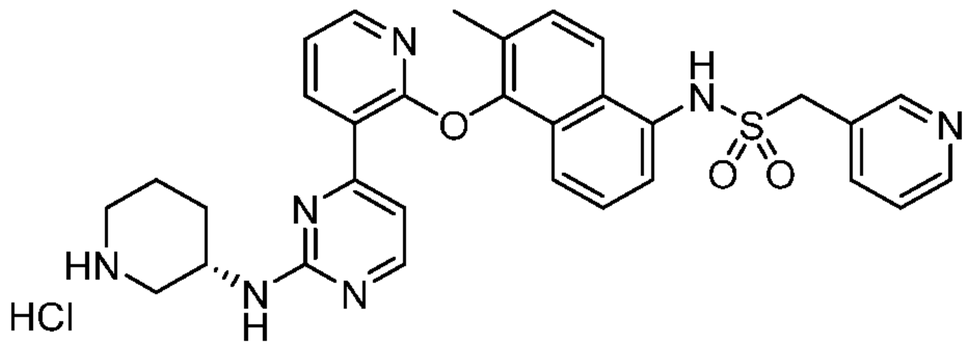
Example 125 (S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-(pyridin-3-yl)methanesulfonamide hydrochloride ***125***

[0313] Step 1: *tert*-Butyl (S)-3-((4-(2-((2-methyl-5-((pyridin-3-ylmethyl)sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0314] The General Procedure A was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (100 mg, 0.19 mmol), pyridine (2 mL) and 3-pyridylmethanesulfonyl chloride (200 mg, 1.04 mmol). The crude was then purified by Prep-TLC (petroleum ether/ethyl acetate = 1 / 1) to yield 25 mg (19% yield) of the title compound as a white solid. LCMS (ESI) [M+H]+ = 682.

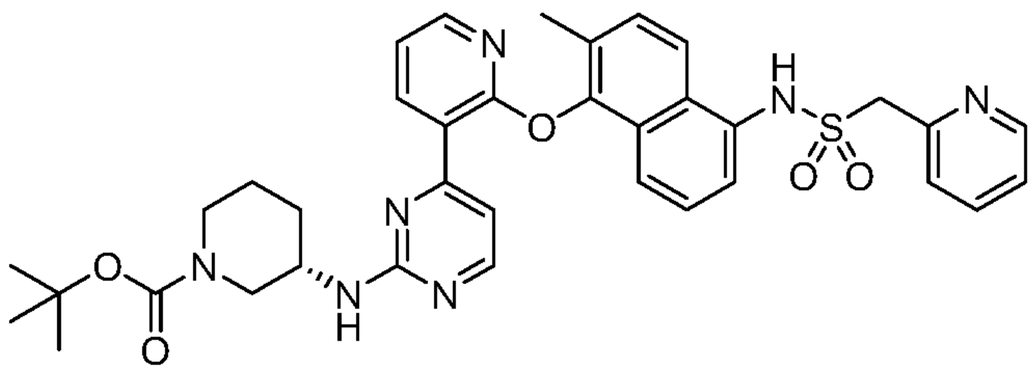
[0315] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-(pyridin-3-yl)methanesulfonamide hydrochloride



[0316] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-((pyridin-3-ylmethyl)sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (25 mg, 0.04 mmol), DCM (4 mL) and hydrochloric acid (4 M in dioxane, 1 mL, 4 mmol). The residue was purified by Prep-HPLC to yield 97 mg (89% yield) of **125** as a yellow solid. LCMS (ESI): $[M+H]^+$ = 582; ^{1}H-NMR : (400 MHz, CD_3OD) δ 8.86-8.79 (m, 3H), 8.59 (d, J = 8.0 Hz, 1H), 8.49 (d, J = 5.2 Hz, 1H), 8.11 (d, J = 4.0 Hz, 1H), 8.04-7.98 (m, 2H), 7.91-7.87 (m, 1H), 7.69-7.58 (m, 3H), 7.45-7.41 (m, 1H), 7.34-7.31 (m, 1H), 4.92-4.83 (m, 2H), 4.62-4.47 (m, 1H), 3.69-3.62 (m, 1H), 3.43-3.36 (m, 1H), 3.13-3.09 (m, 2H), 2.31-2.13 (m, 5H), 1.98-1.81 (m, 2H).

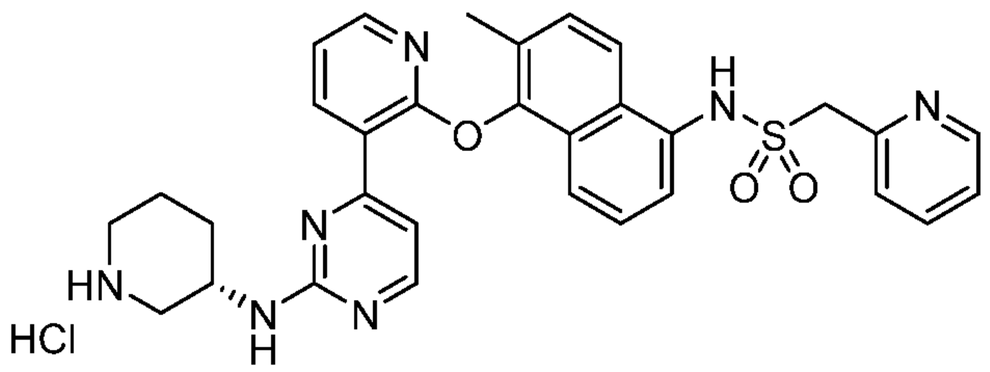
Example 126 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-(pyridin-2-yl)methanesulfonamide hydrochloride* ***126***

[0317] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-((pyridin-2-ylmethyl)sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0318] The General Procedure A was followed, using *tert*-butyl *(S)*-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (100 mg, 0.19 mmol), pyridine (2 mL) and 2-pyridylmethanesulfonyl chloride (200 mg, 1.04 mmol). After addition completed, the reaction mixture was stirred at 40 °C overnight. The crude was then purified by Prep-TLC (petroleum ether/ethyl acetate = 1 / 1) to yield 85 mg (65% yield) of the title compound as a white solid. LCMS (ESI) [M+H]+ = 682.

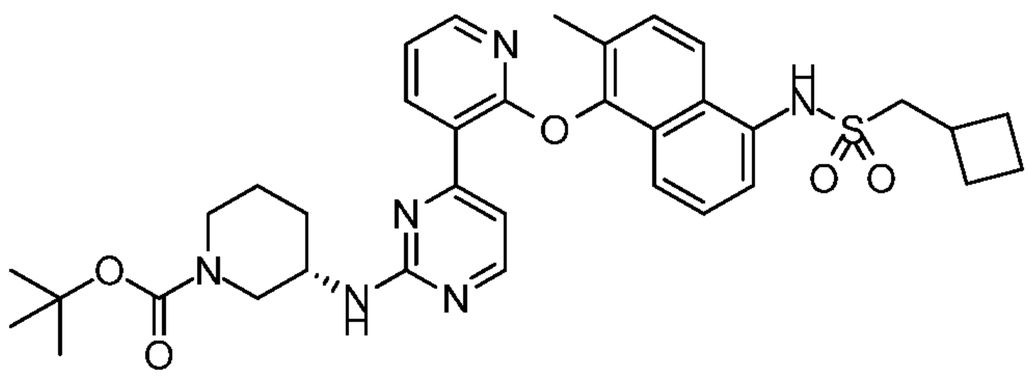
[0319] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-(pyridin-2-yl)methanesulfonamide hydrochloride



[0320] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-((pyridin-2-ylmethyl)sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (25 mg, 0.04 mmol), DCM (4 mL) and hydrochloric acid (4 M in dioxane, 1 mL, 4 mmol). The residue was purified by Prep-HPLC to yield 25 mg (32% yield) of **126** as a yellow solid. LCMS (ESI): [M+H]+ = 582; ^{1}H-NMR : (400 MHz, CD_3OD) δ 8.86-8.79 (m, 3H), 8.59 (d, J = 8.0 Hz, 1H), 8.49 (d, J = 5.2 Hz, 1H), 8.11 (d, J = 4.0 Hz, 1H), 8.04-7.98 (m, 2H), 7.91-7.87 (m, 1H), 7.69-7.58 (m, 3H), 7.45-7.41 (m, 1H), 7.34-7.31 (m, 1H), 4.92-4.83 (m, 2H), 4.62-4.47 (m, 1H), 3.69 - 3.62 (m, 1H), 3.43-3.36 (m, 1H), 3.13-3.09 (m, 2H), 2.31-2.13 (m, 5H), 1.98-1.81 (m, 2H).

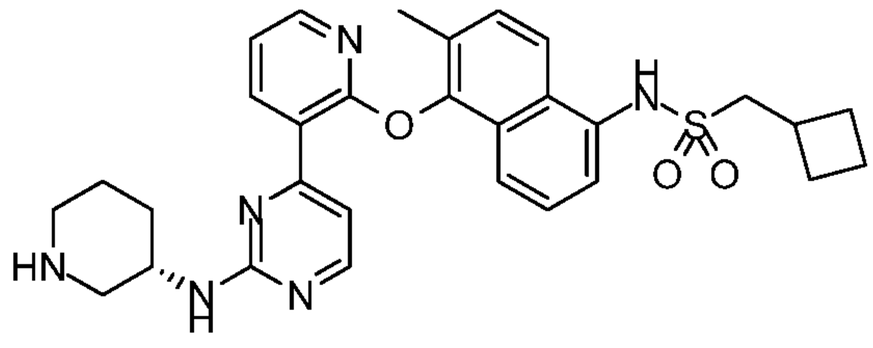
Example 127 *(S)-1-Cyclobutyl-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl) pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide* ***127***

[0321] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-(cyclobutylmethylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0322] The General Procedure A was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.19 mmol), pyridine (2 mL) and cyclobutylmethanesulfonyl chloride (38 mg, 0.23 mmol). The mixture was concentrated, dissolved in dichloromethane (20 mL) and washed with H_2O (15 mL x 2). The organic phase was dried over anhydrous sodium sulfate, concentrated to yield 100 mg (crude) of the title compound as a brown oil. LCMS (ESI) $[M+H]^+$ = 659.2.

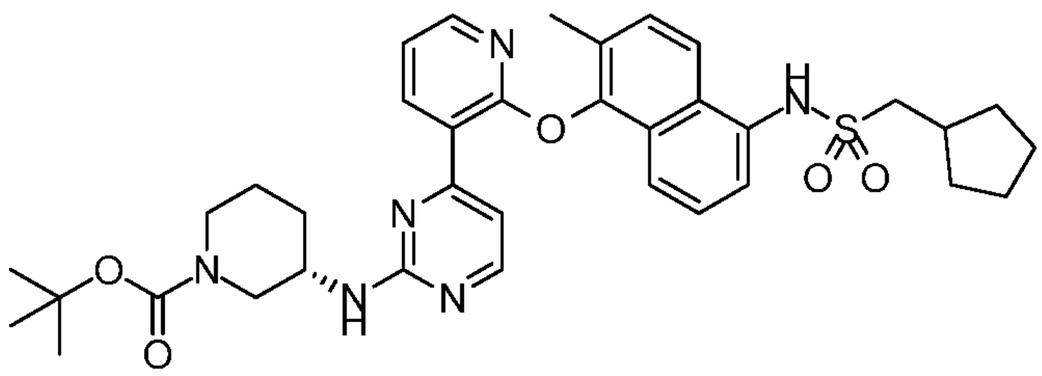
[0323] Step 2: (*S*)-1-Cyclobutyl-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide



[0324] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-(cyclobutylmethylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.15 mmol), dichloromethane (1 mL) and hydrochloric acid (4 M in ethyl acetate, 0.4 mL, 1.6 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05%HCl); B: ACN) to yield 28 mg (30%, HCl salt) of **127** as a brown solid. LCMS (ESI) $[M+H]^+$ = 559.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.79 (s, 1H), 9.31- 9.01 (m., 2H), 8.85 - 8.59 (m, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.09 - 8.04 (m, 1H), 7.76 - 7.58 (m, 2H), 7.56 - 7.49 (m, 2H), 7.48 - 7.38 (m, 2H), 7.31 - 7.24 (m, 1H), 4.50 - 4.05 (m, 1H), 3.47 - 3.38 (m, 1H), 3.30 - 3.26 (m, 2H), 3.24 - 3.15 (m, 1H), 2.91 - 2.73 (m, 3H), 2.21 (s, 3H), 2.11 - 2.00 (m, 3H), 1.94 - 1.74 (m, 6H), 1.69 - 1.58 (m, 1H).

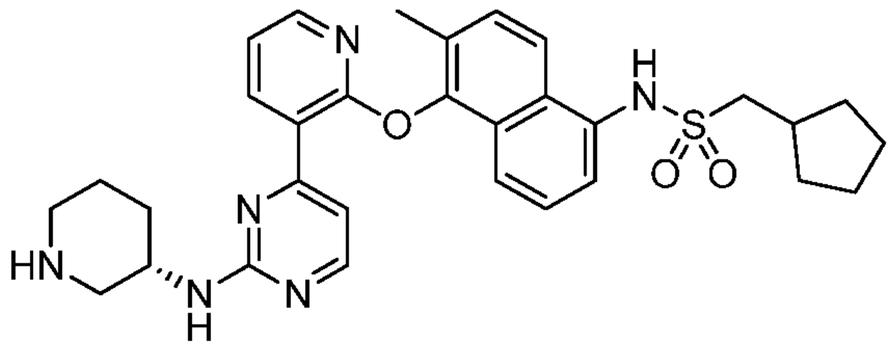
Example 128 *(S)-1-Cyclopentyl-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide* ***128***

[0325] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-(cyclopentylmethylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0326] The General Procedure A was followed, using *tert*-butyl (3S)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol), pyridine (2 mL) and cyclopentylmethanesulfonyl chloride (38 mg, 0.21 mmol). The resulting solution was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, and concentrated *in vacuo* to yield 110 mg of the crude title compound as a yellow solid. LCMS (ESI) $[M+Na]^+$ = 695.1.

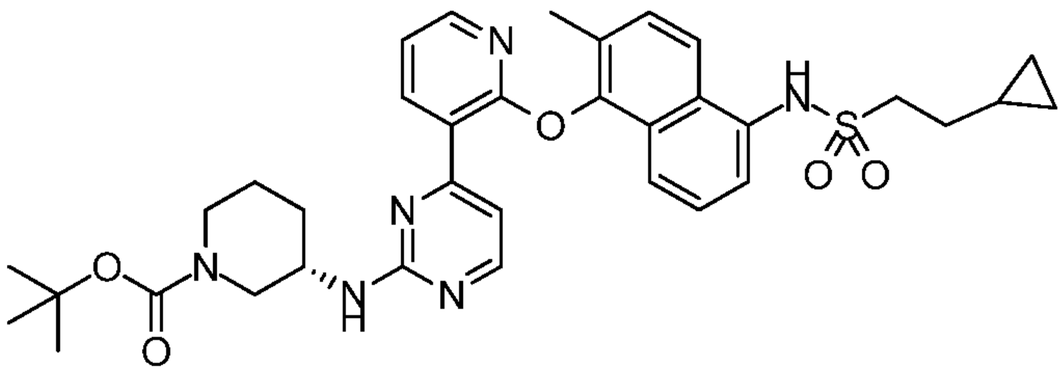
[0327] Step 2: (S)-*tert*-Butyl 3-((4-(2-((5-(cyclopentylmethylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0328] The General Procedure B was followed, using *tert*-butyl (3S)-3-[[4-[2-[[2-methyl-5-(sec-butylsulfonylamino)-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (110 mg, 0.16 mmol), dichloromethane (2 mL) and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05%HCl); B: ACN) to yield 22.8 mg (22%, yield HCl salt) of **128** as a yellow solid. LCMS (ESI) $[M+H]^+ = 573.1$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.82 (s, 1H), 9.22 (s, 2H), 8.49 (d, J = 4.8 Hz, 1H), 8.14 (d, J = 8.8 Hz, 1H), 8.07 (s., 1H), 7.65 (s., 1H), 7.57-7.54 (m, 2H), 7.48 - 7.38 (m, 2H), 7.30 - 7.27 (m, 1H), 4.38 (s, 1H), 3.80 (s, 1H), 3.45 - 3.40 (m, 1H), 3.19 (d, J = 6.4 Hz, 2H), 2.89 - 2.78 (m, 2H), 2.33 - 2.27 (m, 1H), 2.21 (s, 3H), 2.06 - 1.77 (m, 5H), 1.68 - 1.43 (m, 5H), 1.32 - 1.19 (m, 2H).

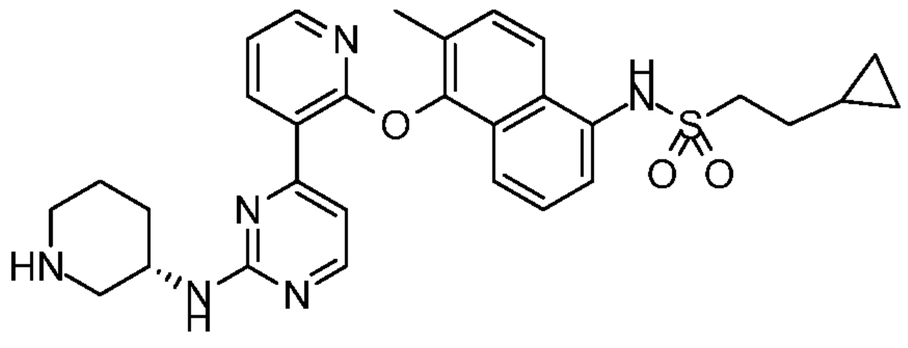
Example 129 *(S)-2-Cyclopropyl-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)ethanesulfonamide* ***129***

[0329] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-(2-cyclopropylethylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0330] The General Procedure A was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.19 mmol), pyridine (2 mL) and 2-cyclopropylethanesulfonyl chloride (38 mg, 0.23 mmol). The mixture was concentrated, dissolved in dichloromethane (20 mL), and washed with H_2O (15 mL x 2). The organic phase was dried over anhydrous sodium sulfate, concentrated to give 100 mg (crude) of the title compound as a brown oil. LCMS (ESI) $[M+H]^+ = 659.1$.

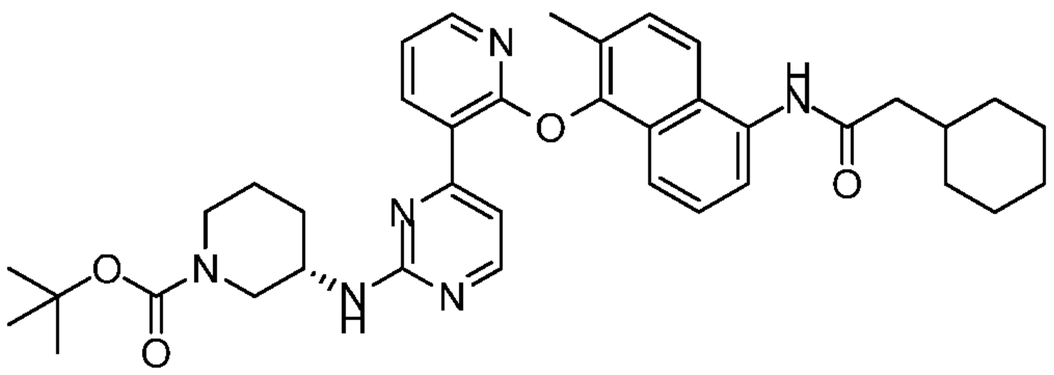
[0331] Step 2: (*S*)-2-Cyclopropyl-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)ethanesulfonamide



[0332] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-(2-cyclopropylethylsulfonamido) -2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino) piperidine-1-carboxylate (100 mg, 0.15 mmol), dichloromethane (1 mL) and hydrochloric acid (4 M in ethyl acetate, 0.4 mL, 1.6 mmol). The residue was purified *via* Prep-HPLC (mobile phase: A: water (0.05%HCl); B: ACN) to yield 26 mg (28%, yield HCl salt) of **129** as a brown solid. LCMS (ESI) $[M+H]^+$ = 559.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 9.51 - 9.14 (m, 2H), 8.90 - 8.67 (m, 1H), 8.50 (d, J = 5.2 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 8.09 - 8.06 (m, 1H), 7.94 - 7.62 (m, 2H), 7.59 - 7.53 (m, 2H), 7.48 - 7.40 (m, 2H), 7.31 - 7.25 (m, 1H), 4.51 - 4.27 (m, 1H), 3.47 - 3.37 (m, 1H), 3.26 - 3.15 (m, 3H), 2.89 - 2.79 (m, 2H), 2.22 (s, 3H), 2.07 - 1.98 (m, 1H), 1.96 - 1.87 (m, 1H), 1.85 - 1.72 (m, 1H), 1.70 - 1.60 (m, 3H), 0.86 - 0.72 (m, 1H), 0.42 - 0.35 (m, 2H), 0.09 - 0.01 (m, 2H).

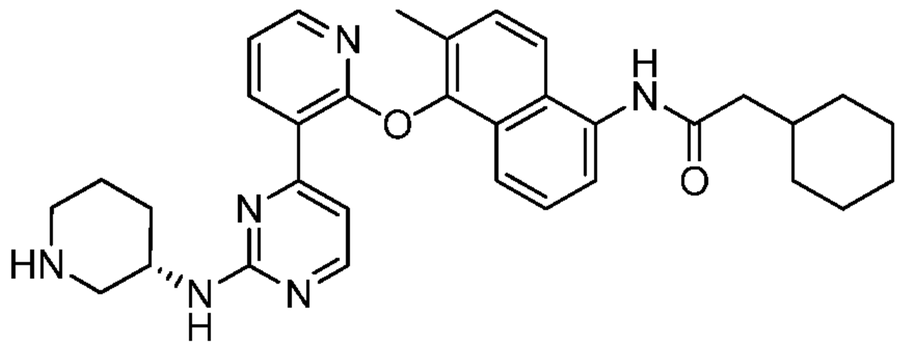
Example 130 *(S)-2-Cyclohexyl-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)acetamide* ***130***

[0333] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-(2-cyclohexylacetamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0334] The General Procedure A was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.19 mmol), pyridine (2 mL) and 2-cyclohexylacetyl chloride (46 mg, 0.28 mmol). The mixture was concentrated, dissolved in dichloromethane (20 mL) and washed with H_2O (15 mL x 2). The organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo* to give 100 mg (crude) of the title compound as a brown oil. LCMS (ESI) $[M+H]^+$ = 651.3

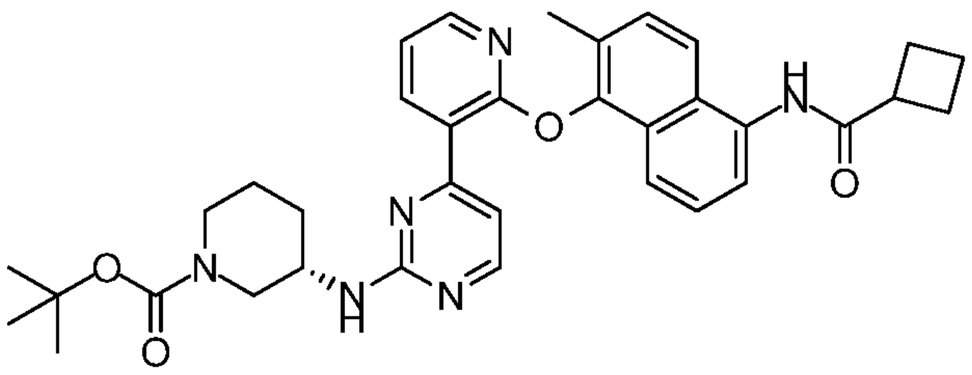
[0335] Step 2: (*S*)-2-Cyclohexyl-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)acetamide



[0336] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-(2-cyclohexylacetamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.15 mmol), dichloromethane (1 mL) and hydrochloric acid (4 M in ethyl acetate, 0.4 mL, 1.6 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% HCl); B: ACN) to yield 54 mg (59%, yield HCl salt) of **130** as a brown solid. LCMS (ESI) $[M+H]^+$ = 551.3; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 9.45 - 9.11 (m, 2H), 8.90 - 8.67 (m, 1H), 8.50 (d, J = 5.2 Hz, 1H), 8.07(d, J = 4.8 Hz, 1H), 7.95 - 7.89 (m, 1H), 7.87 - 7.73 (m, 1H), 7.67 - 7.57 (m, 2H), 7.54 - 7.45 (m, 2H), 7.42 - 7.37 (m, 1H), 7.30 - 7.25 (m, 1H), 4.46 - 4.33 (m, 1H), 3.49 - 3.36 (m, 1H), 3.25 - 3.14 (m, 1H), 2.91 - 2.76 (m, 2H), 2.40 - 2.36 (m, 2H), 2.22 (s, 3H), 2.07 - 1.98 (m, 1H), 1.96 - 1.88 (m, 1H), 1.83 - 1.61 (m, 8H), 1.32 - 1.15 (m, 3H), 1.12 - 1.00 (m, 2H).

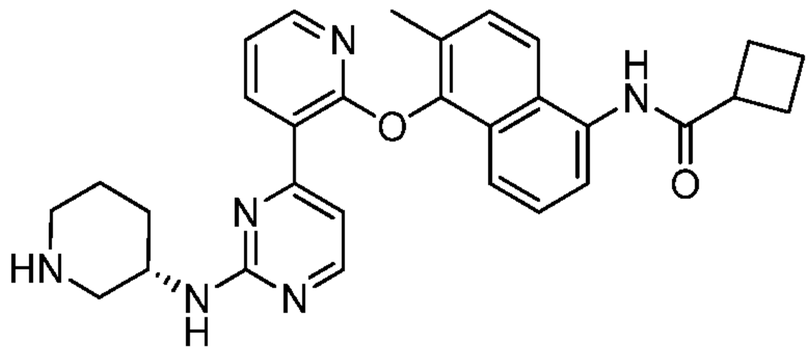
Example 131 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclobutanecarboxamide* ***131***

[0337] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-(cyclobutanecarboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0338] The General Procedure A was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.19 mmol), pyridine (2 mL) and cyclobutanecarbonyl chloride (34 mg, 0.28 mmol). The mixture was concentrated, dissolved in dichloromethane (20 mL) and washed with H_2O (15 mL x 2). The organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo* to yield 100 mg (crude) of the title compound as a yellow oil.

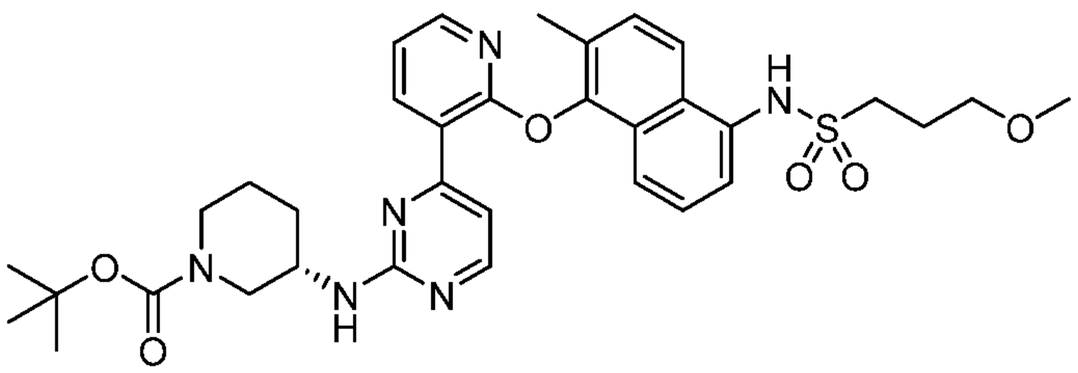
[0339] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclobutanecarboxamide



[0340] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-(cyclobutanecarboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.16 mmol), dichloromethane (1 mL) and hydrochloric acid (4 M in ethyl acetate, 0.4 mL, 1.6 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05%HCl); B: ACN) to yield 66 mg (72%, yield HCl salt) of **131** as a yellow solid. LCMS (ESI) $[M+H]^+$ = 509.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (s, 1H), 9.77 - 9.53 (m, 1H), 9.45 - 9.27 (m, 1H), 9.00 - 8.81 (m, 1H), 8.53 (d, *J* = 4.8 Hz, 1H), 8.42 - 8.22 (m, 1H), 8.16 - 8.06 (m, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.83 - 7.71 (m, 1H), 7.61 (d, *J* = 6.8 Hz, 1H), 7.53 - 7.46 (m, 2H), 7.43 - 7.37 (m, 1H), 7.31 - 7.26 (m, 1H), 4.61 - 4.35 (m, 1H), 3.54 - 3.38 (m, 2H), 3.24 - 3.14 (m, 1H), 2.92 - 2.79 (m, 2H), 2.35 - 2.26 (m, 2H), 2.24 - 2.15 (m, 5H), 2.08 - 1.78 (m, 5H), 1.74 - 1.59 (m, 1H).

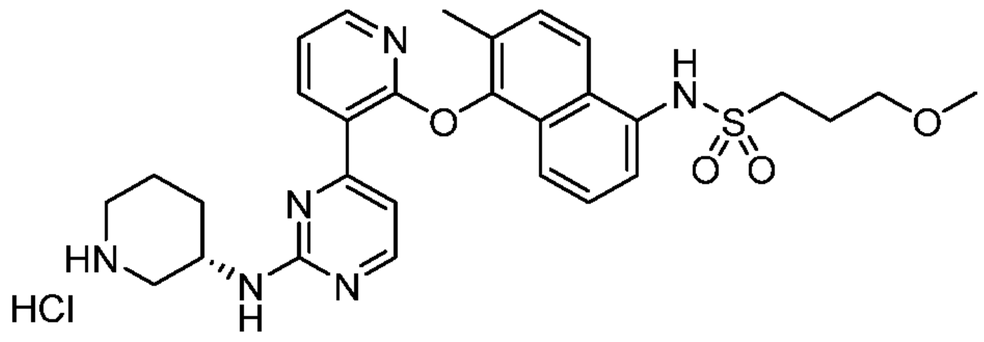
<u>Example 132</u> (S)-3-Methoxy-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide hydrochloride ***132***

[0341] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((5-((3-methoxypropyl)sulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0342] The General Procedure A was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (100 mg, 0.19 mmol), pyridine (3 mL) and 3-methoxypropane-1-sulfonyl chloride (32 mg, 0.19 mmol). LCMS (ESI) [M+H]+ = 689.

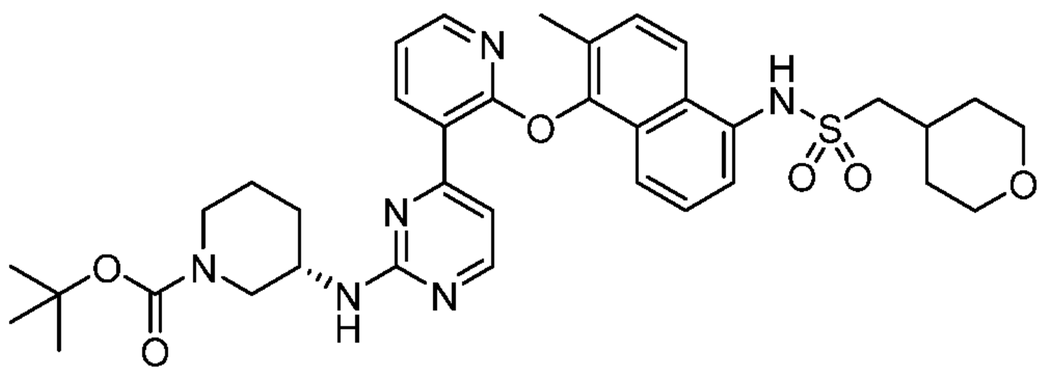
[0343] Step 2: (*S*)-3-Methoxy-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide hydrochloride



[0344] The General Procedure B was followed, using crude *tert*-butyl (*S*)-3-((4-(2-((5-((3-methoxypropyl)sulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate, DCM (4 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). The residue was purified by Prep-HPLC to yield 59 mg (52% yield over 2 steps) of **132** as a white solid. LCMS (ESI): [M+H]+ = 589; ^{1}H-NMR : (400 MHz, CD_3OD) 1HNMR (400 MHz, CD3OD) δ 8.68(d, J = 6.9 Hz, 1 H), 8.47(d, J = 5.5 Hz, 1 H), 8.15(d, J = 9.7 Hz, 1 H), 8.01 (d, J = 4.7 Hz, 1 H), 7.73 (s, 1 H), 7.65 (d, J = 8.5 Hz, 1 H), 7.56 (d, J = 8.1 Hz, 2 H), 7.40 (t, J = 7.9 Hz, 1 H), 7.27-7.23 (m, 1 H), 4.38 (s, 1 H), 3.64 (dd, J = 12.2, 2.8 Hz, 1 H), 3.47 (t, J = 6.0 Hz, 2 H), 3.37 (s, 1 H), 3.29 (s, 1 H), 3.25 - 3.22(m, 2 H), 3.10 - 3.03 (m, 2 H), 2.29 (s, 3 H), 2.23 - 2.07(m, 4 H), 1.93 - 1.80 (m, 2 H).

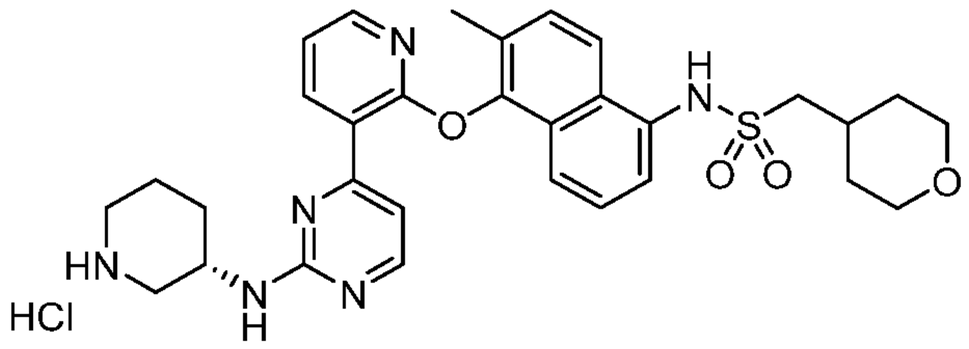
Example 133 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-(tetrahydro-2H-pyran-4-yl)methanesulfonamide hydrochloride* ***133***

[0345] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-(((tetrahydro-2H-pyran-4-yl)methyl)sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0346] The General Procedure A was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (100 mg, 0.19 mmol), pyridine (2 mL) and tetrahydropyran-4-ylmethanesulfonyl chloride (45 mg, 0.19 mmol). LCMS (ESI) [M+H]+ = 689.

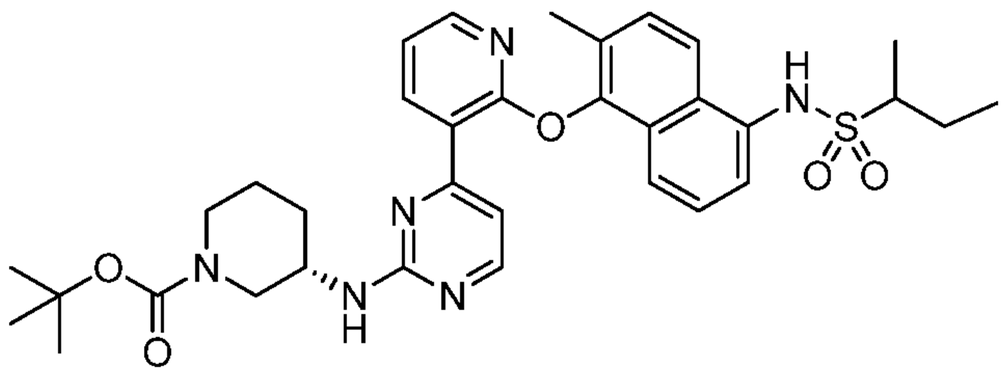
[0347] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-(tetrahydro-2H-pyran-4-yl)methanesulfonamide hydrochloride



[0348] The General Procedure B was followed, using crude *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-(((tetrahydro-2H-pyran-4-yl)methyl)sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate, DCM (4 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). The residue was purified by Prep-HPLC to yield 59 mg (52% yield over 2 steps) of **133** as a white solid. LCMS (ESI): [M+H]+ = 589; ^{1}HNMR (400 MHz, CD_3OD) δ 8.70 (s, 1H), 8.46 (d, J = 5.4 Hz, 1H), 8.14 (d, *J* = 8.8 Hz, H), 8.02 (d, *J* = 4.5 Hz, 1H), 7.77 (s, 1 H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 740 (t, *J* =7.5 Hz, 1H), 7.25 (q, *J* = 4.8 Hz, 1H), 4.41 (s, 1H), 3.91 - 3.88 (m, 2H), 3.65 (d, *J* = 11.5 Hz, 1H), 3.40 (t, *J* = 11.8 Hz, 3H), 3.12 - 3.04 (m, 4H), 2.29 (s, 3H), 2.26 - 2.11(m, 3H), 1.96 - 1.80 (m, 4H), 1.45 - 1.35 (m, 2H).

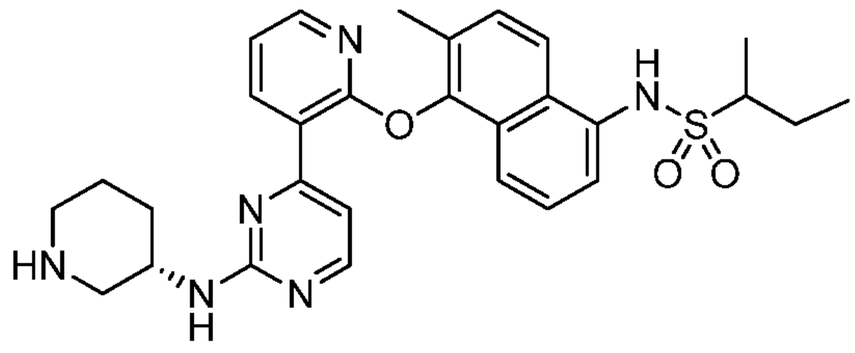
Example 134 *N-(6-Methyl-5-((3-(2-((S)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)butane-2-sulfonamide* ***134***

[0349] Step 1: (3*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-5-(1-methylpropylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0350] The General Procedure A was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol), pyridine (2 mL) and butane-2-sulfonyl chloride (45 mg, 0.28 mmol). The resulting solution was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, and concentrated *in vacuo* to yield 110 mg of the crude title compound as a yellow solid. LCMS (ESI) $[M+H]^+$ = 647.1.

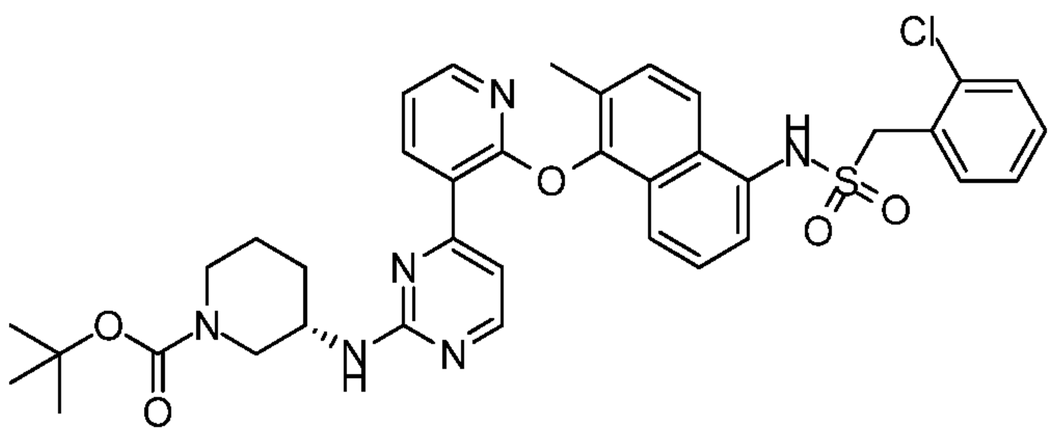
[0351] Step 2: *N*-(6-Methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalene-1-yl)butane-2-sulfonamide



[0352] The General Procedure B was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[[2-methyl-5-(*sec*-butylsulfonylamino)-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.15 mmol), dichloromethane (2 mL) and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05%HCl); B: ACN) to yield 38.4 mg (42%, yield HCl salt) of **134** as a yellow solid and as a racemic mixture of enantiomers. LCMS (ESI) $[M+H]^+$ = 547.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.81 (s, 1H), 9.49 (s, 1H), 9.22 (s, 1H), 8.84 (s, 1H), 8.50 (d, *J* = 5.2 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 8.08 (s, 1H), 7.70 (s, 1H), 7.58 - 7.52 (m, 2H), 7.50 - 7.45 (m, 1H), 7.44 - 7.37 (m, 1H), 7.32 - 7.26 (m, 1H), 4.50 - 4.30 (m, 1H), 3.45 - 3.40 (m, 1H), 3.25 - 3.16 (m, 1H), 3.15 - 3.05 (m, 1H), 2.95 - 2.80 (m, 2H), 2.23 (s, 3H), 2.02 - 1.82 (m, 3H), 1.81 - 1.70 (m, 1H), 1.69 - 1.55 (m, 1H), 1.51 - 1.47 (m, 1H), 1.31 (d, *J* = 6.4 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H).

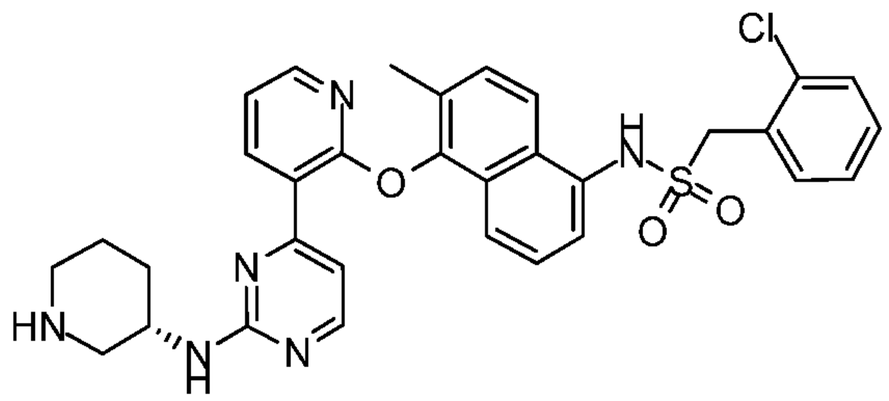
Example 135 *(S)-1-(2-Chlorophenyl)-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino) pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide* ***135***

[0353] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-((2-chlorophenyl)methylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0354] The General Procedure A was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol), pyridine (2 mL) and (2-chlorophenyl)methanesulfonyl chloride (47 mg, 0.21 mmol). The reaction mixture was concentrated and the residue taken up in ethyl acetate (20 mL) and then washed with water (10 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo* to yield (140 mg crude) of the title compound as a pale brown oil. LCMS (ESI) $[M+H]^+$ = 715. 2.

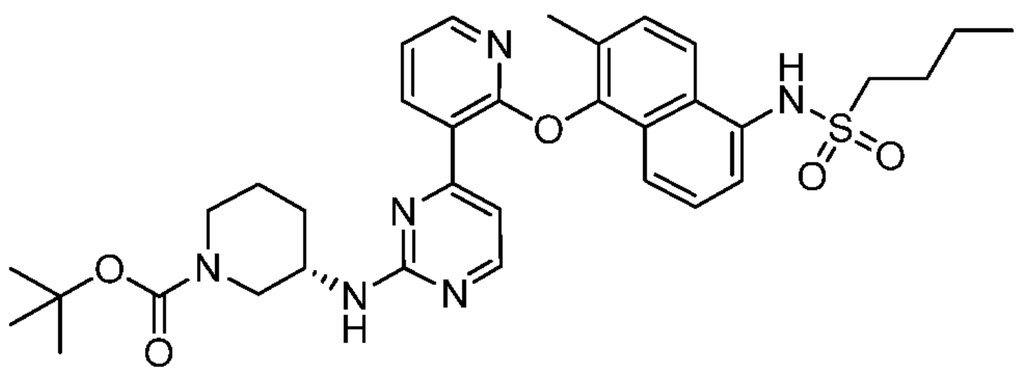
[0355] Step 2: (*S*)-1-(2-Chlorophenyl)-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl) pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide



[0356] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-((2-chlorophenyl) methylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino) piperidine-1-carboxylate ((140 mg, 0.20 mmol)), ethyl acetate (2 mL) and hydrochloric acid (4 M in ethyl acetate, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05%HCl); B: ACN) to yield 59 mg (46%, yield HCl salt) of **135** as a white solid. LCMS (ESI): $[M+H]^+$ = 615.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H), 9.35 - 8.78 (m, 2H), 8.49 (d, J = 5.6 Hz, 1H), 8.10 - 8.06 (m, 2H), 7.80 - 7.60 (m, 1H), 7.58 - 7.32 (m, 8H), 7.30 - 7.25 (m, 1H), 4.72 (s, 2H), 4.40 - 4.35 (m, 1H), 3.45 - 3.40 (m, 1H), 3.22 - 3.17 (m, 1H), 2.80 - 2.70 (m, 2H), 2.22 (s, 3H), 2.05 - 1.90 (m, 2H), 1.88 - 1.63 (m, 2H).

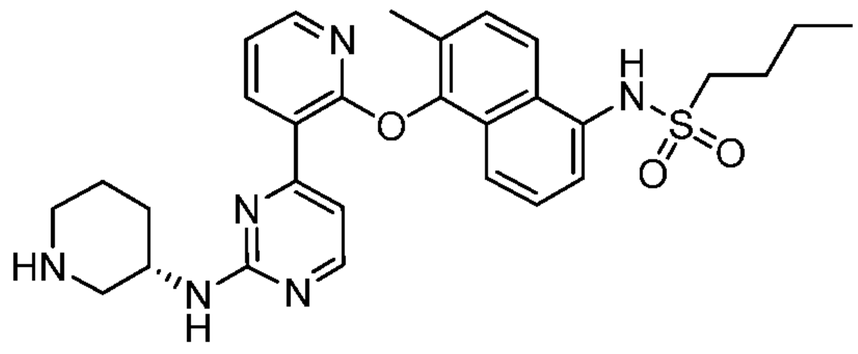
Example 136 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)butane-1-sulfonamide* ***136***

[0357] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-(butylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0358] The General Procedure A was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol), pyridine (3 mL) and 1-butanesulfonyl chloride (36 mg, 0.23 mmol). The solution was concentrated to afford 120 mg of the crude title compound as a brown solid. LCMS (ESI) $[M+H]^+$ = 647.1.

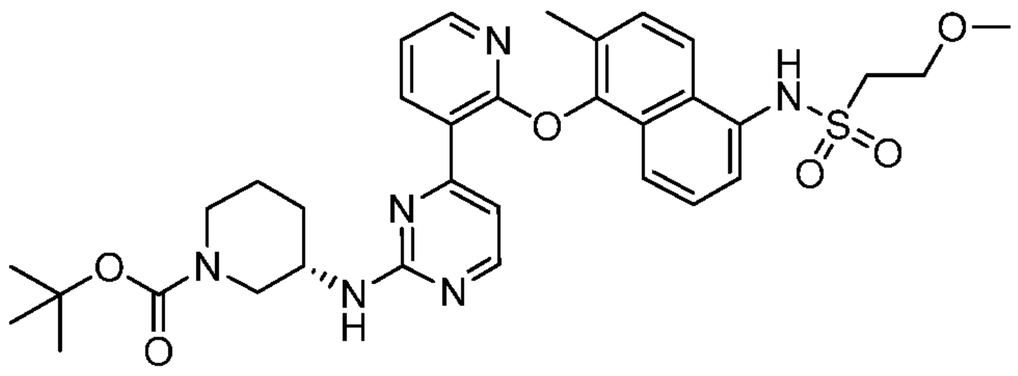
[0359] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalene-1-yl)butane-1-sulfonamide



[0360] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-(butylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.15 mmol), dichloromethane (5 mL) and hydrochloric acid (4 M in ethyl acetate, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05%HCl); B: ACN) to yield 67 mg (80%, yield HCl salt) of **136** as a white solid. LCMS (ESI): $[M+H]^+$ = 547.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 9.72 (s, 1H), 9.36 (s, 1H), 8.92(s, 1H), 8.53 (d, *J* = 5.2 Hz, 1H), 8.18 - 8.06 (m, 2H), 7.79 (s, 1H), 7.60 - 7.51 (m, 2H), 7.48 - 7.39 (m, 2H), 7.31 - 7.26 (m, 1H), 4.66 - 4.41 (m, 1H), 3.48 - 3.36 (m, 2H), 3.17 - 3.10 (m, 2H), 2.86 (d, *J* = 10.0 Hz, 2H), 2.22 (s, 3H), 2.08 - 1.88 (m, 2H), 1.87 - 1.59 (m, 4H), 1.42 - 1.38 (m, 2H), 0.85 (t, *J* = 7.2 Hz, 3H).

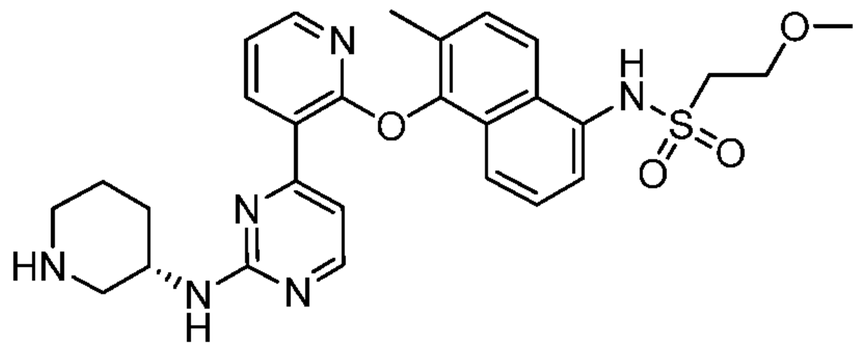
Example 137 *(S)-2-Methoxy-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)ethanesulfonamide* ***137***

[0361] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-(2-methoxyethylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0362] The General Procedure A was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol), pyridine (3 mL) and 2-methoxy-1-ethanesulfonyl chloride (36 mg, 0.23 mmol). The solution was concentrated to yield 100 mg of the crude title compound as a yellow solid. LCMS (ESI) $[M+H]^+$ = 649.1.

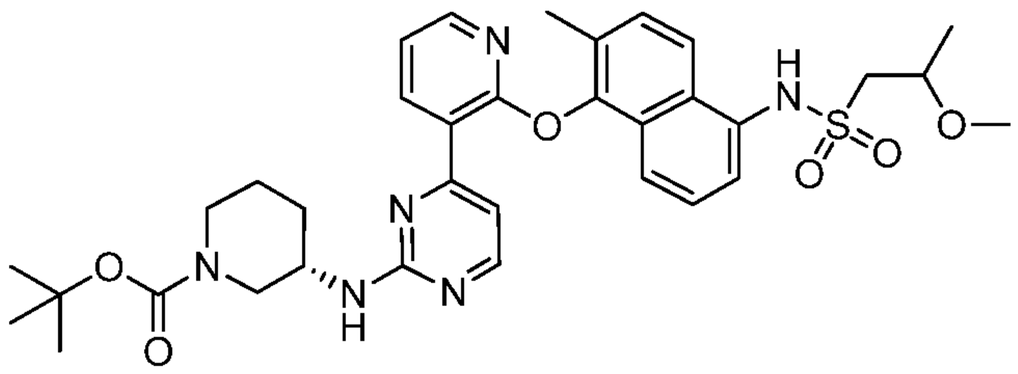
[0363] Step 2: (*S*)-2-Methoxy-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)ethanesulfonamide



[0364] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-(2-methoxyethylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.15 mmol), dichloromethane (5 mL) and hydrochloric acid (4 M in ethyl acetate, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05%HCl); B: ACN) to yield 76 mg (84%, yield HCl salt) of **137** as a white solid. LCMS (ESI): $[M+H]^+$ = 549.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 9.57 (s, 1H), 9.28 (s, 1H), 8.86 (s, 1H), 8.51 (d, J = 5.4 Hz, 1H), 8.15 (d, J = 8.5 Hz, 1H), 8.10 (d, J = 3.5 Hz, 1H), 7.80 - 7.52 (m, 2H), 7.52 - 7.46 (m, 1H), 7.46 - 7.38 (m, 1H), 7.32 - 7.27 (m, 1H), 4.60 - 4.20 (m, 1H), 3.73 (t, J = 6.0 Hz, 2H), 3.43 (t, J = 6.4 Hz, 3H), 3.23 (s, 3H), 3.20 - 3.16 (m, 1H), 2.90 - 2.80 (m, 2H), 2.22 (s, 3H), 2.08 - 1.57 (m, 4H).

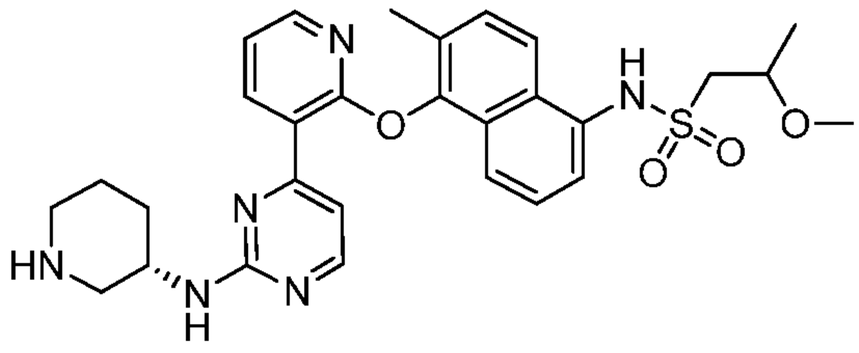
Example 138 *2-Methoxy-N-(6-methyl-5-((3-(2-((S)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide* ***138***

[0365] Step 1: (3*S*)-*tert*-Butyl 3-((4-(2-((5-(2-methoxypropylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0366] The General Procedure A was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol), pyridine (3 mL) and 2-methoxypropane-1-sulfonyl chloride (33 mg, 0.19 mmol). The solution was concentrated to afford 130 mg of the crude title compound as a yellow solid. LCMS (ESI) $[M+H]^+$ = 663.1.

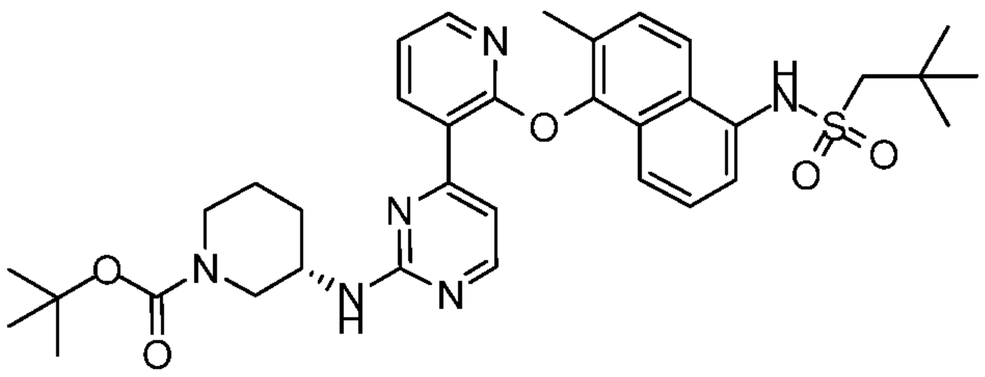
[0367] Step 2: 2-Methoxy-*N*-(6-methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide



[0368] The General Procedure B was followed, using (3*S*)-*tert*-butyl 3-((4-(2-((5-(2-methoxypropylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.15 mmol), dichloromethane (5 mL) and hydrochloric acid (4 M in ethyl acetate, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% HCl); B: ACN) to yield 73 mg (81%, yield HCl salt) of **138** as a yellow solid. LCMS (ESI): $[M+H]^+$ = 563.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 - 9.80 (m, 1H), 9.68 (s, 1H), 9.34 (s, 1H), 8.89 (s, 1H), 8.52 (d, J = 4.8 Hz, 1H), 8.16 (d, J = 8.8 Hz, 1H), 8.10 (s, 1H), 7.76 (s, 1H), 7.56 (t, J = 9.2 Hz, 2H), 7.52 - 7.47 (m, 1H), 7.47 - 7.36 (m, 1H), 7.33 - 7.26 (m, 1H), 4.47 - 4.53 (m, 1H), 3.85 - 3.76 (m, 1H), 3.46 - 3.35 (m, 2H), 3.27 - 3.20 (m, 2H), 3.19 (s, 3H), 2.85 (d, J = 9.6 Hz, 2H), 2.22 (s, 3H), 2.07 - 1.61 (m, 4H), 1.20 (d, J = 6.4 Hz, 3H).

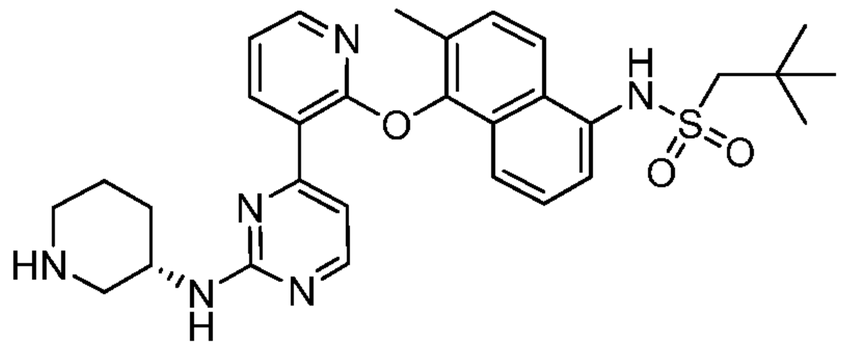
Example 139 *((S)-2,2-Dimethyl-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide* ***139***

[0369] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-(2,2-dimethylpropylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0370] The General Procedure A was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol), pyridine (2 mL) and 2,2-dimethylpropane-1-sulfonyl chloride (39 mg, 0.230 mmol). The resulting solution was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, and concentrated *in vacuo* to yield 120 mg of the crude title compound as a yellow solid. LCMS (ESI) $[M+H]^+$ = 661.2.

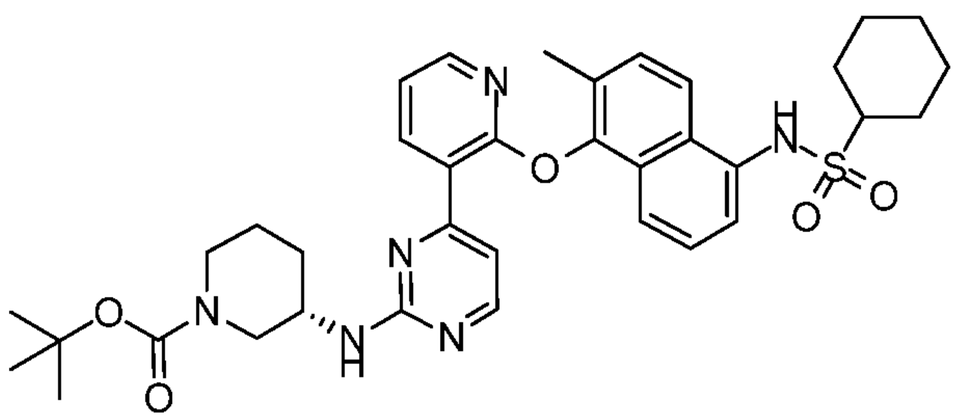
[0371] Step 2: (*S*)-2, 2-Dimethyl-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide



[0372] The General Procedure B was followed, using (*S*)-*tert*-butyl-3-((4-(2-((5-(2,2-dimethylpropylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (110 mg, 0.16 mmol), dichloromethane (2 mL) and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% HCl); B: ACN) to yield 31 mg (30%, yield HCl salt) of **139** as a yellow solid. LCMS (ESI) $[M+H]^+ = 561.3$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.82 (s, 1H), 9.05 (s, 1H), 8.48 (d, $J = 4.8$ Hz, 1H), 8.13 (d, $J = 8.8$ Hz, 1H), 8.07 (s, 1H), 7.70 - 7.61 (m, 2H), 7.54 (d, $J = 5.2$ Hz, 2H), 7.50 - 7.40 (m, 2H), 7.31 - 7.25 (m, 1H), 3.45 - 3.40 (m, 1H), 3.22 - 3.18 (m, 1H), 3.13 (s, 2H), 2.90 - 2.80 (m, 3H), 2.21 (s, 3H), 2.04 -1.97 (m, 1H), 1.95 - 1.85 (m, 1H), 1.83 - 1.76 (m, 1H), 1.72 - 1.65 (m, 1H), 1.09 (s, 9H).

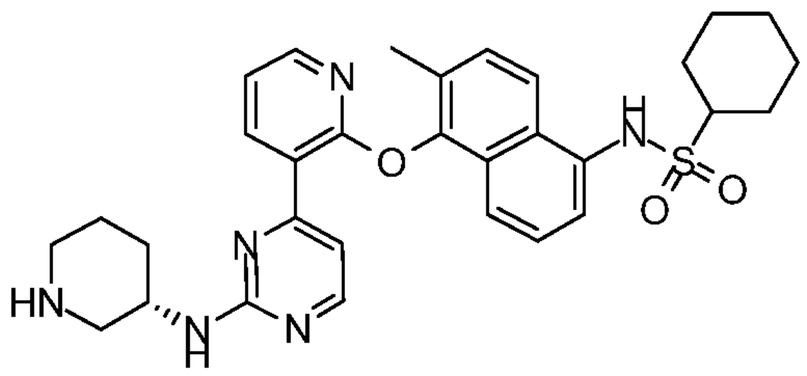
Example 140 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclohexanesulfonamide* ***140***

[0373] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-(cyclohexanesulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0374] The General Procedure A was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.19 mmol), pyridine (2 mL) and cyclohexanesulfonylchloride (42 mg, 0.23 mmol). The mixture was concentrated *in vacuo* and dissolved in dichloromethane (15 mL) and washed with H_2O (15 mL x 2). The organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo* to yield 100 mg (crude) of the title compound as a yellow oil.

[0375] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclohexanesulfonamide

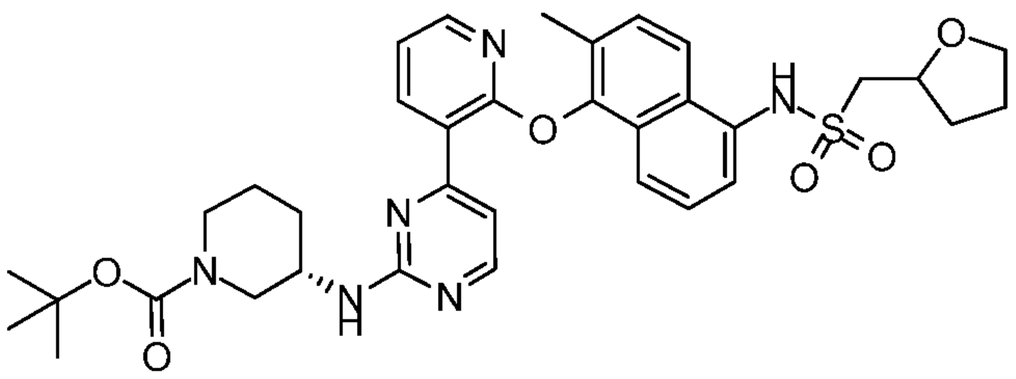


[0376] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-(cyclohexanesulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.15 mmol), dichloromethane (1 mL) and hydrochloric acid (4 M in ethyl acetate, 0.4 mL, 1.6 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% HCl); B: ACN) to yield 78 mg (85%, yield HCl salt) of **140** as a yellow solid. LCMS (ESI) $[M+H]^+ = 573.1$; ^1H NMR (400 MHz, DMSO-d_6) δ 9.80 (s, 1H), 9.50 - 9.31 (m, 1H), 9.02 - 8.81 (m, 1H), 8.59 - 8.27 (m, 2H), 8.19 - 8.08 (m, 2H), 7.87 - 7.67 (m, 1H), 7.59 - 7.53 (m, 2H), 7.50 - 7.45 (m, 1H), 7.44 - 7.38 (m, 1H), 7.32 - 7.26 (m, 1H), 4.69 - 4.40 (m, 1H), 3.48 - 3.37 (m, 1H), 3.24 - 3.13 (m, 1H), 3.12 - 3.02 (m, 1H), 2.94 - 2.78 (m, 2H), 2.22 (s, 3H), 2.16 - 1.99 (m, 3H), 1.94 - 1.59 (m, 6H), 1.52 - 1.38 (m, 2H), 1.32 - 1.04 (m, 3H).

Example 141 *N-(6-Methyl-5-((3-(2-((S)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-(tetrahydrofuran-2-yl)methanesulfonamide* ***141***

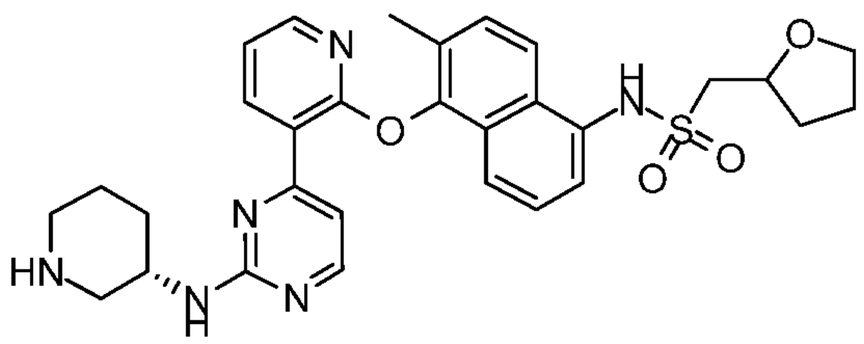
[0377]

[0378] Step 1: (3*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-5-((tetrahydrofuran-2-yl)methylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0379] The General Procedure A was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.19 mmol), pyridine (2 mL) and tetrahydrofuran-2-ylmethanesulfonyl chloride (70 mg, 0.38 mmol). The mixture was concentrated and dissolved in dichloromethane (20 mL), washed with H_2O (15 mL x 2). The organic phase was dried over anhydrous sodium sulfate and concentrated to yield 100 mg (crude) of the title compound as a brown oil.

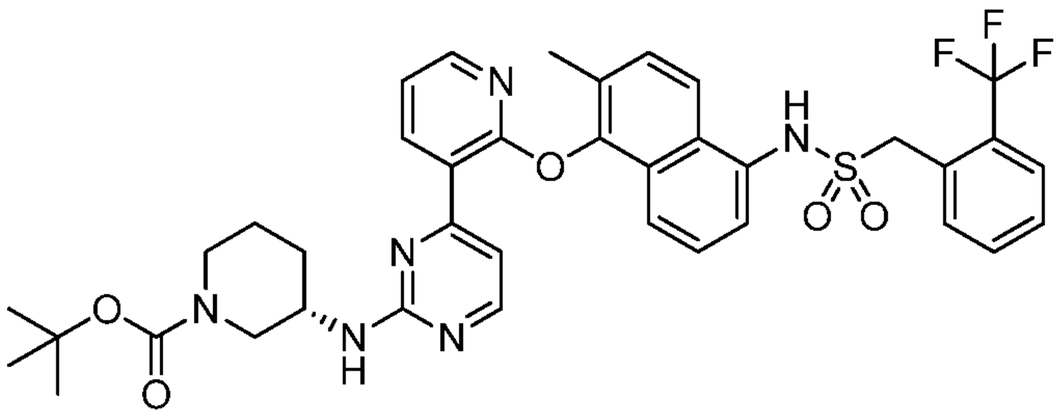
[0380] Step 2: *N*-(6-Methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-(tetrahydrofuran-2-yl)methanesulfonamide



[0381] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-(cyclobutanecarboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.15 mmol), dichloromethane (2 mL) and hydrochloric acid (4 M in ethyl acetate, 0.37 mL, 1.48 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05%HCl); B: ACN) to yield 55 mg (65%, yield HCl salt) of **141** as a yellow solid. LCMS (ESI) $[M+H]^+$ = 575.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (s, 1H), 9.73 - 9.23 (m, 1H), 8.99 - 8.76 (m, 1H), 8.56 - 8.47 (m, 1H), 8.25 - 8.15 (m, 3H), 7.75 - 7.25 (m, 7H), 4.45 - 4.22 (m, 2H), 3.78 - 3.58 (m, 2H), 3.35 - 3.33 (m, 3H), 3.25 - 3.13 (m, 1H), 2.93 - 2.80 (m, 2H), 2.29 - 2.18 (m, 3H), 2.10 - 1.99 (m, 2H), 1.97 - 1.76 (m, 4H), 1.72 - 1.60 (m, 2H).

Example 142 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-(2-(trifluoromethyl)phenyl)methanesulfonamide* ***142***

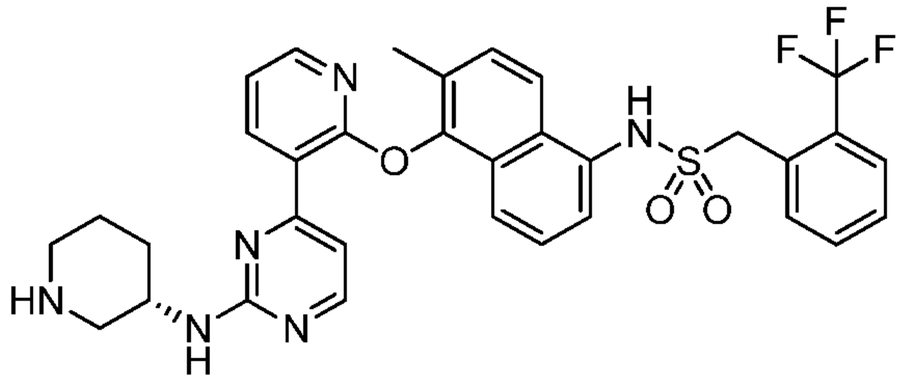
[0382] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-5-((2-(trifluoromethyl)phenyl)methylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0383] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (400 mg, 0.760 mmol), pyridine (1 mL), DCM (3 mL), and (2-(trifluoromethyl)phenyl)methanesulfonyl chloride (295 mg, 1.14 mmol). After 20 h, the mixture was diluted with DCM (75 mL) and washed with saturated $NaHCO_3$(aq) (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude was purified by flash chromatography through silica gel (0 – 100% EtOAc/hexanes) to provide

392 mg (69 % yield) of the title compound as a light yellow gum. LCMS (ESI) [M+H]+ = 749.1, rt = 2.02 min.

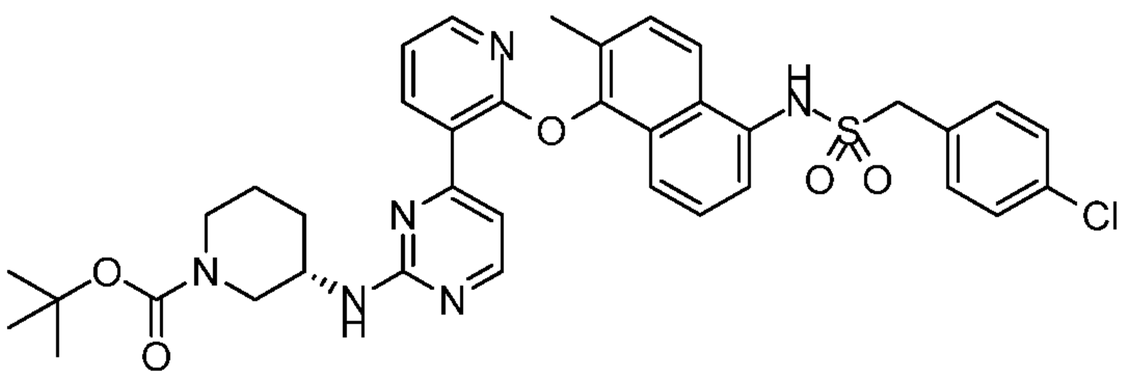
[0384] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-(2-(trifluoromethyl)phenyl)methanesulfonamide



[0385] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((2-methyl-5-((2-(trifluoromethyl)phenyl)methylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (392 mg, 0.524 mmol), EtOAc (3 mL), and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). After 3 h, the mixture was concentrated *in vacuo* and the crude solid was washed with EtOAc (3 x 3 mL) and then MeCN (3 x 3 mL). The solid product was then sonicated, concentrated *in vacuo* with MeCN (3 x 3 mL) and then dissolved in H_2O and MeCN. Lyophilization provided 292 mg (81% yield) of **142** as a fluffy white solid. LCMS (ESI) [M+H]+ = 649.3, rt = 1.48 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.96 – 8.73 (m, 2H), 8.69 – 8.54 (m, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.13 – 8.04 (m, 2H), 7.78 (d, J = 7.9 Hz, 1H), 7.74 – 7.66 (m, 2H), 7.64 – 7.51 (m, 5H), 7.49 – 7.40 (m, 2H), 7.28 (dd, J = 7.5, 4.8 Hz, 1H), 4.72 (s, 2H), 4.38 – 4.16 (m, 1H), 3.21 (d, J = 11.3 Hz, 2H), 2.95 – 2.76 (m, 2H), 2.22 (s, 3H), 2.09 – 1.84 (m, 2H), 1.83 – 1.55 (m, 2H).

Example 143 *(S)-1-(4-Chlorophenyl)-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide* ***143***

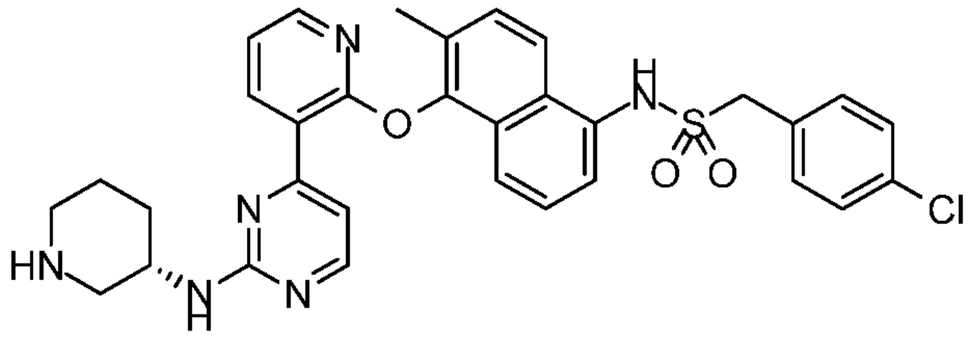
[0386] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-((4-chlorophenyl)methylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0387] The General Procedure A was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.19 mmol), pyridine (2 mL) and (4-chlorophenyl)methanesulfonylchloride (64 mg, 0.28

mmol). The mixture was concentrated, dissolved in ethyl acetate (20 mL), and washed with H_2O (15 mL x 2). The organic phase was dried over anhydrous sodium sulfate, concentrated to yield 100 mg (crude) of the title compound as a brown oil.

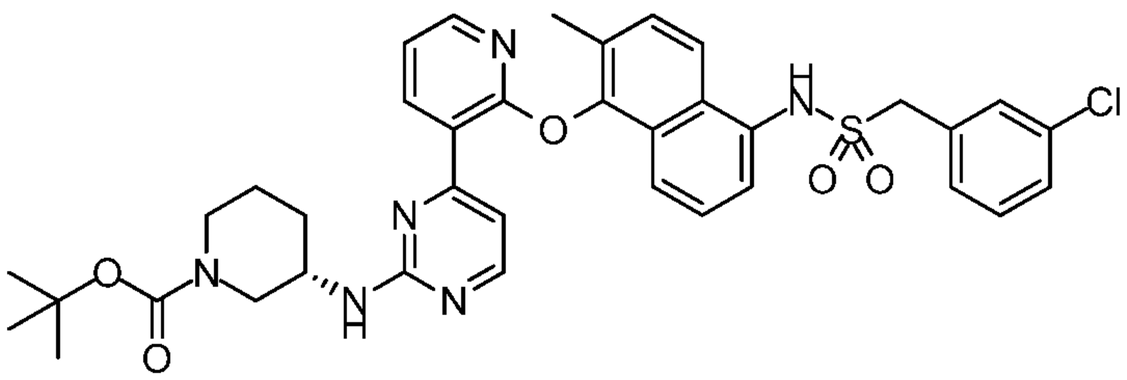
[0388] Step 2: (*S*)-1-(4-Chlorophenyl)-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide



[0389] The General Procedure B was followed, using (*S*)-1-(4-chlorophenyl)-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide (100 mg, 0.14 mmol), dichloromethane (1 mL) and hydrochloric acid (4 M in ethyl acetate, 0.4 mL, 1.6 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% HCl); B: ACN) to yield 42 mg (46%, yield HCl salt) of **143** as a brown solid. LCMS (ESI) $[M+H]^+$ = 615.1; ^1H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 9.23 - 8.83 (m, 2H), 8.78 - 8.61 (m, 1H), 8.53 - 8.42 (m, 1H), 8.13 - 7.96 (m, 2H), 7.66 - 7.49 (m, 3H), 7.48 - 7.36 (m, 4H), 7.30 - 7.25 (m, 1H), 4.66 - 4.48 (m, 2H), 4.40 - 4.21 (m, 1H), 3.46 - 3.18 (m, 2H), 2.93 - 2.77 (m, 2H), 2.24 - 2.07 (m, 3H), 2.06 - 1.86 (m, 2H), 1.84 - 1.58 (m, 2H).

Example 144 *(S)-1-(3-Chlorophenyl)-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide* ***144***

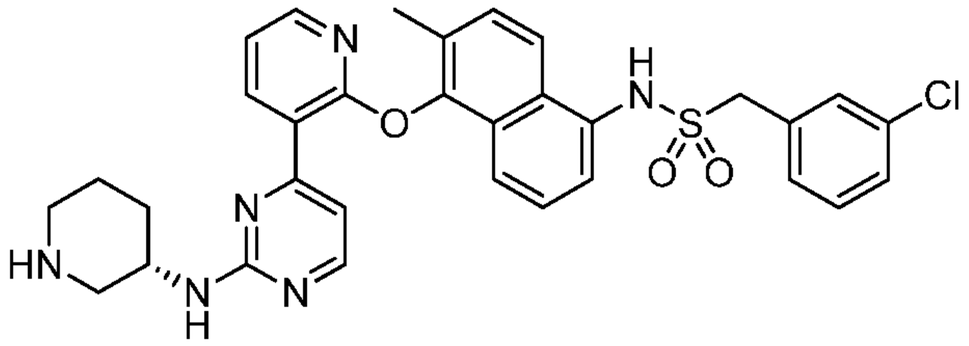
[0390] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-((3-Chlorophenyl)methylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0391] The General Procedure A was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol), pyridine (2 mL) and (3-chlorophenyl)methanesulfonyl chloride (51 mg, 0.22 mmol). The resulting solution was extracted with ethyl acetate. The combined organic layers

were dried over anhydrous sodium sulfate, and concentrated *in vacuo* to yield 115 mg of the crude title compound as a yellow solid. LCMS (ESI) $[M+H]^+$ = 715.0.

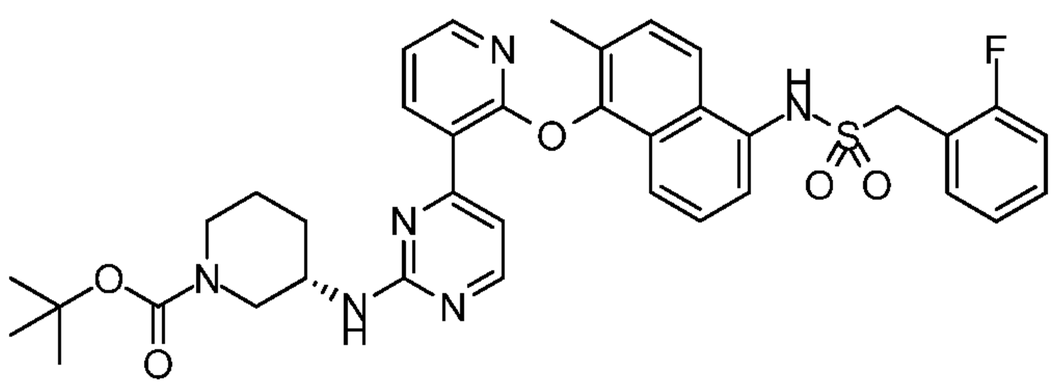
Step 2: (*S*)-1-(3-Chlorophenyl)-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide



[0392] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-((3-chlorophenyl)methylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (110 mg, 0.15 mmol), dichloromethane (2 mL) and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05%HCl); B: ACN) to yield 99 mg (95%, yield HCl salt) of **144** as a yellow solid. LCMS (ESI) $[M+H]^+$ = 615.3. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.91 (s, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.09 - 8.05 (m, 1H), 8.02 (d, J = 8.8 Hz, 1H), 7.50 - 7.60 (m, 4H), 7.48 - 7.34 (m, 6H), 7.29 - 7.26 (m, 1H), 4.60 (s, 2H), 4.28 (s, 1H), 3.21 (d, J = 12.0 Hz, 2H), 2.85 - 2.81 (m, 2H), 2.21 (s, 3H), 2.04 - 1.96 (m, 1H), 1.92 - 1.85 (m, 1H), 1.75 -1.66 (m, 1H), 1.65 -1.55 (m, 1H).

Example 145 *(S)-1-(2-Fluorophenyl)-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide* ***145***

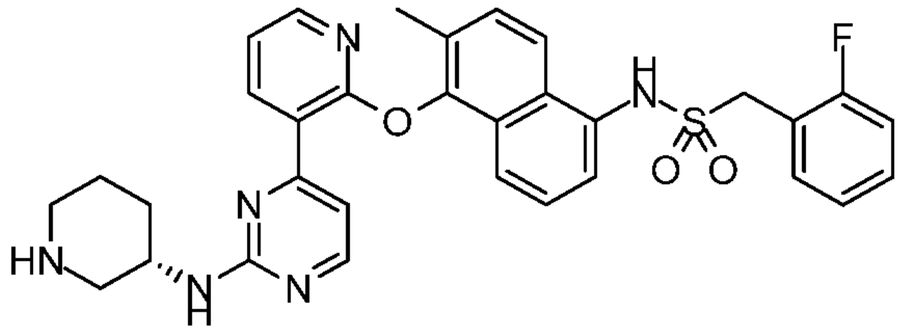
[0393] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-((2-fluorophenyl)methylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0394] The General Procedure A was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.19 mmol), pyridine (4 mL) and (2-fluorophenyl)methanesulfonyl chloride (47.5 mg, 0.23 mmol). The mixture was concentrated, dissolved in dichloromethane (30 mL) and washed

with H_2O (40 mL x 2). The organic phase was dried over anhydrous sodium sulfate and concentrated to give 110 mg (83% yield) of the title compound as a brown oil.

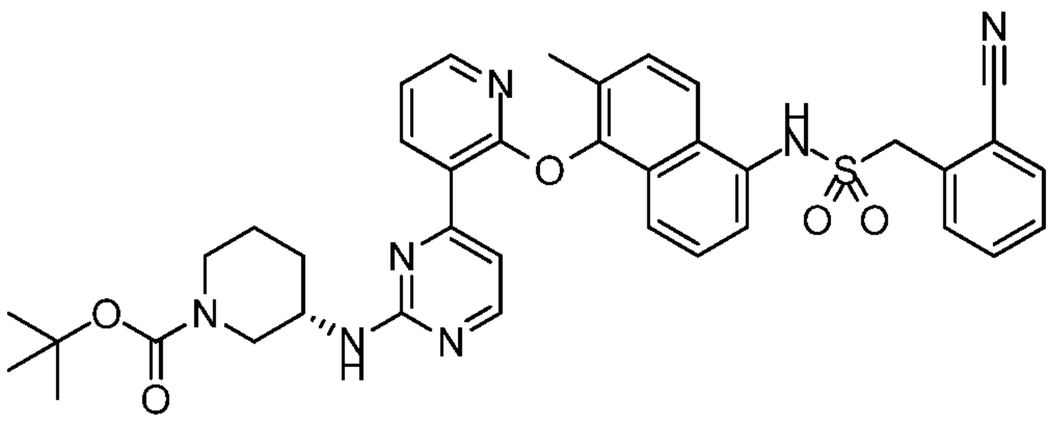
[0395] Step 2: (*S*)-1-(2-Fluorophenyl)-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide



[0396] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-((2-fluorophenyl)methylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (110 mg, 0.16 mmol), ethyl acetate (1 mL) and hydrochloric acid (4 M in ethyl acetate, 3 mL, 12 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% HCl); B: ACN) to yield 45.7 mg (46%, yield HCl salt) of **145** as a white solid. LCMS (ESI) $[M+H]^+$ = 599.2.; ^1H NMR (400 MHz, DMSO-d_6) δ 10.07 (s, 1H), 9.69 - 9.00 (m, 2H), 8.85 (s, 1H), 8.51 (d, *J* = 5.2 Hz, 1H), 8.14 - 8.04 (m, 2H), 7.72 (m, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.50 - 7.37 (m, 4H), 7.31 - 7.27 (m, 1H), 7.24 - 7.19 (m, 2H), 4.60 (s, 2H), 4.54 - 4.44 (m, 1H), 3.53 - 3.37 (m, 1H), 3.28 - 3.13 (m, 1H), 2.93 - 2.79 (m, 2H), 2.22 (s, 3H), 2.09 - 1.98 (m, 1H), 1.97 - 1.86 (m, 1H), 1.85 - 1.73 (m, 1H), 1.72 - 1.56 (m, 1H).

Example 146 *(S)-1-(2-Cyanophenyl)-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide* ***146***

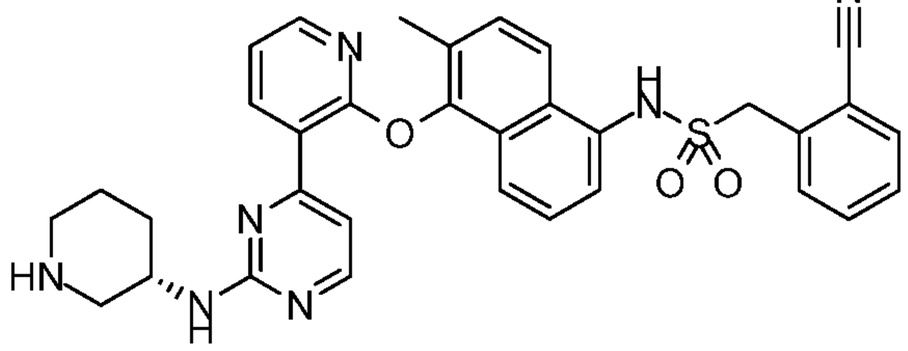
[0397] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-((2-chlorophenyl)methylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0398] The General Procedure A was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol), pyridine (2 mL) and (2-cyanophenyl)methanesulfonyl chloride (49 mg, 0.23 mmol) (47 mg, 0.21mmol). The reaction mixture was concentrated and the residue was taken

up in ethyl acetate (20 mL) and washed with water (10 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo* to yield (130 mg crude) of the title compound as a pale brown oil. LCMS (ESI) $[M+H]^+$ = 705.1.

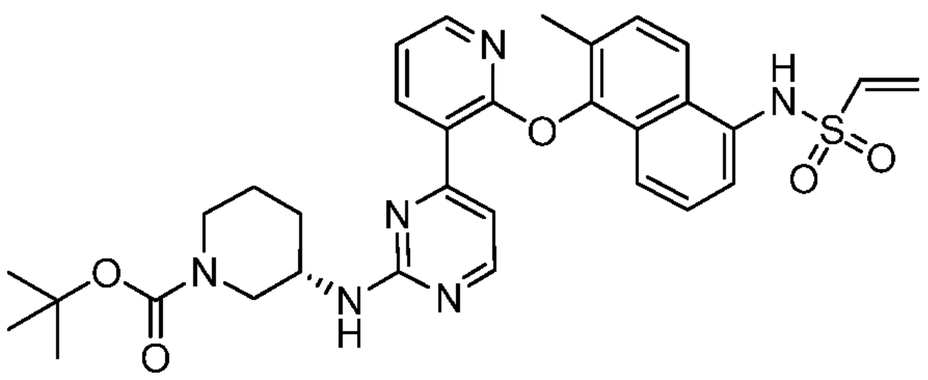
[0399] Step 2: (*S*)-1-(2-Cyanophenyl)-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide



[0400] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-((2-chlorophenyl) methylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (130 mg, 0.18 mmol), ethyl acetate (2 mL) and hydrochloric acid (4 M in ethyl acetate, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% NH_4OH); B: ACN) to yield 32 mg (30%, yield HCl salt) of **146** as a white solid. LCMS (ESI): $[M+H]^+$ = 606.1; ^1H NMR (400 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.46 (d, J = 5.2 Hz, 1H), 8.19 (d, *J* = 8.8 Hz, 1H), 8.06 - 8.04 (m, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 4.8 Hz, 1H), 7.56 - 7.49 (m, 3H), 7.40 - 7.30 (m, 3H), 7.15 - 7.11 (m, 2H), 4.44 (s, 2H), 4.14 - 4.09 (m, 1H), 3.08 - 3.04 (m, 2H), 2.71 - 2.65 (m, 2H), 2.20 (s, 3H), 2.02 - 1.98 (m, 1H), 1.85 - 1.80 (m, 1H), 1.65 -1.55 (m, 2H).

Example 147 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)ethenesulfonamide* ***147***

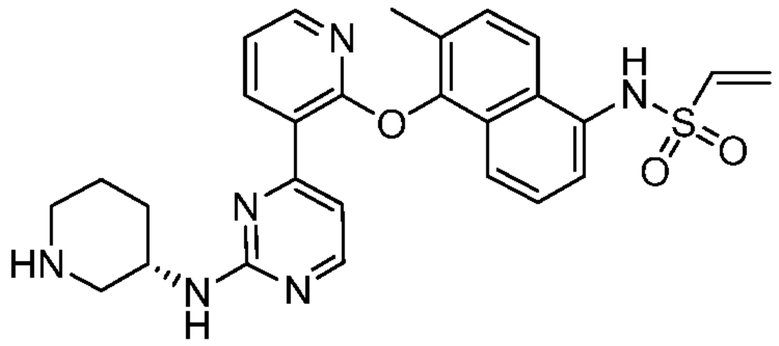
[0401] Step 1: (S)-*tert*-Butyl 3-((4-(2-((2-methyl-5-(vinylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0402] The General Procedure A was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol), pyridine (3 mL) and 2-methoxypropane-1-sulfonyl chloride (33 mg, 0.19 mmol).

The solution was concentrated to yield 140 mg of the crude title compound as a yellow solid. LCMS (ESI) $[M+H]^+ = 617.1$.

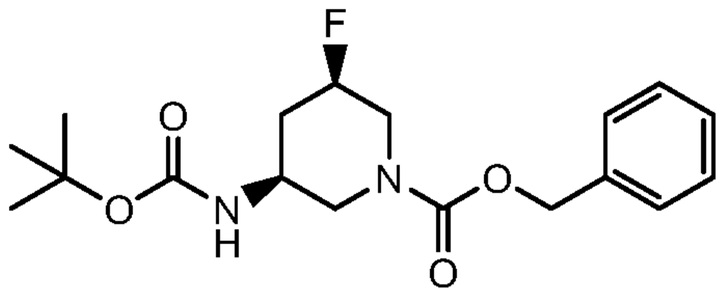
[0403] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)ethenesulfonamide



[0404] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((2-methyl-5-(vinylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.16 mmol), dichloromethane (5 mL) and hydrochloric acid (4 M in ethyl acetate, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05%HCl); B: ACN) to yield 3 mg (4%, yield HCl salt) of **147** as a yellow solid. LCMS (ESI): $[M+H]^+ = 517.1$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (s, 1H), 8.49 (d, J = 6.0 Hz, 1H), 8.12 (d, J = 8.8 Hz, 3H), 7.62 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.47 (d, J = 7.5 Hz, 1H), 7.41 - 7.29 (m, 2H), 6.79 (dd, J = 16.4, 10.0, 1H), 6.08 (d, J = 16.8 Hz, 1H), 5.91 (d, J = 9.6 Hz, 1H), 4.63 (s, 1H), 3.68 (d, J = 11.6 Hz, 1H), 3.40 (d, J = 12.8 Hz, 1H), 3.18 - 3.03 (m, 2H), 2.34 - 2.09 (m, 5H), 2.05 - 1.81 (m, 2H).

Example 148 *N-(5-((3-(2-(((3S, 5R)-5-Fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)-1-phenylmethanesulfonamide* ***148***

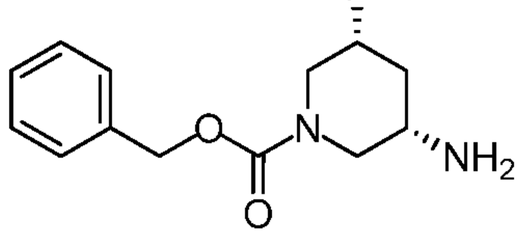
[0405] Step 1: (3*S*, 5*R*)-Benzyl 3-((*tert*-butoxycarbonyl)amino)-5-fluoropiperidine-1-carboxylate



[0406] To a solution of *tert*-butyl ((3*S*, 5*R*)-5-fluoropiperidin-3-yl) carbamate (500 mg, 0.23 mmol) in THF (2 mL) and H_2O (1 mL) was added sodium carbonate (48.6 mg, 0.46 mmol). Benzyl chloroformate (0.03 ml, 0.23 mmol) was added dropwise at 0 °C and stirred at 0 °C to rt for 1 h. The mixture was concentrated to dryness and the residue was dissolved in dichloromethane (20 mL) and washed with H_2O (10 mL x 2). The organic phase was dried over anhydrous sodium sulfate, concentrated and purified by silica gel chromatography

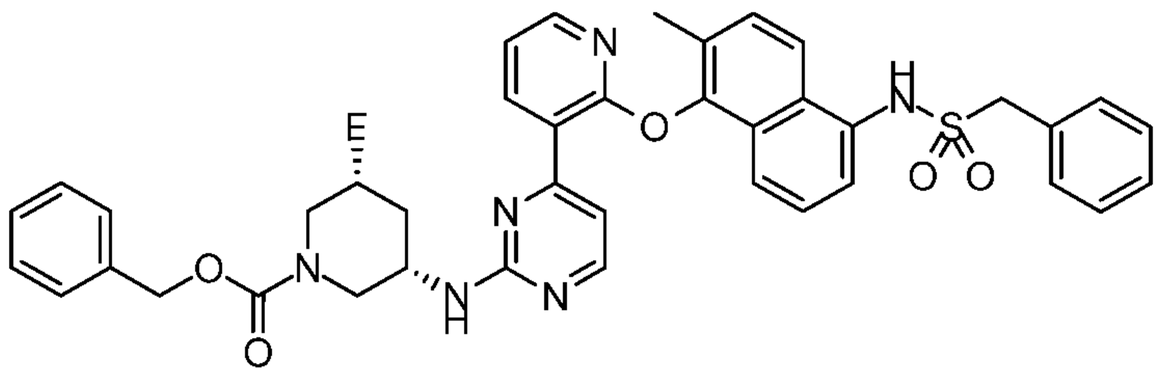
(eluting with 0-1% methanol in dichloromethane) to yield 200 mg (82% yield) of the title compound as a colorless oil; LCMS (ESI) $[M+H]^+$ = 398.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 - 7.29 (m, 5H), 5.28 - 5.03 (m, 3H), 4.95 - 4.63 (m, 1H), 4.45 - 4.25 (m, 1H), 4.19 - 3.97 (m, 1H), 3.95 - 3.81 (m, 1H), 3.35 - 3.02 (m, 2H), 2.17 - 1.82 (m, 2H), 1.40 (s, 9H).

[0407] Step 2: (3*S*, 5*R*)-Benzyl 3-amino-5-fluoropiperidine-1-carboxylate

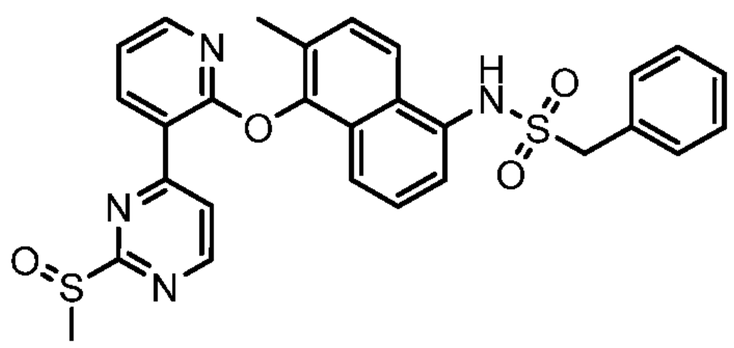


[0408] To a solution of benzyl (3*S*,5*R*)-3-(*tert*-butoxycarbonylamino)-5-fluoro-piperidine-1-carboxylate (200 mg, 0.57 mmol) in ethyl acetate (1 mL) was added (4 M in ethyl acetate, 3 mL, 12 mmol) and stirred at 25 °C for 1 h. The mixture was concentrated to yield 138 mg (84% yield) of the title compound as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.44 - 7.29 (m, 5H), 5.28 - 5.07 (m, 2H), 4.96 (s, 1H), 4.31 - 4.08 (m, 2H), 3.60 - 3.35 (m, 3H), 2.30 - 2.10 (m, 2H).

[0409] Step 3: (3*R*, 5*S*)-Benzyl 3-fluoro-5-((4-(2-((2-methyl-5-(phenylmethylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0410] To a stirred solution of *N*-[6-methyl-5-[[3-(2-methylsulfinylpyrimidin-4-yl)-2-pyridyl]oxy]-1-naphthyl]-1-phenyl-methanesulfonamide, made following the procedures of Example 101 (100 mg, 0.18 mmol):

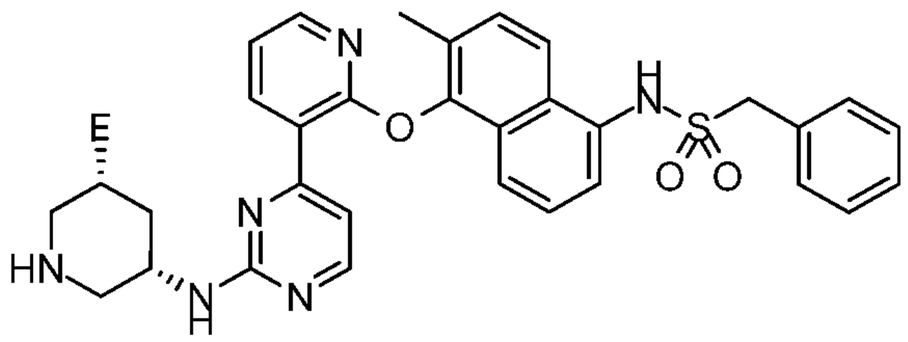


,

in 1,4-dioxane (3 mL) was added *N*,*N*-diethylpropan-2-amine (0.16 mL, 0.92 mmol) and (3*S*,5*R*)-benzyl 3-amino-5-fluoropiperidine-1-carboxylate (64 mg, 0.22 mmol), the mixture was stirred at 140 °C for 88 h. After cooling down, the mixture was concentrated and the

residue was dissolved in ethyl acetate (20 mL) and washed with H_2O (20 mL). The organic phase was dried over anhydrous sodium sulfate, concentrated and purified by Prep-TLC (5% methanol in dichloromethane, R_f = 0.5) to give 65 mg (48% yield) of the title compound as a white solid. LCMS (ESI) $[M+H]^+$= 733.1.

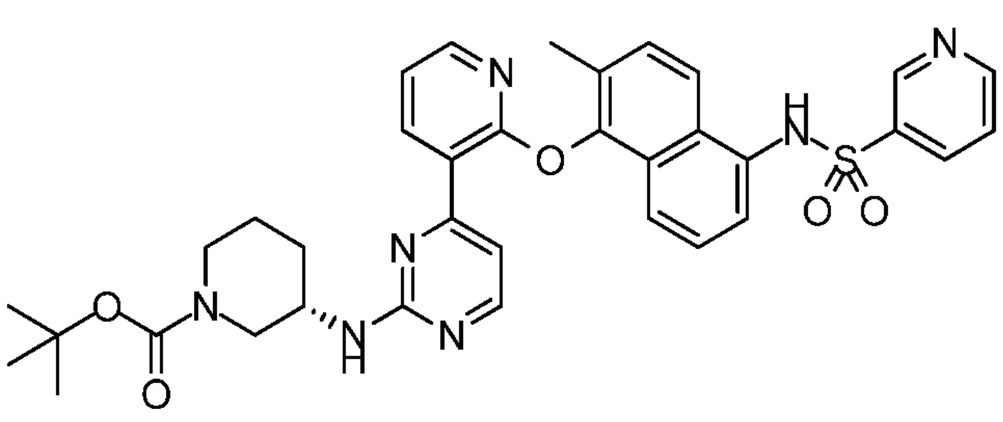
[0411] Step 4: *N*-(5-((3-(2-(((3*S*, 5*R*)-5-Fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)-1-phenylmethanesulfonamide



[0412] To a solution of (3*R*,5*S*)-benzyl 3-fluoro-5-((4-(2-((2-methyl-5-(phenylmethylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (80 mg, 0.11 mmol) in methanol (10 mL) was added 10% wet palladium (30 mg) on carbon followed by stirring at 40 °C under hydrogen gas (35 Psi) for 12 h. The mixture was filtered and purified by Prep-HPLC (mobile phase: A: water (0.05%HCl); B: ACN) to yield 2.6 mg (3.9% yield) of **148** as a white solid; LCMS (ESI) $[M+H]^+$ = 599.1; ^1H NMR (400MHz, DMSO-d_6) δ 9.87 (s, 1H), 9.37 - 9.19 (m, 1H), 8.51 (d, *J* = 5.2 Hz, 1H), 8.12 - 8.02 (m, 2H), 7.65 - 7.55 (m, 2H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.45 - 7.40 (m, 2H), 7.38 - 7.33 (m, 5H), 7.29 - 7.26 (m, 1H), 5.16 - 4.98 (m, 1H), 4.54 (s, 2H), 4.50 - 4.41 (m, 1H), 3.53 - 3.42 (m, 2H), 3.26 - 3.18 (m, 1H), 3.08 - 3.02 (m, 1H), 2.21 (s, 3H), 2.13 - 2.00 (m, 2H).

Example 149 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyridine-3-sulfonamide* ***149***

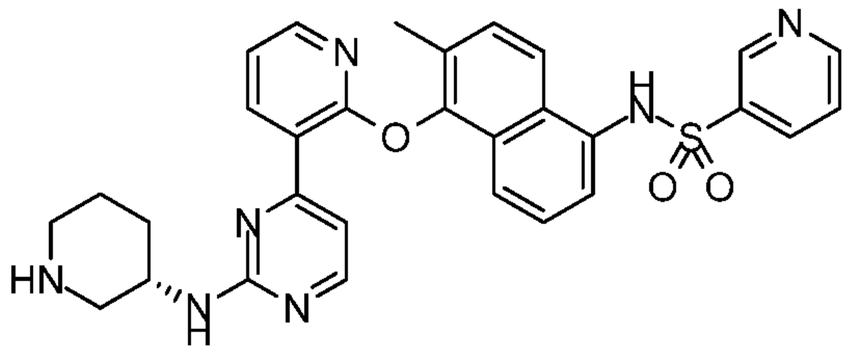
[0413] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-5-(pyridine-3-sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0414] The General Procedure A was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100

mg, 0.19 mmol), pyridine (3 mL) and pyridine-3-sulfonylchloride (37.1 mg, 0.21mmol). The mixture was concentrated, dissolved in ethyl acetate (20 mL) and washed with H_2O (15 mL x 2). The organic phase was dried over anhydrous sodium sulfate and concentrated to give 100 mg (crude) of the title compound as a brown solid.

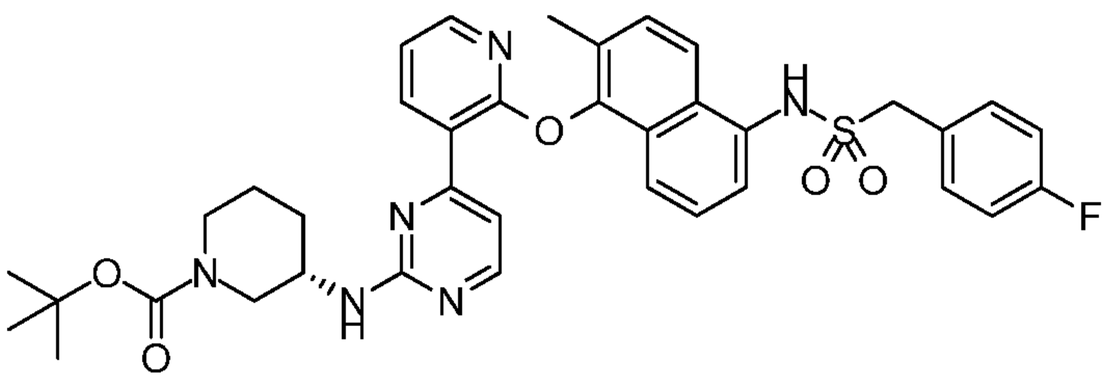
[0415] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyridine-3-sulfonamide



[0416] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-(cyclobutanecarboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.15 mmol), dichloromethane (2 mL) and hydrochloric acid (4 M in ethyl acetate, 0.4 mL, 1.6 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% HCl); B: ACN) to yield 29.4 mg (32%, yield as HCl salt) of **149** as a yellow solid. LCMS (ESI) $[M+H]^+$ = 568.1; ^1H NMR (400 MHz, DMSO-d_6) δ 10.69 - 10.60 (m, 1H), 9.18 - 9.05 (m, 1H), 8.85 - 8.73 (m, 2H), 8.51 - 8.43 (m, 1H), 8.14 - 8.01 (m, 2H), 7.88 - 7.79 (m, 1H), 7.70 - 7.53 (m, 3H), 7.45 - 7.40 (m, 1H), 7.38 - 7.31 (m, 1H), 7.30 - 7.23 (m, 1H), 7.15 - 7.09 (m, 1H), 3.48 - 3.14 (m, 2H), 2.92 - 2.75 (m, 2H), 2.16 (s, 3H), 2.06 - 1.86 (m, 2H), 1.84 - 1.57 (m, 2H).

Example 150 *(S)-1-(4-Fluorophenyl)-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide* ***150***

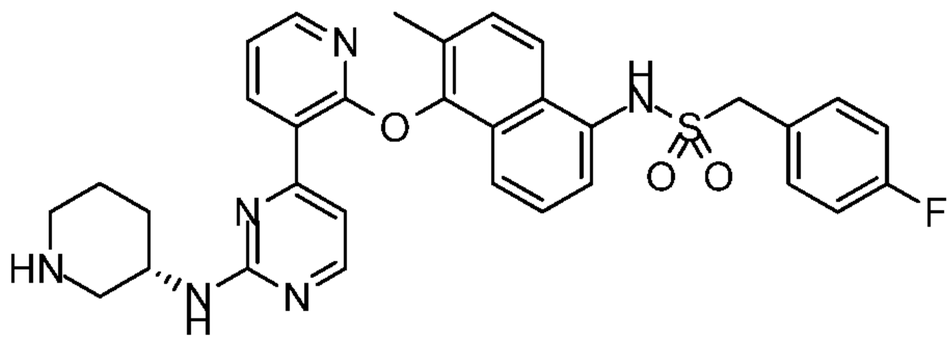
[0417] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-((4-fluorophenyl)methylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0418] The General Procedure A was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol), pyridine (2 mL) and 4-fluorophenyl)methanesulfonylchloride (48 mg, 0.23

mmol). The reaction mixture was concentrated *in vacuo* and the residue taken up in ethyl acetate (20 mL) and washed with water (10 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo* to yield (130 mg crude) of the title compound as a pale brown oil. LCMS (ESI) $[M+H]^+$ = 699.3.

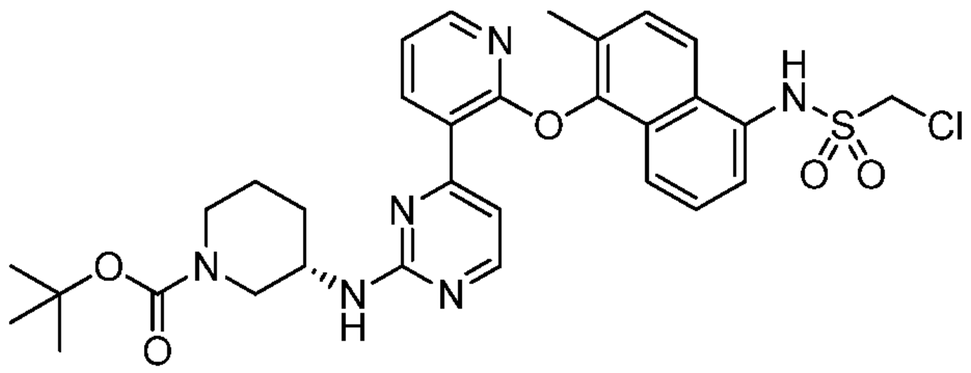
[0419] Step 2: (*S*)-1-(4-Fluorophenyl)-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide



[0420] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-((4-fluorophenyl) methylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (130 mg, 0.19 mmol), ethyl acetate (2 mL) and hydrochloric acid (4 M in ethyl acetate, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% HCl); B: ACN) to yield 47 mg (40% yield) of **150** as a white solid. LCMS (ESI): $[M+H]^+$ = 599.3; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 9.17 (s, 1H), 8.50 (d, J = 5.2 Hz, 1H), 8.13 - 8.00 (m, 2H), 7.65 (s, 1H), 7.58 - 7.50 (m, 2H), 7.47 - 7.34 (m, 3H), 7.30 - 7.27(m, 1H), 7.20 (t, J = 8.8 Hz, 2H), 4.56 (s, 2H), 4.40 - 4.35 (m, 1H), 3.45 - 3.38 (m, 1H), 3.22 - 3.15 (m, 1H), 2.90 - 2.80 (m, 2H), 2.22 (s, 3H), 2.07 - 2.00 (m, 1H), 1.96 - 1.88 (m, 1H), 1.85 - 1.71 (m, 1H), 1.69 - 1.62 (m, 1H).

Example 151 *(S)-1-Chloro-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide* ***151***

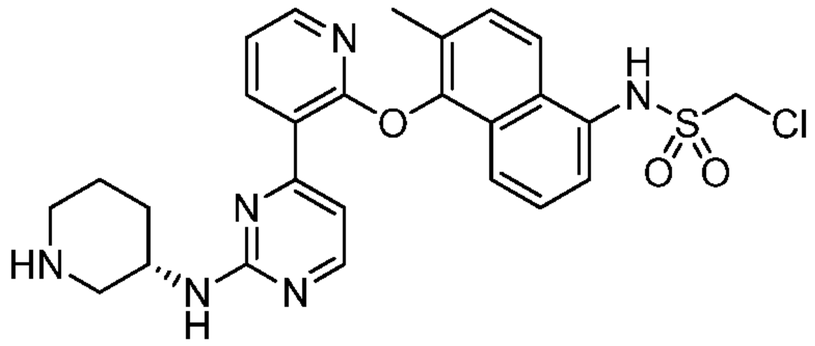
[0421] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-(chloromethylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0422] The General Procedure A was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (300 mg, 0.57 mmol), pyridine (2 mL) and chloromethanesulfonylchloride (0.06 mL, 0.68 mmol). The mixture was concentrated and dissolved in dichloromethane (100 mL) and washed with

H_2O (80 mL x 2). The organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo* to yield 110 mg (83% yield) of the title compound as a brown oil. LCMS (ESI) $[M+H]^+ = 639.1$.

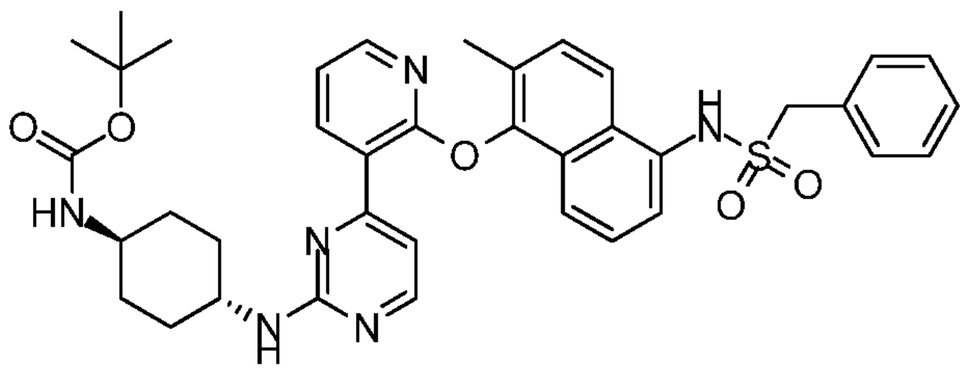
[0423] Step 2: (*S*)-1-Chloro-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide



[0424] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-(chloromethylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (110 mg, 0.17 mmol), ethyl acetate (1 mL) and hydrochloric (4 M in ethyl acetate, 0.6 mL, 2.4 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05%HCl); B: ACN) to yield 34 mg (34% yield) of **151** as a yellow solid. LCMS (ESI) $[M+H]^+ = 539.1$; ^1H NMR (400 MHz, DMSO-d_6) δ 10.44 (s, 1H), 9.10 - 8.60 (m, 2H), 8.48 (d, J = 5.6 Hz, 1H), 8.14 (d, J = 8.8 Hz, 1H), 8.06 (d, J = 3.2 Hz, 1H), 7.65 - 7.54 (m, 4H), 7.52 - 7.47 (m, 1H), 7.46 - 7.40 (m, 1H), 7.29 - 7.26 (m, 1H), 5.05 (s, 2H), 4.36 - 4.25 (m, 1H), 3.48 - 3.38 (m, 1H), 3.26 - 3.14 (m, 1H), 2.90 - 2.80 (m, 2H), 2.22 (s, 3H), 2.07 - 1.97 (m, 1H), 1.95 - 1.85 (m, 1H), 1.81 - 1.70 (m, 1H), 1.67 - 1.55 (m, 1H).

Example 152 *N-(5-((3-(2-(((trans)-4-Aminocyclohexyl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)-1-phenylmethanesulfonamide* ***152***

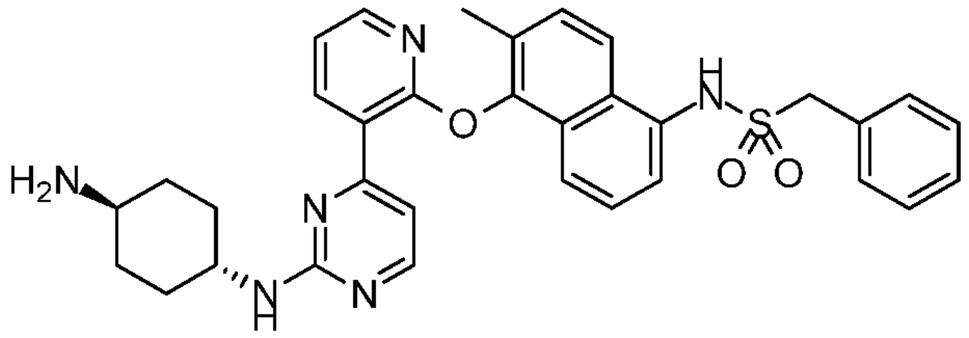
[0425] Step 1: *tert*-Butyl ((*trans*)-4-((4-(2-((2-methyl-5-(phenylmethylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)cyclohexyl)carbamate



[0426] To a stirred solution of *N*-[6-methyl-5-[[3-(2-methylsulfinylpyrimidin-4-yl)-2-pyridyl]oxy]-1-naphthyl]-1-phenyl-methanesulfonamide from Example 148 (100 mg, 0.18 mmol) in 1,4-dioxane (3 mL) was added *N,N*-diisopropylethylamine (0.1 mL, 0.55 mmol) and *tert*-butyl *N*-(4-aminocyclohexyl)carbamate (39 mg, 0.18 mmol). The mixture was stirred at

130 °C for 3 days and then concentrated *in vacuo* and purified by flash column chromatography eluting with 0-2% methanol in dichloromethane (Rf = 0.5) to yield 100 mg (78% yield) of the title compound as a brown solid. LCMS (ESI) $[M+H]^+$ = 695.4.

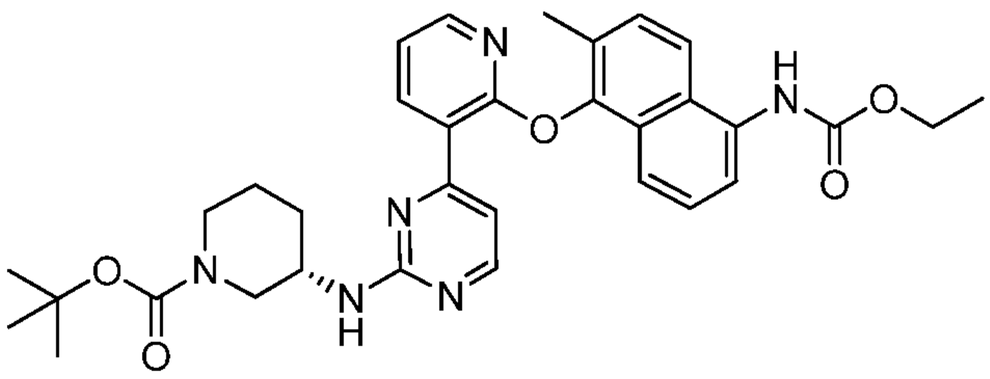
[0427] Step 2: *N*-(5-((3-(2-(((*trans*)-4-Aminocyclohexyl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)-1-phenylmethanesulfonamide



[0428] The General Procedure B was followed, using *tert*-butyl ((1r,4r)-4-((4-(2-((2-methyl-5-(phenylmethylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)cyclohexyl) carbamate (100 mg, 0.14 mmol), dichloromethane (5 mL) and hydrochloric acid (4 M in ethyl acetate, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05%HCl); B: ACN) to yield 73 mg (80% yield) of **152** as a yellow solid. LCMS (ESI): $[M+H]^+$ = 595.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.59 - 8.43 (m, 2H), 8.25 - 8.04 (m, 5H), 7.74 - 7.27 (m, 12H), 4.58 - 4.51 (m, 2H), 3.99 - 3.84 (m, 1H), 3.09 - 2.97 (m, 1H), 2.22 (s, 3H), 2.15 - 1.98 (m, 4H), 1.60 - 1.39 (m, 4H).

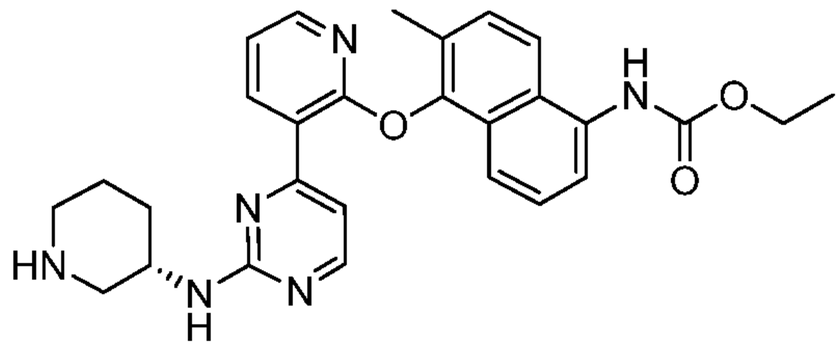
Example 153 *(S)-Ethyl (6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)carbamate* ***153***

[0429] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-((ethoxycarbonyl)amino)-2-methylnaphthalen-1-yl)oxy) pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0430] The General Procedure A was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (150 mg, 0.28 mmol), triethylamine (0.16 mL, 1.14 mmol) and ethyl chloroformate (0.26 mL, 2.76 mmol). The solution was concentrated to afford 200 mg of the crude title compound as a yellow solid. LCMS (ESI) $[M+Na]^+$ = 621.1.

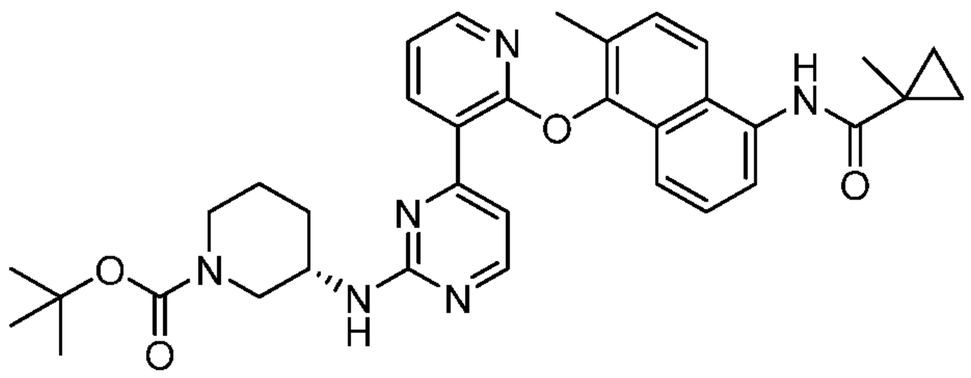
[0431] Step 2: (*S*)-Ethyl (6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl) oxy)naphthalen-1-yl)carbamate



[0432] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-((ethoxycarbonyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.17 mmol), dichloromethane (5 mL) and hydrochloric acid (4 M in ethyl acetate, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% HCl); B: ACN) to yield 29 mg (34% yield) of **153** as a yellow solid. LCMS (ESI): $[M+H]^+$ = 517.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.59 (s, 1H), 9.22 (s, 1H), 8.50 (d, *J* = 5.2 Hz, 1H), 8.07 (d, *J* = 3.2 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.67 (s, 1H), 7.56 (d, *J* = 7.1 Hz, 1H), 7.48 (t, *J* = 8.8 Hz, 2H), 7.43 - 7.36 (m, 1H), 7.27 (d, *J* = 7.7 Hz, 1H), 4.42 (s, 1H), 4.14 (s, 2H), 3.43 (d, *J* = 8.4 Hz, 1H), 3.19 (d, *J* = 12.0 Hz, 1H), 2.85 (t, *J* = 9.6 Hz, 2H), 2.27 - 2.13 (m, 3H), 2.03 (d, *J* = 9.2 Hz, 1H), 1.96 - 1.87 (m, 1H), 1.86 - 1.72 (m, 1H), 1.65 (d, *J* = 9.6 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 3H).

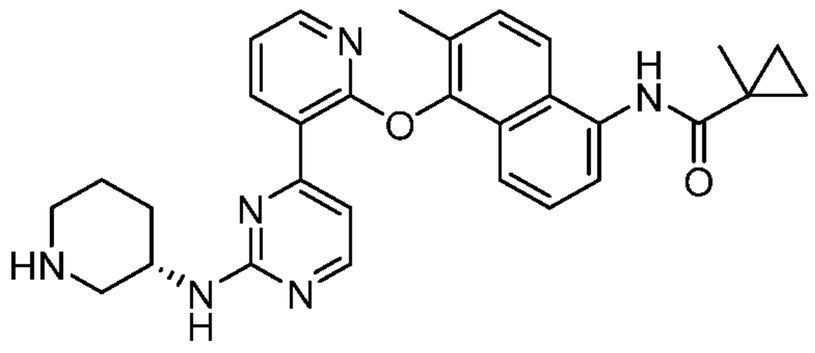
Example 154 *(S)-1-Methyl-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide* ***154***

[0433] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-(1-methylcyclopropane-1-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0434] The General Procedure C was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (138 mg, 0.25 mmol), 1-methycyclopropane carboxylic acid (25 mg, 0.25 mmol), DIPEA (0.131 mL, 0.75 mmol), HATU (194 mg, 0.50 mmol) and DCM (4 mL). The crude was used in the next steps without further purification.

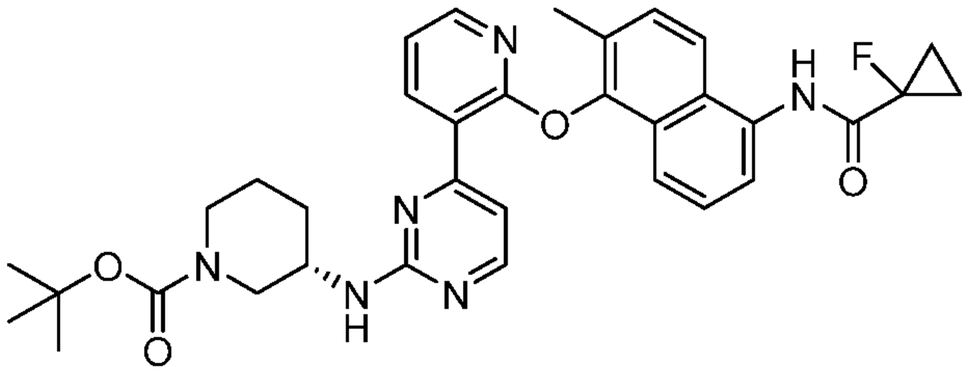
[0435] Step 2: (*S*)-1-Methyl-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide



[0436] The General Procedure B was followed, using crude *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-(1-methylcyclopropane-1-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate, DCM (4 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). The residue was purified *via* reverse-phase HPLC and lyophilized to yield 50 mg (39% yield over 2 steps) of **154**. LCMS (ESI): $[M+H]^+$ = 509.2;^{1}H NMR (400 MHz, DMSO-d_6) δ 9.47 (s, 1H), 8.54 – 8.47 (m, 1H), 8.42 (d, J = 5.1 Hz, 1H), 8.03 (dd, J = 4.8, 2.0 Hz, 1H), 7.71 (d, J = 8.7 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.51 – 7.45 (m, 2H), 7.42 – 7.34 (m, 2H), 7.25 (dd, J = 7.6, 4.8 Hz, 1H), 7.19 (d, J = 7.9 Hz, 1H), 3.96 (s, 1H), 3.20 – 3.12 (m, 1H), 2.87 (d, J = 12.8 Hz, 1H), 2.22 (s, 3H), 1.99 – 1.90 (m, 1H), 1.73 – 1.65 (m, 1H), 1.52 (s, 3H), 1.54 – 1.46 (m, 1H), 1.18- 1.13 (m, 2H), 0.72 – 0.68 (m, 2H).

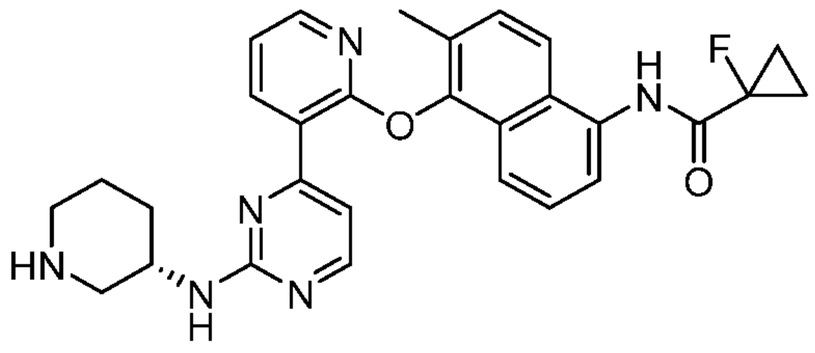
Example 155 *(S)-1-Fluoro-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide* ***155***

[0437] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((5-(1-fluorocyclopropane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0438] The General Procedure C was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (133 mg, 0.25 mmol), 1-fluorocyclopropanecarboxylic acid (25 mg, 0.24 mmol), DIPEA (0.126 mL, 0.72 mmol), HATU (186 mg, 0.48 mmol) and DCM (4 mL). The crude was directly used in the next step.

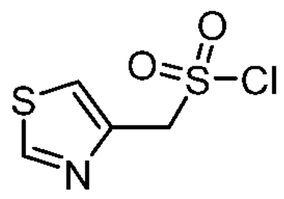
[0439] Step 2: (*S*)-1-Fluoro-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide



[0440] The General Procedure B was followed, using crude *tert*-butyl (*S*)-3-((4-(2-((5-(1-fluorocyclopropane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate, DCM (4 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). The residue was purified *via* reverse-phase HPLC and lyophilized to yield 68 mg (55% yield over 2 steps) of **155**. LCMS (ESI): $[M+H]^+$ = 513.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.45 (d, J = 2.0 Hz, 1H), 8.50 (d, J = 7.6 Hz, 1H), 8.41 (d, J = 5.1 Hz, 1H), 8.04 (dd, J = 4.8, 2.0 Hz, 1H), 7.75 (d, J = 8.7 Hz, 1H), 7.65 – 7.58 (m, 1H), 7.52 (d, J = 8.7 Hz, 1H), 7.48 – 7.40 (m, 3H), 7.26 (dd, J = 7.5, 4.8 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 3.90 (s, 1H), 3.14 – 3.05 (m, 1H), 2.85 – 2.75 (m, 1H), 2.48 – 2.41 (m, 2H), 2.22 (s, 3H), 1.97 – 1.88 (m, 1H), 1.68 – 1.59 (m, 1H), 1.58 – 1.27 (m, 6H).

Example 156 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-(thiazol-4-yl)methanesulfonamide* ***156***

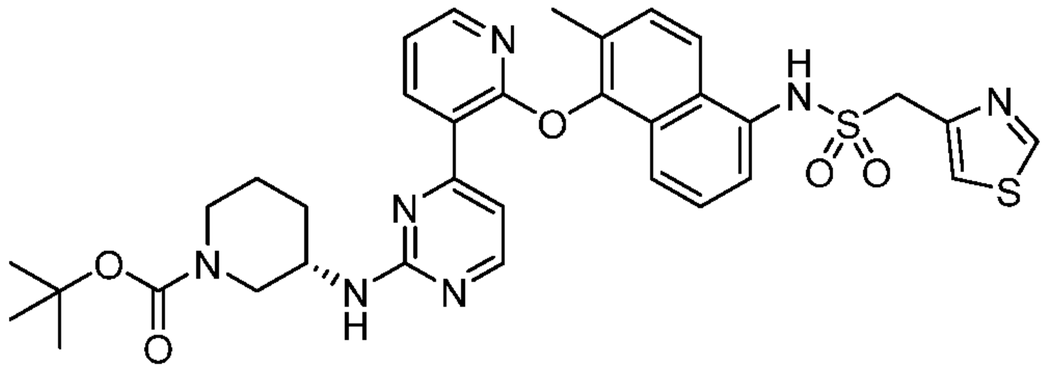
[0441] Step 1: Thiazol-4-ylmethanesulfonyl chloride



[0442] A mixture of 4-(chloromethyl)thiazole (1.0 g, 7.5 mmol), sodium sulfite (1.10 g, 9.0 mmol), and tetrabutylammonium bromide (120 mg, 0.37 mmol) in water (10 mL) was heated at 80 °C overnight, concentrated *in vacuo*, azeotroped with toluene (2x), and dried under high vacuum to afford thiazol-4-ylmethylsulfonyloxysodium. The crude product was used in the next step without further purification.

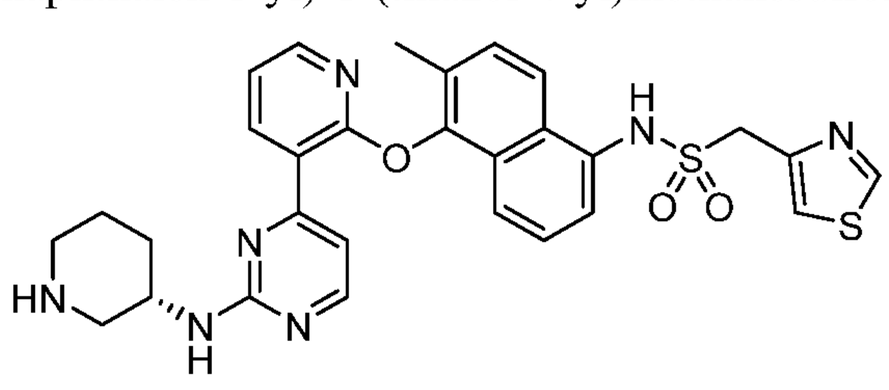
[0443] Thiazol-4-ylmethylsulfonyloxysodium (1.3 g, 6.5 mmol) was suspended in DMF (10 mL) cooled in ice bath. Thionyl chloride (0.71 mL, 9.7 mmol) was added dropwise. The resulting yellow mixture was allowed to warm to room temperature, stirred for 30 min. It was poured into crushed ice (~75 mL), extracted with iPrOAc (2 x 40 mL), washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 523 mg (41% yield) of the title compound as off-white solid. LCMS (ESI) $[M+H]^+$ = 198. The material obtained after work-up was used immediately in the next step.

[0444] Step 2: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-((thiazol-4-ylmethyl)sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0445] The General Procedure A was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol), pyridine (2 mL), DCM (2 mL), and thiazol-4-ylmethanesulfonyl chloride (523 mg, 2.64 mmol). After work up, the title compound was obtained as a brown solid (145 mg, 100% yield). The product was used in the next step without further purification. LCMS (ESI) $[M+H]^+ = 688$.

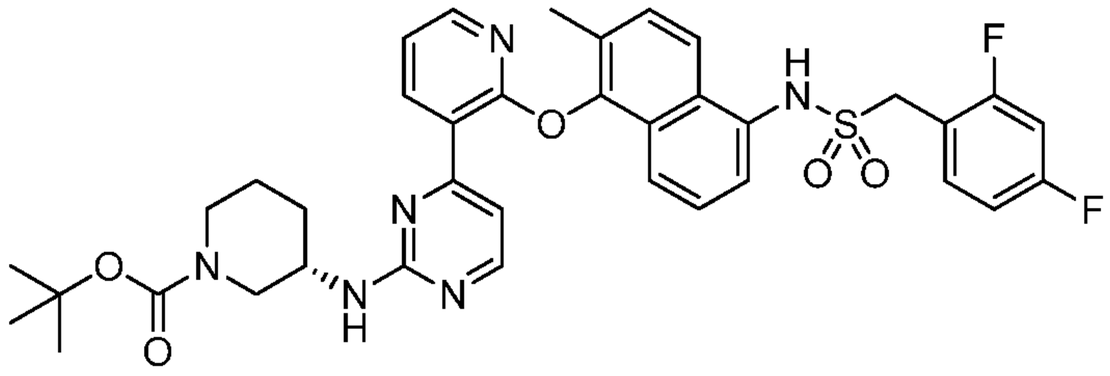
[0446] Step 4: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-(thiazol-4-yl)methanesulfonamide



[0447] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-((thiazol-4-ylmethyl)sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (145 mg, 211 mmol). The crude product was purified *via* reverse-phase HPLC and lyophilized to yield 20.3 mg (16.5% yield) of **156** as an off-white solid. LCMS (ESI) [M+H]+ = 588; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (d, J = 2.0 Hz, 1H), 8.51 (d, J = 7.7 Hz, 1H), 8.42 (d, J = 5.1 Hz, 1H), 8.13 (d, J = 8.7 Hz, 1H), 8.05 (dd, J = 4.8, 2.0 Hz, 1H), 7.68 (d, J = 2.0 Hz, 1H), 7.50 – 7.39 (m, 3H), 7.36 – 7.29 (m, 1H), 7.25 (dd, J = 7.6, 4.8 Hz, 1H), 7.21 (d, J = 7.9 Hz, 1H), 4.59 (s, 2H), 3.98 (s, 1H), 3.20 (d, J = 16.6 Hz, 2H), 2.90 (d, J = 12.2 Hz, 1H), 2.61 – 2.53 (m, 1H), 2.20 (s, 3H), 1.99 – 1.92 (m, 1H), 1.75 – 1.68 (m, 1H), 1.57 – 1.46 (m, 2H).

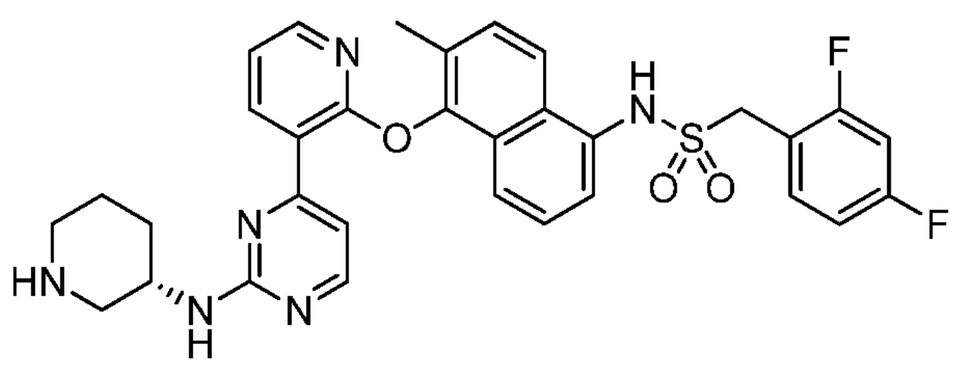
Example 157 *(S)-1-(2, 4-Difluorophenyl)-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide* ***157***

[0448] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-((2, 4-difluorophenyl)methylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0449] The General Procedure A was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (150 mg, 0.28 mmol), pyridine (3 mL) and 2,4-difluorophenyl)methanesulfonyl chloride (65 mg, 0.28 mmol). The solution was concentrated to afford 150 mg (74% yield) of the crude title compound as a yellow solid. LCMS (ESI) $[M+H]^+$ = 717.1.

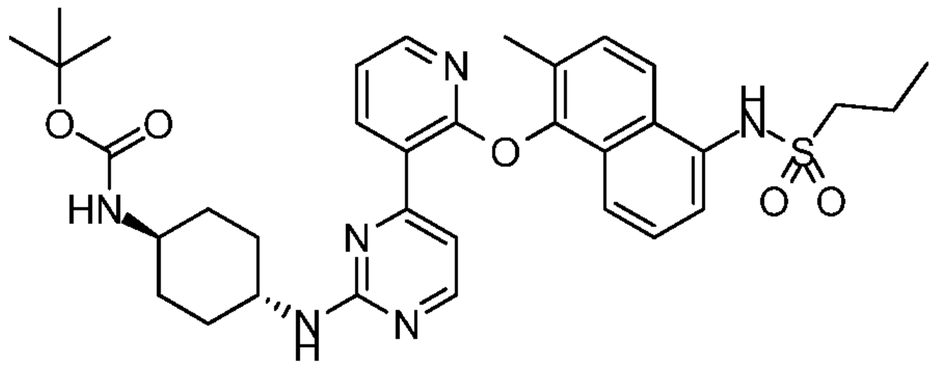
[0450] Step 2: (*S*)-1-(2, 4-Difluorophenyl)-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide



[0451] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-((2,4-difluorophenyl)methylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino) piperidine-1-carboxylate (150 mg, 0.21 mmol), dichloromethane (5 mL) and hydrochloric acid (4 M in ethyl acetate, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% HCl); B: ACN) to yield 38 mg (29% yield) of **157** as a yellow solid. LCMS (ESI): $[M+H]^+$ = 517.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 - 10.02 (m, 1H), 9.67 (s, 1H), 9.35 (s, 1H), 8.89 (s, 1H), 8.52 (d, J = 5.6 Hz, 1H), 8.15 - 8.02 (m, 2H), 7.74 (s, 1H), 7.60 - 7.38 (m, 5H), 7.34 - 7.23 (m, 2H), 7.12 (t, J = 8.4 Hz, 1H), 4.59 (s, 2H), 4.49 (s, 1H), 3.51 - 3.13 (m, 2H), 2.94 - 2.78 (m, 2H), 2.21 (s, 3H), 2.09 - 1.56 (m, 4H).

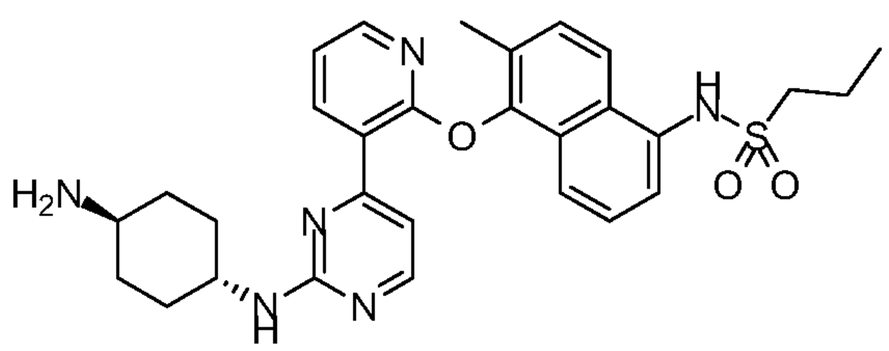
Example 158 *N-(5-((3-(2-(((trans)-4-Aminocyclohexyl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)propane-1-sulfonamide* ***158***

[0452] Step 1: *tert*-Butyl ((*trans*)-4-((4-(2-((2-methyl-5-(propylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)cyclohexyl)carbamate



[0453] To a stirred solution of *N*-(6-methyl-5-((3-(2-(methylsulfinyl)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide (100 mg, 0.20 mmol) in 1,4-dioxane (3 mL) was added *N,N*-diisopropylethylamine (0.1 mL, 0.55 mmol) and *tert*-butyl *N*-(4-aminocyclohexyl)carbamate (65 mg, 0.30 mmol). The mixture was stirred at 130 °C for 16 h. The reaction was concentrated to dryness and purified by flash column chromatography eluting with 0-10% methanol in dichloromethane (Rf = 0.5) to yield 100 mg (77% yield) of the title compound as a yellow solid. LCMS (ESI) $[M+H]^+$ = 647.1.

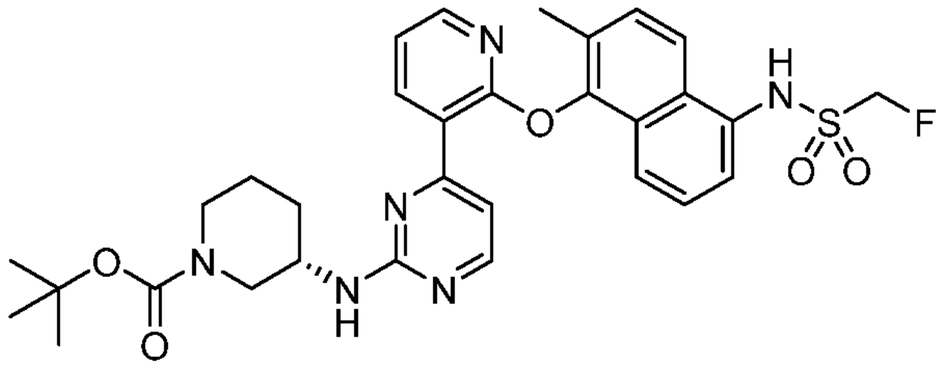
[0454] Step 2: *N*-(5-((3-(2-(((*trans*)-4-Aminocyclohexyl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)propane-1-sulfonamide



[0455] The General Procedure B was followed, using *tert*-butyl ((1r,4r)-4-((4-(2-((2-methyl-5-(propylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)cyclohexyl)carbamate (100 mg, 0.15 mmol), dichloromethane (5 mL) and hydrochloric acid (4 M in ethyl acetate, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05%HCl); B: ACN) to yield 45 mg (49% yield) of **158** as a yellow solid. LCMS (ESI): $[M+H]^+$ = 547.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.84 (s, 1H), 8.63 - 8.43 (m, 3H), 8.24 - 8.13 (m, 5H), 7.70 - 7.66 (m, 1H), 7.63 - 7.54 (m, 2H), 7.49 - 7.41 (m, 2H), 7.36 - 7.31 (m, 1H), 3.96 - 3.85 (m, 1H), 3.17 - 3.10 (m, 2H), 3.08 - 2.97 (m, 1H), 2.23 (s, 3H), 2.14 - 1.99 (m, 4H), 1.83 - 1.71 (m, 2H), 1.62 - 1.38 (m, 4H), 0.97 (t, *J* = 7.2 Hz, 3H).

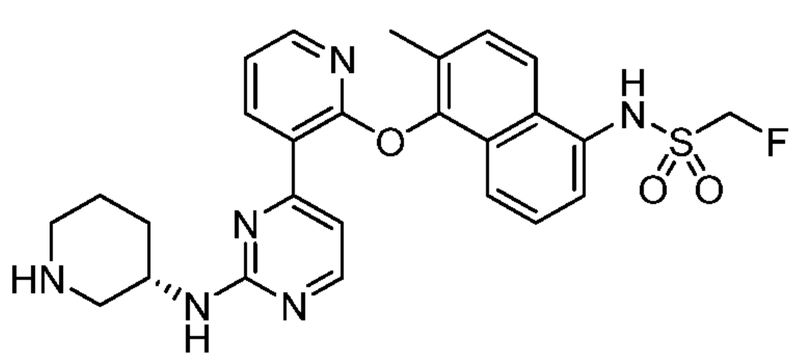
Example 159 *(S)-1-Fluoro-N-(6-methyl-5-(3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yloxy)naphthalen-1-yl)methanesulfonamide* ***159***

[0456] Step 1: (*S*)-*tert*-Butyl 3-(4-(2-(5-(fluoromethylsulfonamido)-2-methylnaphthalen-1-yloxy)pyridin-3-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate



[0457] The General Procedure A was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (50 mg, 0.095 mmol), pyridine (1 mL) and fluoromethanesulfonyl chloride (81 mg, 0.61 mmol). The crude was then purified by flash chromatography (gradient 0 to 80% of 1:4 MeOH/DCM in DCM) to yield 38 mg (64% yield) of the title compound as a brown solid. LCMS (ESI) $[M+H]^+ = 623.3$.

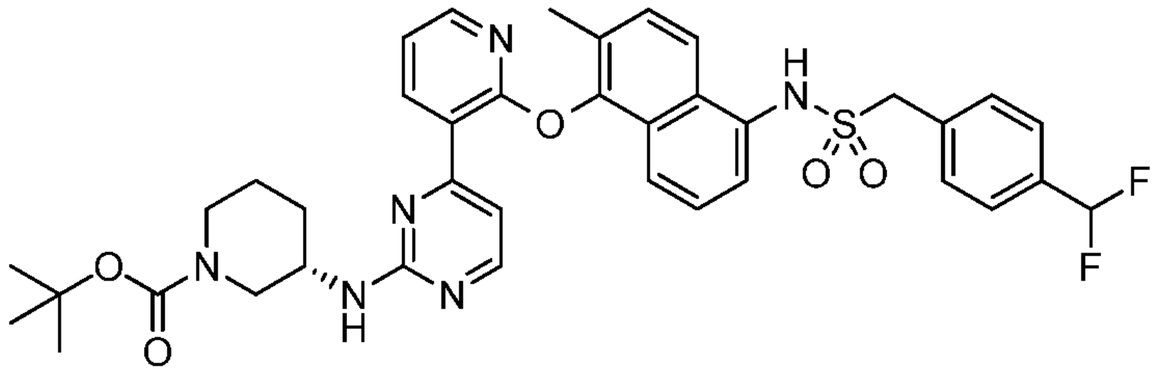
[0458] Step 2: (*S*)-1-Fluoro-*N*-(6-methyl-5-(3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yloxy)naphthalen-1-yl)methanesulfonamide



[0459] To (*S*)-*tert*-butyl 3-(4-(2-(5-(fluoromethylsulfonamido)-2-methylnaphthalen-1-yloxy)pyridin-3-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate (38 mg, 0.061 mmol) in DCM (6 mL) was added trifluoroacetic acid (1 mL). The mixture was concentrated and the residue purified by Prep-HPLC to yield 19.8 mg (40% yield) of **159** as a white solid. LCMS (ESI): $[M+H]^+ = 523.1$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (d, J = 5.2 Hz, 2H), 8.23 (m, 1H), 8.04 (dd, J = 4.8, 2.0 Hz, 1H), 7.54 (d, J = 5.2 Hz, 1H), 7.37 (d, J = 7.5 Hz, 1H), 7.29 (d, J = 8.7 Hz, 1H), 7.23 (dd, J = 7.6, 4.8 Hz, 1H), 7.21 – 7.10 (m, 2H), 7.01 (d, J = 8.1 Hz, 1H), 5.03 (d, J = 47.8 Hz, 2H), 4.14 (s, 1H), 3.09 (dd, J = 10.4, 6.4 Hz, 1H), 2.82-2.68 (m, 2H), 2.18 (s, 3H), 2.00 (s, 1H), 1.84 (s, 1H), 1.62 (q, J = 10.7 Hz, 2H).

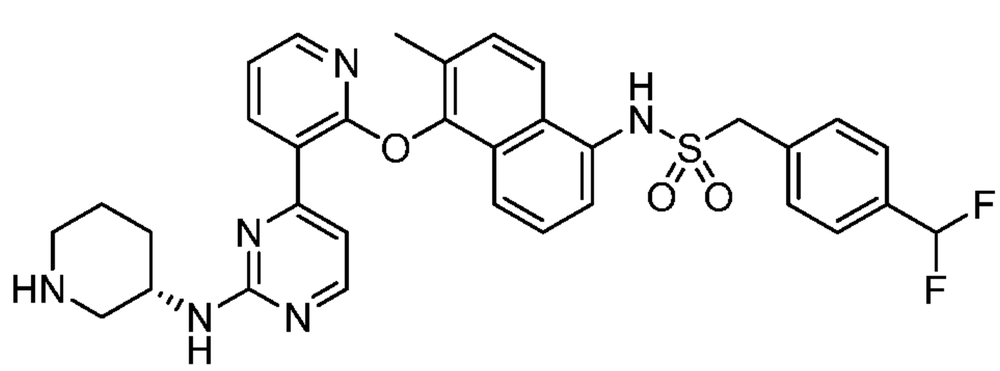
Example 160 *(S)-1-(4-(Difluoromethyl)phenyl)-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide* ***160***

[0460] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-((4-(difluoromethyl)phenyl)methylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0461] The General Procedure A was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol), pyridine (2 mL) and [4-(difluoromethyl)phenyl]methanesulfonyl chloride (91 mg, 0.38 mmol). The resulting solution was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, and concentrated *in vacuo* to yield 80 mg of the crude title compound as a yellow solid. LCMS (ESI) $[M+Na]^+ = 753.1$.

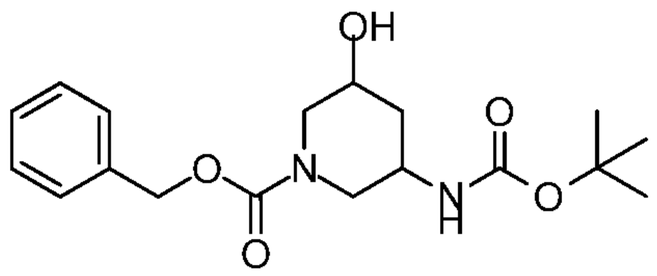
[0462] Step 2: (*S*)-1-(4-(Difluoromethyl)phenyl)-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide



[0463] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-((4-(difluoromethyl)phenyl)methylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (80 mg, 0.11 mmol), dichloromethane (2 mL) and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% HCl); B: ACN) to yield 33 mg (45% yield) of **160** as a yellow solid. LCMS (ESI) $[M+H]^+ = 631.1$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (s, 1H), 9.44 (s, 1H), 9.22 (s, 1H), 8.82 (s, 1H), 8.50 (d, J = 5.4 Hz, 1H), 8.09 (d, J = 3.2 Hz, 1H), 8.04 (d, J = 8.8 Hz, 1H), 7.90 (s, 1H), 7.68 (s, 1H), 7.60 - 7.50 (m, 5H), 7.49 - 7.38 (m, 2H), 7.31 - 7.26 (m, 1H), 7.05 (t, J = 56.0 Hz 1H), 4.64 (s, 2H), 4.45 - 4.35 (m, 1H), 3.46 - 3.42 (m, 1H), 3.22 - 3.18 (m, 1H), 2.90 - 2.80 (m, 2H), 2.22 (s, 3H), 2.04 - 1.97 (m, 1H), 1.95 - 1.88 (m, 1H), 1.85 - 1.75 (m, 1H), 1.65 (m, 1H).

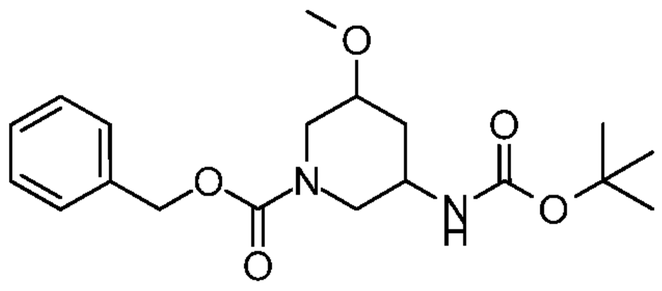
Example 161 *N-(5-((3-(2-(((3S, 5R)-5-Methoxypiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)-1-phenylmethanesulfonamide* ***161***

[0464] Step 1: Benzyl 3-((*tert*-butoxycarbonyl)amino)-5-hydroxypiperidine-1-carboxylate



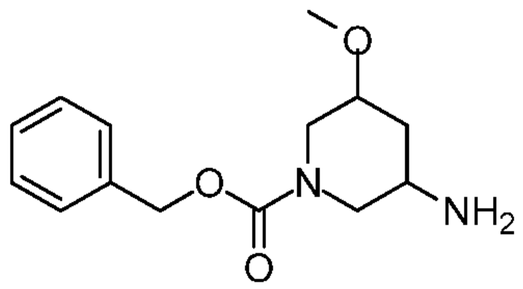
[0465] To a solution of benzyl chloroformate, Cbz-Cl (1.03 mL, 7.21 mmol), and sodium bicarbonate (505 mg, 6.01 mmol) in tetrahydrofuran (5 mL) was added tert-butyl-*N*-(5-hydroxy-3-piperidyl)carbamate (1.3 g, 6.01 mmol). The mixture was stirred at 21 °C for 4 h. The solution was concentrated and purified by chromatography on silica (solvent gradient: methanol in dichloromethane) to yield 2 g (95% yield) of the title compound as a white solid. LCMS (ESI) $[M+Na]^+$ = 372.9.

[0466] Step 2: Benzyl 3-((*tert*-butoxycarbonyl)amino)-5-methoxypiperidine-1-carboxylate



[0467] To a solution of benzyl 3-((*tert*-butoxycarbonyl)amino)-5-hydroxypiperidine-1-carboxylate (3.0 g, 8.6 mmol), silver oxide, Ag_2O (2 g, 8.6 mmol) in acetonitrile (60 mL) and *N*,*N*-dimethylformamide (15 mL) was added iodomethane, MeI (7.0 mL, 111.46 mmol). The mixture was stirred at 25 °C for 24 h. The solution was filtered and concentrated. The residue was purified by chromatography on silica (solvent gradient: 0-40% ethyl acetate in petroleum ether) to yield 2.3 g (74% yield) of the title compound as a colorless oil. LCMS (ESI) $[M+Na]^+$ = 387.1.

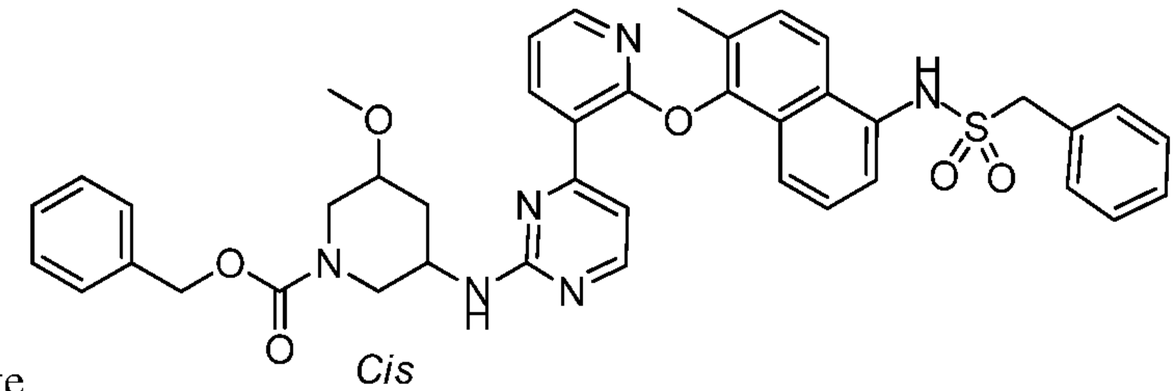
[0468] Step 3: Benzyl 3-amino-5-methoxypiperidine-1-carboxylate



[0469] To a solution of benzyl 3-((*tert*-butoxycarbonyl)amino)-5-methoxypiperidine-1-carboxylate (2.2 g, 6.04 mmol) in dichloromethane (20 mL) was added 4M hydrochloric acid (10 mL, 44 mmol) in ethyl acetate and the mixture was stirred at 25 °C for 1 h. The reaction

solution was concentrated *in vacuo* to yield 2 g of the crude title compound as a white solid. LCMS (ESI) $[M+H]^+ = 264.9$.

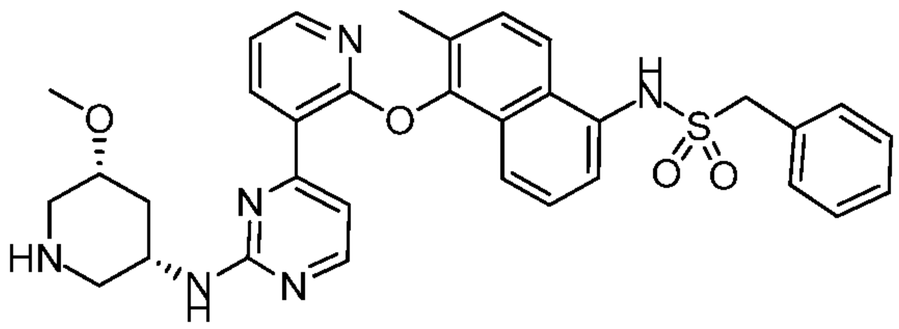
Step 4: Benzyl 3-methoxy-5-((4-(2-((2-methyl-5-(phenylmethylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



Cis

[0470] To a solution of *N*-[6-methyl-5-[[3-(2-methylsulfinylpyrimidin-4-yl)-2-pyridyl]oxy]-1-naphthyl]-1-phenyl-methanesulfonamide from Example 148 (600 mg, 1.1 mmol) in 1,4-dioxane (5 mL) was added *N,N*-di*iso*propylethylamine (0.59 mL, 3.3 mmol) and benzyl 3-amino-5-methoxypiperidine-1-carboxylate (420.0 mg, 1.59 mmol). The mixture was stirred at 130 °C for 16 h. The solution was concentrated and purified by prep-TLC (5% methanol in dichloromethane, Rf = 0.5) and then purified by using chiral SFC (SFC80; Chiralpak AD 250 × 30 mm I.D.,10 μm; supercritical CO_2 / MeOH+NH_3•H_2O = 55/55; 80 mL/min) to afford (3*S*,5*R*)-benzyl 3-methoxy-5-((4-(2-((2-methyl-5-(phenylmethylsulfonamido) naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (300 mg, 40% yield, Rt = 1.80 min) and (3*R*,5*S*)-benzyl-3-methoxy-5-((4-(2-((2-methyl-5-(phenylmethylsulfonamido)naphthalen-1-yl)oxy) pyridine-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (250 mg, 33.3% yield, Rt = 3.06 min) as a yellow solid. LCMS (ESI) $[M+H]^+ = 745.2$.

Step 5: *N*-(5-((3-(2-(((3*S*, 5*R*)-5-Methoxypiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)-1-phenylmethanesulfonamide

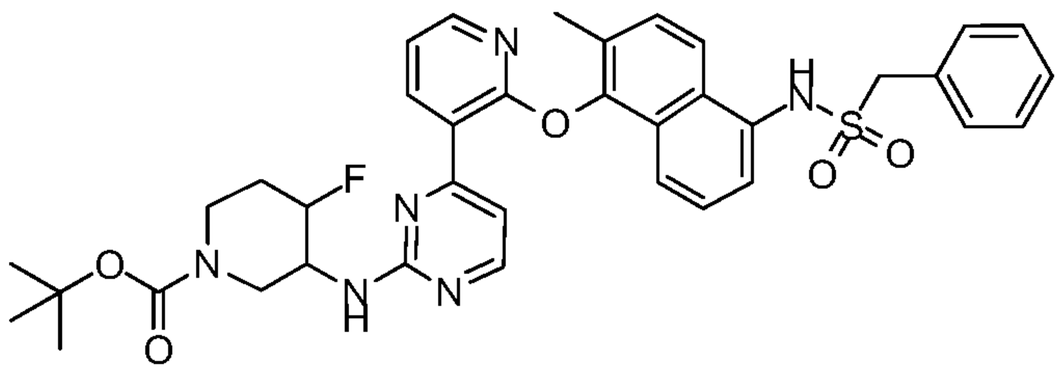


[0471] To a solution of thiourea (77 mg, 1.01 mmol), 1-methylimidazole (66 mg, 0.81 mmol) and (3*R*,5*S*)-benzyl3-methoxy-5-((4-(2-((2-methyl-5-(phenylmethylsulfonamido)naphthalen-1-yl)oxy)pyridin -3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (150 mg, 0.20 mmol, the second peak in step 2) in redistilled acetonitrile (2 mL) was added iodotrimethylsilane (0.23 mL, 1.65 mmol) dropwise.

Then the mixture was stirred for 16 h. Then the mixture was quenched with water (15 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic extracts were concentrated *in vacuo* and the residue was purified by Prep-HPLC (mobile phase: A: water (0.05% NH_4OH); B: ACN) to afford **161** (37 mg, 29.5% yield) as a white solid (*ee* = 95%). LCMS (ESI) $[M+H]^+$ = 611.1; ^1H NMR (400 MHz,$CDCl_3$) δ 8.63 - 8.54 (m, 1H), 8.37 (d, *J* = 5.4 Hz, 1H), 8.01 (d, *J* = 4.8 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.65 - 7.56 (m, 3H), 7.44 - 7.28 (m, 6H), 7.26 (d, *J* = 2.0 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 6.21 (s, 1H), 4.39 (s, 2H), 4.20 - 4.15 (m, 1H), 3.44 (s, 3H), 3.41 - 3.35 (m, 1H), 3.09 - 2.91 (m, 4H), 2.30 (s, 3H), 2.20 - 2.16 (m, 1H), 1.93 - 1.88 (m, 1H).

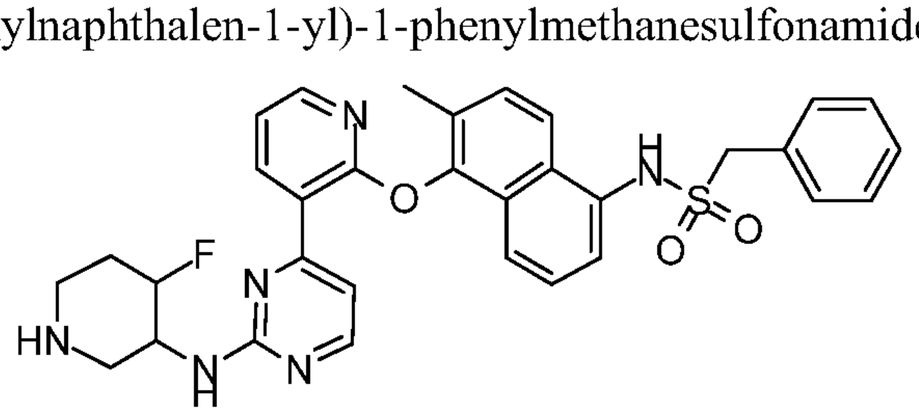
Example 162 *N-(5-((3-(2-((4-Fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)-1-phenylmethanesulfonamide* ***162***

[0472] Step 1: *tert*-Butyl 4-fluoro-3-((4-(2-((2-methyl-5-(phenylmethylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0473] To a stirred solution of *N*-(6-methyl-5-((3-(2-(methylsulfinyl)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide (100 mg, 0.18 mmol) in 1,4-dioxane (3 mL) was added *N,N*-diisopropylethylamine (0.1 mL, 0.55 mmol) and *trans-tert*-butyl *N*-(4-aminocyclohexyl)carbamate (40 mg, 0.18 mmol), the mixture was stirred at 135 °C for 4 days. The reaction was concentrated *in vacuo* and purified by flash column chromatography eluting with 0-10% methanol in dichloromethane (Rf = 0.5) to yield 100 mg (78% yield) of the title compound as a yellow solid. LCMS (ESI) $[M+H]^+$ = 699.1.

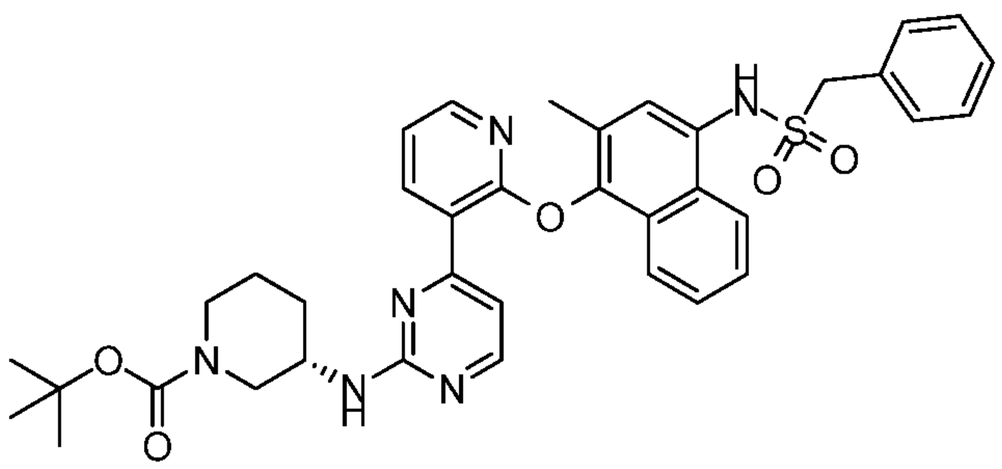
[0474] Step 2: *N*-(5-((3-(2-((4-Fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)-1-phenylmethanesulfonamide



[0475] The General Procedure B was followed, using *tert*-butyl ((1*r*,4*r*)-4-((4-(2-((2-methyl-5-(propylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)cyclohexyl)carbamate (100 mg, 0.14 mmol), dichloromethane (5 mL) and hydrochloric acid (4 M in ethyl acetate, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% HCl); B: ACN) to yield 17 mg (18% yield) of **162** as a yellow solid (as mixture of enantiomers). LCMS (ESI): $[M+H]^+$ = 599.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 9.44 (s, 1H), 8.98 - 8.42 (m, 2H), 8.13 - 7.92 (m, 3H), 7.80 - 7.62 (m, 1H), 7.59 - 7.49 (m, 2H), 7.44 - 7.33 (m, 7H), 7.31 - 7.25 (m, 1H), 5.03 - 4.74 (m, 2H), 4.59 - 4.48 (m, 2H), 3.53 - 3.26 (m, 2H), 3.11 - 2.89 (m, 2H), 2.39 - 2.29 (m, 1H), 2.21 (s, 3H), 2.13 - 1.98 (m, 1H).

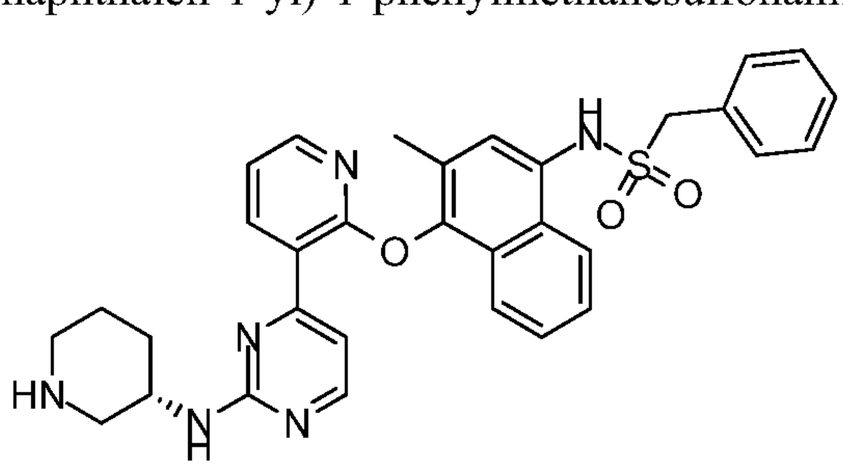
Example 163 *(S)-N-(3-Methyl-4-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-phenylmethanesulfonamide* ***163***

[0476] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-4-(phenylmethylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0477] The General Procedure A was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(4-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (200 mg, 0.38 mmol), pyridine (2 mL) and phenylmethanesulfonyl chloride (108 mg, 0.57 mmol). The reaction was then concentrated *in vacuo* to yield 200 mg of the crude title compound as a brown solid. LCMS (ESI) $[M+Na]^+$ = 703.1.

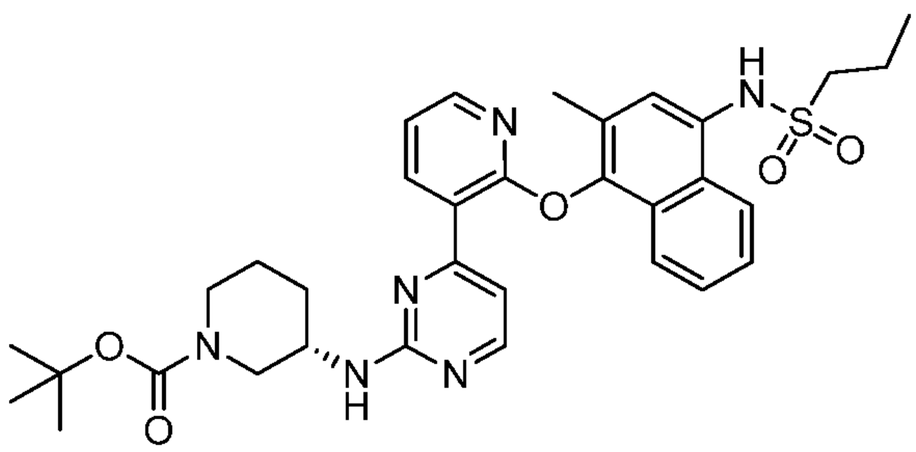
[0478] Step 2: (*S*)-*N*-(3-Methyl-4-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-phenylmethanesulfonamide



[0479] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((2-methyl-4-(phenylmethylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (200 mg, 0.29 mmol), dichloromethane (5 mL) and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% HCl); B: ACN) to yield 56 mg (30% yield) of **163** as a yellow solid. LCMS (ESI): $[M+H]^+$ = 581.1; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.89 - 9.78 (m, 1H), 9.60 - 9.18 (m, 2H), 8.94 - 8.70 (m, 1H), 8.55 - 8.46 (m, 1H), 8.40 - 8.07 (m, 2H), 8.05 - 7.62 (m, 3H), 7.54 - 7.37 (m, 6H), 7.33 - 7.26 (m, 2H), 4.58 (s, 2H), 4.46 - 4.38 (m, 1H), 3.49 - 3.38 (m, 1H), 3.26 - 3.14 (m, 1H), 2.93 - 2.77 (m, 2H), 2.18 (s, 3H), 2.07 - 1.87 (m, 2H), 1.86 - 1.59 (m, 2H).

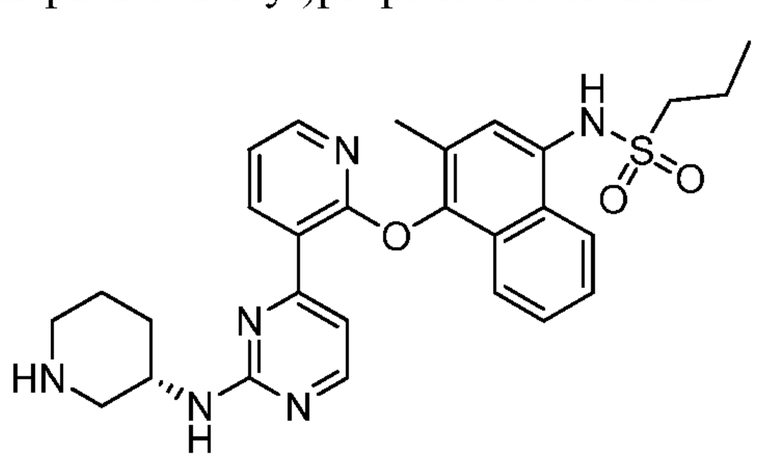
Example 164 *(S)-N-(3-Methyl-4-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide* ***164***

[0480] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-4-(propylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0481] The General Procedure A was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(4-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (200 mg, 0.38 mmol), pyridine (2 mL) and 1-propanesulfonyl chloride (82 mg, 0.57 mmol). The reaction mixture was then concentrated to yield 200 mg of the crude title compound as a brown oil. LCMS (ESI) $[M+Na]^+$ = 655.1.

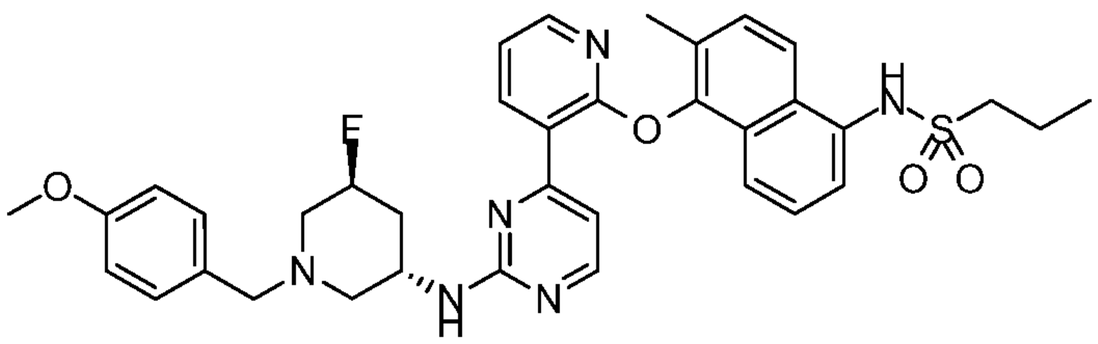
[0482] Step 2: (*S*)-*N*-(3-Methyl-4-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide



[0483] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((2-methyl-4-(propylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (200 mg, 0.31 mmol), dichloromethane (5 mL) and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05%HCl); B: ACN) to yield 56 mg (30% yield) of **164** as a yellow solid. LCMS (ESI): $[M+H]^+$ = 533.1; ^1H NMR (400 MHz, DMSO-*d6*) δ 9.83 - 9.47 (m, 2H), 9.41 - 9.19 (m, 1H), 9.02 - 8.74 (m, 1H), 8.56 - 8.46 (m, 1H), 8.30 - 8.05 (m, 3H), 7.83 - 7.62 (m, 2H), 7.59 - 7.52 (m, 1H), 7.48 - 7.42 (m, 2H), 7.32 - 7.27 (m, 1H), 4.67 - 4.33 (m, 1H), 3.48 - 3.38 (m, 1H), 3.24 - 3.11 (m, 3H), 2.92 - 2.79 (m, 2H), 2.22 (s, 3H), 2.09 - 1.99 (m, 1H), 1.96 - 1.87 (m, 1H), 1.86 - 1.74 (m, 3H), 1.73 - 1.60 (m, 1H), 0.99 (t, *J* = 7.2 Hz, 3H).

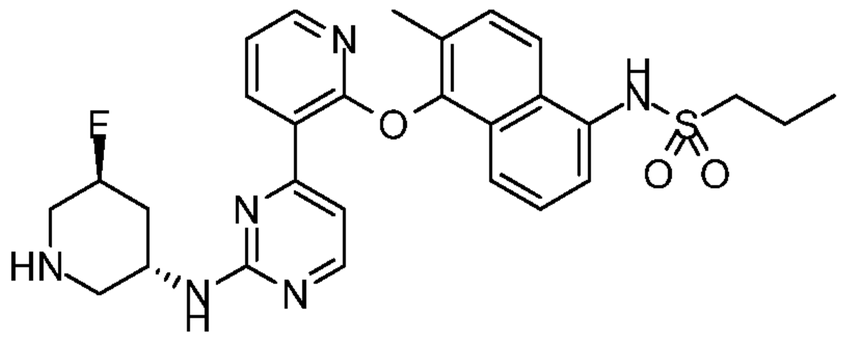
Example 165 *N-(5-((3-(2-(((3S, 5S)-5-Fluoropiperidin-3-yl)amino) pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)propane-1-sulfonamide* ***165***

[0484] Step 1: *N*-(5-((3-(2-(((3*S*,5*S*)-5-Fluoro-1-(4-methoxybenzyl)piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)propane-1-sulfonamide



[0485] To a solution of *N*-[6-methyl-5-[[3-(2-methylsulfinylpyrimidin-4-yl)-2-pyridyl]oxy]-1-naphthyl]propane-1-sulfonamide (100 mg, 0.2 mmol) in 1,4-dioxane (3 mL) was added *N,N*-diisopropylethylamine (0.11 mL, 0.6 mmol) and (3*S*,5*S*)-5-fluoro-1-[(4-methoxyphenyl)methyl]piperidin-3-amine (52.8 mg, 0.22 mmol). The mixture was stirred at 120 °C for 64 h. After cooling down, the mixture was concentrated *in vacuo*, dissolved in dichloromethane (30 mL) and washed with H_2O (30 mL x 2). The organic phase was dried over anhydrous sodium sulfate, concentrated *in vacuo* and the residue was purified by Prep-TLC (5% methanol in dichloromethane, Rf = 0.6) to yield 34 mg (25% yield) of the title compound as a yellow solid; LCMS (ESI) $[M+H]^+$ = 671. 0

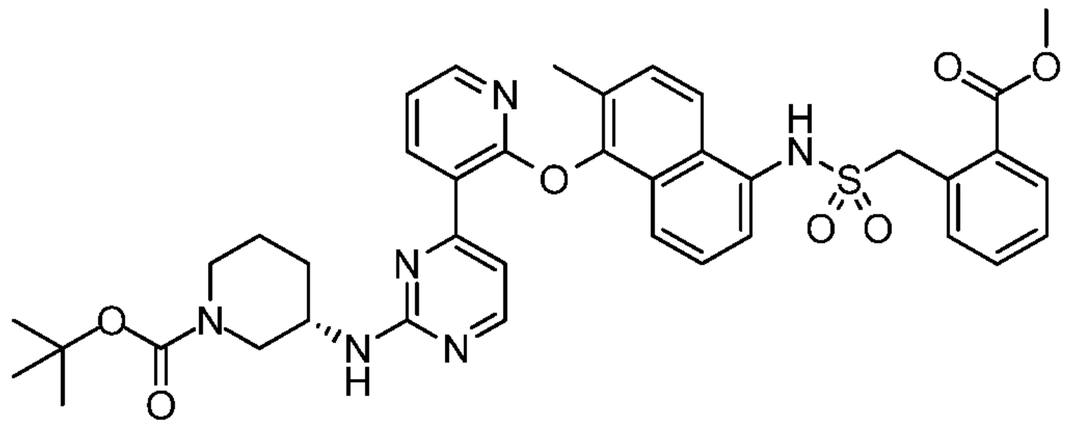
[0486] Step 2: *N*-(5-((3-(2-(((3*S*, 5*S*)-5-Fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)propane-1-sulfonamide



[0487] To a solution of *N*-[5-[[3-[2-[[(3*S*,5*S*)-5-fluoro-1-[(4-methoxyphenyl)methyl]-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-6-methyl-1-naphthyl]propane-1-sulfonamide (24 mg, 0.04 mmol) in 1,2-dichloroethane (1 mL) was added triethylamine (6.8 mL, 0.36 mmol) and 1-chloroethyl chloroformate (51.2 mg, 0.36 mmol). The mixture was stirred at 20 °C for 4 h and then concentrated and dissolved in methanol (20 mL). Heating at 70 °C for 16 h, followed by concentration in vacuum and purification by Prep-HPLC (mobile phase: A: water (0.05% NH_4OH); B: ACN) yielded 5.1 mg (18% yield) of **165** as a white solid; LCMS (ESI) $[M+H]^+ = 551.3$; ^1H NMR (400 MHz, DMSO-d_6) δ 8.58 - 8.47 (m, 1H), 8.42 (d, J = 4.8 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.04 - 8.03 (m, 1H), 7.60 - 7.51 (m, 2H), 7.49 - 7.38 (m, 3H), 7.30 - 7.19 (m, 2H), 4.92 - 4.71 (m, 1H), 4.28 - 4.09 (m, 1H), 3.15 - 3.00 (m, 3H), 2.95 - 2.82 (m, 1H), 2.77 - 2.70 (m, 1H), 2.42 - 2.39 (m, 1H), 2.26 - 2.08 (m, 4H), 1.95 - 1.67 (m, 3H), 0.96 (t, J = 7.6 Hz, 3H).

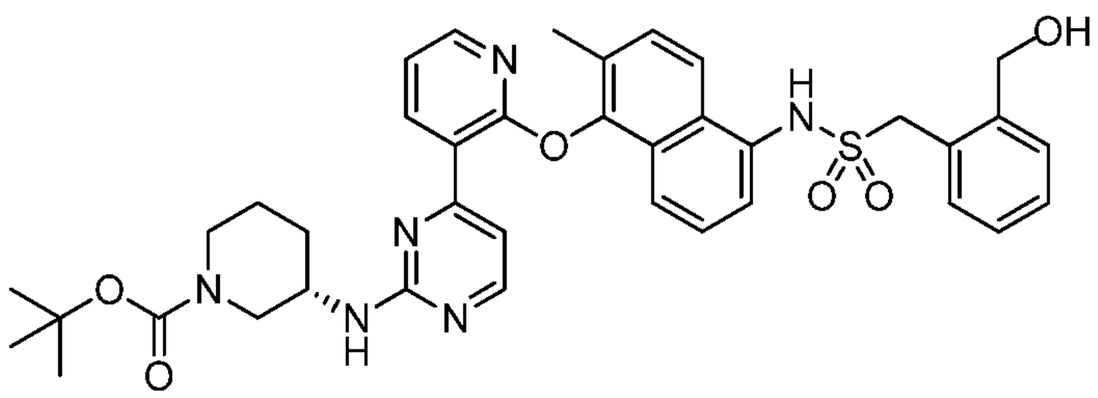
Example 166 *(S)-1-(2-(Hydroxymethyl)phenyl)-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide* ***166***

Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-((2-(methoxycarbonyl)phenyl)methylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



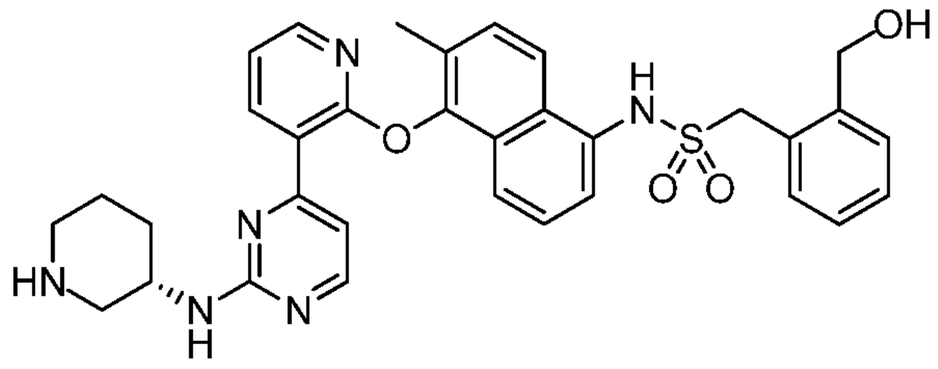
[0488] The General Procedure A was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (400 mg, 0.76 mmol), pyridine (10 mL) and 2,4-difluorophenyl methanesulfonyl chloride (189 mg, 0.76 mmol). The organic layer was concentrated and purified by column chromatography on silica (solvent gradient: methanol in dichloromethane) to yield 500 mg (89% yield) of the title compound as a yellow solid. LCMS (ESI) $[M+H]^+ = 739.1$.

[0489] Step 2: (*S*)-*tert*-Butyl 3-((4-(2-((5-((2-(hydroxymethyl)phenyl)methylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0490] To a solution of (*S*)-*tert*-butyl 3-((4-(2-((5-((2-(methoxycarbonyl)phenyl)methylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (400 mg, 0.54 mmol) in tetrahydrofuran (20 mL) was added lithium aluminum hydride (21 mg, 0.54 mmol) at -40 °C. The mixture was stirred at -40 °C for 5 h. The solution was added water (10 mL) and anhydrous sodium sulfate (10 g). The solution was filtered and concentrated *in vacuo* to yield 300 mg (78% yield) as a yellow solid. LCMS (ESI) $[M+H]^+$ = 711.3.

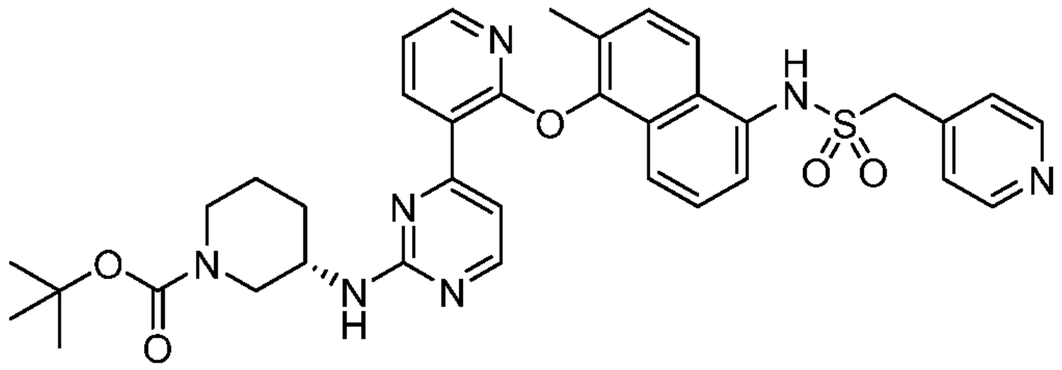
[0491] Step 3: (*S*)-1-(2-(Hydroxymethyl)phenyl)-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide



[0492] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-((2-(hydroxymethyl)phenyl)methylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (50 mg, 0.07 mmol), dichloromethane (5 mL) and hydrochloric acid (4 M in ethyl acetate, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% NH_4OH); B: ACN) to yield 13 mg (28% yield) of **166** as a yellow solid. LCMS (ESI): $[M+H]^+$ = 611.1; ^1H NMR (400 MHz, DMSO-d_6) δ 9.97 (s, 1H), 9.08 (s, 1H), 8.49 (d, J = 5.6 Hz, 1H), 8.13 - 8.04 (m, 2H), 7.63 (s, 1H), 7.59 - 7.50 (m, 2H), 7.47 - 7.38 (m, 3H), 7.34 (t, J = 7.2 Hz, 1H), 7.31 - 7.21 (m, 3H), 4.65 (s, 2H), 4.62 (s, 2H), 4.36 - 4.30 (m, 1H), 3.45 - 3.40 (m, 1H), 3.22 - 3.18 (m, 1H), 2.90 - 2.80 (m, 2H), 2.25 (s, 3H), 2.09 - 1.58 (m, 4H).

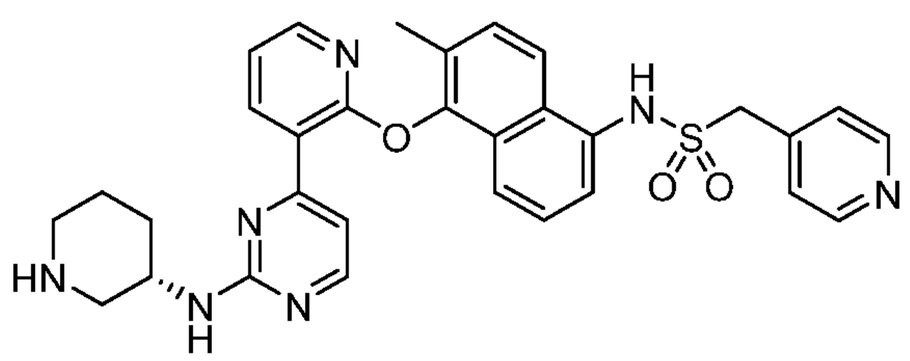
Example 167 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-(pyridin-4-yl)methanesulfonamide* ***167***

[0493] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-((pyridin-4-ylmethyl)sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0494] The General Procedure A was followed. To a solution of *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol) in pyridine (1.25 mL) was added (4-pyridylmethyl)sulfonyl chloride triflate (97.3 mg, 0.29 mmol) followed by stirring at room temperature for 72 h with an extra (1.45 mmol) of (4-pyridylmethyl)sulfonyl chloride triflate added in between. The mixture was diluted with 10% citric acid, extracted with iPrOAc (2 x 10 mL), dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography (24 g column) eluting with 0-5% MeOH/DCM to give 32 mg (25% yield) of a brown solid. This product was used in the next step without further purification. LCMS (ESI) $[M+H]^+ = 682$.

[0495] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-(pyridin-4-yl)methanesulfonamide

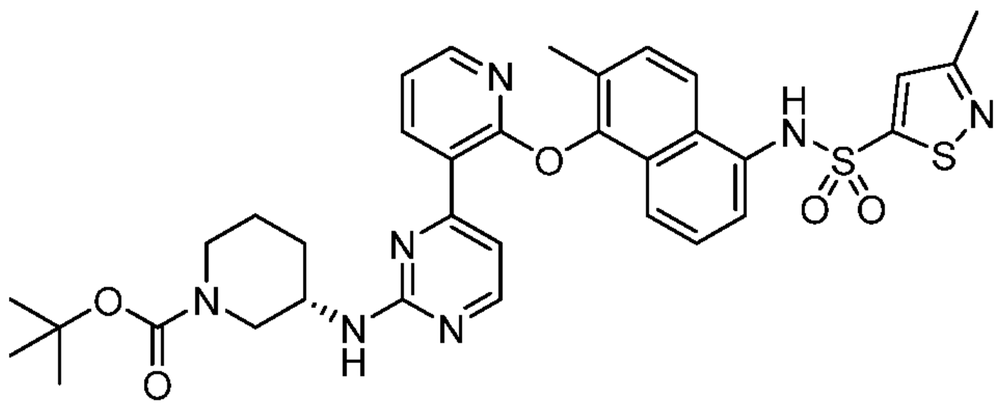


[0496] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-((pyridin-4-ylmethyl)sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (32 mg, 0.047 mmol). The crude product was purified *via* reverse-phase HPLC and lyophilized to yield 11.8 mg (43% yield) of **167** as an off-white solid. LCMS (ESI) [M+H]+ = 582; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 – 8.50 (m, 2H), 8.45 (d, J = 5.2 Hz, 1H), 8.09 (d, J = 8.7 Hz, 1H), 8.05 (dd, J = 4.8, 2.0 Hz, 1H), 7.53 (d, J = 5.2 Hz, 1H), 7.43 – 7.39 (m, 1H), 7.39 – 7.30 (m, 5H), 7.26 (dd, J = 7.6, 4.8 Hz, 1H),

4.44 (s, 2H), 4.12 (s, 1H), 3.06 (d, *J* = 12.4 Hz, 1H), 2.77 – 2.65 (m, 2H), 2.20 (s, 3H), 2.02 – 1.94 (m, 1H), 1.86 – 1.78 (m, 1H), 1.69 – 1.54 (m, 2H).

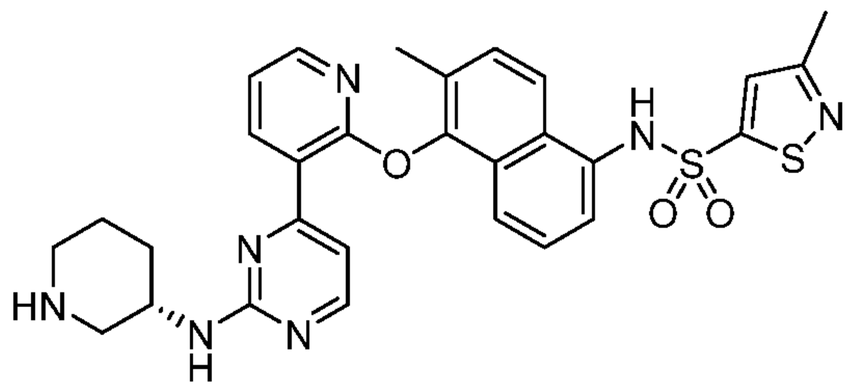
Example 168 *(S)-3-Methyl-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)isothiazole-5-sulfonamide* ***168***

[0497] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-((3-methylisothiazole)-5-sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0498] The General Procedure A was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (50 mg, 0.09 mmol) and 3-methylisothiazole-5-sulfonyl chloride (28.16 mg, 0.14 mmol) in pyridine (1 mL) to afford 55 mg (65.3% yield) of the title compound as a brown solid. It was carried on as is. LCMS (ESI) [M+H]+ = 688.

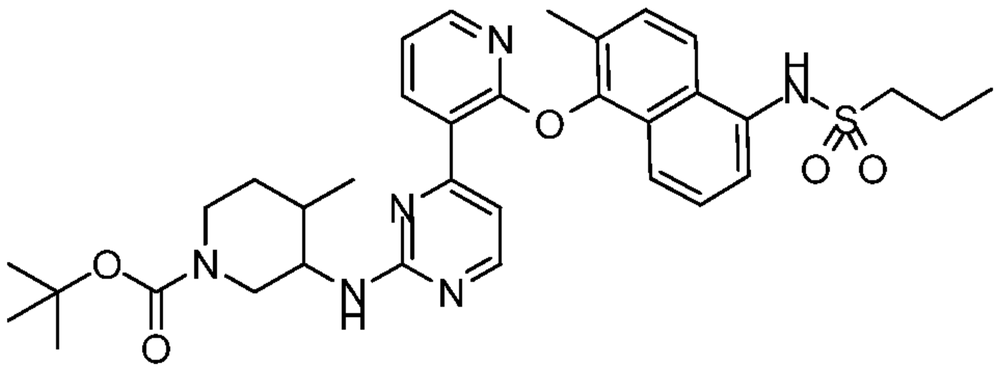
[0499] Step 2: (*S*)-3-Methyl-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)isothiazole-5-sulfonamide



[0500] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-((3-methylisothiazole)-5-sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (55 mg, 0.08 mmol). The crude product was purified *via* reverse-phase HPLC and lyophilized to yield 11.5 mg (24.5% yield) of **168** as an off-white solid. LCMS (ESI) [M+H]+ = 588; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (s, 2H), 8.45 (d, *J* = 5.2 Hz, 1H), 8.25 (d, *J* = 8.6 Hz, 1H), 8.04 (dd, *J* = 4.8, 2.0 Hz, 1H), 7.55 (d, *J* = 5.2 Hz, 1H), 7.43 (d, *J* = 7.4 Hz, 1H), 7.25 – 7.18 (m, 3H), 7.10 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.04 (t, *J* = 7.9 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 4.21 (s, 1H), 3.43 (d, *J* = 12.6 Hz, 2H), 3.18 (d, *J* = 12.8 Hz, 1H), 2.89-2.78 (m, 2H), 2.31 (s, 3H), 2.16 (s, 3H), 2.04 – 1.97 (m, 1H), 1.94 – 1.86 (m, 1H), 1.74 – 1.58 (m, 2H).

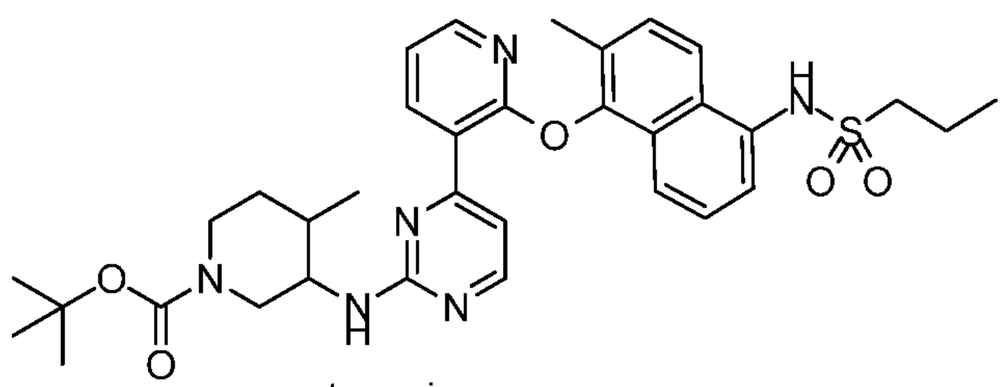
Example 169 *N-(6-Methyl-5-((3-(2-((4-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide* ***169***

[0501] Step 1: *tert*-Butyl 4-methyl-3-((4-(2-((2-methyl-5-(propylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0502] To a 100 mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed *N*-[6-methyl-5-[[3-(2-methylsulfinylpyrimidin-4-yl)-2-pyridyl]oxy]-1-naphthyl]propane-1-sulfonamide (2.0 g, 4.03 mmol), *tert*-butyl 3-amino-4-methyl-piperidine-1-carboxylate (1.0 g, 4.83 mmol), 1,4-dioxane (20 mL) and *N,N*-diisopropylethylamine (2.11 mL, 12.08 mmol). The resulting solution was stirred at 130 °C in an oil bath for 36 h, cooled to room temperature and concentrated *in vacuo*. The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% NH_4OH); B: ACN) to give two major products. First HPLC peak: 950 mg (16% yield); second HPLC peak: 170 mg (3% yield). The second peak corresponds to the title product which was obtained as a white solid. LCMS (ESI) $[M+H]^+ = 647.1$. The *trans* relative stereochemistry of the title compound was based on 2D-NMR analysis.

Step 2: *tert*-Butyl 4-methyl-3-((4-(2-((2-methyl-5-(propylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate

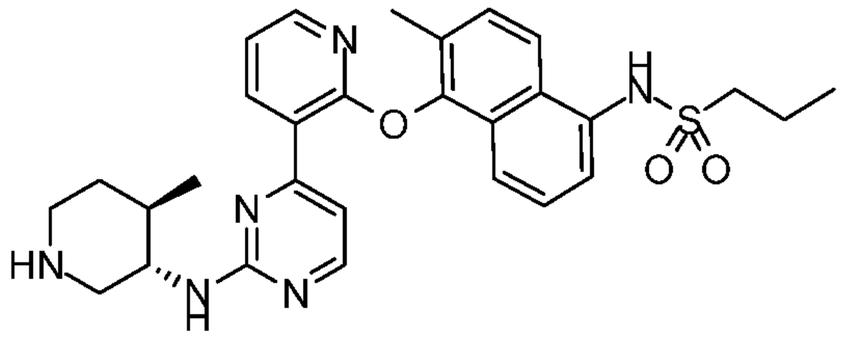


trans isomer

[0503] *tert*-Butyl4-methyl-3-[[4-[2-[[2-methyl-5-(propylsulfonylamino)-1-naphthyl]oxy]-3-pyridyl] pyrimidin-2-yl]amino]piperidine-1-carboxylate (170 mg, 0.26 mmol) (second peak on HPLC in step 1) was purified by SFC(AS (250 mm x 30 mm,10 μm); 0.1% NH_3H_2O EtOH: 40%; flow rate (80 mL / min) to give *trans-tert*-butyl 4-methyl-3-[[4-[2-[[2-methyl-5-(propylsulfonylamino)-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (70 mg, 41% yield) (first peak on SFC, Rt = 4.49 min) and *trans-tert*-butyl 4-

methyl-3-[[4-[2-[[2-methyl-5-(propylsulfonylamino)-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (70 mg, 41% yield) (second peak on SFC, Rt = 4.82 min) as a white solid.

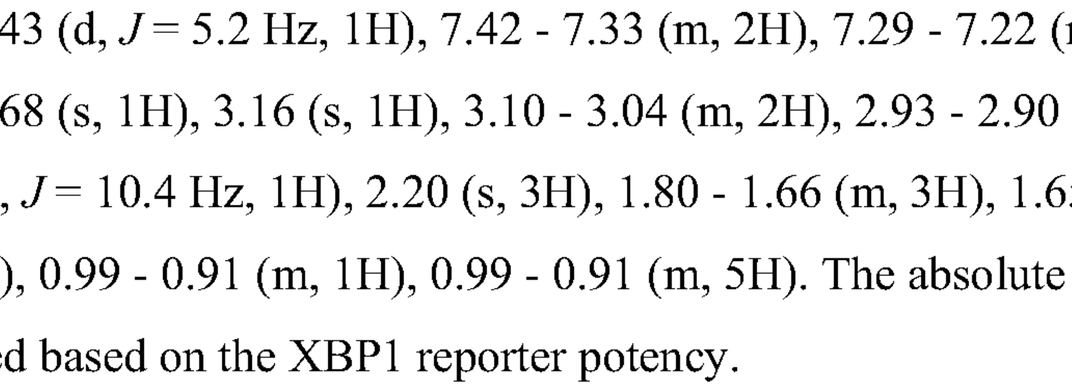
[0504] Step 3: *N*-(6-Methyl-5-((3-(2-(((3S, 4R)-4-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide



[0505] The General Procedure B was followed, using 4-methyl-3-[[4-[2-[[2-methyl-5-(propylsulfonylamino)-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (70 mg, 0.11 mmol) (second peak on SFC in step 2), dichloromethane (2 mL) and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% ammonia hydroxide) B: ACN) to yield 45 mg (74% yield) of **169** as a white solid. LCMS (ESI): $[M+H]^+$ = 547.1;^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (s, 1H), 8.39 (d, J = 5.2 Hz, 1H), 8.14 (d, J = 8.8 Hz, 1H), 8.05 - 8.01 (m, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.43 (d, J = 5.2 Hz, 1H), 7.42 - 7.33 (m, 2H), 7.29 - 7.22 (m, 1H), 7.17 (d, J = 8.8 Hz, 1H), 3.68 (s, 1H), 3.16 (s, 1H), 3.10 - 3.04 (m, 2H), 2.93 - 2.90 (m, 1H), 2.52 - 2.52 (m, 1H), 2.31 (d, J = 10.4 Hz, 1H), 2.20 (s, 3H), 1.80 - 1.66 (m, 3H), 1.65 - 1.54 (m, 1H), 1.27 - 1.12 (m, 1H), 0.99 - 0.91 (m, 1H), 0.99 - 0.91 (m, 5H). The absolute stereochemistry was tentatively assigned based on the XBP1 reporter potency.

Example 170 *(S)-1-(2-(Fluoromethyl)phenyl)-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide* ***170***

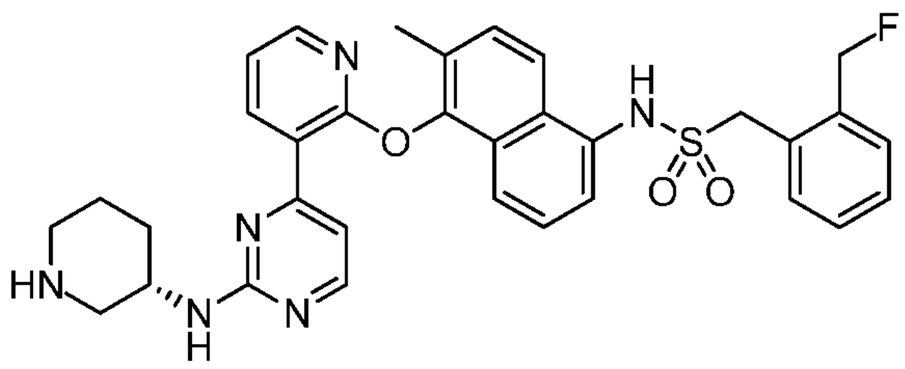
[0506] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-((2-(fluoromethyl)phenyl)methylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0507] To a solution of *tert*-butyl (3*S*)-3-[[4-[2-[[5-[[2-(hydroxymethyl)phenyl]methylsulfonylamino]-2-methyl-1-naphthyl]oxy]-3-pyridyl]pyrimidin-

2-yl]amino]piperidine-1-carboxylate (200 mg, 0.28 mmol) in dichloromethane (2 mL) was added diethylaminosulfur trifluoride (59 mg, 0.37 mmol) in dichloromethane (2 mL) dropwised at -78 °C. The mixture was stirred at -78 °C for 0.5 h. The solution was washed with water (10 mL) and extracted with dichloromethane (20 mL x 3). The organic layer was concentrated to yield 200 mg (99% yield) of the title compound as a yellow solid. LCMS (ESI): $[M+H]^+$ = 713.0.

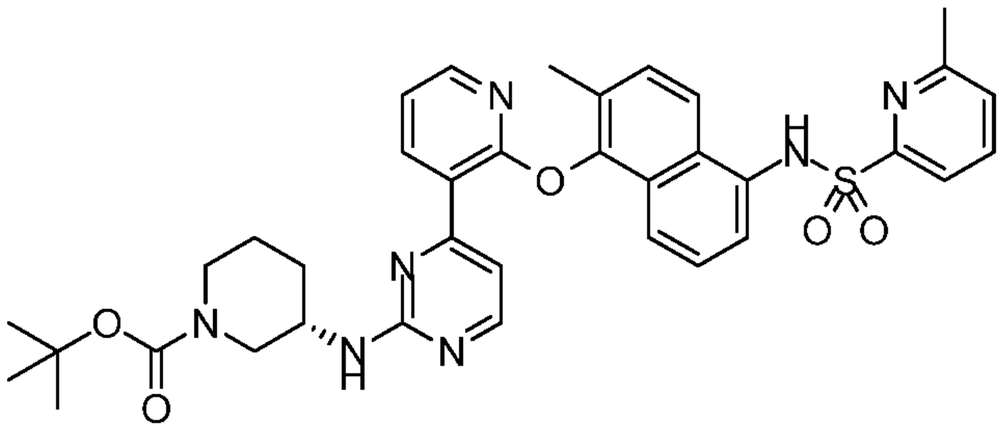
[0508] Step 2: (*S*)-1-(2-(Fluoromethyl)phenyl)-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide



[0509] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-((2-(fluoromethyl)phenyl)methylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (200 mg, 0.28 mmol), dichloromethane (5 mL) and hydrochloric acid (4 M in ethyl acetate, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% HCl) B: ACN) to yield 13 mg (7 %) yield of **170** as a yellow solid. LCMS (ESI): $[M+H]^+$ = 613.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 - 10.01 (m, 1H), 9.11 (s, 1H), 8.50 (d, *J* = 5.6 Hz, 1H), 8.08 (d, *J* = 7.2 Hz, 2H), 7.70 - 7.51 (m, 3H), 7.51 - 7.36 (m, 6H), 7.29 (d, *J* = 7.2 Hz, 1H), 5.67 - 5.48 (m, 2H), 4.73 - 4.62 (m, 2H), 4.41 - 4.34 (m, 1H), 3.49 - 3.13 (m, 2H), 2.93 - 2.76 (m, 2H), 2.22 (s, 3H), 2.09 - 1.58 (m, 4H).

Example 171 *(S)-6-Methyl-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyridine-2-sulfonamide* ***171***

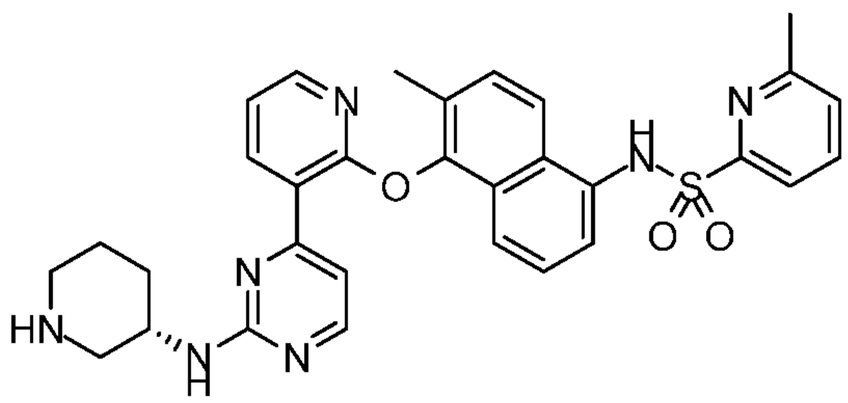
[0510] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-5-(6-methylpyridine-2-sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0511] The General Procedure A was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg,

0.19 mmol), pyridine (2 mL) and 6-methylpyridine-2-sulfonyl chloride (44 mg, 0.23 mmol). The reaction mixture was concentrated *in vacuo* and the residue was taken up in ethyl acetate (20 mL), and washed with water (10 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo* to yield (130 mg crude) of the title compound as a pale brown oil. LCMS (ESI) $[M+H]^+$ = 682.1.

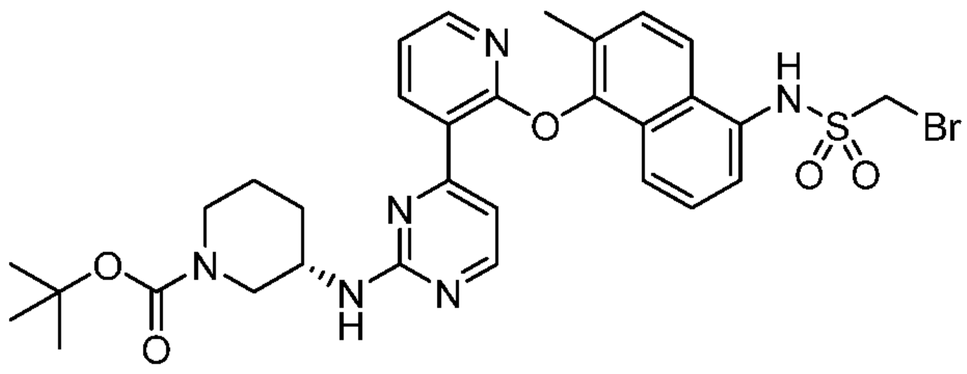
[0512] Step 2: (*S*)-6-Methyl-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyridine-2-sulfonamide



[0513] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((2-methyl-5-(6-methylpyridine-2-sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (130 mg, 0.19 mmol), ethyl acetate (2 mL) and hydrochloric acid (4 M in ethyl acetate, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% HCl) B: ACN) to yield 73 mg (62% yield) of **171** as a white solid. LCMS (ESI): $[M+H]^+$ = 582.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.58 (s, 1H), 9.37 (s, 1H), 8.51 (d, *J* = 4.8 Hz, 1H), 8.12 - 7.99 (m, 2H), 7.91 - 7.81 (m, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.55 - 7.39 (m, 3H), 7.36 - 7.24 (m, 2H), 7.21 (d, *J* = 7.6 Hz, 1H), 4.40 - 4.35 (m, 1H), 3.45 - 3.40 (m, 1H), 3.20 - 3.15 (m, 1H), 2.90 - 2.80 (m, 2H), 2.57 (s, 3H), 2.17 (s, 3H), 2.04 - 1.99 (m, 1H), 1.97 - 1.58 (m, 3H).

Example 172 *(S)-1-Bromo-N-(6-methyl-5-(3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yloxy)naphthalen-1-yl)methanesulfonamide* ***172***

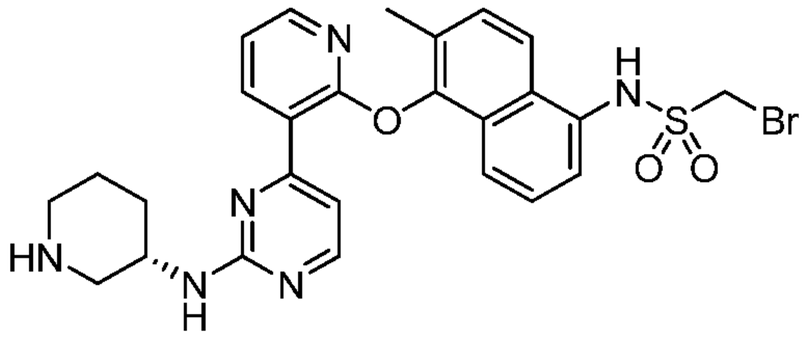
[0514] Step 1: (*S*)-*tert*-Butyl 3-(4-(2-(5-(bromomethylsulfonamido)-2-methylnaphthalen-1-yloxy)pyridin-3-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate



[0515] The General Procedure A was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (50 mg,

0.095 mmol), pyridine (1 mL) and bromomethanesulfonyl chloride (250 mg, 1.3 mmol). The mixture was concentrated and the crude product was directly used in step 2. LCMS (ESI) $[M+H]^+ = 683.2$.

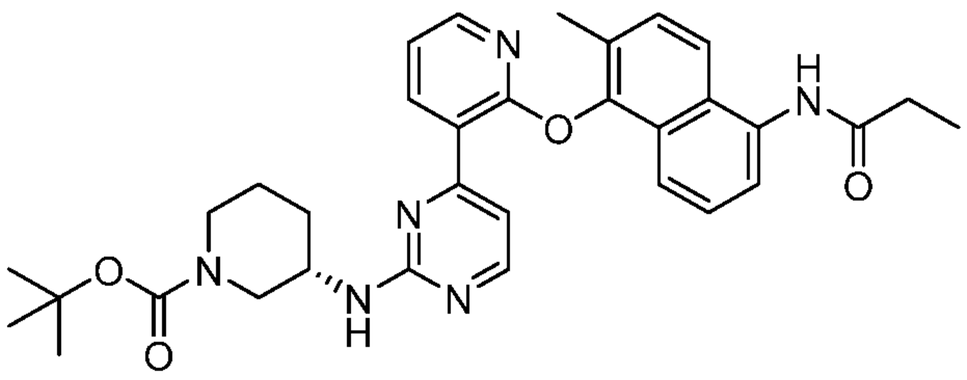
[0516] Step 2: (*S*)-1-Bromo-*N*-(6-methyl-5-(3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yloxy)naphthalen-1-yl)methanesulfonamide



[0517] To the crude (*S*)-*tert*-butyl 3-(4-(2-(5-(bromomethylsulfonamido)-2-methylnaphthalen-1-yloxy)pyridin-3-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate from step 1 in DCM (6 mL) was added trifluoroacetic acid (1 mL). The mixture was concentrated and the residue purified by Prep-HPLC to yield 4.7 mg (9% yield) of **172** as a white solid. LCMS (ESI): $[M+H]^+ = 583.1$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.47 (dd, J = 5.2, 3.4 Hz, 1H), 8.21-8.10 (m, 1H), 8.07-8.00 (m, 1H), 7.63 – 7.27 (m, 6H), 7.11-6.97 (m, 1H), 4.87 (d, J = 27.4 Hz, 2H), 4.23 (s, 1H), 3.21 (d, J = 12.8 Hz, 1H), 2.85 (q, J = 11.7 Hz, 2H), 2.21 (s, 3H), 2.01 (s, 1H), 1.90 (s, 1H), 1.75-1.62 (m, 2H).

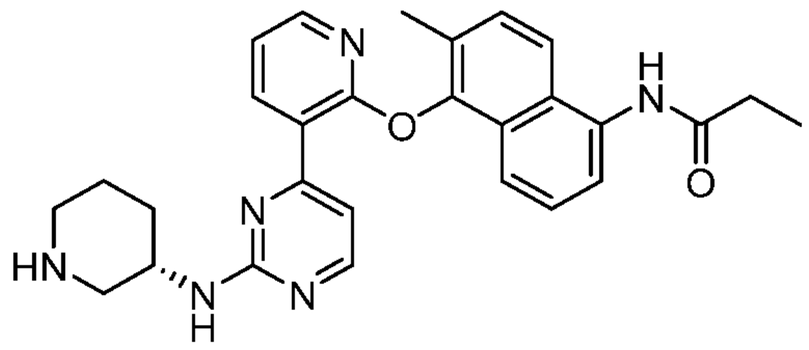
Example 173 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propionamide* ***173***

[0518] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-propionamidonaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0519] The General Procedure C was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (90 mg, 0.17 mmol), propionic acid (19 mg, 0.26 mmol), DIPEA (0.089 mL, 0.51 mmol), HATU (97 mg, 0.26 mmol) and DCM (1.7 mL). The crude was directly used in the next step.

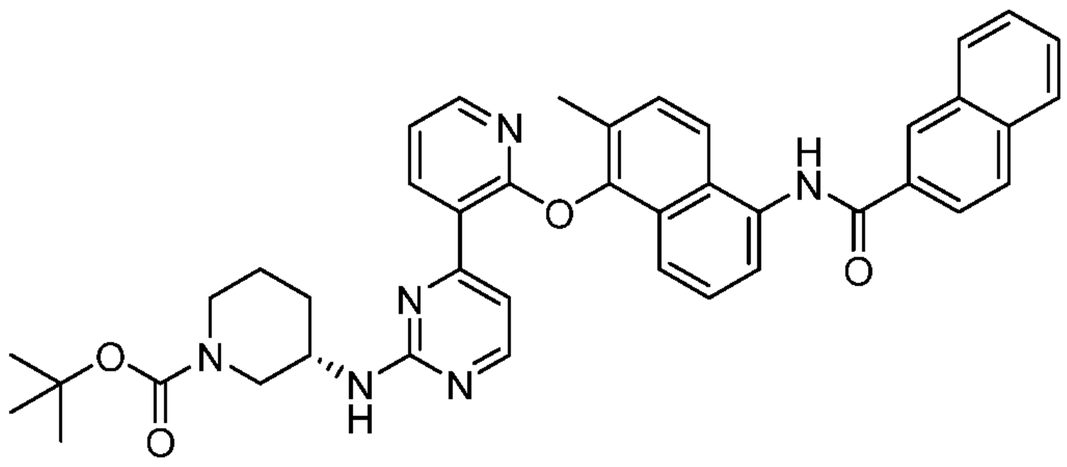
[0520] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propionamide



[0521] The General Procedure B was followed, using crude *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-propionamidonaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate, DCM (1.7 mL) and hydrochloric acid (4 M in dioxane, 0.430 mL, 1.71 mmol). The residue was purified *via* reverse-phase HPLC and lyophilized to yield 16.1 mg of **173**. LCMS (ESI): $[M+H]^+$ = 483.2; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.89 (s, 1H), 8.52 – 8.46 (m, 1H), 8.42 – 8.37 (m, 1H), 8.04 – 8.00 (m, 1H), 7.92 (d, J = 8.7 Hz, 1H), 7.62 (d, J = 7.4 Hz, 1H), 7.50 (d, J = 8.7 Hz, 3H), 7.46 – 7.36 (m, 2H), 7.25 (dd, J = 7.6, 4.8 Hz, 1H), 7.11 (d, J = 7.7 Hz, 1H), 3.96 – 3.59 (m, 1H), 3.13 – 3.03(m, 1H), 2.85 – 2.71 (m, 1H), 2.46 – 2.37 (m, 1H), 2.22 (s, 3H), 1.97 – 1.81 (m, 1H), 1.67 – 1.24 (m, 3H), 1.17 (t, J = 7.6 Hz, 3H).

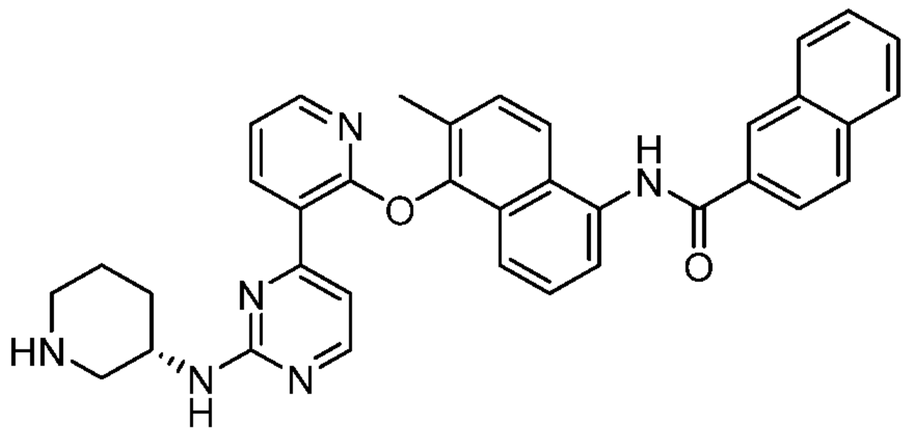
Example 174 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-naphthamide **174***

[0522] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((5-(2-naphthamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0523] The General Procedure C was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (90 mg, 0.17 mmol), naphthalene-2-carboxylic acid (44 mg, 0.26 mmol), DIPEA (0.089 mL, 0.51 mmol), HATU (97 mg, 0.26 mmol) and DCM (1.7 mL). The crude was directly used in the next step.

[0524] Step 2: (S)-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-naphthamide

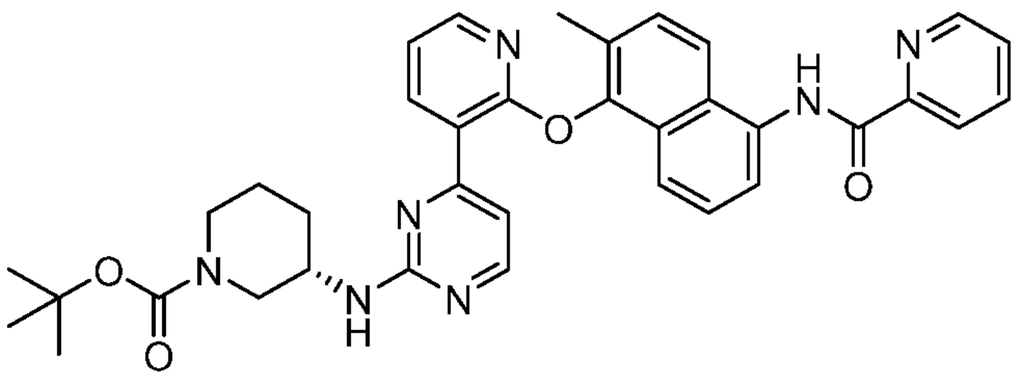


[0525] The General Procedure B was followed, using crude *tert*-butyl (*S*)-3-((4-(2-((5-(2-naphthamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate, DCM (1.7 mL) and hydrochloric acid (4 M in dioxane, 0.430 mL, 1.71 mmol). The residue was purified *via* reverse-phase HPLC and lyophilized to yield 31 mg of **174**. LCMS (ESI): $[M+H]^+$ = 581.2; ^{1}H NMR (400 MHz, DMSO-d6) δ 10.64 (s, 1H), 8.75 (d, J = 1.6 Hz, 1H), 8.55 – 8.48 (m, 1H), 8.43 (d, J = 5.1 Hz, 1H), 8.23 – 8.00 (m, 5H), 7.92 (d, J = 8.7 Hz, 1H), 7.74 – 7.58 (m, 4H), 7.54 – 7.44 (m, 3H), 7.28 (dd, J = 7.6, 4.8 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 3.92 (s, 1H), 3.18 – 3.06 (m, 1H), 2.87 – 2.77 (m, 1H), 2.24 (s, 3H), 2.01 – 1.87 (m, 1H), 1.70 – 1.60 (m, 1H), 1.56 – 1.38 (m, 2H).

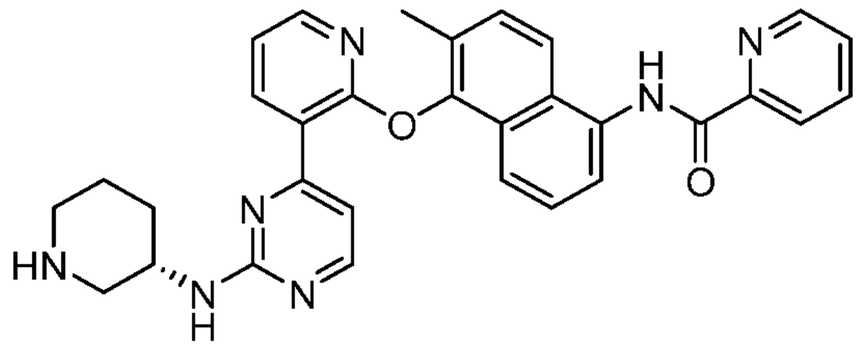
Example 175 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)picolinamide* ***175***

[0526] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-(picolinamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate

[0527] The General Procedure C was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (90 mg, 0.17 mmol), pyridine-2-carboxylic acid (44 mg, 0.26 mmol), DIPEA (0.089 mL, 0.51 mmol), HATU (97 mg, 0.26 mmol) and DCM (1.7 mL). The crude was directly used in the next step.



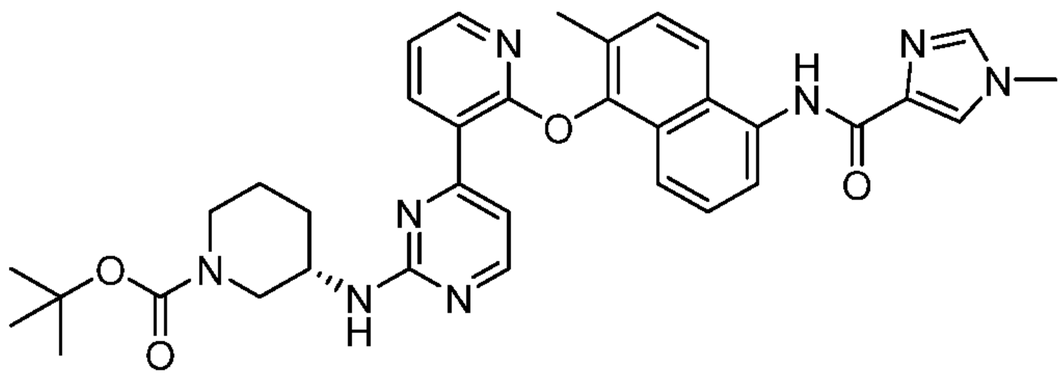
[0528] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)picolinamide



[0529] The General Procedure B was followed, using crude *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-(picolinamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate, DCM (1.7 mL) and hydrochloric acid (4 M in dioxane, 0.430 mL, 1.71 mmol). The residue was purified *via* reverse-phase HPLC and lyophilized to yield 40 mg of **175**. LCMS (ESI): $[M+H]^+$ = 532.2; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.94 (s, 1H), 8.85 – 8.82 (m, 1H), 8.54 – 8.47 (m, 1H), 8.42 (d, J = 5.1 Hz, 1H), 8.23 – 8.19 (m, 1H), 8.12 (td, J = 7.7, 1.7 Hz, 1H), 8.06 (dd, J = 4.8, 1.9 Hz, 1H), 7.85 (t, J = 7.7 Hz, 2H), 7.74 (ddd, J = 7.5, 4.8, 1.3 Hz, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.27 (dd, J = 7.5, 4.8 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 3.89 (s, 1H), 3.16 – 3.01 (m, 1H), 2.85 – 2.76 (m, 1H), 2.47 – 2.38 (m, 2H), 2.24 (s, 3H), 1.97 – 1.86 (m, 1H), 1.70 – 1.61 (m, 1H), 1.56 – 1.37 (m, 2H).

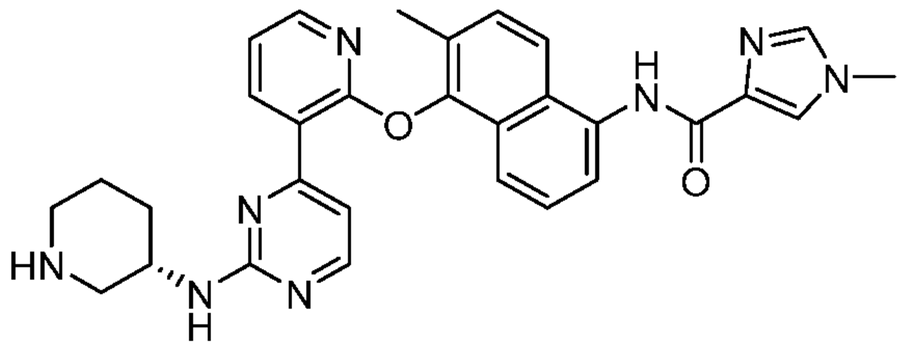
Example 176 *(S)-1-Methyl-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1H-imidazole-4-carboxamide* ***176***

[0530] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-(1-methyl-1H-imidazole-4-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0531] The General Procedure C was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (90 mg, 0.17 mmol), 1-methylimidazole-4-methyl carboxylic acid (32 mg, 0.26 mmol), DIPEA (0.089 mL, 0.51 mmol), HATU (97 mg, 0.26 mmol) and DCM (1.7 mL). The crude was directly used in the next step.

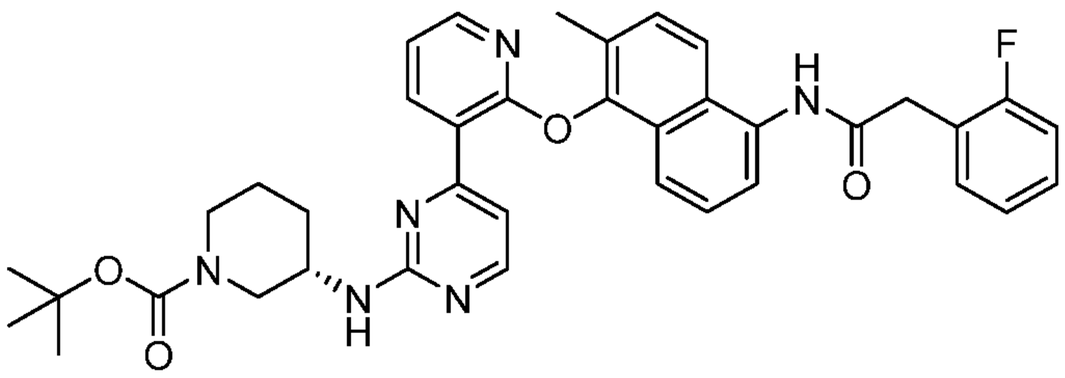
[0532] Step 2: (*S*)-1-Methyl-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1H-imidazole-4-carboxamide



[0533] The General Procedure B was followed, using crude *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-(1-methyl-1H-imidazole-4-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate, (1.7 mL) and hydrochloric acid (4 M in dioxane, 0.430 mL, 1.71 mmol). The residue was purified *via* reverse-phase HPLC and lyophilized to yield 32 mg of **176** as a mixture of two rotamers (ratio = 3:1). LCMS (ESI): $[M+H]^+$ = 535.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02, 9.99 (2s, 1H), 8.57 – 8.47 (m, 1H), 8.43 (d, J = 5.1 Hz, 0.75H), 8.40 (d, J = 5.1 Hz, 0.25H), 8.06 (dd, J = 4.8, 2.0 Hz, 0.75H), 8.01 – 7.74 (m, 4.25H), 7.57 – 7.34 (m, 4H), 7.30 – 7.18 (m, 1.75H), 7.10 – 7.05 (m, 0.25H), 5.75 (s, 1H), 4.13 - 3.91 (m, 1H), 3.77 (s, 3H), 3.23 – 3.15 (m, 1H), 2.98 – 2.86 (m, 1H), 2.63 – 2.50 (m, 1H), 2.23 (s, 3H), 2.18 (s, 1H), 2.12 – 1.90 (m, 2H), 1.76 – 1.63 (m, 1H), 1.60 – 1.37 (m, 2H).

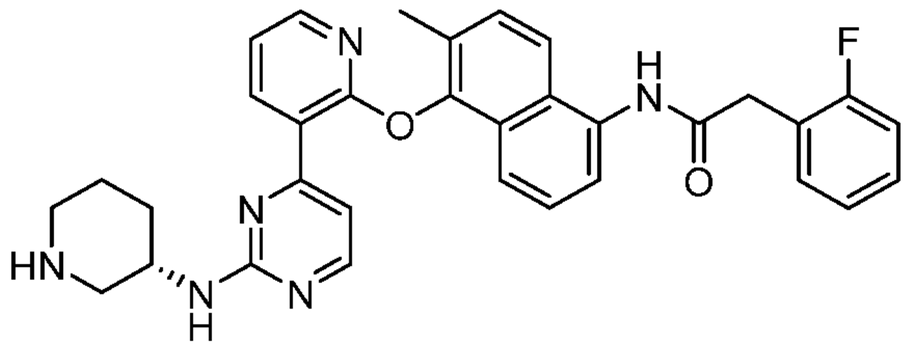
Example 177 *(S)-2-(2-Fluorophenyl)-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)acetamide* ***177***

[0534] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((5-(2-(2-fluorophenyl)acetamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0535] The General Procedure C was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (90 mg, 0.17 mmol), 2-(2-fluorophenyl)acetic acid (39.5 mg, 0.26 mmol), DIPEA (0.089 mL, 0.51 mmol), HATU (97 mg, 0.26 mmol) and DCM (1.7 mL). The crude was directly used in the next step.

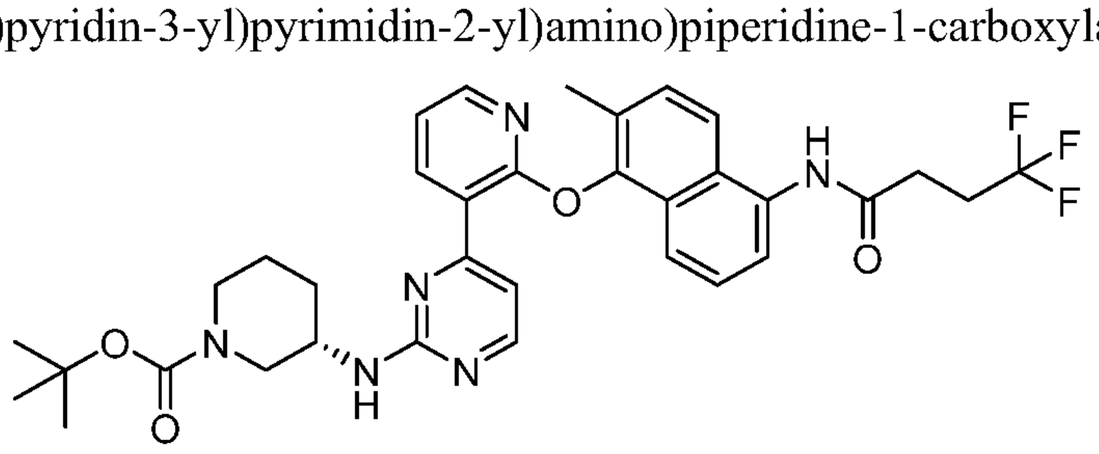
[0536] Step 2: (*S*)-2-(2-Fluorophenyl)-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)acetamide



[0537] The General Procedure B was followed, using crude *tert*-butyl (*S*)-3-((4-(2-((5-(2-(2-fluorophenyl)acetamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate, DCM (1.7 mL) and hydrochloric acid (4 M in dioxane, 0.430 mL, 1.71 mmol). The residue was purified *via* reverse-phase HPLC and lyophilized to yield 33 mg of **177**. LCMS (ESI): $[M+H]^+$ = 563.2; ^1H NMR (400 MHz, DMSO-d_6) δ 10.22 (s, 1H), 8.69 – 8.52 (m, 2H), 8.48 (d, J = 5.2 Hz, 1H), 8.05 (dd, J = 4.8, 2.0 Hz, 1H), 7.97 (d, J = 8.7 Hz, 1H), 7.65 – 7.18 (m, 11H), 4.30 – 4.17 (m, 1H), 3.93 (s, 2H), 3.52 – 3.42 (m, 1H), 3.27 – 3.19 (m, 1H), 2.96 – 2.83 (m, 1H), 2.22 (s, 3H), 2.07 – 1.90 (m, 2H), 1.78 – 1.57 (m, 2H).

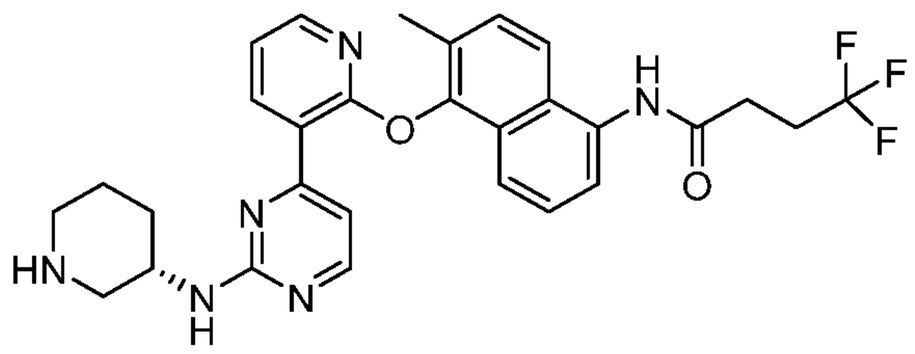
Example 178 *(S)-4,4,4-Trifluoro-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)butanamide* ***178***

[0538] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-(4,4,4-trifluorobutanamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



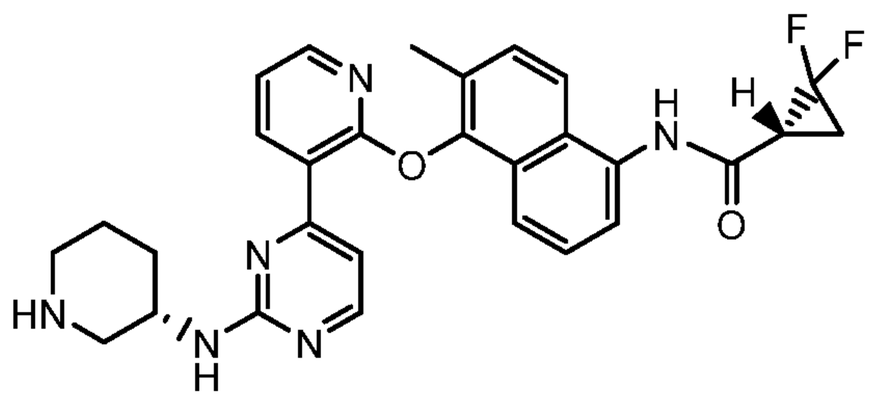
[0539] The General Procedure C was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (90 mg, 0.17 mmol), 4,4,4-trifluorobutanoic acid (36 mg, 0.26 mmol), DIPEA (0.089 mL, 0.51 mmol), HATU (97 mg, 0.26 mmol) and DCM (1.7 mL). The crude was directly used in the next step.

[0540] Step 2: (*S*)-4,4,4-Trifluoro-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)butanamide

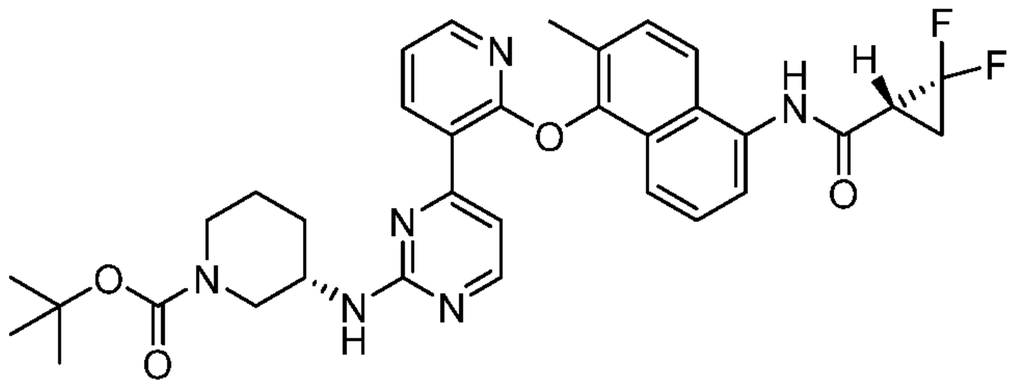


[0541] The General Procedure B was followed, using crude *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-(4,4,4-trifluorobutanamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate, DCM (1.7 mL) and hydrochloric acid (4 M in dioxane, 0.430 mL, 1.71 mmol). The residue was purified *via* reverse-phase HPLC and lyophilized to yield 25 mg of **178**. LCMS (ESI): $[M+H]^+$ = 551.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.69 – 8.51 (m, 2H), 8.48 (d, J = 5.2 Hz, 1H), 8.06 (dd, J = 4.8, 2.0 Hz, 1H), 7.95 (d, J = 8.7 Hz, 1H), 7.66 – 7.46 (m, 4H), 7.41 (dd, J = 8.4, 7.4 Hz, 1H), 7.27 (dd, J = 7.5, 4.8 Hz, 1H), 4.25 (s, 1H), 3.27 – 3.18 (m, 1H), 2.94 – 2.77 (m, 3H), 2.75 – 2.57 (m, 2H), 2.22 (s, 3H), 2.06 – 1.98 (m, 1H), 1.98 – 1.89 (m, 1H), 1.77 – 1.57 (m, 1H), 1.28 – 1.23 (m, 1H).

Example 179 *(R)-2,2-Difluoro-N-(6-methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide* ***179***

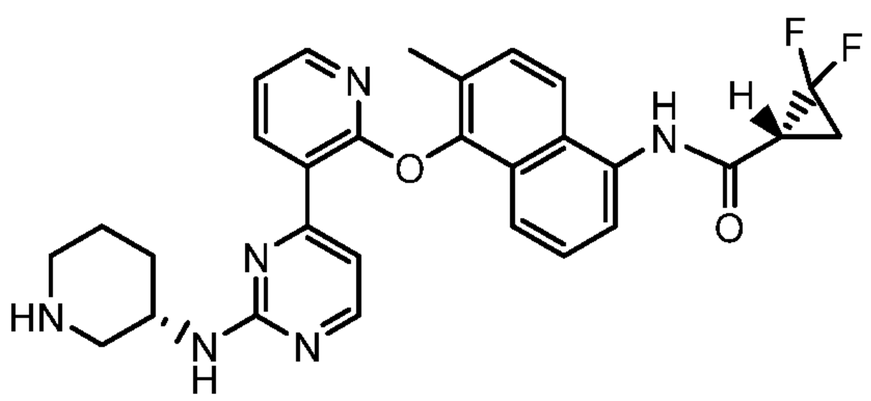


[0542] Step 1: I-Butyl (*S*)-3-((4-(2-((5-((*R*)-2,2-difluorocyclopropane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



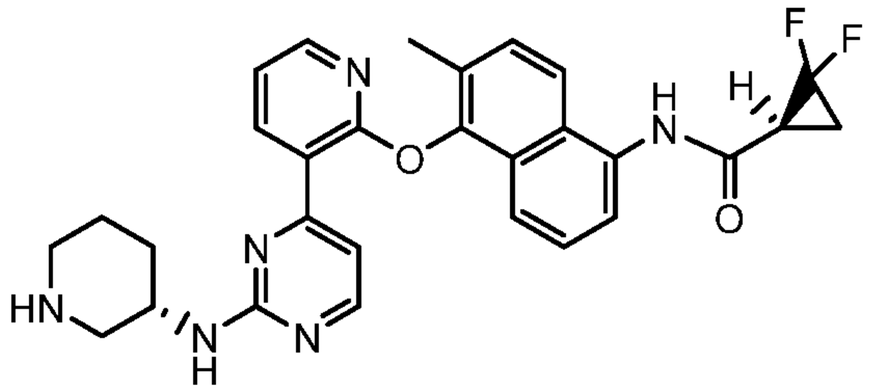
[0543] The General Procedure C was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (207 mg, 0.39 mmol), 2,2-difluorocyclopropanecarboxylic acid (40 mg, 0.33 mmol), DIPEA (0.171 mL, 0.98 mmol), HATU (381 mg, 0.98 mmol) and DCM (8 mL). The residue was purified *via* reverse-phase HPLC to provide a mixture of the two isomers. This mixture was then purified *via* chiral reverse-phase HPLC and lyophilized to yield 82 mg and 85 mg of the two single stereoisomers possessing a stereocenter at the 1 position of the cyclopropyl amide.

[0544] Step 2: (*R*)-2,2-difluoro-N-(6-methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide



[0545] The General Procedure B was followed, using tert-butyl (S)-3-((4-(2-((5-((R)-2,2-difluorocyclopropane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (85 mg, 0.132 mmol), DCM (4 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). The residue was purified via reverse-phase HPLC and lyophilized to yield 39.8 mg (55% yield) of **179**. The stereochemistry was tentatively and arbitrarily assigned. LCMS (ESI): $[M+H]^+$ = 531.2;^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42 (s, 1H), 8.50 (d, J = 7.5 Hz, 1H), 8.41 (d, J = 5.1 Hz, 1H), 8.03 (dd, J = 4.8, 2.0 Hz, 1H), 7.94 (d, J = 8.7 Hz, 1H), 7.66 (d, J = 7.3 Hz, 1H), 7.55 (d, J = 8.7 Hz, 2H), 7.49 – 7.38 (m, 2H), 7.26 (dd, J = 7.5, 4.8 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 3.89 (s, 1H), 3.15 – 3.05 (m, 2H), 2.83 – 2.76 (m, 1H), 2.48 – 2.38 (m, 2H), 2.22 (s, 3H), 2.11 – 1.97 (m, 2H), 1.96 – 1.89 (m, 1H), 1.68 – 1.60 (m, 1H), 1.55 – 1.37 (m, 2H).

Example 180 *(S)-2,2-Difluoro-N-(6-methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide* ***180***

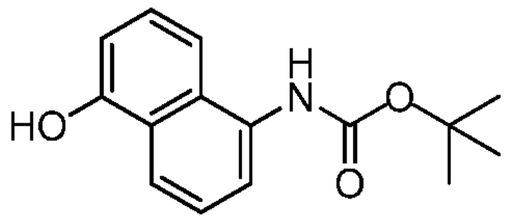


[0546] Following Example 179 and the General Procedure B, tert-butyl (S)-3-((4-(2-((5-((S)-2,2-difluorocyclopropane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (82 mg,0.127 mmol), DCM (4 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol) were reacted. The residue was purified *via* reverse-phase HPLC and lyophilized to yield 23.8 mg (34% yield) of **180**. The stereochemistry was tentatively and arbitrarily assigned. LCMS (ESI): $[M+H]^+$ = 531.2^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42 (s, 1H), 8.50 (d, J = 7.5 Hz, 1H), 8.41 (d, J = 5.1 Hz, 1H), 8.03 (dd, J = 4.8, 2.0 Hz, 1H), 7.94 (d, J = 8.7 Hz, 1H), 7.66 (d, J = 7.3 Hz, 1H), 7.55 (d, J = 8.7 Hz, 2H), 7.49 – 7.38 (m, 2H), 7.26 (dd, J = 7.5, 4.8 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 3.89 (s, 1H), 3.15 – 3.05

(m, 2H), 2.83 – 2.76 (m, 1H), 2.48 – 2.38 (m, 2H), 2.22 (s, 3H), 2.11 – 1.97 (m, 2H), 1.96 – 1.89 (m, 1H), 1.68 – 1.60 (m, 1H), 1.55 – 1.37 (m, 2H).

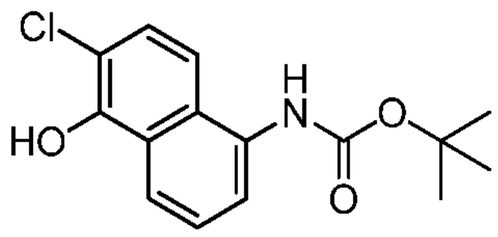
Example 181 *N-(5-((3-(2-(((3S, 5S)-5-Fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)propane-1-sulfonamide* ***181***

[0547] Step 1: *tert*-Butyl (5-hydroxynaphthalen-1-yl)carbamate



[0548] To a solution of 5-amino-1-naphthol (5 g, 31.4 mmol) in 1,4-dioxane (50 mL) was added di-*tert*-butyldicarbonate (8.43 g, 38.6 mmol), the mixture was stirred at 60 °C for 12 h. The reaction mixture was concentrated *in vacuo* and the residuea purified by silica gel chromatography (solvent gradient: 0-50% ethyl acetate in petroleum ether, Rf = 0.8) to yield 8 g (98% yield) of the title compound as red solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 9.06 (s, 1H), 7.94 (d, J = 7.6 Hz, 1H), 7.51 (d, J = 7.2 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.29 (t, J = 8.2 Hz, 1H), 6.86 (d, J = 7.6 Hz, 1H), 1.48 (s, 9H).

[0549] Step 2: *tert*-Butyl (6-chloro-5-hydroxynaphthalen-1-yl)carbamate



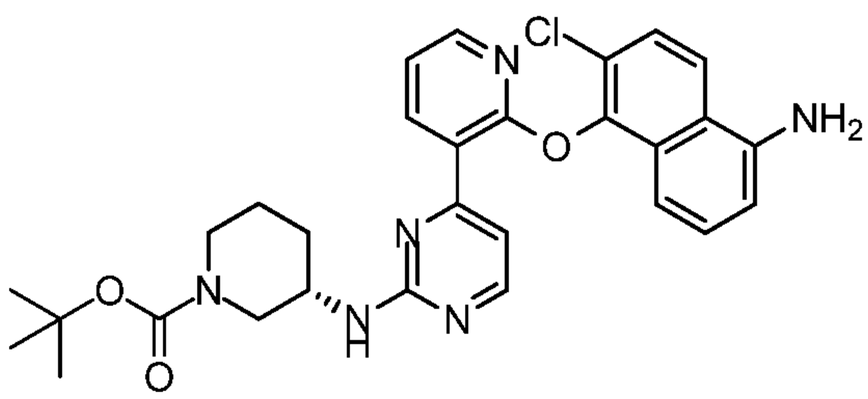
[0550] To a solution of *tert*-butyl *N*-(5-hydroxy-1-naphthyl)carbamate (600 mg, 2.3 mmol) in a solution of sodium hydroxide (1.4 mL, 2.8 mmol, 2N) in H_2O (6 mL) was added sodium hypochloride (1.9 mL, 2.3 mmol, 9%) and the mixture was stirred at 0 °C for 1 h. H_2O (50 mL) and ethyl acetate (60 mL) were added, the organic phase was dried over anhydrous sodium sulfate, concentrated and purified by silica gel chromatography (50% ethyl acetate in petroleum ether, Rf = 0.8) to yield 300 mg (44% yield) of the title compound as a brown solid; ^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.53 - 7.47 (m, 2H), 7.47 - 7.42 (m, 1H), 7.37 (d, J = 9.2 Hz, 1H), 1.54 (s, 9H).

[0551] Step 3: 5-Amino-2-chloronaphthalen-1-ol

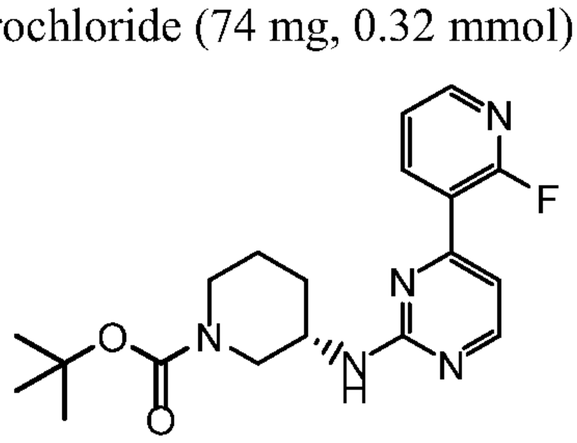
[0552] To a stirred solution of *tert*-butyl *N*-(6-chloro-5-hydroxy-1-naphthyl)carbamate (300 mg, 1.02 mmol) in ethyl acetate (1mL) was added hydrochloric acid (4 M in ethyl acetate, 2.6

mL, 10.4 mmol) followed by stirring at 20 °C for 3 h. The mixture was concentrated and the residue was dissolved in ethyl acetate (50 mL) andwashed with saturated sodium bicarbonate aqueous solution. The organic phase was dried over anhydrous sodium sulfate, concentrated and purified by Prep-TLC (9% ethyl acetate in petroleum ether, Rf = 0.7) to yield 74 mg (37% yield) of the title compound as a tan solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.59 (s, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.38 (d, J = 8.8 Hz, 1H), 7.25 (d, J = 8.8 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 6.67 (d, J = 7.6 Hz, 1H), 5.71 (s, 2H).

[0553] Step 4: (*S*)-*tert*-Butyl 3-((4-(2-((5-amino-2-chloronaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate

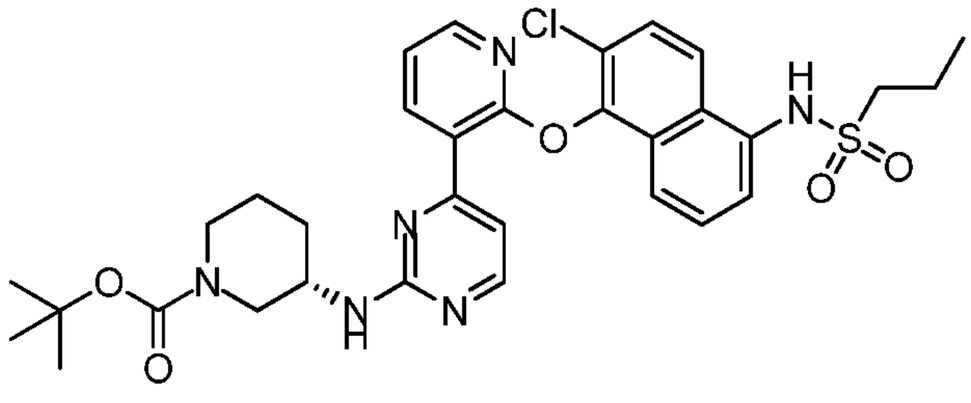


[0554] To a solution of *tert*-butyl (3*S*)-3-[[4-(2-fluoro-3-pyridyl)pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.27 mmol) and 5-amino-2-chloro-naphthalen-1-ol hydrochloride (74 mg, 0.32 mmol):



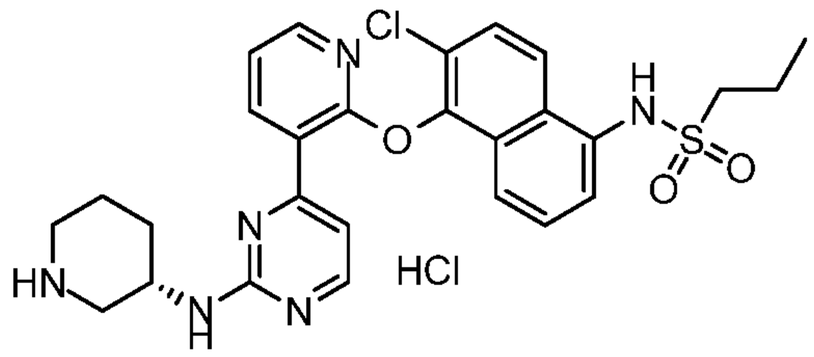
[0555] in 1-methyl-2-pyrrolidinone (6 mL) was added caesium carbonate (262 mg, 0.8 mmol) followed by stirring at 120 °C for 12 h. After cooling down, the mixture was diluted in ethyl acetate (50 mL) and washed with H_2O (40 mL) and brine (40 mL). The organic phase was dried over anhydrous sodium sulfate, concentrated and purified by Prep-TLC (50% ethyl acetate in petroleum ether, Rf = 0.8) to yield 90 mg (61% yield) of the title compound as a tan solid; LCMS (ESI) $[M+H]^+$ = 547.1.

[0556] Step 5: (*S*)-*tert*-Butyl 3-((4-(2-((2-chloro-5-(propylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0557] To a solution of *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-chloro-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (90 mg, 0.16 mmol) in pyridine (3 mL) was added 1-propanesulfonyl chloride (0.02 mL, 0.2 mmol) and stirred at 26 °C for 12 h. The mixture was concentrated, dissolved in dichloromethane (50 mL) and washed with H_2O (40 mL). The organic phase was dried over anhydrous sodium sulfate, concentrated and purified by prep-TLC (50% ethyl acetate in petroleum ether, Rf = 0.6) to yield 60 mg (42% yield) of the title compound as a white solid; LCMS (ESI) $[M+H]^+$ = 653.0.

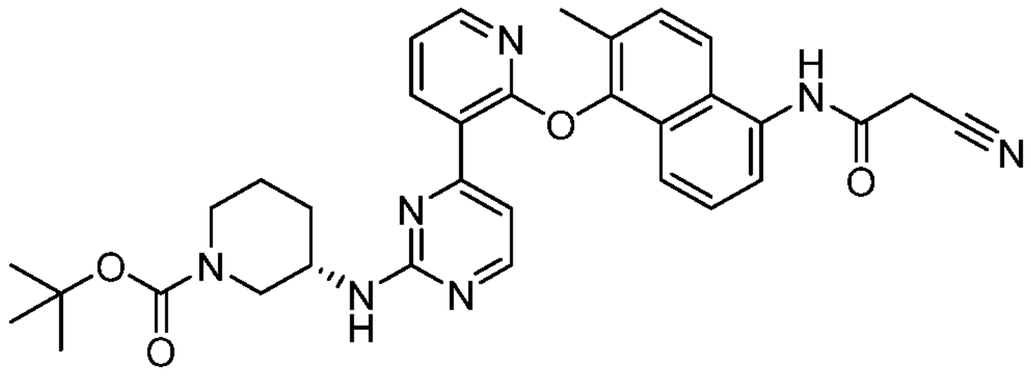
[0558] Step 6: (*S*)-*N*-(6-Chloro-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide



[0559] To a solution of *tert*-butyl (3*S*)-3-[[4-[2-[[2-chloro-5-(propylsulfonylamino)-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (60 mg, 0.09 mmol) in ethyl acetate (0.5 mL) was added hydrochloric acid (4 M in ethyl acetate, 0.2 mL, 0.8 mmol) and stirred at 26 °C for 1 h. The residue was concentrated and purified by Prep-HPLC (mobile phase: A: water (0.05%HCl); B: ACN) to yield 22.7 mg (39% yield) of hydrochloride **181** as a white solid; LCMS (ESI) $[M+H]^+$ = 553.1; ^1H NMR (400MHz, DMSO-d_6) δ 9.95 (s, 1H), 9.20 - 9.00 (m, 2H), 8.82 - 8.63 (m, 1H), 8.49 (d, *J* = 5.2 Hz, 1H), 8.24 (d, *J* = 8.8 Hz, 1H), 8.09 (d, *J* = 3.6 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.66 - 7.51 (m, 4H), 7.34 - 7.31 (m, 1H), 4.43 - 4.19 (m, 1H), 3.49 - 3.37 (m, 1H), 3.26 - 3.11 (m, 3H), 2.94 - 2.75 (m, 2H), 2.06 - 1.98 (m, 1H), 1.96 - 1.87 (m, 1H), 1.83 - 1.69 (m, 3H), 1.68 - 1.58 (m, 1H), 0.98 (t, *J* = 7.2 Hz, 3H).

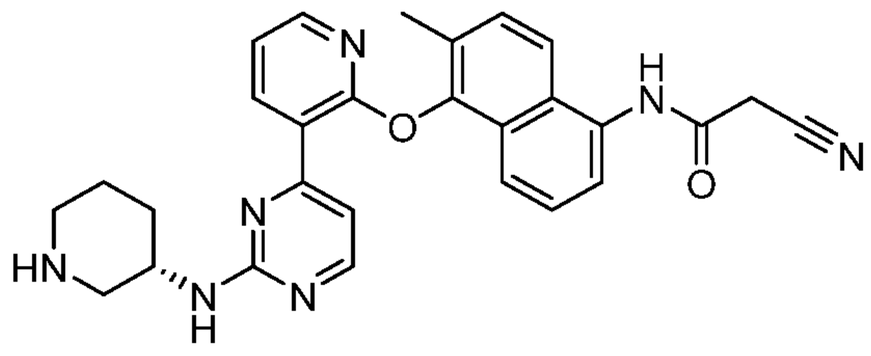
Example 183 *(S)-2-Cyano-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)acetamide* ***183***

[0560] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((5-(2-cyanoacetamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0561] The General Procedure C was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (90 mg, 0.17 mmol), 2-cyanoacetic acid (22 mg, 0.26 mmol), DIPEA (0.089 mL, 0.51 mmol), HATU (97 mg, 0.26 mmol) and DCM (1.7 mL). The crude was directly used in the next step.

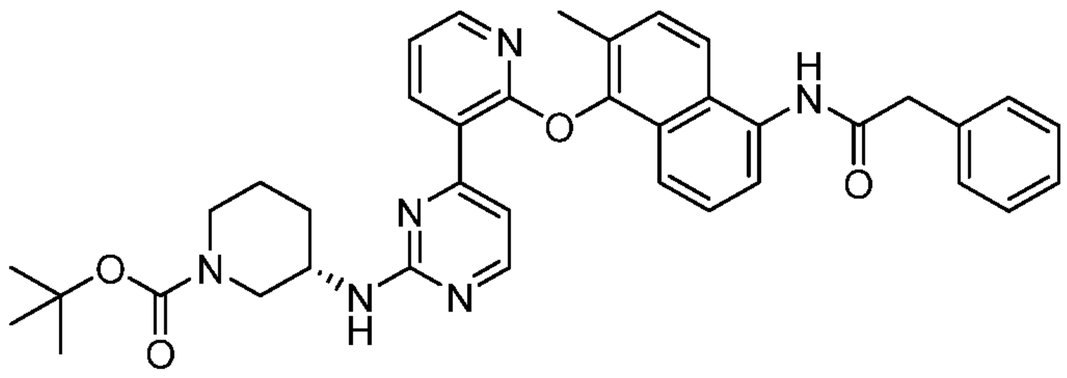
[0562] Step 2: (*S*)-2-Cyano-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)acetamide



[0563] The General Procedure B was followed, using crude *tert*-butyl (*S*)-3-((4-(2-((5-(2-cyanoacetamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate, DCM (1.7 mL) and hydrochloric acid (4 M in dioxane, 0.430 mL, 1.71 mmol). The residue was purified *via* reverse-phase HPLC and lyophilized to yield 8 mg of **183**. LCMS (ESI): $[M+H]^+$ = 494.2; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.30 (s, 1H), 8.50 (d, J = 7.5 Hz, 1H), 8.41 (d, J = 5.1 Hz, 1H), 8.03 (dd, J = 4.8, 2.0 Hz, 1H), 7.94 (d, J = 8.7 Hz, 1H), 7.64 – 7.60 (m, 1H), 7.58 – 7.53 (m, 2H), 7.45 – 7.41 (m, 2H), 7.26 (dd, J = 7.5, 4.8 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 4.10 (s, 2H), 3.90 (s, 1H), 3.14 – 3.06 (m, 1H), 2.84 – 2.77 (m, 1H), 2.49 – 2.40 (m, 2H), 1.97 – 1.87 (m, 1H), 1.69 – 1.61 (m, 1H), 1.57 – 1.36 (m, 2H).

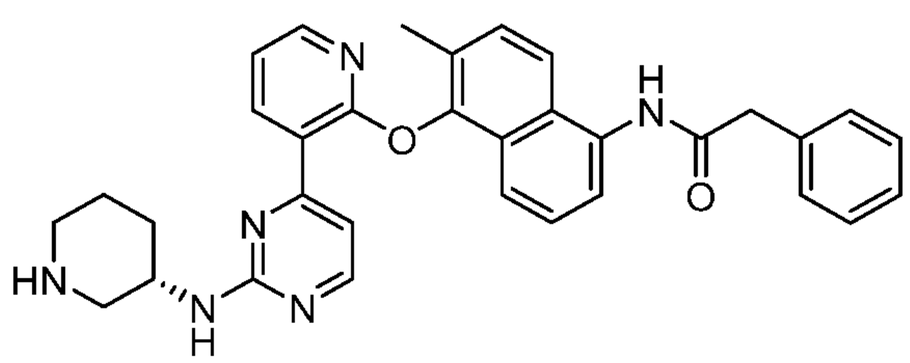
Example 184 *N-[6-Methyl-5-[[3-[2-[[(3S)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]-2-phenyl-acetamide* ***184***

[0564] Step 1: *tert*-Butyl (S)-3-((4-(2-((2-methyl-5-(2-phenylacetamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0565] The General Procedure C was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (90 mg, 0.17 mmol), 2-phenylacetic acid (35 mg, 0.26 mmol), DIPEA (0.089 mL, 0.51 mmol), HATU (97 mg, 0.26 mmol) and DCM (1.7 mL). The crude was directly used in the next step.

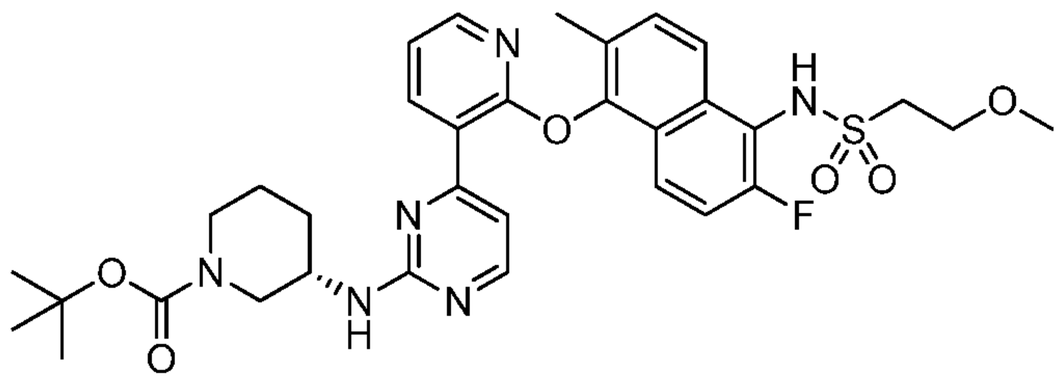
[0566] Step 2: *N*-[6-Methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]-2-phenyl-acetamide



[0567] The General Procedure B was followed, using crude *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-(2-phenylacetamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate, DCM (1.7 mL) and hydrochloric acid (4 M in dioxane, 0.430 mL, 1.71 mmol).The residue was purified *via* reverse-phase HPLC and lyophilized to yield 13 mg of **184**. LCMS (ESI): $[M+H]^+$ = ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.17 (s, 1H), 8.49 (d, J = 7.2 Hz, 1H), 8.41 (d, J = 5.2 Hz, 1H), 8.02 (dd, J = 4.8, 2.0 Hz, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.62 (d, J = 7.4 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.47 – 7.20 (m, 9H), 7.14 (d, J = 7.9 Hz, 1H), 3.91 (s, 1H), 3.83 (s, 2H), 3.69 – 3.62 (m, 1H), 3.15 – 3.07 (d, J = 11.6 Hz, 1H), 2.85 – 2.76 (m, 1H), 2.46 – 2.41 (m, 1H), 2.20 (s, 3H), 1.97 – 1.88 (m, 1H), 1.70 – 1.59 (m, 1H), 1.55 – 1.37 (m, 2H).

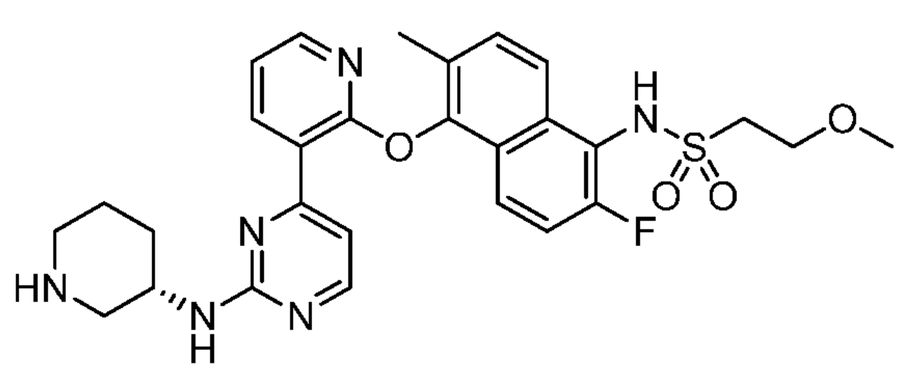
Example 185 *(S)-N-(2-Fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-methoxyethanesulfonamide* ***185***

[0568] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((6-fluoro-5-(2-methoxyethylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0569] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 275 (75 mg, 0.138 mmol), pyridine (0.167 mL, 2.07 mmol), DCM (0.9 mL), 2-methoxyethanesulfonyl chloride (43.7 mg, 0.275 mmol) and DMAP (1.68 mg, 0.014 mmol). After 16 h, the mixture was diluted with 1M $KHSO_4$(aq), extracted twice with DCM, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude was purified by flash chromatography through silica gel (0 – 55% EtOAc/DCM) to provide 42 mg (46% yield) of the title compound. LCMS (ESI) $[M+H]^+$ = 667.4, rt = 1.82 min.

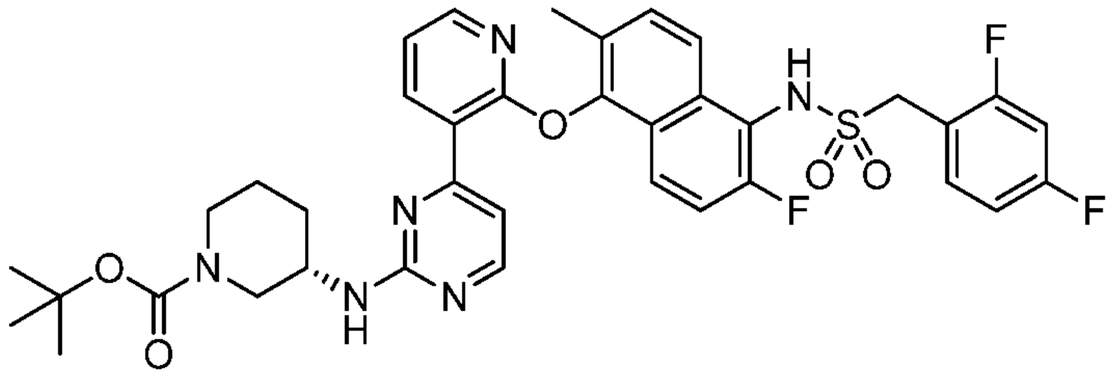
[0570] Step 2: (*S*)-*N*-(2-Fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-methoxyethanesulfonamide



[0571] Prepared according to General Procedure B using (*S*)-*tert*-butyl 3-((4-(2-((6-fluoro-5-(2-methoxyethylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (42 mg, 0.063 mmol), 1,4-dioxane (0.5 mL) and hydrochloric acid (4 M in dioxane, 0.53 mL, 2.11 mmol). After 1h, the reaction was diluted with Et_2O and sonicated for a few seconds. The solid was collected by filtration, washed with Et_2O, dissolved in H_2O and MeCN and lyophilized to provide 36 mg (95 % yield) of **185**. LCMS (ESI) $[M+H]^+$ = 567.4, rt = 1.29 min; ^{1}H NMR (400 MHz, DMSO-*d*$_6$)δ 9.80 (s, 1H), 8.92 (bs, 2H), 8.69 (s, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.11 – 8.00 (m, 2H), 7.72 (dd, J = 9.3, 5.2 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.57 (d, J = 5.5 Hz, 2H), 7.46 (t, J = 9.5 Hz, 1H), 7.29 (dd, J = 7.6, 4.8 Hz, 1H), 3.82 (t, J = 6.5 Hz, 2H), 3.49 (t, J = 6.5 Hz, 2H), 3.46 – 3.38 (m, 1H), 3.29 (s, 3H), 3.20 (d, J = 12.2 Hz, 1H), 2.94 – 2.76 (m, 2H), 2.19 (s, 3H), 2.06 – 1.97 (m, 1H), 1.95 – 1.85 (m, 1H), 1.84 – 1.54 (m, 2H).

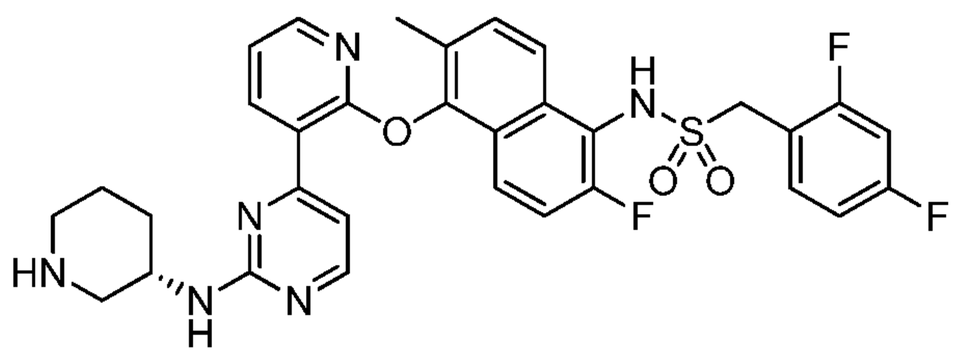
Example 186 *(S)-1-(2,4-Difluorophenyl)-N-(2-fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide* ***186***

[0572] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-((2,4-difluorophenyl)methylsulfonamido)-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0573] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 275 (50 mg, 0.092 mmol), pyridine (0.5 mL, 6.18 mmol), DCM (1 mL), and (2,4-difluorophenyl)methanesulfonyl chloride (52 mg, 0.23 mmol). After 16 h, the mixture was diluted with DCM (50 mL), washed with saturated $NaHCO_3$(aq) (10mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude was purified by flash chromatography through silica gel (0 – 75% EtOAc/Hexanes) to provide 45 mg (67% yield) of the title compound. LCMS (ESI) $[M+H]^+$ = 735.3, rt = 2.00 min.

[0574] Step 2: (*S*)-1-(2,4-Difluorophenyl)-*N*-(2-fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide

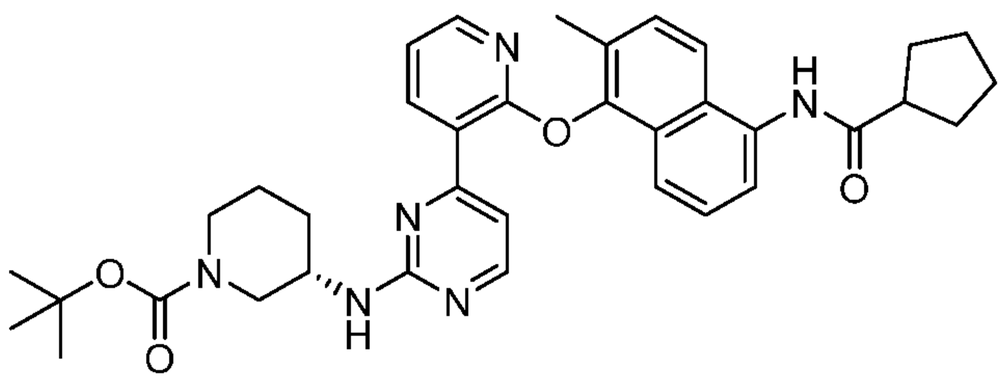


[0575] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-((2,4-difluorophenyl)methylsulfonamido)-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (45 mg, 0.061 mmol), EtOAc (2 mL), and hydrochloric acid (4 M in dioxane, 1 mL, 4 mmol). After 4 h, volatiles were removed *in vacuo* and the residue was washed with EtOAc (3 x 3 mL), then with MeCN (3 x 3 mL). The residue was then sonicated and concentrated *in vacuo* with MeCN (3 x 3 mL) and the resulting solid dissolved in water and MeCN and lyophilized to provide 28 mg (68% yield) of **186** as a white solid. LCMS (ESI) $[M+H]^+$ = 635.2, rt = 1.50 min; ^1H NMR (400 MHz, DMSO-d_6)δ 9.96 (s, 1H), 8.87 – 8.67 (m, 2H), 8.66 – 8.53 (m, 1H), 8.47 (d, J = 7.0 Hz, 1H), 8.09 (dd, J = 4.8, 1.9 Hz, 1H), 8.01 (d, J = 8.7 Hz, 1H), 7.73 (dd, J = 12.7, 6.5 Hz, 1H), 7.64 – 7.45 (m, 5H), 7.39 – 7.26 (m, 2H), 7.17 (td,

J = 8.5, 2.1 Hz, 1H), 4.62 (s, 2H), 4.16 – 4.33 (m, 1H), 3.47 – 3.42 (m, 1H), 3.21 (d, J = 12.5 Hz, 1H), 2.96 – 2.76 (m, 2H), 2.19 (s, 3H), 2.08 – 1.97 (m, 1H), 1.97 – 1.85 (m, 1H), 1.81 – 1.56 (m, 2H).

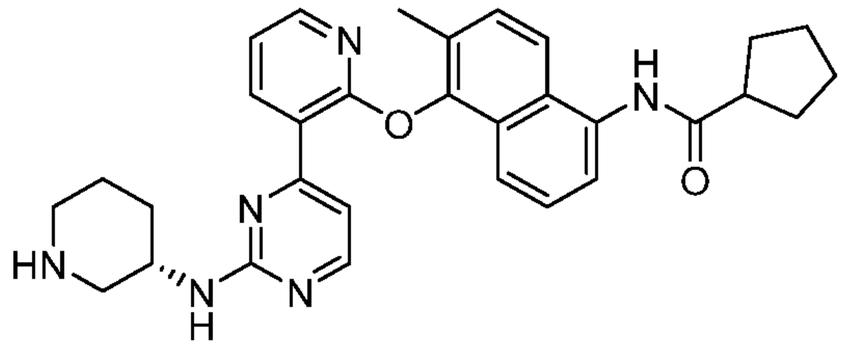
[0576] Example187 (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentanecarboxamide **187**

[0577] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((5-(cyclopentanecarboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0578] The General Procedure C was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (90 mg, 0.17 mmol), cyclopentanecarboxylic acid (29 mg, 0.26 mmol), DIPEA (0.089 mL, 0.51 mmol), HATU (97 mg, 0.26 mmol) and DCM (1.7 mL). The crude was directly used in the next step.

[0579] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentanecarboxamide

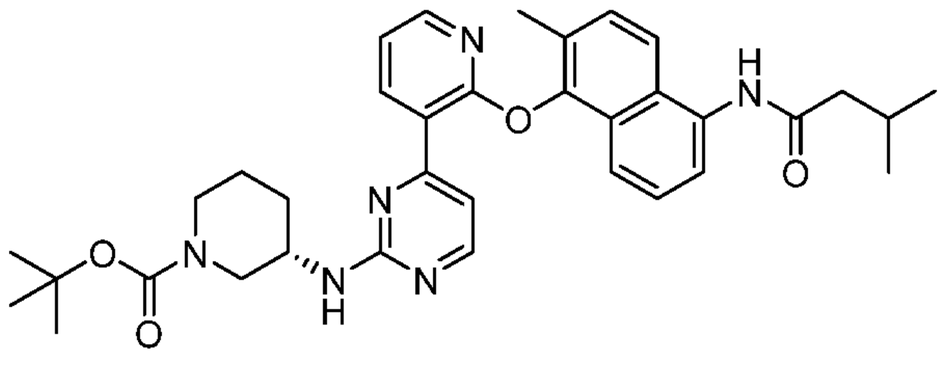


[0580] The General Procedure B was followed, using crude *tert*-butyl (*S*)-3-((4-(2-((5-(cyclopentanecarboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate, DCM (1.7 mL) and hydrochloric acid (4 M in dioxane, 0.430 mL, 1.71 mmol).The residue was purified *via* reverse-phase HPLC and lyophilized to yield 16 mg of **187**. LCMS (ESI): $[M+H]^+$ = 523.3; ^1H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 8.49 (d, J = 7.5 Hz, 1H), 8.41 (d, J = 5.1 Hz, 1H), 8.02 (dd, J = 4.8, 2.0 Hz, 1H), 7.89 (d, J = 8.6 Hz, 1H), 7.59 (d, J = 7.4 Hz, 1H), 7.50 (d, J = 8.7 Hz, 3H), 7.35 – 7.46 (m, 2H), 7.25 (dd, J = 7.5, 4.8 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 3.88 (s, 1H), 2.97 – 3.11 (m, 2H), 2.82 – 2.74 (d, J = 12.1 Hz, 1H), 2.35 – 2.46 (m, 2H), 2.22 (s, 3H), 1.88 - 2.02 (m, 3H), 1.36 – 1.87 (m, 9H).

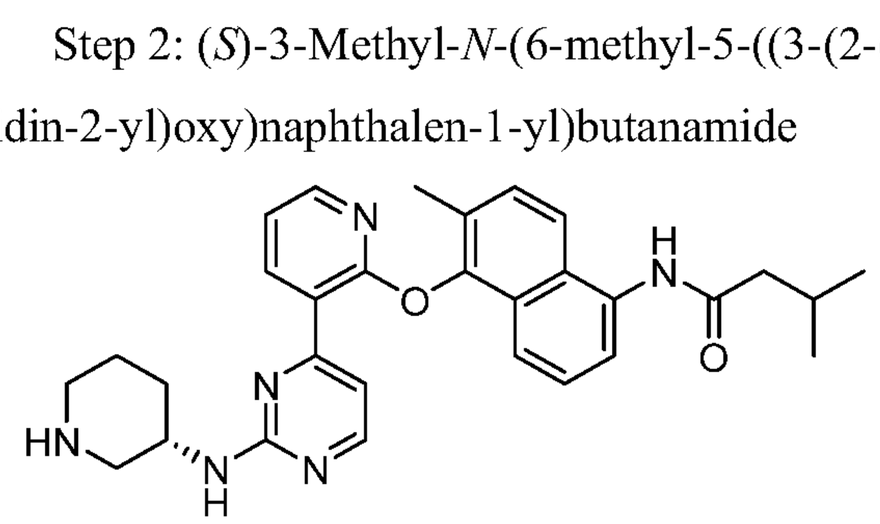
Example 188 *(S)-3-Methyl-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)butanamide* ***188***

[0581] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((5-isobutyramido-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate

[0582] The General Procedure C was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (90 mg, 0.17 mmol), 3-methylbutanoic acid (26 mg, 0.26 mmol), DIPEA (0.089 mL, 0.51 mmol), HATU (97 mg, 0.26 mmol) and DCM (1.7 mL). The crude was directly used in the next step.



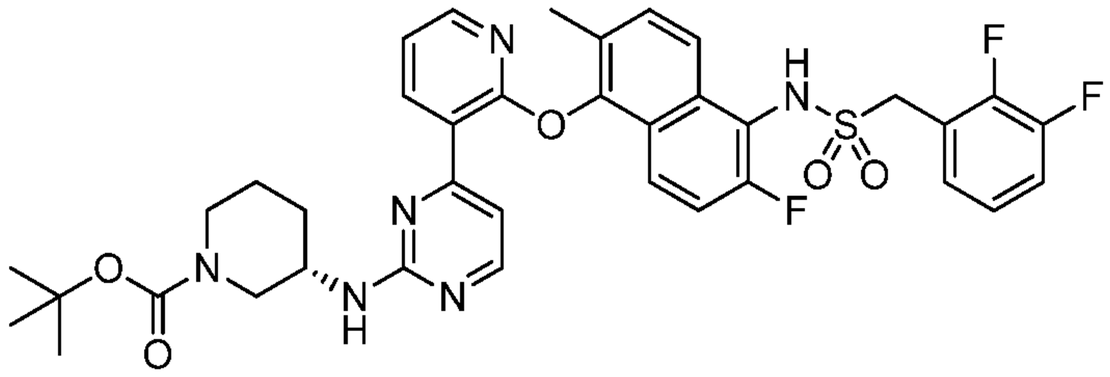
[0583] Step 2: (*S*)-3-Methyl-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)butanamide



[0584] The General Procedure B was followed, using crude (*S*)-3-Methyl-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)butanamide, DCM (1.7 mL) and hydrochloric acid (4 M in dioxane, 0.430 mL, 1.71 mmol). The residue was purified *via* reverse-phase HPLC and lyophilized to yield 11 mg of **188**. LCMS (ESI): $[M+H]^+$ = 511.2; ^1H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.49 (d, J = 7.6 Hz, 1H), 8.41 (d, J = 5.1 Hz, 1H), 8.02 (dd, J = 4.8, 2.0 Hz, 1H), 7.91 (d, J = 8.7 Hz, 1H), 7.60 (d, J = 7.3 Hz, 1H), 7.51 (d, J = 8.7 Hz, 2H), 7.46 – 7.39 (m, 2H), 7.25 (dd, J = 7.6, 4.8 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 3.88 (s, 1H), 3.13 – 3.05 (m, 1H), 2.82 – 2.74 (m, 1H), 2.47 – 2.30 (m, 4H), 2.22 (s, 3H), 2.19 – 2.10 (m, 1H), 1.96 – 1.88 (m, 1H), 1.68 – 1.60 (m, 1H), 1.54 – 1.37 (m, 2H), 1.02 (d, J = 6.6 Hz, 6H).

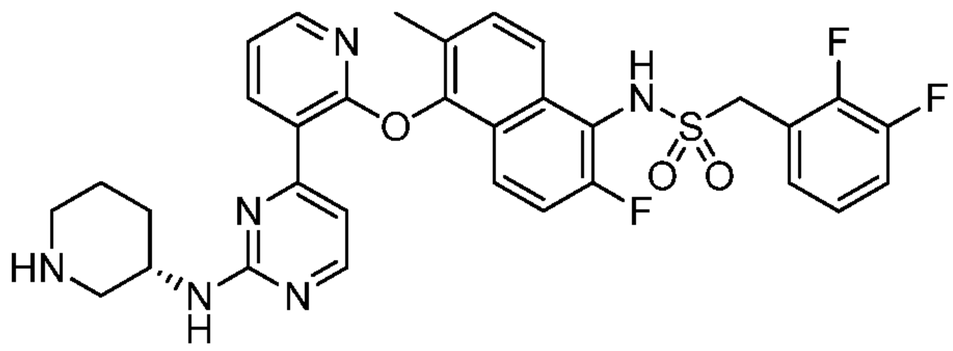
Example 189 *(S)-1-(2,3-Difluorophenyl)-N-(2-fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide* ***189***

[0585] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-((2,3-difluorophenyl)methylsulfonamido)-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0586] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 275 (50 mg, 0.092 mmol), pyridine (0.5 mL, 6.18 mmol), DCM (1 mL), and (2,3-difluorophenyl)methanesulfonyl chloride (52 mg, 0.23 mmol). After 16 h, the mixture was diluted DCM (50 mL), washed with saturated $NaHCO_3$(aq) (10mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude was purified by flash chromatography through silica gel (0 – 70% EtOAc/Hexanes) to provide 45 mg (67% yield) of the title compound. LCMS (ESI) $[M+H]^+$ = 735.3, rt = 1.99 min.

[0587] Step 2: (*S*)-1-(2,3-Difluorophenyl)-*N*-(2-fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide

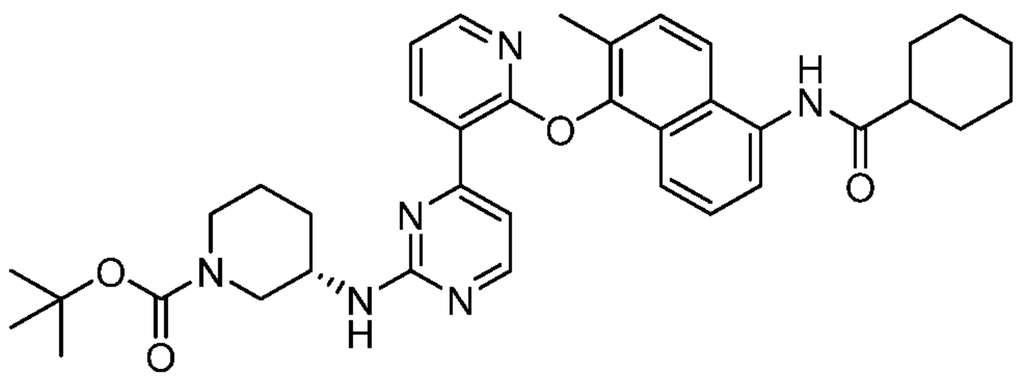


[0588] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-((2,3-difluorophenyl)methylsulfonamido)-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (45 mg, 0.061 mmol), EtOAc (1 mL), and hydrochloric acid (4 M in dioxane, 1 mL, 4 mmol). After 90 min, volatiles were removed *in vacuo* and the residue was washed with EtOAc (3 x 3 mL), then with MeCN (3 x 3 mL). The residue was then sonicated and concentrated *in vacuo* with MeCN (3 x 3 mL) and the resulting solid dissolved in water and MeCN and lyophilized to provide 26 mg (63% yield) of **189** as a white solid. LCMS (ESI) $[M+H]^+$ = 635.2, rt = 1.51 min; 1H NMR (400 MHz, d6-dmso) δ 10.04 (s, 1H), 8.95 – 8.72 (m, 2H), 8.69 – 8.53 (m, 1H), 8.47 (d, J = 7.0 Hz, 1H), 8.09 (dd, J = 4.8, 1.8 Hz, 1H), 8.01 (d, J = 8.7 Hz, 1H), 7.74 (dd, J = 9.3, 5.1 Hz, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.59 – 7.43 (m, 4H), 7.40

– 7.20 (m, 3H), 4.70 (s, 2H), 4.34 – 4.18 (m, 1H), 3.44 (d, J = 10.1 Hz, 1H), 3.21 (d, J = 12.0 Hz, 1H), 2.96 – 2.78 (m, 2H), 2.19 (s, 3H), 2.07 – 1.87 (m, 2H), 1.81 – 1.54 (m, 2H).

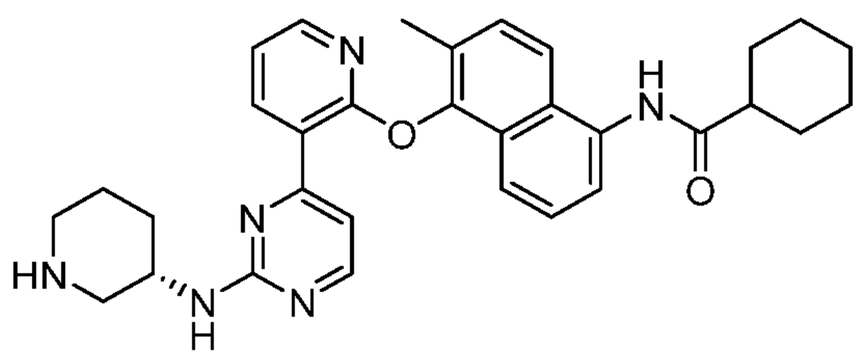
Example 190 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclohexanecarboxamide* ***190***

[0589] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((5-(cyclohexanecarboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0590] The General Procedure C was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (90 mg, 0.17 mmol), cyclopentanecarboxylic acid (mg, 0.26 mmol), DIPEA (0.089 mL, 0.51 mmol), HATU (97 mg, 0.26 mmol) and DCM (1.7 mL). The crude was directly used in the next step.

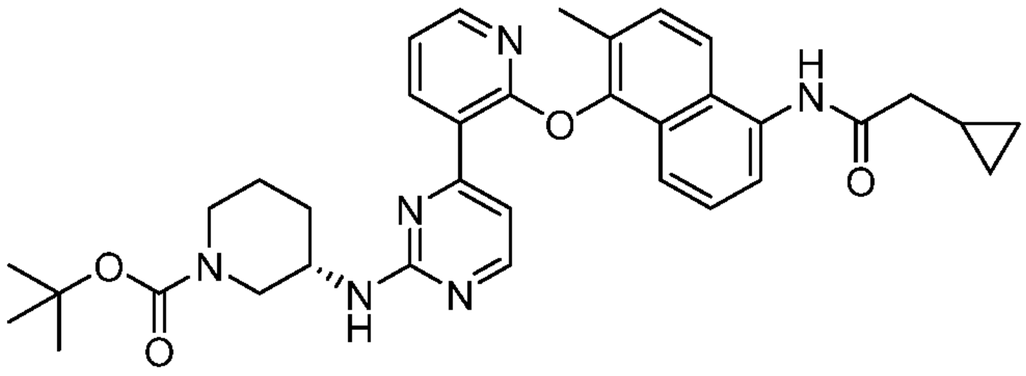
[0591] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclohexanecarboxamide



[0592] The General Procedure B was followed, using crude *tert*-butyl (*S*)-3-((4-(2-((5-(cyclohexanecarboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate, DCM (1.7 mL) and hydrochloric acid (4 M in dioxane, 0.430 mL, 1.71 mmol).The residue was purified *via* reverse-phase HPLC and lyophilized to yield 22 mg of **190**. LCMS (ESI): $[M+H]^+$ = 537.3; ^{1}H NMR (400 MHz, DMSO-d6) δ 9.80 (s, 1H), 8.49 (d, J = 7.6 Hz, 1H), 8.41 (d, J = 5.0 Hz, 1H), 8.02 (dd, J = 4.8, 2.0 Hz, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.58 (d, J = 7.4 Hz, 1H), 7.50 (dd, J = 8.7, 4.3 Hz, 2H), 7.43 (d, J = 5.1 Hz, 1H), 7.39 (dd, J = 8.5, 7.3 Hz, 1H), 7.25 (dd, J = 7.5, 4.8 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 3.88 (s, 1H), 3.08 (d, J = 11.6 Hz, 1H), 2.82 – 2.75 (m, 1H), 2.47 – 2.38 (m, 2H), 2.21 (s, 3H), 1.99 - 1.89 (m, 3H), 1.84 – 1.76 (m, 1H), 1.73 – 1.60 (m, 2H), 1.54 – 1.18 (m, 7H).

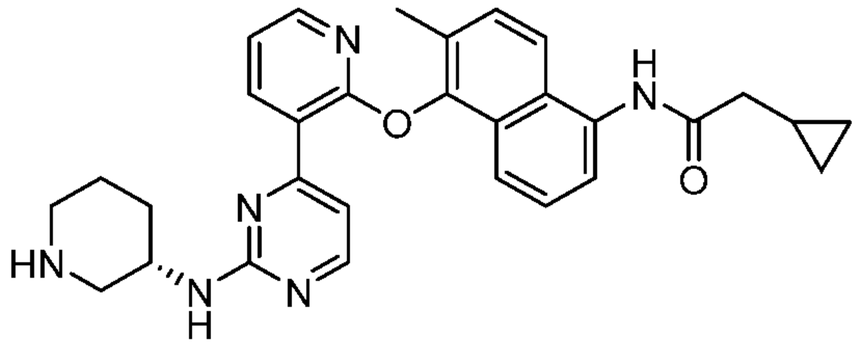
Example 191 *(S)-2-Cyclopropyl-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)acetamide* ***191***

[0593] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((5-(2-cyclopropylacetamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0594] The General Procedure C was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (90 mg, 0.17 mmol), 2-cyclopropyl acetic acid (26 mg, 0.26 mmol), DIPEA (0.089 mL, 0.51 mmol), HATU (97 mg, 0.26 mmol) and DCM (1.7 mL). The crude was directly used in the next step.

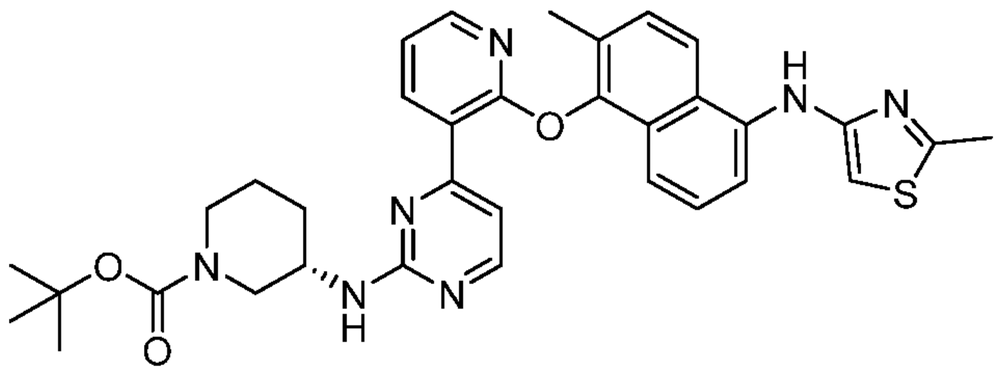
[0595] Step 2: (*S*)-2-Cyclopropyl-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)acetamide



[0596] The General Procedure B was followed, using, DCM (1.7 mL) and hydrochloric acid (4 M in dioxane, 0.430 mL, 1.71 mmol).The residue was purified via reverse-phase HPLC and lyophilized to yield 15 mg of **191**. LCMS (ESI): $[M+H]^+$ = 509.2; ^{1}H NMR (400 MHz, DMSO-d6) δ 9.82 (s, 1H), 8.49 (d, J = 7.5 Hz, 1H), 8.41 (d, J = 5.1 Hz, 1H), 8.03 (dd, J = 4.8, 2.0 Hz, 1H), 7.92 (d, J = 8.7 Hz, 1H), 7.63 (d, J = 7.4 Hz, 1H), 7.51 (d, J = 8.8 Hz, 2H), 7.48 – 7.36 (m, 2H), 7.25 (dd, J = 7.6, 4.8 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 3.89 (s, 1H), 3.13 – 3.06 (m, 1H), 2.82 – 2.76 (m, 1H), 2.45 – 2.32 (m, 3H), 2.22 (s, 3H), 1.96 – 1.89 (m, 1H), 1.67 – 1.60 (m 1H), 1.59 – 1.37 (m, 2H), 1.20 – 1.10 (m, 1H), 0.57 – 0.52 (m, 2H), 0.32 – 0.26 (m, 2H).

Example 192 *(S)-2-Methyl-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)thiazol-4-amine* ***192***

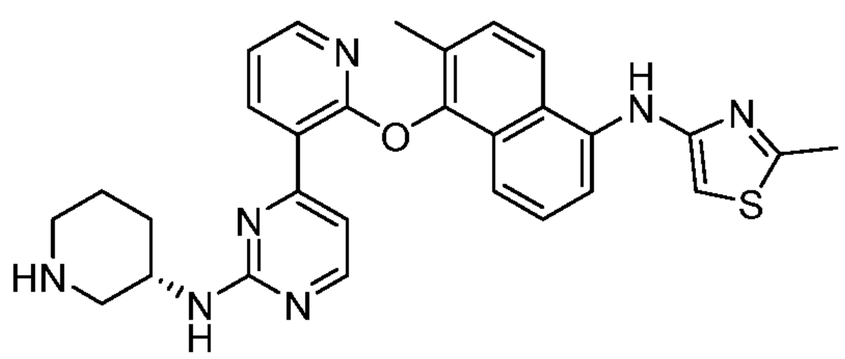
[0597] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-((2-methylthiazol-4-yl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0598] A mixture of *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol), 4-bromo-2-methylthiazole (53.4 mg, 0.28 mmol), Brettphos Pd G3 (18.1 mg, 0.019 mmol), Brettphos (16.10 mg, 0.028 mmol), and sodium tert-butoxide (28.2 mg, 0.28 mmol) in 1,4-dioxane (1.5 mL) was capped in a microwave vial, degassed with N_2, and heated in a microwave reactor at 120 °C for 45 min. Additional 4-bromo-2-methylthiazole (53.4 mg), Brettphos Pd G3 (18 mg), Brettphos (16.0 mg), and sodium tert-butoxide (28.2 mg) were added followed by heating at 120 °C for 45 min. Additional Brettphos Pd G3 (18 mg) and Brettphos (16.0 mg) were added followed by additional heating at 120 °C for 45 min.

[0599] The mixture was diluted with iPrOAc (10 mL), filtered through Celite® (Johns Manville). The crude material was purified by chromatography (silica gel chromatography), 24 g column, eluting with 0-5% MeOH/DCM to afford 22 mg (18.6% yield) of the title compound as a brown solid. LCMS (ESI) $[M+H]^+ = 624$.

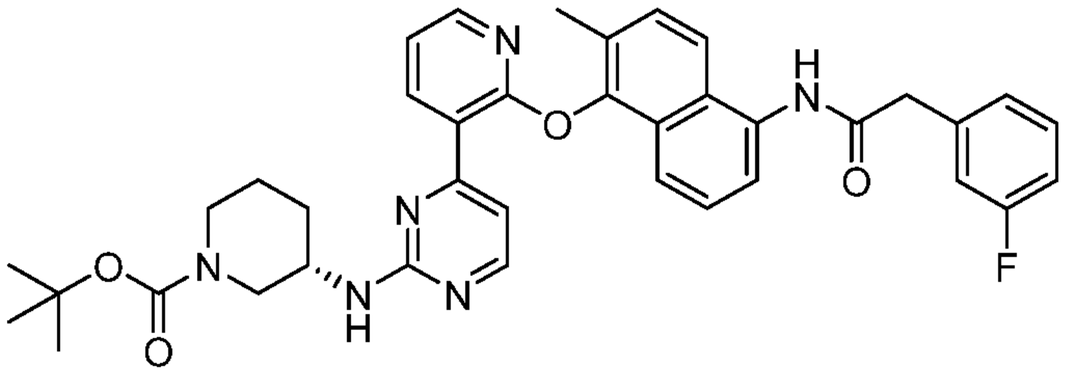
[0600] Step 2: (*S*)-2-Methyl-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)thiazol-4-amine



[0601] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-((2-methylthiazol-4-yl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (22 mg, 0.03 mmol). The crude product was purified *via* reverse-phase HPLC and lyophilized to yield 6.7 mg (18.5% yield) of **192** as an off-white solid. LCMS (ESI) $[M+H]^+ = 524$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.49 (s, 1H), 8.41 (d, J = 5.1 Hz, 1H), 8.13 (d, J = 8.7 Hz, 1H), 8.03 (dd, J = 4.8, 1.9 Hz, 1H), 7.48 – 7.40 (m, 2H), 7.37 – 7.32 (m, 1H), 7.31 – 7.22 (m, 2H), 7.18 (d, J = 8.3 Hz, 1H), 7.15 – 7.08 (m, 1H), 3.90 (s, 1H), 3.10 (s, 1H), 2.81 (d, J = 12.0 Hz, 1H), 2.64 (s, 3H), 2.45 (s, 1H), 2.21 (s, 3H), 1.97 – 1.90 (m, 1H), 1.69 – 1.63 (m, 1H), 1.55 – 1.40 (m, 2H).

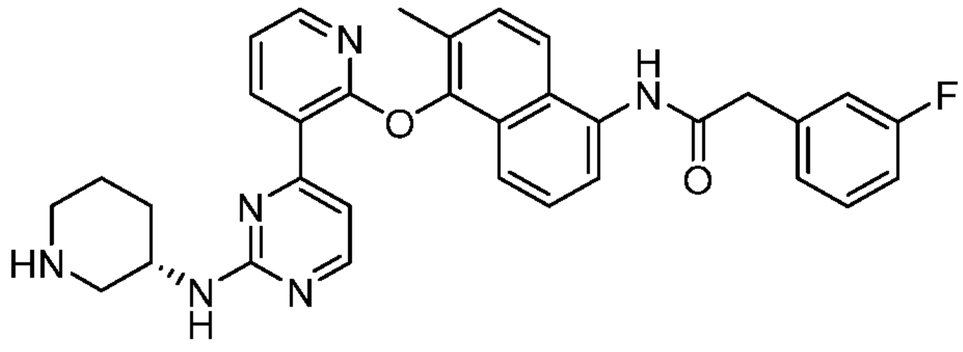
Example 193 *(S)-2-(3-Fluorophenyl)-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)acetamide* ***193***

[0602] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((5-(2-(3-fluorophenyl)acetamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0603] The General Procedure C was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (90 mg, 0.17 mmol), 2-(3-fluorophenyl)acetic acid (39.5 mg, 0.26 mmol), DIPEA (0.089 mL, 0.51 mmol), HATU (97 mg, 0.26 mmol) and DCM (1.7 mL). The crude was directly used in the next step.

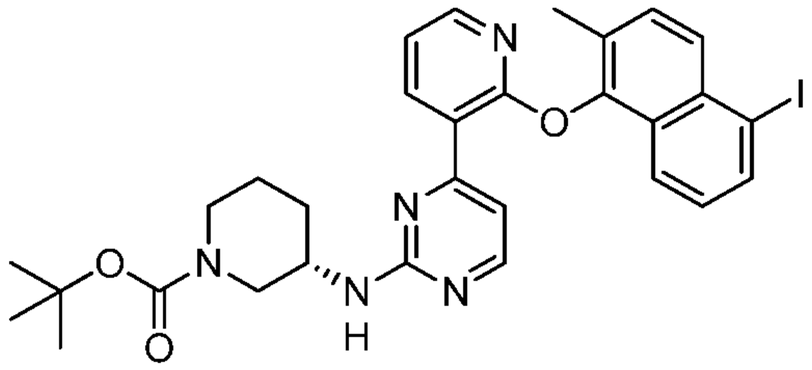
[0604] Step 2: (*S*)-2-(3-Fluorophenyl)-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)acetamide



[0605] The General Procedure B was followed, using crude *tert*-butyl (*S*)-3-((4-(2-((5-(2-(3-fluorophenyl)acetamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate, DCM (1.7 mL) and hydrochloric acid (4 M in dioxane, 0.430 mL, 1.71 mmol).The residue was purified *via* reverse-phase HPLC and lyophilized to yield 6 mg of **193**. LCMS (ESI): $[M+H]^+$ = 563.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.49 (d, J = 7.5 Hz, 1H), 8.40 (d, J = 5.1 Hz, 1H), 8.02 (dd, J = 4.8, 2.0 Hz, 1H), 7.91 (d, J = 8.6 Hz, 0H), 7.62 (d, J = 7.3 Hz, 1H), 7.55 – 7.50 (m, 2H), 7.46 – 7.35 (m, 3H), 7.30 – 7.21 (m, 3H), 7.14 – 7.08 (m, 2H), 3.87 (s, 3H), 3.12 – 3.05 (d, J = 11.9 Hz, 1H), 2.81 – 2.74 (m, 1H), 2.46 – 2.37 (m, 1H), 2.22 (s, 3H), 1.96 – 1.88 (m, 1H), 1.67 – 1.58 (m, 1H), 1.55 – 1.35 (m, 2H).

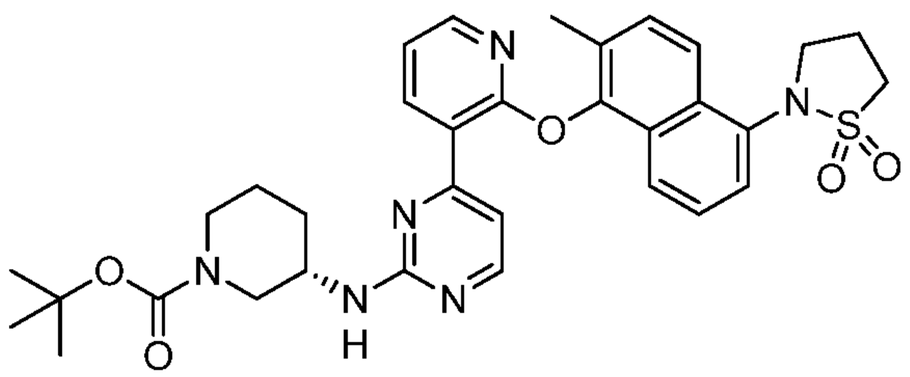
Example 194 *(S)-tert-Butyl 3-((4-(2-((5-(1,1-dioxidoisothiazolidin-2-yl)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate* ***194***

[0606] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-iodo-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0607] To a solution of *tert*-butyl (3S)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (4 g, 7.6 mmol) in acetonitrile (200 mL) was added 4-methylbenzenesulfonic acid hydrate (4.3 g, 22.8 mmol) and the mixure was cooled to 0 °C. Then a solution of potassium iodide (3.2 g, 19 mmol) and sodium nitrite (1.05 g, 15.2 mmol) in H_2O (60 mL) was added followed by stirring at 20 °C for 2 h. To the reaction mixture was then added H_2O (150 mL), sodium bicarbonate (1 M; until pH = 9 ~ 10) and sodium thiosulfate (2 M, 120 mL). The precipitated was filtered off and the filtrate was extracted with ethyl acetate (30 mL). The organic extract was dried over anhydrous sodium sulfate and purified by silica gel chromatography (50% ethyl acetate in petroleum ether, Rf = 0.6) to yield 1.5 g (31% yield) of the title compound as a white solid; LCMS (ESI) $[M+H]^+$ = 638.0.

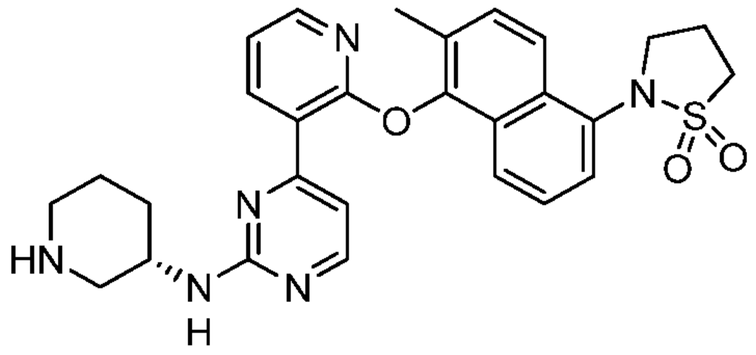
[0608] Step 2: (*S*)-*tert*-Butyl 3-((4-(2-((5-(1,1-dioxidoisothiazolidin-2-yl)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0609] To a solution of *tert*-butyl (3*S*)-3-[[4-[2-[(5-iodo-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (110 mg, 0.17 mmol) in CH_3CN (2 mL) was added 1,3-propanesultam (209.1 mg, 1.73 mmol), copper iodide (1.6 mg, 0.01 mmol), *N*,*N*'-dimethyl-1,2-ethanediamine (7.6 mg, 0.09 mmol) and potassium carbonate (47.8 mg, 0.34 mmol). The mixture was purged with N_2 and stirred at 80 °C for 88 h. After cooling down, the mixture was filtered, concentrated, dissolved in ethyl acetate (60 mL) and washed with H_2O (50 mL x 2). The organic phase was dried over anhydrous sodium sulfate and

concentrated and the residue was purified by Prep-TLC (50% ethyl acetate in petroleum ether, Rf = 0.1) to yield 55 mg (51%) of the title compound as a brown oil. LCMS (ESI) $[M+H]^+$ = 631.0.

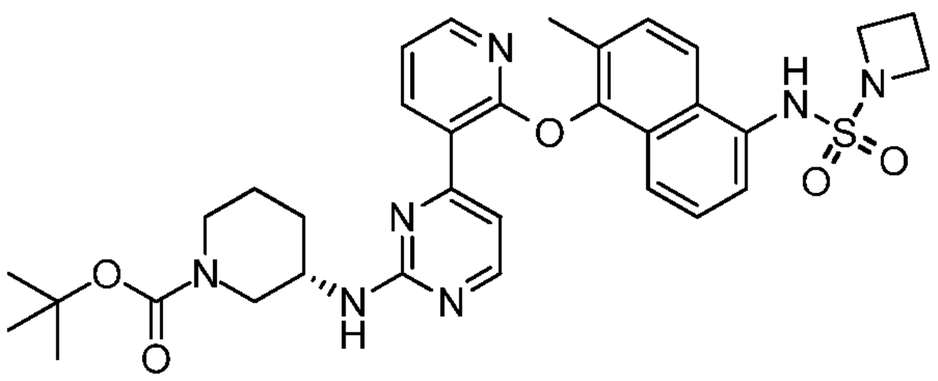
[0610] Step 3: (*S*)-2-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)isothiazolidine 1,1-dioxide



[0611] The General Procedure B was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[[5-(1,1-dioxo-1,2-thiazolidin-2-yl)-2-methyl-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (110 mg, 0.17 mmol), ethyl acetate (0.5 mL) and hydrochloric acid (4 M in ethyl acetate, 0.4 mL,1.6 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05%HCl); B: ACN) to yield 20 mg (21% yield) of **194** as a white solid. LCMS (ESI): $[M+H]^+$ = 531.3; ^{1}H NMR (400 MHz, DMSO-*d*6) δ 8.50 (s, 1H), 8.41 (d, *J* = 5.2 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 8.06 - 8.04 (m, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.62 - 7.59 (m, 1H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.53 - 7.48 (m, 1H), 7.45 (d, *J* = 5.6 Hz, 1H), 7.28 - 7.25 (m, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 4.02 - 3.87 (m, 1H), 3.81 (t, *J* = 6.4 Hz, 2H), 3.56 (t, *J* = 7.2 Hz, 2H), 3.18 - 3.08 (m, 1H), 2.88 - 2.78 (m, 1H), 2.57 - 2.54 (m, 1H), 2.53 - 2.52 (m, 1H), 2.48 - 2.45 (m, 2H), 2.22 (s, 3H), 1.98 - 1.90 (m, 1H), 1.71 - 1.63 (m, 1H), 1.57 - 1.40 (m, 2H).

Example 195 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)azetidine-1-sulfonamide* ***195***

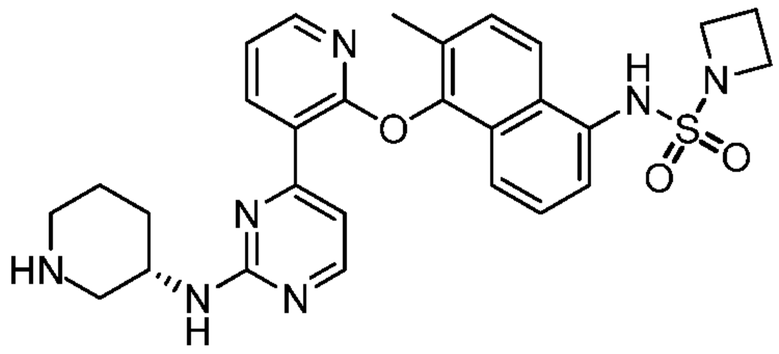
[0612] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-(azetidine-1-sulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0613] The General Procedure A was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol), pyridine (2 mL) and azetidine-1-sulfonyl chloride (38 mg, 0.25 mmol). The

residue was purified by Prep-TLC (normal phase, petroleum ether/ethyl acetate = 2 / 1) to yield 60 mg (49% yield) of the title compound as a brown oil. LCMS (ESI) $[M+H]^+$ = 646.1.

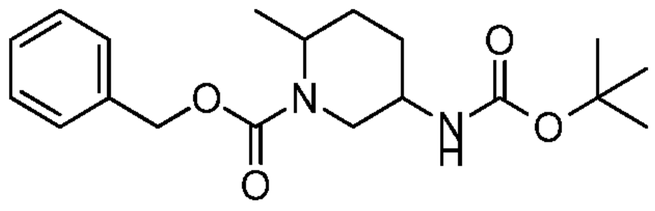
[0614] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)azetidine-1-sulfonamide



[0615] The General Procedure B was followed, using *tert*-butyl (3S)-3-[[4-[2-[[5-(azetidin-1-ylsulfonylamino)-2-methyl-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (40 mg, 0.06 mmol), dichloromethane (1 mL) and 2,2,2-trifluoroacetic acid (0.1 mL, 1.34 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% NH_4OH) B: ACN) to yield 16 mg (46% yield) of **195** as a yellow solid. LCMS (ESI): $[M+H]^+$ = 546.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (s, 1H), 8.43-8.39 (m, 1H), 8.15 (m, 1H), 8.05 - 8.00 (m, 1H), 7.48 - 7.43 (m, 2H), 7.37 - 7.28 (m, 2H), 7.27 -7.22 (m, 1H), 7.21 - 7.17 (m, 1H), 3.97 - 3.91 (m, 1H), 3.80 - 3.69 (m, 4H), 3.17 (s, 2H), 2.89 - 2.87 (m, 1H), 2.56 - 2.55 (m, 1H), 2.44 - 2.40 (m, 1H), 2.19 (s, 3H), 2.15 - 2.02 (m, 2H), 1.96 - 1.90 (m, 1H), 1.70 - 1.65 (m, 1H), 1.54 - 1.45 (m, 2H).

Example 196 *N-(6-Methyl-5-((3-(2-(((3S, 6S)-6-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide* ***196***

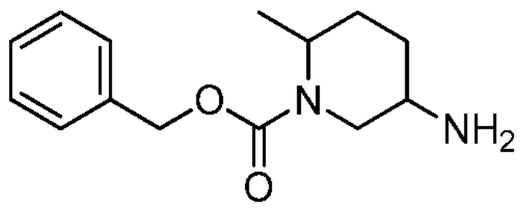
[0616] Step 1: Benzyl 5-((*tert*-butoxycarbonyl)amino)-2-methylpiperidine-1-carboxylate



[0617] To a 100 mL 3-necked round-bottom flask was placed benzyl chloroformate (0.8mL, 5.6mmol), sodium bicarbonate (392 mg, 4.67 mmol), *tert*-butyl *N*-(6-methyl-3-piperidyl)carbamate (1.0 g, 4.67 mmol) and tetrahydrofuran (5 mL). The resulting solution was stirred at rt for 4 h. The reaction mixture was then cooled to room temperature and concentrated *in vacuo*. The residue was purified chromatography on silica (solvent gradient: 0-20% ethyl acetate in petroleum ether) to yield 1.1 g (68% yield) of the title compound as a colorless oil. ^{1}H-NMR: (400 MHz, DMSO-d_6) δ 7.36 - 7.33 (m, 4H), 6.86 (d, J = 7.2 Hz, 1H),

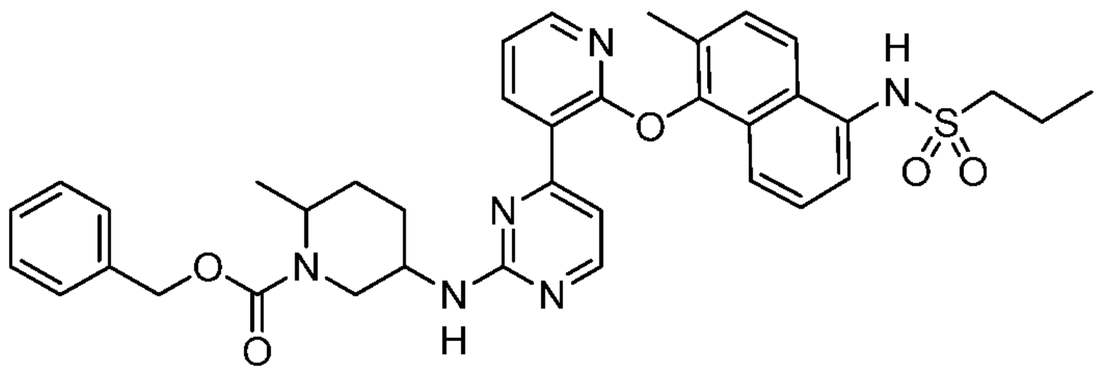
5.07 (s, 2H), 4.29 (s, 1H), 3.93 (d, *J* = 13.2 Hz, 1H), 3.20 (s, 1H), 2.57 (s, 1H), 1.63 - 1.49 (m, 4H), 1.38 (s, 9H), 1.07 (d, *J* = 7.2 Hz, 3H)

[0618] Step 2: Benzyl 5-amino-2-methylpiperidine-1-carboxylate



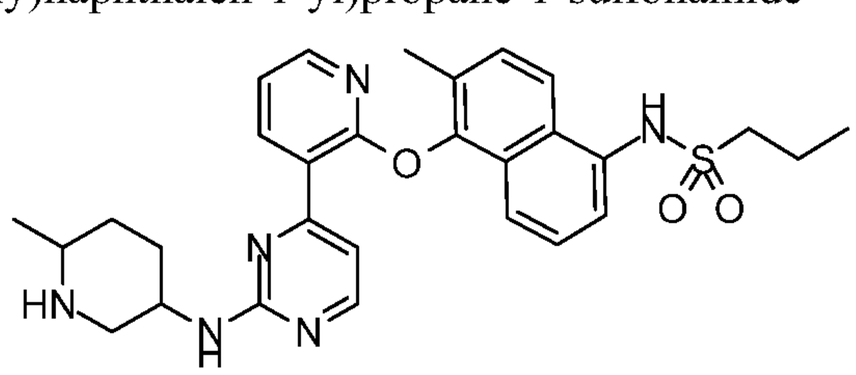
[0619] The General Procedure B was followed, using benzyl 5-((*tert*-butoxycarbonyl)amino)-2-methylpiperidine-1-carboxylate (1.0 g, 2.87 mmol), dichloromethane (5 mL) and hydrochloric acid (4 M in dioxane, 20 mL, 80 mmol). The organic phase was dried over anhydrous sodium sulfate, concentrated to yield 610 mg of the title crude product as a white solid.

[0620] Step 3: Benzyl 2-methyl-5-((4-(2-((2-methyl-5-(propylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0621] To a 100 mL 3-necked round-bottom flask was placed *N*-[6-methyl-5-[[3-(2-methylsulfinylpyrimidin-4-yl)-2-pyridyl]oxy]-1-naphthyl]propane-1-sulfonamide (0.8 g, 1.61 mmol), *N*,*N*-diisopropylethylamine (0.84 mL, 4.83mmol), benzyl 5-amino-2-methyl-piperidine-1-carboxylate (400.0 mg, 1.61 mmol) and 1,4-dioxane (10 mL). The resulting solution was stirred at 130 °C for 36 h. The solution was concentrated and purified by flash chromatography on silica gel eluting with 0-10% methanol/ dichloromethane to yield 0.7 g (61% yield) of the title compound as a brown solid. LCMS (ESI) $[M+H]^+$ = 681.1.

[0622] Step 4: *N*-(6-Methyl-5-((3-(2-((6-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide



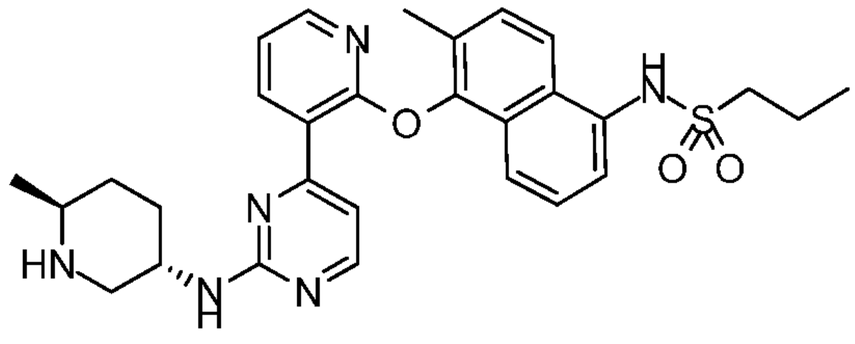
[0623] A solution of benzyl 2-methyl-5-[[4-[2-[[2-methyl-5-(propylsulfonylamino)-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (600 mg, 0.88 mmol),

10% wet palladium (47 mg, 0.040 mmol) on carbon in methanol (20 mL) at 30 °C was exposed to a hydrogen atmosphere (15 Psi). The reaction was sitrred at 30 °C for 14 h. Then the mixture was filtered and concentrated and the residue was purified by Prep-HPLC (mobile phase: A: water (0.05% NH_4OH) B: ACN) to give

[0624] Peak 1: *cis* isomer mixture, *N*-[6-Methyl-5-[[3-[2-[(6-methyl-3-piperidyl)amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]propane-1-sulfonamide (80 mg, 17% yield) (peak 1 on HPLC). LCMS (ESI) $[M+H]^+$ = 547.1; ^1H NMR (400 MHz, DMSO-d_6) δ 8.50 (s, 1H), 8.40 (d, J = 4.8 Hz, 1H), 8.14 (d, J = 8.8 Hz, 1H), 8.05-8.00 (m, 1H), 7.50 (d, J = 8.8 Hz, 2H), 7.46 - 7.35 (m, 3H), 7.29 - 7.23 (m, 1H), 7.16 (d, J = 7.2 Hz, 1H), 3.87 (s, 1H), 3.24 (s, 1H), 3.11 - 3.04 (m, 2H), 2.56 - 2.54 (m, 1H), 2.44 (s, 1H), 2.20 (s, 3H), 1.97 (d, J = 10.8 Hz, 1H), 1.79 - 1.72 (m, 2H), 1.68 (d, J = 12.4 Hz, 1H), 1.47 - 1.41 (m, 1H), 1.21 - 1.14 (m, 1H), 1.02 (d, J = 6.4 Hz, 3H), 0.96 (t, J = 7.6 Hz, 3H).

[0625] Peak 2: *trans* isomer mixture, *N*-[6-methyl-5-[[3-[2-[(6-methyl-3-piperidyl)amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]propane-1-sulfonamide (40 mg, 8% yield) (peak 2 on HPLC), obtained as a white solid. LCMS (ESI) $[M+H]^+$ = 547.1; ^1H NMR (400 MHz, DMSO-d_6) δ 8.54 - 8.47 (m, 1H), 8.43 (d, J = 5.2 Hz, 1H), 8.14 (d, J = 8.8 Hz, 1H), 8.03 (d, J = 3.2 Hz, 1H), 7.50 (d, J = 8.6 Hz, 1H), 7.47 (d, J = 5.0 Hz, 1H), 7.43 - 7.34 (m, 2H), 7.26 - 7.20 (m, 1H), 6.98 (d, J = 7.6 Hz, 1H), 4.04 (s, 1H), 3.11 - 3.05 (m, 2H), 3.01 (d, J = 12.4 Hz, 1H), 2.85 (d, J = 10.8 Hz, 1H), 2.67 (s, 1H), 2.20 (s, 3H), 1.92 (s, 1H), 1.78 - 1.68 (m, 2H), 1.63 (t, J = 12.4 Hz, 1H), 1.50 - 1.42 (m, 1H), 1.37 (d, J = 12.8 Hz, 1H), 1.04 (d, J = 6.4 Hz, 3H), 0.96 (t, J = 7.2 Hz, 3H).

[0626] Step 5: *N*-(6-methyl-5-((3-(2-(((3*S*, 6*S*)-6-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide

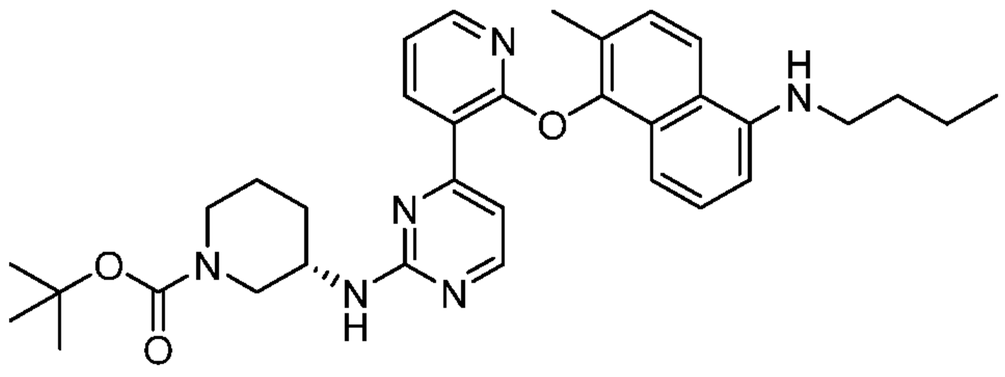


[0627] *N*-[6-methyl-5-[[3-[2-[(6-methyl-3-piperidyl)amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]propane-1-sulfonamide (40 mg, 0.070 mmol) was purified by SFC (AD (250 mm x 30 mm, 5 μm); Base-EtOH: 40%; (flow rate 60 mL / min) to give **196** (10 mg, 24.5% yield) (second peak on SFC, Rt = 6.64 min) as a white solid. The absolute stereochemistry inferred based on the activity in the XBP1 reporter potency. LCMS (ESI) $[M+H]^+$ = 547.1; ^1H NMR (400 MHz, DMSO-d_6) δ 8.54 - 8.47 (m, 1H), 8.43 (d, J = 5.2 Hz, 1H), 8.14 (d, J = 8.8 Hz, 1H),

8.03 (d, *J* = 3.2 Hz, 1H), 7.50 (d, *J* = 8.6 Hz, 1H), 7.47 (d, *J* = 5.0 Hz, 1H), 7.43 - 7.34 (m, 2H), 7.26 - 7.20 (m, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 4.04 (s, 1H), 3.11 - 3.05 (m, 2H), 3.01 (d, *J* = 12.4 Hz, 1H), 2.85 (d, *J* = 10.8 Hz, 1H), 2.67 (s, 1H), 2.20 (s, 3H), 1.92 (s, 1H), 1.78 - 1.68 (m, 2H), 1.63 (t, *J* = 12.4 Hz, 1H), 1.50 - 1.42 (m, 1H), 1.37 (d, *J* = 12.8 Hz, 1H), 1.04 (d, *J* = 6.4 Hz, 3H), 0.96 (t, *J* = 7.2 Hz, 3H).

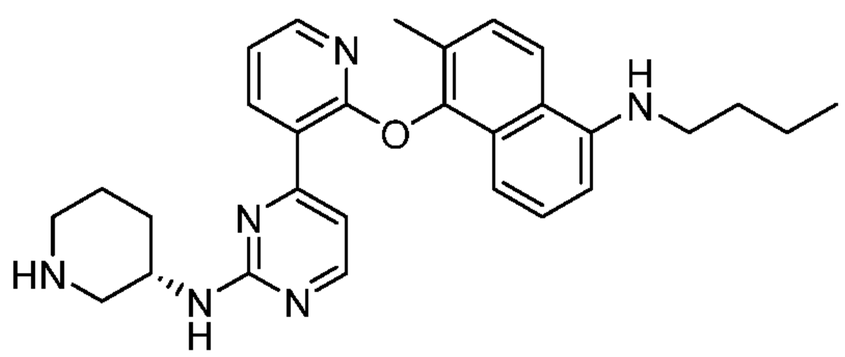
Example 197 *(S)-4-(2-((5-(Butylamino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine* ***197***

[0628] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((5-(butylamino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0629] The General Procedure E was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol) and DIPEA (0.083 mL, 0.48 mmol) in DMF (1 mL), together with, 1-bromobutane (0.031 mL, 0.29 mmol). The reaction mixture was purified by silica gel chromatography (12 g column), eluting with 0-5% MeOH/DCM to afford 67 mg (60% yield) of the title compound as a brown solid. LCMS (ESI) $[M+H]^+$ = 583.

[0630] Step 2: (*S*)-4-(2-((5-(Butylamino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-2-amine

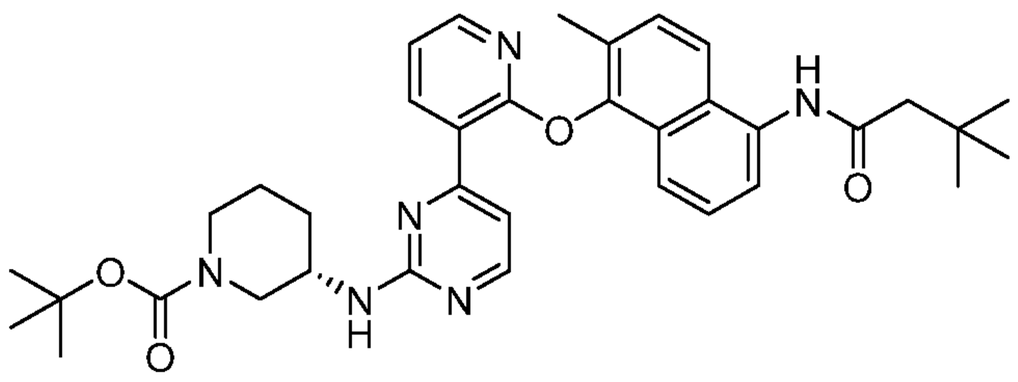


[0631] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-(butylamino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (67 mg, 0.11 mmol). The crude product was purified *via* reverse-phase HPLC and lyophilized to yield 9.3 mg (17% yield) of **197** as a light brown solid. LCMS (ESI) $[M+H]^+$ = 524; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (s, 1H), 8.40 (d, *J* = 5.1 Hz, 1H), 8.03 – 7.99 (m, 2H), 7.45 (d, *J* = 5.2 Hz, 1H), 7.32 (d, *J* = 8.7 Hz, 1H), 7.23 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.16 (t, *J* = 8.2 Hz, 2H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.42 (dd, *J* = 7.7, 0.9 Hz, 1H), 6.15 (t, *J* = 5.3 Hz, 1H),

3.93 (s, 1H), 3.23 – 3.18 (m, 1H), 3.14 (d, *J* = 13.8 Hz, 3H), 2.84 (d, *J* = 12.3 Hz, 1H), 2.18 (s, 3H), 1.98 – 1.89 (m, 1H), 1.72 – 1.63 (m, 3H), 1.54 – 1.38 (m, 4H), 0.95 (t, *J* = 7.4 Hz, 3H).

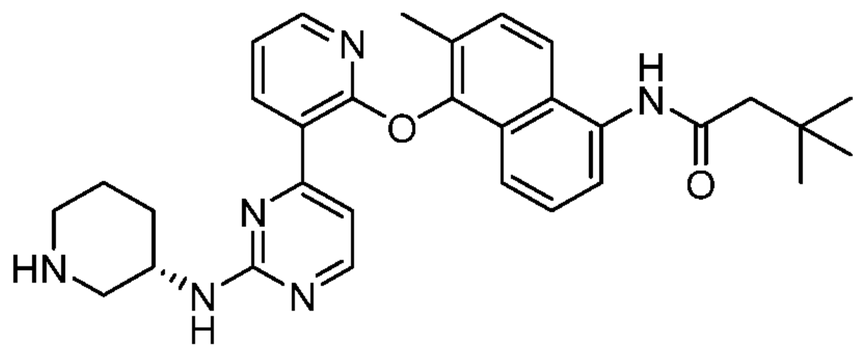
Example 198 *(S)-3,3-Dimethyl-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)butanamide* ***198***

[0632] Step 1: *tert*-Butyl (S)-3-((4-(2-((5-(3,3-dimethylbutanamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0633] The General Procedure C was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (90 mg, 0.17 mmol), 3,3-dimethylbutanoic acid (30 mg, 0.26 mmol), DIPEA (0.089 mL, 0.51 mmol), HATU (97 mg, 0.26 mmol) and DCM (1.7 mL). The crude was directly used in the next step.

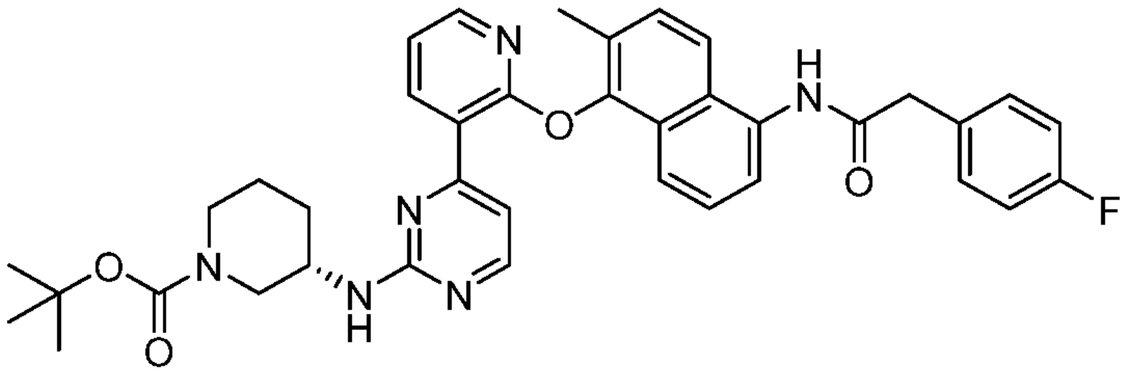
[0634] Step 2: (*S*)-3,3-Dimethyl-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)butanamide



[0635] The General Procedure B was followed, using crude *tert*-butyl (*S*)-3-((4-(2-((5-(3,3-dimethylbutanamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate, DCM (1.7 mL) and hydrochloric acid (4 M in dioxane, 0.430 mL, 1.71 mmol).The residue was purified *via* reverse-phase HPLC and lyophilized to yield 27 mg of **198**. LCMS (ESI): $[M+H]^+$ = 525.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.83 (s, 1H), 8.54 (s, 1H), 8.47 (d, J = 5.2 Hz, 1H), 8.04 (dd, J = 4.8, 2.0 Hz, 1H), 7.95 – 7.91 (m, 1H), 7.62 (d, J = 7.2, 1H), 7.58 – 7.36 (m, 5H), 7.27 (dd, J = 7.6, 4.8 Hz, 1H), 4.18 (s, 1H), 3.44 – 3.36 (m, 2H), 3.20 – 3.12 (m, 1H), 2.86 – 2.74 (m, 2H), 2.38 (s, 2H), 2.22 (s, 3H), 2.03 – 1.97 (m, 1H), 1.93 – 1.84 (m, 1H), 1.73 – 1.56 (m, 2H), 1.10 (s, 9H).

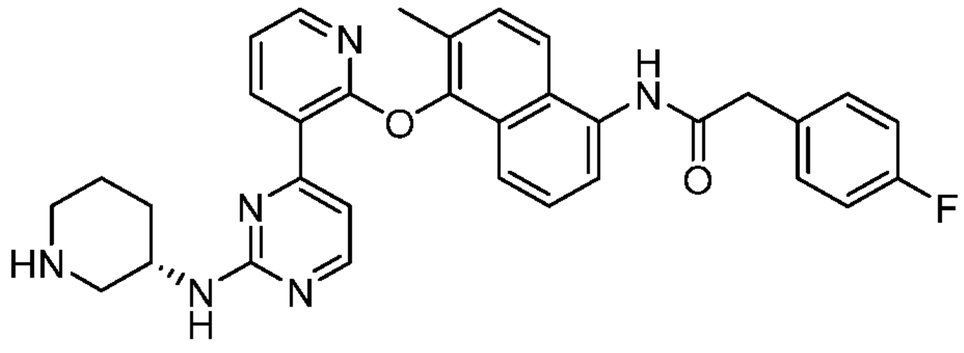
Example 199 *(S)-2-(4-Fluorophenyl)-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)acetamide* ***199***

[0636] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((5-(2-(4-fluorophenyl)acetamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0637] The General Procedure C was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (90 mg, 0.17 mmol), 2-(4-fluorophenyl)acetic acid (39.5 mg), DIPEA (0.302 mL, 1.72 mmol), HATU (97 mg, 0.26 mmol) and DCM (1.7 mL). The crude was directly used in the next step.

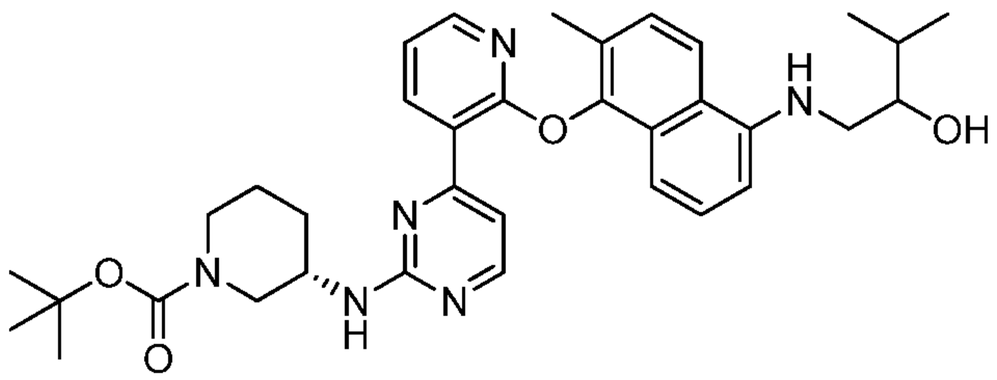
[0638] Step 2: (*S*)-2-(4-Fluorophenyl)-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)acetamide



[0639] The General Procedure B was followed, using crude (*S*)-2-(4-fluorophenyl)-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)acetamide, DCM (1.7 mL) and hydrochloric acid (4 M in dioxane, 0.430 mL, 1.71 mmol). The residue was purified *via* reverse-phase HPLC and lyophilized to yield 7 mg of **199**. LCMS (ESI): $[M+H]^+$ = 563.2;^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.20 (s, 1H), 8.49 (d, J = 7.5 Hz, 1H), 8.40 (d, J = 5.1 Hz, 1H), 8.02 (dd, J = 4.8, 2.0 Hz, 1H), 7.91 (d, J = 8.6 Hz, 1H), 7.62 (d, J = 7.3 Hz, 1H), 7.57 – 7.43 (m, 2H), 7.48 – 7.37 (m, 3H), 7.31 – 7.21 (m, 3H), 7.14 – 7.07 (m, 2H), 3.87 (s, 3H), 3.13 – 3.05 (m, 1H), 2.82 – 2.74 (m, 1H), 2.46 – 2.38 (m, 3H), 2.22 (s, 3H), 1.96 – 1.88 (m, 1H), 1.67 – 1.60 (m, 1H), 1.52 – 1.36 (m, 2H).

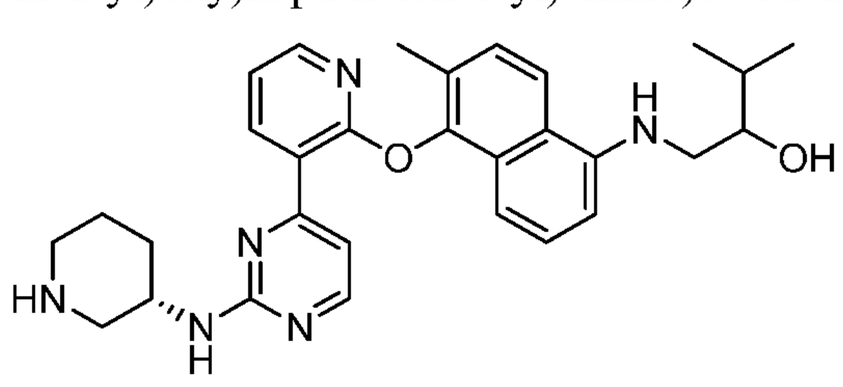
Example 200 *3-Methyl-1-((6-methyl-5-((3-(2-((S)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)butan-2-ol* ***200***

[0640] Step 1: (3*S*)-*tert*-Butyl 3-((4-(2-((5-((2-hydroxy-3-methylbutyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0641] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (200 mg, 0.380 mmol), 2-isopropyloxirane (0.052 mL, 0.492 mmol), in acetic acid (0.5 mL), at rt. After 16 h, the mixture was placed in a 75 °C bath overnight. After a further 16 h, acetic acid was evaporated *in vacuo* and the residue purified directly by C18 reverse phase flash chromatography (0 - 65% MeCN/10mM aqueous ammonium formate, pH = 3.8). The product fractions were combined and lyophilized to provide 84 mg (36% yield) of the title compound. LCMS (ESI) $[M+H]^+$ = 613.4, rt = 2.02 min.

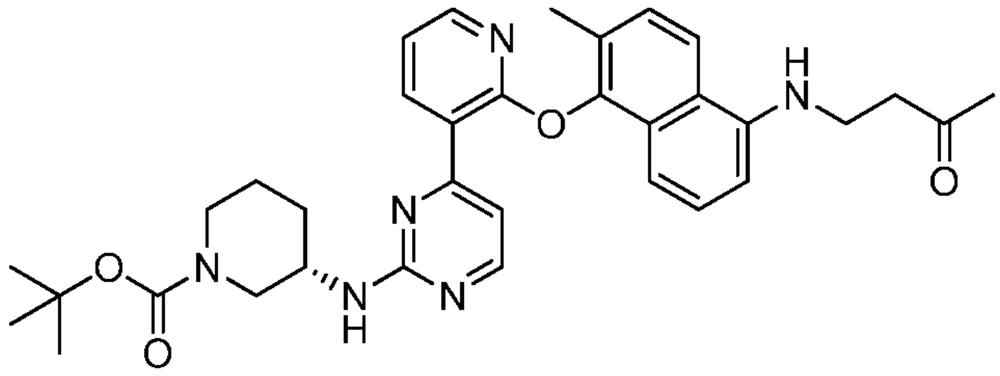
[0642] Step 2: 3-Methyl-1-((6-methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)butan-2-ol



[0643] Prepared using (3*S*)-*tert*-butyl 3-((4-(2-((5-((2-hydroxy-3-methylbutyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (20 mg, 0.033 mmol), 1,4-dioxane (1 mL) and hydrochloric acid (4 M in dioxane, 0.5 mL, 2 mmol). After 4 h, the mixture was concentrated *in vacuo*. The residue was triturated in MeCN and the resulting solids collected by filtration, dissolved in MeCN and water and lyophilized to provide 17 mg (95% yield) of **200** as a mixture of the two isomers of the aminoalcohol. LCMS (ESI) $[M+H]^+$ = 513.2, r.t.= 1.43 min; ^{1}H NMR (400 MHz, d4-MeOH) δ 8.83 – 8.73 (m, 1H), 8.48 (d, J = 5.6 Hz, 1H), 8.07 – 7.99 (m, 2H), 7.86 (s, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.57 – 7.46 (m, 2H), 7.29 (dd, J = 7.6, 4.9 Hz, 1H), 4.48 (s, 1H), 3.78 – 3.57 (m, 3H), 3.48 – 3.34 (m, 2H), 3.17 – 3.00 (m, 2H), 2.31 (s, 3H), 2.28 – 2.18 (m, 1H), 2.17 – 2.06 (m, 1H), 2.01 – 1.70 (m, 3H), 0.99 (dd, J = 17.5, 6.8 Hz, 6H).

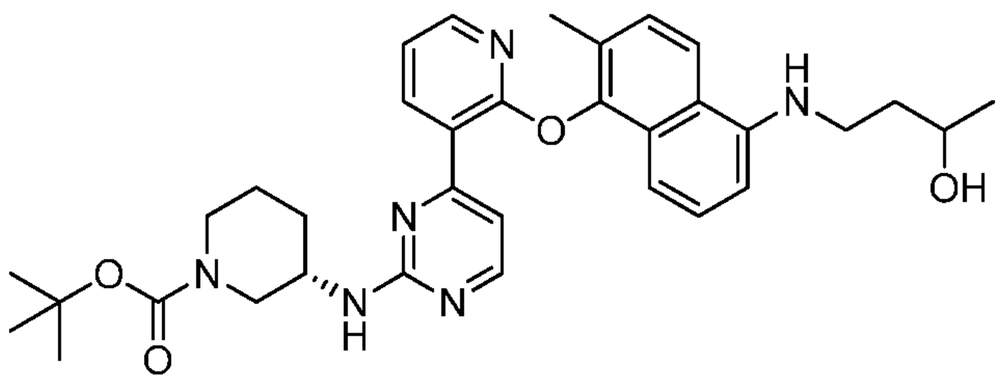
Example 201 *(R)-4-((6-Methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)butan-2-ol* ***201***

[0644] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-5-((3-oxobutyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0645] Following the procedures of Example 390, to a suspension of (*S*)-*tert*-butyl 3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (140 mg, 0.266 mmol) in methanol (1.3 mL), was added but-3-en-2-one (65 µL, 0.80 mmol) followed by triethylamine (111 µL, 0.80 mmol) and the mixture stirred at rt. After 18 h, a further portion of but-3-en-2-one (32 µL, 0.40 mmol) was added and after a further 16 h at rt, the reaction mixture was diluted with H_2O and extracted twice with DCM, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude was purified by flash chromatography through Si (silica) gel (0 – 60% EtOAc/DCM) to provide 156 mg (98% yield) of the title compound. LCMS (ESI) $[M+H]^+$ = 597.6, rt = 1.96 min.

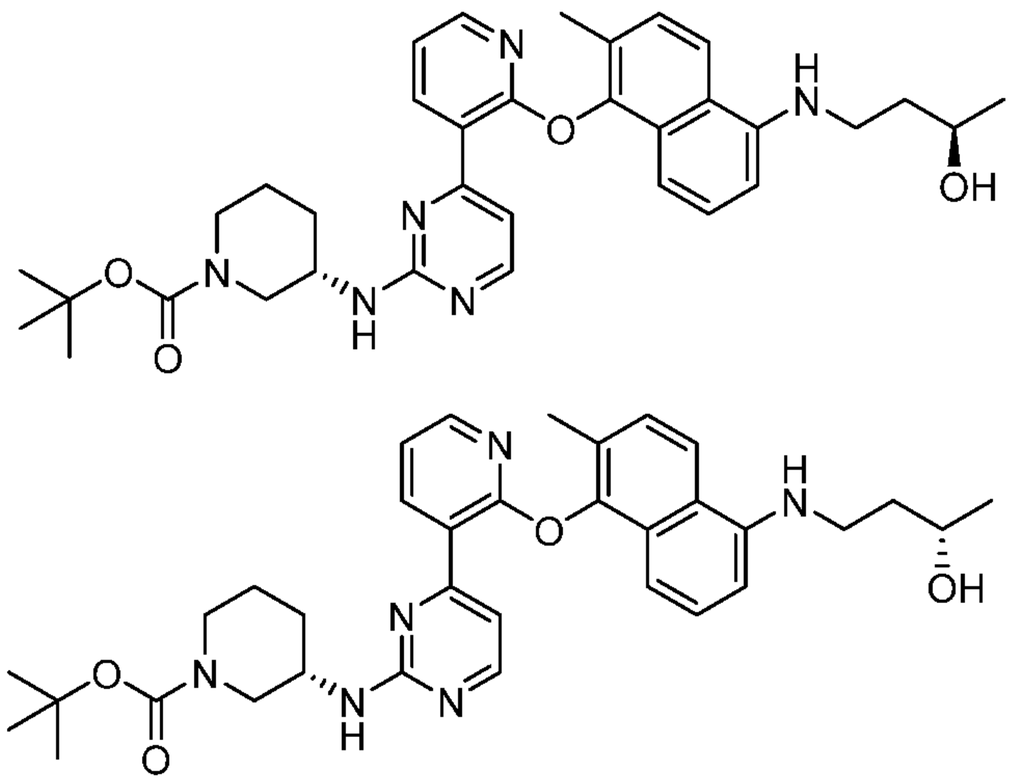
[0646] Step 2: (3*S*)-*tert*-Butyl 3-((4-(2-((5-((3-hydroxybutyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0647] A solution of (*S*)-*tert*-butyl 3-((4-(2-((2-methyl-5-((3-oxobutyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (156 mg, 0.261 mmol) in THF (0.45 mL) and methanol (0.45 mL) was cooled 0 °C and to this was then added sodium borohydride (34 mg, 0.91 mmol). The mixture was stirred 30 min at 0 °C, then diluted with H_2O and extracted three times with DCM, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude was purified by C18 reverse phase flash chromatography (55 – 100% MeCN/10 mM aqueous ammonium formate, pH = 3.8). The appropriate fractions were combined,

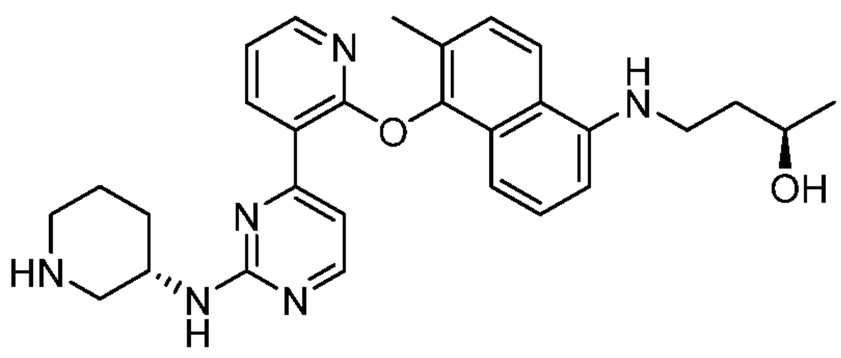
concentrated to remove some MeCN, and lyophilized to provide 89 mg (57% yield) of the title compound. LCMS (ESI) $[M+H]^+$ = 599.7, rt = 1.89 min.

[0648] Step 3: *tert*-Butyl (*S*)-3-((4-(2-((5-(((R)-3-hydroxybutyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-1) and tert-butyl (S)-3-((4-(2-((5-(((S)-3-hydroxybutyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-2)



[0649] The stereoisomers from Step 2 (89 mg, 0.15 mmol), were subjected to chiral normal phase semi-prep purification (Conditions: Chiralpak IB, 5 uM, 20 x 250 mm, 6:6:88 MeOH:EtOH:Hexanes, 2-4mg/inj.) to provide two stereoisomers possessing a stereocenter at the alcohol position: (isomer-1), 25 mg (16% yield), ee = 98.4%, (ESI) $[M+H]^+$ = 599.7, rt = 1.89 min; and (isomer-2), 27 mg (17% yield), ee = 97.7%, (ESI) $[M+H]^+$ = 599.7, rt = 1.89 min.

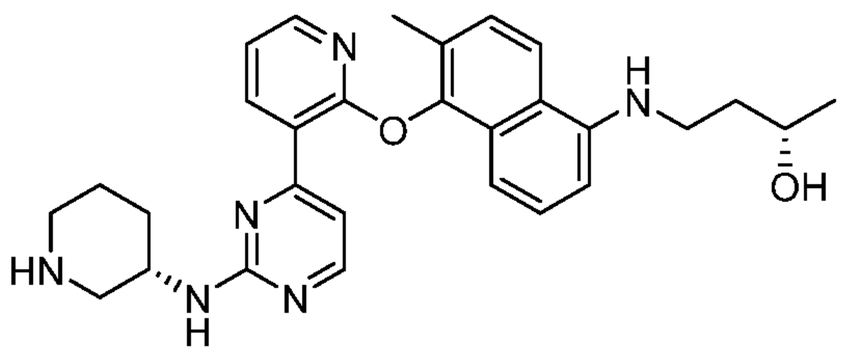
[0650] Step 4: (*R*)-4-((6-Methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)butan-2-ol (isomer-1)



[0651] Prepared according to General Procedure B using tert-butyl (S)-3-((4-(2-((5-(((R)-3-hydroxybutyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-1) (25 mg, 0.042 mmol), 1,4-dioxane (0.5 mL) and hydrochloric acid (4 M in dioxane, 0.5 mL, 2 mmol). After 45 min, the reaction was diluted with Et_2O, and the resulting solids collected by filtration, dissolved in a mixture of MeCN and

H_2O, and lyophilized to provide 15 mg (68% yield) of **201**. The stereochemistry was tentatively and arbitrarily assigned. LCMS (ESI) $[M+H]^+$ = 499.2, rt = 1.30min; ^1H NMR (400 MHz, d6-dmso) δ 9.02 (br.s, 2H), 8.69 (s, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.19 – 7.95 (m, 2H), 7.61 (s, 2H), 7.41 (d, J = 8.8 Hz, 1H), 7.36 – 7.16 (m, 2H), 7.00 (s, 1H), 6.70 (s, 1H), 3.87 – 3.69 (m, 1H), 3.51 – 3.35 (m, 1H), 3.35 – 3.25 (m, 2H), 3.20 (d, J = 12.1 Hz, 1H), 2.96 – 2.75 (m, 2H), 2.19 (s, 3H), 2.10 – 1.97 (m, 1H), 1.97 – 1.86 (m, 1H), 1.86 – 1.50 (m, 4H), 1.13 (d, J = 6.2Hz, 3H).

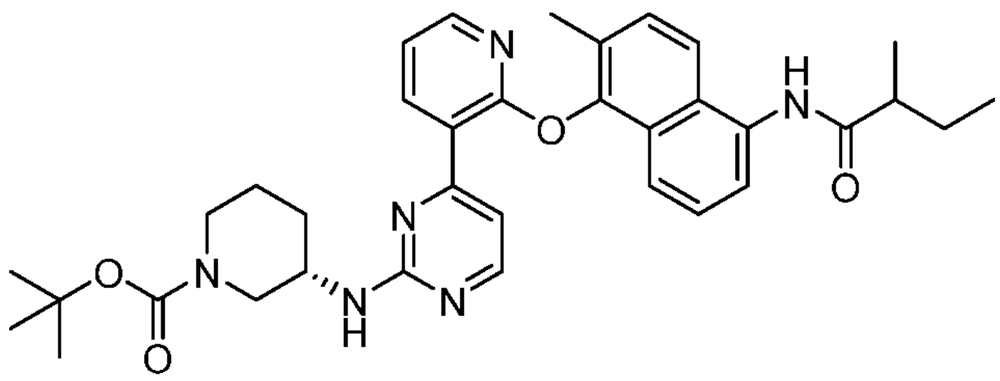
Example 202 *(S)-4-((6-Methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)butan-2-ol* ***202***



[0652] Prepared according to Example 201 and General Procedure B using tert-butyl (S)-3-((4-(2-((5-(((S)-3-hydroxybutyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-2) (27 mg, 0.045 mmol), 1,4-dioxane (0.5 mL) and hydrochloric acid (4 M in dioxane, 0.5 mL, 2 mmol). After 45 min, the reaction mixture was diluted with Et_2O, and the resulting solids collected by filtration, dissolved in a mixture of MeCN and H_2O, and lyophilized to provide 16 mg (64% yield) of **202**. The stereochemistry was tentatively and arbitrarily assigned. LCMS (ESI) $[M+H]^+$ = 499.2, rt = 1.30min; ^1H NMR (400 MHz, d6-dmso) δ 9.01 (br.s, 2H), 8.71 (s, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.13 – 7.91 (m, 2H), 7.60 (s, 2H), 7.40 (d, J = 8.6 Hz, 1H), 7.32 – 7.14 (m, 2H), 7.00 (s, 1H), 6.69 (s, 1H), 3.96 – 3.71 (m, 2H), 3.50 – 3.34 (m, 1H), 3.34 – 3.24 (m, 2H), 3.20 (d, J = 12.3 Hz, 1H), 2.97 – 2.74 (m, 2H), 2.19 (s, 3H), 2.11 – 1.96 (m, 1H), 1.96 – 1.84 (m, 1H), 1.86 – 1.50 (m, 4H), 1.13 (d, J = 6.2 Hz, 3H).

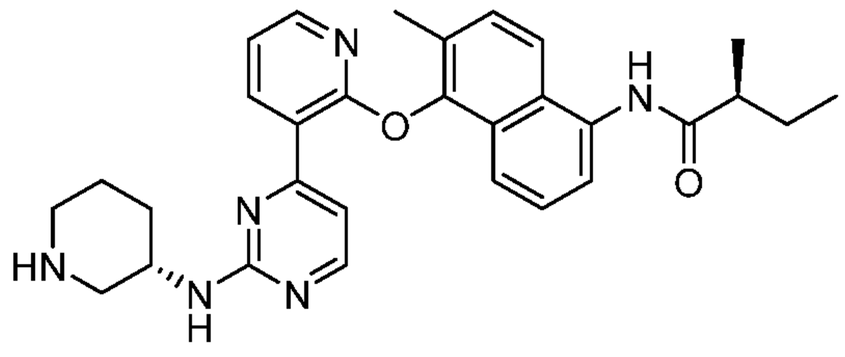
Example 203 *(S)-2-methyl-N-(6-methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)butanamide* ***203***

[0653] Step 1: *tert*-Butyl (3*S*)-3-((4-(2-((2-methyl-5-(2-methylbutanamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0654] The General Procedure C was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (90 mg, 0.17 mmol), 2-methylbutanoic acid (23 mg, 0.26 mmol), DIPEA (0.089 mL, 0.51 mmol), HATU (91 mg, 0.24 mmol) and DCM (1.7 mL). The crude mixture of diastereomers was directly used in the next step.

[0655] Step 2: (S)-2-methyl-N-(6-methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)butanamide



[0656] The General Procedure B was followed, using crude (*S*)-2-(4-fluorophenyl)-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)acetamide, DCM (1.7 mL) and hydrochloric acid (4 M in dioxane, 0.430 mL, 1.71 mmol). The residue was purified *via* reverse-phase HPLC to provide a mixture of the two isomers, this mixture was then purified *via* chiral reverse-phase HPLC and lyophilized to yield 11.7 mg of **203** and 10.1 mg of **204**, the two single stereoisomers enantiomeric at the 2 position of the butanamide. The stereochemical assignments of **203** and **204** were randomly assigned and may be determined later.

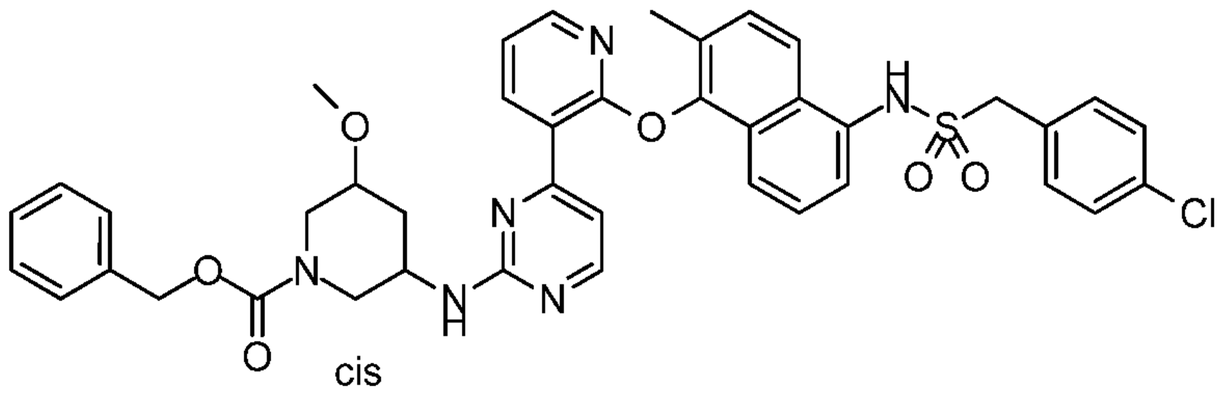
[0657] **203:** LCMS (ESI): $[M+H]^+$ = 511.2; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.87 (s, 1H), 8.50 (d, J = 7.6 Hz, 1H), 8.41 (d, J = 5.1 Hz, 1H), 8.02 (dd, J = 4.8, 2.0 Hz, 1H), 7.89 (d, J = 8.6 Hz, 1H), 7.60 – 7.40 (m, 3H), 7.46 – 7.36 (m, 2H), 7.25 (dd, J = 7.5, 4.8 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 3.89 (s, 1H), 3.13 3.07 (m, 1H), 2.83 – 2.76 (m, 1H), 2.69 – 2.60(m, 1H), 2.46 – 2.37 (m, 2H), 2.22 (s, 3H), 1.97 – 1.87 (m, 1H), 1.75 – 1.61 (m, 2H), 1.58 – 1.38 (m, 3H), 1.18 (d, J = 6.8 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H).

Example 204 *(R)-2-methyl-N-(6-methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)butanamide* ***204***

[0658] The procedures of Example 203 were followed to give **204**: LCMS (ESI): $[M+H]^+$ = 511.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 8.50 (d, J = 7.6 Hz, 1H), 8.41 (d, J = 5.1 Hz, 1H), 8.02 (dd, J = 4.8, 2.0 Hz, 1H), 7.89 (d, J = 8.6 Hz, 1H), 7.60 – 7.40 (m, 3H), 7.46 – 7.36 (m, 2H), 7.25 (dd, J = 7.5, 4.8 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 3.89 (s, 1H), 3.13 3.07 (m, 1H), 2.83 – 2.76 (m, 1H), 2.69 – 2.60(m, 1H), 2.46 – 2.37 (m, 2H), 2.22 (s, 3H), 1.97 – 1.87 (m, 1H), 1.75 – 1.61 (m, 2H), 1.58 – 1.38 (m, 3H), 1.18 (d, J = 6.8 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H).

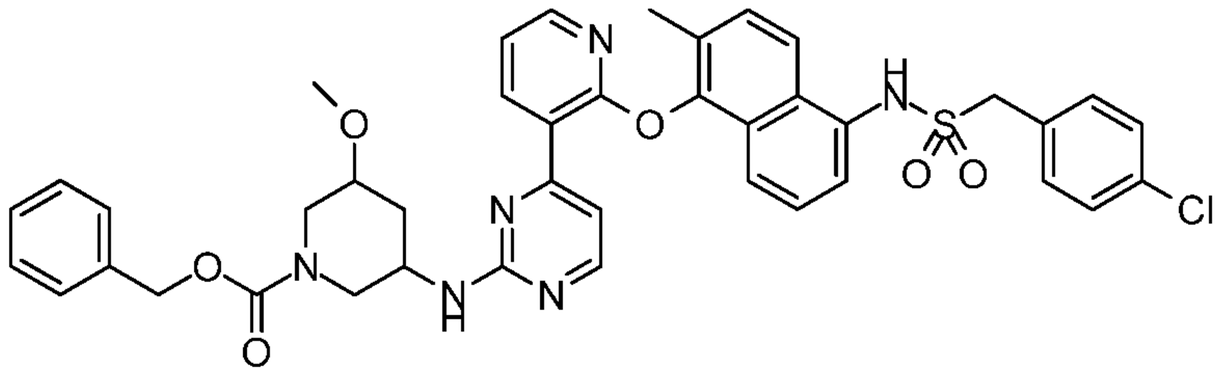
Example 205 *1-(4-Chlorophenyl)-N-(5-((3-(2-(((3S, 5R)-5-methoxypiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)methanesulfonamide* ***205***

[0659] Step 1: Benzyl 3-((4-(2-((5-((4-chlorophenyl)methylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)-5-methoxypiperidine-1-carboxylate



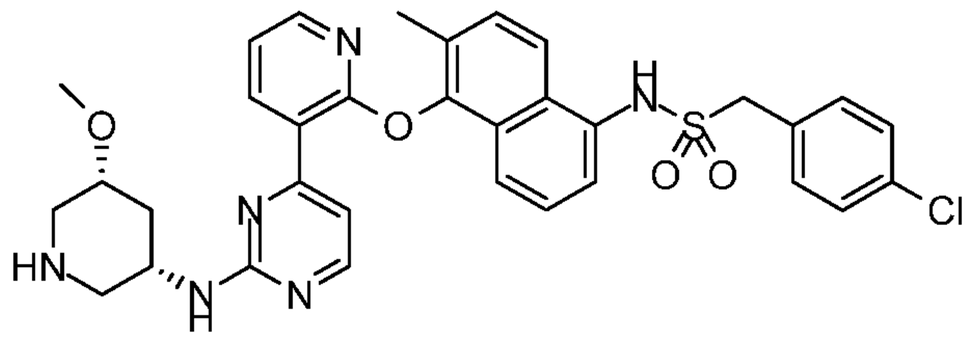
[0660] To a 100 mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 1-(4-chlorophenyl)-*N*-[6-methyl-5-[[3-(2-methylsulfinylpyrimidin-4-yl)-2-pyridyl]oxy]-1-naphthyl]methanesulfonamide (500 mg, 0.86 mmol), benzyl 3-amino-5-methoxy-piperidine-1-carboxylate (273 mg, 1.04 mmol), 1,4-dioxane (8 mL) and *N,N*-diisopropylethylamine (0.21 mL, 1.21 mmol). The resulting solution was stirred at 130 ºC in an oil bath overnight, cooled to rt and concentrated *in vacuo*. The residue was purified *via* flash silica chromatography (solvent gradient: 2% methanol in dichloromethane) to yield 430 mg (64% yield) of the title compound as a yellow solid. LCMS: (ES, m/z): $[M+H]^+$ = 779.1.

[0661] Step 2: Benzyl 3-((4-(2-((5-((4-chlorophenyl)methylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)-5-methoxypiperidine-1-carboxylate



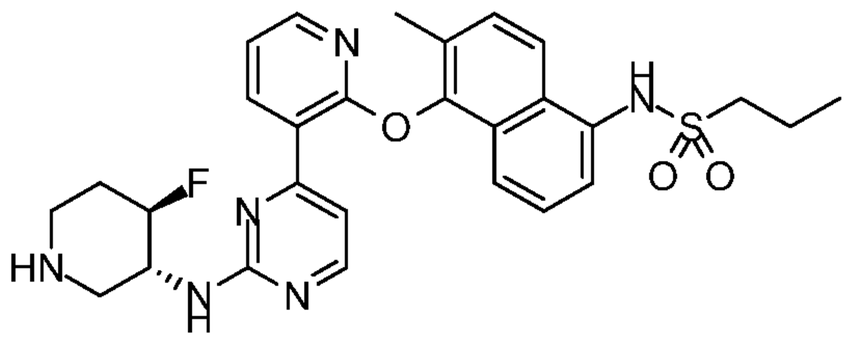
[0662] Benzyl 3-[[4-[2-[[5-[(4-chlorophenyl)methylsulfonylamino]-2-methyl-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]-5-methoxy-piperidine-1-carboxylate (360 mg, 0.46 mmol) was purified by SFC (AD (250mm x 30mm,10 μm); Base-EtOH: 40%; flow rate (80 ml / min) to give benzyl3-[[4-[2-[[5-[(4-chlorophenyl)methylsulfonylamino]-2-methyl-1-naphthyl]oxy]-3-pyridyl] pyrimidin-2-yl]amino]-5-methoxy-piperidine-1-carboxylate (120 mg, 33 % yield) (first peak on SFC) and benzyl 3-[[4-[2-[[5-[(4-chlorophenyl)methylsulfonylamino]-2-methyl-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]-5-methoxy-piperidine-1-carboxylate (200 mg, 56% yield) (second peak on SFC) as a white solid.

[0663] Step 3: 1-(4-Chlorophenyl)-*N*-(5-((3-(2-(((3*S*, 5*R*)-5-methoxypiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)methanesulfonamide

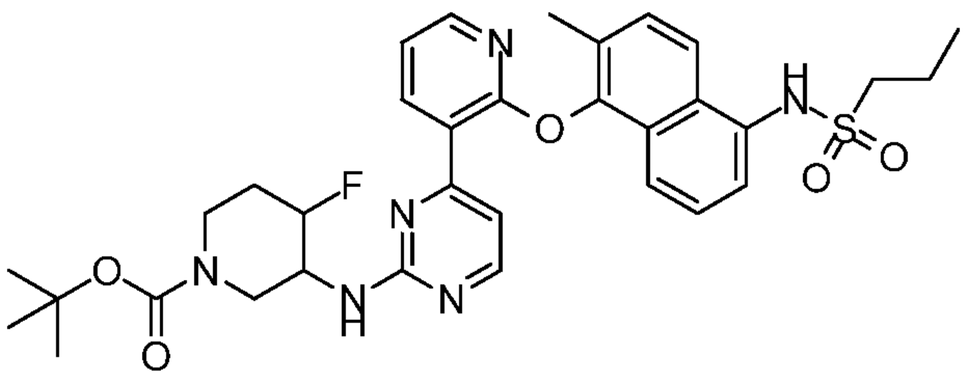


[0664] To a 100 mL 3-necked round-bottom flask was placed benzyl 3-[[4-[2-[[5-[(4-chlorophenyl)methylsulfonylamino]-2-methyl-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]-5-methoxy-piperidine-1-carboxylate (196 mg, 0.25 mmol) (second peak on SFC in step 2), 1-methylimidazole (33 mg, 0.42 mmol), thiourea (97 mg, 1.29 mmol), iodotrimethylane (0.30 mL, 2.1 mmol) and acetonitrile (2 mL). The mixture was stirred at room temperature for 12 h and concentrated in a vacuum. The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% NH_4OH) B: ACN) to yield 42 mg (25% yield) of **205** as a white solid. LCMS (ESI): $[M+H]^+ = 645.2$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.49 (s, 1H), 8.42 (d, $J = 4.8$ Hz, 1H), 8.06 - 8.01 (m, 2H), 7.51 - 7.48 (m, 1H), 7.46 - 7.43 (m, 2H), 7.41 - 7.38 (m, 4H), 7.37 (s, 1H), 7.28 - 7.19 (m, 2H), 4.53 (s, 2H), 4.10 - 3.90 (m, 1H), 3.25 (s, 3H), 3.15 - 3.10 (m, 2H), 2.56 - 2.53 (m, 2H), 2.45 - 2.40 (m, 1H), 2.27 (m, 1H), 2.21 (s, 3H), 1.40 - 1.29 (m, 1H). The absolute stereochemistry was tentatively assigned based on the potency in the XBP1 reporter assay.

Example 206 *N-(5-((3-(2-(((3R,4R)-4-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)propane-1-sulfonamide* ***206***

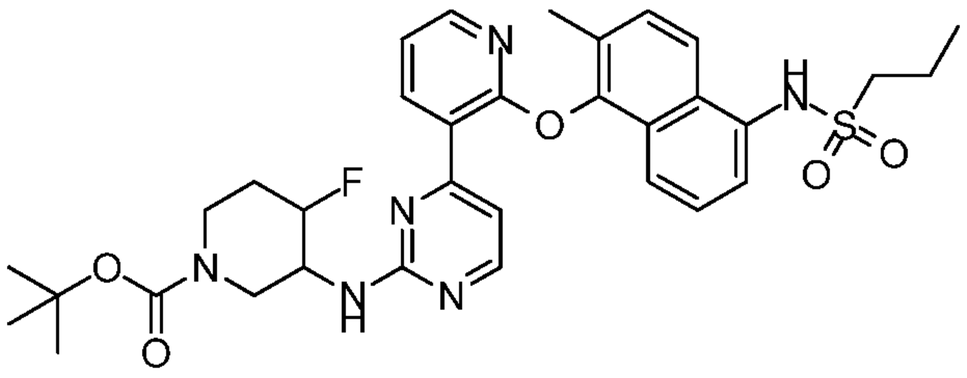


[0665] Step 1: *tert*-Butyl 4-fluoro-3-((4-(2-((2-methyl-5-(propylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0666] To a solution of *N*-[6-methyl-5-[[3-(2-methylsulfinylpyrimidin-4-yl)-2-pyridyl]oxy]-1-naphthyl]propane-1-sulfonamide (500 mg, 1.01 mmol) in 1,4-dioxane (5 mL) was added *N,N*-diisopropylethylamine (0.53 mL, 3.02mmol) and *tert*-butyl 3-amino-4-fluoro-piperidine-1-carboxylate (263.7 mg, 1.21 mmol), the mixture was stirred at 120 °C for 80 h. After cooling, the mixture was concentrated to dryness and the residue was dissolved in DCM (50 mL) and washed with H_2O (40 mL x 2). The organic phase was dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated and purified by silica gel chromatography (solvent gradient: 0 - 50% ethyl acetate in petroleum ether, Rf = 0.7) and prep-TLC (50% ethyl acetate in petroleum ether, Rf = 0.7) to yield 100 mg (15% yield) of the title compound of the trans mixture product as a white solid. LCMS (ESI) $[M+H]^+$ = 651.0.

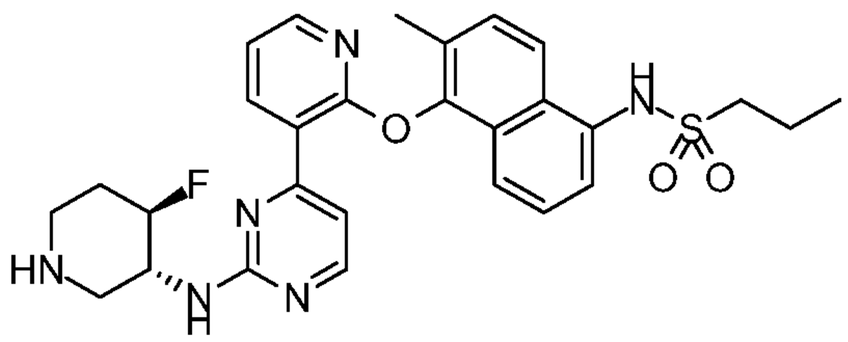
[0667] Step 2: *tert*-Butyl 4-fluoro-3-((4-(2-((2-methyl-5-(propylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0668] The trans mixture of *tert*-butyl 4-fluoro-3-((4-(2-((2-methyl-5-(propylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (300 mg, 0.46 mmol) was separated by chiral SFC (SFC 13, AS(250mm x 30mm,5

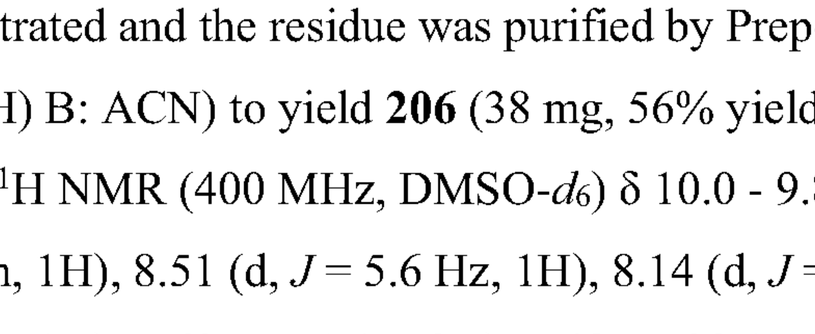
μm), 40% 40 mL/min, 0.1% NH_3H_2O in methanol) to yield *tert*-butyl 4-fluoro-3-[[4-[2-[[2-methyl-5-(propylsulfonylamino)-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (90 mg, 14% yield) (first peak on SFC, Rt = 4.95 min) as a white solid. LCMS (ESI) $[M+H]^+$ = 651.1; and *tert*-butyl 4-fluoro-3-[[4-[2-[[2-methyl-5-(propylsulfonylamino)-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (80 mg, 12% yield) (second peak on SFC, Rt = 5.15 min) as a white solid. LCMS (ESI) $[M+H]^+$ = 651.1.

[0669] Step 3: *N*-(5-((3-(2-(((3*R*,4*R*)-4-Fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)propane-1-sulfonamide

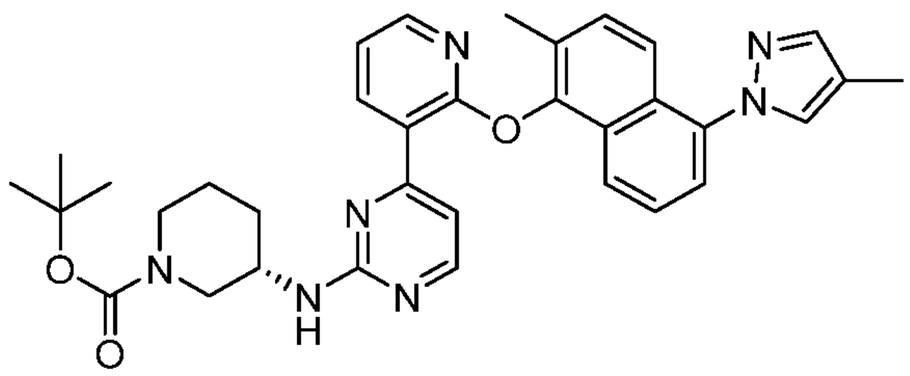


[0670] To a solution of *tert*-butyl 4-fluoro-3-[[4-[2-[[2-methyl-5-(propylsulfonylamino)-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (80 mg, 0.12 mmol) (second peak on SFC in step 2) in ethyl acetate (1 mL) was added 4M of HCl (0.35 mL, 1.38 mmol) in ethyl acetate and the mixture was stirred at 20 °C for 2 h. The mixture was concentrated and the residue was purified by Prep-HPLC (mobile phase: A: water (0.05% NH_4OH) B: ACN) to yield **206** (38 mg, 56% yield) as a white solid; LCMS (ESI) $[M+H]^+$ = 551.2; ^1H NMR (400 MHz, DMSO-d_6) δ 10.0 - 9.88 (m, 1H), 9.83 (s, 1H), 9.45 (s, 1H), 9.03 - 8.77 (m, 1H), 8.51 (d, *J* = 5.6 Hz, 1H), 8.14 (d, *J* = 8.8 Hz, 1H), 8.08 (d, *J* = 3.2 Hz, 1H), 7.80 - 7.65 (m, 1H), 7.60 - 7.51 (m, 2H), 7.48 - 7.39 (m, 2H), 7.30 - 7.26 (m, 1H), 5.01 - 4.46 (m, 2H), 3.56 - 3.26 (m, 2H), 3.21 - 3.08 (m, 2H), 3.07 - 2.89 (m, 2H), 2.42 - 2.29 (m, 1H), 2.21 (s, 3H), 2.15 - 1.96 (m, 1H), 1.85 - 1.68 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H). The absolute stereochemistry was tentitiavely assigned based on potency in the XBP1 reporter assay.

Example 207 *(S)-4-(2-((2-Methyl-5-(4-methyl-1H-pyrazol-1-yl)naphthalen-1-yl)oxy)pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine* ***207***

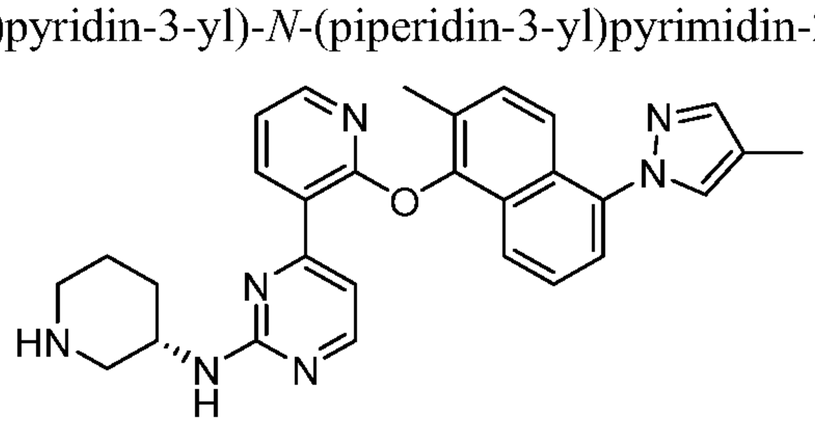


[0671] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-(4-methyl-1H-pyrazol-1-yl)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0672] A mixture of 4-methyl-1H-pyrazole (23 mg, 0.28 mmol), tert-butyl (3S)-3-[[4-[2-[(5-iodo-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (120 mg, 0.188 mmol), cuprous iodide 911 mg, 0.057 mmol), cesium carbonate (123 mg, 0.38 mmol) in DMF (1.5 mL) was evacuated and filled with nitrogen twice. The reaction mixture was stirred at rt for 30 min, and then at 120 °C overnight. After 16 hours, the mixture was cooled to room temperature and the mixture diluted with DCM and water, followed by separation of the layers. The organic phase was washed with saturated NaCl(aq), dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified on a silica column 5 to 80% (isopropylacetate/MeOH (3:1):heptanes) to provide 92 mg of the title compound (74% yield).

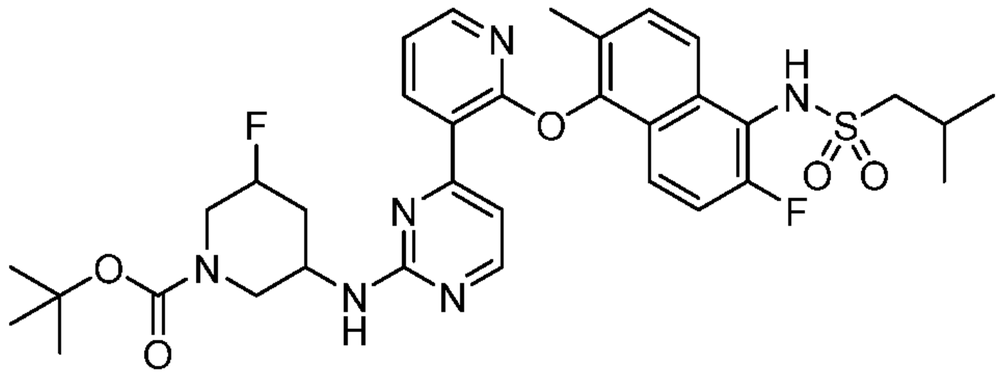
[0673] Step 2: (*S*)-4-(2-((2-Methyl-5-(4-methyl-1H-pyrazol-1-yl)naphthalen-1-yl)oxy)pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-2-amine



[0674] The General Procedure B was followed using *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-(4-methyl-1H-pyrazol-1-yl)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (82 mg, 0.14 mmol), DCM (4 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). The residue was purified *via* reverse-phase HPLC and lyophilized to yield 3.2 mg (5% yield) of **207**. LCMS (ESI): $[M+H]^+$ = 492.2; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.57 – 8.48 (m, 1H), 8.43 (d, J = 5.1 Hz, 1H), 8.07 – 8.02 (m, 1H), 7.99 – 7.97 (m, 1H), 7.81 – 7.62 (m, 3H), 7.58 – 7.41 (m,4H), 7.32 – 7.22 (m, 1H), 7.20 (d, J = 7.8 Hz, 1H), 4.01 – 3.88 (m, 1H), 3.19 – 3.13 (m, 1H), 2.87 (d, J = 12.3 Hz, 1H), 2.22 (s, 3H), 2.18 (s, 3H), 1.99 – 1.89 (m, 1H), 1.73 – 1.68 (m, 1H), 1.55 – 1.42 (m, 1H).

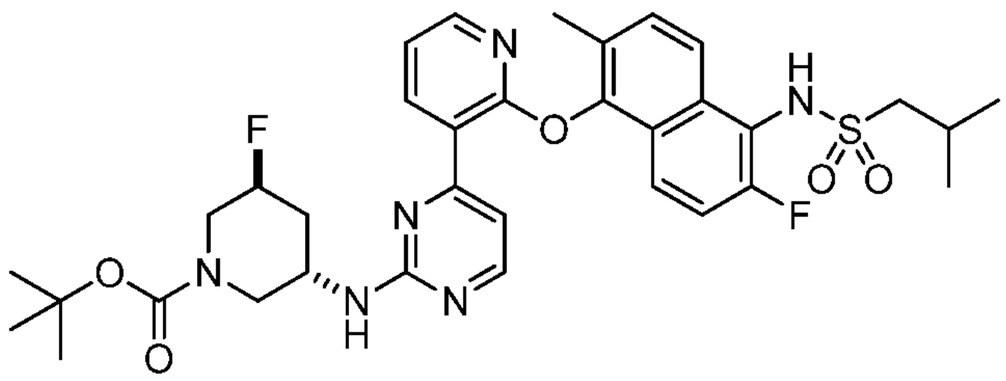
Example 208 *N-(2-Fluoro-5-((3-(2-(((trans)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)-2-methylpropane-1-sulfonamide* ***208***

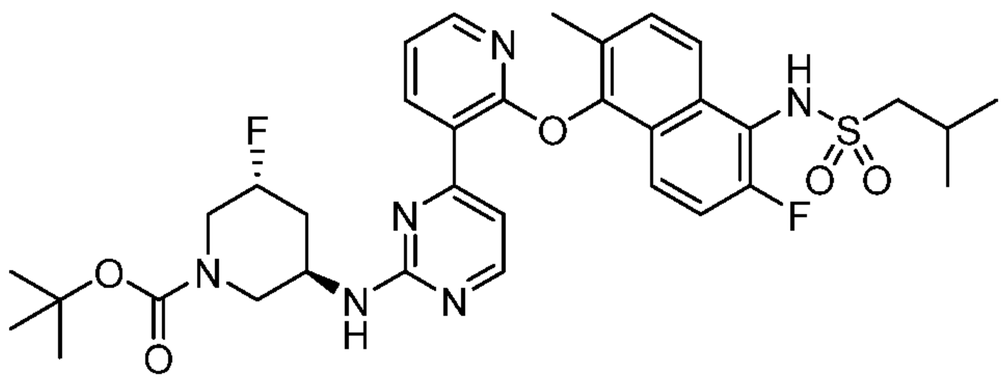
[0675] Step 1: *trans-tert*-Butyl 3-fluoro-5-((4-(2-((6-fluoro-2-methyl-5-(2-methylpropylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0676] Prepared using *trans-tert*-butyl 3-((4-(2-((5-amino-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)-5-fluoropiperidine-1-carboxylate (150 mg, 0.267 mmol), pyridine (0.323 mL, 4.00 mmol), DCM (0.89 mL), 2-methylpropane-1-sulfonyl chloride (0.070 mL, 0.533 mmol) and DMAP (1.63 mg, 0.013 mmol). After 16 h, a further portion of 2-methylpropane-1-sulfonyl chloride (0.070 mL, 0.533 mmol) was added and the reaction mixture stirred a further 6 h. The reaction mixture was diluted with 1M $KHSO_4$(aq), extracted twice with DCM, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude was purified by flash chromatography through silica gel (0 – 50% EtOAc/DCM) to provide 92 mg (50% yield) of the title compound. LCMS (ESI) $[M+H]^+$ = 683.6, rt = 1.93 min.

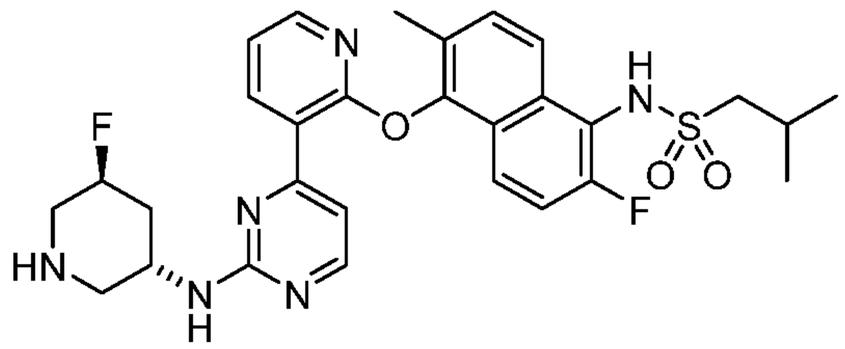
[0677] Step 2: tert-butyl (3S,5S)-3-fluoro-5-((4-(2-((6-fluoro-2-methyl-5-((2-methylpropyl)sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-1) and tert-butyl (3R,5R)-3-fluoro-5-((4-(2-((6-fluoro-2-methyl-5-((2-methylpropyl)sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-2)





[0678] The trans enantiomers from Step 1 were subjected to chiral normal phase semi-prep purification (Conditions: Chiralpak IA, 5 uM, 20 x 250 mm, 10:5:85 MeOH:iPrOH:Hexanes, 7-10mg/inj.) to provide two *trans*-piperidine enantiomers: (isomer-1), 65 mg (36% yield), ee = 97.2%, (ESI) $[M+H]^+$ = 683.3, rt = 1.91 min; and (isomer-2), 66 mg (37% yield), ee = 97.7%, (ESI) $[M+H]^+$ = 683.3, rt = 1.91 min.

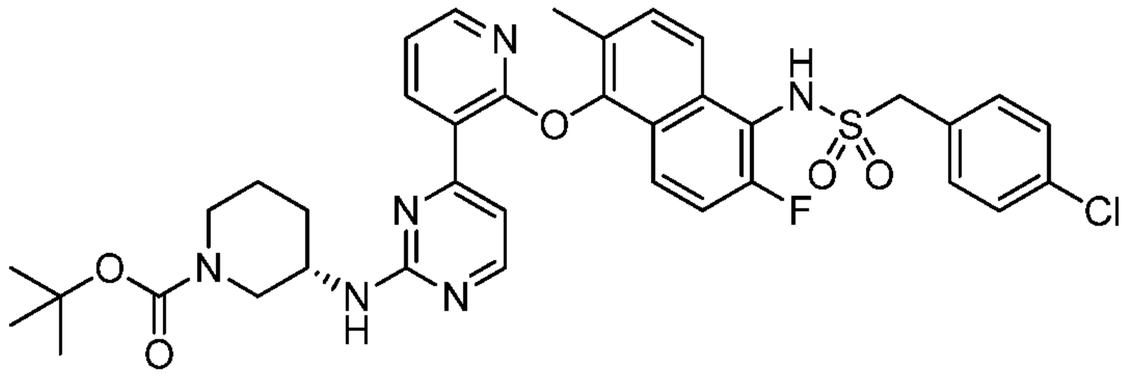
[0679] Step 3: *N*-(2-Fluoro-5-((3-(2-(((3S,5S)-5-fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)-2-methylpropane-1-sulfonamide (isomer-1)



[0680] Prepared according to General Procedure B using tert-butyl (3S,5S)-3-fluoro-5-((4-(2-((6-fluoro-2-methyl-5-((2-methylpropyl)sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-1) (66 mg, 0.097 mmol), 1,4-dioxane (0.5 mL) and hydrochloric acid (4 M in dioxane, 1 mL, 4 mmol). After 3 h, the reaction mixture was diluted with Et_2O and the resulting solids collected by filtration and washed with Et_2O. The collected solids were dissolved in a mixture of MeCN and H_2O and lyophilized to provide 54 mg (91% yield) of **208**. LCMS (ESI) $[M+H]^+$ = 583.4, rt = 1.44 min; ^1H NMR (400 MHz, DMSO-*d6*)δ 9.70 (s, 1H), 9.61 (d, J = 11.4 Hz, 1H), 9.34 – 9.06 (m, 1H), 8.79 – 8.56 (m, 1H), 8.49 (d, J = 5.2 Hz, 1H), 8.08 (dd, J = 4.7, 1.9 Hz, 1H), 8.06 (d, J = 9.0 Hz, 1H), 7.71 (dd, J = 9.3, 5.1 Hz, 1H), 7.66 – 7.55 (m, 3H), 7.45 (t, J = 9.5 Hz, 1H), 7.29 (dd, J = 7.6, 4.8 Hz, 1H), 5.24 (d, J = 45.4 Hz, 1H), 4.52 (s, 1H), 3.57 – 3.39 (m, 2H), 3.34 – 3.14 (m, 1H), 3.11 (d, J = 6.4 Hz, 2H), 2.83 (q, J = 10.9 Hz, 1H), 2.42 – 2.22 (m, 2H), 2.19 (s, 3H), 1.94 (dt, J = 24.6, 12.8 Hz, 1H), 1.07 (d, J = 6.7 Hz, 6H).

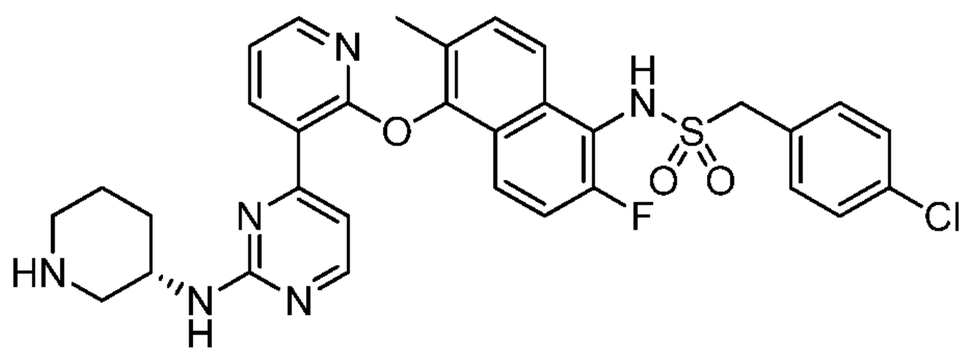
Example 209 *(S)-1-(4-Chlorophenyl)-N-(2-fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide* ***209***

[0681] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-((4-chlorophenyl)methylsulfonamido)-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0682] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 275 (60 mg, 0.11 mmol), pyridine (0.090 mL, 1.11 mmol), DCM (1.5 mL), and (4-chlorophenyl)methanesulfonyl chloride (50 mg, 0.22 mmol). After 16 h, the reaction mixture was concentrated *in vacuo* and the residue diluted with EtOAc, then washed twice with 1M HCl(aq), followed by saturated $NaHCO_3$(aq) and brine. The solution was dried ($MgSO_4$), filtered and concentrated *in vacuo*, and the resulting crude product purified purified by C18 reverse phase flash chromatography (0 - 70% MeCN/10 mM aqueous ammonium formate, pH = 3.8). The product fractions were combined, concentrated, and lyophilized to provide 54 mg (67% yield) of the title compound. LCMS (ESI) $[M+H]^+$ = 733.3, rt = 2.06 min.

[0683] Step 2: (*S*)-1-(4-Chlorophenyl)-*N*-(2-fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide

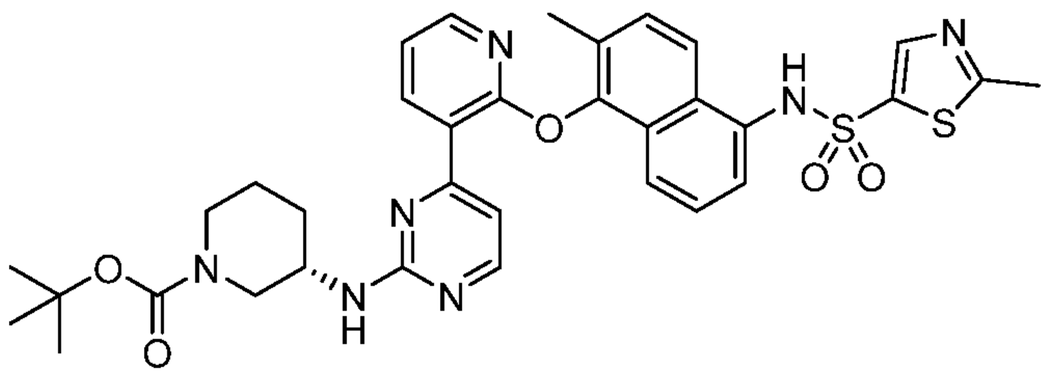


[0684] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-((4-chlorophenyl)methylsulfonamido)-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (54 mg, 0.074 mmol), 1,4-dioxane (1.5 mL), and hydrochloric acid (4 M in dioxane, 0.5 mL, 2 mmol). After 4 h, the reaction mixture was diluted with MTBE (5 mL), and the resulting solids collected by filtration and washed with MTBE. The solids were then dissolved in a mixture of MeCN and H_2O, and lyophilized to provide 42 mg (85% yield) of **209**. LCMS (ESI) $[M+H]^+$ = 633.1, rt = 1.56 min. ^{1}H NMR (400 MHz, d4-MeOH) δ 8.69 (d, J = 6.7 Hz, 1H), 8.46 (d, J = 5.4 Hz, 1H), 8.09 (d, J = 8.8 Hz, 1H), 8.02 (dd, J = 4.8, 1.9 Hz, 1H),

7.78 (dd, J = 9.3, 4.9 Hz, 1H), 7.73 (d, J = 5.4 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.50 – 7.45 (m, 2H), 7.43 – 7.32 (m, 3H), 7.25 (dd, J = 7.6, 4.8 Hz, 1H), 4.56 (s, 2H), 4.47 – 4.32 (m, 1H), 3.63 (dd, J = 12.2, 3.6 Hz, 1H), 3.39 – 3.33 (m, 1H), 3.11 – 2.99 (m, 2H), 2.24 (s, 3H), 2.23 – 2.06 (m, 2H), 1.98 – 1.74 (m, 2H).

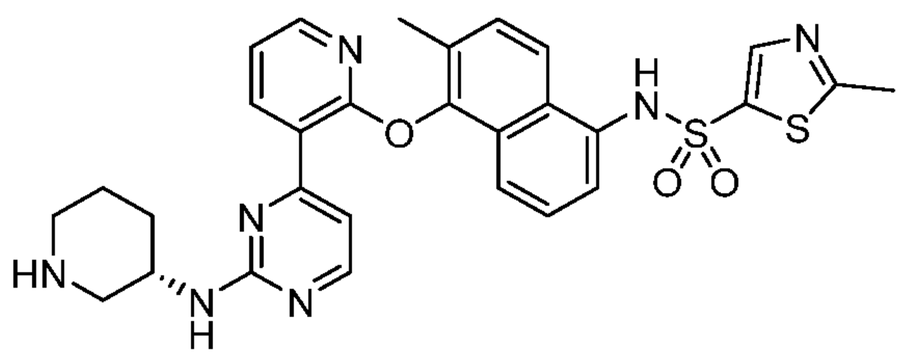
Example 210 *(S)-2-Methyl-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)thiazole-5-sulfonamide* ***210***

[0685] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-((2-methylthiazole)-5-sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0686] The General Procedure A was followed, using *tert*-butyl (3S)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol) and 2-methylthiazole-5-sulfonyl chloride (56.31 mg, 0.56 mmol) in pyridine (1 mL), stirred at room temperature for 48 h. Purification was conducted by silica gel chromatography (12 g column) eluting with 0-5% MeOH/DCM to afford 50 mg (38% yield) of the title compound as a brown solid. LCMS (ESI) $[M+H]^+ = 688$.

[0687] Step 2: (*S*)-2-Methyl-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)thiazole-5-sulfonamide

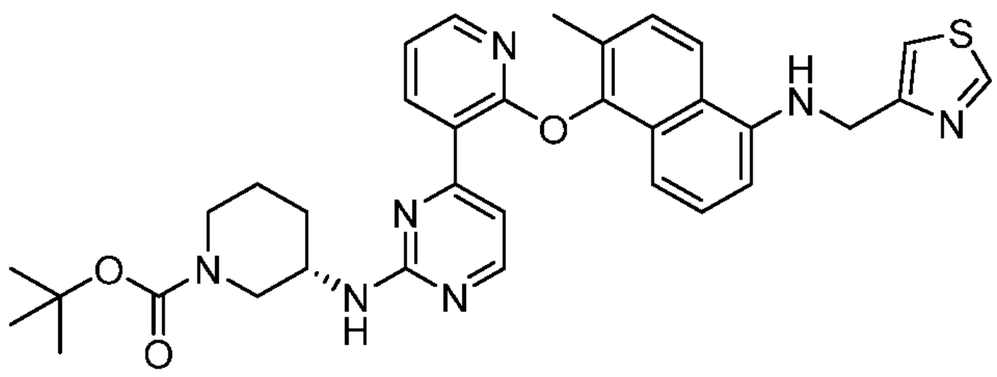


[0688] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-((2-methylthiazole)-5-sulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (50 mg, 0.08 mmol). The crude product was purified *via* reverse-phase HPLC and lyophilized to yield 30.7 mg (72% yield) of **210** as a light gray solid: LCMS (ESI) $[M+H]^+ = 588$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (s, 1H), 8.44 (d, J = 5.2 Hz, 1H), 8.24 (d, J = 8.7 Hz, 1H), 8.04 (dd, J = 4.8, 2.0 Hz, 1H), 7.65 (s, 1H), 7.54 (d, J = 5.2 Hz, 1H), 7.41 (d, J = 7.5 Hz, 1H), 7.22 (dt, J = 7.6, 4.8 Hz, 2H), 7.10 – 7.00 (m, 2H), 6.84 (s, 1H), 4.18 (s, 1H), 3.40 (d, J = 11.0 Hz, 1H), 3.15 (d, J = 12.9 Hz, 1H), 2.86 –2.75

(m, 2H), 2.56 – 2.53 (m, 3H), 2.16 (s, 3H), 2.03 – 1.97 (m, 1H), 1.92 – 1.86 (m, 1H), 1.71 – 1.57 (m, 1H).

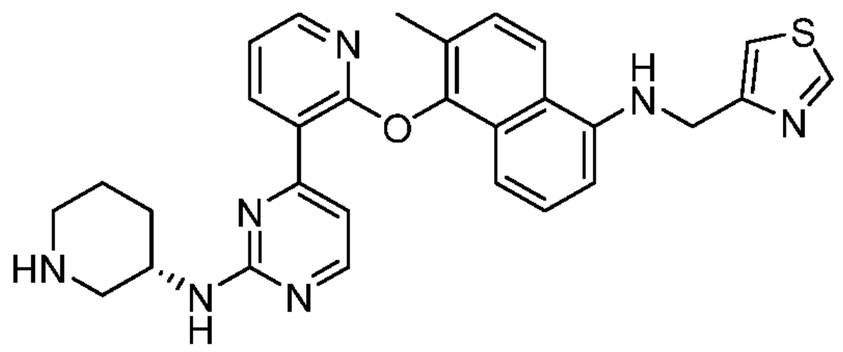
Example 211 *(S)-4-(2-((2-Methyl-5-((thiazol-4-ylmethyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine* ***211***

[0689] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-((thiazol-4-ylmethyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0690] To a solution of *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol) and DIPEA (0.13 mL, 0.7596 mmol) in DMF (1 mL) was added 4-(chloromethyl)thiazole hydrochloride (64.59 mg, 0.38 mmol). The mixture was heated at 65 °C for 48 h. It was then diluted with 10% citric acid, extracted with iPrOAc (2 x 10 ml), dried over $MgSO_4$ and filtered. The crude material was purified by silica gel chromatography (12 g column) eluting with 0-5% MeOH/DCM to afford 51 mg (43% yield) of the title compound as a brown sticky gum. LCMS (ESI) $[M+H]^+ = 624$.

[0691] Step 2: (*S*)-4-(2-((2-Methyl-5-((thiazol-4-ylmethyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-2-amine

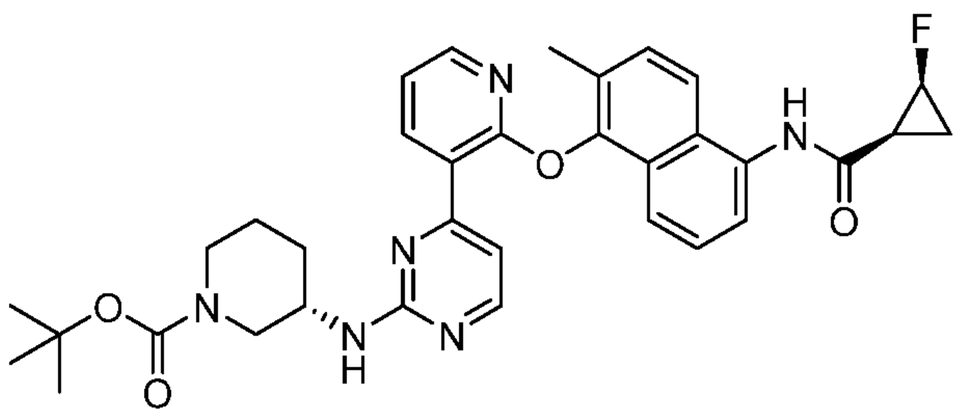


[0692] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-((thiazol-4-ylmethyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (51 mg, 0.08 mmol). The crude product was purified *via* reverse-phase HPLC and lyophilized to yield 2.5 mg (6% yield) of **211** as a pale brown solid. LCMS (ESI) $[M+H]^+ = 524$; ^1H NMR (400 MHz, DMSO-d_6) δ 8.48 (s, 1H), 8.39 (d, J = 5.1 Hz, 1H), 8.08 (d, J = 8.8 Hz, 1H), 8.01 (dd, J = 4.8, 2.0 Hz, 1H), 7.48 – 7.41 (m, 2H), 7.37 (d, J = 8.7 Hz, 1H), 7.22 (dd, J = 7.6, 4.8 Hz, 1H), 7.14 – 7.07 (m, 2H), 6.95 (t, J = 5.9 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 6.42 (dd, J = 7.6, 1.0 Hz, 1H), 4.62 (d, J = 5.8 Hz, 2H),

3.89 (s, 1H), 3.14 – 3.07 (m, 1H), 2.80 (d, *J* = 12.2 Hz, 1H), 2.19 (s, 3H), 1.96 – 1.87 (m, 1H), 1.68 – 1.62 (m, 1H), 1.52 – 1.40 (m, 2H).

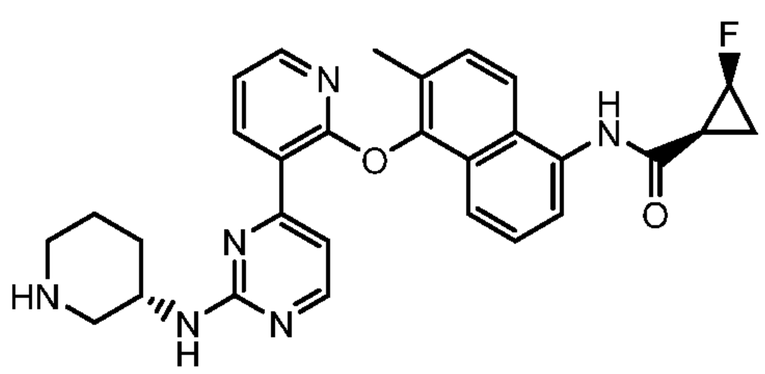
Example 212 (1S,2S)-2-Fluoro-N-[6-methyl-5-[[3-[2-[[(3S)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]cyclopropanecarboxamide ***212***

[0693] Step 1: *tert*-Butyl (S)-3-((4-(2-((5-((1S,2S)-2-fluorocyclopropane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0694] The General Procedure C was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (243 mg, 0.46 mmol), (*cis*)-2-fluorocyclopropanecarboxylic acid (40 mg, 0.38 mmol), DIPEA (0.201 mL, 1.15 mmol), HATU (671 mg, 1.73 mmol) and DCM (10 mL). The residue was purified *via* reverse-phase HPLC to provide a mixture of the two isomers. This mixture was then purified *via* chiral reverse-phase HPLC and lyophilized to yield 50 mg and 52 mg of the two single cis stereoisomers possessing a stereocenter at the 1 and 2 positions of the cyclopropyl amide moiety.

[0695] Step 2: (1*S*,2*S*)-2-Fluoro-*N*-[6-methyl-5-[[3-[2-[[(3*S*)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]cyclopropanecarboxamide

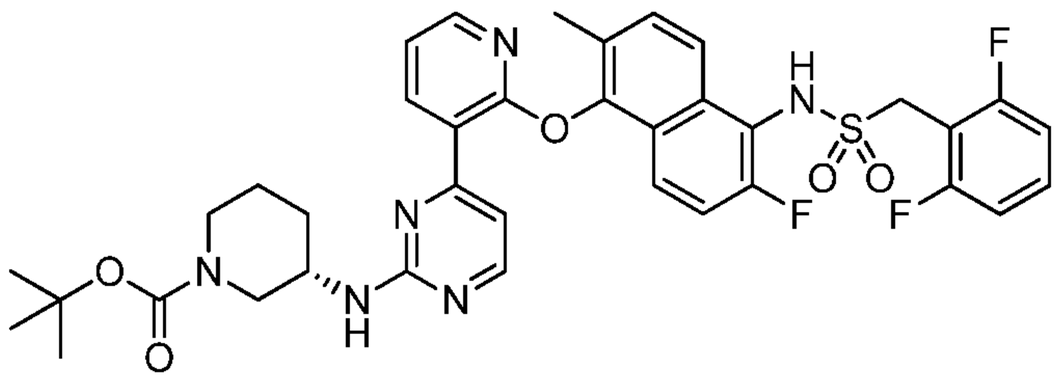


[0696] The General Procedure B was followed, using *tert*-butyl (3*S*)-3-((4-(2-((5-(2-fluorocyclopropane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (50 mg), DCM (4 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). The residue was purified via reverse-phase HPLC and lyophilized to yield 17.8 mg of **212**. The stereochemistry was tentatively and randomly assigned. LCMS (ESI): $[M+H]^+$ = 513.2; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.24 (s, 1H), 8.55 – 8.50 (m, 1H), 8.42 (d, J = 5.1 Hz, 1H), 8.03 (dd, J = 4.8, 2.0 Hz, 1H), 7.94 (d, J = 8.5 Hz, 1H), 7.64 (d, J =

7.4 Hz, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 5.1 Hz, 1H), 7.44 – 7.37 (m, 1H), 7.26 (dd, J = 7.6, 4.8 Hz, 1H), 7.18 (d, J = 7.9 Hz, 1H), 5.12 – 4.89 (m, 1H), 3.95 (s, 1H), 3.19 – 3.10 (m, 1H), 2.88 – 2.82 (m, 1H), 2.31 – 2.25 (m, 1H), 2.22 (s, 3H), 2.01 – 1.88 (m, 1H), 1.73 – 1.62 (m, 2H), 1.56 – 1.42 (m, 2H), 1.23 – 1.14 (m, 1H).

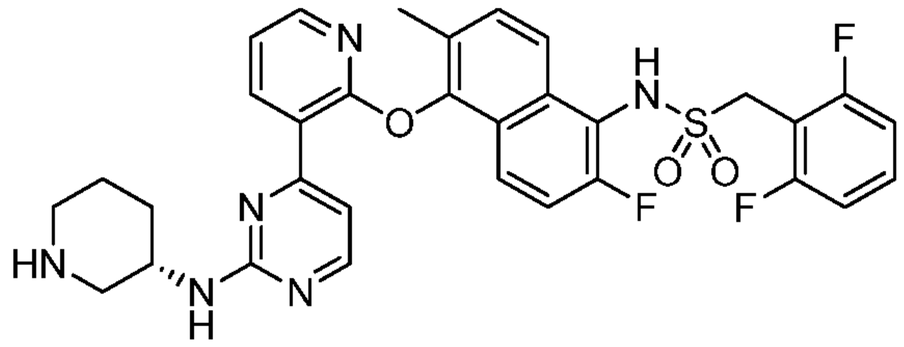
Example 213 *(S)-1-(2,6-Difluorophenyl)-N-(2-fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide* ***213***

[0697] Step 1: (S)-*tert*-butyl 3-((4-(2-((5-((2,6-difluorophenyl)methylsulfonamido)-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0698] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 275 (60 mg, 0.11 mmol), pyridine (0.090 mL, 1.11 mmol), DCM (1.5 mL), and (2,6-difluorophenyl)methanesulfonyl chloride (50 mg, 0.22 mmol). After 16 h, the reaction mixture was concentrated *in vacuo* and the residue was diluted with EtOAc, washed twice with 1M HCl(aq), then with saturated $NaHCO_3$(aq), then brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude was purified purified by C18 reverse phase flash chromatography (0 - 70% MeCN/10 mM aqueous ammonium formate, pH = 3.8). The product fractions were combined and concentrated to remove some MeCN, and lyophilized to provide 58 mg (72% yield) of the title compound. LCMS (ESI) $[M+H]^+$ = 735.3, rt = 1.97 min.

[0699] Step 2: (*S*)-1-(2,6-Difluorophenyl)-*N*-(2-fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)methanesulfonamide

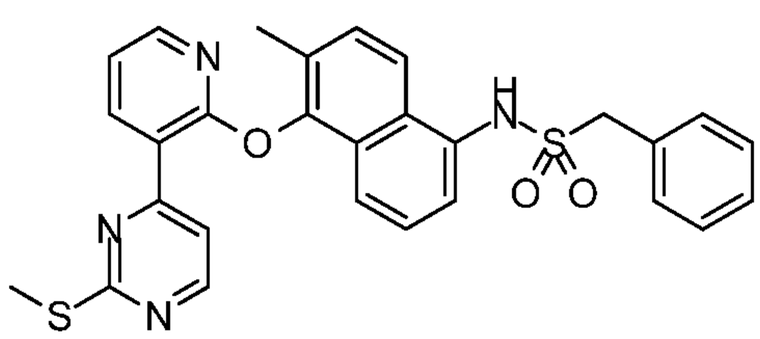


[0700] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-((2,6-difluorophenyl)methylsulfonamido)-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (58 mg, 0.079 mmol), 1,4-dioxane (1.5 mL), and hydrochloric acid (4 M in

dioxane, 0.5 mL, 2 mmol). After 4 h, the reaction mixture was diluted with MTBE (5 mL), and the resulting solids collected by filtration and washed with MTBE. The resulting solids were dissolved in a mixture of MeCN and H_2O, and lyophilized to provide 39 mg (74% yield) of **213**. LCMS (ESI) $[M+H]^+$ = 635.2, rt = 1.47 min. ^1H NMR (400 MHz, CD_3OD) δ 8.72 (d, J = 6.5 Hz, 1H), 8.47 (d, J = 5.6 Hz, 1H), 8.12 (d, J = 8.8 Hz, 1H), 8.05 (dd, J = 4.8, 1.8 Hz, 1H), 7.84 – 7.75 (m, 2H), 7.57 (d, J = 8.8 Hz, 1H), 7.51 – 7.40 (m, 1H), 7.36 (t, J = 9.5 Hz, 1H), 7.27 (dd, J = 7.6, 4.9 Hz, 1H), 7.10 – 6.99 (m, 2H), 4.74 (s, 2H), 4.50 – 4.34 (m, 1H), 3.66 – 3.60 (m, 1H), 3.41 – 3.34 (m, 1H), 3.12 – 2.99 (m, 2H), 2.25 (s, 3H), 2.23 – 2.07 (m, 2H), 1.98 – 1.74 (m, 2H).

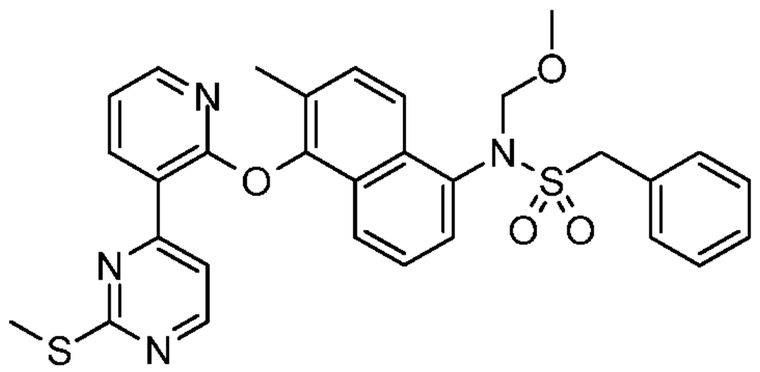
Example 214 *(S)-N-(6-Methyl-5-((3-(2-((S)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-phenylethanesulfonamide* ***214***

[0701] Step 1: *N*-(6-Methyl-5-((3-(2-(methylthio)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-phenylmethanesulfonamide



[0702] The General Procedure A was followed, using 6-methyl-5-[[3-(2-methylsulfanylpyrimidin-4-yl)-2-pyridyl]oxy]naphthalen-1-amine (2.0 g, 5.34 mmol), pyridine (10 mL) and benzyl sulfonyl chloride (1.2 g, 6.41 mmol). The organic layer was concentrated and purified by chromatography on silica (solvent gradient: 0-30% ethyl acetate in petroleum ether) to yield 2.6 g (92% yield) of the title compound as a yellow solid.

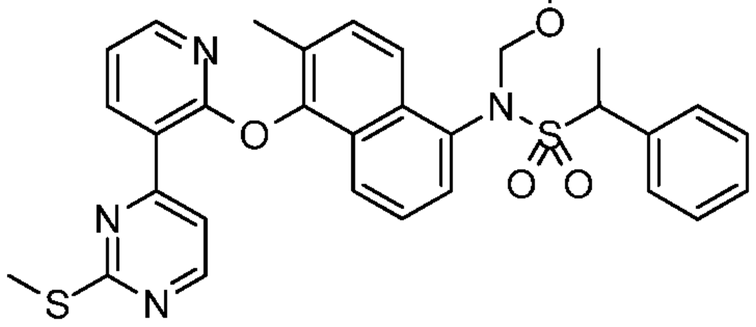
[0703] Step 2: *N*-(methoxymethyl)-*N*-(6-methyl-5-((3-(2-(methylthio)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-phenylmethanesulfonamide



[0704] To a solution of *N*-[6-methyl-5-[[3-(2-methylsulfanylpyrimidin-4-yl)-2-pyridyl]oxy]-1-naphthyl]-1-phenyl-methanesulfonamide (2.4 g, 4.54 mmol), *N,N*-diisopropylethylamine (0.87 mL, 4.99 mmol) in dichloromethane (20 mL) was added chloromethyl methyl ether (0.85 mL, 11.18 mmol) at 25 °C. The mixture was warmed to 25 °C for 1 h. The solution was

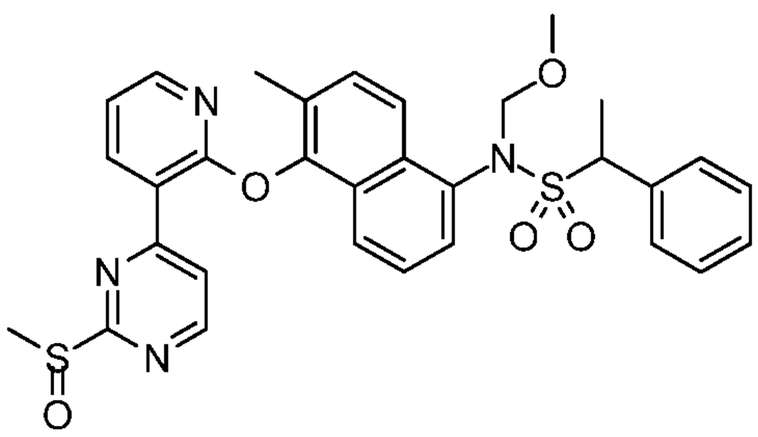
concentrated and purified by chromatography on silica (solvent gradient: 0-50% ethyl acetate in petroleum ether) to yield 2.3 g (88% yield) of the title compound as a yellow solid.

[0705] Step 3: *N*-(Methoxymethyl)-*N*-(6-methyl-5-((3-(2-(methylthio)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-phenylethanesulfonamide



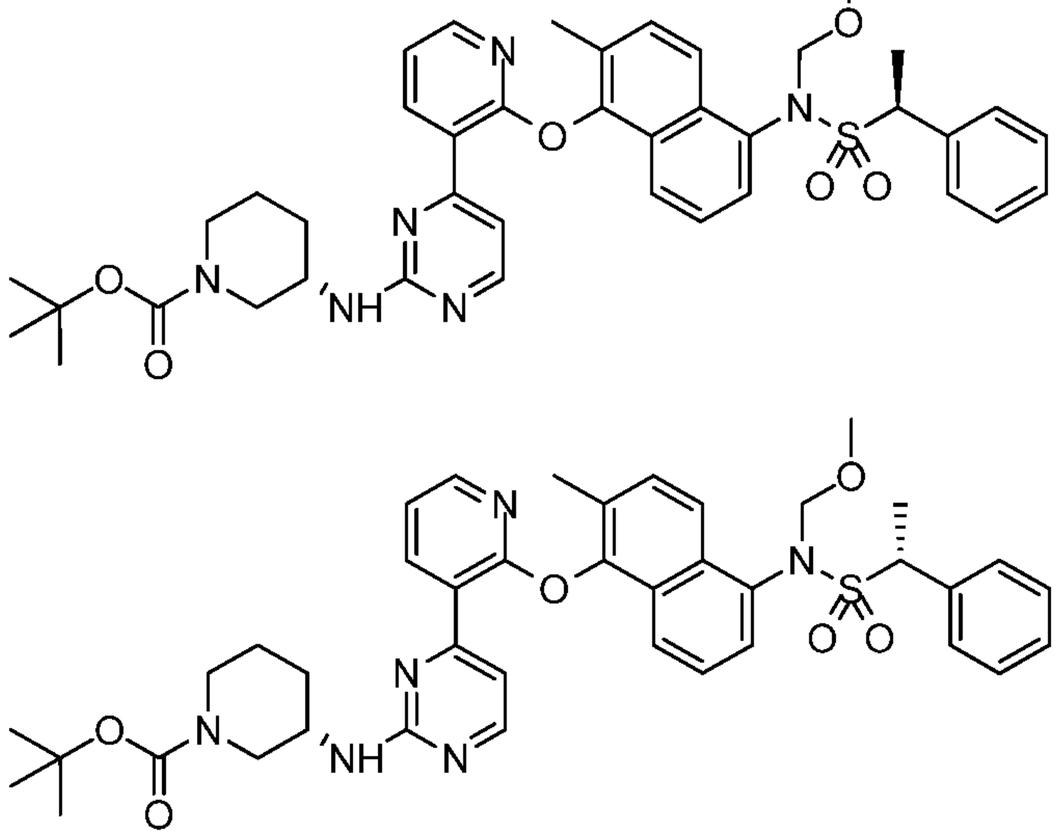
[0706] To a solution of *N*-(methoxymethyl)-*N*-[6-methyl-5-[[3-(2-methylsulfanylpyrimidin-4-yl)-2-pyridyl]oxy]-1-naphthyl]-1-phenyl-methanesulfonamide (1.2 g, 2.10 mmol) in tetrahydrofuran (5 mL) was added lithium bis(trimethylsilyl)azanide (4.19 mL, 4.19 mmol) at -78 °C and stirred for 30 min at -78 °C. The solution was warmed to 18 °C and cooled to -78 °C. Iodomethane (0.16 mL, 2.51 mmol) was added into the solution. The mixture was stirred at -78 °C for 2 h. Water (30 mL) was added and extracted by dichloromethane (50 mL x 3). The organic layer was concentrated and purified by chromatography on silica (solvent gradient: 0-30% ethyl acetate in petroleum ether) to yield 2.0 g (95% yield) of the title compound as a white solid.

[0707] Step 4: *N*-(Methoxymethyl)-*N*-(6-methyl-5-((3-(2-(methylsulfinyl)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-phenylethanesulfonamide



[0708] To a solution of *N*-(methoxymethyl)-*N*-[6-methyl-5-[[3-(2-methylsulfanylpyrimidin-4-yl)-2-pyridyl]oxy]-1-naphthyl]-1-phenyl-ethanesulfonamide (1.0 g, 1.70 mmol) in dichloromethane (3 mL) at 0 °C was added 80% 3-chloroperoxybenzoicacid (404 mg, 1.87 mmol). The resulting mixture was stirred at 0 °C for 0.5 h. To the solution was added saturated sodium bicarbonate to pH = 9 and then sodium sulfite until the starch potassium iodide test does not change color. The solution was extracted by dichloromethane (30 mL x 3) and water (30 mL x 2) and the organic layer was concentrated to yield 1.0 g (97% yield) of the title compound as a yellow solid.

[0709] Step 5: (*S*)-*tert*-Butyl 3-((4-(2-((5-((*S*)-*N*-(methoxymethyl)-1-phenylethylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate & (*S*)-*tert*-butyl 3-((4-(2-((5-((*R*)-*N*-(methoxymethyl)-1-phenylethylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate

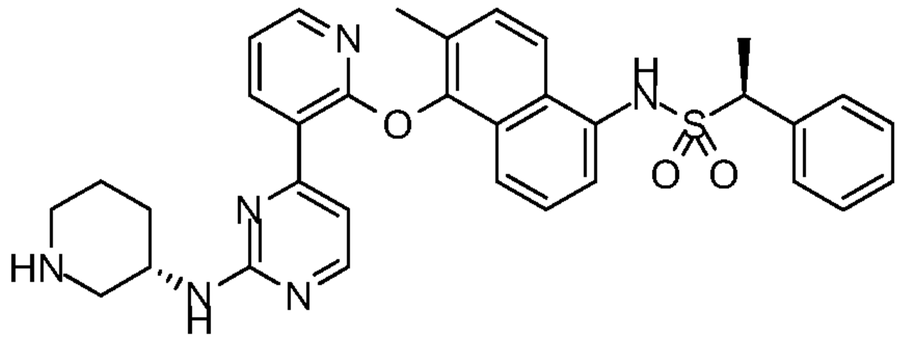


[0710] To a stirred solution of *N*,*N*-di*iso*propylethylamine (0.44 mL, 2.49 mmol) in 1,4-dioxane (5 mL) was added *N*-(methoxymethyl)-*N*-[6-methyl-5-[[3-(2-methylsulfinylpyrimidin-4-yl)-2-pyridyl]oxy]-1-naphthyl]-1-phenyl-ethanesulfonamide (500 mg, 0.83 mmol) and *tert*-butyl (3*S*)-3-amino-1-piperidinecarboxylate (249 mg, 1.24 mmol), the mixture was stirred at 130 °C for 16 h. The solution was concentrated and purified by chromatography on silica (solvent gradient: 0-50% ethyl acetate in petroleum ether) and separated using chiral SFC (SFC80; Chiralpak AD 250 × 30 mm I.D.,10 μm; Supercritical CO_2 / MEOH+NH_3•H_2O= 40 / 40; 80 mL / min) to yield *tert*-butyl (3*S*)-3-[[4-[2-[[2-methyl-5-(1-phenylethylsulfonylamino)-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (210 mg, 48% yield) as a white solid and *tert*-butyl (3*S*)-3-[[4-[2-[[2-methyl-5-(1-phenylethylsulfonylamino)-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (180 mg, 41% yield) as a white solid. LCMS (ESI): $[M+Na]^+$ = 761.0.

[0711] Step 6: (*S*)-*N*-(6-methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-phenylethanesulfonamide

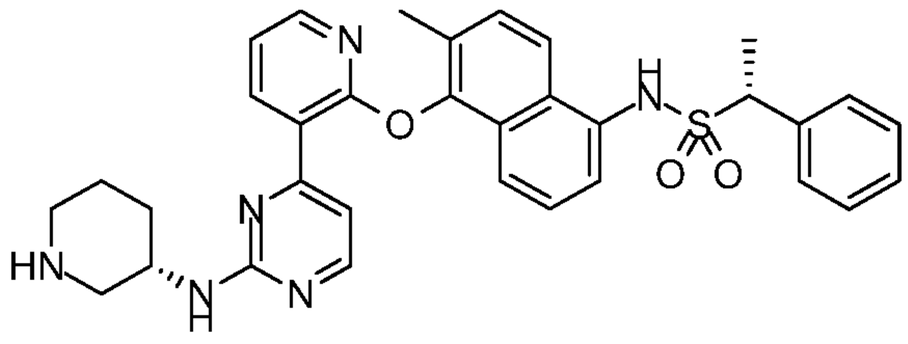
[0712] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-((*S*)-*N*-(methoxymethyl)-1-phenylethylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.14 mmol) or (*R*)-*tert*-butyl 3-((4-

(2-((5-((*R*)-*N*-(methoxymethyl)-1-phenylethylsulfonamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.14 mmol), dichloromethane (5 mL) and trifluoroacetic acid (2 mL, 14 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% ammonia) B: ACN) to yield two separate isomers. The absolute stereochemistry of **214** and **215** was assigned arbitrarly.



[0713] **214:** (*S*)-*N*-(6-Methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-phenylethanesulfonamide (3.2 mg 3.6% yield) as a yellow solid. LCMS (ESI): $[M+H]^+$ = 595.2. ^1H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 7.2 Hz, 1H), 8.35 (d, *J* = 5.6 Hz, 1H), 8.01 (d, *J* = 4.8 Hz, 1H), 7.67 (d, *J* = 5.6 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 7.2 Hz, 1H), 7.40 - 7.27 (m, 8H), 7.11 (d, *J* = 4.8 Hz, 1H), 5.69 (s, 1H), 4.45 (q, *J* = 7.2 Hz, 1H), 4.30 (s, 1H), 3.44 (d, *J* = 10.4 Hz, 1H), 3.05 (s, 1H), 2.93 - 2.86 (m, 2H), 2.27 (s, 3H), 2.08 - 1.94 (m, 2H), 1.84 (d, *J* = 7.2 Hz, 3H), 1.79 - 1.68 (m, 2H).

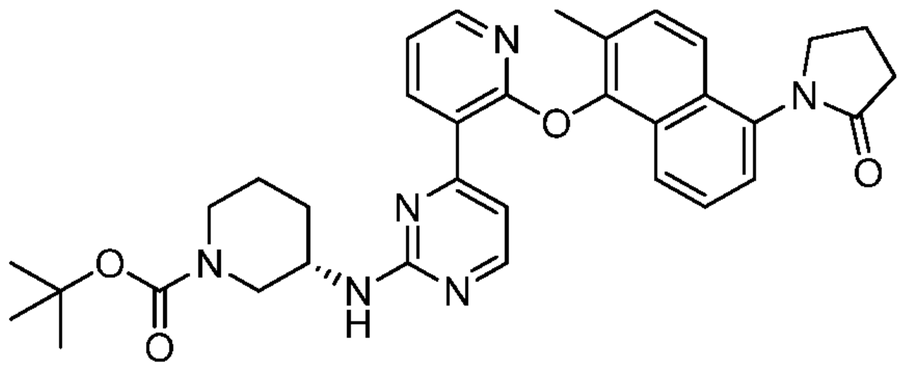
Example 215 *(R)-N-(6-methyl-5-((3-(2-((S)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-phenylethanesulfonamide* ***215***



[0714] Following the procedures of Example 214, **215** was isolated (11.4 mg, 13% yield) as a white solid. LCMS (ESI): $[M+H]^+$ = 595.2. ^1H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 7.2 Hz, 1H), 8.38 (d, *J* = 5.2 Hz, 1H), 8.04 (d, *J* = 5.2 Hz, 1H), 7.67 - 7.54 (m, 3H), 7.43 - 7.28 (m, 8H), 7.12 (d, *J* = 7.2 Hz, 1H), 5.43 (d, *J* = 7.2 Hz, 1H), 4.45 (q, *J* = 7.2 Hz, 1H), 4.11 (s, 1H), 3.32 (d, *J* = 10.4 Hz, 1H), 3.00 - 2.89 (m, 1H), 2.80 - 2.67 (m, 2H), 2.29 (s, 3H), 2.05 - 1.94 (m, 2H), 1.85 (d, *J* = 7.2 Hz, 3H), 1.74 - 1.72 (m, 2H).

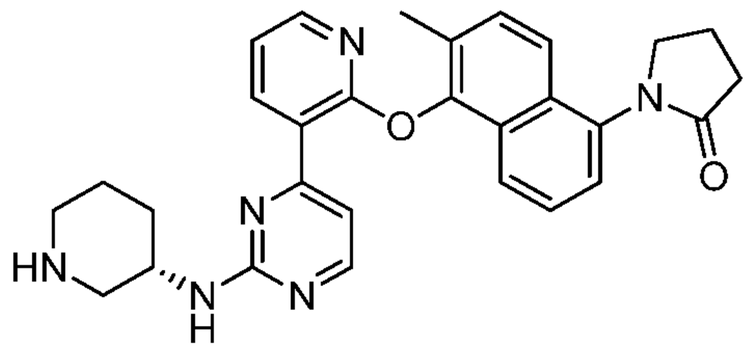
Example 216 *(S)-1-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidin-2-one* ***216***

[0715] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-5-(2-oxopyrrolidin-1-yl)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0716] To a solution of *tert*-butyl (3*S*)-3-[[4-[2-[(5-iodo-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.16 mmol) in 1,4-dioxane (2 mL) was added 2-pyrrolidone (100 mg, 1.18 mmol), copper (I) iodide (1.5 mg, 0.01 mmol), *N*, *N*'-dimethyl-1,2-ethanediamine (1.38 mg, 0.02 mmol) and potassium carbonate (65 mg, 0.47 mmol). The mixture was stirred at 110 °C for 12 h and then concentrated, dissolved in ethyl acetate (50 mL), and washed with H_2O (30 mL) and brine (30 mL). The organic phase was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated and purified by Prep-TLC (50% ethyl acetate in petroleum ether, Rf = 0.2) to yield 60 mg (64% yield) of the title compound as a white solid. LCMS (ESI) $[M+H]^+$ = 595.2.

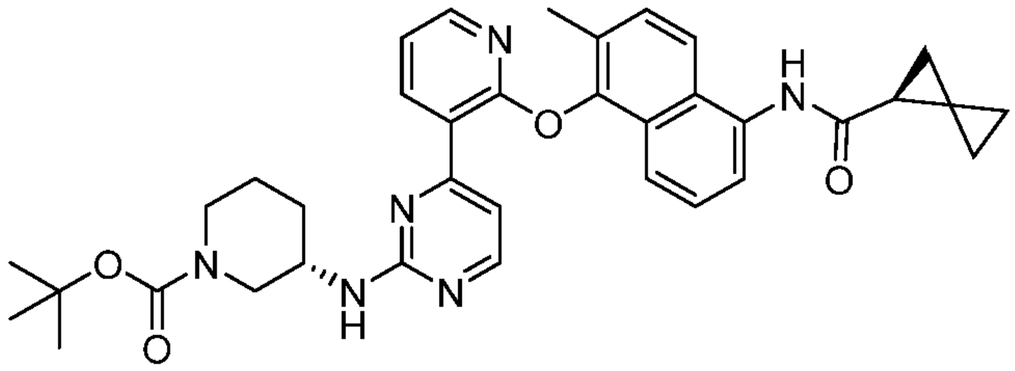
[0717] Step 2: (*S*)-1-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidin-2-one



[0718] To a solution of *tert*-butyl (3S)-3-[[4-[2-[[2-methyl-5-(2-oxopyrrolidin-1-yl)-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (90 mg, 0.15 mmol) in ethyl acetate (1 mL) was added 4M hydrochloric acid (0.38 mL, 1.51 mmol) in ethyl acetate and the mixture was stirred at 20 °C for 1 h. The mixture was concentrated and ethyl acetate (50 mL) and was added followed by washing with saturated sodium bicarbonate aqueous solution (50 mL) and H_2O (40 mL x 2). The organic phase was dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated and purified by prep-TLC (50% ethyl acetate in petroleum ether, Rf = 0.2) to yield 17.3 mg (22%) yield of **216** as a white solid. LCMS (ESI) $[M+H]^+$ = 495.2; ^1H NMR (400 MHz, DMSO-d_6) δ 8.55 - 8.46 (m, 1H), 8.41 (d, *J* = 5.2 Hz, 1H), 8.08 - 8.03 (m, 1H), 7.70 - 7.61 (m, 2H), 7.55 - 7.39 (m, 4H), 7.29 - 7.24 (m, 1H), 7.21 - 7.13 (m, 1H), 4.00 - 3.78 (m, 3H), 3.19 - 3.07 (m, 1H), 2.86 - 2.77 (m, 1H), 2.59 - 2.54 (m, 2H), 2.54 - 2.54 (m, 1H), 2.47 - 2.40 (m, 2H), 2.30 - 2.18 (m, 5H), 1.99 - 1.89 (m, 1H), 1.71 - 1.61 (m, 1H), 1.55 - 1.39 (m, 2H).

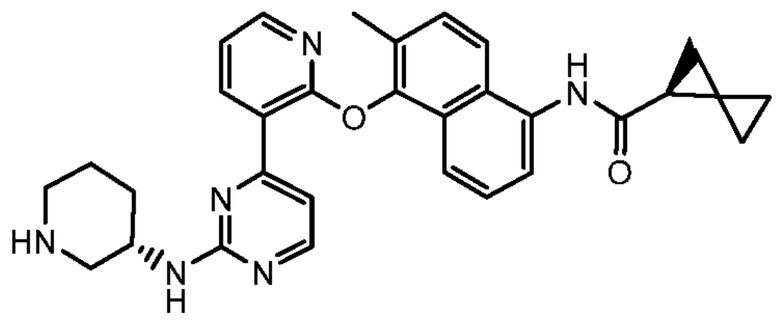
Example 217 *(S)-N-(6-Methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)spiro[2.2]pentane-1-carboxamide* ***217***

[0719] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-((S)-spiro[2.2]pentane-1-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



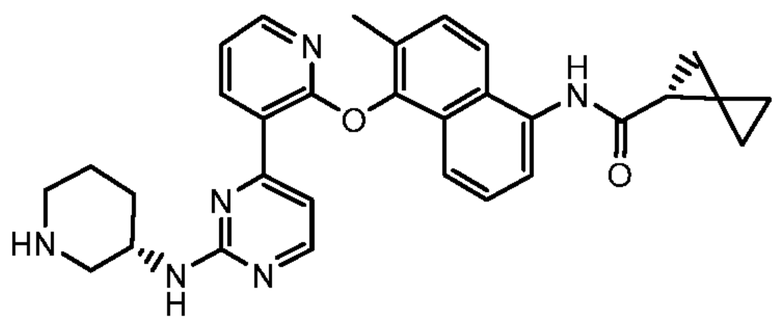
[0720] The General Procedure C was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (300 mg, 0.57 mmol), spiro[2.2]pentane-1-carboxylic acid (95.8 mg, 0.85 mmol), DIPEA (0.29 mL, 1.71 mmol), and HATU (442 mg, 1.14 mmol) in DMF (3 mL) was stirred at room temperature overnight to afford 325 mg (91.9% yield) of the title compound as a brown solid. The crude product was purified *via* reverse-phase HPLC and chiral SFC separation, isomer-1 (t_R= 1.107 min) affording the desired product in a yield of 124 mg and isomer-2 (t_R= 1.503 min) in a yield of 145 mg. LCMS (ESI) $[M+H]^+$ = 621.

[0721] Step 2: *N*-(6-Methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)spiro[2.2]pentane-1-carboxamide



[0722] The General Procedure B was followed, using tert-butyl (S)-3-((4-(2-((2-methyl-5-((S)-spiro[2.2]pentane-1-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-1, 124 mg, 0.20 mmol). The crude product was lyophilized to yield 111 mg (99.5% yield) of **217** (isomer-1) as an off-white solid. The absolute configuration of **217** and **218** was randomly assigned and may be later determined. LCMS (ESI) $[M+H]^+$ = 521; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.00 (s, 1H), 8.82 – 8.53 (m, 4H), 8.48 (d, *J* = 5.2 Hz, 1H), 8.05 (dd, *J* = 4.8, 2.0 Hz, 1H), 7.94 (d, *J* = 8.7 Hz, 1H), 7.67 (s, 1H), 7.58 (d, *J* = 5.2 Hz, 1H), 7.54 – 7.44 (m, 3H), 7.38 (dd, *J* = 8.5, 7.4 Hz, 1H), 7.27 (dd, *J* = 7.6, 4.8 Hz, 1H), 4.26 (s, 1H), 3.23 (s, 1H), 2.86 (s, 2H), 2.46 (s, 1H), 2.22 (s, 3H), 2.07 – 1.89 (m, 2H), 1.81 – 1.59 (m, 2H), 1.44 (t, *J* = 3.9 Hz, 1H), 1.36 (s, 1H), 1.00 – 0.76 (m, 4H).

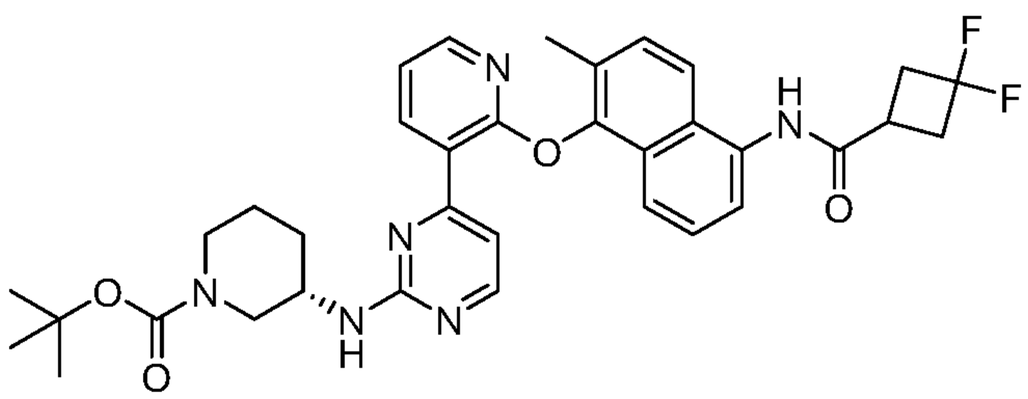
Example 218 *(R)-N-(6-Methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)spiro[2.2]pentane-1-carboxamide* ***218***



[0723] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-((*R*)-spiro[2.2]pentane-1-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-2, 145 mg, 0.26 mmol). The crude product was lyophilized to yield 109 mg (83.5% yield) of **218** (isomer-2) as an off-white solid. LCMS (ESI) [M+H]+ = 521; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H), 8.83 – 8.53 (m, 4H), 8.48 (d, J = 5.2 Hz, 1H), 8.05 (dd, J = 4.8, 2.0 Hz, 1H), 7.94 (d, J = 8.7 Hz, 1H), 7.66 (s, 1H), 7.58 (d, J = 5.2 Hz, 1H), 7.55 – 7.43 (m, 3H), 7.38 (dd, J = 8.5, 7.4 Hz, 1H), 7.27 (dd, J = 7.6, 4.8 Hz, 1H), 4.26 (s, 1H), 3.21 (d, J = 12.5 Hz, 1H), 2.85 (d, J = 13.7 Hz, 2H), 2.48 – 2.40 (m, 1H), 2.22 (s, 3H), 2.07 – 1.98 (m, 1H), 1.97 – 1.88 (m, 1H), 1.79 – 1.57 (m, 2H), 1.44 (t, J = 3.8 Hz, 1H), 1.41 – 1.32 (m, 1H), 1.01 – 0.78 (m, 4H).

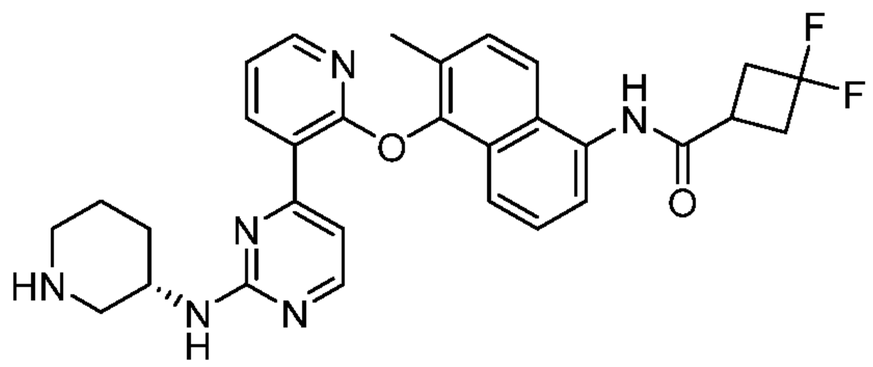
Example 219 *(S)-3,3-Difluoro-N-(6-methyl-5-(3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yloxy)naphthalen-1-yl)cyclobutanecarboxamide* ***219***

[0724] Step 1: (*S*)-*tert*-Butyl 3-(4-(2-(5-(3,3-difluorocyclobutanecarboxamido)-2-methylnaphthalen-1-yloxy)pyridin-3-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate



[0725] The General Procedure C was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (50 mg, 0.095 mmol), HATU (72 mg, 0.19 mmol), diisopropylethylamine (36 mg, 0.29 mmol), and 3,3-difluorocyclobutanecarboxylic acid (26 mg, 0.19 mmol). The product obtained after workup was used in step 2 without further purification. LCMS (ESI) $[M+H]^+$ = 645.4.

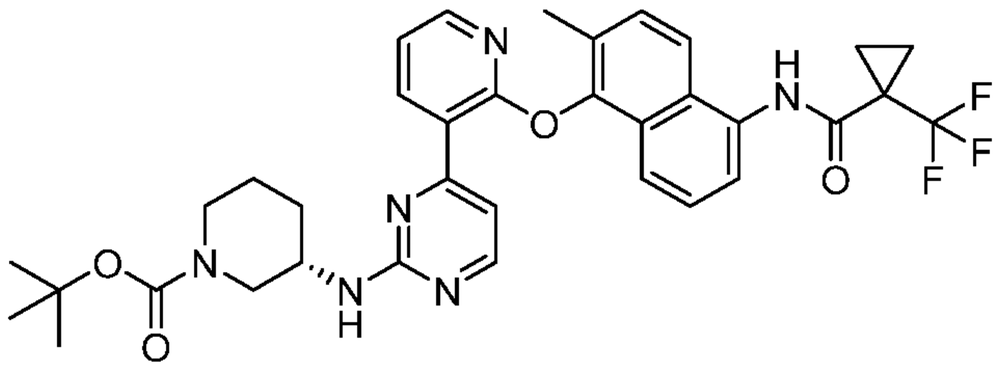
[0726] Step 2: (*S*)-3,3-Difluoro-*N*-(6-methyl-5-(3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yloxy)naphthalen-1-yl)cyclobutanecarboxamide



[0727] To the crude (*S*)-*tert*-butyl 3-(4-(2-(5-(3,3-difluorocyclobutanecarboxamido)-2-methylnaphthalen-1-yloxy)pyridin-3-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate from step 1 in DCM (6 mL) was added trifluoroacetic acid (1 mL). The mixture was concentrated and the residue purified by Prep-HPLC to yield 24 mg (47% yield) of **219** as a white solid. LCMS (ESI): $[M+H]^+$ = 545.2; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.11 (s, 1H), 8.56-8.43 (m, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.03 (dd, *J* = 4.8, 2.0 Hz, 1H), 7.90 (d, *J* = 8.7 Hz, 1H), 7.71-7.60 (m, 1H), 7.55-7.51 (m, 2H), 7.42 (m, 2H), 7.26 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 3.89 (br s, 1H), 3.37 (m, 1H), 3.10 (d, *J* = 11.8 Hz, 1H), 2.96 - 2.73 (m, 5H), 2.48-2.36 (m, 2H), 2.22 (s, 3H), 1.92 - 1.89 (m, 1H), 1.66 - 1.63 (m, 1H), 1.48-1.44 (m, 2H).

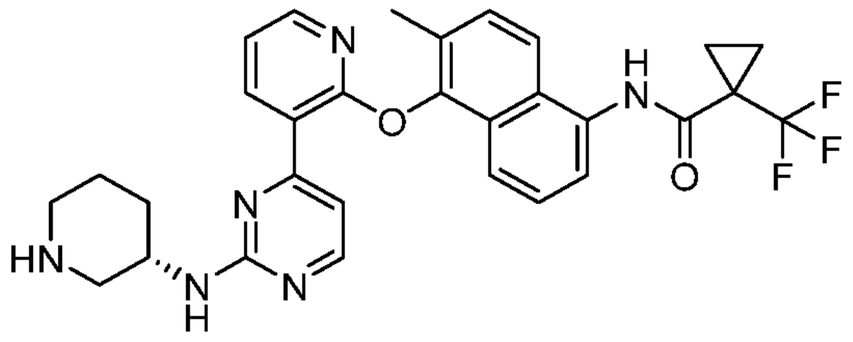
Example 220 *(S)-N-(6-Methyl-5-(3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yloxy)naphthalen-1-yl)-1-(trifluoromethyl)cyclopropanecarboxamide* ***220***

[0728] Step 1: (*S*)-*tert*-Butyl 3-(4-(2-(2-methyl-5-(1-(trifluoromethyl)cyclopropanecarboxamido)naphthalen-1-yloxy)pyridin-3-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate



[0729] The General Procedure C was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (50 mg, 0.095 mmol), HATU (72 mg, 0.19 mmol), diisopropylethylamine (36 mg, 0.29 mmol), and 1-(trifluoromethyl)cyclopropane-1-carboxylic acid (22 mg, 0.14 mmol). The product obtained after workup was used in step 2 without further purification. LCMS (ESI) $[M+H]^+$ = 663.3.

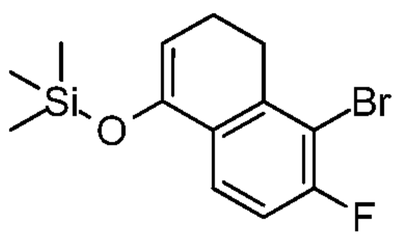
[0730] Step 2: (*S*)-*N*-(6-Methyl-5-(3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yloxy)naphthalen-1-yl)-1-(trifluoromethyl)cyclopropanecarboxamide



[0731] To the crude (*S*)-*tert*-butyl 3-(4-(2-(2-methyl-5-(1-(trifluoromethyl)cyclopropanecarboxamido)naphthalen-1-yloxy)pyridin-3-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate from step 1 in DCM (6 mL) was added trifluoroacetic acid (1 mL). The mixture was concentrated and the residue purified by Prep-HPLC to yield 1.6 mg (3% yield) of **220** as a white solid. LCMS (ESI): $[M+H]^+$ = 563.2.

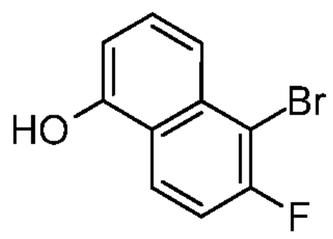
Example 221 *(S)-N-(2-Fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide* ***221***

[0732] Step 1: ((5-Bromo-6-fluoro-3,4-dihydronaphthalen-1-yl)oxy)trimethylsilane



[0733] To a solution of 5-bromo-6-fluoro-tetralin-1-one (5.0 g, 20.57 mmol) and triethylamine (11.56 mL, 82.28 mmol) in anhydrous dichloromethane (50 mL) was added trimethylsilyl trifluoromethanesulfonate (7.45 mL, 41.14 mmol) dropwsie at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at 25 °C for 2 h. The reaction was then quenched with ice water (50 mL) and extracted with methyl *tert* butyl ether (50 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield 6.4 g (crude) of the title compound as a yellow oil.

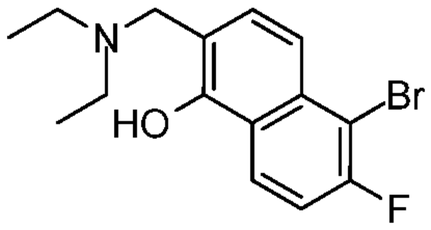
[0734] Step 2: 5-Bromo-6-fluoronaphthalen-1-ol



[0735] To a solution of ((5-bromo-6-fluoro-3,4-dihydronaphthalen-1-yl)oxy)trimethylsilane (6.0 g, 19.03 mmol) in anhydrous dimethyl sulfoxide (180 mL) was added palladium(II)acetate (427 mg, 1.9 mmol). The reaction mixture was stirred at 35 °C for 16 h under an oxygen atmosphere (15 Psi). After the addition of water (200 mL) at 0° C, the reaction mixture was filtered and then extracted with ethyl acetate (100 mL x 2). The combined organic layers were separated, dried over anhydrous sodium sulfate, filtered and concentrated

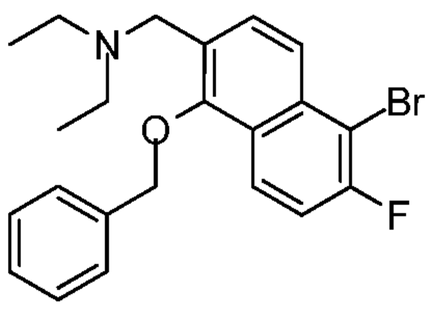
in vacuo. The residue was purified *via* flash silica chromatography (solvent gradient: 0-2% ethyl acetate in petroleum ether) to yield 3.5 g (76% yield) of the title compound as a pale brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 - 8.17 (m, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.41 (t, *J* = 8.4 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H).

[0736] Step 3: 5-Bromo-2-((diethylamino)methyl)-6-fluoronaphthalen-1-ol



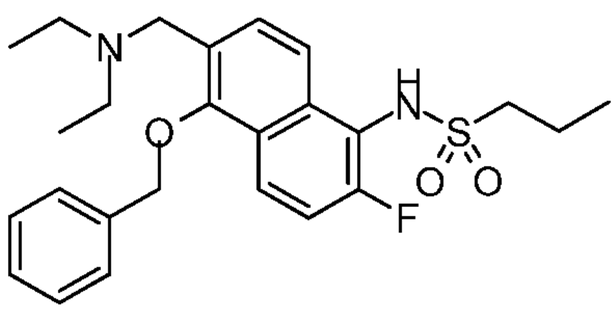
[0737] To a solution of 5-bromo-6-fluoronaphthalen-1-ol (4.0 g, 16.59 mmol) and 38% aqueous formaldehyde (1.34 mL, 18.25 mmol) in methanol (30 mL) was added diethylamine (1.97 mL, 19.08 mmol). The mixture was stirred at 25 °C for 12 h. The mixture was concentrated *in vacuo* and the residue was taken up in ethyl acetate (50 mL), washed with H_2O (50 mL x 2) and saturated brine solution (50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified *via* flash silica chromatography (solvent gradient: 0-25% ethyl acetate in petroleum ether) to yield 3.5 g (65% yield) of the title compound as red brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 - 8.21 (m, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.25 - 7.19 (m, 2H), 3.93 (s, 2H), 2.69 (q, *J* = 7.6 Hz, 4H), 1.16 (t, *J* = 7.6 Hz, 6H).

[0738] Step 4: *N*-((1-(Benzyloxy)-5-bromo-6-fluoronaphthalen-2-yl)methyl)-*N*-ethylethanamine



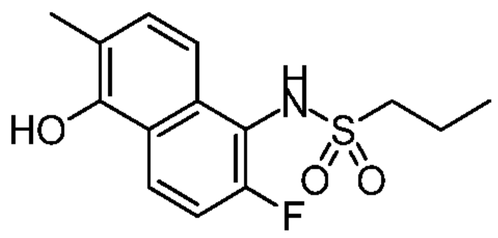
[0739] To a solution of 5-bromo-2-((diethylamino)methyl)-6-fluoronaphthalen-1-ol (3.5 g, 10.73 mmol) and potassium carbonate (2.97 g, 21.46 mmol) in DMF (35 mL) was added benzyl bromide (1.84 g, 10.73 mmol) dropwise. The resulting mixture was stirred at 25 °C for 16 h. The mixture was filtered and concentrated in *vacuo*. The crude product was purified *via* flash silica chromatography (solvent gradient: 0-10% ethyl acetate in petroleum ether) to yield 3.5 g (78% yield) of the title compound as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 - 8.05 (m, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.52 - 7.48 (m, 2H), 7.47 - 7.40 (m, 3H), 7.31 - 7.28 (m, 1H), 5.05 (s, 2H), 3.74 (s, 2H), 2.56 (q, *J* = 7.6 Hz, 4H), 1.04 (t, *J* = 7.6 Hz, 6H).

[0740] Step 5: *N*-(5-(Benzyloxy)-6-((diethylamino)methyl)-2-fluoronaphthalen-1-yl)propane-1-sulfonamide



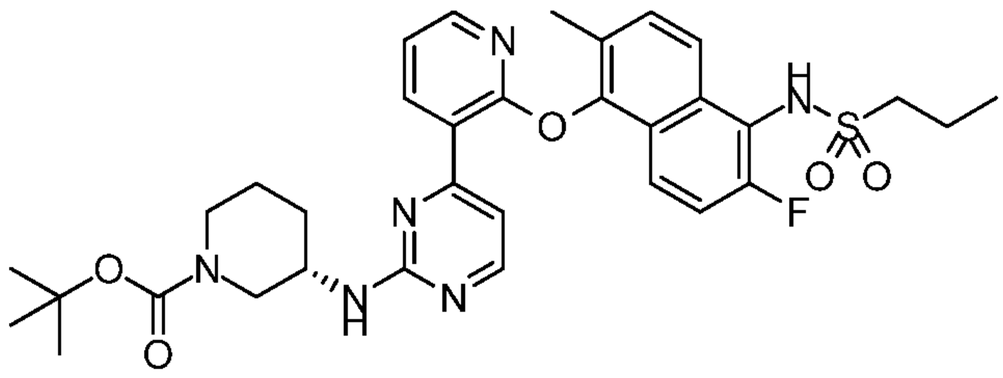
[0741] To a solution of *N*-[(1-benzyloxy-5-bromo-6-fluoro-2-naphthyl)methyl]-*N*-ethyl-ethanamine (1.0 g, 2.4 mmol), propane-1-sulfonamide (355 mg, 2.88 mmol) and potassium carbonate (664 mg, 4.8 mmol) in 2-methyltetrahydrofuran (15 mL) were added 2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl (102 mg, 0.24 mmol) and allyl palladium(II) chloride dimer (44 mg, 0.12 mmol). The mixture was heated to 80 °C for 12 h under an argon atmosphere. The mixture was filtered and concentrated *in vacuo*. The residue was purified *via* flash silica chromatography (solvent gradient: 0-1% methanol in dichloromethane) to yield 500 mg (45% yield) of the title compound as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 - 8.08 (m, 2H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.47 - 7.40 (m, 3H), 7.31 - 7.28 (m, 1H), 5.04 (s, 2H), 3.74 (s, 2H), 3.25 - 3.21 (m, 2H), 2.56 (q, *J* = 7.6 Hz, 4H), 2.05 - 1.98 (m, 2H), 1.11 (t, *J* = 7.6 Hz, 3H), 1.04 (t, *J* = 7.2 Hz, 6H).

[0742] Step 6: *N*-(2-Fluoro-5-hydroxy-6-methylnaphthalen-1-yl)propane-1-sulfonamide



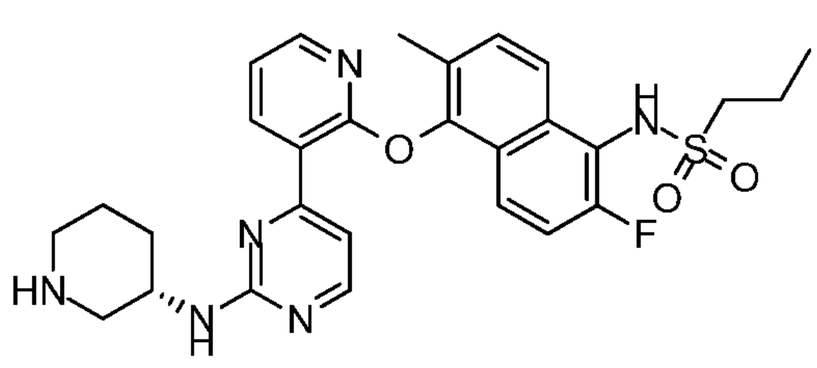
[0743] To a solution of *N*-[5-benzyloxy-6-(diethylaminomethyl)-2-fluoro-1-naphthyl]propane-1-sulfonamide (300 mg, 0.65 mmol) in ethanol (120 mL) was added 10% weight palladium (139 mg, 0.13 mmol) on carbon. The mixture was stirred at 25 °C under hydrogen gas (15 Psi) for 1 h. And acetic acid (0.12 mL, 1.96 mmol) was added and the mixture was stirred at 25 °C under hydrogen gas (15 Psi) for 16 h. The mixture was filtered and concentrated *in vacuo*. The residue was purified by Prep-TLC (50% ethyl acetate in petroleum ether) to 50 mg (26% yield) of the title compound as a yellow solid.

[0744] Step 7: (*S*)-*tert*-Butyl 3-((4-(2-((6-fluoro-2-methyl-5-(propylsulfonamido)naphthalen-1-yl)oxy) pyridine-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0745] To a solution of (*S*)-*tert*-butyl 3-((4-(2-((6-fluoro-2-methyl-5-(propylsulfonamido)naphthalen-1-yl)oxy) pyridine-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (38 mg, 0.10 mmol) and *N*-(2-fluoro-5-hydroxy-6-methyl-1-naphthyl)propane-1-sulfonamide (30 mg, 0.10 mmol) in anhydrous dimethyl sulfoxide (1.5 mL) was added cesium carbonate (66 mg, 0.20 mmol). The mixture was heated to 80 °C for 1 h. The mixture was filtered and water (5 mL) was added. The mixture was extracted with ethyl acetate (10 mL x 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by Prep-TLC (50% ethyl acetate in petroleum ether) to yield 30 mg (46% yield) of the title compound as a pale brown solid. LCMS (ESI) $[M+Na]^+ = 673.1$.

[0746] Step 8: (*S*)-*N*-(2-Fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy) naphthalen-1-yl)propane-1-sulfonamide



[0747] To a solution of (*S*)-*tert*-butyl 3-((4-(2-((6-fluoro-2-methyl-5-(propylsulfonamido)naphthalen-1-yl)oxy) pyridine-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (30 mg, 0.05 mmol) in ethyl acetate (0.50 mL) was added hydrochloricacid (4 M in ethyl acetate, 0.35 mL, 1.38 mmol). The reaction mixture was stirred at 20 °C for 1 h. The mixture was concentrated *in vacuo* and the residue was taken up in ethyl acetate (10 mL) and saturated sodium bicarbonate (5 mL). The orgainc layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by prep-TLC (10% methanol in dichloromethane) to yield 15 mg (59% yield) of **221** as a pale yellow solid. LCMS (ESI): $[M+H]^+ = 551$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 - 8.50 (m, 1H), 8.42 (d, J = 5.2 Hz, 1H), 8.08 - 8.04 (m, 2H), 7.71 - 7.68 (m, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.50 - 7.44 (m, 2H), 7.29 - 7.21 (m, 2H), 3.99 - 3.95 (m, 1H), 3.18 - 3.13 (m, 3H), 2.90 - 2.86 (m, 1H),

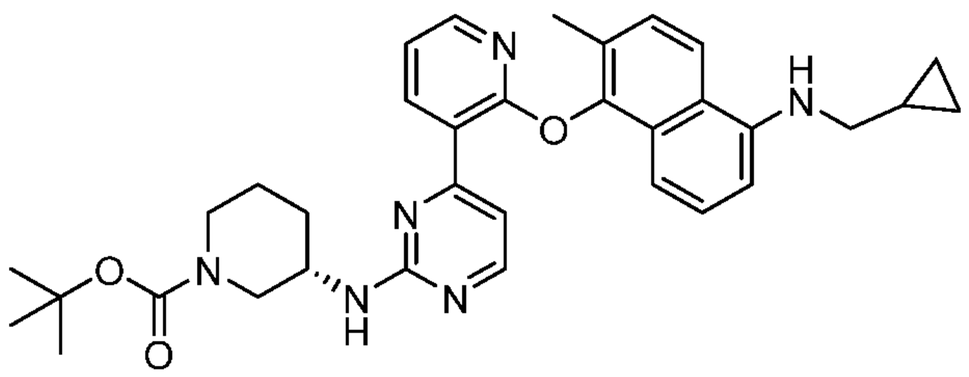
2.54 - 2.51 (m, 2H), 2.19 (s, 3H), 1.98 - 1.92 (m, 1H), 1.88 - 1.82 (m, 2H), 1.73 - 1.69 (m, 1H), 1.54 - 1.46 (2 H), 1.02 (t, J = 7.6 Hz, 3H).

Example 222 *(1R,2R)-2-Fluoro-N-[6-methyl-5-[[3-[2-[[(3S)-3-piperidyl]amino]pyrimidin-4-yl]-2-pyridyl]oxy]-1-naphthyl]cyclopropanecarboxamide* ***222***

[0748] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-((1*R*,2*R*)-2-fluorocyclopropane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example **212** (52 mg), DCM (4 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). The residue was purified via reverse-phase HPLC and lyophilized to yield 19.3 mg of **222**. LCMS (ESI): $[M+H]^+$ = 513.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 1H), 8.55 – 8.50 (m, 1H), 8.42 (d, J = 5.1 Hz, 1H), 8.03 (dd, J = 4.8, 2.0 Hz, 1H), 7.94 (d, J = 8.5 Hz, 1H), 7.64 (d, J = 7.4 Hz, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 5.1 Hz, 1H), 7.43 – 7.37 (m, 1H), 7.26 (dd, J = 7.6, 4.8 Hz, 1H), 7.12 (d, J = 7.9 Hz, 1H), 5.12 – 4.89 (m, 1H), 3.89 (s, 1H), 3.14 – 3.07 (m, 1H), 2.84 – 2.77 (m, 1H), 2.46 – 2.39 (m, 1H), 2.31 – 2.25 (m, 1H), 2.22 (s, 3H), 1.97 – 1.88 (m, 1H), 1.73 – 1.62 (m, 2H), 1.56 – 1.42 (m, 2H), 1.23 – 1.14 (m, 1H).

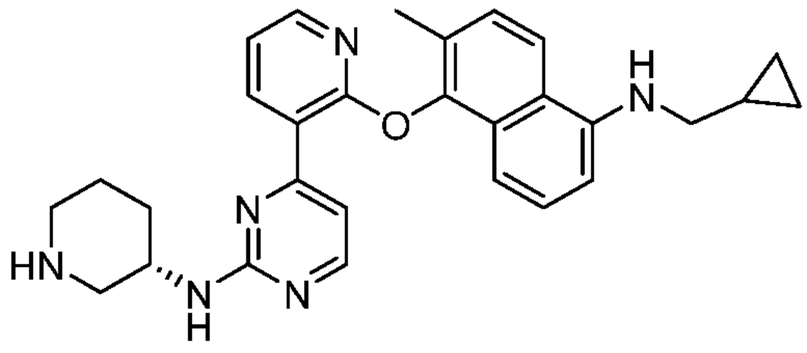
Example 223 *(S)-4-(2-((5-((Cyclopropylmethyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine* ***223***

[0749] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((5-((cyclopropylmethyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0750] The General Procedure E was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol) and (bromomethyl)cyclopropane (77 mg, 0.57 mmol). The crude material was purified by silica gel chromatography (12 g column), eluting with 0-5% MeOH/DCM to afford 46 mg (42% yield) of the title compound as a brown solid. LCMS (ESI) $[M+H]^+$ = 581.

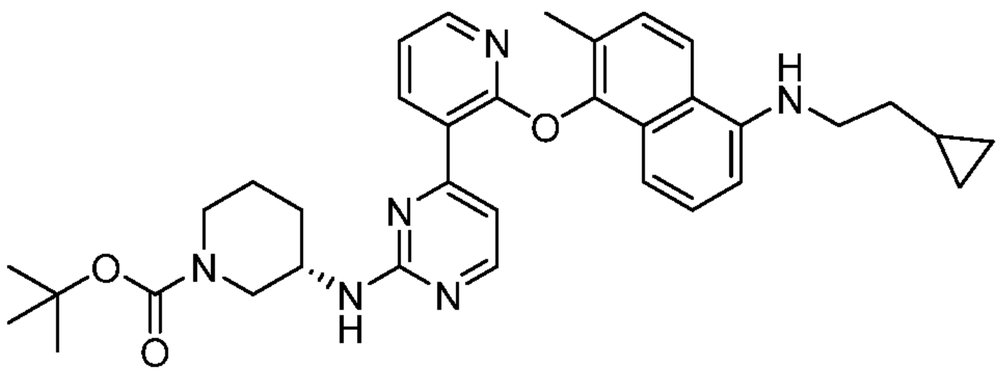
[0751] Step 2: (*S*)-4-(2-((5-((Cyclopropylmethyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine



[0752] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-((cyclopropylmethyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (46 mg, 0.08 mmol). The crude product was purified *via* reverse-phase HPLC and lyophilized to yield 21 mg (55.7% yield) of **223** as an off-white solid. LCMS (ESI) $[M+H]^+ = 481$; ^1H NMR (400 MHz, DMSO-d_6) δ 8.48 (s, 1H), 8.39 (d, J = 5.1 Hz, 1H), 8.04 (d, J = 8.6 Hz, 1H), 8.00 (dd, J = 4.8, 2.0 Hz, 1H), 7.43 (d, J = 5.1 Hz, 1H), 7.34 (d, J = 8.7 Hz, 1H), 7.22 (dd, J = 7.6, 4.8 Hz, 1H), 7.16 (dd, J = 8.3, 7.7 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 6.49 – 6.45 (m, 1H), 6.28 – 6.21 (m, 1H), 3.87 (s, 1H), 3.09 (s, 3H), 2.78 (d, J = 12.2 Hz, 1H), 2.43 (dd, J = 12.8, 4.1 Hz, 3H), 2.18 (s, 3H), 1.92 (s, 1H), 1.64 (d, J = 11.8 Hz, 1H), 1.54 – 1.38 (m, 1H), 1.26 – 1.16 (m, 1H), 0.54 – 0.46 (m, 2H), 0.29 (dd, J = 4.8, 1.6 Hz, 2H).

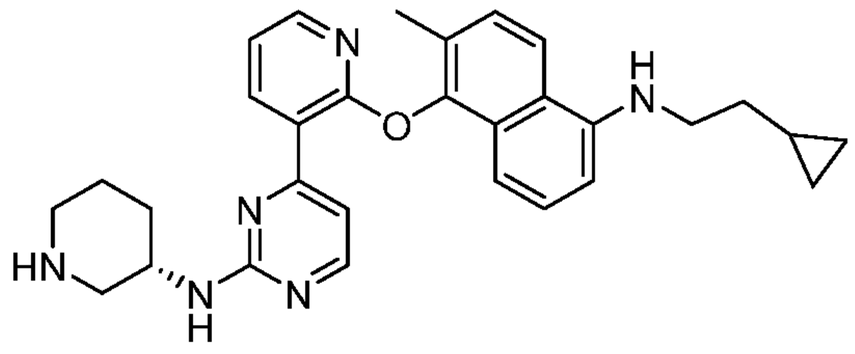
Example 224 *(S)-4-(2-((5-((2-Cyclopropylethyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine* ***224***

[0753] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((5-((2-Cyclopropylethyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0754] The General Procedure E was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol) and (2-bromoethyl)cyclopropane (89 mg, 0.57 mmol) to afford 46 mg (47% yield) of the title compound as a brown solid. It was carried on as is. LCMS (ESI) $[M+H]^+ = 595$.

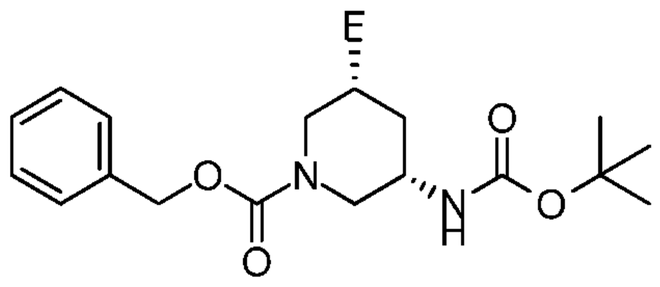
[0755] Step 2: (*S*)-4-(2-((5-((2-Cyclopropylethyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine



[0756] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-((2-cyclopropylethyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (46 mg, 0.08 mmol). The crude product was purified *via* reverse-phase HPLC and lyophilized to yield 21 mg (55% yield) of **224** as an off-white solid. LCMS (ESI) $[M+H]^+ = 495$; ^1H NMR (400 MHz, DMSO-d_6) δ 8.49 (d, J = 11.6 Hz, 1H), 8.39 (d, J = 5.1 Hz, 1H), 8.03 – 7.98 (m, 2H), 7.43 (d, J = 5.1 Hz, 1H), 7.32 (d, J = 8.7 Hz, 1H), 7.22 (dd, J = 7.5, 4.8 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 6.83 (d, J = 8.3 Hz, 1H), 6.46 – 6.42 (m, 1H), 3.88 (s, 1H), 3.09 (d, J = 10.9 Hz, 1H), 2.78 (d, J = 12.2 Hz, 1H), 2.47 – 2.38 (m, 3H), 2.18 (s, 3H), 1.92 (s, 1H), 1.67 – 1.57 (m, 3H), 1.54 – 1.39 (m, 2H), 0.89 – 0.81 (m, 1H), 0.48 – 0.41 (m, 2H), 0.16 – 0.08 (m, 2H).

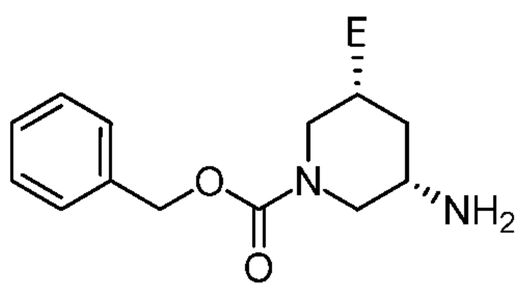
Example 225 *N-(5-((3-(2-(((3S,5R)-5-Fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)-1-(pyridin-2-yl) methanesulfonamide* ***225***

[0757] Step 1: (3*S*, 5*R*)-Benzyl 3-((*tert*-butoxycarbonyl)amino)-5-fluoropiperidine-1-carboxylate



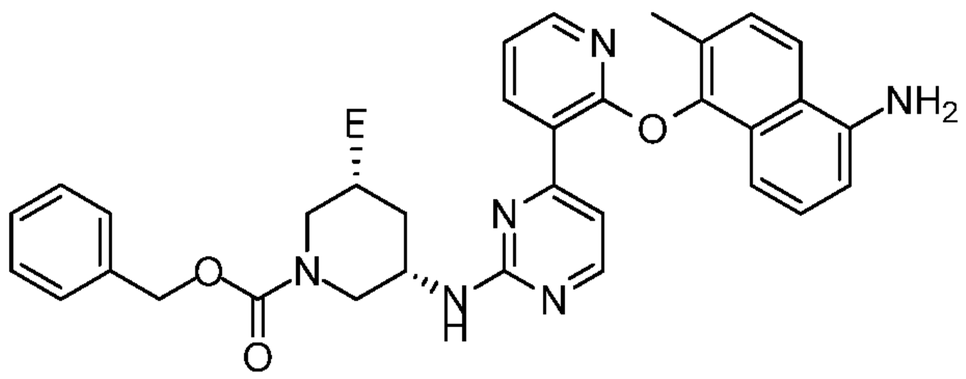
[0758] To a 100 mL 3-necked round-bottom flask was placed benzyl chloroformate (0.16 mL, 5.6 mmol), sodiumbicarbonate (115 mg, 1.37 mmol), *tert*-butyl *N*-[(3*S*,5*R*)-5-fluoro-3-piperidyl]carbamate (300 mg, 1.37 mmol) and tetrahydrofuran (6 mL). The resulting solution was stirred at room temperature for 4 h. TLC (33% ethyl acetate in petroleum ether, Rf = 0.4) showed that the reaction was complete. The residue was purified chromatography by silica gel chromatogaphy (solvent gradient: 0-20% ethyl acetate in petroleum ether) to yield 0.35 g (72% yield) of the title compound as a white solid.

[0759] Step 2: (3*S*, 5*R*)- Benzyl 3-amino-5-fluoropiperidine-1-carboxylate



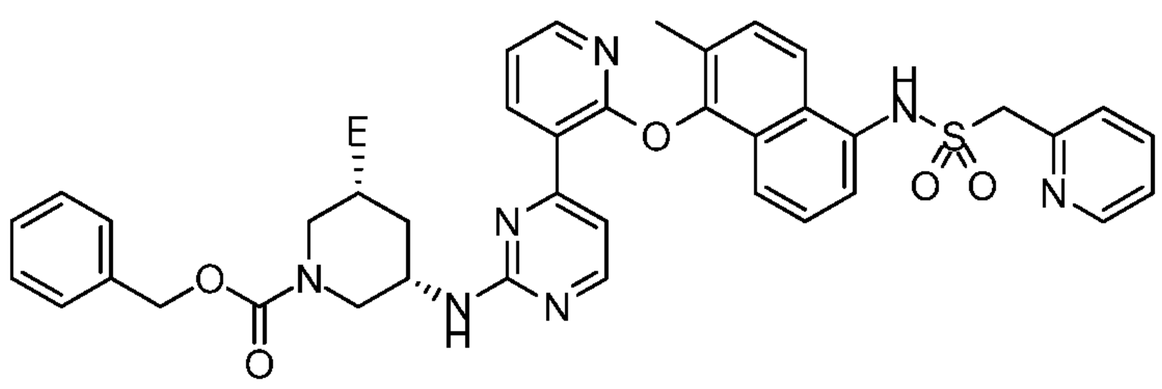
[0760] The General Procedure B was followed, using benzyl (3*S*,5*R*)-3-(*tert*-butoxycarbonylamino)-5-fluoro-piperidine-1-carboxylate (350 mg, 0.99 mmol), dichloromethane (5 mL) and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). The resulting solution was stirred at room temperature for 2 h. The the solution was concentrated to yield 330 mg (crude) of the title product as a white solid.

[0761] Step 3: (3*S*, 5*R*)-Benzyl 3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)-5-fluoropiperidine-1-carboxylate



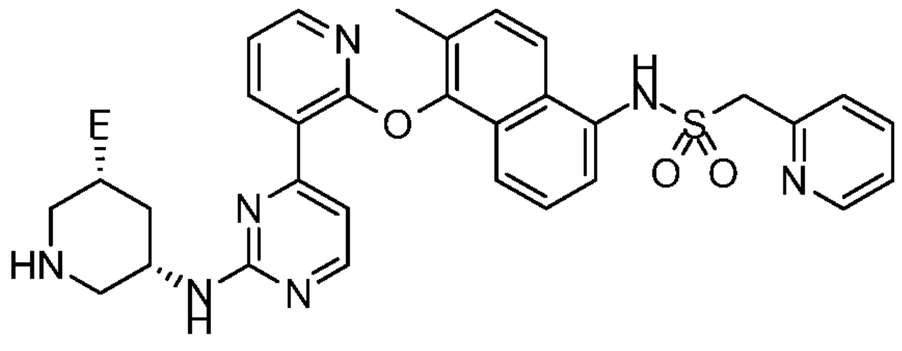
[0762] To a 100 mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 6-methyl-5-[[3-(2-methylsulfinylpyrimidin-4-yl)-2-pyridyl]oxy]naphthalen-1-amine (300 mg, 0.77 mmol), benzyl (3*S*,5*R*)-3-amino-5-fluoro-piperidine-1-carboxylate (252 mg, 1 mmol), 1,4-dioxane (6 mL) and *N,N*-diisopropylethylamine (0.16 mL, 0.91 mmol). The resulting solution was stirred at 110 ºC in an oil bath for 24 h, cooled to room temperature and concentrated *in vacuo*. The residue was purified *via* flash silica chromatography (solvent gradient: 5% methanol in dichloromethane) to yield 0.3 g (67 % yield) of the title compound as a yellow solid. LCMS: (ES, m/z): $[M+H]^+$ = 579.2.

[0763] Step 4: (3*R*, 5*S*)-Benzyl-3-fluoro-5-((4-(2-((2-methyl-5-(pyridin-2-ylmethylsulfonamido) naphthalene-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0764] The General Procedure A was followed, using benzyl (3*S*,5*R*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]-5-fluoro-piperidine-1-carboxylate (300 mg, 0.52 mmol), pyridine (4 mL) and 2-pyridylmethanesulfonyl chloride (119 mg, 0.62 mmol). The residue was purified by Prep-TLC (normal phase, petroleum ether/ethyl acetate = 2 / 1) to yield 60 mg (16% yield) of the title compound as a brown oil. LCMS (ESI) $[M+H]^+$ = 734.1.

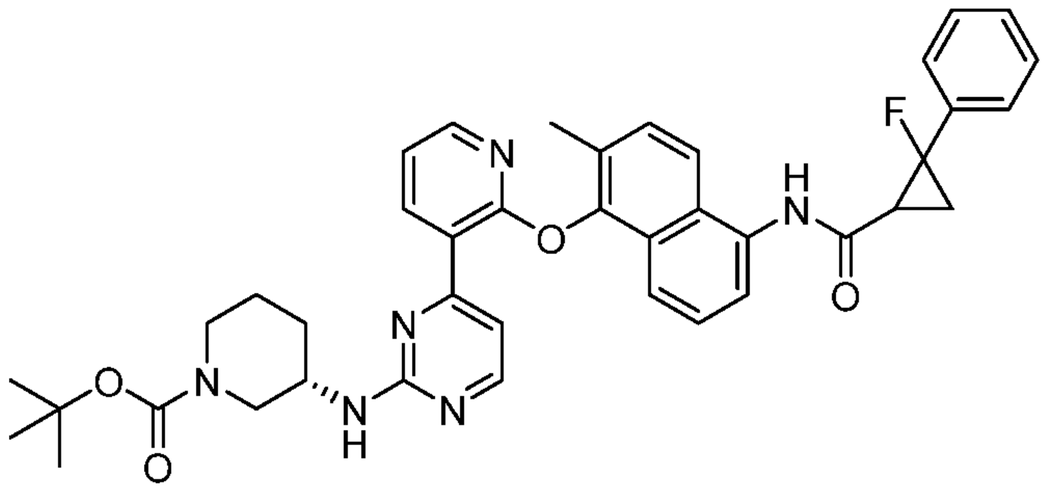
[0765] Step 5: *N*-(5-((3-(2-(((3*S*, 5*R*)-5-Fluoropiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)-1-(pyridin-2-yl)methanesulfonamide



[0766] To a 100 mL 3-necked round-bottom flask was placed benzyl (3*R*,5*S*)-3-fluoro-5-[[4-[2-[[2-methyl-5-(2-pyridylmethylsulfonylamino)-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (45 mg, 0.06 mmol), 1-methylimidazole (20 mg, 0.25 mmol), thiourea (23 mg, 0.31 mmol), iodotrimethylsilane (0.07 mL, 0.49 mmol) and acetonitrile (1 mL). The mixture was then stirred at room temperature for 1 h and concentrated *in vacuo*. The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% NH_4OH) B: ACN) to yield 6.3 mg (17% yield) of **225** as a white solid. LCMS (ESI): $[M+H]^+$ = 600.2. ^1H NMR (400 MHz, DMSO-d_6) δ 8.56 (d, *J* = 4.6 Hz, 1H), 8.50 (s, 1H), 8.42 (d, *J* = 5.2 Hz, 1H), 8.11 - 8.02 (m, 2H), 7.86 - 7.77 (m, 1H), 7.62 - 7.55 (m, 2H), 7.54 - 7.49 (m, 2H), 7.47 (d, *J* = 5.2 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.41 - 7.35 (m, 1H), 7.28 - 7.19 (m, 2H), 4.64 (s, 3H), 3.99 (s, 1H), 3.10 (m, 2H), 2.45 (m, 1H), 2.39 - 2.29 (m, 2H), 2.21 (s, 3H), 1.75-1.55 (m, 1H).

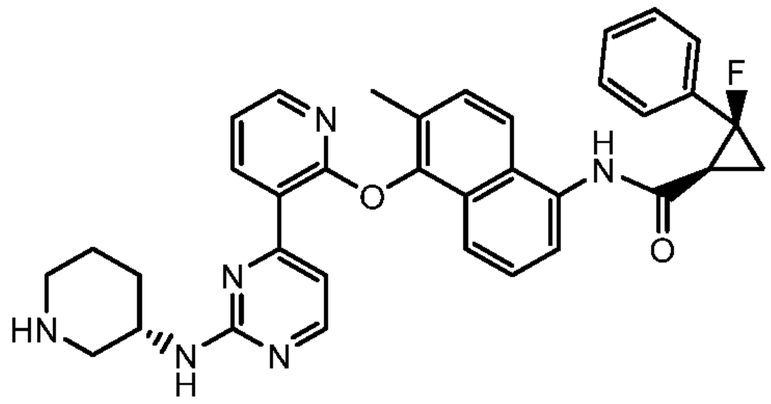
Example 226 2-Fluoro-N-(6-methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-phenylcyclopropane-1-carboxamide ***226***

[0767] Step 1: *tert*-Butyl (3*S*)-3-((4-(2-((5-(2-fluoro-2-phenylcyclopropane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0768] The General Procedure C was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (210 mg, 0.40 mmol), 2-fluoro-2-phenyl-cyclopropanecarboxylic acid (60 mg, 0.33 mmol), DIPEA (0.174 mL, 1.0 mmol), HATU (388 mg, 1.73 mmol) and DCM (10 mL). The residue was purified *via* reverse-phase HPLC to provide a mixture of the two isomers. This mixture was purified *via* chiral reverse-phase HPLC and lyophilized to yield 31.6 mg and 34.4 mg of the two single stereoisomers enantiomeric at the 1 and 2 positions of the cyclopropyl amide.

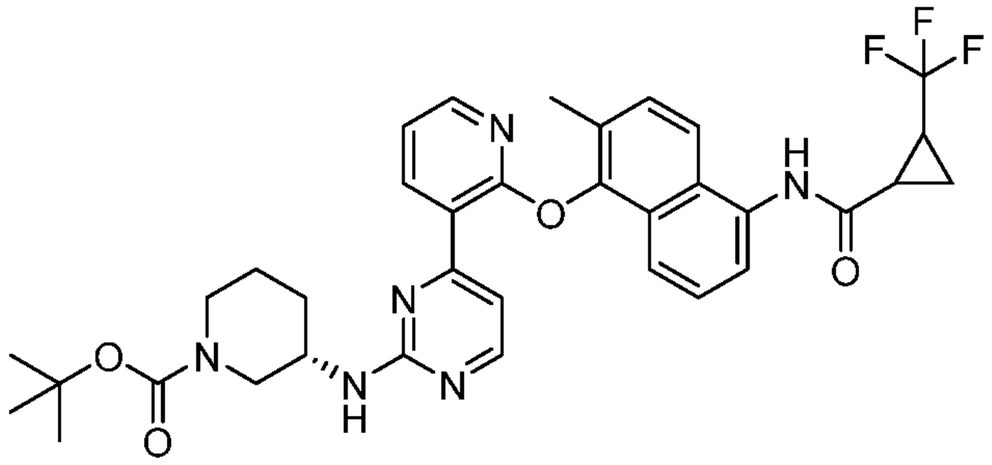
[0769] Step 2: 2-Fluoro-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-phenylcyclopropane-1-carboxamide



[0770] The General Procedure B was followed using *tert*-butyl (3*S*)-3-((4-(2-((5-(2-fluoro-2-phenylcyclopropane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (31.6 mg, 0.046 mmol), DCM (4 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). The residue was purified *via* reverse-phase HPLC and lyophilized to yield 20.1 mg (74% yield) of **226**. The stereochemistry was tentatively and randomly assigned. LCMS (ESI): $[M+H]^+$ = 589.2; ^{1}H NMR (400 MHz, DMSO-d6) δ 10.35 (s, 1H), 8.50 – 8.45 (m, 1H), 8.43 – 8.39 (m, 1H), 8.00 (dd, J = 4.9, 2.0 Hz, 1H), 7.61 – 7.53 (m, 3H), 7.47 – 7.36 (m, 7H), 7.31 – 7.27 (m, 1H), 7.25 (dd, J = 7.5, 4.8 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 3.90 (s, 1H), 2.84 – 2.78 (m, 1H), 2.81 (d, J = 12.7 Hz, 1H), 2.50 – 2.40 (m, 1H), 2.19 (s, 3H), 2.07 – 1.99 (m,12H), 1.95 – 1.83 (m, 2H), 1.68 – 1.61 (m, 1H), 1.53 – 1.39 (m, 2H).

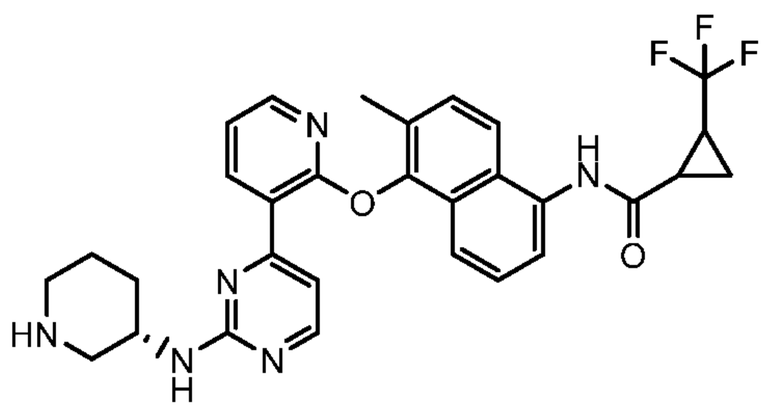
Example 227 *N-(6-Methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-(trifluoromethyl)cyclopropane-1-carboxamide* ***227***

[0771] Step 1: *tert*-Butyl (3*S*)-3-((4-(2-((2-methyl-5-(2-(trifluoromethyl)cyclopropane-1-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0772] The General Procedure C was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (357 mg, 0.40 mmol), 2-(trifluoromethyl)cyclopropanecarboxylic acid (95 mg, 0.62 mmol), DIPEA (0.323 mL, 1.85 mmol), HATU (718 mg, 1.85 mmol) and DCM (10 mL). The residue was purified *via* reverse-phase HPLC to provide a mixture of the two isomers. This mixture was then purified *via* chiral reverse-phase HPLC and lyophilized to yield 71 mg and 61 mg of the two single stereoisomers possessing stereocenters at the 1 and 2 positions of the cyclopropyl amide.

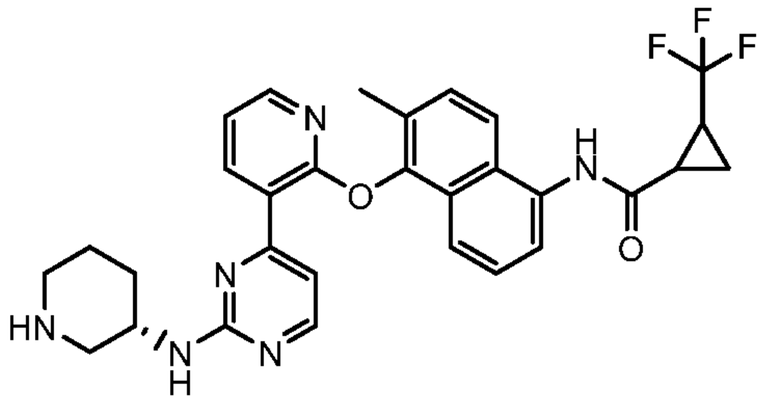
[0773] Step 2: *N*-(6-Methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-(trifluoromethyl)cyclopropane-1-carboxamide



[0774] The General Procedure B was followed, using *tert*-butyl (3*S*)-3-((4-(2-((2-methyl-5-(2-(trifluoromethyl)cyclopropane-1-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (71 mg, 0.11 mmol), DCM (4 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). The residue was purified *via* reverse-phase HPLC and lyophilized to yield 40.9 mg of **227**. The stereochemistry was tentatively and randomly assigned. LCMS (ESI): $[M+H]^+$ = 563.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.45 (s, 1H), 8.52 – 8.47 (m, 1H), 8.41 (d, J = 5.1 Hz, 1H), 8.03 (dd, J = 4.8, 2.0 Hz, 1H), 7.98 (d, J = 8.7 Hz, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.57 – 7.51 (m, 2H), 7.45 – 7.36 (m, 2H), 7.26 (dd, J = 7.6, 4.8

Hz, 1H), 7.11 (d, J = 8.1 Hz, 1H), 3.88 (s, 1H), 3.13 – 3.05 (m, 1H), 2.81 – 2.75 (m, 1H), 2.71 – 2.60 (m, 1H), 2.48 – 2.36 (m, 2H), 2.36 – 2.27 (m, 1H), 2.22 (s, 3H), 1.96 – 1.88 (m, 1H), 1.68 – 1.57 (m, 1H), 1.53 – 1.40 (m, 2H), 1.35 (t, J = 7.4 Hz, 2H).

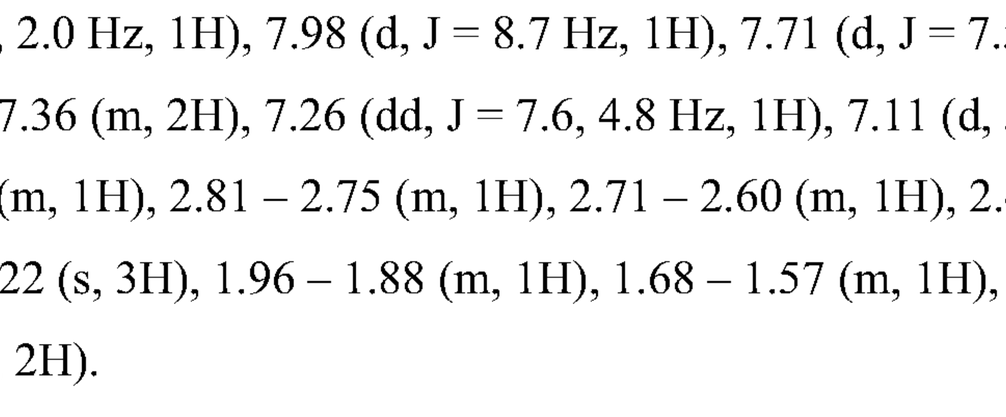
Example 228 *N-(6-Methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-(trifluoromethyl)cyclopropane-1-carboxamide* ***228***



[0775] The General Procedure B was followed, using *tert*-butyl (3*S*)-3-((4-(2-((2-methyl-5-(2-(trifluoromethyl)cyclopropane-1-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 227 (61 mg, 0.092 mmol), DCM (4 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). The residue was purified *via* reverse-phase HPLC and lyophilized to yield 30.1 mg of **228**. LCMS (ESI): $[M+H]^+$ = 563.3; ^1H NMR (400 MHz, DMSO-d_6) δ 10.45 (s, 1H), 8.52 – 8.47 (m, 1H), 8.41 (d, J = 5.1 Hz, 1H), 8.03 (dd, J = 4.8, 2.0 Hz, 1H), 7.98 (d, J = 8.7 Hz, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.57 – 7.51 (m, 2H), 7.45 – 7.36 (m, 2H), 7.26 (dd, J = 7.6, 4.8 Hz, 1H), 7.11 (d, J = 8.1 Hz, 1H), 3.88 (s, 1H), 3.13 – 3.05 (m, 1H), 2.81 – 2.75 (m, 1H), 2.71 – 2.60 (m, 1H), 2.48 – 2.36 (m, 2H), 2.36 – 2.27 (m, 1H), 2.22 (s, 3H), 1.96 – 1.88 (m, 1H), 1.68 – 1.57 (m, 1H), 1.53 – 1.40 (m, 2H), 1.35 (t, J = 7.4 Hz, 2H).

Example 229 *2-Isopropyl-N-(6-methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide* ***229***

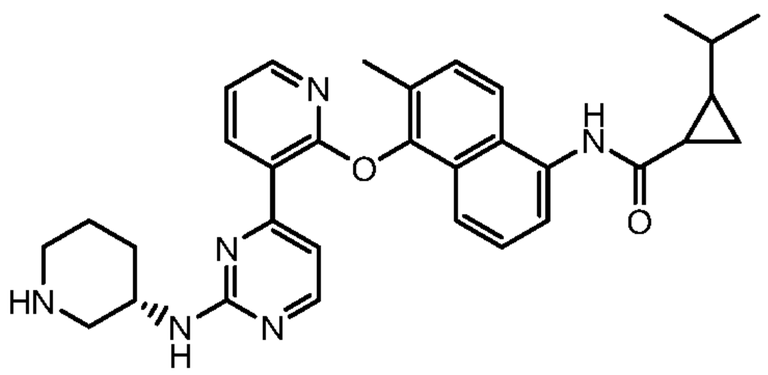
[0776] Step 1: *tert*-Butyl (3*S*)-3-((4-(2-((5-(2-isopropylcyclopropane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0777] The General Procedure C was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from

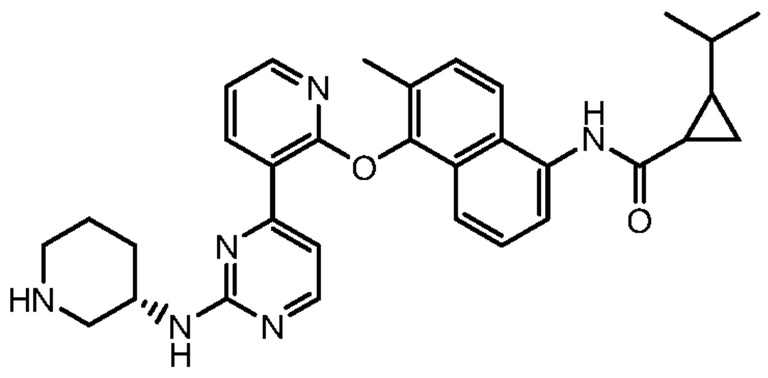
Example 101 (362 mg, 0.69 mmol), 2-isopropylcyclopropanecarboxylic acid (80 mg, 0.62 mmol), DIPEA (0.327 mL, 1.87 mmol), HATU (727 mg, 1.87 mmol) and DCM (10 mL). The residue was purified *via* reverse-phase HPLC to provide a mixture of the two isomers. This mixture was purified *via* chiral reverse-phase HPLC and lyophilized to yield 98 mg and 78 mg of the two single stereoisomers enantiomeric at the 1 and 2 positions of the cyclopropyl amide.

[0778] Step 2: 2-Isopropyl-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide



[0779] The General Procedure B was followed, using *tert*-butyl (3*S*)-3-((4-(2-((5-(2-isopropylcyclopropane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (98 mg, 0.153 mmol), DCM (4 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). The residue was purified *via* reverse-phase HPLC and lyophilized to yield 45 mg of **229**. LCMS (ESI): $[M+H]^+$ = 537.2;^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.53 – 8.47 (m, 1H), 8.42 (d, J = 5.1 Hz, 1H), 8.03 (dd, J = 4.8, 2.0 Hz, 1H), 7.97 (d, J = 8.6 Hz, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.50 – 7.45 (m, 1H), 7.45 (d, J = 5.1 Hz, 1H), 7.38 (dd, J = 8.5, 7.5 Hz, 1H), 7.25 (dd, J = 7.6, 4.8 Hz, 1H), 7.16 (d, J = 7.9 Hz, 1H), 3.93 (s, 1H), 3.17 – 3.09 (m, 1H), 2.87 – 2.80 (m, 1H), 2.22 (s, 3H), 1.98 – 1.90 (m, 2H), 1.70 – 1.63 (m, 1H), 1.56 – 1.41 (m, 2H), 1.24 – 1.08 (m, 2H), 1.07 – 0.96 (m, 8H), 0.80 – 0.73 (m, 1H).

Example 230 *2-Isopropyl-N-(6-methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide* ***230***

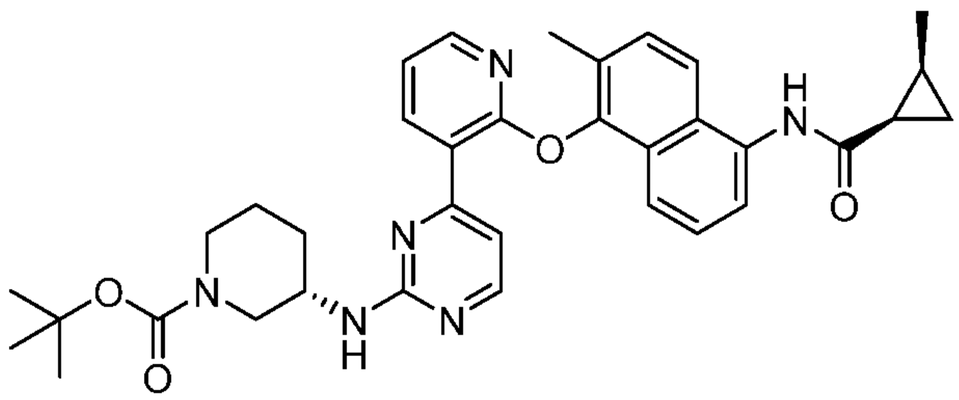


[0780] The General Procedure B was followed using *tert*-butyl (3*S*)-3-((4-(2-((5-(2-isopropylcyclopropane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (78 mg, 0.20 mmol), DCM (4 mL) and hydrochloric acid

(4 M in dioxane, 3 mL, 12 mmol). The residue was purified *via* reverse-phase HPLC and lyophilized to yield 39.9 mg of **230**. LCMS (ESI): $[M+H]^+$ = 537.3; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.53 – 8.47 (m, 1H), 8.42 (d, J = 5.1 Hz, 1H), 8.03 (dd, J = 4.8, 2.0 Hz, 1H), 7.97 (d, J = 8.6 Hz, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.50 – 7.45 (m, 1H), 7.44 (d, J = 5.1 Hz, 1H), 7.38 (dd, J = 8.5, 7.5 Hz, 1H), 7.25 (dd, J = 7.6, 4.8 Hz, 1H), 7.12 (d, J = 7.9 Hz, 1H), 3.88 (s, 1H), 3.13 – 3.05 (m, 1H), 2.83 – 2.77 (m, 1H), 2.47 – 2.39 (m, 1H), 2.22 (s, 3H), 1.98 – 1.90 (m, 2H), 1.68 – 1.61 (m, 1H), 1.56 – 1.41 (m, 2H), 1.24 – 1.08 (m, 2H), 1.07 – 0.96 (m, 8H), 0.80 – 0.73 (m, 1H).

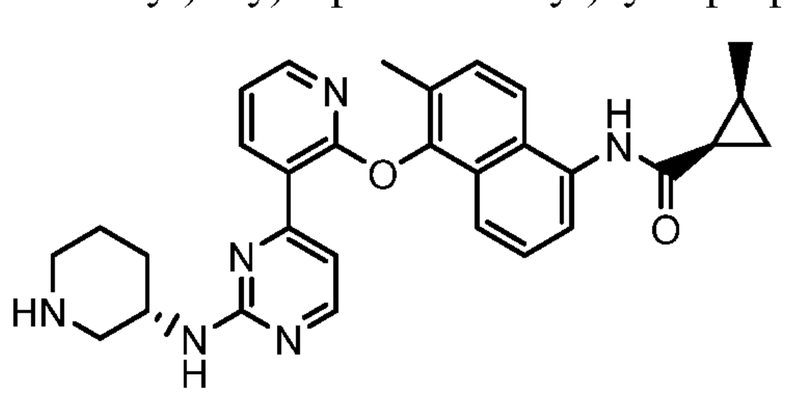
Example 231 *(1R,2S)-2-Methyl-N-(6-methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide* ***231***

[0781] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-((1*R*,2*S*)-2-methylcyclopropane-1-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



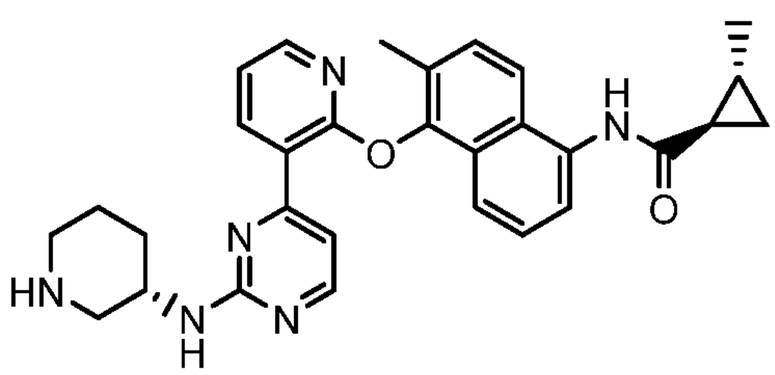
[0782] The General Procedure C was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (405 mg, 0.77 mmol), 2-methylcyclopropanecarboxylic acid (70 mg, 0.70 mmol), DIPEA (0.366 mL, 2.10 mmol), HATU (814 mg, 2.10 mmol) and DCM (10 mL). The residue was purified *via* reverse-phase HPLC to provide a mixture of the two isomers, this mixture was then purified *via* chiral reverse-phase HPLC and lyophilized to yield 8 mg, 57 mg, 32 mg and 13 mg of the four single stereoisomers at the 1 and 2 positions of the cyclopropyl amide.

[0783] Step 2: (1*R*,2*S*)-2-Methyl-*N*-(6-methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide



[0784] Prepared according to Example 233, following General Procedure B, and using tert-butyl (*S*)-3-((4-(2-((2-methyl-5-((1*R*,2*S*)-2-methylcyclopropane-1-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-2) (43 mg, 0.071 mmol), 1,4-dioxane (1 mL) and hydrochloric acid (4 M in dioxane, 1 mL, 4 mmol). After 60 min reaction time, the resulting suspension was diluted with MTBE (15 mL) and the precipitate was filtered and washed with MTBE. The collected solids were dissolved in MeCN and water and lyophilized to provide 34 mg (88% yield) of **231** as a fluffy light yellow solid. LCMS (ESI) $[M+H]^+$ = 509.5, rt = 1.37 min; ^{1}H NMR (400 MHz, d6-dmso) δ 10.15 (s, 1H), 9.06 - 8.51 (m, 3H), 8.48 (d, J = 5.2 Hz, 1H), 8.05 (dd, J = 4.8, 2.0 Hz, 1H), 7.96 (d, J = 8.7 Hz, 1H), 7.63 (d, J = 7.1 Hz, 1H), 7.59 (d, J = 4.9 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.52 (d, J = 8.9 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.43 - 7.36 (m, 1H), 7.27 (dd, J = 7.6, 4.8 Hz, 1H), 4.28 (s, 1H), 3.21 (d, J = 12.1 Hz, 1H), 2.96 - 2.73 (m, 2H), 2.22 (s, 3H), 2.16 - 2.06 (m, 1H), 2.06 - 1.98 (m, 1H), 1.98 - 1.86 (m, 1H), 1.75 (q, J = 12.5 Hz, 1H), 1.63 (d, J = 10.7 Hz, 1H), 1.38 - 1.27 (m, 1H), 1.17 (d, J = 6.1 Hz, 3H), 1.05 - 0.93 (m, 1H), 0.82 (dd, J = 10.6, 5.4 Hz, 1H).

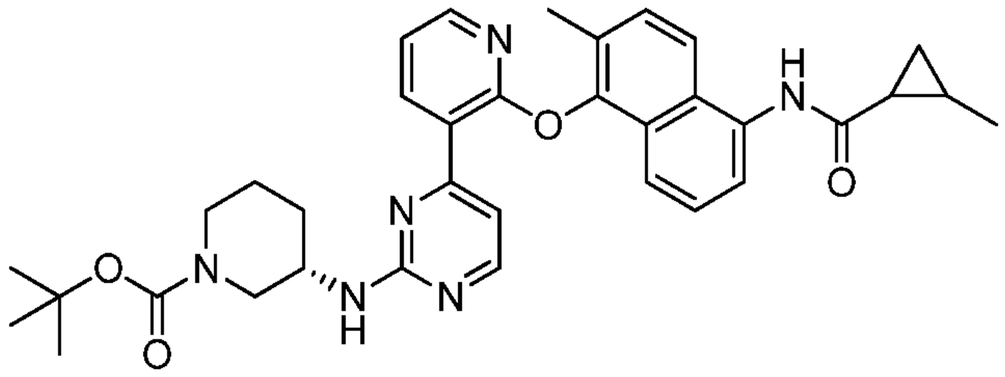
Example 232 *(1R,2R)-2-Methyl-N-(6-methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide* ***232***



[0785] The General Procedure B was followed using *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-((1*R*,2*R*)-2-methylcyclopropane-1-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (57 mg, 0.094 mmol), DCM (4 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). The residue was purified *via* reverse-phase HPLC and lyophilized to yield 38.6 mg (81% yield) of **232**. LCMS (ESI): $[M+H]^+$ = 509.2;^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 8.50 (d, *J* = 7.7 Hz, 1H), 8.41 (d, J = 5.1 Hz, 1H), 8.05 – 7.98 (m, 2H), 7.98 – 7.96 (m, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.53 – 7.36 (m, 4H), 7.25 (dd, J = 7.5, 4.9 Hz, 1H), 7.13 (d, J = 7.9 Hz, 1H), 3.90 (s, 1H), 3.11 (d, J = 12.0 Hz, 1H), 2.86 – 2.76 (m, 1H), 2.47 – 2.42 (m, 2H), 2.22 (s, 3H), 2.14 – 2.03 (m, 1H), 1.96 – 1.90 (m, 1H), 1.70 – 1.60 (m, 1H), 1.55 – 1.40 (m, 2H), 1.37 – 1.24 (m, 1H), 1.17 (d, J = 6.1 Hz, 3H), 1.02 – 0.95(m, 1H), 0.85 – 0.80 (m, 1H).

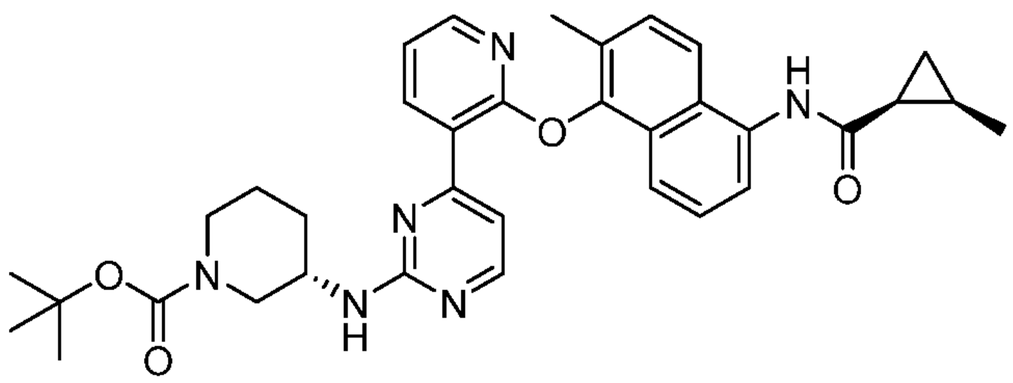
Example 233 *(1S,2R)-2-Methyl-N-(6-methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide* ***233***

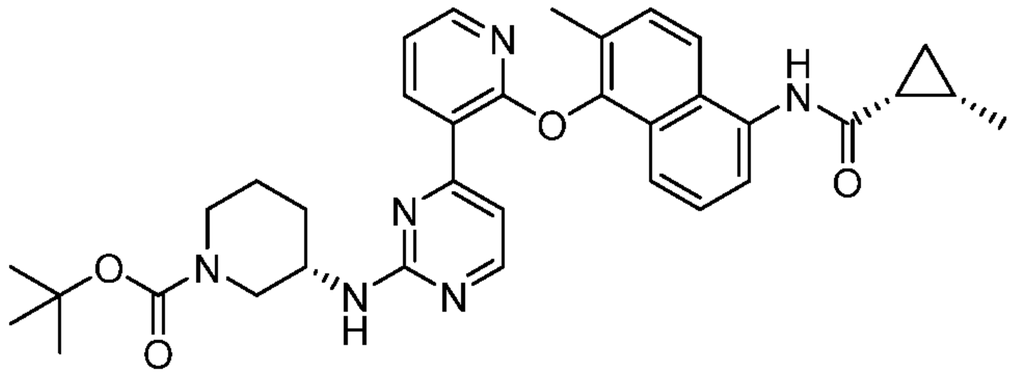
[0786] Step 1: (3*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-5-(2-methylcyclopropanecarboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0787] To a solution of cis-2-methylcyclopropanecarboxylic acid (0.07 mL, 0.67 mmol) in DCM (3mL) cooled to 0 °C was added oxalyl chloride (86 µL, 1.0 mmol). The mixture was stirred for 30 min and then *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (529 mg, 1.0 mmol) and pyridine (0.32 mL, 4.02 mmol) were added. The reaction mixture was stirred for 3 days and then diluted with water (10 mL) and EtOAc (30 mL), followed by separation of the layers. The organic phase was washed with saturated $NaHCO_3$(aq) (20 mL), then brine (20 mL), then saturated NH_4Cl(aq) (10 mL). The organic phase was then dried ($MgSO_4$), filtered and concentrated to dryness. The crude product was purified by flash chromatography through silica gel (0 - 100% EtOAc/DCM) followed by further purification by C18 reverse phase flash chromatography (40 - 70% MeCN/0.1% TFA in water). The product fractions were combined, 5 mL of ammonium hydroxide was added and most of the acetonitrile was removed on the rotavap. The product suspension in water was extracted with DCM (2 x 50 mL), dried ($MgSO_4$), filtered and concentrated to provide 103 mg (25% yield) of the title compound. LCMS (ESI) $[M+H]^+$ = 609.6, rt = 1.93 min.

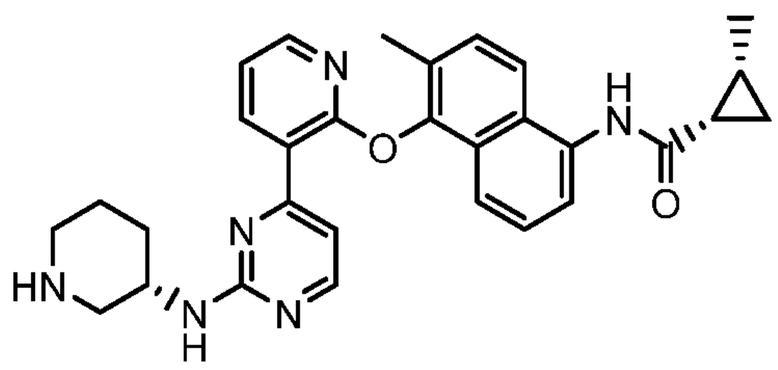
[0788] Step 2: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-((1*S*,2*R*)-2-methylcyclopropane-1-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-1) and *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-((1*R*,2*S*)-2-methylcyclopropane-1-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-2)





[0789] The mixture of stereoisomers from Step 1 were subjected to chiral normal phase semi-prep purification (conditions: Chiralpak IB, 5 uM, 20 x 250 mm, Isocratic 5% MeOH, 5% EtOH, 90% hexane, 15 mL/min, 5-10 mg/inj.) to provide two stereoisomers enantiomeric with respect to the cyclopropane: (isomer-1), 47 mg (46% yield), white solid, ee = 99.4%, rt = 15.2 min, LCMS (ESI) $[M+H]^+$ = 609.6, rt = 1.90 min; and (isomer-2), 43 mg (42% yield), white solid, ee = 98.9%, rt = 17.8 min, LCMS (ESI) $[M+H]^+$ = 609.6, rt = 1.91 min.

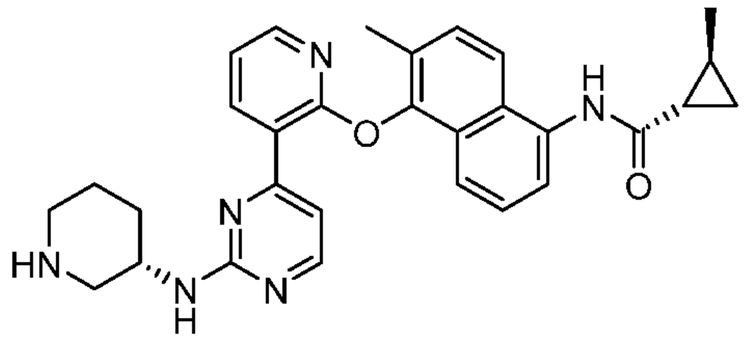
[0790] Step 3: (1*S*,2*R*)-2-Methyl-*N*-(6-methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide (isomer-1)



[0791] Prepared following General Procedure B and using tert-butyl (S)-3-((4-(2-((2-methyl-5-((1S,2R)-2-methylcyclopropane-1-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-1) (47 mg, 0.077 mmol), 1,4-dioxane (1 mL) and hydrochloric acid (4 M in dioxane, 1 mL, 4 mmol). After 60 min, the resulting suspension was diluted with MTBE (15 mL) and the precipitate was filtered and washed with MTBE. The collected solids were dissolved in MeCN and water and lyophilized to provide 36 mg (85% yield) of **233** as a fluffy light yellow solid. LCMS (ESI) $[M+H]^+$ = 509.5, rt = 1.37 min; ^{1}H NMR (400 MHz, d6-dmso) δ 10.15 (s, 1H), 9.11 - 8.51 (m, 3H), 8.48 (d, J = 5.2 Hz, 1H), 8.05 (dd, J = 4.8, 2.0 Hz, 1H), 7.96 (d, J = 8.6 Hz, 1H), 7.63 (d, J = 7.2 Hz, 1H), 7.59 (d, J = 4.9 Hz, 1H), 7.53 (t, J = 8.2 Hz, 2H), 7.47 (d, J = 8.3 Hz, 1H), 7.43 - 7.34 (m, 1H), 7.27 (dd, J = 7.6, 4.8 Hz, 1H), 4.28 (s, 1H), 3.21 (d, J = 12.1 Hz, 1H), 2.89 - 2.79 (m, 2H),

2.22 (s, 3H), 2.16 - 2.07 (m, 1H), 2.07 - 1.97 (m, 1H), 1.97 - 1.85 (m, 1H), 1.74 (q, J = 10.3 Hz, 1H), 1.63 (q, J = 9.4 Hz, 1H), 1.37 - 1.26 (m, 1H), 1.17 (d, J = 6.1 Hz, 3H), 1.06 - 0.94 (m, 1H), 0.82 (dd, J = 10.7, 5.3 Hz, 1H).

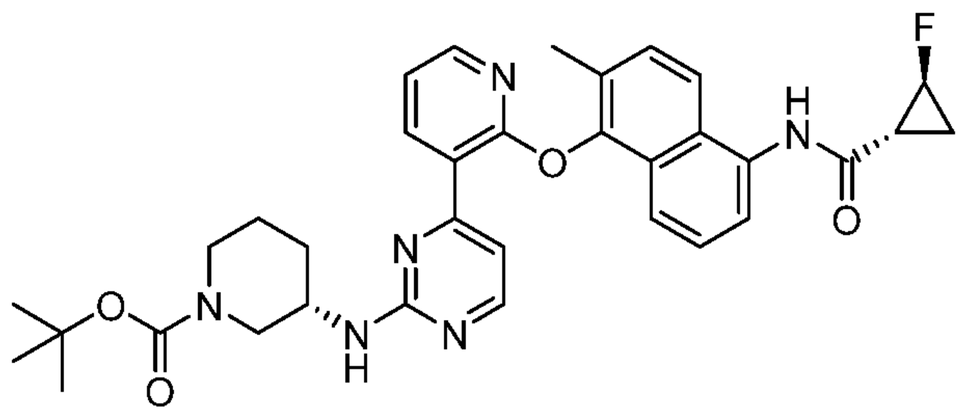
Example 234 *(1S,2S)-2-Methyl-N-(6-methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide* ***234***



[0792] The General Procedure B was followed using tert-butyl (S)-3-((4-(2-((2-methyl-5-((1S,2S)-2-methylcyclopropane-1-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (13 mg, 0.021 mmmol), DCM (4 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). The residue was purified *via* reverse-phase HPLC and lyophilized to yield 5.2 mg (48% yield) of **234**. LCMS (ESI): $[M+H]^+$ = 509.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 8.50 (d, J = 7.7 Hz, 1H), 8.41 (d, J = 5.1 Hz, 1H), 8.05 – 7.98 (m, 2H), 7.98 – 7.96 (m, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.53 – 7.36 (m, 4H), 7.25 (dd, J = 7.5, 4.8 Hz, 1H), 7.12 (d, J = 7.9 Hz, 1H), 3.90 (s, 1H), 3.18 – 3.09 (m, 1H), 2.87 – 2.79 (m, 1H), 2.48 – 2.40 (m, 2H), 2.22 (s, 3H), 2.14 – 2.03 (m, 1H), 1.96 – 1.90 (m, 1H), 1.70 – 1.60 (m, 1H), 1.57 – 1.38 (m, 2H), 1.36 – 1.24 (m, 1H), 1.17 (d, J = 6.1 Hz, 3H), 1.02 – 0.95(m, 1H), 0.85 – 0.80 (m, 1H).

Example 235 *(1R,2S)-2-Fluoro-N-(6-methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide* ***235***

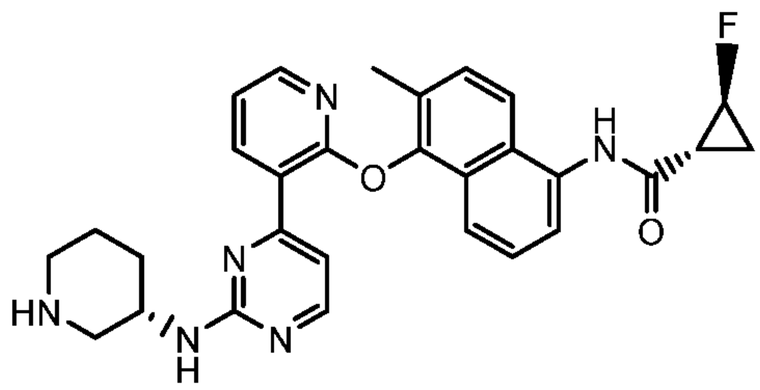
Step1: *tert*-Butyl (*S*)-3-((4-(2-((5-((1*R*,2*S*)-2-fluorocyclopropane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0793] The General Procedure C was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example **101** (364 mg, 0.69 mmol), (*trans*)-2-fluorocyclopropanecarboxylic acid (60 mg, 0.58

mmol), DIPEA (0.302 mL, 0.51 mmol), HATU (671 mg, 1.73 mmol) and DCM (10 mL). The residue was purified *via* reverse-phase HPLC to provide a mixture of the two isomers. This mixture was then purified *via* chiral reverse-phase HPLC and lyophilized to yield 62 mg and 56 mg of the two single trans stereoisomers enantiomeric at the 1 and 2 positions of the cyclopropyl amide.

[0794] Step 2: (1*R*,2*S*)-2-Fluoro-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide

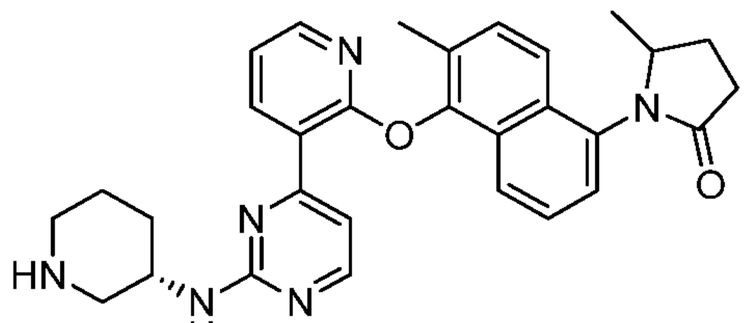


[0795] The General Procedure B was followed, using *tert*-butyl (3*S*)-3-((4-(2-((5-(2-fluorocyclopropane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (56 mg, 0.091 mmol), DCM (4 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). The residue was purified *via* reverse-phase HPLC and lyophilized to yield 31.6 mg of **235**. LCMS (ESI): $[M+H]^+$ = 513.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 8.60 – 8.50 (m, 1H), 8.45 (d, J = 5.1 Hz, 1H), 8.06 – 7.96 (m, 2H), 7.67 (d, J = 7.5 Hz, 1H), 7.56 – 7.47 (m, 2H), 7.46 – 7.32 (m, 2H), 7.27 (dd, J = 7.5, 4.8 Hz, 1H), 5.12 – 4.89 (m, 1H), 4.14 (s, 1H), 3.15 – 3.07 (m, 1H), 2.78 – 2.59 (m, 3H), 2.22 (s, 3H), 1.97 – 1.89 (m, 1H), 1.88 – 1.80 (m, 1H), 1.69 – 1.40 (m, 3H), 1.33 – 1.22 (m, 1H).

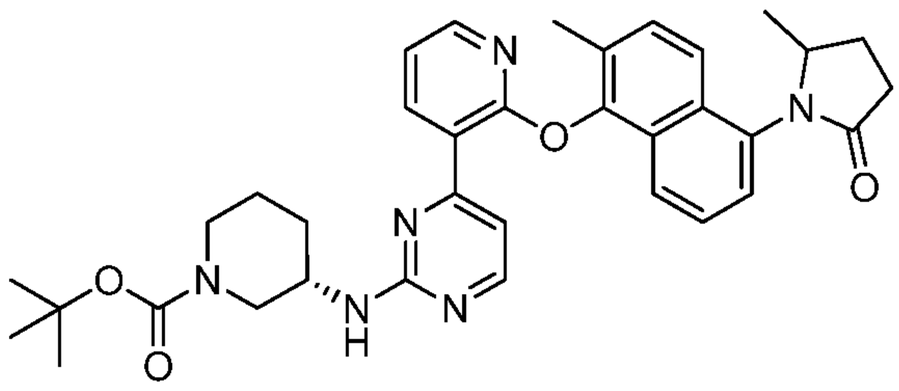
Example 236 *(1S,2R)-2-Fluoro-N-(6-methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide* ***236***

[0796] The General Procedure B was followed, using tert-butyl (S)-3-((4-(2-((5-((1S,2R)-2-fluorocyclopropane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (62 mg, 0.10 mmol), DCM (4 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). The residue was purified *via* reverse-phase HPLC and lyophilized to yield 36.8 mg of **236**. LCMS (ESI): $[M+H]^+$ = 513.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 8.53 – 8.47(m, 1H), 8.41 (d, J = 5.1 Hz, 1H), 8.04 – 7.96 (m, 2H), 7.67 (d, J = 7.5 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.46 – 7.37 (m, 2H), 7.26 (dd, J = 7.5, 4.8 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 5.12 – 4.89 (m, 1H), 3.90 (s, 1H), 3.15 – 3.07 (m, 1H), 2.85 – 2.80 (m, 1H), 2.70 – 2.59 (m, 1H), 2.46 – 2.41 (m, 1H), 2.22 (s, 3H), 1.97 – 1.89 (m, 1H), 1.69 – 1.40 (m, 3H), 1.33 – 1.22 (m, 1H).

Example 237 *5-Methyl-1-(6-methyl-5-((3-(2-((S)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidin-2-one* ***237***

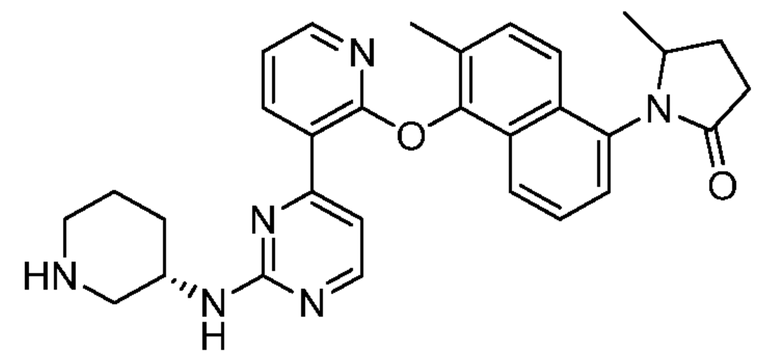


[0797] Step 1: (3*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-5-(2-methyl-5-oxopyrrolidin-1-yl)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0798] To a solution of *tert*-butyl (3*S*)-3-[[4-[2-[(5-iodo-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (110 mg, 0.17 mmol) in 1,4-dioxane (2 mL) was added copper (I) iodide (3 mg, 0.02 mmol), potassium carbonate (65 mg, 0.47 mmol), 5-methyl-2-pyrrolidinone (31 mg, 0.31 mmol) and *N*, *N*'-dimethyl-1,2-ethanediamine (2.77 mg, 0.03 mmol). The mixture was purged with N_2 and stirred at 110 °C for 12 h. After cooling, the mixture was filtered, concentrated and dissolved in ethyl acetate (60 mL), and subsequently washed with H_2O (50 mL x 2). The organic phase was dried over anhydrous sodium sulfate and filtered and the filtrate was concentrated and purified by prep-TLC (50% ethyl acetate in petroleum ether, Rf = 0.1) to yield 80 mg (83% yield) of the title compound as a white solid. LCMS (ESI) $[M+H]^+$ = 609.1.

[0799] Step 2: 5-Methyl-1-(6-methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidin-2-one

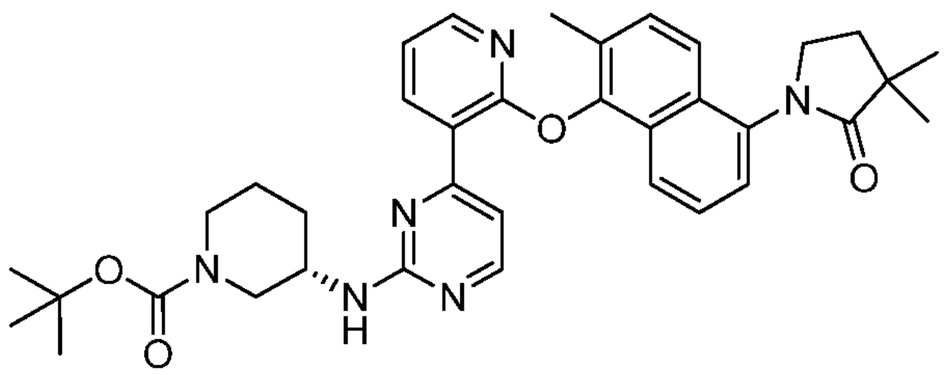


[0800] The General Procedure B was followed, using (3*S*)-*tert*-butyl 3-((4-(2-((2-methyl-5-(2-methyl-5-oxopyrrolidin-1-yl)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (80 mg, 0.13 mmol), dichloromethane (2 mL) and

hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05%HCl); B: ACN) to yield 25.8 mg (36% yield) of **237** as a yellow solid and as mixture of diastereomers. LCMS (ESI) $[M+H]^+$ = 509.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.99 (s, 1H), 9.51 (s, 1H), 9.15 - 8.75 (m, 1H), 8.57 (s, 1H), 8.18 (s, 1H), 7.93 (s, 1H), 7.67 (s, 2H), 7.53 - 7.43 (m, 2H), 7.33-7.30 (m, 1H), 4.65 (s, 1H), 4.28 (s, 1H), 3.43 (s, 1H), 3.19 (s, 1H), 2.89 (t, J = 9.6 Hz, 2H), 2.56 (s, 2H), 2.48 - 2.36 (m, 1H), 2.22 (s, 3H), 2.09 - 2.00 (m, 1H), 1.97 - 1.64 (m, 4H), 1.03 (s, 3H).

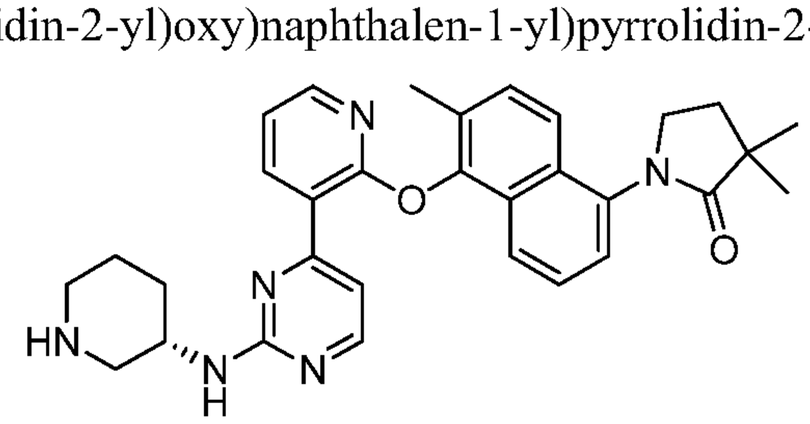
Example 238 *(S)-3,3-Dimethyl-1-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidin-2-one* ***238***

[0801] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-(3,3-dimethyl-2-oxopyrrolidin-1-yl)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0802] To a solution of *tert*-butyl (3*S*)-3-[[4-[2-[(5-iodo-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.16 mmol) in 1,4-dioxane (2 mL) was added copper (I) iodide CuI (3 mg, 0.02 mmol), potassium carbonate (65 mg, 0.47 mmol), 3,3-dimethylpyrrolidin-2-one (35 mg, 0.31 mmol) and *N*,*N*'-dimethyl-1,2-ethanediamine (3 mg, 0.03 mmol), the mixture was subjected to a nitrogen atmosphere and stirred at 110 °C for 12 h. After cooling down, the mixture was filtered, concentrated and dissolved in ethyl acetate (60 mL), and then washed with H_2O (50 mL x 2). The organic phase was dried over anhydrous sodium sulfate and filtered and the filtrate was concentrated and purified by prep-TLC (50% ethyl acetate in petroleum ether, Rf = 0.1) to yield 80 mg (82% yield) of the title compound as a white solid. LCMS (ESI) $[M+H]^+$ = 623.1.

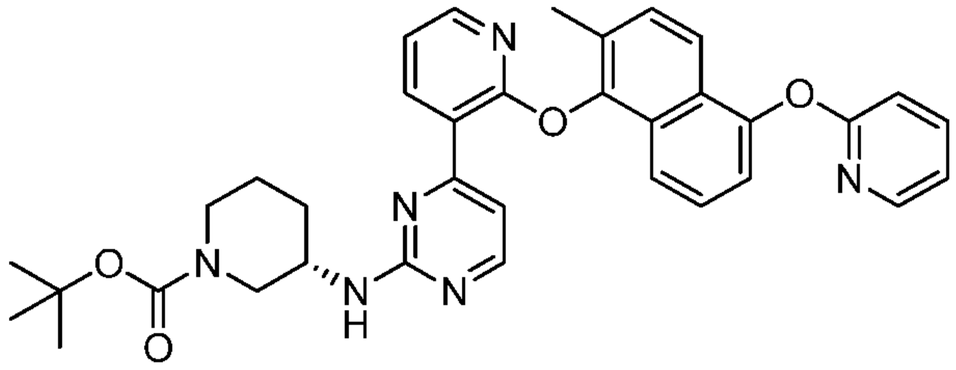
[0803] Step 2: (*S*)-3,3-Dimethyl-1-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidin-2-one



[0804] The General Procedure B was followed, using (S)-*tert*-butyl 3-((4-(2-((5-(3,3-dimethyl-2-oxopyrrolidin-1-yl)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (80 mg, 0.13 mmol), dichloromethane (2 mL) and hydrochloric acid (4 M in dioxane, 0.32 mL, 1.28 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% HCl); B: ACN) to yield 42.2 mg (58% yield) of **238** as a white solid. LCMS (ESI) $[M+H]^+$ = 523.1. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.06 (s, 1H), 8.49 (d, *J* = 5.2 Hz, 1H), 8.10 - 8.01 (m, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.60 - 7.52 (m, 2H), 7.51 - 7.46 (m, 1H), 7.44 - 7.39 (m, 1H), 7.30-7.27 (m, 1H), 4.35 (s, 1H), 3.78 (s, 2H), 3.43 (d, *J* = 9.2 Hz, 1H), 3.20 (d, *J* = 11.2 Hz, 1H), 2.92 - 2.77 (m, 2H), 2.22 (s, 3H), 2.15 (t, *J* = 6.8 Hz, 2H), 2.02 (d, *J* = 8.8 Hz, 1H), 1.92 (m, 1H), 1.81 - 1.71 (m, 1H), 1.64 (m, 1H), 1.26 (s, 6H).

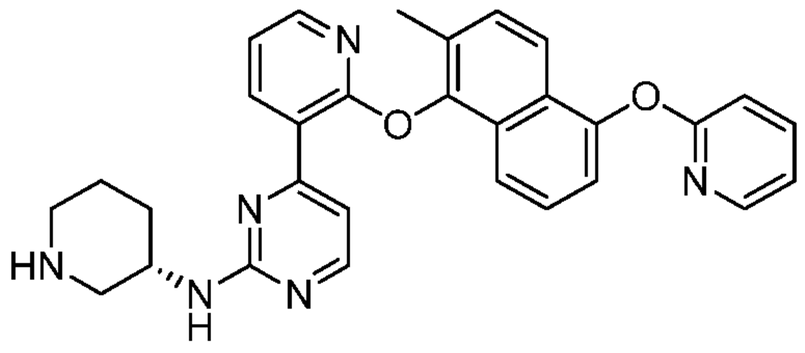
Example 239 *(S)-4-(2-((2-Methyl-5-(pyridin-2-yloxy)naphthalen-1-yl)oxy)pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine* ***239***

[0805] Step 1: (*S*)-*tert*-butyl 3-((4-(2-((2-methyl-5-(pyridin-2-yloxy)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0806] To a solution of *tert*-butyl (3*S*)-3-[[4-[2-[(5-iodo-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.16 mmol), 8-hydroxyquinoline (3 mg, 0.02 mmol), potassium carbonate (43 mg, 0.31 mmol), copper(I) iodide (3 mg, 0.02 mmol) in dimethyl sulfoxide (1 mL) was added 1*H*-pyridin-2-one (18 mg, 0.19 mmol). The mixture was stirred at 120 °C under nitrogen atmosphere for 24 h. The solution was concentrated and purified by prep-TLC (50% ethyl acetate in petroleum ether, Rf = 0.5) to yield 50 mg (53 % yield) of the title compound as a yellow solid. LCMS (ESI): $[M+H]^+$ = 605.2.

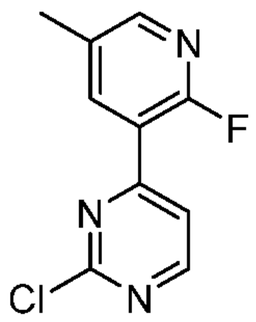
[0807] Step 2: (*S*)-4-(2-((2-methyl-5-(pyridin-2-yloxy)naphthalen-1-yl)oxy)pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-2-amine



[0808] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((2-methyl-5-(pyridin-2-yloxy)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (50 mg, 0.08 mmol), dichloromethane (5 mL) and hydrochloric acid (4 M in ethyl acetate, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% HCl); B: ACN) to yield 13 mg (29 % yield) of **239** as a yellow solid. LCMS (ESI): $[M+H]^+$ = 505.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.81 (s, 1H), 9.41 (s, 1H), 8.97 (s, 1H), 8.54 (s, 2H), 8.15 (s, 1H), 8.07 (d, *J* = 3.6 Hz, 1H), 7.95 - 7.86 (m, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.60 - 7.51 (m, 1H), 7.46 (dd, *J* = 4.0, 8.0 Hz, 2H), 7.37 - 7.28 (m, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.17 - 7.09 (m, 1H), 4.58 (s, 1H), 3.43 (s, 1H), 3.19 (s, 1H), 2.90 - 2.80 (m, 2H), 2.21 (s, 3H), 2.10 - 1.62 (m, 4H).

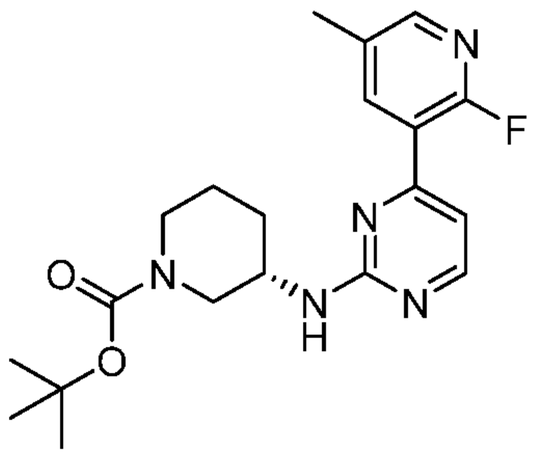
Example 240 *(S)-N-(6-Methyl-5-((5-methyl-3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide* ***240***

[0809] Step 1: 2-Chloro-4-(2-fluoro-5-methylpyridin-3-yl)pyrimidine



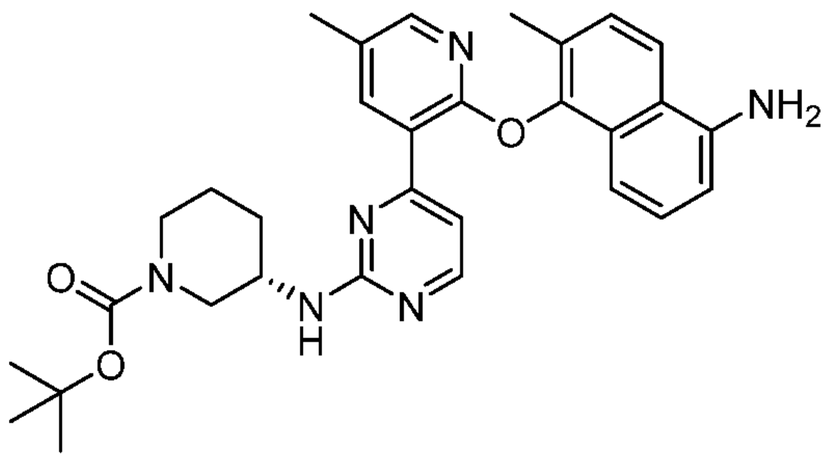
[0810] To the mixture of 2,4-dichloropyrimidine (149 mg, 1.0 mmol), 2-fluoro-5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (237 mg, 1.0 mmol) and potassium carbonate (346 mg, 2.5 mmol) in 1,4-dioxane (3 mL) and water (1 mL) was added tetrakis(triphenylphosphine)palladium (0) (58 mg, 0.05 equiv). The reaction mixture was purged with nitrogen, heated to 90 °C, stirred at the same temperature overnight, cooled to room temperature, filtered, and concentrated under vacuum. To the residue was added ethyl acetate and water. The organic layer was separated, washed with water and brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified *via* silica gel column chromatography (isopropylacetate in heptanes, 0 to 80%) to yield 170 mg of the title compound (76% yield).

[0811] Step 2: *tert*-Butyl (*S*)-3-((4-(2-fluoro-5-methylpyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



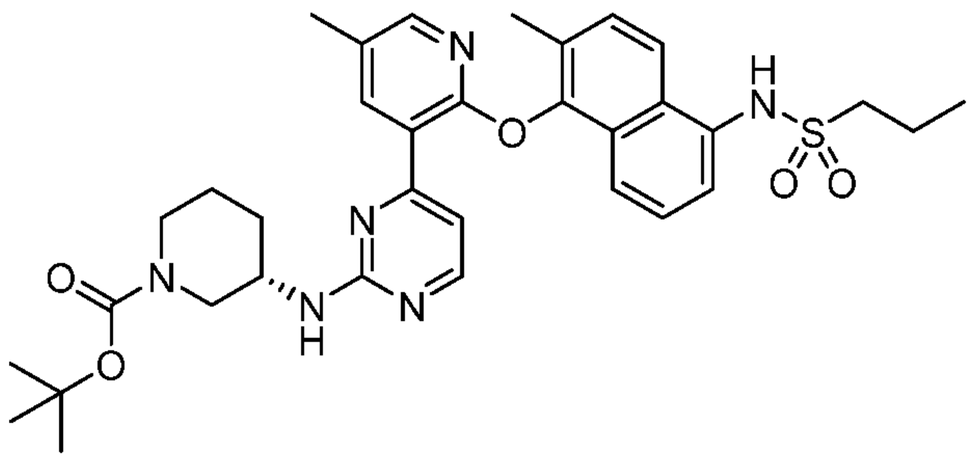
[0812] The solution of 2-chloro-4-(2-fluoro-5-methyl-3-pyridyl)pyrimidine (170 mg, 0.76 mmol), tert-butyl (3*S*)-3-[[4-(2-fluoro-5-methyl-3-pyridyl)pyrimidin-2-yl]amino]piperidine-1-carboxylate (138 mg, 0.36 mmol) and triethylamine (0.212 mL, 1.52 mmol) in dimethylsulfoxide (1.5 mL) was stirred at 100 °C overnight. To the solution was added water and ethyl acetate. The organic layer was separated, washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under vacuum to afford an oily residue. The residue was purified *via* silica gel column chromatography (isopropylacetate/methanol (3:1) in heptanes, 0 to 80%) to yield 138 mg of the title compound (47% yield).

[0813] Step 3: *tert*-Butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)-5-methylpyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



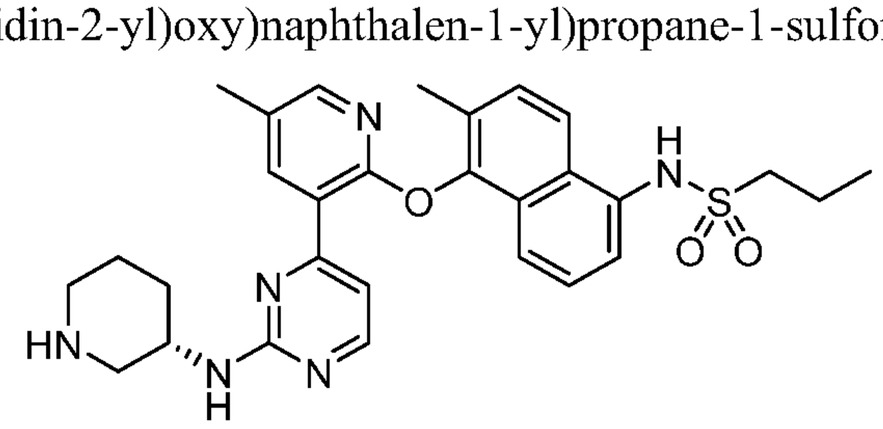
[0814] To a round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed *tert*-butyl (3*S*)-3-[[4-(2-fluoro-5-methyl-3-pyridyl)pyrimidin-2-yl]amino]piperidine-1-carboxylate (139 mg, 0.36 mmol), 5-amino-2-methylnaphathalene-1-ol HCl (72 mg, 0.33 mmol), cesium carbonate (0.98 mmol, 319 mg) and 1-methyl-2-pyrrolidinone (2 mL). The resulting mixture was stirred overnight at 125 °C, cooled to room temperature, diluted with water, and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified *via* silica column chromatography (isopropylacetate/methanol (3:1) in heptanes, 0 to 80%) to yield 160 mg of the title compound (91% yield).

[0815] Step 4: *tert*-Butyl (*S*)-3-((4-(5-methyl-2-((2-methyl-5-(propylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0816] The General Procedure A was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (160 mg, 0.30 mmol), pyridine (3 mL) and 1-propanesulfonyl chloride (50 mg, 0.36 mmol). The crude was then purified by silica column chromatography (isopropylacetate/methanol (3:1) in heptanes, 0 to 80%) to yield 90 mg (47% yield) of the title compound as a white solid. LCMS (ESI) $[M+H]^+ = 647$.

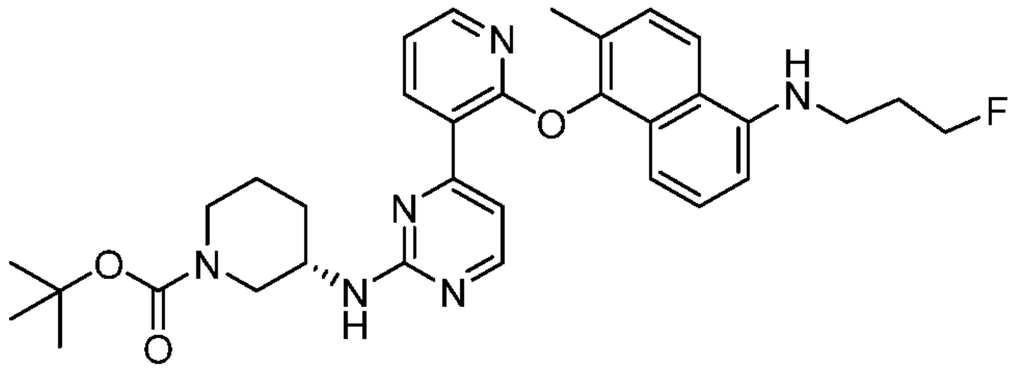
[0817] Step 5: (*S*)-*N*-(6-Methyl-5-((5-methyl-3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide



[0818] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(5-methyl-2-((2-methyl-5-(propylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (90 mg, 0.14 mmol), DCM (4 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). The residue was purified via reverse-phase HPLC and lyophilized to yield 23.3 mg (14% yield) of **240**; LCMS (ESI): $[M+H]^+ = 547.2$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (d, J = 5.1 Hz, 1H), 8.32 (d, J = 3.5 Hz, 1H), 8.12 (d, J = 8.8 Hz, 1H), 7.84 (d, J = 2.4 Hz, 1H), 7.54 – 7.34 (m, 5H), 7.17 (d, J = 7.9 Hz, 1H), 3.93 (s, 1H), 3.18 – 3.10 (m, 1H), 2.90 – 2.82 (m, 1H), 2.28 (s, 3H), 2.20 (s, 3H), 1.97-1.90 (m, 1H), 1.81 – 1.65 (m, 3H), 1.55 – 1.45 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H).

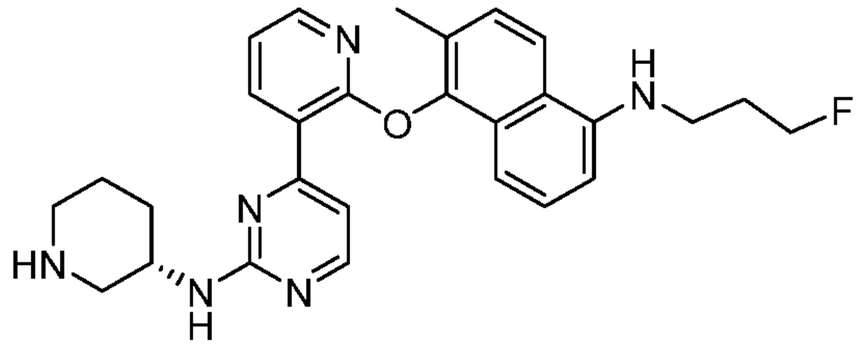
Example 241 *(S)-4-(2-((5-((3-Fluoropropyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine* ***241***

[0819] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((5-((3-fluoropropyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0820] The General Procedure E was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (150 mg, 0.28 mmol) and 1-bromo-3-fluoro-propane (120.5 mg, 0.85 mmol) to afford 156 mg (93% yield) of the title compound as a brown gum. It was carried on as is. LCMS (ESI) $[M+H]^+$ = 587.

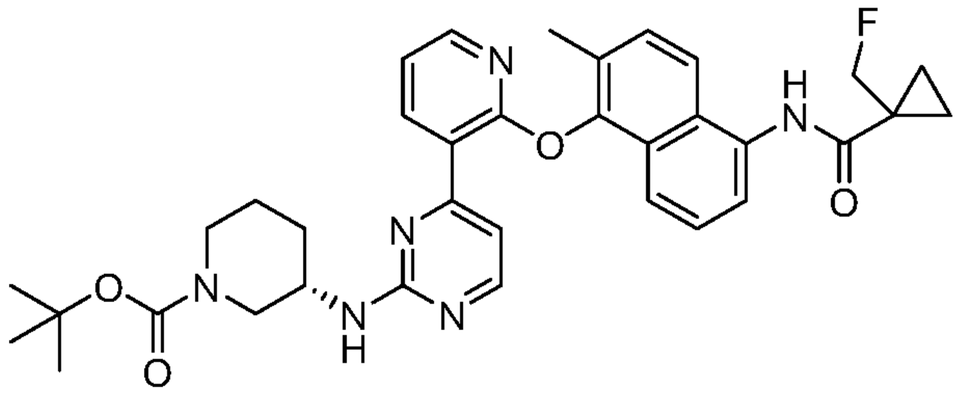
[0821] Step 2: (*S*)-4-(2-((5-((3-Fluoropropyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-2-amine



[0822] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-((3-fluoropropyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (156 mg, 0.26 mmol). The crude product was purified *via* reverse-phase HPLC and lyophilized to yield 3.8 mg (3% yield) of **241** as an off-white solid. LCMS (ESI) [M+H]+ = 487; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (s, 1H), 8.40 (d, J = 5.1 Hz, 1H), 8.03 – 7.99 (m, 2H), 7.43 (d, J = 5.1 Hz, 1H), 7.34 (d, J = 8.7 Hz, 1H), 7.23 (dd, J = 7.6, 4.8 Hz, 1H), 7.18 (t, J = 8.0 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.48 – 6.43 (m, 1H), 6.28 – 6.22 (m, 1H), 4.68 (t, J = 5.8 Hz, 1H), 4.56 (t, J = 5.9 Hz, 1H), 3.89 (s, 1H), 3.15 – 3.06 (m, 1H), 2.84 – 2.76 (m, 2H), 2.45 – 2.42 (m, 2H), 2.18 (s, 3H), 2.11 (q, J = 6.3 Hz, 1H), 2.04 (p, J = 6.6 Hz, 1H), 1.96 – 1.89 (m, 2H), 1.69 – 1.60 (m, 1H), 1.52 – 1.41 (m, 2H).

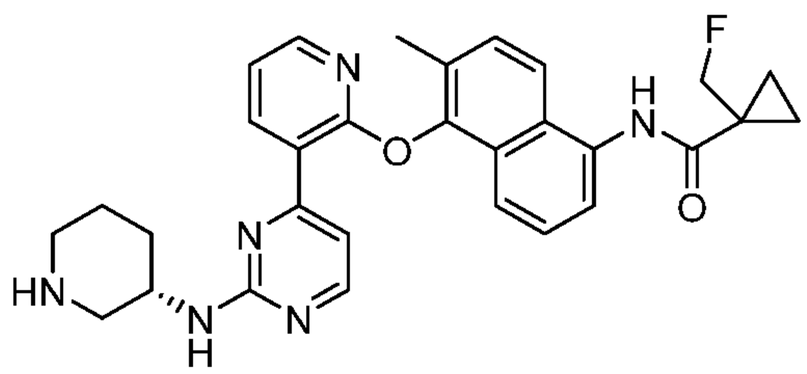
Example 242 *(S)-1-(Fluoromethyl)-N-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide* ***242***

[0823] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((5-(1-(fluoromethyl)cyclopropane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0824] The General Procedure C was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (150 mg, 0.28 mmol) and 1-(fluoromethyl)cyclopropanecarboxylic acid (50.4 mg, 0.43 mmol), HATU (221.0 mg, 0.57 mmol), DIPEA (0.15 mL, 0.85 mmol), and DMF (1.5 mL). The crude material was purified by silica gel chromatographyt (12 g column), eluted with 0-5% MeOH/DCM to afford 123 mg (69% yield) of the title compound as a brown solid. LCMS (ESI) $[M+H]^+ = 627$.

[0825] Step 2: (*S*)-1-(Fluoromethyl)-*N*-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide

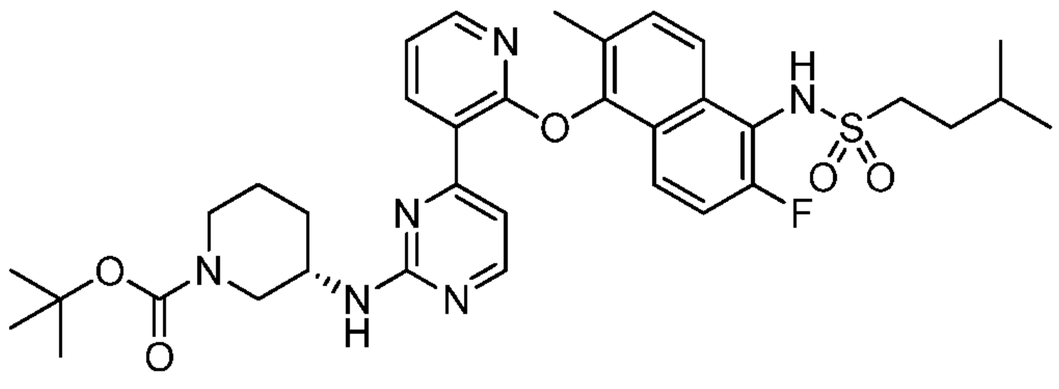


[0826] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-(1-(fluoromethyl)cyclopropane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (123 mg, 0.19 mmol). The crude product was purified *via* reverse-phase HPLC and lyophilized to yield 90 mg (87% yield) of **242** as a brown solid. LCMS (ESI) $[M+H]^+ = 487$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.65 (s, 1H), 8.49 (d, J = 7.4 Hz, 1H), 8.41 (d, J = 5.1 Hz, 1H), 8.03 (dd, J = 4.8, 2.0 Hz, 1H), 7.70 (dd, J = 8.5, 0.8 Hz, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.50 (d, J = 8.7 Hz, 1H), 7.46 – 7.42 (m, 2H), 7.41 – 7.39 (m, 1H), 7.25 (dd, J = 7.6, 4.8 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 4.79 (d, J = 48.5 Hz, 2H), 3.89 (s, 1H), 3.10 (d, J = 11.9 Hz, 1H), 2.85 – 2.75 (m, 1H), 2.46 – 2.39 (m, 2H), 2.22 (s,

3H), 1.97 – 1.89 (m, 1H), 1.68 – 1.61 (m, 1H), 1.54 – 1.41 (m, 2H), 1.38 – 1.32 (m, 2H), 1.05 – 0.99 (m, 2H).

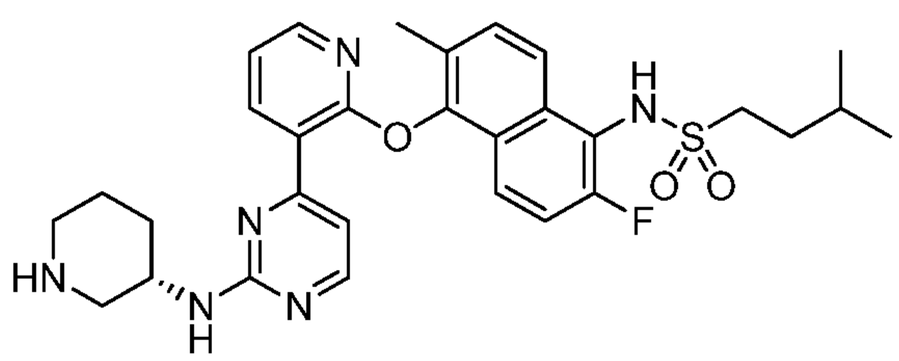
Example 243 *(S)-N-(2-Fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-3-methylbutane-1-sulfonamide* ***243***

[0827] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((6-fluoro-2-methyl-5-(3-methylbutylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0828] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 275 (85 mg, 0.16 mmol), pyridine (0.19 mL, 2.3 mmol), DCM (0.78 mL), 3-methylbutane-1-sulfonyl chloride (53 mg, 0.31 mmol) and DMAP (1.9 mg, 0.016 mmol). After 18 h, a further portion of 3-methylbutane-1-sulfonyl chloride (53 mg, 0.31 mmol) was added and after a further 16 h, the mixture was diluted with 1M $KHSO_4$(aq), extracted twice with DCM, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude was purified by flash chromatography through silica gel (0 – 50% EtOAc/DCM) to provide 53 mg (50% yield) of the title compound. LCMS (ESI) $[M+H]^+$ = 679.4, rt = 2.03 min.

[0829] Step 2: (*S*)-*N*-(2-fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-3-methylbutane-1-sulfonamide

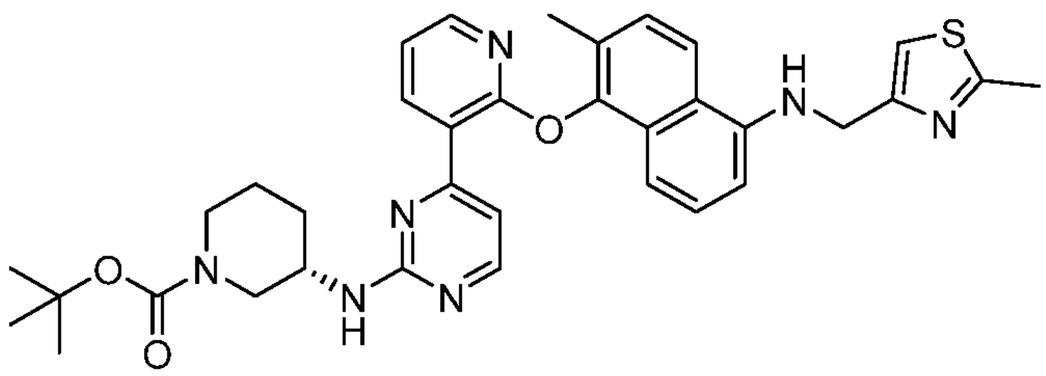


[0830] Prepared according to General Procedure B using (*S*)-*tert*-butyl 3-((4-(2-((6-fluoro-2-methyl-5-(3-methylbutylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (53 mg, 0.078 mmol), 1,4-dioxane (0.3 mL) and hydrochloric acid (4 M in dioxane, 0.4 mL, 1.60 mmol). After 45 min, the reaction was diluted with Et_2O and the resulting solids collected by filtration, washed with Et_2O, dissolved in a

mixture of H_2O and MeCN and lyophilized to provide 42 mg (88% yield) of **243**. LCMS (ESI) $[M+H]^+$ = 579.4, rt = 1.52 min; ^1H NMR (400 MHz, DMSO-d_6) δ 9.70 (s, 1H), 8.91 (bs, 2H), 8.69 (s, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.11 – 8.01 (m, 2H), 7.71 (dd, J = 9.2, 5.2 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.57 (s, 2H), 7.46 (t, J = 9.5 Hz, 1H), 7.29 (dd, J = 7.6, 4.8 Hz, 1H), 4.29 (s, 1H), 3.50 – 3.36 (m, 1H), 3.28 – 3.10 (m, 3H), 3.01 – 2.73 (m, 2H), 2.19 (s, 3H), 2.06 – 1.85 (m, 2H), 1.83 – 1.52 (m, 5H), 0.92 (d, J = 6.3 Hz, 6H).

Example 244 *(S)-4-(2-((2-Methyl-5-(((2-methylthiazol-4-yl)methyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine* ***244***

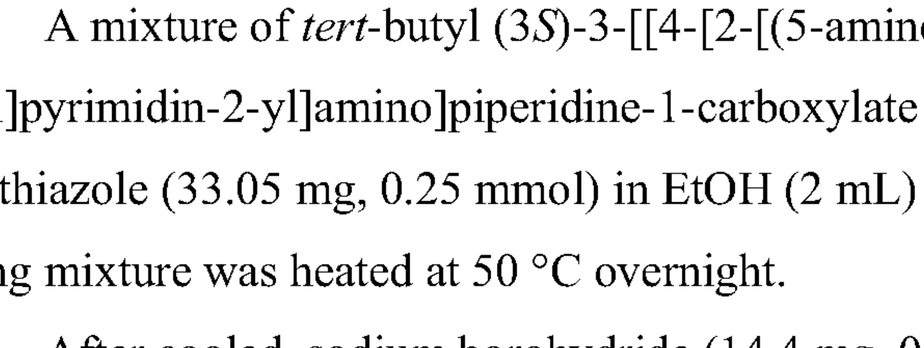
[0831] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-(((2-methylthiazol-4-yl)methyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0832] A mixture of *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol) and 4-formyl-2-methylthiazole (33.05 mg, 0.25 mmol) in EtOH (2 mL) was added AcOH (3 drops). The resulting mixture was heated at 50 °C overnight.

[0833] After cooled, sodium borohydride (14.4 mg, 0.38 mmol) was added at once, followed by stirring at room temperature for 3 h. The reaction mixture was diluted with water, extracted with iPrOAc (2 x 10 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo*. It was purified by silica gel chromatography (12 g column), eluting with 0-5% MeOH/DCM to afford 43 mg (35.5% yield) of the title compound as a brown solid. LCMS (ESI) $[M+H]^+$ = 638.

[0834] Step 2: (*S*)-4-(2-((2-Methyl-5-(((2-methylthiazol-4-yl)methyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-2-amine

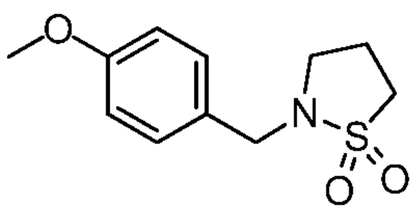


[0835] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-(((2-methylthiazol-4-yl)methyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-

yl)amino)piperidine-1-carboxylate (43 mg, 0.07 mmol). The crude product was purified *via* reverse-phase HPLC and lyophilized to yield 37.2 mg (96% yield) of **244** as a yellow solid. LCMS (ESI) $[M+H]^+ = 538$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.76 (s, 2H), 8.46 (d, $J = 5.2$ Hz, 1H), 8.08 (d, $J = 8.7$ Hz, 1H), 8.03 (dd, $J = 4.8, 2.0$ Hz, 1H), 7.56 (d, $J = 5.2$ Hz, 1H), 7.50 (d, $J = 7.4$ Hz, 1H), 7.38 (d, $J = 8.7$ Hz, 1H), 7.27 – 7.20 (m, 2H), 7.15 – 7.07 (m, 1H), 6.82 (d, $J = 8.4$ Hz, 1H), 6.46 – 6.39 (m, 1H), 4.52 (s, 2H), 4.26 (s, 1H), 3.21 (d, $J = 12.9$ Hz, 2H), 2.84 (d, $J = 14.5$ Hz, 2H), 2.64 (s, 3H), 2.19 (s, 3H), 2.06-1.97 (m, 1H), 1.96-1.88 (m, 1H), 1.79 – 1.56 (m, 2H).

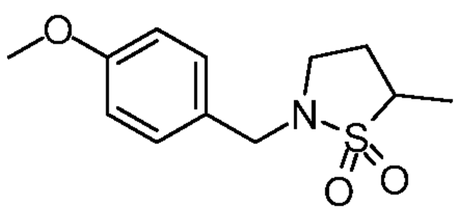
Example 245 *5-Methyl-2-(6-methyl-5-((3-(2-((S)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)isothiazolidine 1,1-dioxide* ***245***

[0836] Step 1: 2-(4-Methoxybenzyl)isothiazolidine 1,1-dioxide



[0837] To a solution of isothiazolidine 1,1-dioxide (500 mg, 4.13 mmol) in acetonitrile (10 mL) was added potassium carbonate (1.14 g, 8.25 mmol), 4-methoxybenzyl chloride (646 mg, 4.13 mmol). The mixture was heated to 80 °C for 12 h under nitrogen atmosphere. The mixture was poured into H_2O (50 mL) and extracted with ethyl acetate (50 mL). The organic layer was washed with H_2O (50 mL x 2) and saturated brine solution (50 mL). The organic layers was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified *via* flash silica chromatography (solvent gradient: 0-40% ethyl acetate in petroleum ether) to yield 1.0 g (99% yield) of the title compound as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, $J = 8.4$ Hz, 2H), 9.89 (d, $J = 8.8$ Hz, 2H), 4.13 (s, 2H), 3.82 (s, 3H), 3.23 - 3.18 (t, $J = 8.8$ Hz, 2H), 3.12 - 3.07 (m, 2H), 2.34 - 2.25 (m, 2H).

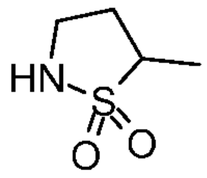
[0838] Step 2: 2-(4-Methoxybenzyl)-5-methylisothiazolidine 1,1-dioxide



[0839] To a solution of 2-(4-methoxybenzyl)isothiazolidine 1,1-dioxide (800 mg, 3.32 mmol) in THF (10 mL) was added *n*-BuLi (2.5 M in hexanes, 1.99 mL, 4.97 mmol) dropwise at-78 °C under nitrogen atmosphere. After stirring at -78 °C for 1 h, iodomethane (600 mg, 4.23 mmol) was added at -78 °C. After stirring at -78 °C for 1 h, the mixture was poured into saturated ammonium chloride solution (40 mL), extracted with ethyl acetate (2 x 30 mL) and

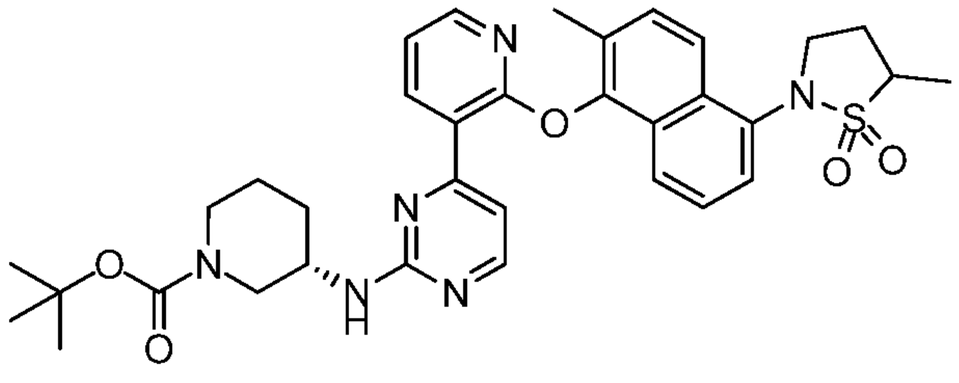
the organic phase was washed with water (50 mL x 2) and saturated brine solution (50 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by pre-TLC (50% ethyl acetate in petroleum ether) to yield 250 mg (30% yield) of the title compound as a yellow oil.

[0840] Step 3: 5-Methylisothiazolidine 1,1-dioxide



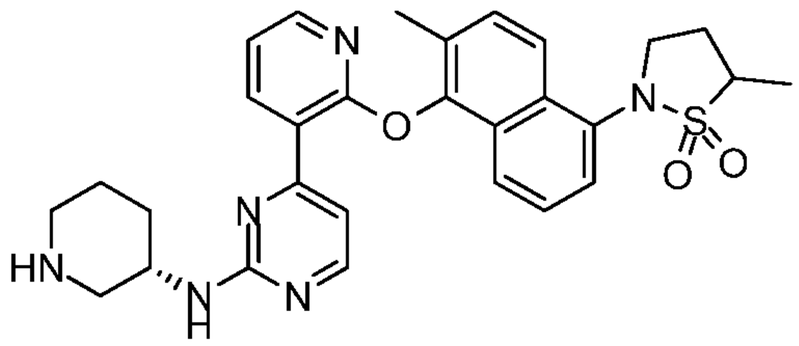
[0841] To a solution of 2-(4-methoxybenzyl)-5-methylisothiazolidine 1,1-dioxide (350 mg, 1.37 mmol) in anhydrous DCM (2 mL) was added trifluoroacetic acid (2.03 mL, 27.42 mmol). The mixture was stirred at for 1 h at room temparature. The mixture was concentrated *in vacuo* and the residue was dissolved in ethyl acetate (10 mL) and washed with saturated sodium bicarbonate (5 mL). The orgainc phase was separated, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by prep-TLC (50% ethyl acetate in petroleum ether) to yield 120 mg (65% yield) of the title compound. as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (s, 1H), 3.38 - 3.34 (m, 2H), 3.20 - 3.17 (m, 1H), 2.59 - 2.54 (m, 1H), 2.11 - 2.06 (m, 1 H), 4.43 (d, J = 7.2 Hz, 3H).

[0842] Step 4: (3*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-5-(5-methyl-1,1-dioxidoisothiazolidin-2-yl)naphthalen -1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0843] To a stirred solution of (*S*)-*tert*-butyl 3-((4-(2-((5-iodo-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.16 mmol) and 5-methyl-1,2-thiazolidine 1,1-dioxide (42 mg, 0.31 mmol) in *N*,*N*-dimethylacetamide (3 mL) was added tribasic potassium phosphate (100 mg, 0.47 mmol), CuI (12 mg, 0.06mmol) and 2-(dimethylamino)acetic acid (6 mg, 0.06 mmol). The mixture was stirred at 130 °C for 40 h. After cooling to room temperature, the mixture was filtered and concentrated in vacuo. The residue was dissolved in ethyl acetate (50 mL) and washed with H_2O (40 mL x 2). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by prep-TLC (50% ethyl acetate in petroleum ether) to yield 25 mg (25% yield) of the title compound as pale brown oil. LCMS (ESI): $[M+H]^+$ = 645.3.

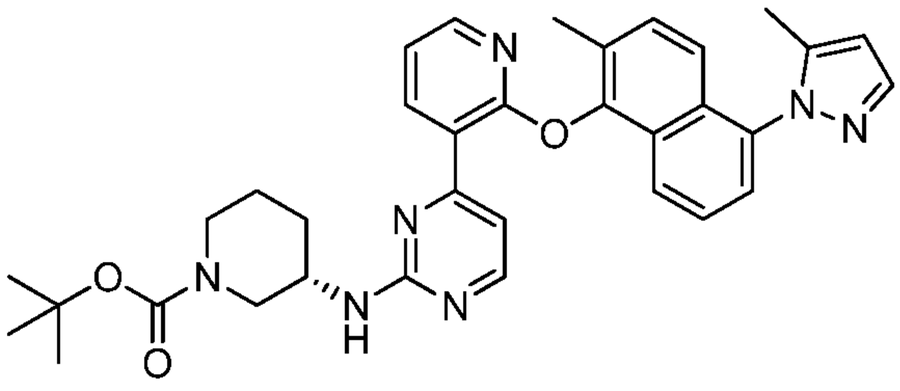
[0844] Step 5: 5-Methyl-2-(6-methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)isothiazolidine 1,1-dioxide



[0845] The General Procedure B was followed, using (3*S*)-*tert*-butyl 3-((4-(2-((2-methyl-5-(5-methyl-1,1-dioxidoisothiazolidin-2-yl)naphthalen -1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (25 mg, 0.04 mmol), dichloromethane (2 mL) and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05%NH_4OH); B: ACN) to yield 8 mg (38% yield) of the title compound as a white solid (mixture of diastereomers). LCMS (ESI): $[M+H]^+$ = 545.3; ^1H NMR (400 MHz, DMSO-d_6) δ 8.53 - 8.51 (m, 2H), 8.41 (d, J = 5.2 Hz, 1H), 8.09 (d, J = 8.8 Hz, 1H), 8.07 - 8.04 (m, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.65 - 7.49 (m, 3H), 7.44 (d, J = 5.2 Hz, 1H), 7.29 - 7.25 (m, 1H), 7.14 (d, J = 8.0 Hz, 1H), 3.98 - 3.76 (m, 2H), 3.76 - 3.58 (m, 2H), 3.13 - 3.04 (m, 1H), 2.72 - 2.60 (m, 3H), 2.48 - 2.39 (m, 1H), 2.22 - 2.16 (m, 4H), 1.96 - 1.90 (m, 1H), 1.66 - 1.63 (m, 1H), 1.51 - 1.40 (m, 5H).

Example 246 *(S)-4-(2-((2-Methyl-5-(5-methyl-1H-pyrazol-1-yl)naphthalen-1-yl)oxy)phenyl)-N-(piperidin-3-yl)pyrimidin-2-amine* ***246***

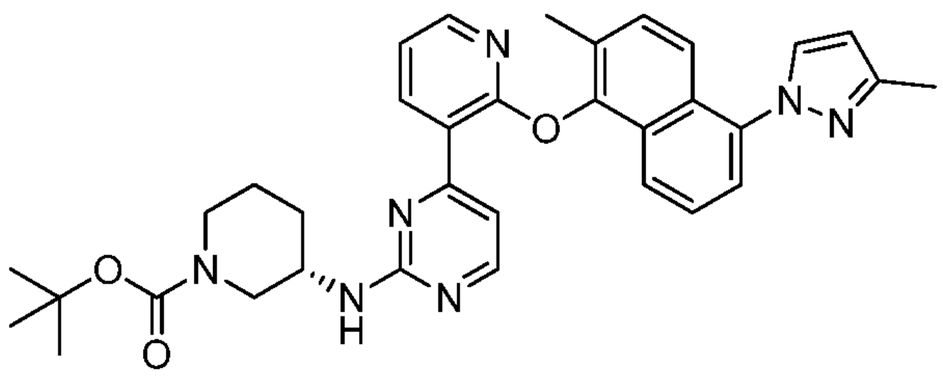
[0846] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-5-(5-methyl-1*H*-pyrazol-1-yl)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0847] To a solution of *tert*-butyl (3*S*)-3-[[4-[2-[(5-iodo-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (150 mg, 0.24 mmol) in DMSO (2 mL) was added 5-methyl-1*H*-pyrazole (23.2 mg, 0.28 mmol), copper (I) iodide (4.5 mg, 0.02 mmol), 8-hydroxyquinoline (6.8 mg, 0.05 mmol) and potassium carbonate (97.6 mg, 0.71 mmol) and stirred at 120 °C for 40 h. The mixture was concentrated and the residue was dissolved in ethyl acetate (50 mL), washed with H_2O (50 mL) and brine (50 mL). The organic

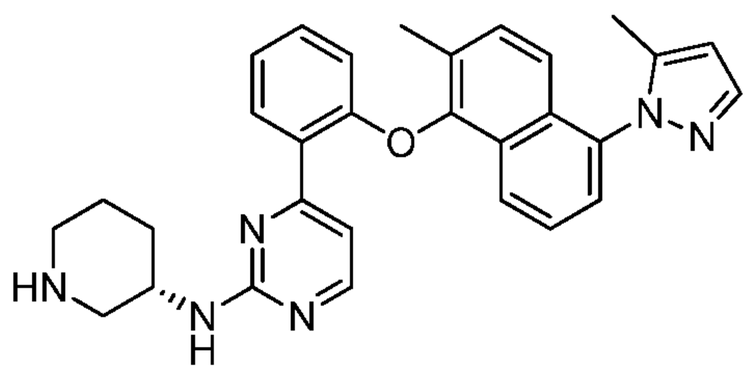
phase was dried over anhydrous sodium sulfate, concentrated and purified by prep-TLC (50% ethyl acetate in petroleum ether, Rf = 0.5) to give a mixture of the title compound and its 5-methyl pyrazole isomer (10 mg, 7% yield) as a white solid. LCMS (ESI) $[M+H]^+$ = 592.3; ^1H NMR (400 MHz, $CDCl_3$) δ 8.89 - 8.57 (m, 1H), 8.42 (s, 1H), 8.10 - 8.02 (m, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.70 (s, 2H), 7.50 - 7.35 (m, 3H), 7.18 - 7.10 (m, 2H), 6.29 (s, 1H), 5.27 (s, 1H), 4.20 - 4.08 (m, 1H), 4.03 - 3.76 (m, 1H), 3.69 - 3.52 (m, 1H), 3.47 - 3.10 (m, 1H), 2.30 (s, 3H), 2.15 (s, 3H), 2.10 - 2.00 (m, 1H), 1.89 - 1.77 (m, 2H), 1.75 - 1.67 (m, 3H), 1.42 (s, 9H);

[0848] and the 3-methyl pyrazole isomer: (*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-5-(3-methyl-1*H*-pyrazol-1-yl)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0849] (an intermediate for Example 250) as a white solid (13 mg, 9% yield). LCMS (ESI) $[M+H]^+$ = 592.3; ^1H NMR (400 MHz, $CDCl_3$) δ 8.83 - 8.54 (m, 1H), 8.42 (s, 1H), 8.05 (d, *J* = 4.8 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.77 - 7.63 (m, 3H), 7.51 - 7.36 (m, 3H), 7.27 - 7.23 (m, 1H), 7.14 - 7.11 (m, 1H), 6.33 (s, 1H), 6.38 - 6.26 (m, 1H), 5.34 - 5.15 (m, 1H), 4.25 - 4.05 (m, 1H), 3.98 - 3.74 (m, 1H), 3.68 -3.53 (m, 1H), 3.47 - 3.20 (m, 1H), 2.45 (s, 3H), 2.30 (s, 3H), 2.14 - 1.97 (m, 1H), 1.86 - 1.77 (m, 1H), 1.75 - 1.64 (m, 3H), 1.42 (s, 9H).

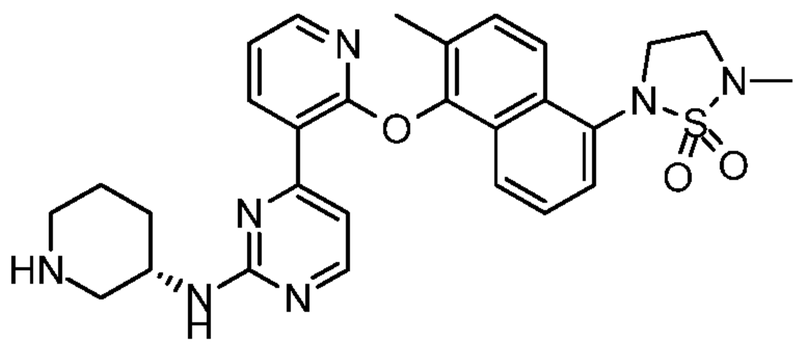
[0850] Step 2: (*S*)-4-(2-((2-Methyl-5-(5-methyl-1*H*-pyrazol-1-yl)naphthalen-1-yl)oxy)phenyl)-*N*-(piperidin-3-yl)pyrimidin-2-amine



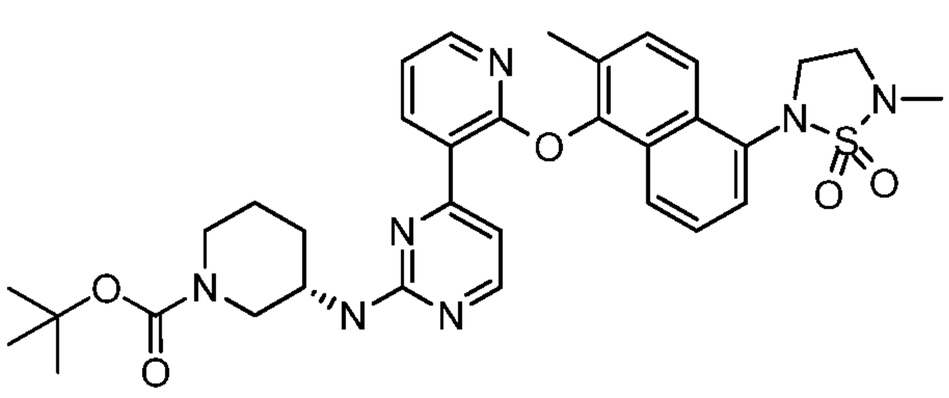
[0851] The General Procedure B was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[[2-methyl-5-(5-methylpyrazol-1-yl)-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (10 mg, 0.02 mmol) in ethyl acetate (0.5 mL). To this mixture was added hydrochloric acid (4 M in ethyl acetate, 0.04 mL, 0.16 mmol) followed by stirring at 25 °C for 1 h. The mixture was concentrated and dissolved in ethyl acetate (30 mL), washed with saturated sodium bicarbonate aqueous solution (30 mL). The organic phase was concentrated and purified by prep-TLC(10% methanol in dichloromethane, Rf = 0.4) to yield 3 mg (31%

yield) of **246** as a white solid. LCMS (ESI) $[M+H]^+$ = 492.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 - 8.47(m, 1H), 8.43 (d, J = 5.2 Hz, 1H), 8.08 - 8.06 (m, 1H), 7.86 (d, J = 8 Hz, 1H), 7.69 (d, J = 1.6 Hz, 1H), 7.62 - 7.45 (m, 3H), 7.31 - 7.28 (m, 1H), 7.16 (d, J = 8.0 Hz, 1H), 7.01 (d, J = 8.8 Hz, 1H), 6.39 (s, 1H), 4.02 - 3.80 (m, 1H), 3.17 - 3.05(m, 1H), 2.86 - 2.76 (m, 1H), 2.47 - 2.37 (m, 2H), 2.22 (s, 3H), 2.10 (s, 3H), 2.01 - 1.88 (m, 1H), 1.70 - 1.61(m, 1H), 1.54 - 1.41 (m, 2H).

Example 247 *(S)-2-Methyl-5-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1,2,5-thiadiazolidine 1,1-dioxide* ***247***

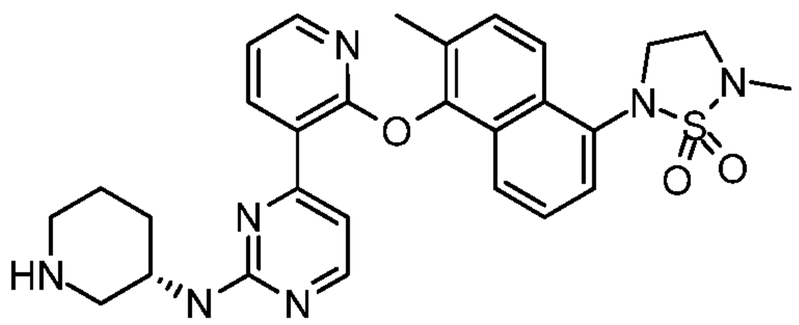


[0852] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-5-(5-methyl-1,1-dioxido-1,2,5-thiadiazolidin-2-yl)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



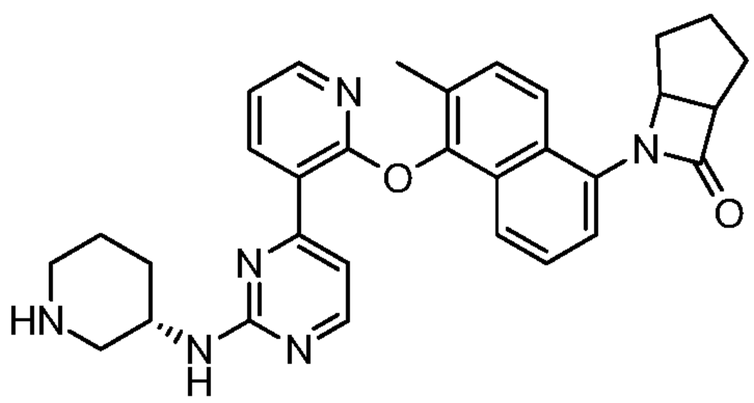
[0853] To a solution of *tert*-butyl (3*S*)-3-[[4-[2-[(5-iodo-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (150 mg, 0.24 mmol) in acetonitrile (2 mL) was added 2-methyl-1,2,5-thiadiazolidine 1,1-dioxide (64.1 mg, 0.47 mmol), copper (I) iodide (22.4 mg, 0.12 mmol), *N*,*N*'-dimethyl-1,2-ethanediamine (20.7 mg, 0.24 mmol) and potassium carbonate (97.6 mg, 0.71 mmol) followed by stirring at 80 °C for 40 h. After cooling, the mixture was filtered, concentrated and dissolved in ethyl acetate (50 mL) and subsequently washed with H_2O (40 mL x 2). The organic phase was dried over anhydrous sodium sulfate and filtered and the filtrate was concentrated *in vacuo* and purified by prep-TLC (50% ethyl acetate in petroleum ether, Rf = 0.1) to yield 22 mg (15% yield) of the title compound as a white solid. LCMS (ESI) $[M+Na]^+$= 646.1.

[0854] Step 2: (*S*)-2-Methyl-5-(6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1,2,5-thiadiazolidine 1,1-dioxide

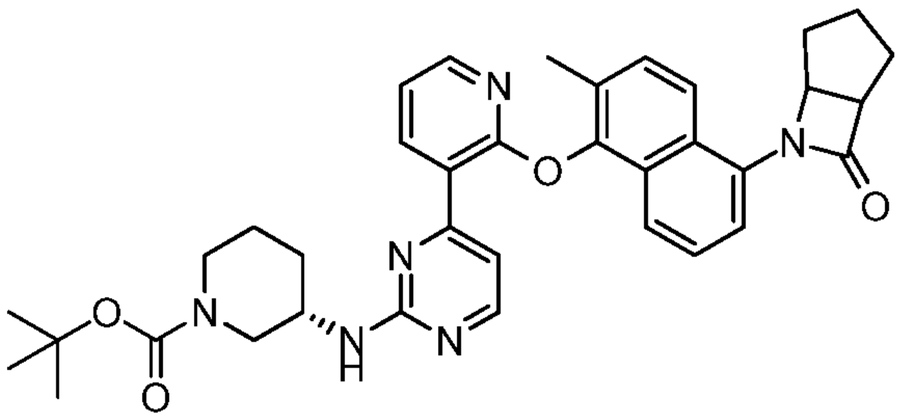


[0855] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((2-methyl-5-(5-methyl-1,1-dioxido-1,2,5-thiadiazolidin-2-yl)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (22 mg, 0.03 mmol) in ethyl acetate (1 mL). To this mixture was added hydrochloric acid (4 M in ethyl acetate, 0.09 mL, 0.36 mmol) followed by stirring at 25 °C for 1 h. The mixture was diluted with ethyl acetate (30 mL) and washed with saturated sodium bicarbonate aqueous solution (30 mL) and the organic phase was dried over anhydrous sodium sulfate, concentrated, and purified by prep-TLC (50% ethyl acetate in petroleum ether, Rf = 0.1) to yield 2.1 mg (11% yield) of **247** as a white solid. LCMS (ESI) $[M+Na]^+$= 546.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 - 8.48 (m, 1H), 8.42 (d, J = 5.6 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 8.06 - 8.04 (m, 1H), 7.73 (d, J = 9.2 Hz, 1H), 7.66 (d, J = 6.8 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.56 - 7.50 (m, 1H), 7.46 (d, J = 5.2 Hz, 1H), 7.29 - 7.25 (m, 1H), 7.22 - 7.17 (m, 1H), 4.00 - 3.91 (m, 3H), 3.62 - 3.56 (m, 2H), 3.26 - 3.20 (m, 1H), 3.26 - 3.18 (m, 1H), 2.91 - 2.84 (m, 1H), 2.79 (s, 3H), 2.67 (t, J = 2.0 Hz, 1H), 2.33 (t, J = 2.0 Hz, 1H), 2.23 (s, 3H), 1.99 - 1.88 (m, 1H), 1.72 - 1.62 (m, 1H), 1.57 - 1.41 (m, 2H).

<u>Example 248</u> *6-(6-Methyl-5-((3-(2-((S)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-6-azabicyclo[3.2.0]heptan-7-one* ***248***



[0856] Step 1: (3*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-5-(7-oxo-6-azabicyclo[3.2.0]heptan-6-yl)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0857] To a solution of (*S*)-*tert*-butyl 3-((4-(2-((5-iodo-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (50 mg, 0.08 mmol) in 1,4-dioxane (2 mL) was added 6-azabicyclo[3.2.0]heptan-7-one (17.4 mg, 0.16 mmol), copper (I) iodide (1.5 mg, 0.01 mmol), *N*,*N*'-dimethyl-1,2-ethanediamine (1.4 mg, 0.02 mmol), and potassium carbonate (32.5 mg, 0.24 mmol) and the mixture was stirred at 110 °C for 12 h. The mixture was concentrated and dissolved in ethyl acetate (50 mL) and subsequently washed with H_2O (30 mL) and brine (30 mL). The organic phase was dried over anhydrous sodium sulfate, concentrated and purified by prep-TLC (50% ethyl acetate in petroleum ether, Rf = 0.2) to yield 35 mg (72% yield) of the title compound as a white solid. LCMS (ESI) $[M+H]^+$ = 621.1.The isomers were separated by chiral SFC (OD (250 mm x 30 mm, 5 μm), 0.1%NH_3H_2O EtOH, 40% 60 mL/min) to give:

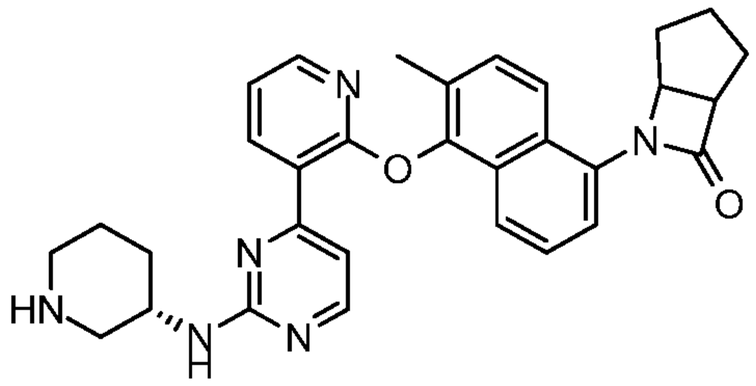
[0858] first peak on SFC: white solid; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.83 - 8.53 (m, 1H), 8.44 - 8.36 (m, 1H), 8.11 - 8.04 (m, 1H), 8.10 - 7.92 (m, 1H), 7.74 - 7.64 (m, 2H), 7.51 - 7.47 (m, 1H), 7.45 - 7.39 (m, 1H), 7.38 - 7.30 (m, 1H), 7.17 - 7.09 (m, 1H), 5.30 - 5.18 (m, 1H), 4.87 - 4.76 (m, 1H), 4.18 - 4.08 (m, 1H), 3.79 - 3.71 (m, 1H), 3.65 - 3.52 (m, 1H), 3.47 - 3.05 (m, 1H), 2.38 - 2.26 (m, 4H), 2.11 - 2.02 (m, 1H), 1.99 - 1.76 (m, 5H), 1.75 - 1.65 (m, 8H), 1.51 - 1.38 (m, 9H),

[0859] second peak on SFC: 31 mg, 44% yield), white solid; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.80 - 8.54 (m, 1H), 8.39 (d, *J* = 5.2 Hz, 1H), 8.10 - 8.02 (m, 1H), 7.99 - 7.91 (m, 1H), 7.74 - 7.64 (m, 2H), 7.53 - 7.46 (m, 1H), 7.45 - 7.38 (m, 1H), 7.45 - 7.38 (m, 1H), 7.38 - 7.31 (m, 1H), 7.30 - 7.24 (m, 2H), 7.17 - 7.07 (m, 1H), 5.31 - 5.24 (m, 1H), 4.81 (t, *J* = 4.0 Hz, 1H), 4.20 - 4.05 (m, 1H), 3.79 - 3.70 (m, 1H), 3.67 - 3.49 (m, 1H), 3.47 - 3.16 (m, 1H), 2.35 - 2.26 (m, 4H), 2.11 - 2.00 (m, 1H), 1.98 - 1.79 (m, 5H), 1.75 - 1.63 (m, 8H), 1.51 - 1.35 (s, 9H).

[0860] Step 3: The first peak on SFC compound from Step 2 was deprotected by the General Procedure B (29 mg, 0.05 mmol) in dichloromethane (0.5 mL) and trifluoroacetic acid (0.5 mL, 6.53 mmol) and stirring at 25 °C for 1 h. The mixture was dissolved in dichloromethane (30 mL) and washed with saturated sodium bicarbonate aqueous solution (30 mL x 2). The organic phase was dried over anhydrous sodium sulfate, and purified by prep-TLC (50% ethyl acetate in petroleum ether, Rf = 0.2) to yield 10.3 mg (41% yield) as a white solid. LCMS (ESI) $[M+H]^+$ = 521.1; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.54 - 8.43 (m, 1H), 8.37 (d, *J* = 4.8 Hz, 1H), 8.01 - 7.97 (m, 1H), 7.90 (d, *J* = 8.8 Hz, 1H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.53 - 7.38 (m, 4H), 7.24 - 7.21 (m, 1H), 7.12 - 7.05 (m, 1H), 4.88 (t, *J* = 4.0 Hz, 1H), 3.97 - 3.84 (m, 1H),

3.71 - 3.66 (m, 1H), 3.12 - 3.03 (m, 1H), 2.82 - 2.73 (m, 1H), 2.46 - 2.35 (m, 2H), 2.18 (s, 3H), 2.08 - 2.00 (m, 1H), 1.96 - 1.81 (m, 2H), 1.76 - 1.54 (m, 4H), 1.51 - 1.38 (m, 3H).

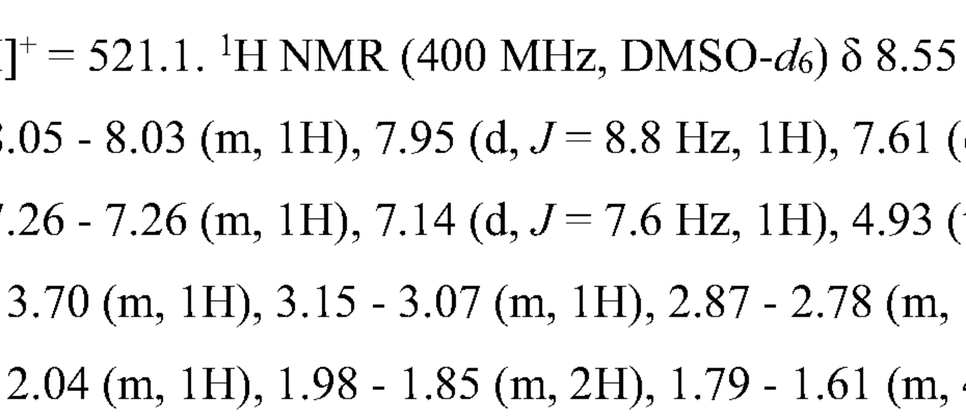
[0861] Step 4: 6-(6-Methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-6-azabicyclo[3.2.0]heptan-7-one



[0862] The second peak on SFC compound, (3*S*)-*tert*-butyl 3-((4-(2-((2-methyl-5-(7-oxo-6-azabicyclo[3.2.0]heptan-6-yl)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (31 mg, 0.05 mmol) from Step 2 was deprotected using General Procedure B in dichloromethane (0.5 mL) and trifluoroacetic acid (0.5 mL, 6.53 mmol) and stirring at 25 °C for 1 h. The mixture was dissolved in dichloromethane (30 mL) and washed with saturated sodium bicarbonate aqueous solution (30 mL x 2). The organic phase was dried over anhydrous sodium sulfate, and purified by prep-TLC (50% ethyl acetate in petroleum ether, Rf = 0.2) to yield 15 mg (57% yield) of **248** as a white solid. LCMS (ESI) $[M+H]^+$ = 521.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 - 8.48 (m, 1H), 8.42 (d, *J* = 4.8 Hz, 1H), 8.05 - 8.03 (m, 1H), 7.95 (d, *J* = 8.8 Hz, 1H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.55 - 7.43 (m, 3H), 7.26 - 7.26 (m, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 4.93 (t, *J* = 4.0 Hz, 1H), 3.97 - 3.84 (m, 1H), 3.73 - 3.70 (m, 1H), 3.15 - 3.07 (m, 1H), 2.87 - 2.78 (m, 1H), 2.48 - 2.40 (m, 2H), 2.22 (s, 3H), 2.12 - 2.04 (m, 1H), 1.98 - 1.85 (m, 2H), 1.79 - 1.61 (m, 4H), 1.56 - 1.37 (m, 3H).

Example 249 *(S)-1-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)azepan-2-one* ***249***

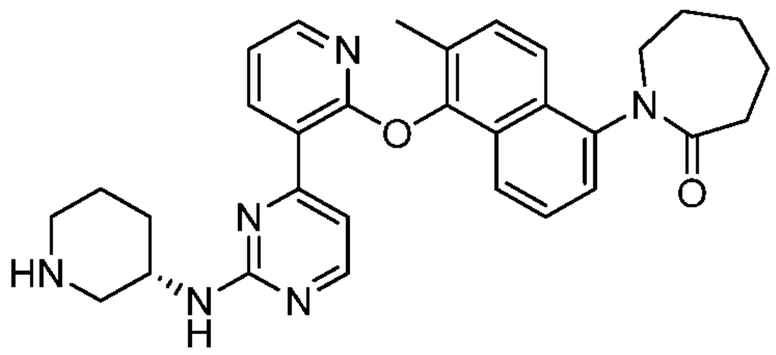
[0863] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-5-(2-oxoazepan-1-yl)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0864] To a solution of *tert*-butyl (3*S*)-3-[[4-[2-[(5-iodo-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.16 mmol) in 1,4-dioxane (2

mL) was added copper (I) iodide (2 mg, 0.01 mmol), potassium carbonate (65 mg, 0.47 mmol), *N,N'*-dimethyl-1,2-ethanediamine (1 mg, 0.02 mmol) and 2-azepanone (36 mg, 0.31 mmol). The mixture was stirred at 110 °C for 36 h. The reaction was concentrated and purified by pre-TLC (50% ethyl acetate in petroleum ether, Rf = 0.2) to yield 80 mg (82% yield) of the title compound as a yellow solid. LCMS (ESI): $[M+H]^+$ = 623.2.

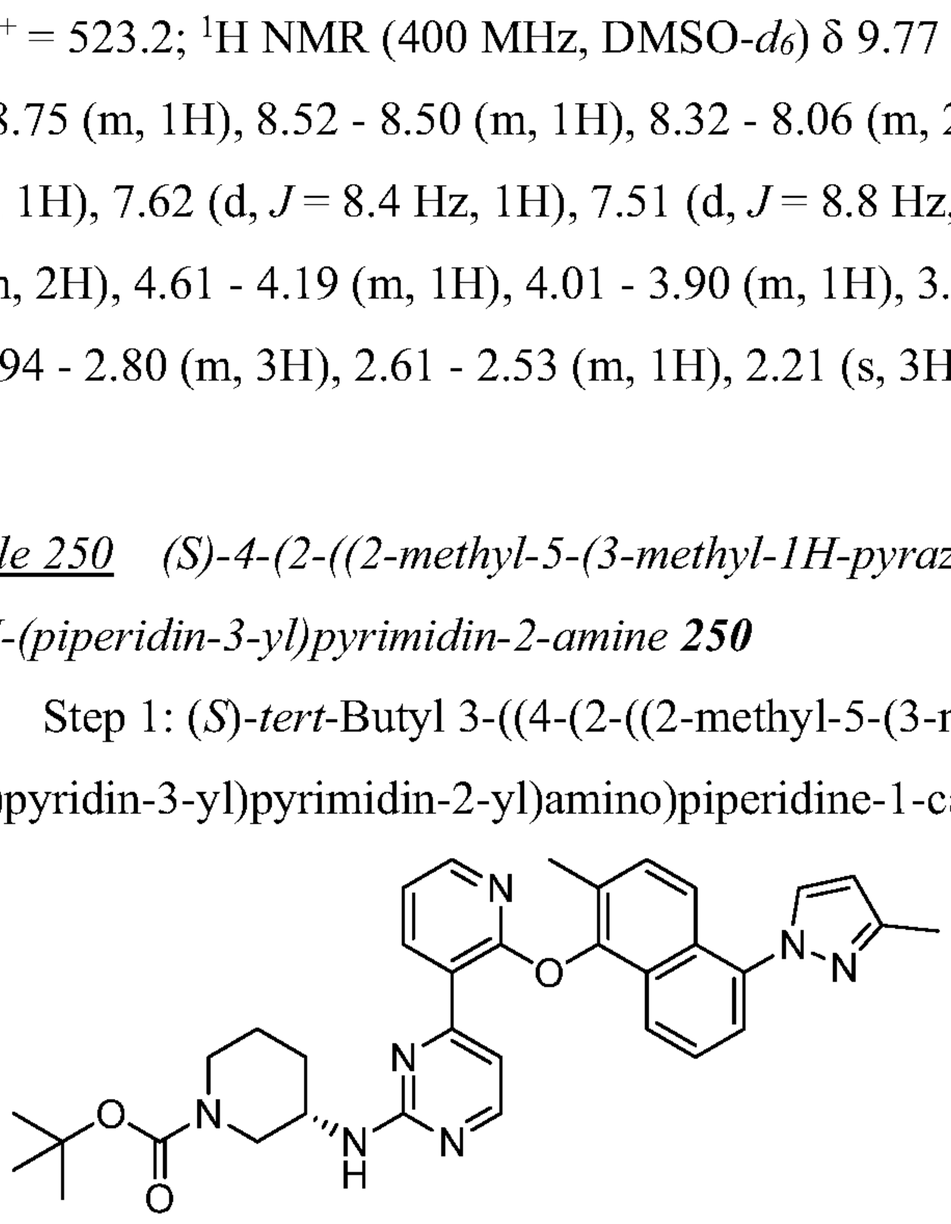
[0865] Step 2: (*S*)-1-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)azepan-2-one



[0866] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((2-methyl-5-(2-oxoazepan-1-yl)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (80 mg, 0.13 mmol), dichloromethane (5 mL) and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05%HCl) B: ACN) to yield 14 mg (19% yield) of **249** as a yellow solid. LCMS (ESI): $[M+H]^+$ = 523.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.77 - 9.43 (m, 1H), 9.42 - 9.24 (m, 1H), 8.98 - 8.75 (m, 1H), 8.52 - 8.50 (m, 1H), 8.32 - 8.06 (m, 2H), 7.82 - 7.71 (m, 1H), 7.67 (d, *J* = 8.6 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.34 - 7.27 (m, 2H), 4.61 - 4.19 (m, 1H), 4.01 - 3.90 (m, 1H), 3.59 - 3.37 (m, 2H), 3.25 - 3.13 (m, 1H), 2.94 - 2.80 (m, 3H), 2.61 - 2.53 (m, 1H), 2.21 (s, 3H), 2.08 - 1.99 (m, 1H), 1.95 - 1.64 (m, 9H).

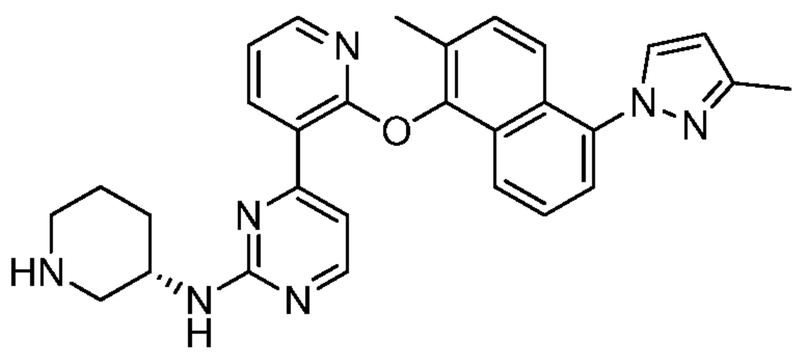
Example 250 *(S)-4-(2-((2-methyl-5-(3-methyl-1H-pyrazol-1-yl)naphthalen-1-yl)oxy)pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine* ***250***

[0867] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-5-(3-methyl-1*H*-pyrazol-1-yl)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0868] Following the procedures of Example 246, the 3-methyl pyrazole isomer was obtained as a white solid (13 mg, 9% yield). LCMS (ESI) $[M+H]^+$ = 592.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 - 8.54 (m, 1H), 8.42 (s, 1H), 8.05 (d, *J* = 4.8 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.77 - 7.63 (m, 3H), 7.51 - 7.36 (m, 3H), 7.27 - 7.23 (m, 1H), 7.14 - 7.11 (m, 1H), 6.33 (s, 1H), 6.38 - 6.26 (m, 1H), 5.34 - 5.15 (m, 1H), 4.25 - 4.05 (m, 1H), 3.98 - 3.74 (m, 1H), 3.68 - 3.53 (m, 1H), 3.47 - 3.20 (m, 1H), 2.45 (s, 3H), 2.30 (s, 3H), 2.14 - 1.97 (m, 1H), 1.86 - 1.77 (m, 1H), 1.75 - 1.64 (m, 3H), 1.42 (s, 9H).

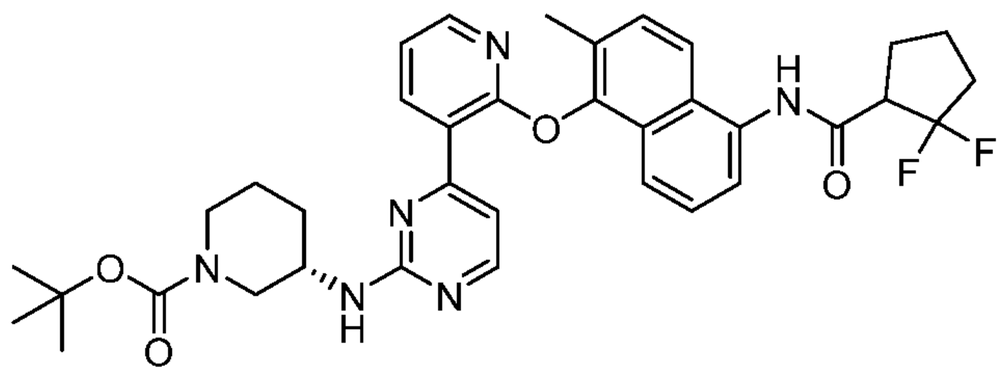
[0869] Step 2: (*S*)-4-(2-((2-Methyl-5-(3-methyl-1*H*-pyrazol-1-yl)naphthalen-1-yl)oxy)pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-2-amine



[0870] The General Procedure B was followed, using (*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-5-(3-methyl-1*H*-pyrazol-1-yl)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (13 mg, 0.02 mmol) in ethyl acetate (0.5 mL). To this mixture was added hydrochloric acid (4 M in ethyl acetate, 0.05 mL, 0.2 mmol) followed by stirring at 25 °C for 1 h. The mixture was concentrated *in vacuo*, dissolved in ethyl acetate (30 mL), and washed with saturated sodium bicarbonate aqueous solution (30 mL). The organic phase was concentrated and purified by prep-TLC (10% methanol in dichloromethane, Rf = 0.4) to yield 2 mg (17% yield) of **250**. LCMS (ESI) $[M+H]^+$ = 492.2; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.55 - 8.46 (m, 1H), 8.42 (d, *J* = 5.2 Hz, 1H), 8.08 (d, *J* = 2.0 Hz, 1H), 8.05 - 8.03 (m, 1H), 7.84 - 7.75 (m, 1H), 7.72 (d, *J* = 8.8 Hz, 1H), 7.57 - 7.48 (m, 3H), 7.45 (d, *J* = 5.2 Hz, 1H), 7.29 - 7.26 (m, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 6.40 (d, *J* = 2.4 Hz, 1H), 3.98 - 3.78 (m, 1H), 3.14 - 3.04 (m, 1H), 2.84 - 2.73 (m, 1H), 2.46 - 2.36 (m, 2H), 2.33 (s, 3H), 2.23 (s, 3H), 1.98 - 1.88 (m, 1H), 1.69 - 1.59 (m, 1H), 1.56 - 1.37 (m, 2H).

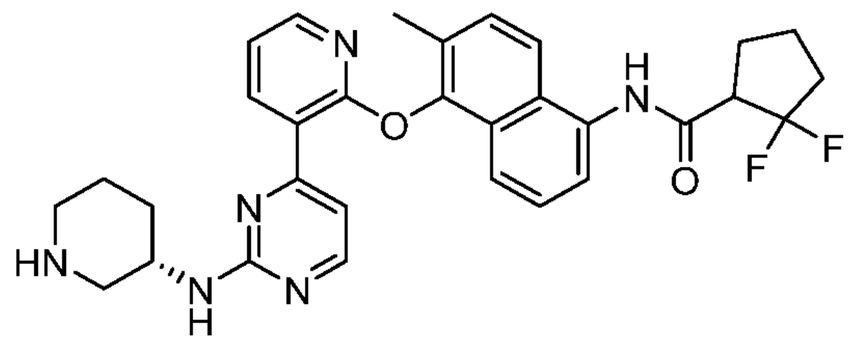
Example 251 *2,2-Difluoro-N-(6-methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentane-1-carboxamide* ***251***

[0871] Step 1: (3*S*)-*tert*-Butyl 3-(4-(2-(5-(2,2-difluorocyclopentanecarboxamido)-2-methylnaphthalen-1-yloxy)pyridin-3-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate



[0872] The General Procedure C was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (50 mg, 0.095 mmol), HATU (72 mg, 0.19 mmol), diisopropylethylamine (36 mg, 0.29 mmol), and 2,2-difluorocyclopentane-1-carboxylic acid (22 mg, 0.14 mmol). The product obtained after workup was used in step 2 without further purification. LCMS (ESI) $[M+H]^+$ = 659.3.

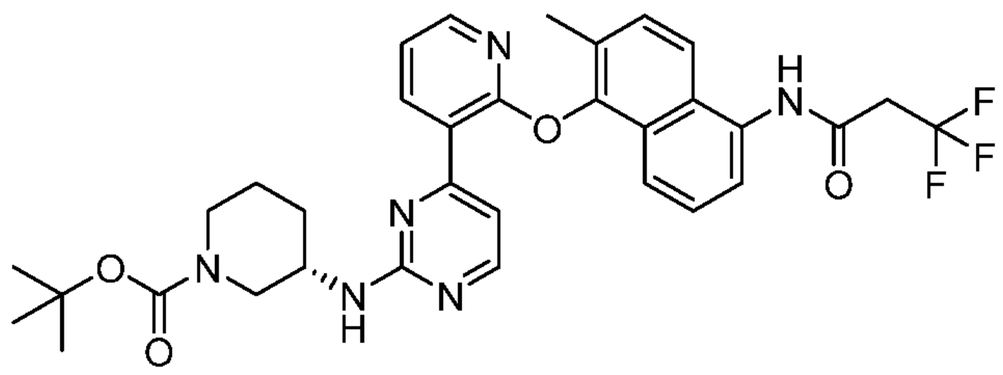
[0873] Step 2: 2,2-Difluoro-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentane-1-carboxamide



[0874] To the crude (3*S*)-*tert*-Butyl 3-(4-(2-(5-(2,2-difluorocyclopentanecarboxamido)-2-methylnaphthalen-1-yloxy)pyridin-3-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate from step 1 in DCM (6 mL) was added trifluoroacetic acid (1 mL). The mixture was concentrated and the residue purified by Prep-HPLC to yield 17.9 mg (34% yield) of **251** as a white solid. LCMS (ESI): $[M+H]^+$ = 559.2. ^{1}H NMR (400 MHz, DMSO-*d*6) δ 10.18 (s, 1H), 8.52 (s, 1H), 8.43 (d, *J* = 5.1 Hz, 1H), 8.03 (dd, *J* = 4.8, 2.0 Hz, 1H), 7.90 (m, 1H), 7.59 – 7.49 (m, 2H), 7.48 (d, *J* = 5.1 Hz, 1H), 7.42 (dd, *J* = 8.6, 7.3 Hz, 1H), 7.26 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.21 (d, *J* = 7.9 Hz, 1H), 3.98 (s, 1H), 3.55 (m, 2H), 2.90 (d, *J* = 12.3 Hz, 1H), 2.55 (d, *J* = 6.1 Hz, 1H), 2.22 (s, 3H), 1.94 (m, 2H), 1.82 – 1.66 (m, 2H), 1.52 (d, *J* = 8.6 Hz, 2H).

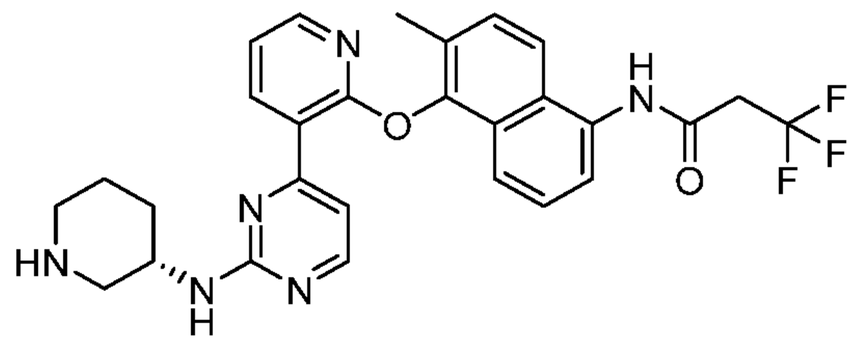
Example 252 (S)-3,3,3-Trifluoro-N-(6-methyl-5-(3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yloxy)naphthalen-1-yl)propanamide ***252***

[0875] Step 1: (*S*)-*tert*-Butyl 3-(4-(2-(2-methyl-5-(3,3,3-trifluoropropanamido)naphthalen-1-yloxy)pyridin-3-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate



[0876] The General Procedure C was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (50 mg, 0.095 mmol), HATU (72 mg, 0.19 mmol), diisopropylethylamine (36 mg, 0.29 mmol), and 3,3,3-trifluoropropionic acid (19 mg, 0.14 mmol). The product obtained after workup was used in step 2 without further purification. LCMS (ESI) $[M+H]^+ = 637.3$.

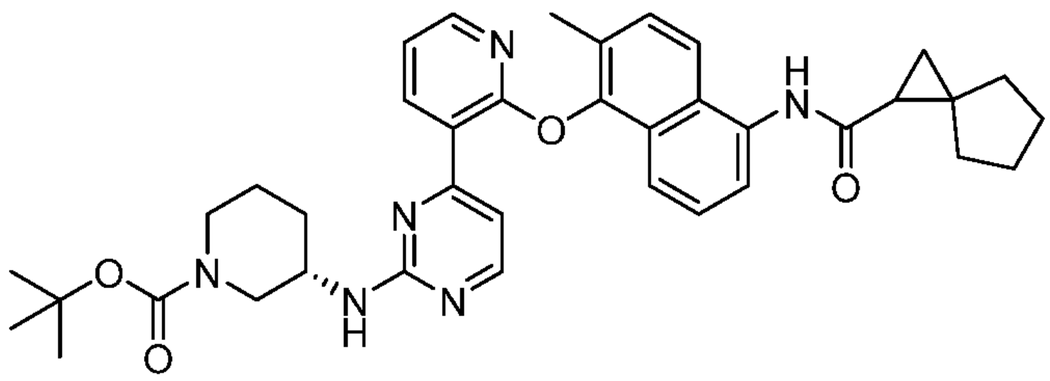
[0877] Step 2: (*S*)-3,3,3-Trifluoro-*N*-(6-methyl-5-(3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yloxy)naphthalen-1-yl)propanamide



[0878] To the crude (*S*)-*tert*-butyl 3-(4-(2-(2-methyl-5-(3,3,3-trifluoropropanamido)naphthalen-1-yloxy)pyridin-3-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate from step 1 in DCM (6 mL) was added trifluoroacetic acid (1 mL). The mixture was concentrated and the residue purified by Prep-HPLC to yield 23.6 mg (46% yield) of **252** as a white solid. LCMS (ESI): $[M+H]^+ = 537.2$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 8.50 (s, 1H), 8.42 (d, J = 5.1 Hz, 1H), 8.03 (dd, J = 4.8, 2.0 Hz, 1H), 7.91 (d, J = 8.6 Hz, 1H), 7.63 (dd, J = 7.4, 1.0 Hz, 1H), 7.56 (dd, J = 8.6, 6.1 Hz, 2H), 7.44 (m, 2H), 7.26 (dd, J = 7.6, 4.8 Hz, 1H), 7.16 (d, J = 7.9 Hz, 1H), 3.93 (s, 1H), 3.71 (q, J = 11.2 Hz, 2H), 3.14 (d, J = 11.4 Hz, 1H), 2.84 (d, J = 12.5 Hz, 1H), 2.22 (s, 3H), 1.97-1.91 (m, 1H), 1.69-1.66 (m, 1H), 1.53-1.47 (m, 2H).

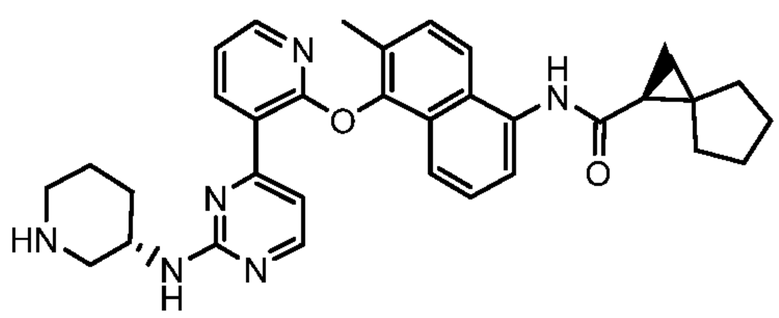
Example 253 *(S)-N-(6-Methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)spiro[2.4]heptane-1-carboxamide* ***253***

[0879] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-spiro[2.4]heptane-1-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



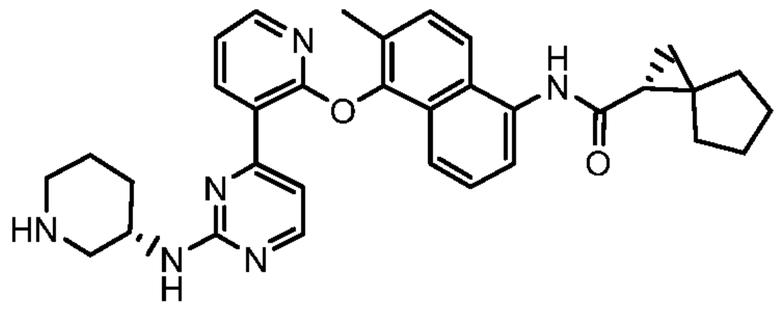
[0880] The General Procedure C was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (150 mg, 0.28 mmol) and spiro[2.4]heptane-1-carboxylic acid (63.05 mg, 0.43 mmol), HATU (221.0 mg, 0.57 mmol), DIPEA (0.15 mL, 0.85 mmol), and DMF (1.5 mL) to afford 142 mg (76.8% yield) of the title compound as a light brown solid. It was carried on as is. LCMS (ESI) $[M+H]^+ = 649$.

[0881] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)spiro[2.4]heptane-1-carboxamide



[0882] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-((*S*)-spiro[2.4]heptane-1-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (142 mg, 0.22 mmol). The crude product was purified *via* reverse-phase HPLC, chiral SFC, and lyophilized to yield 44.9 mg (37% yield) of **253** (isomer-1) as an off-white solid. LCMS (ESI) $[M+H]^+ = 549$. t_R: 1.191 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.49 (s, 1H), 8.41 (d, J = 5.1 Hz, 1H), 8.02 (dd, J = 4.8, 1.9 Hz, 1H), 7.95 (d, J = 8.7 Hz, 1H), 7.64 (s, 1H), 7.50 (t, J = 9.0 Hz, 2H), 7.46 – 7.33 (m, 2H), 7.29 – 7.21 (m, 1H), 7.10 (d, J = 8.0 Hz, 1H), 3.85 (s, 1H), 3.07 (d, 1H), 2.78 (d, J = 12.4 Hz, 1H), 2.44 – 2.39 (m, 1H), 2.22 (s, 3H), 2.15 – 2.09 (m, 1H), 1.96 (s, 2H), 1.75 – 1.57 (m, 10H), 1.52 – 1.40 (m, 1H), 1.17 (dd, J = 5.5, 3.8 Hz, 1H), 1.05 – 0.99 (m, 1H).

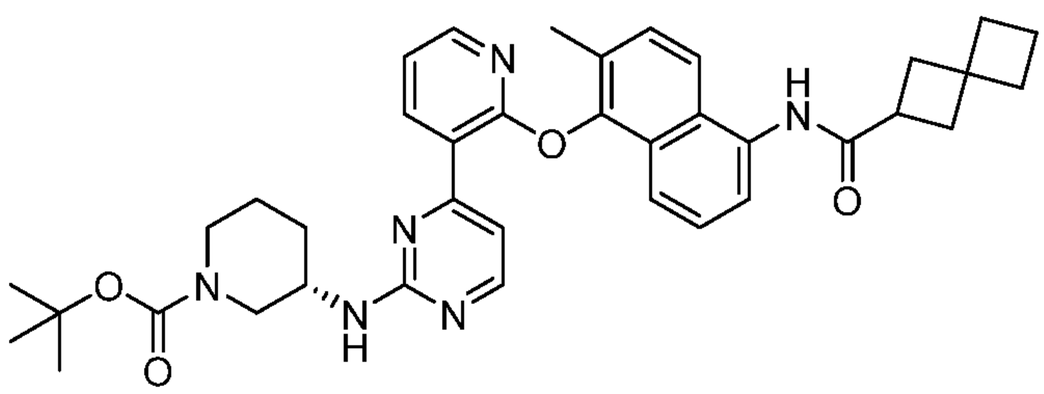
Example 254 *(R)-N-(6-Methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)spiro[2.4]heptane-1-carboxamide* ***253***



[0883] Following Example 253 and General Procedure B was followed, *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-((*R*)-spiro[2.4]heptane-1-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate was converted to **254** as isomer-2 was obtained 47 mg (39% yield) as an off-white solid. LCMS (ESI) $[M+H]^+$ = 549. t_R: 1.557 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.49 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.02 (dd, *J* = 4.8, 2.0 Hz, 1H), 7.95 (d, *J* = 8.7 Hz, 1H), 7.64 (d, 1H), 7.54 – 7.47 (m, 2H), 7.44 (d, *J* = 5.1 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.25 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 3.89 (s, 1H), 3.09 (s, 1H), 2.80 (d, *J* = 12.4 Hz, 1H), 2.46 – 2.40 (m, 1H), 2.22 (s, 3H), 2.14 – 2.07 (m, 5H), 1.96 – 1.89 (m, 1H), 1.76 – 1.59 (m, 7H), 1.53 – 1.39 (m, 1H), 1.17 (dd, *J* = 5.4, 3.8 Hz, 1H), 1.02 (s, 1H).

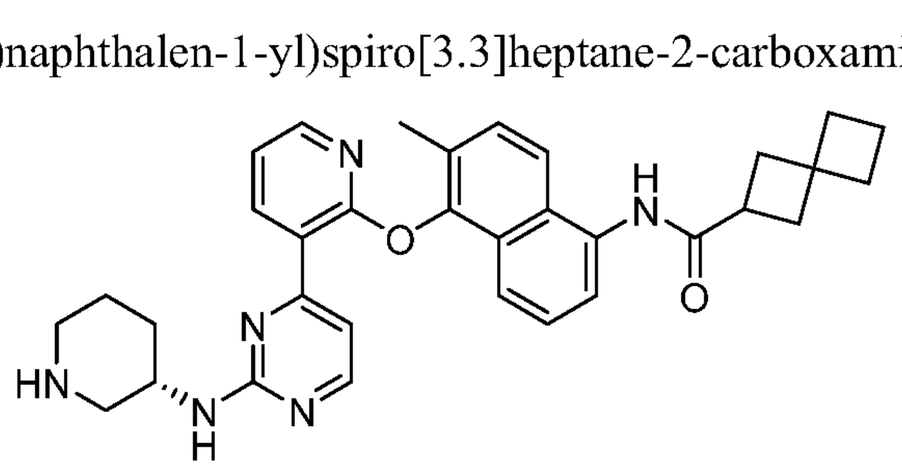
Example 255 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)spiro[3.3]heptane-2-carboxamide* ***255***

[0884] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-(spiro[3.3]heptane-2-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0885] The General Procedure of Example 217 was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (150 mg, 0.28 mmol) and spiro[3.3]heptane-2-carboxylic acid (61.7 mg, 0.43 mmol), HATU (221.0 mg, 0.57 mmol), DIPEA (0.15 mL, 0.85 mmol), and DMF (1.5 mL). The crude material was purified by silica gel chromatography (12 g column) eluting with 0-5% MeOH/DCM to afford 185 mg (100% yield) of the title compound as a brown solid. LCMS (ESI) $[M+H]^+$ = 649.

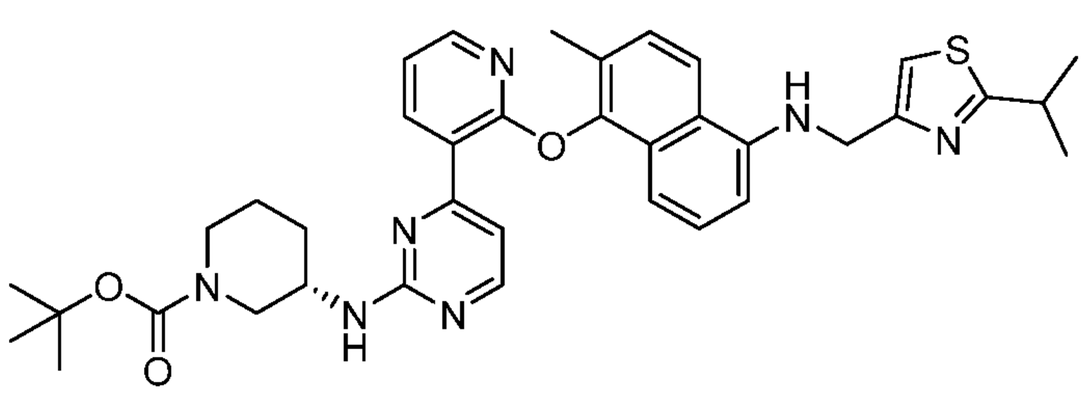
[0886] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)spiro[3.3]heptane-2-carboxamide



[0887] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-(spiro[3.3]heptane-2-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (185 mg, 0.28 mmol). The crude product was purified *via* reverse-phase HPLC and lyophilized to yield 79.1 mg (50.6% yield) of **255** as an off-white solid. LCMS (ESI) $[M+H]^+ = 549$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 8.49 (d, J = 7.4 Hz, 1H), 8.40 (d, J = 5.1 Hz, 1H), 8.02 (dd, J = 4.8, 2.0 Hz, 1H), 7.86 (d, J = 8.7 Hz, 1H), 7.61 (d, J = 7.4 Hz, 1H), 7.49 (d, J = 8.8 Hz, 2H), 7.45 – 7.32 (m, 2H), 7.25 (dd, J = 7.6, 4.8 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 3.87 (s, 1H), 3.08 (d, J = 11.6 Hz, 1H), 2.78 (d, J = 12.4 Hz, 1H), 2.42 (dd, J = 12.4, 3.6 Hz, 3H), 2.24 (d, J = 8.5 Hz, 4H), 2.21 (s, 3H), 2.08 (t, J = 7.4 Hz, 2H), 1.91 (t, J = 7.4 Hz, 3H), 1.81 (q, J = 7.5 Hz, 2H), 1.67 – 1.59 (m, 1H), 1.54 – 1.37 (m, 2H).

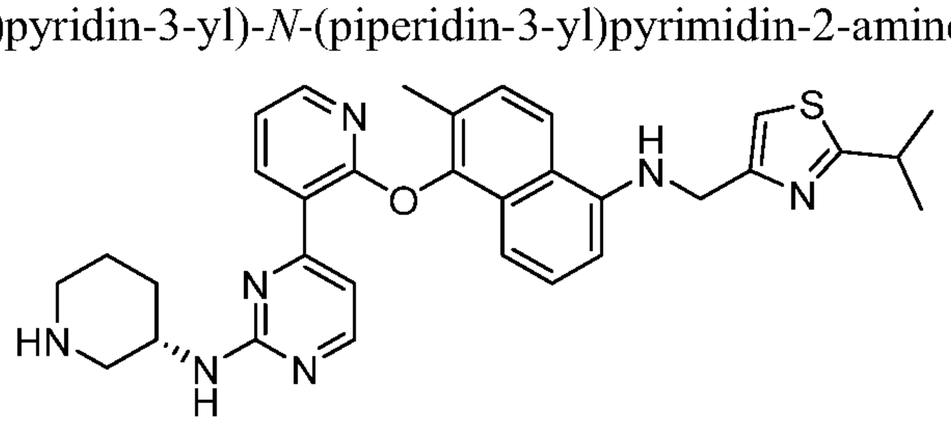
Example 256 *(S)-4-(2-((5-(((2-Isopropylthiazol-4-yl)methyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine* ***256***

[0888] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((5-(((2-isopropylthiazol-4-yl)methyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0889] The General Procedure E was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (150 mg, 0.28 mmol) and 4-(chloromethyl)-2-isopropyl-thiazole (150 mg, 0.85 mmol). The crude material was purified by silica gel chromatography (12 g column) eluting with 0-5% MeOH/DCM to afford 69 mg (36.4% yield) of the title compound as a brown solid. LCMS (ESI) $[M+H]^+ = 666$.

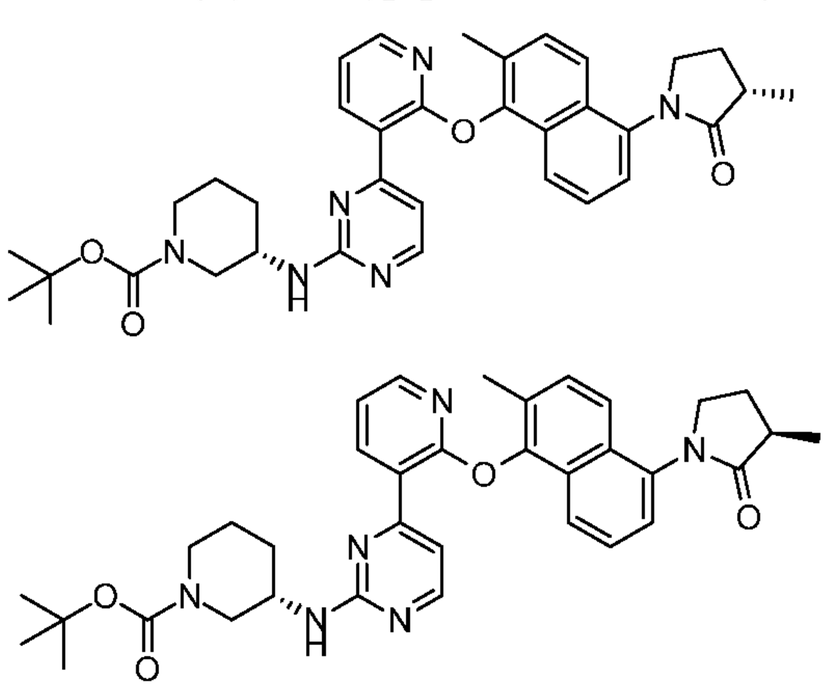
[0890] Step 2: (*S*)-4-(2-((5-(((2-Isopropylthiazol-4-yl)methyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-2-amine



[0891] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-(((2-isopropylthiazol-4-yl)methyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (69 mg, 0.10 mmol). The crude product was purified *via* reverse-phase HPLC and lyophilized to yield 24.1 mg (41% yield) of **256** as an off-white solid. LCMS (ESI) $[M+H]^+$ = 566. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50-8.46 (m, 1H), 8.39 (d, *J* = 5.1 Hz, 1H), 8.07 (d, *J* = 8.7 Hz, 1H), 8.01 (dd, *J* = 4.8, 2.0 Hz, 1H), 7.43 (d, *J* = 5.2 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.30 (s, 1H), 7.25 – 7.20 (m, 2H), 7.10 (dd, *J* = 8.1, 2.2 Hz, 2H), 6.92 – 6.83 (m, 2H), 6.43 (dd, *J* = 7.8, 1.0 Hz, 1H), 4.53 (d, *J* = 5.5 Hz, 2H), 3.87 (s, 1H), 3.09 (d, *J* = 11.7 Hz, 1H), 2.85 – 2.75 (m, 2H), 2.47 – 2.40 (m, 2H), 2.19 (s, 3H), 1.90 (d, *J* = 7.2 Hz, 1H), 1.64 (d, *J* = 12.2 Hz, 1H), 1.54 – 1.38 (m, 2H), 1.33 (d, *J* = 6.9 Hz, 6H).

Example 257 *(S)-3-Methyl-1-(6-methyl-5-((3-(2-((S)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidin-2-one* ***257***

[0892] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-5-((*S*)-3-methyl-2-oxopyrrolidin-1-yl)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate & (*S*)-tert-butyl 3-((4-(2-((2-methyl-5-((*R*)-3-methyl-2-oxopyrrolidin-1-yl)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



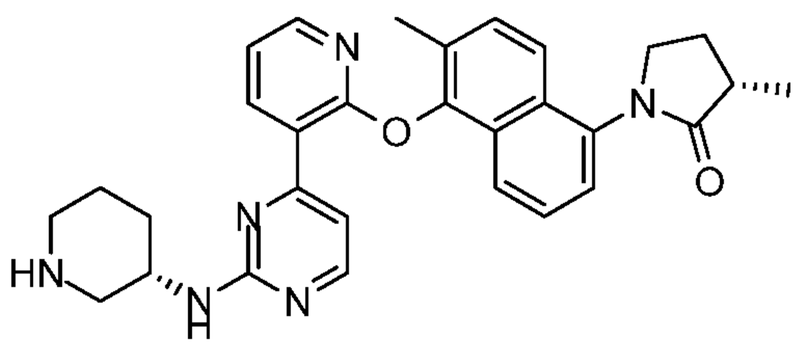
[0893] To a stirred solution of *tert*-butyl (3*S*)-3-[[4-[2-[(5-iodo-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (150 mg, 0.24 mmol) in 1,4-dioxane (2 mL) was added copper(I) iodide (5 mg, 0.02 mmol), potassium carbonate (98 mg, 0.71 mmol), *N*, *N*'-dimethyl-1,2-ethanediamine (4 mg, 0.05 mmol) and 3-methyl-2-pyrrolidinone (23 mg, 0.24 mmol), the mixture was stirred at 110 °C for 12 h. The combined mixture was concentrated and dissolved in ethyl acetate (50 mL) and subsequently washed with H_2O (30 mL) and brine (30 mL). The organic phase was dried over anhydrous sodium sulfate and filtered and the filtrate was concentrated. The residue was purified by chromatography on silica (solvent gradient: 0-50% ethyl acetate in petroleum ether) and separated using chiral SFC

(SFC80; Chiralpak AD 250×30 mm I.D.,10 μm; supercritical CO_2 / MeOH+NH_3•H_2O = 40 / 40; 60 mL / min) to afford

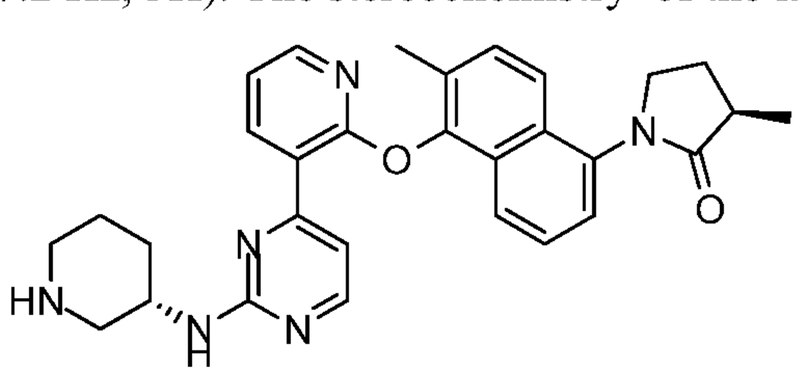
[0894] Peak 1: *tert*-butyl (3*S*)-3-[[4-[2-[[2-methyl-5-[(3*S*)-3-methyl-2-oxo-pyrrolidin-1-yl]-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (70 mg, 53.8% yield) as a white solid (first peak).

[0895] Peak 2: *tert*-butyl (3*S*)-3-[[4-[2-[[2-methyl-5-[(3*R*)-3-methyl-2-oxo-pyrrolidin-1-yl]-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (60 mg, 46.2% yield) as a white solid (second peak). LCMS (ESI): $[M+H]^+$ = 609.3.

[0896] Step 2: (*S*)-3-Methyl-1-(6-methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidin-2-one & (*R*)-3-methyl-1-(6-methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidin-2-one



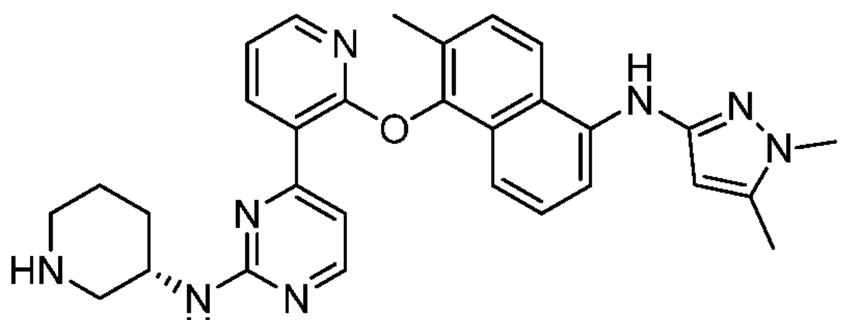
[0897] The General Procedure B was followed, using (*S*)-3-methyl-1-(6-methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidin-2-one (70 mg, 0.12 mmol) (first peak on SFC in step 1), dichloromethane (5 mL) and hydrochloric acid (4 M in ethyl acetate, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% TFA) B: ACN) to yield 19 mg (31 % yield) of **257** as a yellow solid. LCMS (ESI): $[M+H]^+$ = 509.3; ^1H NMR (400 MHz, DMSO-*d6*) δ 9.68 (s, 1H), 9.35 (s, 1H), 8.91 (s, 1H), 8.53 (s, 1H), 8.34 (s, 1H), 8.14 (s, 1H), 7.80 (s, 1H), 7.69 - 7.58 (m, 2H), 7.55 - 7.45 (m, 2H), 7.45 - 7.39 (m, 1H), 7.31 (dd, *J* = 5.2, 7.6 Hz, 1H), 4.53 (s, 1H), 3.83 (s, 1H), 3.71 (s, 1H), 3.44 (d, *J* = 6.4 Hz, 1H), 3.19 (s, 1H), 2.93 - 2.81 (m, 2H), 2.80 - 2.71 (m, 1H), 2.46 (s, 1H), 2.23 (s, 3H), 2.06 - 2.00 (m, 1H), 1.99 - 1.88 (m, 2H), 1.88 - 1.60 (m, 2H), 1.25 (d, *J* = 7.2 Hz, 3H). The stereochemistry of the lactam was tentatively and randomly assigned.



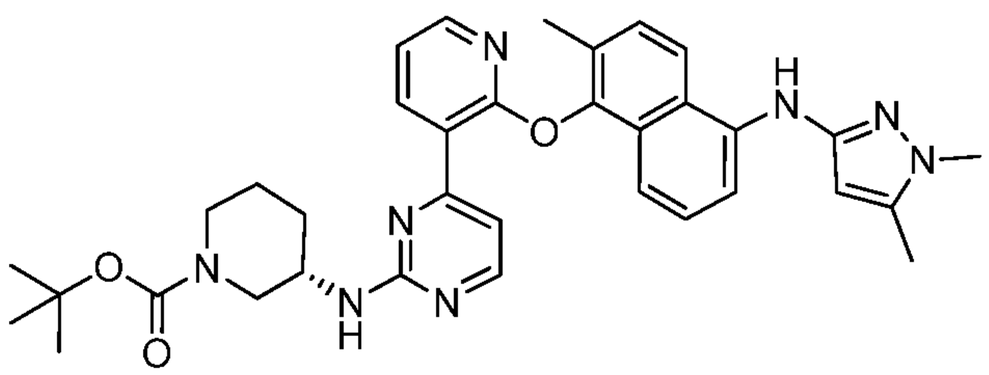
[0898] The R methyl isomer was also obtained using the General Procedure B, using (*R*)-3-methyl-1-(6-methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-

yl)oxy)naphthalen-1-yl)pyrrolidin-2-one (60 mg, 0.10 mmol)) (second peak on SFC in step 1), dichloromethane (5 mL) and hydrochloric acid (4 M in ethyl acetate, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% TFA) B: ACN) to yield 11 mg (22% yield) of (*R*)-3-methyl-1-(6-methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidin-2-one as a yellow solid. LCMS (ESI): $[M+H]^+$ = 509.2; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.78 (s, 1H), 9.41 (s, 1H), 8.94 (s, 1H), 8.53 (s, 1H), 8.40 (s, 1H), 8.13 (s, 1H), 7.82 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.63 - 7.57 (m, 1H), 7.54 - 7.44 (m, 2H), 7.44 - 7.37 (m, 1H), 7.30 (dd, *J* = 5.2, 7.6 Hz, 1H), 4.74 - 4.45 (m, 1H), 3.90 - 3.63 (m, 2H), 3.50 - 3.35 (m, 1H), 3.18 (s, 1H), 2.93 - 2.80 (m, 2H), 2.79 - 2.69 (m, 1H), 2.48 - 2.40 (m, 1H), 2.22 (s, 3H), 2.06 - 2.00 (m, 1H), 1.99 - 1.88 (m, 2H), 1.87 - 1.59 (m, 2H), 1.24 (d, *J* = 7.2 Hz, 3H). The stereochemistry of the lactam was tentatively and randomly assigned.

Example 258 *(S)-4-(2-((5-((1, 5-Dimethyl-1H-pyrazol-3-yl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine* ***258***



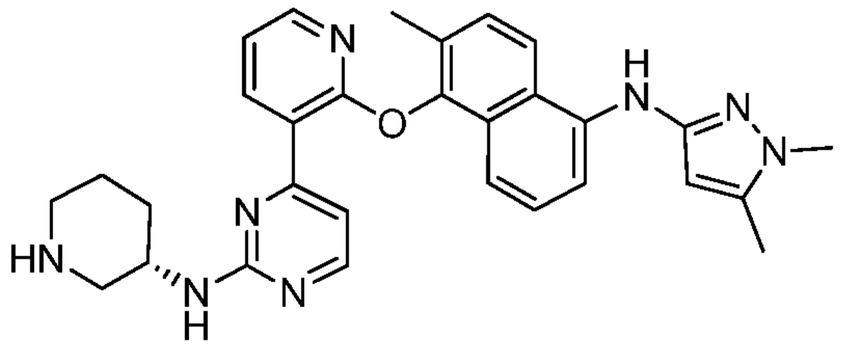
[0899] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-((1,5-dimethyl-1*H*-pyrazol-3-yl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0900] To a solution of *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol), 3-bromo-1,5-dimethyl-pyrazole (50 mg, 0.28 mmol), 2-methylpropan-2-olate; sodium hydride (46 mg, 0.47 mmol) in 1,4-dioxane were added [2-(2-aminophenyl)phenyl]-methylsulfonyloxy-palladium; dicyclohexyl-[3,6-dimethoxy-2-(2,4,6-triisopropylphenyl)phenyl]phosphane (17 mg, 0.02 mmol), 2-(dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl (20 mg, 0.04 mmol) under nitrogen atmosphere. The mixture was stirred at 120 °C for 12 h. The

solution was concentrated and purified by prep-TLC (50% ethyl acetate in petroleum ether, Rf = 0.4) to yield 50 mg (42% yield) of the title compound as a white solid.

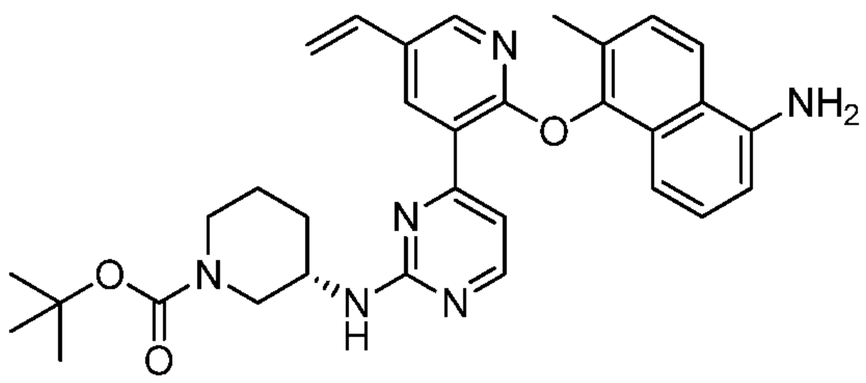
[0901] Step 2: (*S*)-4-(2-((5-((1,5-Dimethyl-1*H*-pyrazol-3-yl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine



[0902] The General Procedure B was followed, using (*S*)-*tert*-butyl 3-((4-(2-((5-((1,5-dimethyl-1H-pyrazol-3-yl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (50 mg, 0.08 mmol), dichloromethane (5 mL) and hydrochloric acid (4 M in ethyl acetate, 2 mL, 8 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05% HCl) B: ACN) to yield 14 mg (32% yield) of **258** as a yellow solid. LCMS (ESI): $[M+H]^+$ = 521.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 9.38 (s, 1H), 8.91 (s, 1H), 8.53 (s, 1H), 8.18 - 8.02 (m, 2H), 7.80 (s, 1H), 7.64 (d, *J* = 7.4 Hz, 1H), 7.46 (d, *J* = 8.8 Hz, 1H), 7.34 - 7.25 (m, 2H), 7.21 (d, *J* = 8.4 Hz, 1H), 5.90 (s, 1H), 4.64 - 4.47 (m, 1H), 3.69 (s, 3H), 3.42 (s, 1H), 3.18 (s, 1H), 2.93 - 2.79 (m, 2H), 2.26 (s, 3H), 2.21 (s, 3H), 2.09 - 1.60 (m, 4H).

Example 259 *(S)-N-(5-((5-ethyl-3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)propane-1-sulfonamide* ***259***

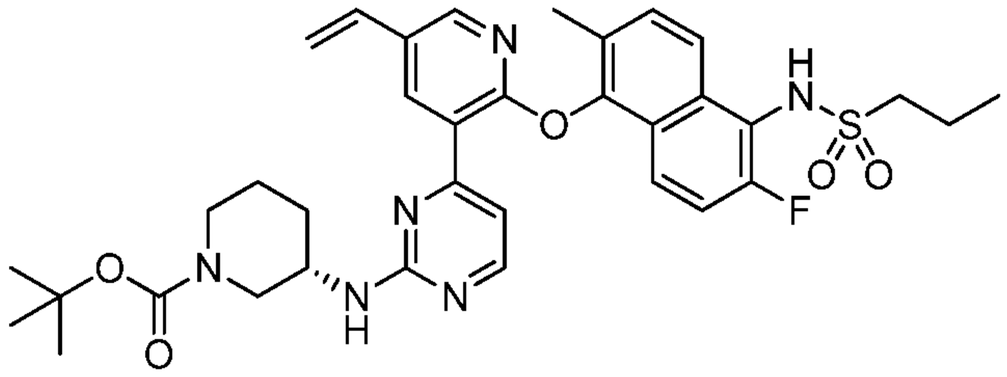
[0903] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)-5-vinylpyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0904] To a mixture of *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-5-bromo-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (50 mg, 0.083 mmol), palladium(II) acetate (1.8 mg, 0.0083 mmol) and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (6.8 mg, 0.016 mmol)(S-Phos) was added degassed 1,4-dioxane (0.41 mL) followed by tributyl(vinyl)tin (34 μL, 0.12 mmol). The reaction mixture was heated in a

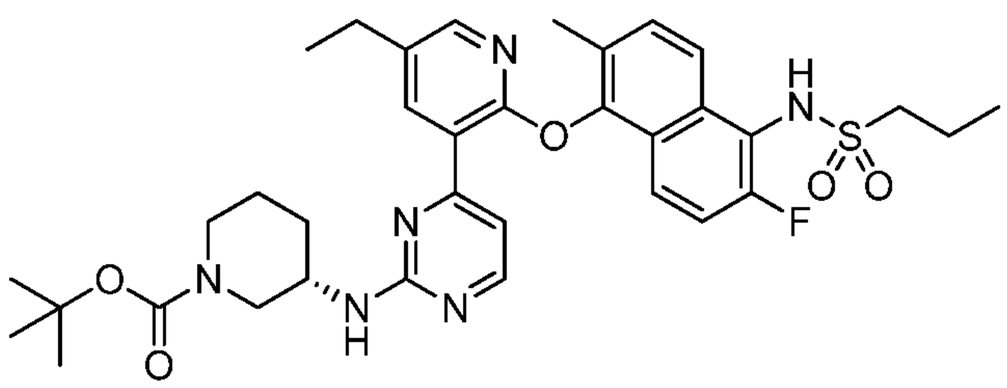
microwave reactor for 35 min at 130 °C and then cooled to rt. The reaction mixture was used directly in the next step as is. LCMS (ESI) $[M+H]^+$ = 553.3, rt = 1.95 min.

[0905] Step 2: (*S*)-*tert*-Butyl 3-((4-(2-((6-fluoro-2-methyl-5-(propylsulfonamido)naphthalen-1-yl)oxy)-5-vinylpyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0906] Prepared using the crude solution of (*S*)-*tert*-butyl 3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)-5-vinylpyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (51 mg, 0.092 mmol) prepared in the previous step, pyridine (0.28 mL, 3.46 mmol), 1,4-dioxane (0.4 mL), and 1-propanesulfonyl chloride (71 mg, 0.50 mmol). After 4 h, the reaction mixture was diluted with EtOAc (50 mL) and H_2O (2 mL), washed with saturated NH_4Cl(aq), then saturated $NaHCO_3$(aq) and brine. The organic phase was dried ($MgSO_4$) filtered and concentrated *in vacuo*. The crude mixture was dissolved in MeCN, extracted with heptanes and concentrated *in vacuo*. The crude was purified by flash chromatography through silica gel (0 – 40% EtOAc/DCM) to provide 33 mg (54% yield) of the title compound. LCMS (ESI) $[M+H]^+$ = 659.6, rt = 2.05 min.

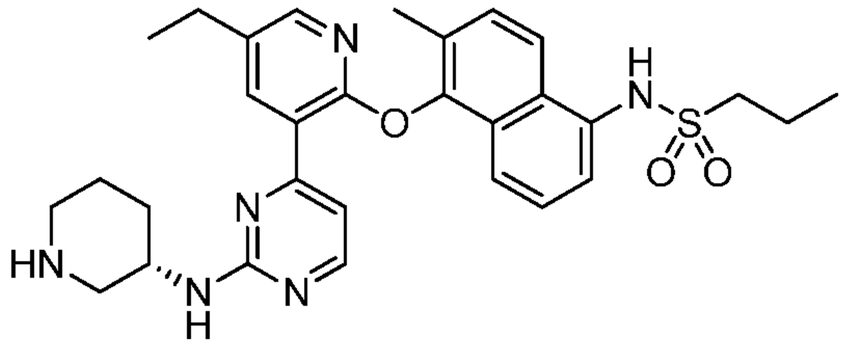
[0907] Step 3: (*S*)-*tert*-butyl 3-((4-(5-ethyl-2-((6-fluoro-2-methyl-5-(propylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0908] A solution of (*S*)-*tert*-butyl 3-((4-(2-((6-fluoro-2-methyl-5-(propylsulfonamido)naphthalen-1-yl)oxy)-5-vinylpyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (50 mg, 0.076 mmol), in EtOAc (3 mL), was added to a flask containing 10 % w/w Pd/C (26 mg, wet). The flask was purged for 5 min with N_2 and then purged for 10 min with H_2. Then a fresh H_2 balloon was attached followed by stirring at rt. After 18 h, the reaction mixture was filtered through celite eluting EtOAc (40 mL). The

solution was concentrated *in vacuo* to provide 40 mg (80% yield) of the title compound as a clear wax which was used in the next step without further purification. LCMS (ESI) $[M+H]^+$ = 661.4, rt = 2.04 min.

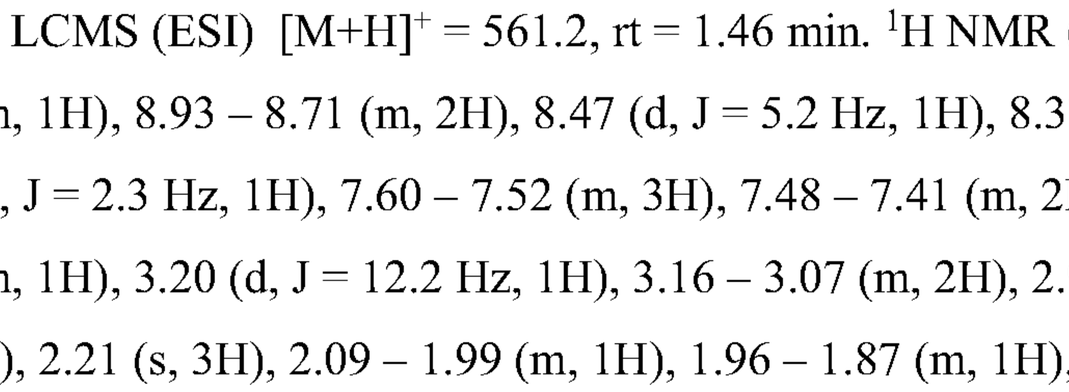
[0909] Step 4: (*S*)-*N*-(5-((5-ethyl-3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)-6-methylnaphthalen-1-yl)propane-1-sulfonamide



[0910] Prepared according to General Procedure B using (*S*)-*tert*-butyl 3-((4-(5-ethyl-2-((6-fluoro-2-methyl-5-(propylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (40 mg, 0.060 mmol), EtOAc (2 mL) and hydrochloric acid (4 M in dioxane, 1 mL, 4 mmol). After 16 h, the mixture was concentrated *in vacuo* and the residue was washed with EtOAc (3 x 3 mL) and then with MeCN (3 x 3 mL). The residue was then sonicated and concentrated *in vacuo* with MeCN (3 x 3 mL) and the resulting solid residue dissolved in water and MeCN followed by lyophilization to provide 30 mg (88% yield) of **259**. LCMS (ESI) $[M+H]^+$ = 561.2, rt = 1.46 min. ^{1}H NMR (400 MHz, d6-dmso) δ 9.90 – 9.75 (m, 1H), 8.93 – 8.71 (m, 2H), 8.47 (d, J = 5.2 Hz, 1H), 8.37 (s, 1H), 8.16 – 8.09 (m, 1H), 7.90 (d, J = 2.3 Hz, 1H), 7.60 – 7.52 (m, 3H), 7.48 – 7.41 (m, 2H), 4.33 – 4.18 (m, 1H), 3.42 – 3.37 (m, 1H), 3.20 (d, J = 12.2 Hz, 1H), 3.16 – 3.07 (m, 2H), 2.95 – 2.81 (m, 2H), 2.67 - 2.58 (m, 2H), 2.21 (s, 3H), 2.09 – 1.99 (m, 1H), 1.96 – 1.87 (m, 1H), 1.82 – 1.53 (m, 4H), 1.20 (t, J = 7.5 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H).

Example 260 *(S)-4-(2-((2-Methyl-5-((2-(thiazol-4-yl)ethyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine* ***260***

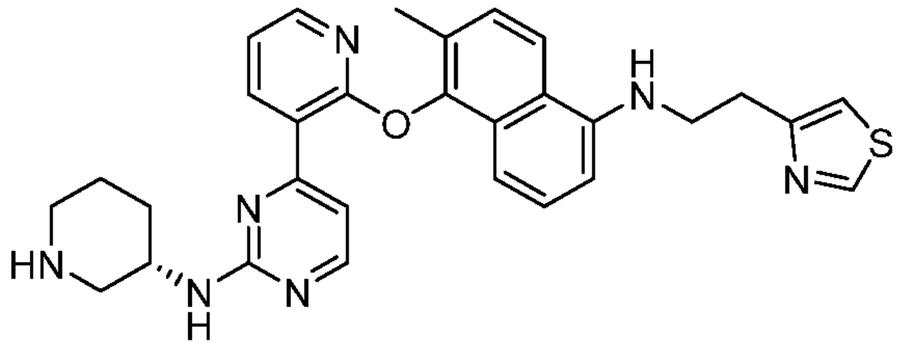
[0911] Step 1: *tert*-Butyl (S)-3-((4-(2-((2-methyl-5-((2-(thiazol-4-yl)ethyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0912] The General Procedure E was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (150 mg,

0.28 mmol) and 4-(2-chloroethyl)thiazole (126.2 mg, 0.85 mmol). The crude material was purified by silica gel chromatography (12 g column) eluting with 0-5% MeOH/DCM to afford 34 mg (19% yield) of the title compound as a brown solid. LCMS (ESI) $[M+H]^+ = 638$.

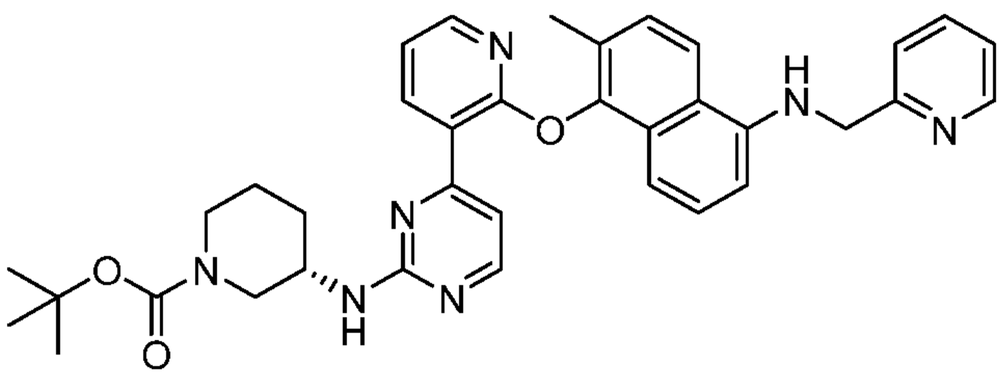
[0913] Step 2: (*S*)-4-(2-((2-Methyl-5-((2-(thiazol-4-yl)ethyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-2-amine



[0914] The General Procedure B was followed, using *tert*-butyl (S)-3-((4-(2-((2-methyl-5-((2-(thiazol-4-yl)ethyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (34 mg, 0.05 mmol). The crude product was purified *via* reverse-phase HPLC and lyophilized to yield 11 mg (39% yield) of **260** as a light brown solid. LCMS (ESI) $[M+H]^+ = 538$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (d, J = 2.0 Hz, 1H), 8.49 (s, 1H), 8.40 (d, J = 5.1 Hz, 1H), 8.01 (dd, J = 4.8, 2.0 Hz, 1H), 7.97 (d, J = 8.8 Hz, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.45 (d, J = 5.2 Hz, 1H), 7.35 (d, J = 8.7 Hz, 1H), 7.26 – 7.12 (m, 4H), 6.86 (d, J = 8.3 Hz, 1H), 6.57 – 6.50 (m, 1H), 6.38 (t, J = 5.5 Hz, 1H), 3.92 (s, 1H), 3.55 (q, J = 6.8 Hz, 2H), 3.18 (t, J = 7.3 Hz, 2H), 3.12 (d, 1H), 2.83 (d, J = 12.4 Hz, 1H), 2.47 – 2.43 (m, 2H), 2.18 (s, 3H), 1.97 – 1.91 (m, 1H), 1.67 (d, J = 11.7 Hz, 1H), 1.54 – 1.41 (m, 2H).

Example 261 *(S)-4-(2-((2-Methyl-5-((pyridin-2-ylmethyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine* ***261***

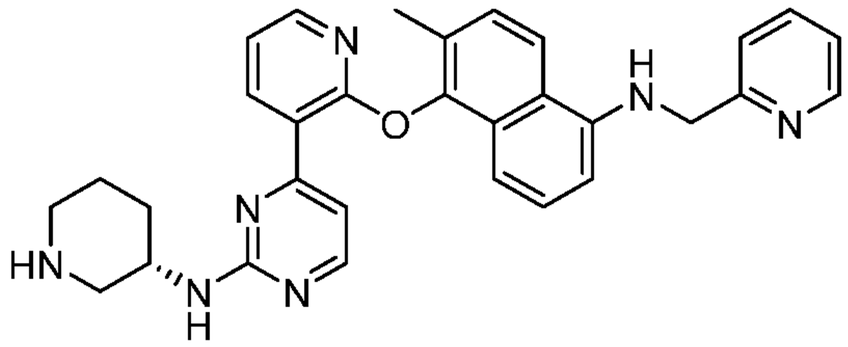
[0915] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-((pyridin-2-ylmethyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0916] The General Procedure E was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (150 mg, 0.28 mmol) and 2-(chloromethyl)pyridine hydrochloride (70.1 mg, 0.43 mmol). (Additional 2-(chloromethyl)pyridine hydrochloride, 35 mg, was added followed by heating for 48 h. The

crude material was purified by silica gel chromatography (12 g column) eluting with 0-5% MeOH/DCM to afford 26 mg (15% yield) of the title compound as a brown solid. LCMS (ESI) $[M+H]^+ = 618$.

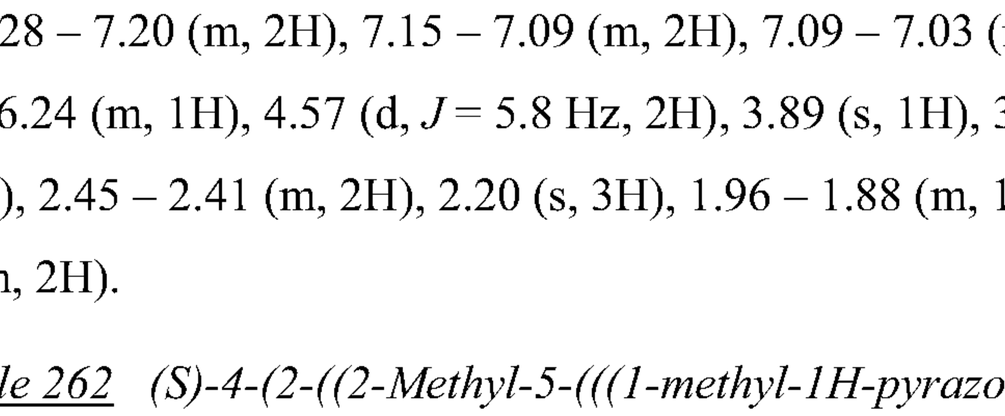
[0917] Step 2: (*S*)-4-(2-((2-Methyl-5-((pyridin-2-ylmethyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-2-amine



[0918] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-((pyridin-2-ylmethyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (26 mg, 0.04 mmol). The crude product was purified *via* reverse-phase HPLC and lyophilized to yield 3.2 mg (15% yield) of **261** as a yellow solid. LCMS (ESI) $[M+H]^+ = 518$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H), 8.51 – 8.44 (m, 1H), 8.42 – 8.36 (m, 1H), 8.10 (d, J = 8.7 Hz, 1H), 8.01 (dd, J = 4.8, 2.0 Hz, 1H), 7.70 (td, J = 7.7, 1.9 Hz, 1H), 7.46 – 7.41 (m, 4H), 7.41 – 7.34 (m, 1H), 7.28 – 7.20 (m, 2H), 7.15 – 7.09 (m, 2H), 7.09 – 7.03 (m, 1H), 6.84 (d, J = 8.5 Hz, 1H), 6.31 – 6.24 (m, 1H), 4.57 (d, J = 5.8 Hz, 2H), 3.89 (s, 1H), 3.16 – 3.05 (m, 1H), 2.87 – 2.77 (m, 1H), 2.45 – 2.41 (m, 2H), 2.20 (s, 3H), 1.96 – 1.88 (m, 1H), 1.70 – 1.63 (m, 1H), 1.54 – 1.39 (m, 2H).

Example 262 *(S)-4-(2-((2-Methyl-5-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine* ***262***

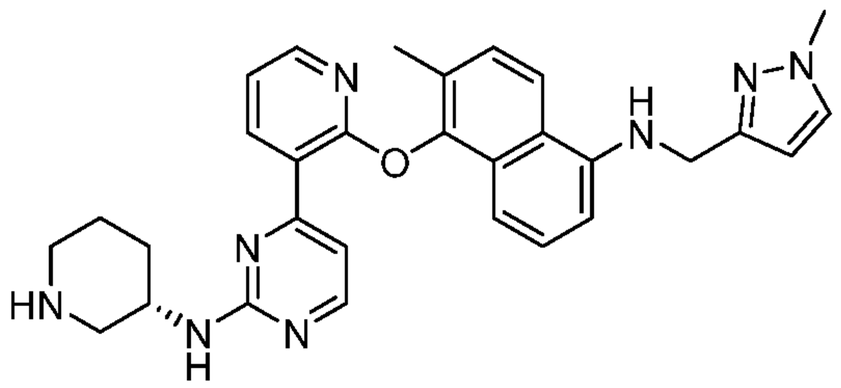
[0919] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0920] The General Procedure E was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (150 mg,

0.28 mmol) and 3-(chloromethyl)-1-methyl-pyrazole (74.4 mg, 0.57 mmol). The crude material was purified by silica gel chromatography (12 g column) eluting with 0-5% MeOH/DCM to afford 44 mg (25% yield) of the title compound as a brown solid. LCMS (ESI) $[M+H]^+ = 621$.

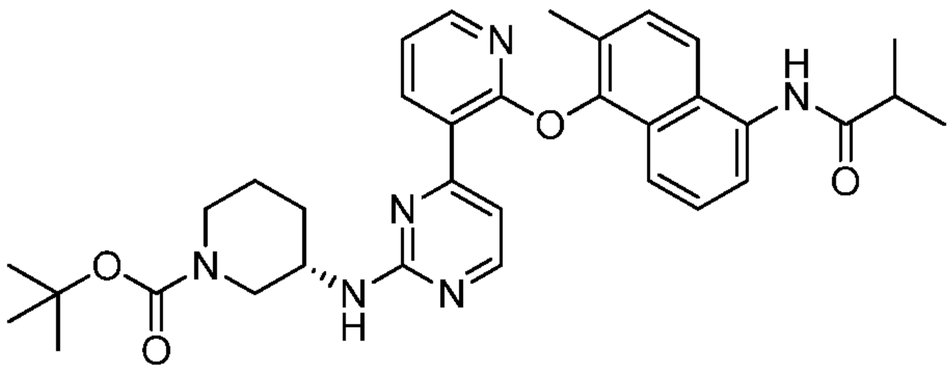
[0921] Step 2: (*S*)-4-(2-((2-Methyl-5-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-2-amine



[0922] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (44 mg, 0.07 mmol). The crude product was purified *via* reverse-phase HPLC and lyophilized to yield 19.3 mg (53% yield) of **262** as a light brown solid. LCMS (ESI) $[M+H]^+ = 521$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (s, 1H), 8.39 (d, J = 5.1 Hz, 1H), 8.00 (dd, J = 4.8, 2.0 Hz, 1H), 7.55 (d, J = 2.2 Hz, 1H), 7.43 (d, J = 5.1 Hz, 1H), 7.34 (d, J = 8.7 Hz, 1H), 7.22 (dd, J = 7.6, 4.8 Hz, 1H), 7.15 – 7.08 (m, 2H), 6.82 (d, J = 8.4 Hz, 1H), 6.72 (t, J = 5.9 Hz, 1H), 6.48 (dd, J = 7.9, 1.0 Hz, 1H), 6.14 (d, J = 2.2 Hz, 1H), 4.38 (d, J = 5.7 Hz, 2H), 3.91 (s, 1H), 3.79 (s, 3H), 3.12 (d, J = 12.0 Hz, 1H), 2.83 (d, J = 12.2 Hz, 1H), 2.47 – 2.42 (m, 2H), 2.18 (s, 3H), 1.96 – 1.89 (m, 1H), 1.71 – 1.63 (m, 1H), 1.55 – 1.42 (m, 2H).

Example 263 *(S)-N-(6-M -5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)isobutyramide hydrochloride* ***263***

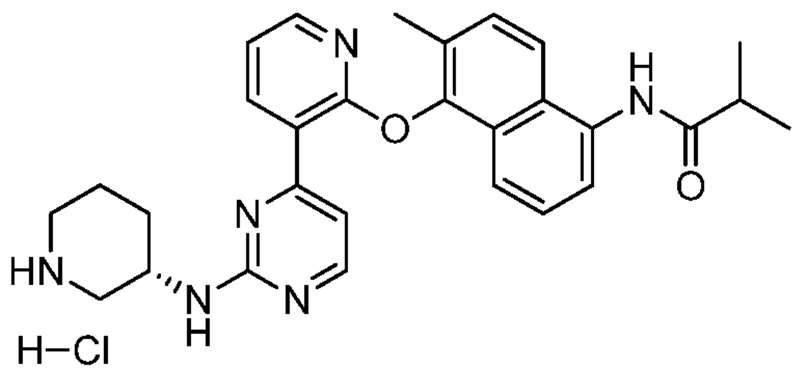
[0923] Step 1: (*S*)-*tert*-butyl 3-((4-(2-((5-Isobutyramido-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0924] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (70 mg, 0.133 mmol),

pyridine (0.11 mL, 1.36 mmol), CH_2Cl_2 (1 mL), and isobutyryl chloride (28 mg, 0.26 mmol). After 16 h, the mixture was concentrated *in vacuo* and the crude was purified by C18 reverse phase flash chromatography (0 – 70% MeCN/10mM pH= 3.8 aqueous ammonium formate). The product fractions were collected and lyophilized to provide 68 mg (86% yield) of the title compound. LCMS (ESI) $[M+H]^+$ = 597.2, rt = 1.83 min.

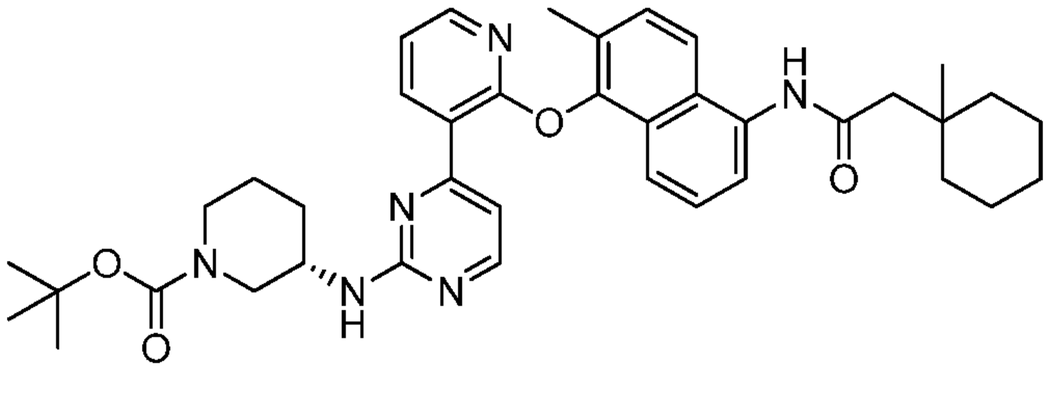
[0925] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)isobutyramide hydrochloride **263**



[0926] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-isobutyramido-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (68 mg, 0.114 mmol), 1,4-dioxane (2 mL), and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). After 5 h, the mixture was diluted with Et_2O and the solids were filtered off, washed with Et_2O then dissolved in H_2O and MeCN. Lyophilization provided 58 mg (95% yield) of **263** as a white solid. LCMS (ESI) $[M+H]^+$ = 497.1, rt = 1.29 min; ^1H NMR (400 MHz, d_6-DMSO) δ 9.90 (s, 1H), 9.13 - 8.60 (m, 2H), 8.48 (d, J = 5.2 Hz, 1H), 8.06 (dd, J = 4.8, 2.0 Hz, 1H), 7.89 (d, J = 8.7 Hz, 1H), 7.63 - 7.57 (m, 3H), 7.51 (d, J = 8.9 Hz, 1H), 7.49 (d, J = 8.6 Hz, 1H), 7.43 – 7.36 (m, 1H), 7.27 (dd, J = 7.6, 4.8 Hz, 1H), 4.29 (s, 1H), 3.51 – 3.39 (m, 1H), 3.25 – 3.14 (m, 1H), 2.95 – 2.77 (m, 3H), 2.22 (s, 3H), 2.07 - 1.87 (m, 2H), 1.83 – 1.55 (m, 2H), 1.20 (d, J = 6.8 Hz, 6H).

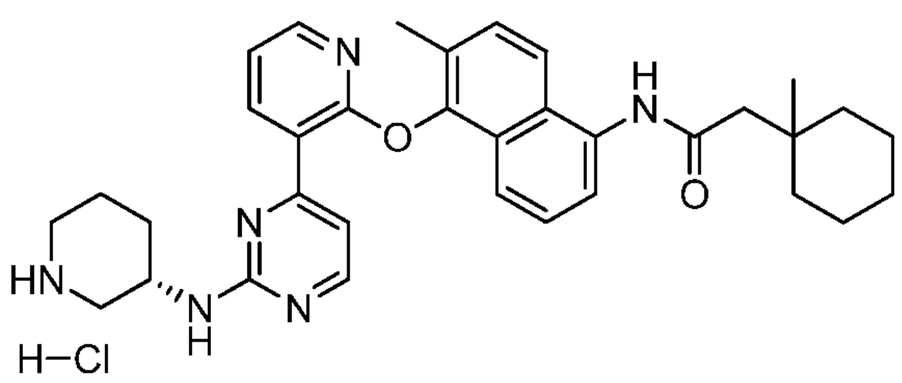
Example 264 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-(1-methylcyclohexyl)acetamide hydrochloride* ***264***

[0927] Step 1: (*S*)-t*ert*-Butyl 3-((4-(2-((2-methyl-5-(2-(1-methylcyclohexyl)acetamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0928] Prepared using (*S*)-tert-butyl 3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.190 mmol), triethylamine (0.10 mL, 0.76 mmol), HATU (144 mg, 0.38 mmol), and 2-(1-methylcyclohexyl)acetic acid (74 mg, 0.47 mmol) in DMF (2 mL). After 16 h, a further portion of triethylamine (0.10 mL, 0.76 mmol), 2-(1-methylcyclohexyl)acetic acid (74 mg, 0.47 mmol), and HATU (144 mg, 0.38 mmol) were added and stirring at rt was continued. After 3 days, the mixture was diluted with EtOAc (50 mL) and washed with sat'd $NaHCO_3$(aq) (10mL), 50% sat'd NaCl(aq) (4 x 10mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography through silica gel (0-100% EtOAc/hex) to provide 42 mg (33% yield) of the title compound as a tan powder. LCMS (ESI) $[M+H]^+$ = 665.4, rt = 2.16 min.

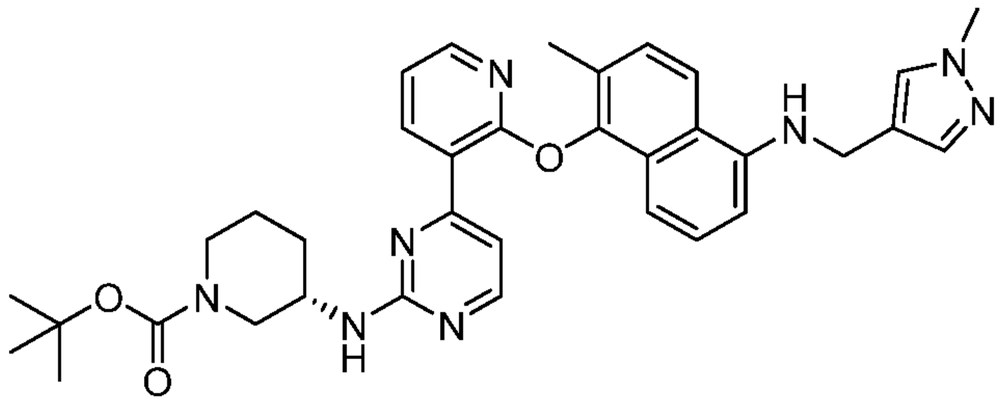
[0929] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-(1-methylcyclohexyl)acetamide hydrochloride **264**



[0930] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((2-methyl-5-(2-(1-methylcyclohexyl)acetamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (42 mg, 0.063 mmol), EtOAc (4 mL), and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). After 4 h, the mixture was concentrated *in vacuo* and the crude HCl salt solid was washed with EtOAc (3 x 3 mL) and then with MeCN (3 x 3 mL). The solid product was then sonicated and concentrated *in vacuo* with MeCN (3 x 3 mL) and then dissolved in H_2O and MeCN. Lyophilization provided 25 mg (68% yield) of **264** as a fluffy light yellow solid. LCMS (ESI) $[M+H]^+$ = 565.3, rt = 1.58 min; ^1H NMR (400 MHz, *d*$_6$-DMSO) δ 9.87 (s, 1H), 9.01 – 8.75 (m, 2H), 8.73 – 8.53 (m, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.05 (dd, J = 4.8, 2.0 Hz, 1H), 7.93 (d, J = 8.7 Hz, 1H), 7.67 – 7.44 (m, 5H), 7.39 (dd, J = 8.4, 7.4 Hz, 1H), 7.27 (dd, J = 7.6, 4.8 Hz, 1H), 4.40 – 4.13 (m, 1H), 3.39 – 3.31 (m, 1H), 3.21 (d, J = 13.5 Hz, 1H), 2.94 – 2.75 (m, 2H), 2.42 (s, 2H), 2.21 (s, 3H), 2.08 – 1.84 (m, 2H), 1.82 – 1.60 (m, 2H), 1.60 – 1.29 (m, 10H), 1.11 (s, 3H).

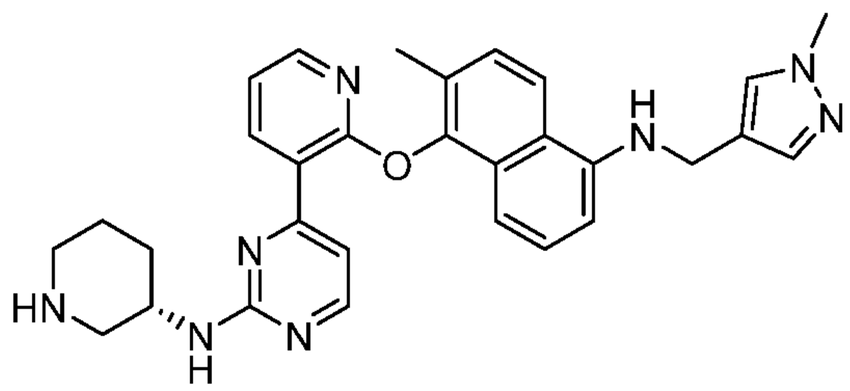
Example 265 *(S)-4-(2-((2-Methyl-5-(((1-methyl-1H-pyrazol-4-yl)methyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine* ***265***

[0931] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-(((1-methyl-1H-pyrazol-4-yl)methyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0932] The General Procedure E was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (200 mg, 0.38 mmol) and 4-(chloromethyl)-1-methyl-1H-pyrazole hydrochloride (95.2 mg, 0.57 mmol). The crude material was purified by silica gel chromatography (12 g column), eluting with 0-5% MeOH/DCM to afford 50 mg (22% yield) of the title compound as a brown solid. LCMS (ESI) $[M+H]^+ = 621$.

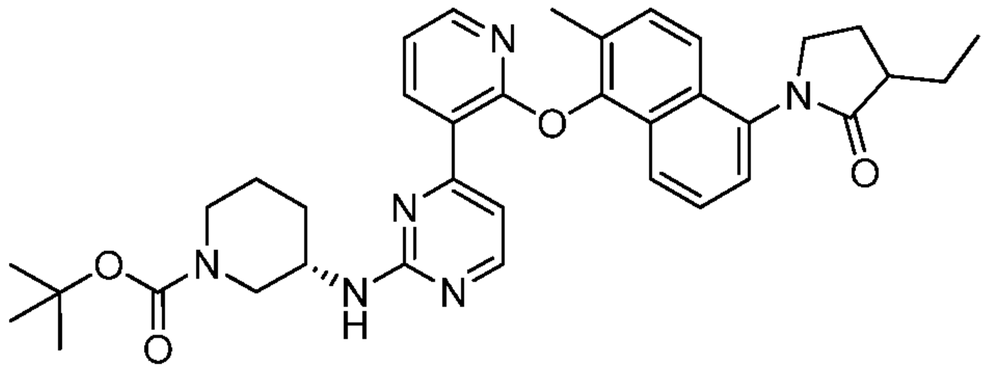
[0933] Step 2: (*S*)-4-(2-((2-Methyl-5-(((1-methyl-1H-pyrazol-4-yl)methyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-2-amine



[0934] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-(((1-methyl-1H-pyrazol-4-yl)methyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (50 mg, 0.08 mmol). The crude product was purified *via* reverse-phase HPLC and lyophilized to yield 24.2 mg (58% yield) of **265** as an off-white solid. LCMS (ESI) $[M+H]^+ = 521$. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.48 (s, 1H), 8.40 (d, *J* = 5.1 Hz, 1H), 8.04 – 7.98 (m, 2H), 7.62 (d, *J* = 0.9 Hz, 1H), 7.44 (d, *J* = 5.2 Hz, 1H), 7.40 (s, 1H), 7.33 (d, *J* = 8.7 Hz, 1H), 7.22 (dd, *J* = 7.5, 4.8 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 1H), 6.58 (d, *J* = 5.9 Hz, 1H), 6.48 (d, *J* = 7.7 Hz, 1H), 4.29 (d, *J* = 5.5 Hz, 2H), 3.93 (s, 1H), 3.77 (s, 3H), 3.13 (s, 1H), 2.84 (d, *J* = 10.8 Hz, 1H), 2.43 (s, 2H), 2.18 (s, 3H), 1.97 – 1.89 (m, 1H), 1.70 – 1.65 (m, 1H), 1.54 – 1.43 (m, 2H).

Example 266 *(R)-3-Ethyl-1-(6-methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidin-2-one* ***266***

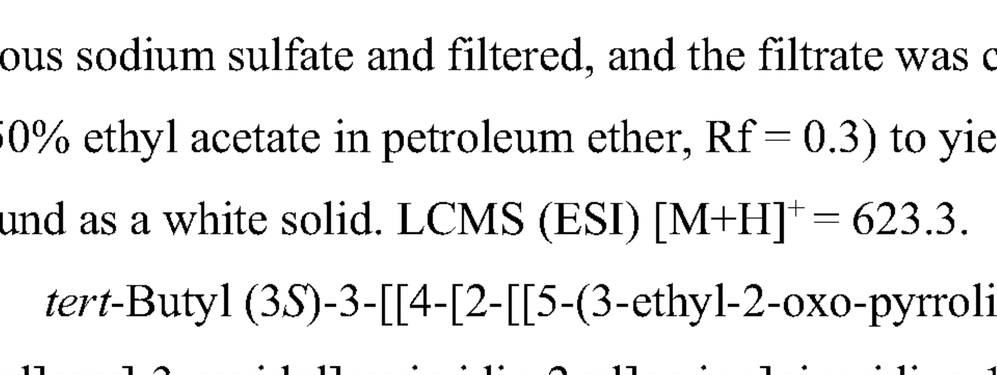
[0935] Step 1: *tert*-butyl (3*S*)-3-((4-(2-((5-(3-Ethyl-2-oxopyrrolidin-1-yl)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



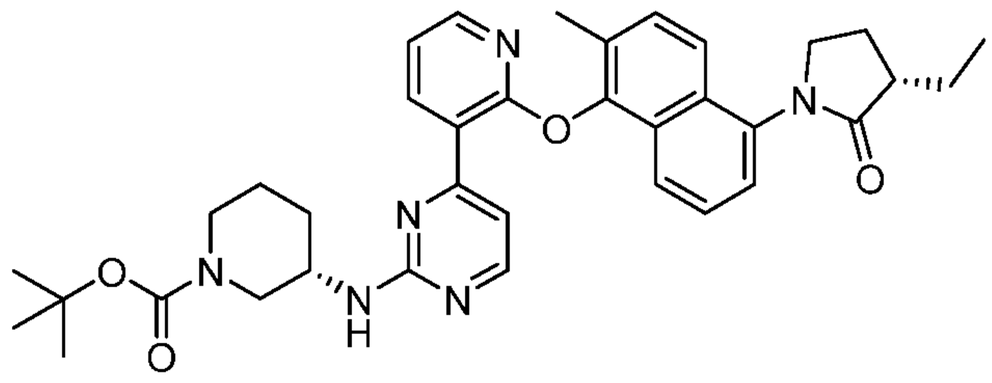
[0936] To a 100 mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed *tert*-butyl (3*S*)-3-[[4-[2-[(5-iodo-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (120 mg, 0.19 mmol), 1,4-dioxane (2 mL), copper (I) iodide (4 mg, 0.02 mmol), potassium carbonate (78 mg, 0.56 mmol), 3-ethylpyrrolidin-2-one (21 mg, 0.19 mmol) and *N*,*N*'-dimethyl-1,2-ethanediamine (3.3 mg, 0.04 mmol), the mixture was purged with nitrogen atmosphere and stirred at 110 °C for 12 h. After cooling down, the mixture was filtered, concentrated and dissolved in ethyl acetate (60 mL), and subsequently washed with H_2O (50 mL x 2). The organic phase was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated and purified by prep-TLC (50% ethyl acetate in petroleum ether, Rf = 0.3) to yield 110 mg (93% yield) of the title compound as a white solid. LCMS (ESI) $[M+H]^+ = 623.3$.

[0937] *tert*-Butyl (3*S*)-3-[[4-[2-[[5-(3-ethyl-2-oxo-pyrrolidin-1-yl)-2-methyl-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (110.0mg, 0.18 mmol) was purified by SFC (AD (250 mm x 30 mm,10 μm); 0.1% NH_3H_2O EtOH: 40%; flow rate (mL/min): 60) to give

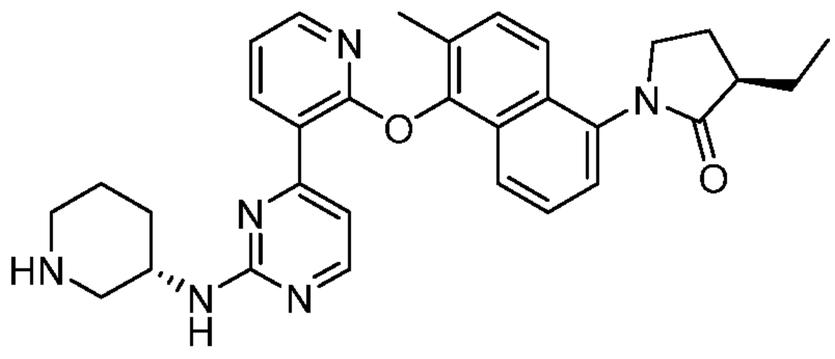
[0938] Peak 1: *tert*-butyl (*S*)-3-((4-(2-((5-((*R*)-3-ethyl-2-oxopyrrolidin-1-yl)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (35 mg, 32% yield) (first peak on SFC) as a white solid:



[0939] Peak 2: *tert*-Butyl (*S*)-3-((4-(2-((5-((*S*)-3-ethyl-2-oxopyrrolidin-1-yl)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (35 mg, 32% yield) (second peak on SFC) as a white solid and used in Example 355:



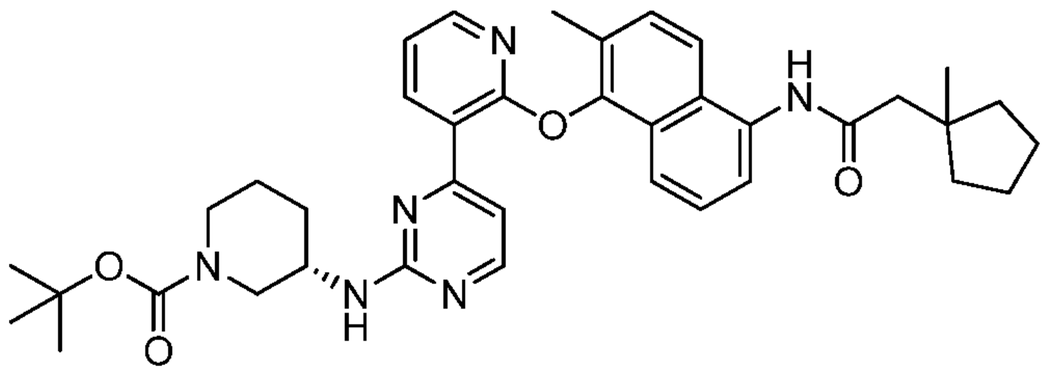
[0940] Step 2: (*R*)-3-Ethyl-1-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)pyrrolidin-2-one



[0941] The General Procedure B was followed, using (3*S*)-*tert*-butyl 3-((4-(2-((5-(3-ethyl-2-oxopyrrolidin-1-yl)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (30 mg, 0.05 mmol) (first peak on SFC in step 1), dichloromethane (2 mL) and hydrochloric acid (4 M in dioxane, 0.32 mL, 1.28 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05%HCl); B: ACN) to yield 27 mg (99 % yield) of **266** as a white solid. LCMS (ESI) $[M+H]^+$= 523.3. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51(s, 1H), 8.42 (d, *J* = 5.2 Hz, 1H), 8.05 - 8.00 (m, 1H), 7.65 (d, *J* = 7.2 Hz, 1H), 7.59 - 7.53 (m, 1H), 7.51 - 7.44 (m, 2H), 7.42 (d, *J* = 5.2 Hz, 1H), 7.40 - 7.37 (m, 1H), 7.27 - 7.22 (m, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 3.91 - 3.64 (m, 3H), 3.06 (m, 1H), 2.77 (m, 1H), 2.64 - 2.58 (m, 1H), 2.41 (d, *J* = 14.8 Hz, 3H), 2.20 (s, 3H), 2.02 - 1.87 (m, 2H), 1.86 - 1.77 (m, 1H), 1.61 (m, 1H), 1.57 - 1.35 (m, 3H), 1.01 (t, *J* = 7.2 Hz, 3H). The absolute stereochemistry of the lactam was assigned based on a crystal structure.

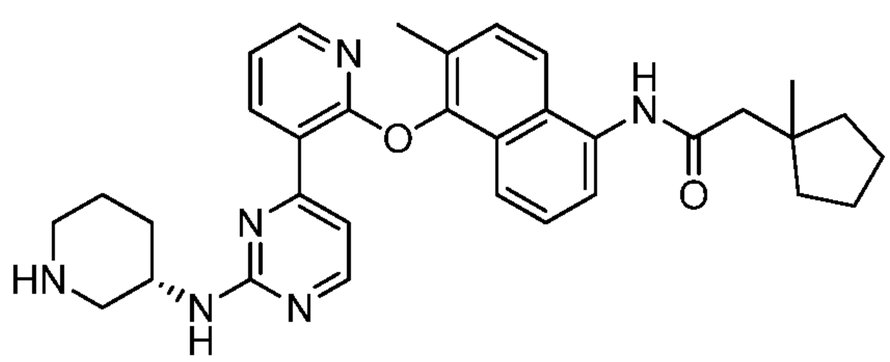
Example 267 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-(1-methylcyclopentyl)acetamide* ***267***

[0942] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-5-(2-(1-methylcyclopentyl)acetamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0943] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.190 mmol), triethylamine (58 mg, 0.08 mL, 0.57 mmol), HATU (108 mg, 0.285 mmol), and 2-(1-methylcyclopentyl)acetic acid (35 mg, 0.25 mmol) in DMF (0.63 mL). After 96 h, the mixture was diluted with EtOAc and washed with saturated NaCl(aq), then H_2O, then saturated NH_4Cl(aq). The organic extract was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography through silica gel (0-100% EtOAc/DCM) to provide 90% pure material which was further purified by C18 reverse phase flash chromatography (40 – 90% MeCN/10mM pH= 3.8 aqueous ammonium formate). Appropriate fractions were combined and MeCN removed on a rotovap and the resulting aqueous solution was diluted with saturated NaCl(aq) and organics extracted with EtOAc, dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide 104 mg (84% yield) of the title compound as a beige solid. LCMS (ESI) $[M+H]^+$ = 651.3, rt = 2.08 min.

[0944] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-(1-methylcyclopentyl)acetamide

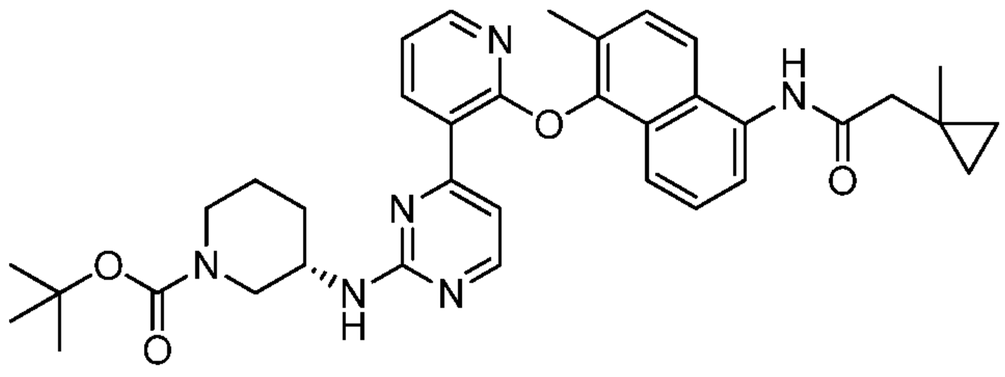


[0945] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((2-methyl-5-(2-(1-methylcyclopentyl)acetamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (104 mg, 0.160 mmol), 1,4-dioxane (1 mL), and hydrochloric acid (4 M in dioxane, 2.5 mL, 9.9 mmol). After 4 h, the heterogeneous mixture was filtered and the collected solids were washed with 1,4-dioxane then Et_2O and dried. The solids were then dissolved in H_2O and MeCN and lyophilized to provide 92 mg (98% yield) of **267** as a pale yellow solid. LCMS (ESI) $[M+H]^+$ = 551.2, rt = 1.53 min; ^1H NMR (400 MHz, d6-dmso) δ 9.92 (s, 1H), 9.26 (br s, 1H), 9.12 (s, 1H), 8.74 (br s, 1H), 8.49 (d, J = 5.3 Hz, 1H), 8.06 (dd, J = 4.7, 1.8 Hz, 1H), 7.93 (d, J = 8.7 Hz, 1H), 7.82 – 7.61 (m, 2H), 7.60 (d, J = 7.3

Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.45 – 7.35 (m, 1H), 7.27 (dd, J = 7.6, 4.8 Hz, 1H), 4.36 (s, 1H), 3.43 (d, J = 9.1 Hz, 1H), 3.20 (d, J = 11.5 Hz, 1H), 2.92 – 2.74 (m, 2H), 2.48 (s, 2H), 2.21 (s, 3H), 2.07 – 1.97 (m, J = 8.9 Hz, 1H), 1.97 – 1.86 (m, J = 14.2 Hz, 1H), 1.86 – 1.54 (m, 8H), 1.50 – 1.32 (m, 2H), 1.14 (s, 3H).

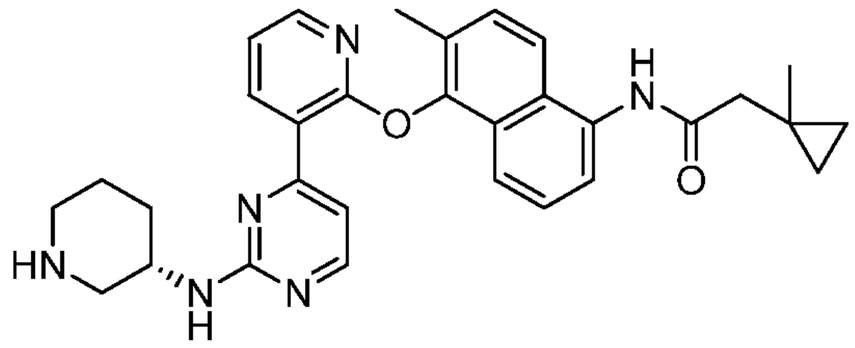
Example 268 *(S)-N-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-(1-methylcyclopropyl)acetamide* ***268***

[0946] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-5-(2-(1-methylcyclopropyl)acetamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0947] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.190 mmol), triethylamine (77 mg, 0.11 mL, 0.76 mmol), HATU (180 mg, 0.475 mmol), and 2-(1-methylcyclopropyl)acetic acid (54 mg, 0.47 mmol) in DMF (1 mL). After 64 h, the mixture was diluted with EtOAc (50 mL) and washed with saturated $NaHCO_3$(aq) (10 mL) and then 50% saturated NaCl(aq) (4 x 10 mL). The organic extract was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography through silica gel (0-100% EtOAc/hexanes) to provide 111 mg (94% yield) of the title compound as tan solid. LCMS (ESI) $[M+H]^+$ = 623.3, rt = 1.93 min.

[0948] Step 2: (*S*)-*N*-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-(1-methylcyclopropyl)acetamide

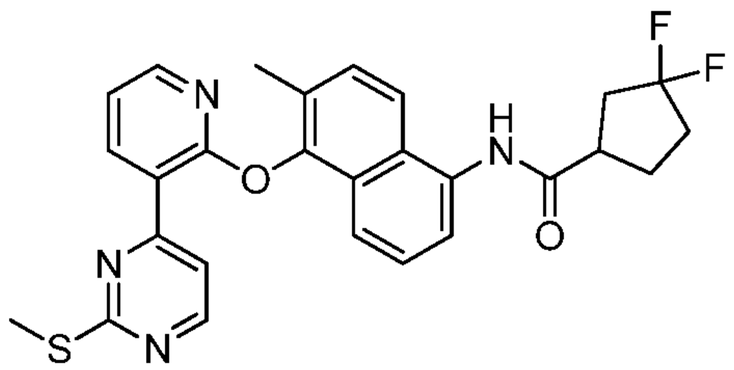


[0949] Prepared using (*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-5-(2-(1-methylcyclopropyl)acetamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (111 mg, 0.178 mmol), EtOAc (6 mL), and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). After 4 h, the solution was concentrated *in vacuo* and the

crude residue purified by C18 reverse phase flash chromatography (20 – 100% MeCN/10mM pH= 3.8 aqueous ammonium formate). The product fractions were combined and lyophilized to provide 6 mg (6% yield) of **268** as a tan powder. LCMS (ESI) $[M+H]^+$ = 523.3, rt = 1.38 min; ^{1}H NMR (400 MHz, d6-dmso) δ 9.82 (s, 1H), 8.55 (br.s, 1H), 8.44 (d, J = 5.1 Hz, 1H), 8.35 (s, 1H), 8.03 (dd, J = 4.8, 1.9 Hz, 1H), 7.92 (d, J = 8.7 Hz, 1H), 7.62 (d, J = 7.3 Hz, 1H), 7.56 – 7.46 (m, 3H), 7.41 (d, J = 7.6 Hz, 1H), 7.31 (d, J = 7.7 Hz, 1H), 7.26 (dd, J = 7.5, 4.8 Hz, 1H), 4.18 – 3.94 (m, 1H), 3.24 (d, J = 9.0 Hz, 1H), 2.97 (d, J = 11.9 Hz, 1H), 2.60 (dd, J = 22.3, 12.3 Hz, 2H), 2.40 (s, 2H), 2.22 (s, 3H), 2.04 – 1.91 (m, 1H), 1.81 – 1.71 (m, 1H), 1.64 – 1.50 (m, 2H), 1.19 (s, 3H), 0.59 (s, 2H), 0.36 (s, 2H).

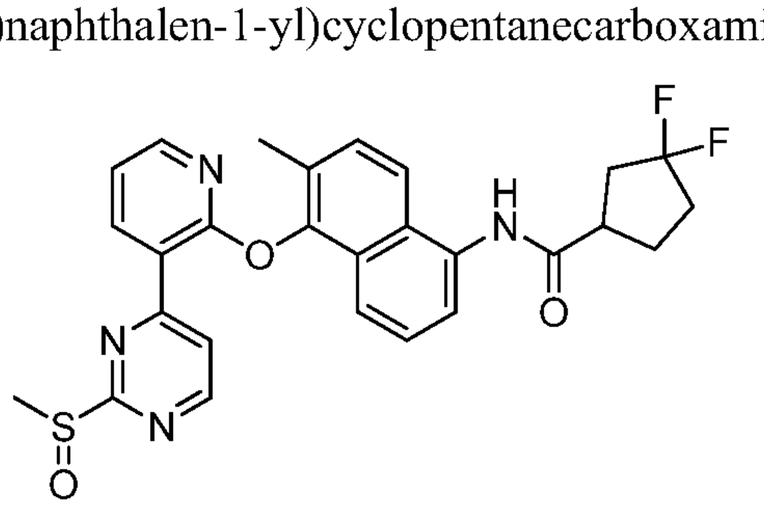
Example 269 *(R)-3,3-difluoro-N-(6-methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentane-1-carboxamide* ***269***

[0950] Step 1: 3,3-Difluoro-*N*-(6-methyl-5-((3-(2-(methylthio)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentanecarboxamide



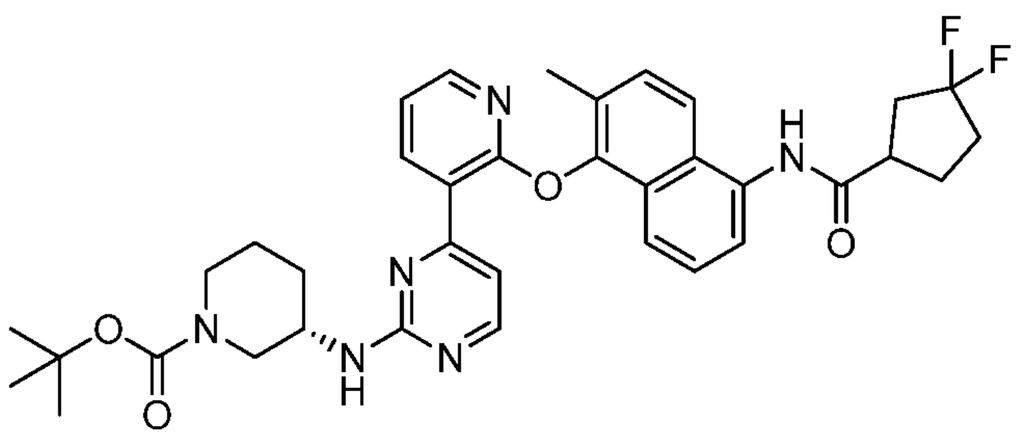
[0951] Prepared using 6-methyl-5-((3-(2-(methylthio)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-amine (150 mg, 0.401 mmol), triethylamine (203 mg, 0.279 mL, 2.00 mmol), HATU (380 mg, 1.00 mmol), and 3,3-difluorocyclopentanecarboxylic acid (180 mg, 1.20 mmol) in DMF (2 mL). After 3 days, the mixture was diluted with EtOAc (75 mL) and washed with saturated $NaHCO_3$(aq) (10 mL), then 50% saturated NaCl(aq) (4 x 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to provide 226 mg (111 % yield) of the title compound as an orange solid which was used crude without further purification in the next step. LCMS (ESI) $[M+H]^+$ = 507.1, rt = 1.88 min.

[0952] Step 2: 3,3-Difluoro-*N*-(6-methyl-5-((3-(2-(methylsulfinyl)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentanecarboxamide



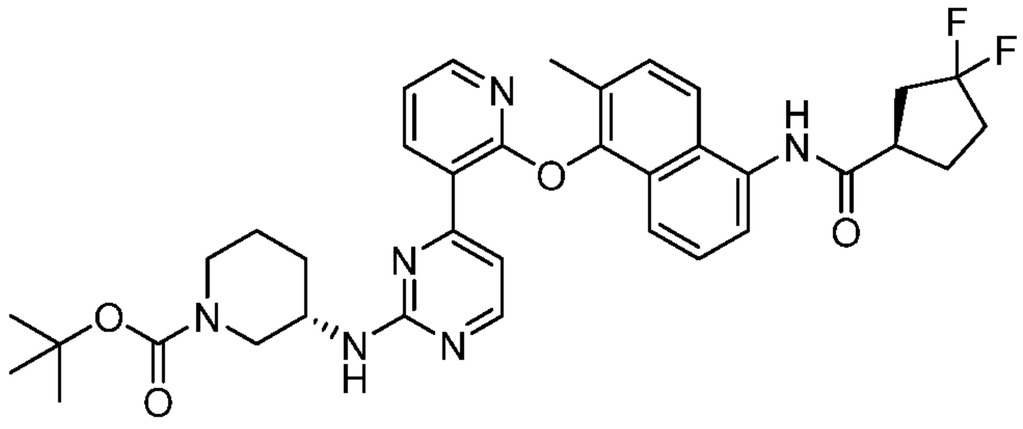
[0953] 3,3-Difluoro-*N*-(6-methyl-5-((3-(2-(methylthio)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentanecarboxamide (226 mg, 0.446 mmol) was suspended in DCM (20 mL) and to this was then added 3-chloroperbenzoic acid (156 mg of 77% pure reagent, 0.710 mmol) and the mixture was stirred at rt. After 1 h, the mixture was diluted with DCM (75 mL) and washed with saturated $NaHCO_3$(aq) (2 x 25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to provide 245 mg (105% yield) of the title compound which was used crude without further purification in the next step. LCMS (ESI) $[M+H]^+$ = 523.1, rt = 1.48 min.

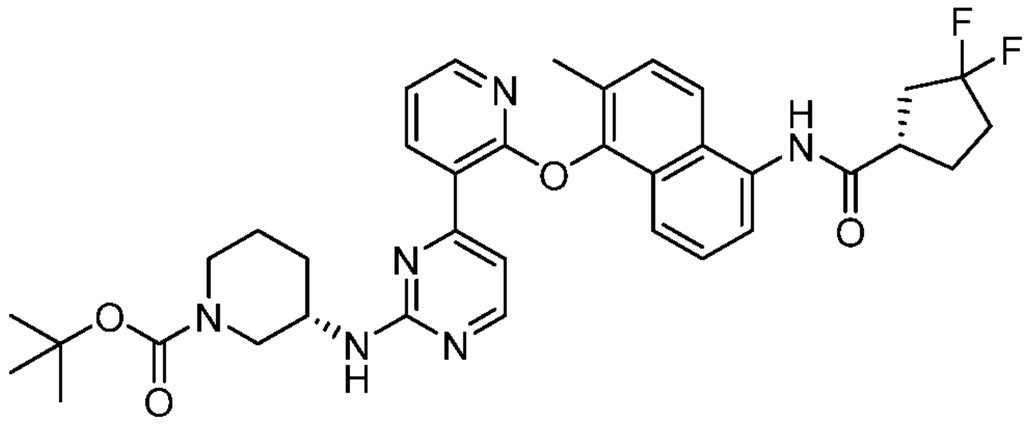
[0954] Step 3: (3*S*)-*tert*-Butyl 3-((4-(2-((5-(3,3-difluorocyclopentanecarboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0955] 3,3-Difluoro-*N*-(6-methyl-5-((3-(2-(methylthio)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentanecarboxamide (245 mg, 0.469 mmol) and (*S*)-*tert*-butyl 3-aminopiperidine-1-carboxylate (141 mg, 0.703 mmol) were combined in 1,4-dioxane (3 mL). Triethylamine (142 mg, 0.196 mL, 1.41 mmol) was then added and the flask was sealed and placed in a 120 °C oil bath. After 20 h, the mixture was diluted with EtOAc (75 mL), and washed with saturated $NaHCO_3$(aq) (25 mL), H_2O (10 mL), and then saturated NaCl(aq) (10 mL). The solution was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude was purified by flash chromatography through silica gel (0 – 100% EtOAc/hexanes) to provide 130 mg (42% yield) of the title compound as an orange wax. LCMS (ESI) $[M+H]^+$ = 659.2, rt = 1.92 min.

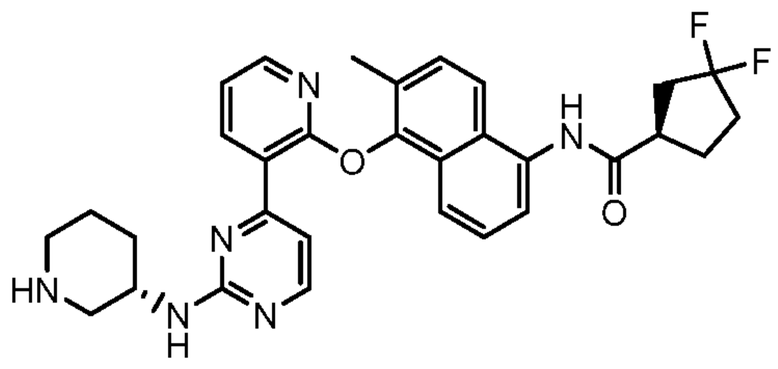
[0956] Step 4: *tert*-Butyl (*S*)-3-((4-(2-((5-((*R*)-3,3-difluorocyclopentane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-1) and *tert*-butyl (*S*)-3-((4-(2-((5-((*S*)-3,3-difluorocyclopentane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-2)





[0957] (3*S*)-*tert*-butyl 3-((4-(2-((5-(3,3-difluorocyclopentanecarboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (128 mg, 0.194 mmol), was subjected to chiral normal phase semi-prep purification (Conditions: Chiralpak IB, 5 uM, 20 x 250 mm, 6:6:88 MeOH:DCM:Hexane + 0.1 % DIPEA, 400 uL (6 mg)/inj) to provide two single stereoisomers enantiomeric at the 4-cyclopentane position: (isomer-1), 43 mg (33% yield), white solid, ee $\geq$ 99%, rt = 14.01 min, LCMS (ESI) $[M+H]^+$ = 659.5, rt = 1.94 min; (isomer-2), 44 mg (34% yield), white solid, ee = 98%, rt = 15.9 min, LCMS (ESI) $[M+H]^+$ = 659.5, rt = 1.94 min. The absolute stereochemistry of the cyclopentane was randomly assigned.

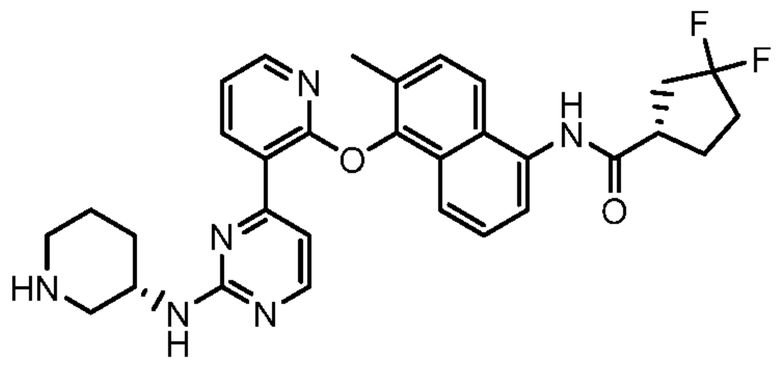
[0958] Step 5: (*R*)-3,3-Difluoro-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentane-1-carboxamide (isomer-1)



[0959] Prepared using *tert*-butyl (*S*)-3-((4-(2-((5-((*R*)-3,3-difluorocyclopentane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-1) (43 mg, 0.065 mmol), EtOAc (2 mL), and hydrochloric acid (4 M in dioxane, 1 mL, 4 mmol). After 16 h, the mixture was concentrated *in vacuo* and the crude HCl salt solid was washed with EtOAc (3 x 3 mL) then with MeCN (3 x 3 mL). The solid product was sonicated and concentrated *in vacuo* with MeCN (3 x 3 mL) and then dissolved in H_2O

and MeCN and lyophilized to provide 29 mg (75% yield) of **269** as a fluffy light yellow solid. The absolute stereochemistries of **269** and **270** were randomly assigned and may be later determined. LCMS (ESI) $[M+H]^+$ = 559.2, rt = 1.38 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.07 (s, 1H), 8.93 – 8.53 (m, 3H), 8.48 (d, J = 5.2 Hz, 1H), 8.05 (dd, J = 4.8, 1.8 Hz, 1H), 7.91 (d, J = 8.7 Hz, 1H), 7.62 (d, J = 7.3 Hz, 1H), 7.58 (d, J = 4.6 Hz, 1H), 7.56 – 7.47 (m, 3H), 7.42 (d, J = 7.6 Hz, 1H), 7.27 (dd, J = 7.5, 4.8 Hz, 1H), 4.38 – 4.15 (m, 1H), 3.34 - 3.29 (m, 1H), 3.21 (d, J = 12.3 Hz, 1H), 2.97 – 2.75 (m, 2H), 2.48 – 2.35 (m, 2H), 2.36 – 2.09 (m, 7H), 2.09 – 1.98 (m, 2H), 1.98 – 1.86 (m, 1H), 1.80 – 1.54 (m, 2H).

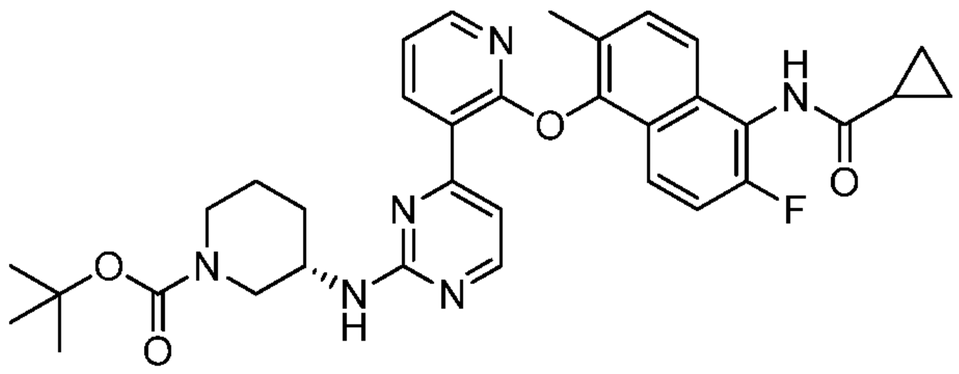
Example 270 *(S)-3,3-Difluoro-N-(6-methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentane-1-carboxamide* ***270***



[0960] Prepared using *tert*-butyl (*S*)-3-((4-(2-((5-((*S*)-3,3-difluorocyclopentane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-2) (44 mg, 0.067 mmol), EtOAc (2 mL), and hydrochloric acid (4 M in dioxane, 1 mL, 4 mmol). After 16 h, the mixture was concentrated *in vacuo* and the crude solid was washed with EtOAc (3 x 3 mL) then with MeCN (3 x 3 mL). The solid product was then sonicated and concentrated *in vacuo* with MeCN (3 x 3 mL) then dissolved in H_2O and MeCN. Lyophilization provided 30 mg (75% yield) of **270** as a fluffy light yellow solid. LCMS (ESI) $[M+H]^+$ = 559.2, rt = 1.40 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.07 (s, 1H), 8.95 – 8.55 (m, 3H), 8.48 (d, J = 5.2 Hz, 1H), 8.05 (dd, J = 4.7, 1.8 Hz, 1H), 7.91 (d, J = 8.7 Hz, 1H), 7.62 (d, J = 7.3 Hz, 1H), 7.58 (d, J = 4.7 Hz, 1H), 7.56 – 7.47 (m, 3H), 7.42 (d, J = 7.7 Hz, 1H), 7.27 (dd, J = 7.5, 4.8 Hz, 1H), 4.38 – 4.14 (m, 1H), 3.35 – 3.26 (m, 1H), 3.21 (d, J = 12.0 Hz, 1H), 2.97 – 2.74 (m, 2H), 2.47 – 2.35 (m, 2H), 2.35 – 2.09 (m, 7H), 2.07 – 1.97 (m, 2H), 1.96 – 1.87 (m, 1H), 1.81 – 1.56 (m, 2H).

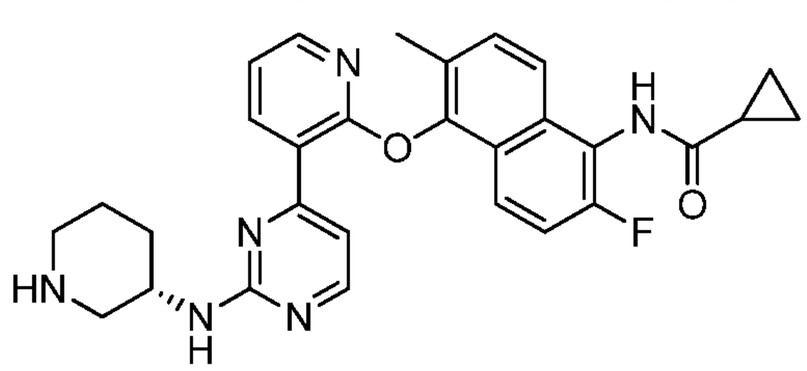
Example 271 *(S)-N-(2-Fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropanecarboxamide* ***271***

[0961] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-(cyclopropanecarboxamido)-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0962] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 275 (40 mg, 0.073 mmol), pyridine (87 mg, 0.089 mL, 1.1 mmol), DCM (0.24 mL), and cyclopropanecarbonyl chloride (15 mg, 0.15 mmol). After 16 h, the mixture was concentrated *in vacuo* and the crude was purified by C18 reverse phase flash chromatography (45 – 70% MeCN/10mM pH= 3.8 aqueous ammonium formate). Appropriate fractions were collected and concentrated *in vacuo* and the resulting residue was diluted with EtOAc and washed with saturated $NaHCO_3$(aq), then saturated NaCl(aq). The solution was dried (Na_2SO_4), filtered and concentrated *in vacuo* to provide 18 mg (40% yield) of the title compound. LCMS (ESI) $[M+H]^+$ = 613.3, rt = 1.81 min.

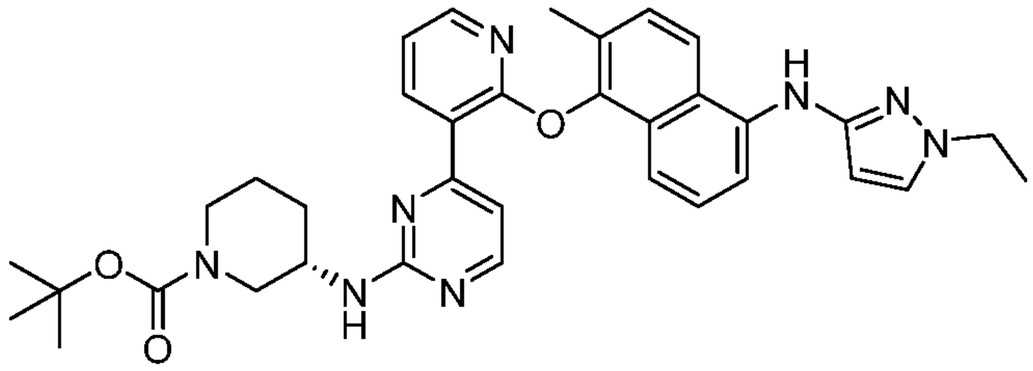
[0963] Step 2: (*S*)-*N*-(2-Fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropanecarboxamide



[0964] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-(cyclopropanecarboxamido)-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (18 mg, 0.114 mmol), 1,4-dioxane (0.3 mL), and hydrochloric acid (4 M in dioxane, 1 mL, 4 mmol). After 1.5 h, the mixture was diluted with Et_2O and the solids were filtered off, followed by washing with Et_2O and then dissolution in H_2O and MeCN. Lyophilization provided 16 mg (99% yield) of **271** as a white solid. LCMS (ESI) $[M+H]^+$ = 513.2, rt = 1.27 min; ^{1}H NMR (400 MHz, d6-dmso) δ 10.18 (s, 1H), 9.13 – 8.83 (m, 2H), 8.67 (s, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.07 (dd, J = 4.8, 2.0 Hz, 1H), 7.75 (d, J = 8.7 Hz, 1H), 7.64 (dd, J = 9.3, 5.1 Hz, 1H), 7.57 (dd, J = 7.8, 5.0 Hz, 3H), 7.41 (t, J = 9.4 Hz, 1H), 7.28 (dd, J = 7.6, 4.8 Hz, 1H), 4.27 (s, 1H), 3.43 (d, J = 9.6 Hz, 1H), 3.20 (d, J = 12.2 Hz, 1H), 2.94 – 2.75 (m, 2H), 2.19 (s, 3H), 2.07 – 1.97 (m, 2H), 1.91 (dt, J = 12.7, 4.1 Hz, 1H), 1.83 – 1.68 (m, 1H), 1.68 – 1.56 (m, 1H), 0.93 – 0.79 (m, 4H).

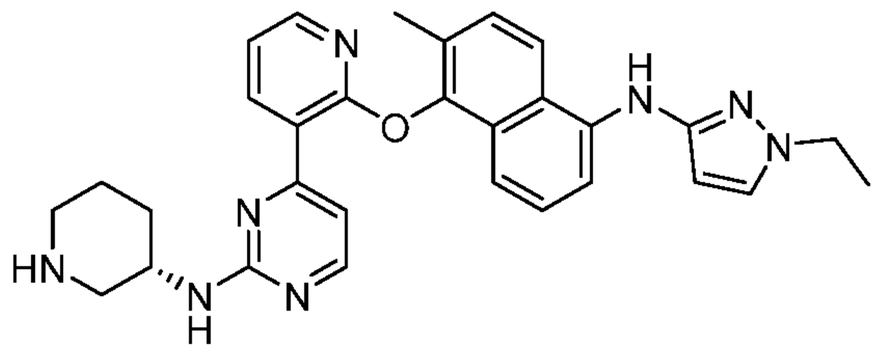
Example 272 *(S)-4-(2-((5-((1-Ethyl-1H-pyrazol-3-yl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine* ***272***

[0965] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((5-((1-ethyl-1H-pyrazol-3-yl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0966] The General Procedure F was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (200 mg, 0.38 mmol) and 3-bromo-1-ethyl-pyrazole (199.4 mg, 1.14 mmol). The crude material was purified by silica gel chromatography (12 g column), eluting with 0-5% MeOH/DCM to afford 162 mg (68.7% yield) of the title compound as a brown solid. LCMS (ESI) $[M+H]^+$ = 621.

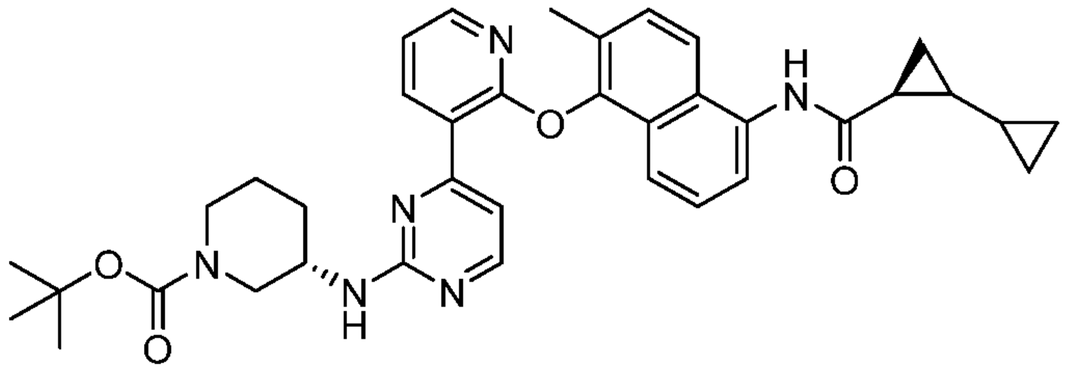
[0967] Step 2: (*S*)-4-(2-((5-((1-Ethyl-1H-pyrazol-3-yl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-2-amine



[0968] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-((1-ethyl-1H-pyrazol-3-yl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (162 mg, 0.26 mmol). The crude product was purified *via* reverse-phase HPLC and lyophilized to yield 82.8 mg (60.9% yield) of **272** as an off-white solid. LCMS (ESI) $[M+H]^+$ = 521; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (s, 1H), 8.40 (d, J = 5.1 Hz, 1H), 8.23 (d, J = 8.9 Hz, 1H), 8.02 (dd, J = 4.8, 2.0 Hz, 1H), 7.73 (dd, J = 7.8, 1.0 Hz, 1H), 7.61 (d, J = 2.3 Hz, 1H), 7.47 – 7.38 (m, 2H), 7.27 – 7.20 (m, 2H), 7.10 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.02 (d, J = 2.3 Hz, 1H), 4.06 (q, J = 7.2 Hz, 2H), 3.88 (s, 1H), 3.10 (d, J = 11.1 Hz, 1H), 2.79 (d, J = 12.4 Hz, 1H), 2.44 (d, J = 9.0 Hz, 2H), 2.21 (s, 3H), 1.92 (s, 1H), 1.64 (s, 1H), 1.47 (d, J = 9.3 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H).

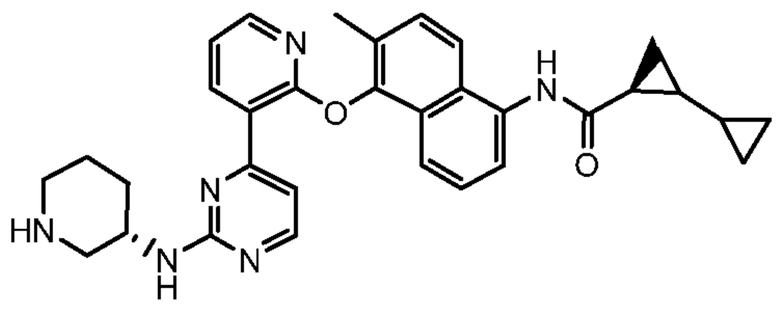
Example 273 *(2S)-N-(6-Methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-[1,1'-bi(cyclopropane)]-2-carboxamide* ***273***

[0969] Step 1: *tert*-butyl (3*S*)-3-((4-(2-((5-((2*S*)-[1,1'-bi(cyclopropane)]-2-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0970] The General Procedure C was followed, using *tert*-butyl (3S)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (300 mg, 0.57 mmol), 2-cyclopropylcyclopropane-1-carboxylic acid (111 mg, 0.85 mmol), HATU (442.1 mg, 1.14 mmol), and DIPEA (0.30 mL, 1.71 mmol) in DMF (3 mL). The crude material was purified by silica gel chromatography (12 g column), eluting with 0-5% MeOH/DCM to afford 313 mg (86.5% yield) of the title compound as a brown solid. LCMS (ESI) $[M+H]^+ = 635$. The enantiomers were separated by chiral SFC to afford isomer-1 (t_R= 1.213 min) 108.5 mg light yellow solid and isomer-2 (t_R= 1.801 min) 110.6 mg light yellow solid. The absolute stereochemistry of the cyclopropyl was randomly assigned.

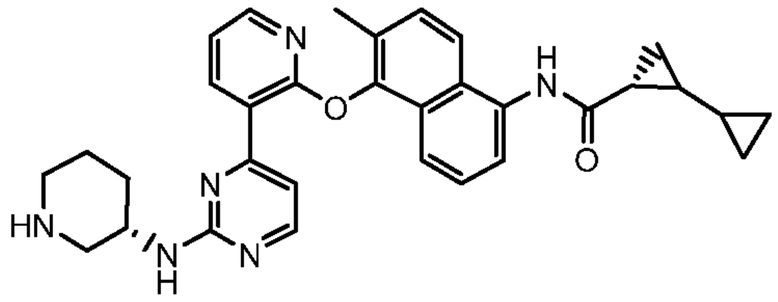
[0971] Step 2: (2*S*)-*N*-(6-Methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-[1,1'-bi(cyclopropane)]-2-carboxamide



[0972] The General Procedure B was followed, using *tert*-butyl (3*S*)-3-((4-(2-((5-((2*S*)-[1,1'-bi(cyclopropane)]-2-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-1, 108.5 mg, 0.17 mmol). The crude product was lyophilized to yield 95 mg (98% yield) of **273** as an off-white solid. The stereochemical assignments of **273** and **274** were randomly assigned and may be later determined. LCMS (ESI) $[M+H]^+ = 535$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H), 8.79 – 8.51 (m, 4H), 8.48 (d, J = 5.2 Hz, 1H), 8.05 (dd, J = 4.8, 2.0 Hz, 1H), 7.99 (d, J = 8.7 Hz, 1H), 7.69 (d, J = 7.4 Hz, 1H), 7.58 (d, J = 5.1 Hz, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.50 (d, J = 7.4 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.42 – 7.34 (m, 1H), 7.27 (dd, J = 7.6, 4.8 Hz, 1H), 4.25 (s, 1H), 3.27 –

3.14 (m, 2H), 2.92 – 2.80 (m, 2H), 2.22 (s, 3H), 2.06 – 1.97 (m, 1H), 1.97 – 1.88 (m, 2H), 1.81 – 1.54 (m, 2H), 1.43 – 1.32 (m, 1H), 0.96 (dt, *J* = 8.8, 4.4 Hz, 2H), 0.75 – 0.66 (m, 1H), 0.47 – 0.39 (m, 2H), 0.20 – 0.13 (m, 2H).

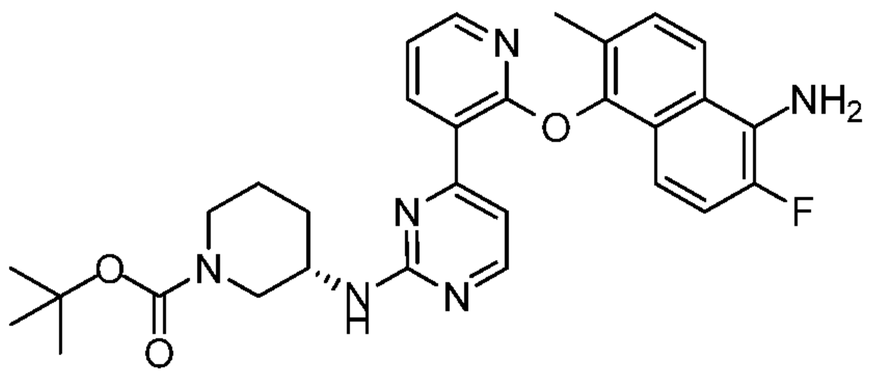
Example 274 *(2R)-N-(6-Methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-[1,1'-bi(cyclopropane)]-2-carboxamide* ***274***



[0973] Following Example 273 and General Procedure B, tert-butyl (3S)-3-((4-(2-((5-((2R)-[1,1'-bi(cyclopropane)]-2-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-2, 110.6 mg, 0.17 mmol) was deprotected. The crude product was lyophilized to yield 98 mg (100%yield) of **274** as an off-white solid. LCMS (ESI) $[M+H]^+$ = 535; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14 (s, 1H), 9.09 – 8.91 (m, 2H), 8.75 – 8.55 (m, 2H), 8.48 (d, *J* = 5.2 Hz, 1H), 8.06 (dd, *J* = 4.8, 2.0 Hz, 1H), 7.99 (d, *J* = 8.7 Hz, 1H), 7.69 (d, *J* = 7.3 Hz, 1H), 7.58 (dd, *J* = 12.6, 6.4 Hz, 2H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.40 – 7.37 (m, 1H), 7.27 (dd, *J* = 7.6, 4.8 Hz, 1H), 4.36 – 4.25 (m, 1H), 3.24 – 3.14 (m, 2H), 2.91 – 2.79 (m, 2H), 2.22 (s, 3H), 2.07 – 1.98 (m, 1H), 1.98 – 1.87 (m, 2H), 1.83 – 1.59 (m, 2H), 1.41 – 1.34 (m, 1H), 1.01 – 0.92 (m, 2H), 0.75 – 0.65 (m, 1H), 0.50 – 0.38 (m, 2H), 0.24 – 0.14 (m, 2H).

Example 275 *(S)-N-(2-Fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-3,3-dimethylbutanamide* ***275***

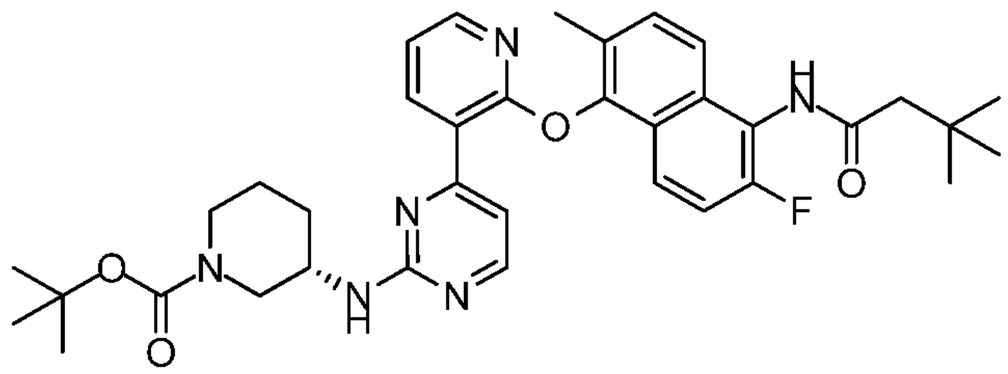
[0974] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-amino-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0975] To a 100 mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed *tert*-butyl (3*S*)-3-[[4-(2-fluoro-3-pyridyl)pyrimidin-2-yl]amino]piperidine-1-carboxylate (150 mg, 0.40 mmol), 5-amino-6-fluoro-2-methylnaphthalen-1-ol (150 mg, 0.52 mmol), cesium carbonate (392 mg, 1.21 mmol), dimethyl

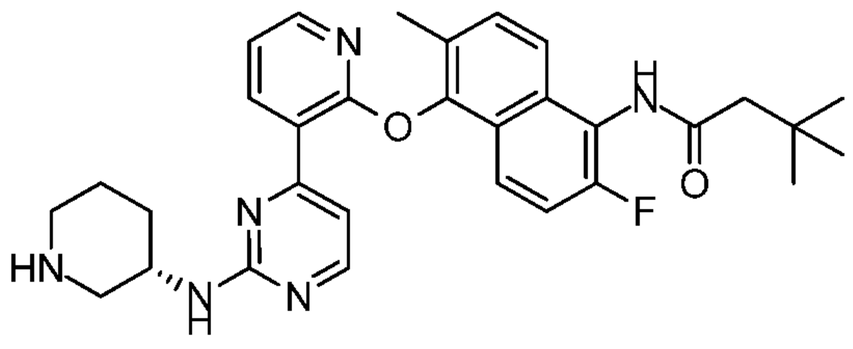
sulfoxide (2 mL). The resulting solution was stirred at 120 ºC in an oil bath for 2 h, cooled to room temperature and concentrated *in vacuo*. The residue was purified prep-TLC (solvent gradient: 50% ethyl acetate in petroleum ether) to yield 160 mg (73% yield) of the title compound as a yellow solid. LCMS: (ES, m/z): $[M+H]^+$= 545.1.

Step 2: (*S*)-*tert*-Butyl 3-((4-(2-((5-(3,3-dimethylbutanamido)-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0976] The General Procedure A was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-6-fluoro-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (80 mg, 0.15 mmol), pyridine (2 mL), dichloromethane (1 mL)and 3,3-dimethylbutanoyl chloride (24 mg, 0.18 mmol). The residue was purified by Prep-TLC (normal phase, petroleum ether/ethyl acetate = 2/1) to yield 90 mg (95% yield) of the title compound as a brown oil. LCMS (ESI) $[M+H]^+$ = 643.3

[0977] Step 3: (*S*)-*N*-(2-fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-3,3-dimethylbutanamide

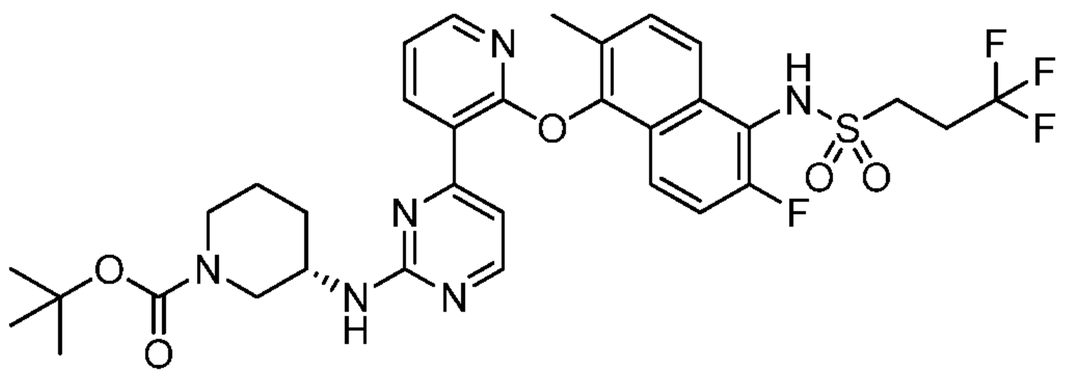


[0978] The General Procedure B was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[[5-(3,3-dimethylbutanoylamino)-6-fluoro-2-methyl-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (90 mg, 0.09 mmol), dichloromethane (2 mL) and hydrochloric acid (4 M in dioxane, 0.23 mL, 0.93 mmol). The residue was purified by Prep-HPLC (mobile phase: A: water (0.05%HCl) B: ACN) to yield 62 mg (83% yield) of **275** as a white solid. LCMS (ESI): $[M+H]^+$ = 543.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 9.38 (s, 1H), 9.15 (s, 1H), 8.79 (s, 1H), 8.50 (d, *J* = 5.4 Hz, 1H), 8.08 (d, *J* = 3.2 Hz, 1H), 7.79 (d, *J* = 8.6 Hz, 1H), 7.70-7.60 (m, 1H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.40 (t, *J* = 9.6 Hz, 1H), 7.30 - 7.24 (m, 1H), 4.40 (s, 1H), 3.41 (m, 1H), 3.18 (m, 1H), 2.89 - 2.78 (m, 2H), 2.36 (s, 2H), 2.19

(s, 3H), 2.02 (m, 1H), 1.95 - 1.87 (m, 1H), 1.75 – 1.87 (m, 1H), 1.75 – 1.60 (m, 1H), 1.10 (s, 9H).

Example 276 *(S)-3,3,3-Trifluoro-N-(2-fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide hydrochloride* ***276***

[0979] Step 1: (S)-*tert*-butyl 3-((4-(2-((6-fluoro-2-methyl-5-(3,3,3-trifluoropropylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0980] The General Procedure A was followed using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example **275** (500 mg, 0.918 mmol), pyridine (2 mL), CH_2Cl_2 (4 mL), and 3,3,3-trifluoropropane-1-sulfonyl chloride (452 mg, 2.30 mmol). After 16 h, the mixture was diluted with CH_2Cl_2 (50 mL) and washed with saturated $NaHCO_3$(aq) (10 mL), dried (Na_2SO_4), filtered and concentrated The crude was purified by flash chromatography through silica gel (0 – 50% EtOAc/CH_2Cl_2) to provide 355 mg (55% yield) of the title compound as a yellow wax. LCMS (ESI) $[M+H]^+$ = 705.2, rt = 1.97 min.

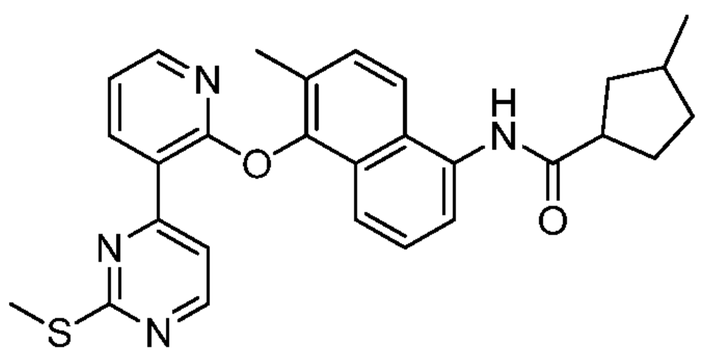
[0981] Step 2: (*S*)-3,3,3-Trifluoro-*N*-(2-fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)propane-1-sulfonamide hydrochloride **276**

[0982] Prepared according to General Procedure B using (*S*)-*tert*-butyl 3-((4-(2-((6-fluoro-2-methyl-5-(3,3,3-trifluoropropylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (355 mg, 0.50 mmol), EtOAc (3 mL), and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). After 16 h, the mixture was concentrated *in vacuo* and the crude HCl salt solid was washed with EtOAc (3 x 3 mL) then with MeCN (3 x 3 mL). The solid product was then sonicated and concentrated *in vacuo* with MeCN (3 x 3 mL) and the resulting solid was dissolved in H_2O and MeCN and lyophilized to provide 265 mg (82% yield) of **276** as a fluffy light yellow powder and as a HCl salt. LCMS (ESI) $[M+H]^+$ = 705.2, rt = 1.97 min; ^{1}H NMR (400 MHz, *d*$_6$-DMSO) δ 10.09 (s, 1H), 9.03 – 8.75 (m, 2H), 8.73 –

8.56 (m, 1H), 8.47 (d, J = 5.2 Hz, 1H), 8.08 (dd, J = 4.8, 1.9 Hz, 1H), 8.04 (d, J = 8.7 Hz, 1H), 7.75 (dd, J = 9.3, 5.1 Hz, 1H), 7.66 (d, J = 8.8 Hz, 1H), 7.60 – 7.52 (m, 2H), 7.49 (t, J = 9.5 Hz, 1H), 7.29 (dd, J = 7.6, 4.8 Hz, 1H), 4.37 – 4.16 (m, 1H), 3.47 – 3.40 (m, 3H), 3.21 (d, J = 11.9 Hz, 1H), 2.99 – 2.75 (m, 4H), 2.18 (s, 3H), 2.08 – 1.86 (m, 2H), 1.80 – 1.56 (m, 2H).

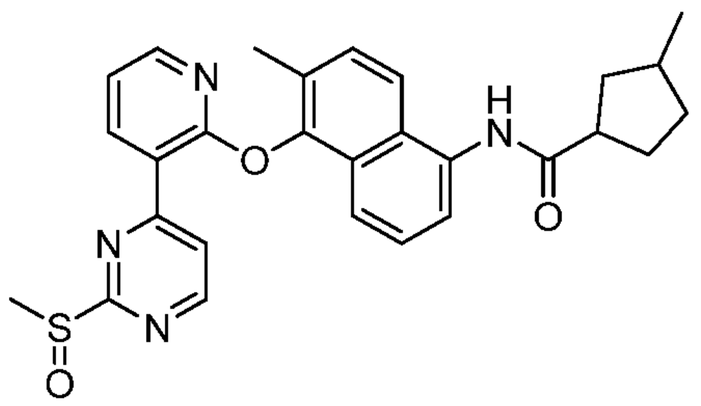
Example 277 *(1R)-3-Methyl-N-(6-methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentane-1-carboxamide* ***277***

[0983] Step 1: 3-Methyl-*N*-(6-methyl-5-((3-(2-(methylthio)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentanecarboxamide



[0984] Prepared using 6-methyl-5-((3-(2-(methylthio)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-amine (260 mg, 0.694 mmol), triethylamine (211 mg, 0.290 mL, 2.08 mmol), HATU (343 mg, 0.903 mmol), and 3-methylcyclopentanecarboxylic acid (98 mg, 0.76 mmol) in DMF (2 mL). After 3 days, the mixture was diluted with EtOAc and H_2O and a precipitate formed which was filtered off, washed with EtOAc and H_2O and vacuum dried to provide 272 mg (80 % yield) of the title compound as a white solid. LCMS (ESI) $[M+H]^+$ = 485.3, rt = 2.01 min.

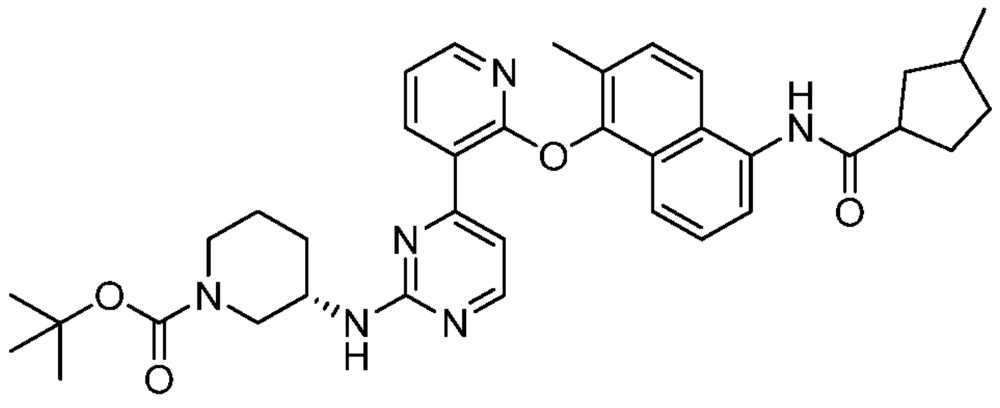
[0985] Step 2: 3-Methyl-*N*-(6-methyl-5-((3-(2-(methylsulfinyl)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentanecarboxamide



[0986] To 3-methyl-*N*-(6-methyl-5-((3-(2-(methylthio)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentanecarboxamide (268 mg, 0.553 mmol) in DCM (18 mL) was added 3-chloroperbenzoic acid (135 mg of 77% pure reagent, 0.610 mmol) and the mixture was stirred at rt. After 1 h, the mixture was diluted with DCM and washed with saturated $NaHCO_3$(aq), dried (Na_2SO_4), filtered and concentrated *in vacuo* to provide 276 mg

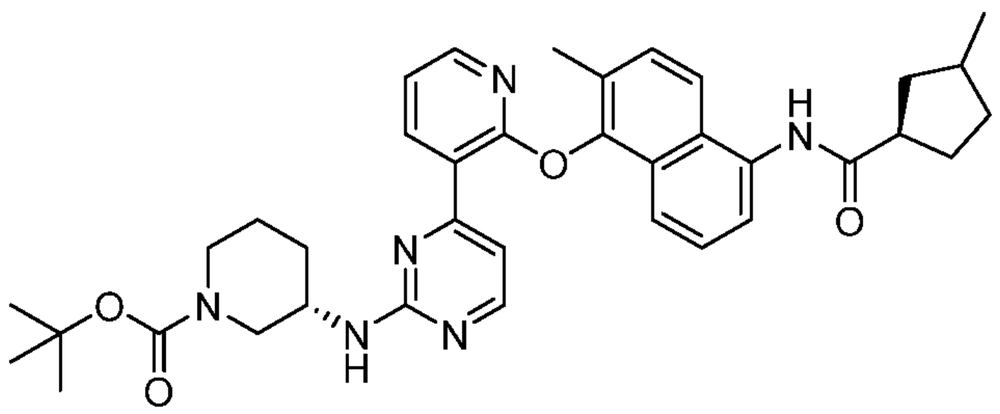
(100% yield) of the title compound which was used without further purification in the next step. LCMS (ESI) $[M+H]^+$ = 501.2, rt = 1.59 min.

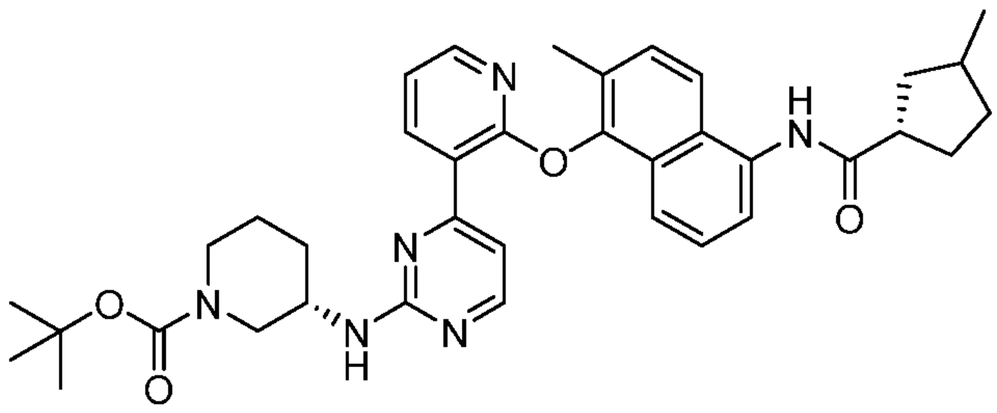
[0987] Step 3: (3*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-5-(3-methylcyclopentanecarboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0988] 3-Methyl-*N*-(6-methyl-5-((3-(2-(methylsulfinyl)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentanecarboxamide (276 mg, 0.551 mmol) and (*S*)-*tert*-butyl 3-aminopiperidine-1-carboxylate (166 mg, 0.827 mmol) were combined in 1,4-dioxane (3 mL). Triethylamine (167 mg, 0.230 mL, 1.65 mmol) was then added and the flask was sealed and placed in a 120 °C oil bath. After 20 h, the mixture was diluted with EtOAc, and washed with saturated $NaHCO_3$(aq), then saturated NaCl(aq), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude was purified by flash chromatography through silica gel (0 – 60% EtOAc/DCM) to provide 254 mg (72% yield) of the title compound as an off-white foam. LCMS (ESI) $[M+H]^+$ = 637.4, rt = 2.04 min.

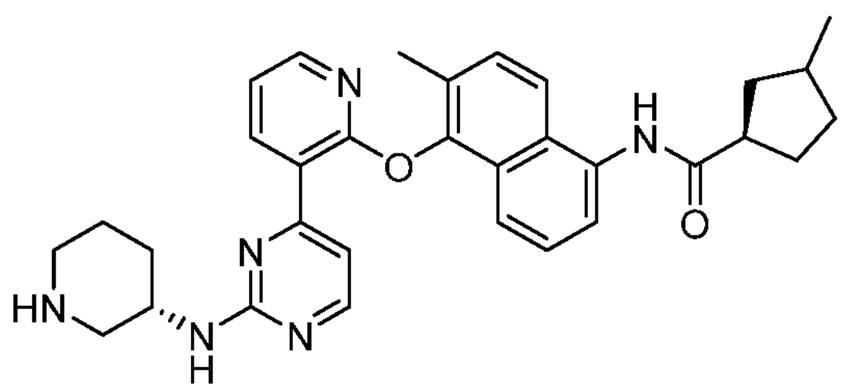
[0989] Step 4: *tert*-Butyl (3*S*)-3-((4-(2-((2-methyl-5-((1*R*)-3-methylcyclopentane-1-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-1) and *tert*-butyl (3*S*)-3-((4-(2-((2-methyl-5-((1*S*)-3-methylcyclopentane-1-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-2)





[0990] The mixture of stereoisomers from Step 3 (254 mg, 0.399 mmol) was subjected to chiral normal phase semi-prep purification (Conditions: Chiral pak IB, 5um, 20 x 250 mm, 6:2:92 MeOH: IPA: hexanes, stached injection, 0.5-0.75 mg/injections) to provide stereoisomers with respect to the cyclopentane ring: (isomer-1), 101 mg (40% yield), ee ≥ 99%, rt = 16.21 min, LCMS (ESI) $[M+H]^+$ = 637.7, rt = 2.04 min; (isomer-2), 105 mg (41% yield), ee = 95%, rt = 16.75 min, LCMS (ESI) $[M+H]^+$ = 637.7, rt = 2.05 min.

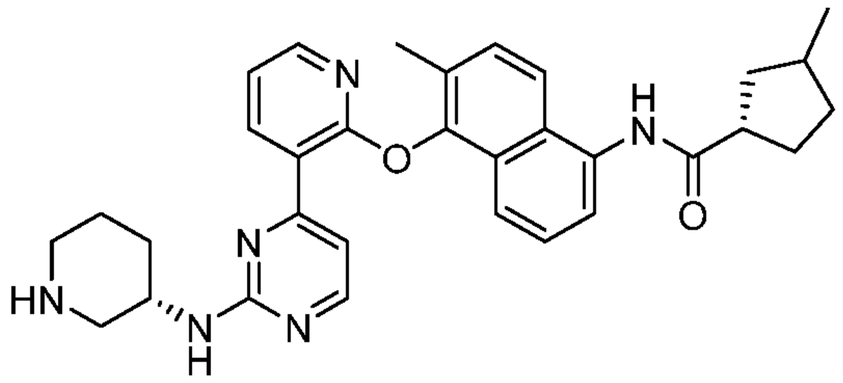
[0991] Step 5: (1*R*)-3-Methyl-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentane-1-carboxamide (isomer-1)



[0992] Prepared using (3*S*)-*tert*-butyl 3-((4-(2-((2-methyl-5-(3-methylcyclopentanecarboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-1) (101 mg, 0.159 mmol), 1,4-dioxane (0.5 mL), and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). After 30 min, the resulting solids were filtered off and washed with Et_2O, and dried. The collected solids were then dissolved in H_2O and MeCN and lyophilized to provide 75 mg (83% yield) of **277**. The stereochemical assignments of **277** and **278** were randomly assigned and may be later determined. LCMS (ESI) $[M+H]^+$ = 537.5, rt = 1.49 min; ^1H NMR (400 MHz, *d*$_6$-DMSO) δ 9.90 (s, 1H), 9.44 – 8.96 (m, 2H), 8.71 (br.s, 1H), 8.49 (d, J = 5.3 Hz, 1H), 8.06 (dd, J = 4.8, 1.9 Hz, 1H), 7.89 (d, J = 8.7 Hz, 1H), 7.74 – 7.55 (m, 3H), 7.49 (dd, J = 12.5, 8.8 Hz, 2H), 7.44 – 7.34 (m, 1H), 7.27 (dd, J = 7.6, 4.8 Hz, 1H), 3.43 (d, J = 10.3 Hz, 1H), 3.28 – 3.03 (m, 2H), 2.95 – 2.74 (m, 2H), 2.21 (s, 3H), 2.18 – 2.07 (m, 1H), 2.08 – 1.96 (m, 2H), 1.98 – 1.87 (m, 3H), 1.87 – 1.68 (m, 2H), 1.70 – 1.55 (m, 1H), 1.39 (dd, J = 21.9, 9.9 Hz, 1H), 1.33 – 1.14 (m, 1H), 1.10 – 0.96 (m, 3H).

Example 278 *(1S)-3-Methyl-N-(6-methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentane-1-carboxamide* ***278***

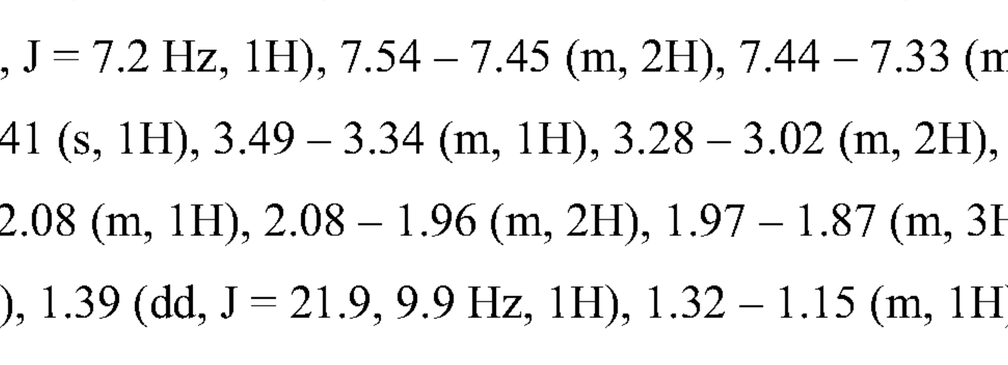
[0993] Step 1: 3-Methyl-*N*-(6-methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopentanecarboxamide (isomer-2)



[0994] Prepared using tert-butyl (3*S*)-3-((4-(2-((2-methyl-5-((1*S*)-3-methylcyclopentane-1-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-2) (105 mg, 0.165 mmol), 1,4-dioxane (0.5 mL), and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). After 30 min, the resulting solids were filtered off and washed with Et_2O, and dried. The collected solids were then dissolved in H_2O and MeCN and lyophilized to provide 74 mg (78% yield) of **278**. LCMS (ESI) $[M+H]^+$ = 537.4, rt = 1.49 min; ^1H NMR (400 MHz, d6-dmso) δ 9.93 (s, 1H), 9.49 (br.s, 1H), 9.27 (s, 1H), 8.81 (br.s, 1H), 8.50 (d, J = 5.4 Hz, 1H), 8.44 (s, 1H), 8.07 (dd, J = 4.7, 1.8 Hz, 1H), 7.90 (d, J = 8.7 Hz, 1H), 7.67 (s, 1H), 7.59 (d, J = 7.2 Hz, 1H), 7.54 – 7.45 (m, 2H), 7.44 – 7.33 (m, 1H), 7.27 (dd, J = 7.6, 4.8 Hz, 1H), 4.41 (s, 1H), 3.49 – 3.34 (m, 1H), 3.28 – 3.02 (m, 2H), 2.96 – 2.73 (m, 2H), 2.21 (s, 3H), 2.19 – 2.08 (m, 1H), 2.08 – 1.96 (m, 2H), 1.97 – 1.87 (m, 3H), 1.87 – 1.72 (m, 2H), 1.72 – 1.56 (m, 1H), 1.39 (dd, J = 21.9, 9.9 Hz, 1H), 1.32 – 1.15 (m, 1H), 1.10 – 0.98 (m, 3H).

Example 279 *(S)-N-(2-Fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-methylpropane-1-sulfonamide* ***279***

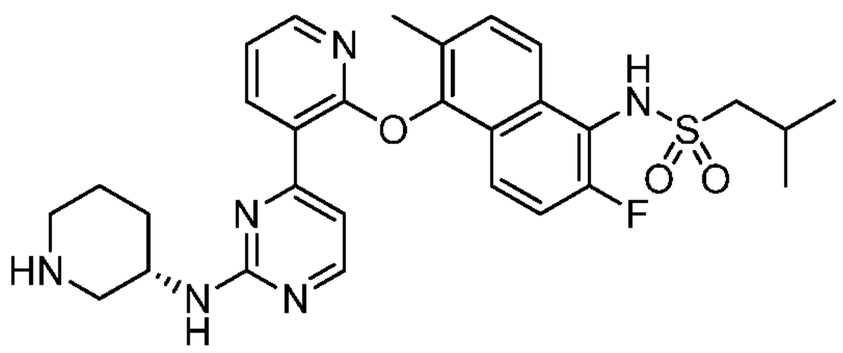
[0995] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((6-fluoro-2-methyl-5-(2-methylpropylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[0996] Prepared using (S)-*tert*-butyl 3-((4-(2-((5-amino-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 275 (45 mg,

0.083 mmol), pyridine (98 mg, 0.10 mL, 1.2 mmol), DCM (0.28 mL), DMAP (3 mg, 0.024 mmol), and 2-methylpropane-1-sulfonyl chloride (26 mg, 0.16 mmol). After 16 h, a further portion of 2-methylpropane-1-sulfonyl chloride (26 mg, 0.16 mmol) added and after stirring a further 20 h the mixture was concentrated *in vacuo* and the crude was purified by C18 reverse phase flash chromatography (25 – 75% MeCN/10mM pH= 10 aqueous ammonium bicarbonate). The product fractions were collected and concentrated *in vacuo* and the resulting residue was diluted with EtOAc and washed with saturated $NaHCO_3$(aq), then saturated NaCl(aq). The solution was dried (Na_2SO_4), filtered and concentrated *in vacuo* to provide 27 mg (49% yield) of the title compound. LCMS (ESI) $[M+H]^+$ = 665.3, rt = 1.96 min.

[0997] Step 2: (*S*)-*N*-(2-Fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-2-methylpropane-1-sulfonamide

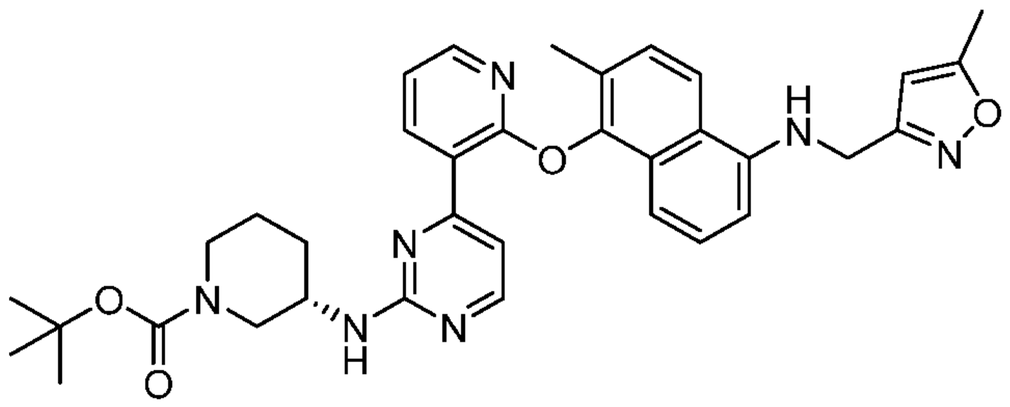


[0998] Prepared according to General Procedure B using (*S*)-*tert*-butyl 3-((4-(2-((6-fluoro-2-methyl-5-(2-methylpropylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (27 mg, 0.041 mmol), 1,4-dioxane (0.2 mL), and hydrochloric acid (4 M in dioxane, 1 mL, 4 mmol). After 1.5 h, the mixture was diluted with Et_2O and the solids were filtered off, washed with Et_2O and then dissolved in H_2O and purified by C18 reverse phase flash chromatography (25 – 45% MeCN/10mM pH= 10 aqueous ammonium bicarbonate). Appropriate fractions were collected and concentrated *in vacuo* and the resulting residue was diluted with EtOAc and washed with saturated $NaHCO_3$(aq), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The material thus obtained was dissolved in 1,4-dioxane (0.2 mL) and treated with hydrochloric acid (4 M in dioxane, 1 mL, 4 mmol) and stirred at rt. After 5 min, the mixture was diluted with Et_2O and the solids were filtered off, washed with Et_2O and then dissolved in H_2O and MeCN. Lyophilization provided 16 mg (64% yield) of the title compound as a white solid. LCMS (ESI) $[M+H]^+$ = 565.1, rt = 1.43 min; ^1H NMR (400 MHz, d_6-DMSO) δ 9.70 (s, 1H), 9.01 – 8.77 (m, 2H), 8.68 (s, 1H), 8.47 (d, J = 5.2 Hz, 1H), 8.10 – 8.04 (m, 2H), 7.71 (dd, J = 9.3, 5.1 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.55 (dd, J = 9.3, 6.4 Hz, 2H), 7.46 (t, J = 9.5 Hz, 1H), 7.29 (dd, J = 7.6, 4.8 Hz, 1H), 4.27 (s, 1H), 3.43 (d, J = 8.7 Hz, 1H), 3.21 (d, J = 12.2 Hz, 1H), 3.11 (d, J = 6.4 Hz, 2H), 2.94 – 2.76 (m, 2H),

2.28 (dt, J = 13.3, 6.6 Hz, 1H), 2.19 (s, 3H), 2.01 (d, J = 12.2 Hz, 1H), 1.92 (dd, J = 14.6, 3.5 Hz, 1H), 1.80 – 1.69 (m, 1H), 1.69 – 1.57 (m, 1H), 1.07 (d, J = 6.7 Hz, 6H).

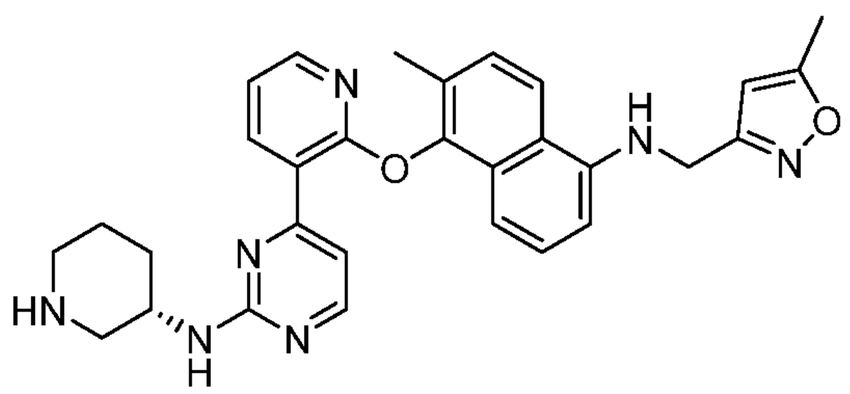
Example 280 *(S)-4-(2-((2-Methyl-5-(((5-methylisoxazol-3-yl)methyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine* ***280***

[0999] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-(((5-methylisoxazol-3-yl)methyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[1000] The General Procedure E was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (200 mg, 0.38 mmol) and 3-(bromomethyl)-5-methylisoxazole (137.8 mg, 0.76 mmol). The crude material was purified by silica gel chromatography (12 g column), eluting with 0-5% MeOH/DCM to afford 69 mg (29% yield) of the title compound as a brown solid. LCMS (ESI) $[M+H]^+ = 622$.

[1001] Step 2: (*S*)-4-(2-((2-Methyl-5-(((5-methylisoxazol-3-yl)methyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-2-amine

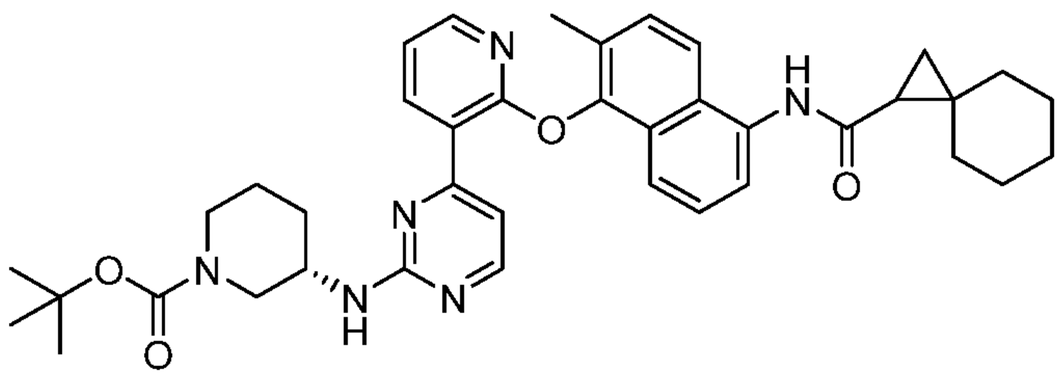


[1002] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-(((5-methylisoxazol-3-yl)methyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (69 mg, 0.07 mmol). The crude product was purified *via* reverse-phase HPLC and lyophilized to yield 19.8 mg (52.6% yield) of **280** as an off-white solid. LCMS (ESI) $[M+H]^+ = 522$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 – 8.45 (m, 1H), 8.39 (d, *J* = 5.2 Hz, 1H), 8.02 – 7.97 (m, 1H), 7.43 (d, *J* = 5.1 Hz, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 7.22 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.14-7.10 (m, 2H), 6.95 – 6.85 (m, 2H), 6.46 (dd, *J* = 7.8, 1.0 Hz, 1H), 6.14 (s, 1H), 4.47 (d, *J* = 6.0 Hz, 2H), 3.96 – 3.82 (m, 1H), 3.16 – 3.08 (m,

1H), 2.86 – 2.77 (m, 1H), 2.47 – 2.40 (m, 2H), 2.33 (d, *J* = 0.9 Hz, 3H), 2.19 (s, 3H), 1.97 – 1.90 (m, 1H), 1.69 – 1.63 (m, 1H), 1.54 – 1.41 (m, 2H).

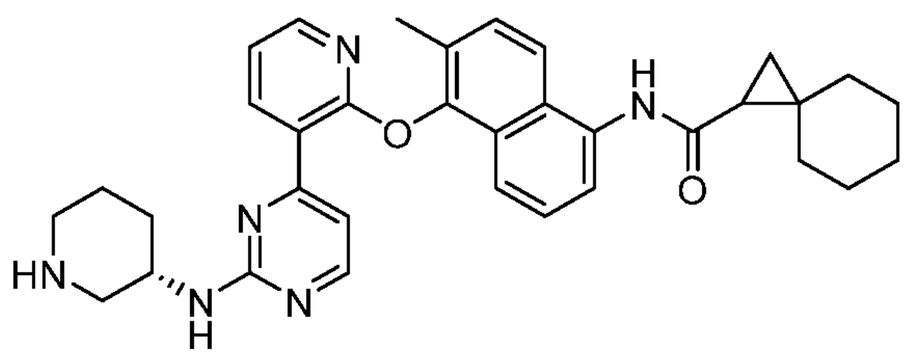
Example 281 *N-(6-Methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)spiro[2.5]octane-1-carboxamide* ***281***

[1003] Step 1: *tert*-Butyl (3*S*)-3-((4-(2-((2-methyl-5-(spiro[2.5]octane-1-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[1004] The General Procedure C was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (200 mg, 0.38 mmol), spiro[2.5]octane-2-carboxylic acid (87.8 mg, 0.57 mmol), HATU (294.7 mg, 0.76 mmol), DMF (2 mL), and DIPEA (0.20 mL, 1.14 mmol). The crude material was purified by chromatography (silica gel chromatography) 12 g column, eluting with 0-5% MeOH/DCM to afford 239 mg (94.5 yield) of the title compound as a yellow solid. LCMS (ESI) $[M+H]^+$ = 663.

[1005] Step 2: *N*-(6-Methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)spiro[2.5]octane-1-carboxamide

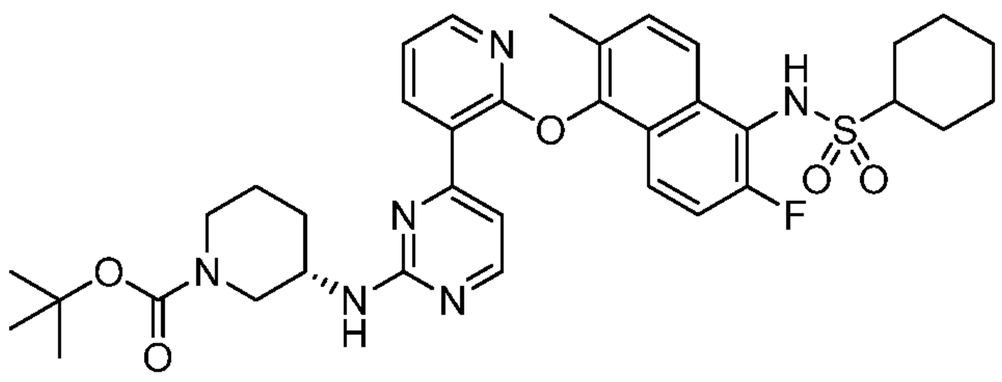


[1006] The General Procedure B was followed, using *tert*-butyl (3*S*)-3-((4-(2-((2-methyl-5-(spiro[2.5]octane-1-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (239 mg, 0.36 mmol). The crude product was purified *via* reverse-phase HPLC and lyophilized to yield 18.8 mg (9.3% yield) of **281** as a white solid and as a mixture of two isomers enantiomeric at the 1-cyclopropane position. LCMS (ESI) $[M+H]^+$ = 563; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H), 8.49 (d, *J* = 7.5 Hz, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.02 (dd, *J* = 4.8, 2.0 Hz, 1H), 7.97 (d, *J* = 8.7 Hz, 1H), 7.60 (d, *J* = 7.3 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.44 (d, *J* = 5.1 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.25 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.13 – 7.07 (m, 1H), 3.94 – 3.82 (m, 1H), 3.12 – 3.02 (m, 1H), 2.82 –

2.72 (m, 1H), 2.47 – 2.36 (m, 2H), 2.22 (s, 3H), 1.97 – 1.90 (m, 2H), 1.73 – 1.27 (m, 14H), 1.06 – 1.00 (m, 1H), 0.85 – 0.78 (m, 1H).

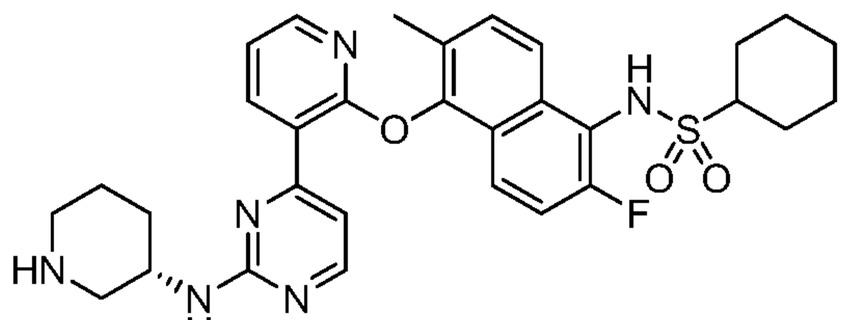
Example 282 *(S)-N-(2-Fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclohexanesulfonamide* ***282***

[1007] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-(cyclohexanesulfonamido)-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[1008] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 275 (50 mg, 0.092 mmol), pyridine (109 mg, 0.11 mL, 1.38 mmol), DCM (0.30 mL), DMAP (3 mg, 0.024 mmol), and cyclohexanesulfonyl chloride (117 mg, 0.643 mmol). After 16 h, a further portion of DMAP (3 mg, 0.024 mmol), and cyclohexanesulfonyl chloride (117 mg, 0.643 mmol) was added and after stirring a further 20 h the mixture was concentrated *in vacuo* and the crude was purified by C18 reverse phase flash chromatography (50 – 80% MeCN/10mM pH= 3.8 aqueous ammonium formate). Appropriate fractions were collected and concentrated *in vacuo* and the resulting residue was diluted with EtOAc and washed with saturated $NaHCO_3$(aq), then saturated NaCl(aq), dried (Na_2SO_4), filtered and concentrated *in vacuo* to provide 12 mg (19% yield) of the title compound. LCMS (ESI) $[M+H]^+$ = 691.3, rt = 2.03 min.

[1009] Step 2: (*S*)-*N*-(2-Fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclohexanesulfonamide

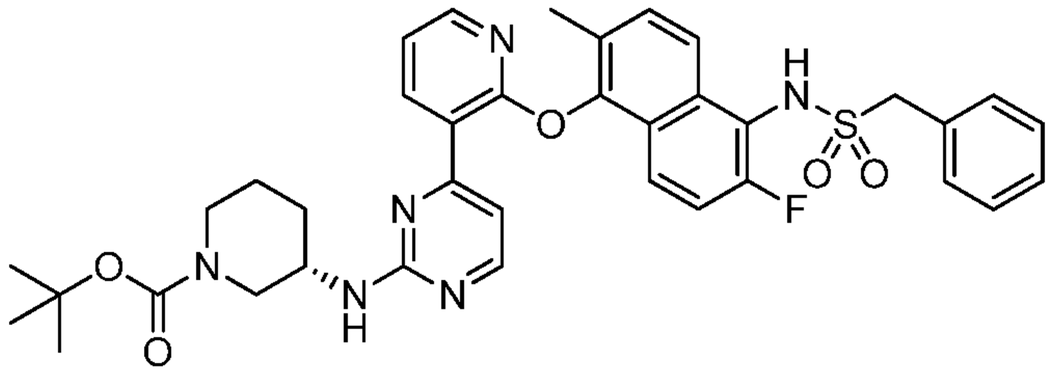


[1010] Prepared according to General Procedure B using (*S*)-*tert*-Butyl 3-((4-(2-((5-(cyclohexanesulfonamido)-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (12 mg, 0.017 mmol), 1,4-dioxane (0.2 mL), and hydrochloric acid (4 M in dioxane, 1 mL, 4 mmol). After 1.5 h, the mixture was diluted with Et_2O and the solids were filtered off, washed with Et_2O and then dissolved in H_2O.

Lyophilization provided 11 mg (103% yield) of **282** as a white solid. LCMS (ESI) $[M+H]^+$ = 591.2, rt = 1.49 min; ^1H NMR (400 MHz, d6-dmso) δ 9.58 (s, 1H), 8.95 – 8.72 (m, 2H), 8.70 – 8.57 (m, 1H), 8.47 (d, J = 5.2 Hz, 1H), 8.10 – 8.04 (m, 2H), 7.70 (dd, J = 9.3, 5.1 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1Hz), 7.55 (dd, J = 11.8, 6.2 Hz, 2H), 7.44 (t, J = 9.5 Hz, 1H), 7.29 (dd, J = 7.6, 4.8 Hz, 1H), 4.27 (s, 1H), 3.45 – 3.30 (m, 2H), 3.21 (d, J = 12.6 Hz, 1H), 3.04 (tt, J = 11.9, 3.0 Hz, 1H), 2.93 – 2.77 (m, 2H), 2.28 – 2.21 (m, 2H), 2.19 (s, 3H), 2.01 (d, J = 9.4 Hz, 1H), 1.97 – 1.82 (m, 3H), 1.78 – 1.57 (m, 3H), 1.50 (qd, J = 12.6, 3.2 Hz, 2H), 1.37 – 1.13 (m, 2H)

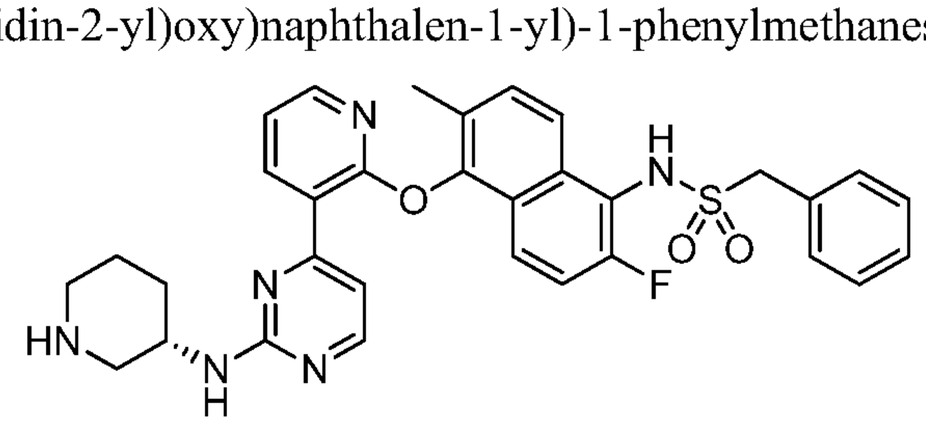
Example 283 *(S)-N-(2-Fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-phenylmethanesulfonamide* ***283***

[1011] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((6-fluoro-2-methyl-5-(phenylmethylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[1012] Prepared using (*S*)-*tert*-Butyl 3-((4-(2-((5-amino-6-fluoro-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 275 (700 mg, 1.28 mmol), pyridine (2 mL), DCM (7 mL), and phenylmethanesulfonyl chloride (367 mg, 1.93 mmol). After 64 h, a further portion of phenylmethanesulfonyl chloride (245 mg, 1.28 mmol) was added and stirring continued at rt. After a further 4 h, the mixture was diluted with DCM (50 mL) and washed with saturated $NaHCO_3$(aq) (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude was purified by flash chromatography through silica gel (0 – 50% EtOAc/DCM) to provide 340 mg (38% yield) of the title compound as a yellow foam. LCMS (ESI) $[M+H]^+$ = 699.3, rt = 1.98 min.

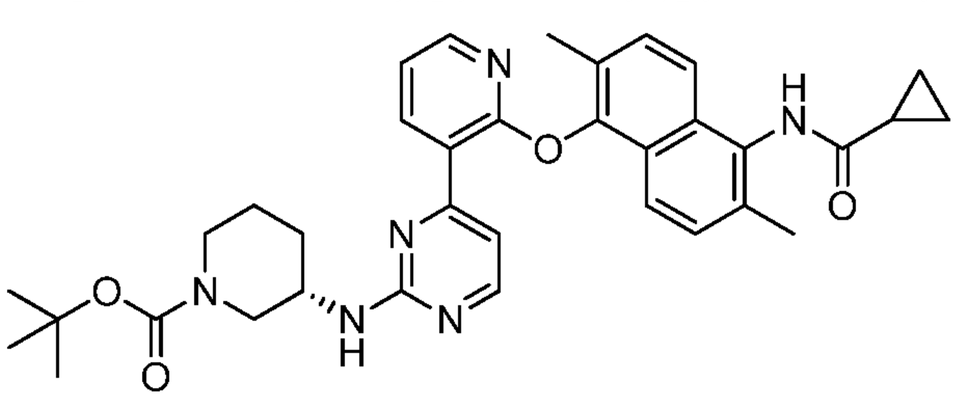
[1013] Step 2: (*S*)-*N*-(2-Fluoro-6-methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-1-phenylmethanesulfonamide



[1014] Prepared according to General Procedure B using (*S*)-*tert*-butyl 3-((4-(2-((6-fluoro-2-methyl-5-(phenylmethylsulfonamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (340 mg, 0.490 mmol), EtOAc (3 mL), and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). After 3 h, the mixture was diluted with Et_2O (10 mL) and the resulting solids were filtered off, washed with Et_2O (2 x 5 mL), and dried. The collected solids were dissolved in H_2O and MeCN and lyophilized to provide 248 mg (80% yield) of **283** as a light yellow powder and as a HCl salt. LCMS (ESI) $[M+H]^+$ = 599.2, rt = 1.45 min; ^{1}H NMR (400 MHz, *d*$_6$-DMSO) δ 9.78 (s, 1H), 8.98 – 8.53 (m, 3H), 8.48 (d, J = 5.2 Hz, 1H), 8.09 (dd, J = 4.8, 1.8 Hz, 1H), 7.99 (d, J = 8.7 Hz, 1H), 7.73 (dd, J = 9.2, 5.1 Hz, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.58 – 7.51 (m, 2H), 7.50 – 7.37 (m, 6H), 7.30 (dd, J = 7.5, 4.8 Hz, 1H), 4.56 (s, 2H), 4.36 – 4.18 (m, 1H), 3.44 (d, J = 9.5 Hz, 1H), 3.21 (d, J = 11.6 Hz, 1H), 2.96 – 2.76 (m, 2H), 2.19 (s, 3H), 2.06 – 1.86 (m, 2H), 1.82 – 1.56 (m, 2H).

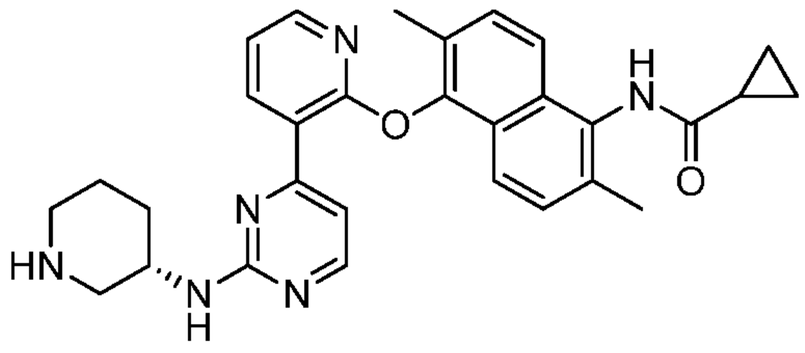
Example 284 *(S)-N-(2,6-Dimethyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)Naphthalen-1-yl)cyclopropanecarboxamide* ***284***

[1015] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-(cyclopropanecarboxamido)-2,6-dimethylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[1016] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-2,6-dimethylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (32 mg, 0.059 mmol), pyridine (0.072 mL), DCM (0.5 mL), and cyclopropanecarbonyl chloride (12 mg, 0.12 mmol). After 3 h, the mixture was diluted with DCM and washed with saturated $NaHCO_3$(aq), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude was purified by flash chromatography through silica gel (20 – 100% EtOAc/hexanes) to provide 32 mg (89% yield) of the title compound. LCMS (ESI) $[M+H]^+$ = 609.6, rt = 1.84 min.

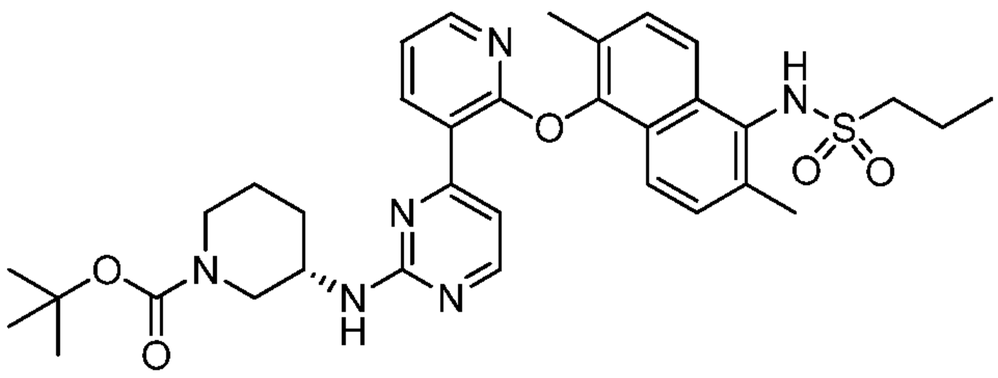
[1017] Step 2: (*S*)-*N*-(2,6-Dimethyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)Naphthalen-1-yl)cyclopropanecarboxamide



[1018] Prepared according to General Procedure B using (*S*)-*tert*-butyl 3-((4-(2-((5-(cyclopropanecarboxamido)-2,6-dimethylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (32 mg, 0.053 mmol), 1,4-dioxane (0.3 mL), and hydrochloric acid (4 M in dioxane, 0.4 mL, 1.6 mmol). After 3h, the mixture was triturated with Et_2O, filtered and washed with Et_2O. The resulting solids were dissolved in H_2O and MeCN and lyophilized to provide 28 mg (97% yield) of **284**. LCMS (ESI) $[M+H]^+ = 509.4$, rt = 1.28 min; ^1H NMR (400 MHz, *d*$_6$-DMSO) δ 10.01 (s, 1H), 8.82 (s, 2H), 8.48 (d, J = 5.2 Hz, 1H), 8.06 (dd, J = 4.8, 2.0 Hz, 1H), 7.71 (d, J = 8.7 Hz, 1H), 7.56 (dd, J = 19.1, 6.1 Hz, 2H), 7.48 (d, J = 8.9 Hz, 2H), 7.32 (d, J = 8.8 Hz, 1H), 7.26 (dd, J = 7.6, 4.8 Hz, 1H), 4.27 (s, 1H), 3.21 (d, J = 12.5 Hz, 1H), 2.96 - 2.75 (m, 2H), 2.25 (s, 3H), 2.19 (s, 3H), 2.09 - 1.98 (m, 2H), 1.95 - 1.86 (m, 1H), 1.82 - 1.55 (m, 2H), 0.93 - 0.77 (m, 4H).

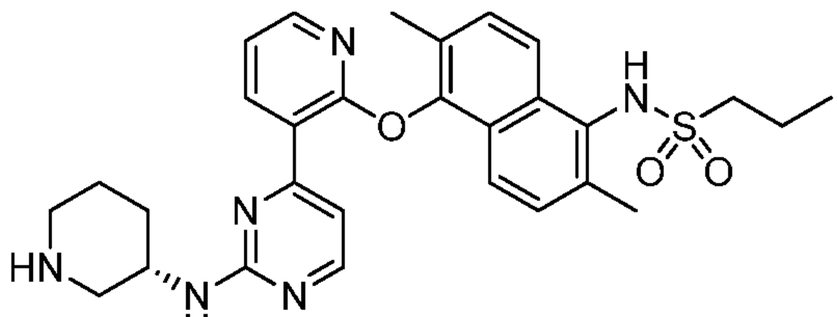
Example 285 *(S)-N-(2,6-Dimethyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)Naphthalen-1-yl)propane-1-sulfonamide* ***285***

[1019] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((2,6-dimethyl-5-(propylsulfoNamido)Naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[1020] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-2,6-dimethylNaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (32 mg, 0.059 mmol), pyridine (0.072 mL), DCM (0.5 mL), and 1-propanesulfonyl chloride (17 mg, 0.12 mmol). After 4 h, a further portion of 1-propanesulfonyl chloride (84 mg, 0.59 mmol) was added. After 72 h, the mixture was diluted with DCM and washed with saturated $NaHCO_3$(aq), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude was purified by flash chromatography through silica gel (15 – 80% EtOAc/hexanes) to provide 17 mg (44% yield) of the title compound. LCMS (ESI) $[M+H]^+ = 647.6$, rt = 1.94 min.

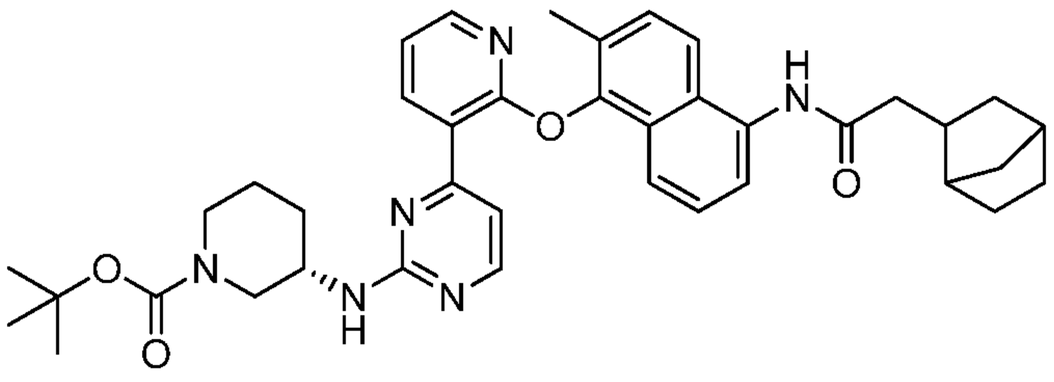
[1021] Step 2: (*S*)-*N*-(2,6-Dimethyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)Naphthalen-1-yl)propane-1-sulfonamide



[1022] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((2,6-dimethyl-5-(propylsulfoNamido)Naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (17 mg, 0.026 mmol), 1,4-dioxane (0.3 mL), and hydrochloric acid (4 M in dioxane, 0.2 mL, 8 mmol). After 3 h, the mixture was diluted with Et_2O and the resulting solids filtered and washed with Et_2O. The collected solids were dissolved in H_2O and MeCN and lyophilized to provide 13 mg (82% yield) of **285**. LCMS (ESI) $[M+H]^+$ = 547.4, rt = 1.38 min; ^1H NMR (400 MHz, dmso) δ 9.38 (s, 1H), 8.75 (br.s, 3H), 8.47 (d, J = 5.2 Hz, 1H), 8.10 – 7.99 (m, 2H), 7.57 (d, J = 5.1 Hz, 2H), 7.53 (d, J = 8.9 Hz, 3H), 7.35 (d, J = 8.8 Hz, 1H), 7.27 (dd, J = 7.6, 4.8 Hz, 1H), 4.25 (s, 1H), 3.26 – 3.09 (m, 3H), 3.00 – 2.74 (m, 2H), 2.48 (s, 4H), 2.19 (s, 3H), 2.01 (d, J = 12.2 Hz, 1H), 1.97 – 1.78 (m, 3H), 1.78 – 1.56 (m, 2H), 1.03 (t, J = 7.4 Hz, 3H).

Example 286 *2-(Bicyclo[2.2.1]heptan-2-yl)-N-(6-methyl-5-((3-(2-((S)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)acetamide* ***286***

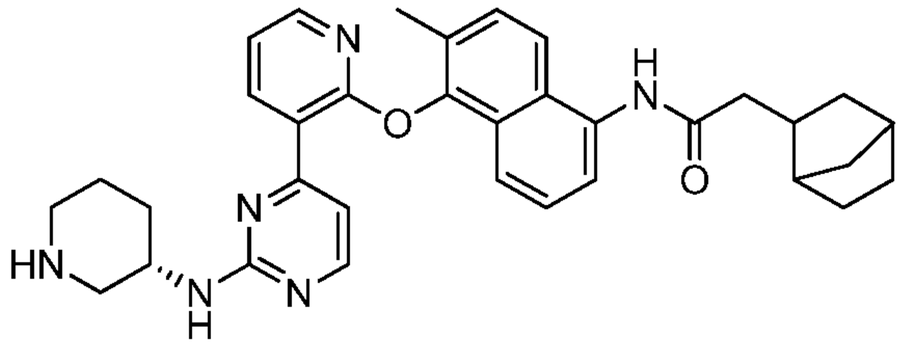
[1023] Step 1: (3*S*)-*tert*-Butyl 3-((4-(2-((5-(2-(bicyclo[2.2.1]heptan-2-yl)acetamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[1024] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (200 mg, 0.38 mmol), 2-norbornaneacetic acid (146 mg, 0.95 mmol), HATU (289 mg, 0.76 mmol), DMF (2 mL) in that order. Triethylamine (154 mg, 1.52 mmol) was then added and after 16 h, the mixture was diluted with ethyl acetate (50 mL) and washed with saturated sodium bicarbonate (10mL) then 50% brine/water (4 x 10mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography through silica gel (0 - 100% EtOAc/hexanes) to

provide 161 mg (64% yield) of the title compound. LCMS (ESI) $[M+H]^+$ = 663.3, rt = 2.10 min.

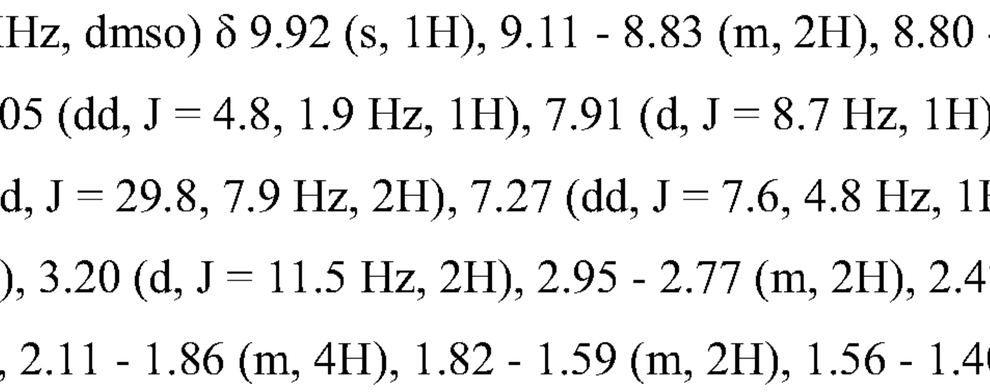
[1025] Step 2: 2-(Bicyclo[2.2.1]heptan-2-yl)-*N*-(6-methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)acetamide



[1026] Prepared using (3*S*)-*tert*-butyl 3-((4-(2-((5-(2-(bicyclo[2.2.1]heptan-2-yl)acetamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (150 mg, 0.226 mmol), EtOAc (6 mL), and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). After 4 h, the mixture was concentrated *in vacuo* and the crude HCl salt solid was washed with EtOAc (3 x 3 mL) then with MeCN (3 x 3 mL). The solid product was then sonicated and concentrated *in vacuo* with MeCN (3 x 3 mL) and the resulting solid was dissolved in H_2O and MeCN and lyophilized to provide 132 mg (97% yield) of **286** of uncharacterized stereochemistry as a light yellow solid. LCMS (ESI) $[M+H]^+$ = 563.3, rt = 1.52 min; ^1H NMR (400 MHz, dmso) δ 9.92 (s, 1H), 9.11 - 8.83 (m, 2H), 8.80 - 8.53 (m, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.05 (dd, J = 4.8, 1.9 Hz, 1H), 7.91 (d, J = 8.7 Hz, 1H), 7.56 (dt, J = 13.7, 8.1 Hz, 4H), 7.44 (dd, J = 29.8, 7.9 Hz, 2H), 7.27 (dd, J = 7.6, 4.8 Hz, 1H), 4.40 - 4.17 (m, 1H), 4.07 - 3.86 (m, 1H), 3.20 (d, J = 11.5 Hz, 2H), 2.95 - 2.77 (m, 2H), 2.47 - 2.29 (m, 2H), 2.24 (s, 1H), 2.21 (s, 3H), 2.11 - 1.86 (m, 4H), 1.82 - 1.59 (m, 2H), 1.56 - 1.40 (m, 4H), 1.27 - 1.11 (m, 4H).

Example 287 *(R)-2,2-Dimethyl-N-(6-methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide*

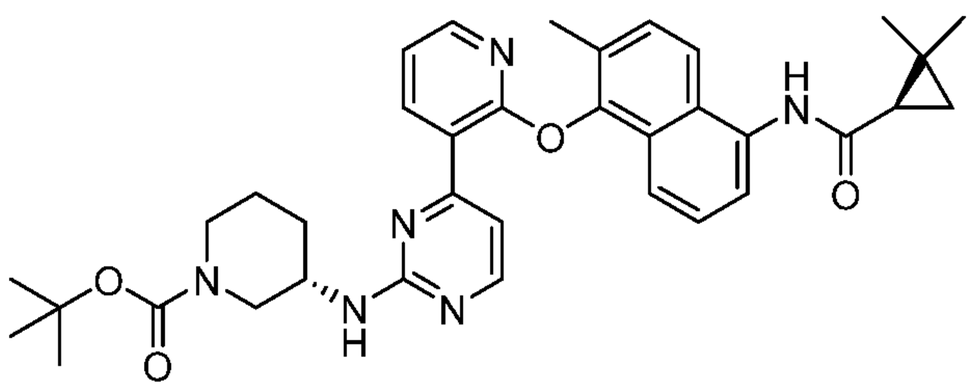
[1027] Step 1: (3*S*)-*tert*-Butyl 3-((4-(2-((5-(2,2-dimethylcyclopropanecarboxamido)-2-methylNaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate

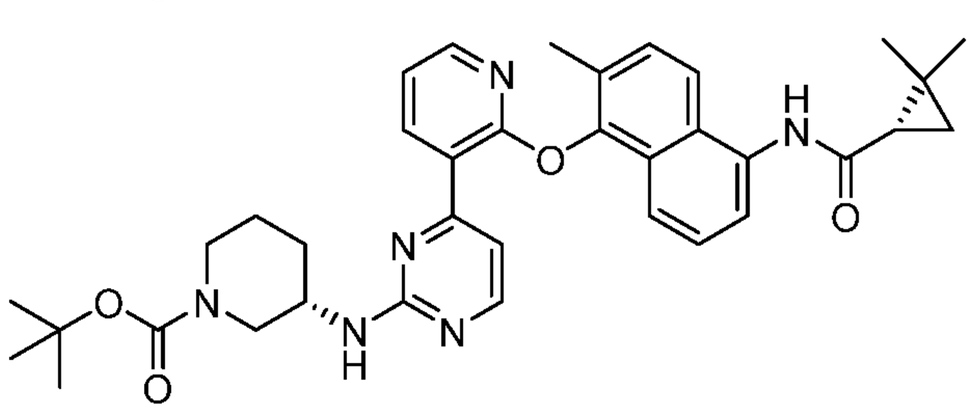


[1028] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (320 mg, 0.608 mmol),

triethylamine (0.85 mL, 6.08 mmol), HATU (1155 mg, 3.04 mmol), and 2,2-dimethylcyclopropanecarboxylic acid (345 mg, 3.04 mmol) in DMF (5 mL). After 16 h, the mixture was diluted with EtOAc (75 mL) and washed with saturated $NaHCO_3$(aq) (25 mL), then with water (10 mL) and 50% saturated NaCl(aq) (4 x 10mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography through silica gel (50 g, 0-100% EtOAc/hex) to provide 363 mg (96% yield) of the title compound as a tan solid. LCMS (ESI) $[M+H]^+$ = 623.3, rt = 1.98 min.

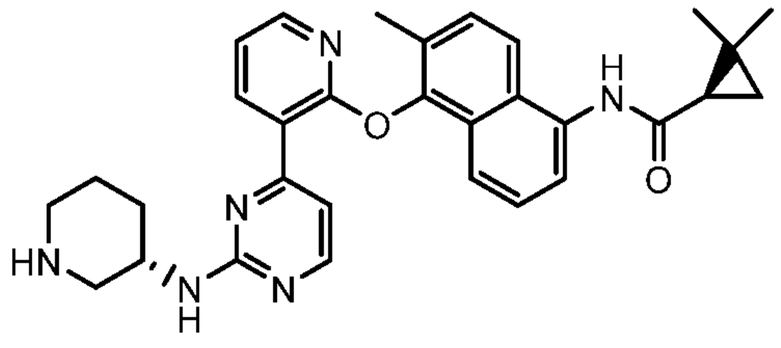
[1029] Step 2: *tert*-**b**utyl (*S*)-3-((4-(2-((5-((*R*)-2,2-dimethylcyclopropane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-1) and *tert*-butyl (*S*)-3-((4-(2-((5-((*S*)-2,2-dimethylcyclopropane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-2)





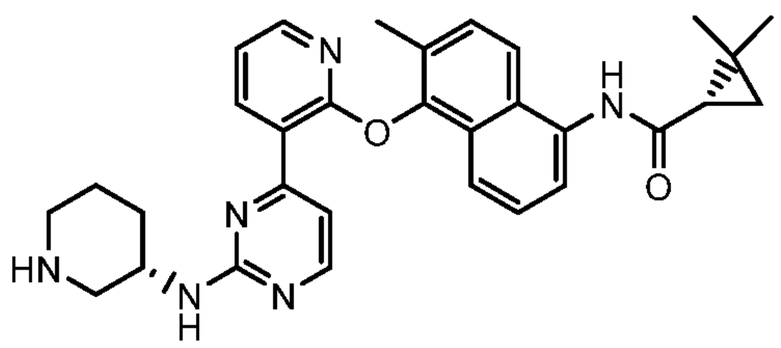
[1030] (3*S*)-*tert*-Butyl 3-((4-(2-((5-(2,2-dimethylcyclopropanecarboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (189 mg, 0.303 mmol), was subjected to chiral normal phase semi-prep purification (Conditions: Chiralpak IA, 5 uM, 20 x 250 mm, 1:10:89 MeOH:IPA:Hexane + 0.1 % DEA, 3.5mg/inj.) to provide two stereoisomers possessing stereocenters at the 1-cyclopropane position. Isomer-1, 58 mg, 31% yield, white solid, ee = 95%, rt = 21.7 min, LCMS (ESI) $[M+H]^+$ = 623.4, rt = 1.98 min. Isomer-2, 53 mg, 28% yield, white solid, ee = 97%, rt = 24.3 min, LCMS (ESI) $[M+H]^+$ = 623.4, rt = 1.98 min.

[1031] Step 3: (*R*)-2,2-Dimethyl-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide (isomer-1)



[1032] Prepared using *tert*-butyl (*S*)-3-((4-(2-((5-((*R*)-2,2-dimethylcyclopropane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-1) (58 mg, 0.093 mmol), EtOAc (5 mL), and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). After 4 h, the mixture was concentrated *in vacuo* and the crude solid was washed with EtOAc (3 x 3 mL) then with MeCN (3 x 3 mL). The solid product was then sonicated and concentrated *in vacuo* with MeCN (3 x 3 mL) then dissolved in H_2O and MeCN and lyophilized to provide 39 mg (75% yield) of **287** as a fluffy light yellow solid. The stereochemical assignments of **287** and **288** were randomly assigned and may be later determined. LCMS (ESI) [M+H]+ = 523.5, rt = 1.42 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 9.08 - 8.78 (m, 2H), 8.75 - 8.54 (m, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.05 (dd, J = 4.7, 1.8 Hz, 1H), 7.96 (d, J = 8.7 Hz, 1H), 7.68 - 7.49 (m, 4H), 7.43 (dd, J = 26.2, 8.0 Hz, 2H), 7.27 (dd, J = 7.5, 4.8 Hz, 1H), 4.40 - 4.12 (m, 1H), 3.21 (d, J = 11.2 Hz, 2H), 2.95 - 2.76 (m, 2H), 2.22 (s, 3H), 2.10 - 1.86 (m, 3H), 1.83 - 1.54 (m, 2H), 1.23 (s, 3H), 1.21 (s, 3H), 1.04 - 0.99 (m, 1H), 0.88 - 0.79 (m, 1H).

Example 288 *(S)-2,2-Dimethyl-N-(6-methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide* ***288***

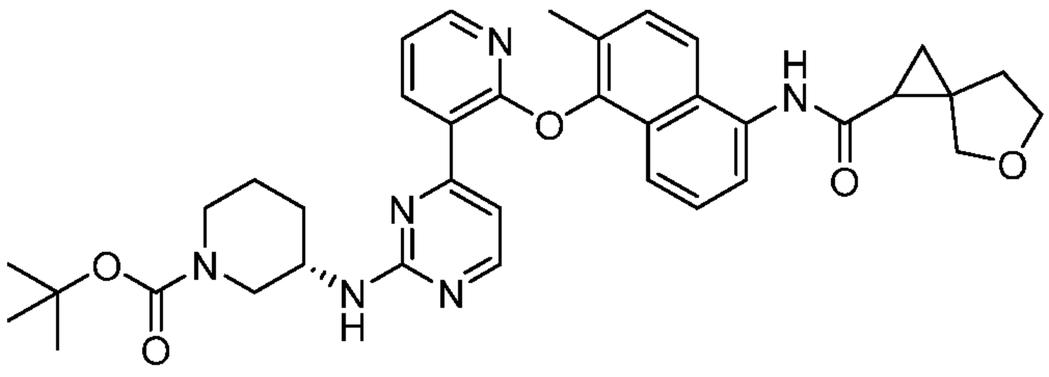


[1033] Prepared according to Example 287 using *tert*-butyl (*S*)-3-((4-(2-((5-((*S*)-2,2-dimethylcyclopropane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-2) (53 mg, 0.085 mmol), EtOAc (5 mL), and hydrochloric acid (4 M in dioxane, 2 mL, 8 mmol). After 4 h, the mixture was concentrated *in vacuo* and the crude solid was washed with EtOAc (3 x 3 mL) then with MeCN (3 x 3 mL). The solid product was sonicated and concentrated *in vacuo* with MeCN (3 x 3 mL) then dissolved in H_2O and MeCN and lyophilized to provide 35 mg (73% yield) of **288** as a fluffy light yellow solid. LCMS (ESI) $[M+H]^+$ = 523.5, rt = 1.42 min; ^{1}H NMR (400 MHz, DMSO-

d6) δ 10.11 (s, 1H), 9.05 - 8.78 (m, 2H), 8.76 - 8.52 (m, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.05 (dd, J = 4.7, 1.8 Hz, 1H), 7.96 (d, J = 8.7 Hz, 1H), 7.68 - 7.49 (m, 4H), 7.43 (dd, J = 26.1, 8.0 Hz, 2H), 7.27 (dd, J = 7.5, 4.8 Hz, 1H), 4.38 - 4.15 (m, 1H), 3.21 (d, J = 12.3 Hz, 2H), 2.96 - 2.76 (m, 2H), 2.22 (s, 3H), 2.08 - 1.86 (m, 3H), 1.82 - 1.56 (m, 2H), 1.23 (s, 3H), 1.21 (s, 3H), 1.04 - 0.99 (m, 1H), 0.90 - 0.78 (m, 1H).

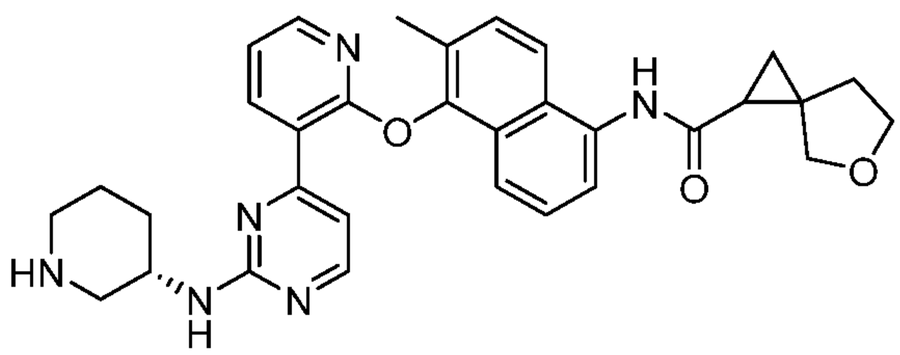
Example 289 *N-(6-Methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-5-oxaspiro[2.4]heptane-1-carboxamide* ***289***

[1034] Step 1: *tert*-Butyl (3*S*)-3-((4-(2-((2-methyl-5-(5-oxaspiro[2.4]heptane-1-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[1035] The General Procedure C was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (200 mg, 0.38 mmol), 5-oxaspiro[2.4]heptane-2-carboxylic acid (80.9 mg, 0.57 mmol), HATU (294.7 mg, 0.76 mmol), DMF (2 mL), and DIPEA (0.20 mL, 1.14 mmol). The crude material was purified by silica gel chromatography (12 g column), eluting with 0-5% MeOH/DCM to afford 250 mg (100% yield) of the title compound as a yellow solid and as a mixture of isomers. LCMS (ESI) $[M+H]^+ = 651$.

[1036] Step 2: *N*-(6-Methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-5-oxaspiro[2.4]heptane-1-carboxamide

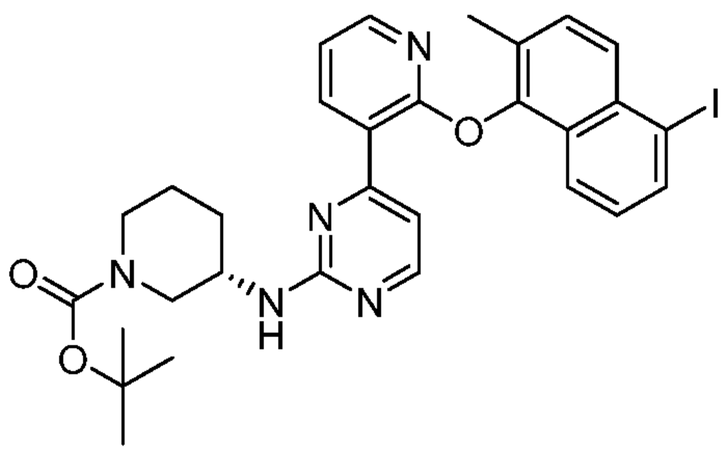


[1037] The General Procedure B was followed, using *tert*-butyl (3*S*)-3-((4-(2-((2-methyl-5-(5-oxaspiro[2.4]heptane-1-carboxamido)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (250 mg, 0.38 mmol). The crude product was lyophilized to yield 108 mg (51% yield) of **289** as an off-white solid and as a mixture of isomers. LCMS (ESI) $[M+H]^+ = 551$; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.19 (d, *J* = 9.8 Hz, 1H), 8.49 (d, *J* = 7.5 Hz, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.02 (dd, *J* = 4.8, 2.0 Hz, 1H), 7.95 (d, *J* = 8.7 Hz, 1H),

7.69 – 7.61 (m, 1H), 7.52 (t, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 5.1 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.25 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 3.94 – 3.80 (m, 2H), 3.70 (q, *J* = 9.2 Hz, 2H), 3.14 – 3.05 (m, 1H), 2.83 – 2.74 (m, 1H), 2.48 – 2.42 (m, 3H), 2.39 – 2.35 (m, 1H), 2.22 (s, 3H), 2.07 – 2.00 (m, 1H), 1.97 – 1.89 (m, 2H), 1.68 – 1.61 (m, 1H), 1.53 – 1.40 (m, 2H), 1.24 (d, *J* = 6.4 Hz, 2H).

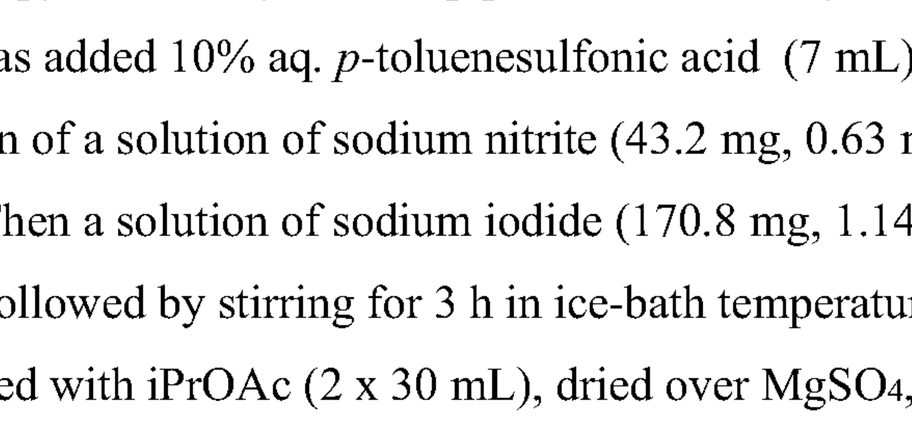
Example 290 *(S)-4-(2-((5-(4-Ethyl-1H-pyrazol-1-yl)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine* ***290***

[1038] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((5-iodo-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[1039] To a solution of *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (300 mg, 0.57 mmol) in acetonitrile (4 mL) was added 10% aq. *p*-toluenesulfonic acid (7 mL) in ice bath temperature followed by the addition of a solution of sodium nitrite (43.2 mg, 0.63 mmol) in water (0.5 mL), stirred for 30 min. Then a solution of sodium iodide (170.8 mg, 1.14 mmol) in water (1 mL) was added at once, followed by stirring for 3 h in ice-bath temperature. The mixture was diluted with water, extracted with iPrOAc (2 x 30 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo*, and dried under high vacuum to afford 310 mg (85% yield) of the title compound as a brown solid. It was carried on without further purification. LCMS (ESI) $[M+H]^+ = 638$.

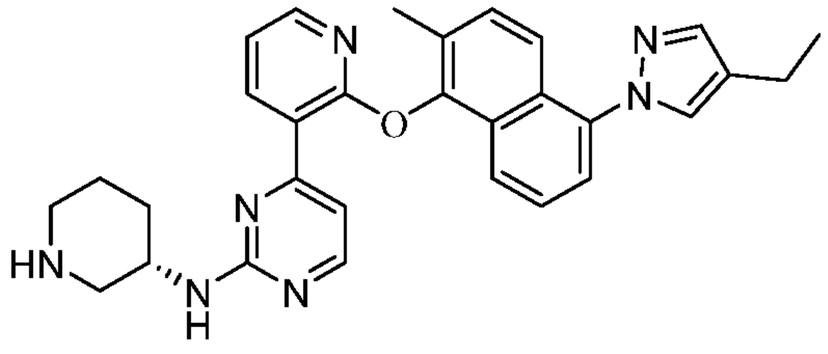
[1040] Step 2: *tert*-Butyl (*S*)-3-((4-(2-((5-(4-ethyl-1H-pyrazol-1-yl)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[1041] A mixture of *tert*-butyl (3*S*)-3-[[4-[2-[(5-iodo-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.16 mmol, 100 mass%), 4-ethyl-1H-pyrazole (30.1 mg, 0.32 mmol), CuI (11.9 mg, 0.063 mmol), (1*R*,2*R*)-*N*,*N*'-dimethyl-1,2-cyclohexanediamine (11.4 mg, 0.078 mmol), and K_2CO_3 (65.0 mg, 0.47 mmol) in 1,4-dioxane (2 mL) was capped in a microwave vial, degassed with N_2, heated in oil bath at 110 °C for 48 h.

[1042] More reagents were added and heated for another of 48 h. It was diluted with iPrOAc, filtered through Celite. The crude product was purified by silica gel chromatography (12 g column), eluting with 0-5% MeOH/DCM to afford 18 mg (18.9% yield) of the title compound as a brown solid. LCMS (ESI) $[M+H]^+ = 606$.

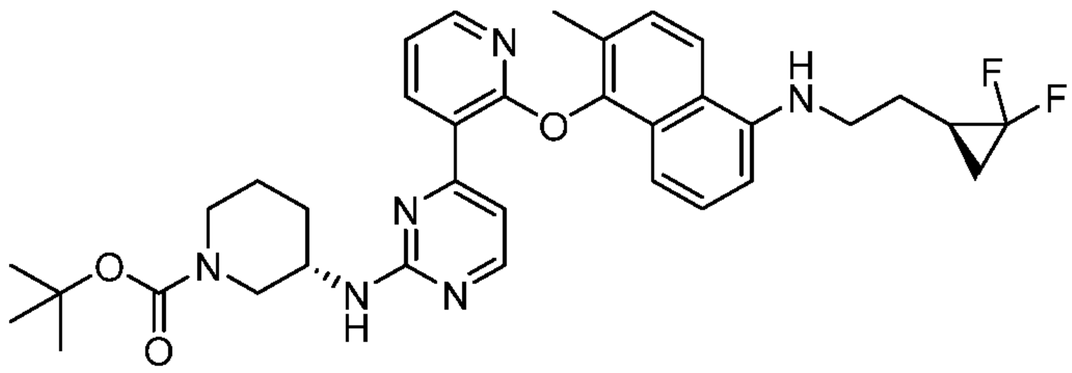
[1043] Step 3: (*S*)-4-(2-((5-(4-Ethyl-1H-pyrazol-1-yl)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-2-amine



[1044] The General Procedure B was followed, using *tert*-Butyl (*S*)-3-((4-(2-((5-(4-ethyl-1H-pyrazol-1-yl)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (18 mg, 0.03 mmol). The crude product was lyophilized to yield 14 mg (86.9% yield) of **290** as a brown solid. LCMS (ESI) $[M+H]^+ = 506$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 – 8.58 (m, 4H), 8.50 (d, J = 5.2 Hz, 1H), 8.08 (dd, J = 4.8, 2.0 Hz, 1H), 8.01 – 7.99 (m, 1H), 7.77 – 7.70 (m, 3H), 7.60 (d, J = 5.2 Hz, 1H), 7.56 – 7.49 (m, 4H), 7.29 (dd, J = 7.6, 4.8 Hz, 1H), 4.33 – 4.21 (m, 1H), 3.26 – 3.19 (m, 1H), 2.93 – 2.81 (m, 3H), 2.59 (q, J = 7.6 Hz, 2H), 2.23 (s, 3H), 2.06 – 1.99 (m, 1H), 1.97 – 1.89 (m, 1H), 1.80 – 1.59 (m, 2H), 1.26 (t, J = 7.6 Hz, 3H).

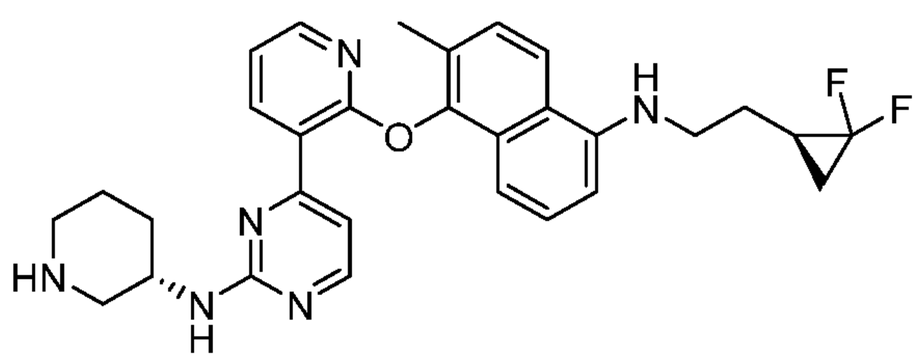
Example 291 *4-(2-((5-((2-((R)-2,2-Difluorocyclopropyl)ethyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-N-((S)-piperidin-3-yl)pyrimidin-2-amine* ***291***

[1045] Step 1: *tert*-butyl (*S*)-3-((4-(2-((5-((2-((*R*)-2,2-Difluorocyclopropyl)ethyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



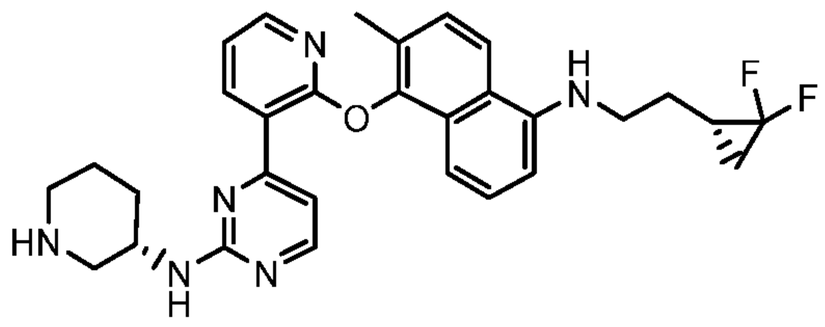
[1046] The General Procedure E was followed, using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (200 mg, 0.38 mmol) and 2-(2-bromoethyl)-1,1-difluorocyclopropane (144.9 mg, 0.76 mmol). The crude material was purified by silica gel chromatogarphy (12 g column), eluting with 0-5% MeOH/DCM to afford 79 mg (33% yield) of the title compound as a brown oil. LCMS (ESI) $[M+H]^+$ = 631. The isomers were separated by chiral SFC to afford 17 mg isomer-1 (t_R= 0.698 min) as an off-white solid and 17.5 mg isomer-2 (t_R= 0.839 min) as an off-white solid.

[1047] Step 2: 4-(2-((5-((2-((*R*)-2,2-Difluorocyclopropyl)ethyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-*N*-((*S*)-piperidin-3-yl)pyrimidin-2-amine



[1048] The General Procedure B was followed, using tert-butyl (*S*)-3-((4-(2-((5-((2-((*R*)-2,2-difluorocyclopropyl)ethyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-1, 17 mg, 0.03 mmol). The crude product was lyophilized to yield 15 mg (95.5% yield) of **291** as a brown solid. The stereochemical assignments of **291** and **292** were randomly assigned and may be later determined. LCMS (ESI) $[M+H]^+$ = 531; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03 – 8.54 (m, 4H), 8.47 (d, J = 5.2 Hz, 1H), 8.06 – 8.00 (m, 2H), 7.59 (d, J = 5.1 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.39 – 7.33 (m, 1H), 7.24 (dd, J = 7.6, 4.8 Hz, 1H), 7.18 (dd, J = 8.4, 7.7 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.50 (d, J = 7.7 Hz, 1H), 4.36 – 4.20 (m, 1H), 3.31 (dd, J = 7.5, 5.8 Hz, 2H), 3.25 – 3.17 (m, 1H), 2.92 – 2.77 (m, 3H), 2.19 (s, 3H), 2.06 – 1.97 (m, 1H), 1.97 – 1.72 (m, 5H), 1.69 – 1.50 (m, 2H), 1.25 – 1.16 (m, 1H).

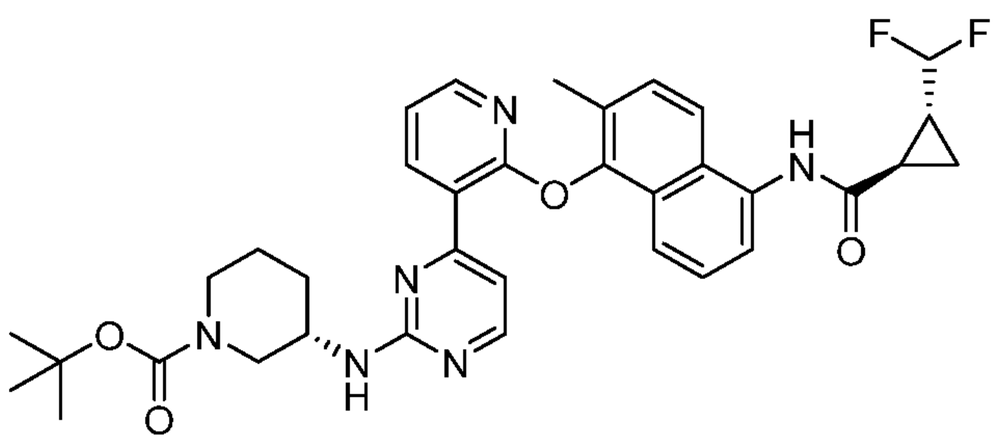
Example 292 *4-(2-((5-((2-((S)-2,2-Difluorocyclopropyl)ethyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-N-((S)-piperidin-3-yl)pyrimidin-2-amine* ***292***



[1049] Following Example 291 and General Procedure B, *tert*-butyl (*S*)-3-((4-(2-((5-((2-((*S*)-2,2-difluorocyclopropyl)ethyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-2, 17.5 mg, 0.03 mmol) was deprotected. The crude product was lyophilized to yield 15 mg (95% yield) of **292** as a brown solid. LCMS (ESI) $[M+H]^+ = 531$; ^1H NMR (400 MHz, DMSO-d_6) δ 8.97 – 8.51 (m, 4H), 8.47 (d, $J = 5.2$ Hz, 1H), 8.06 – 8.00 (m, 2H), 7.58 (d, $J = 4.8$ Hz, 1H), 7.53 (d, $J = 7.5$ Hz, 1H), 7.35 (d, $J = 8.7$ Hz, 1H), 7.24 (dd, $J = 7.6$, 4.8 Hz, 1H), 7.18 (dd, $J = 8.4$, 7.6 Hz, 1H), 6.84 (d, $J = 8.4$ Hz, 1H), 6.49 (d, $J = 7.9$ Hz, 1H), 4.34 – 4.21 (m, 1H), 3.34 – 3.27 (m, 2H), 3.21 (d, $J = 12.2$ Hz, 1H), 2.93 – 2.79 (m, 3H), 2.19 (s, 3H), 2.06 – 1.99 (m, 1H), 1.96 – 1.71 (m, 6H), 1.69 – 1.49 (m, 1H), 1.25 – 1.15 (m, 1H).

Example 293 *(1R,2R)-2-(Difluoromethyl)-N-(6-methyl-5-((3-(2-(((S)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide* ***293***

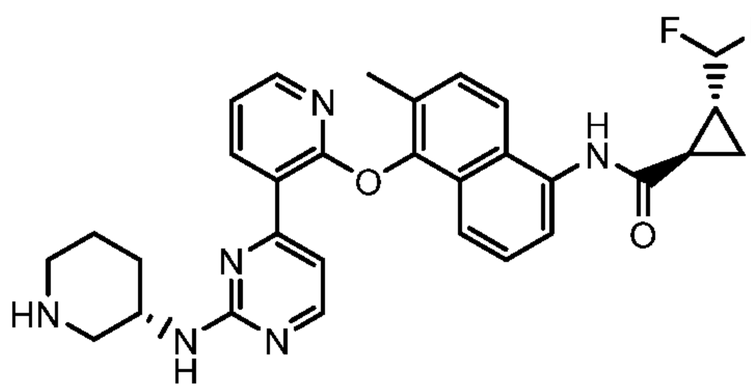
[1050] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((5-((1*R*,2*R*)-2-(difluoromethyl)cyclopropane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[1051] The General Procedure C was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate from Example 101 (90 mg, 0.17 mmol), 2-(difluoromethyl)cyclopropane-1-carboxylic acid (35 mg, 0.26 mmol), DIPEA (0.089 mL, 0.51 mmol), HATU (97 mg, 0.26 mmol) and DCM (1.7 mL). The residue was purified *via* reverse-phase HPLC to provide a mixture of the two isomers.

This mixture was then purified *via* chiral reverse-phase HPLC and lyophilized to yield 44 mg and 43 mg, of the two single stereoisomers at the 1 and 2 positions of the cyclopropyl amide.

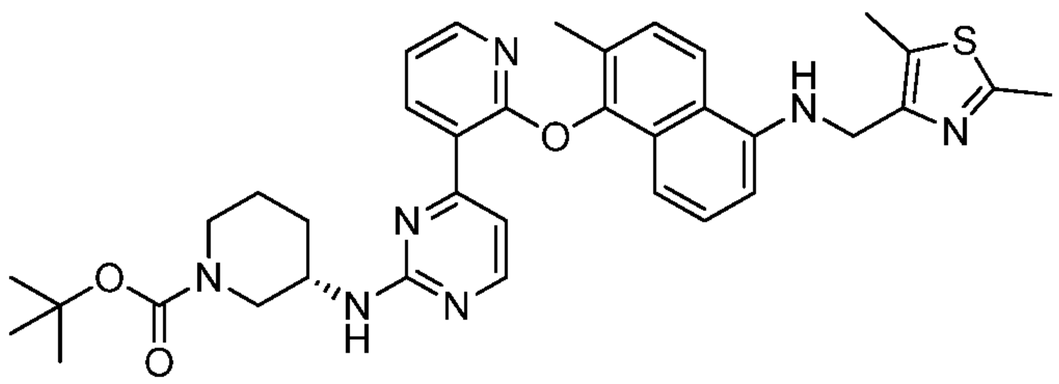
[1052] Step 2: (1*R*,2*R*)-2-(Difluoromethyl)-*N*-(6-methyl-5-((3-(2-(((*S*)-piperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)cyclopropane-1-carboxamide



[1053] The General Procedure B was followed, using *tert*-butyl (*S*)-3-((4-(2-((5-((1R,2R)-2-(difluoromethyl)cyclopropane-1-carboxamido)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (43 mg, 0.067 mmol), DCM (4 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). The residue was purified via reverse-phase HPLC and lyophilized to yield 25 mg (70% yield) of **293**. LCMS (ESI): $[M+H]^+$ = 545.2;^{1}H NMR (400 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.94 – 9.68 (m, 2H), 8.48 (d, J = 5.2 Hz, 1H), 8.06 (dd, J = 4.8, 2.0 Hz, 1H), 7.97 (d, J = 8.7 Hz, 1H), 7.68 (d, J = 7.4 Hz, 1H), 7.59 – 7.48 (m, 5H), 7.40 (dd, J = 8.5, 7.4 Hz, 1H), 7.27 (dd, J = 7.6, 4.8 Hz, 1H), 6.22 – 5.92 (m, 1H), 4.27 (s, 1H), 3.24 – 3.17 (m, 1H), 2.93 – 2.79 (m, 2H), 2.47 – 2.38 (m, 2H), 2.22 (s, 3H), 2.07 – 1.98 (m, 1H), 1.97 – 1.82 (m, 2H), 1.84 – 1.57 (m, 2H), 1.24 – 1.16 (m, 2H).

Example 294 *(S)-4-(2-((5-(((2,5-Dimethylthiazol-4-yl)methyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine* ***294***

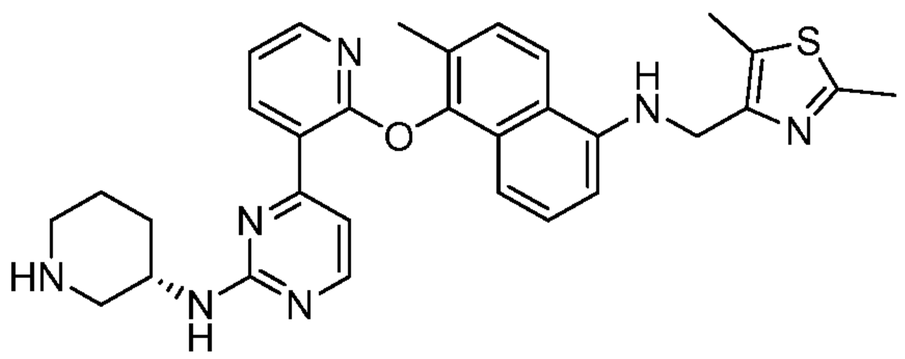
[1054] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-(((2,5-dimethylthiazol-4-yl)methyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[1055] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (100 mg, 0.19 mmol), 1-thiazol-4-ylethanone (241 mg, 1.90 mmol), DCM (1 mL), acetic acid (0.016 mL, 0.28 mmol), and sodium triacetoxyborohydride (60 mg, 0.28 mmol). After 72 h, a further portion of sodium triacetoxyborohydride (60 mg, 0.28 mmol) was added. After 16 h, a further portion of sodium

triacetoxyborohydride (60 mg, 0.28 mmol) and acetic acid (0.016 mL, 0.28 mmol) was added. After another 16 h, the mixture was diluted with water, followed by EtOAc. The phases were separated, and the organic phase was washed with saturated aqueous ammonium chloride solution, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude was purified by flash chromatography through silica gel (0-100% EtOAc/DCM) to provide 101 mg (83% yield) of the title compound as a pale brown oil. LCMS (ESI) $[M+H]^+$ = 638.3, rt = 1.98 min.

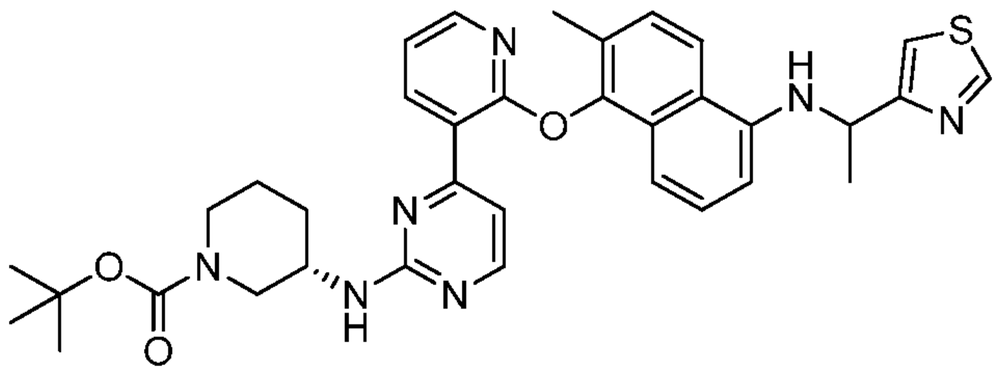
[1056] Step 2: (*S*)-4-(2-((5-(((2,5-Dimethylthiazol-4-yl)methyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-2-amine



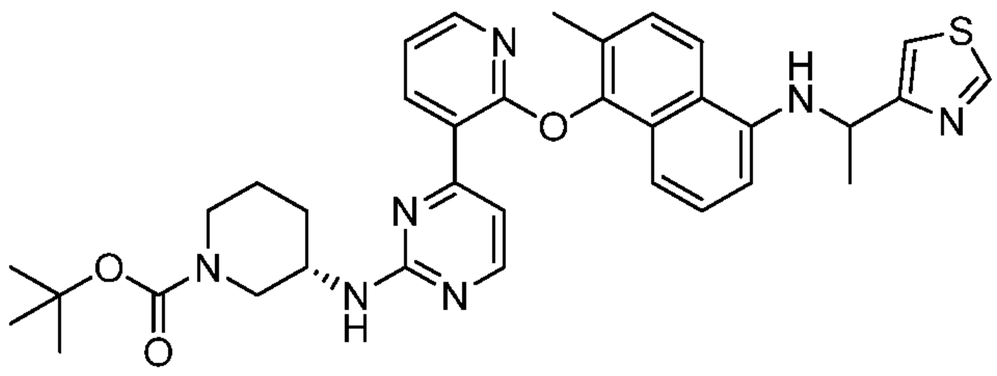
[1057] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-(((2,5-dimethylthiazol-4-yl)methyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (92 mg, 0.14 mmol), EtOAc (1 mL), and hydrochloric acid (4 M in dioxane, 1 mL, 4 mmol). After 3 h, the resulting solids were collected by filtration, washed with DCM, then dissolved in H_2O and lyophilized to provide 81 mg (97% yield) of **294** as an orange solid. LCMS (ESI) $[M+H]^+$ = 552.3, rt = 1.49 min; ^1H NMR (400 MHz, DMSO-d_6) [NH signal hidden under HOD peak] δ 9.44 (s, 1H), 9.19 (s, 1H), 8.81 (s, 1H), 8.49 (d, J = 5.5 Hz, 1H), 8.11 - 8.02 (m, 2H), 7.95 (br s, 1H), 7.68 (br s, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.25 (dd, J = 7.6, 4.8 Hz, 1H), 7.21 - 7.13 (m, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.58 (d, J = 7.6 Hz, 1H), 4.48 (s, 3H), 3.42 (d, J = 8.5 Hz, 1H), 3.19 (d, J = 12.0 Hz, 1H), 2.91 - 2.77 (m, 2H), 2.66 (s, 3H), 2.44 (s, 3H), 2.19 (s, 3H), 2.02 (d, J = 8.9 Hz, 1H), 1.97 - 1.86 (m, 1H), 1.79 (q, J = 10.4 Hz, 1H), 1.65 (q, J = 9.0 Hz, 1H).

Example 295 *4-(2-((2-Methyl-5-((1-(thiazol-4-yl)ethyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)-N-((S)-piperidin-3-yl)pyrimidin-2-amine* ***295***

[1058] Step 1: (3*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-5-((1-(thiazol-4-yl)ethyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



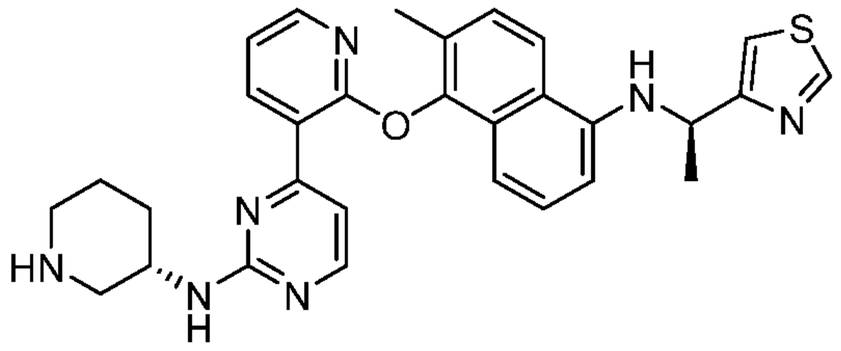
[1059] Prepared using (*S*)-*tert*-butyl 3-((4-(2-((5-amino-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (150 mg, 0.280 mmol), cesium carbonate (310 mg, 0.95 mmol), tetrabutylammonium iodide (11 mg, 0.030 mmol), 4-(chloromethyl)-2,5-dimethyl-thiazole (113 mg, 0.57 mmol), and DMF (1.5 mL). The mixture was stirred at 50 °C for 16h, cooled to room temperature and was dissolved in EtOAc and water. The phases were separated and the organic phase was washed with water, then brine, followed by a solution of aqueous saturated ammonium chloride. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography through silica gel (0-10% MeOH/DCM) followed by C18 reverse phase flash chromatography (40-90% % MeCN/10 mM aqueous ammonium formate, pH 3.8). The appropriate fractions were combined and concentrated *in vacuo* to provide 92 mg (50% yield) of the title compound as an off-white solid. LCMS (ESI) $[M+H]^+ = 652.4$, rt = 2.08 min. (3*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-5-((1-(thiazol-4-yl)ethyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-1) and (3*S*)-*tert*-butyl 3-((4-(2-((2-methyl-5-((1-(thiazol-4-yl)ethyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-2)



[1060] (3*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-5-((1-(thiazol-4-yl)ethyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (87 mg, 0.14 mmol) was subjected to chiral SFC purification (Conditions: Column IB 10 x 250 mm, 5um Isocratic 55% MeOH, 10 mL/min, 100 Bar, Column temp: 35 °C, Run Time (min): 8.00, Injection Volume (uL): 30, Wavelenght (nm): 240 nm) to provide two stereoisomers enantiomeric at the 1-(thiazol-4-yl)ethyl)amino position: (3*S*)-*tert*-butyl 3-((4-(2-((2-methyl-5-((1-(thiazol-4-yl)ethyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-1), 32 mg (37% yield), ee = 98.9%, rt = 4.2 min, (ESI) $[M+H]^+ = 638.4$, rt

= 1.99 min. (3*S*)-*tert*-butyl 3-((4-(2-((2-methyl-5-((1-(thiazol-4-yl)ethyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-2), 28 mg (32% yield), ee = 98.3%, rt = 5.7 min, LCMS (ESI) $[M+H]^+$ = 638.3, rt = 1.98 min.

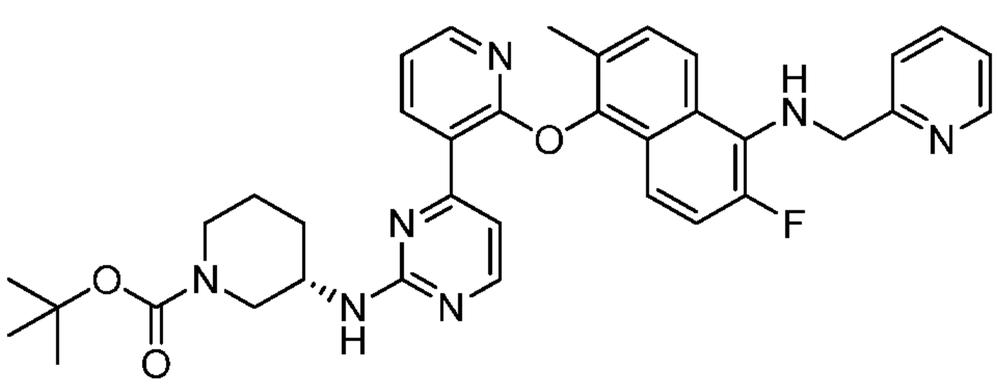
[1061] Step 2: 4-(2-((2-Methyl-5-((1-(thiazol-4-yl)ethyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)-*N*-((*S*)-piperidin-3-yl)pyrimidin-2-amine



[1062] Prepared using (3*S*)-*tert*-butyl 3-((4-(2-((2-methyl-5-((1-(thiazol-4-yl)ethyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (isomer-2) (28 mg, 0.040 mmol), EtOAc (1 mL), and hydrochloric acid (4 M in dioxane, 0.44 mL, 1.75 mmol). After 3 h, the resulting solids were collected by filtration, washed using DCM, then dissolved in H_2O and lyophilized to provide 22 mg (87% yield) of **295** as a brown solid. LCMS (ESI) $[M+H]^+$ = 538.2, rt = 1.41 min; ^1H NMR (400 MHz, DMSO-*d*$_6$) [NH signal hidden under HOD peak] δ 9.22 (br s, 1H), 9.07 (s, 1H), 9.05 (br m, 1H), 8.73 (br s, 1H), 8.47 (s, 1H), 8.22 (d, J = 8.2 Hz, 1H), 8.04 (s, 1H), 7.78 (br s, 1H), 7.62 (br s, 1H), 7.45 (s, 1H), 7.40 (d, J = 8.5 Hz, 1H), 7.24 (s, 1H), 7.08 (t, J = 7.4 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 6.42 (s, 1H), 4.96 (q, J = 6.6 Hz, 1H), 4.35 (s, 1H), 3.43 (d, J = 9.9 Hz, 1H), 3.19 (d, J = 11.0 Hz, 1H), 2.89 - 2.77 (m, 2H), 2.19 (s, 3H), 2.01 (d, J = 12.1 Hz, 1H), 1.91 (d, J = 13.2 Hz, 1H), 1.76 (q, J = 10.1 Hz, 1H), 1.67 (d, J = 6.5 Hz, 4H). The absolute stereochemistry of the methyl was randomly assigned.

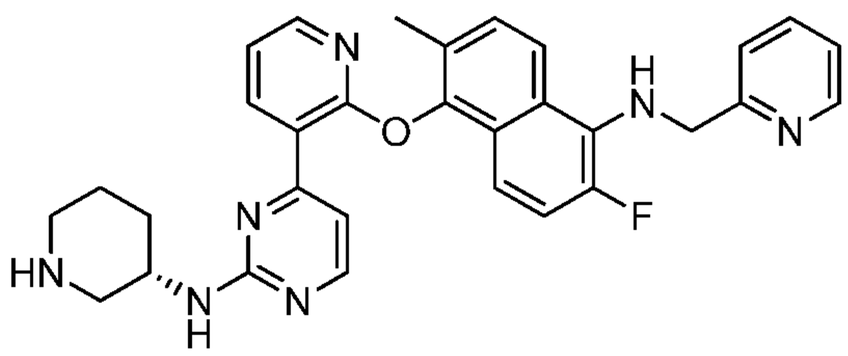
Example 296 *(S)-4-(2-((6-Fluoro-2-methyl-5-((pyridin-2-ylmethyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine* ***296***

[1063] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((6-fluoro-2-methyl-5-((pyridin-2-ylmethyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[1064] Prepared using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (80 mg, 0.15 mmol), 2-pyridine carboxaldehyde (79 mg, 0.73 mmol), acetic acid (25 µL, 0.44 mmol), sodium triacetoxyborohydride (92 mg, 0.44 mmol) in DCM (1 mL). After 18 h at rt, the reaction was still not complete and more sodium triacetoxyborohydride (92 mg, 0.44 mmol) and acetic acid (25 µL, 0.44 mmol) were added and followed by continued stirring at rt. After 5 h, the reaction mixture was diluted with DCM (50 mL), washed with saturated $NaHCO_3$ (aq) (2 x 25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography through silica gel (0-100 EtOAc/Hexanes) to provide 15 mg (16% yield) of the title compound as a yellow wax. LCMS (ESI) $[M+H]^+$ = 636.7, rt = 1.99 min.

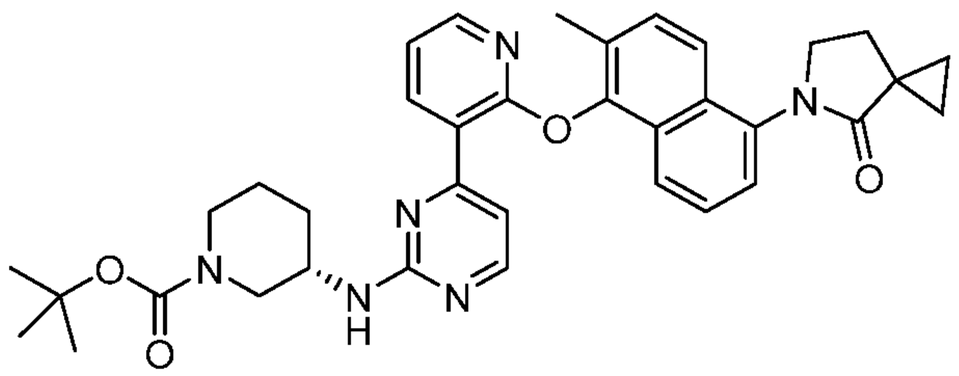
[1065] Step 2: (*S*)-4-(2-((6-Fluoro-2-methyl-5-((pyridin-2-ylmethyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)-*N*-(piperidin-3-yl)pyrimidin-2-amine



[1066] Prepared according to General Procedure B using (*S*)-*tert*-butyl 3-((4-(2-((6-fluoro-2-methyl-5-((pyridin-2-ylmethyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (15 mg, 0.02 mmol), EtOAc (1.0 mL), and hydrochloric acid (4 M in dioxane, 1.0 mL, 4.0 mmol). After 30 min, the volatiles were removed under vacuum. The residue was washed with EtOAc (3 x 3 mL) and MeCN (3 x 3 mL). The resulting solid was dissolved in water and MeCN and lyophilized to provide 13 mg (96% yield) of **296**. LCMS (ESI) [M+H]+ = 536.2, rt = 1.34 min; ^{1}H NMR (400 MHz, d6-dmso) δ 9.06 – 8.77 (m, 3H), 8.69 (d, J = 4.5 Hz, 1H), 8.66 – 8.51 (m, 1H), 8.46 (d, J = 5.2 Hz, 1H), 8.17 (d, J = 8.8 Hz, 2H), 8.05 (dd, J = 4.8, 1.9 Hz, 1H), 7.83 – 7.58 (m, 2H), 7.57 – 7.46 (m, 3H), 7.26 (dd, J = 7.6, 4.8 Hz, 1H), 7.15 (dd, J = 12.9, 9.2 Hz, 1H), 7.03 (dd, J = 9.1, 4.6 Hz, 1H), 4.85 (s, 2H), 4.38 – 4.14 (m, 1H), 3.20 (d, J = 11.8 Hz, 2H), 2.96 – 2.75 (m, 2H), 2.18 (s, 3H), 2.06 – 1.83 (m, 2H), 1.82 – 1.51 (m, 2H).

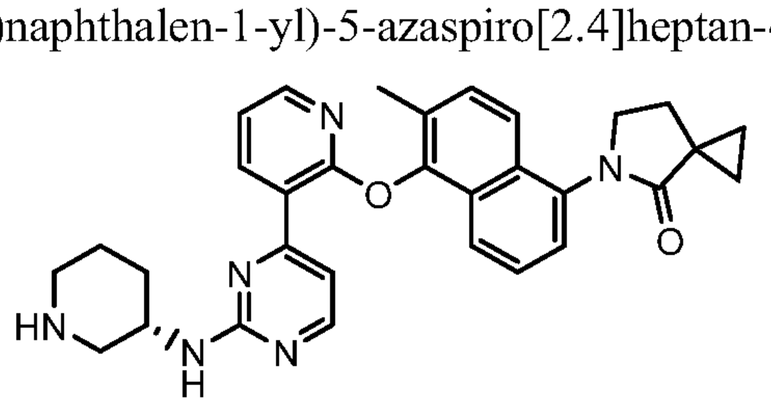
*<u>Example 297</u> (S)-5-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-5-azaspiro[2.4]heptan-4-one **297***

[1067] Step 1: *tert*-Butyl (*S*)-3-((4-(2-((2-methyl-5-(4-oxo-5-azaspiro[2.4]heptan-5-yl)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[1068] A flask containing *tert*-butyl (3S)-3-[[4-[2-[(5-iodo-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (100 mg, 0.157 mmol) was charged with 5-azaspiro[2.4]heptan-4-one (31 mg, 0.214 mmol), copper(I) iodide (6.0 mg, 0.0314 mmol), *N,N'*-dimethylethylenediamine (10 μL, 0.094 mmol), potassium carbonate (54 mg, 0.392 mmol) and 1,4 dioxane (3 mL). The mixture was sparged with nitrogen for 15 min and the flask was heated at reflux overnight. After 16 hours, the mixture was cooled to room temperature and the mixture was diluted with ethyl acetate and water and the phases were separated. The organic extract was washed with saturated NaCl(aq), dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified via reverse-phase HPLC and lyophilized to yield to yield 80 mg (82% yield). LCMS (ESI): $[M+H]^+ = 621.2$.

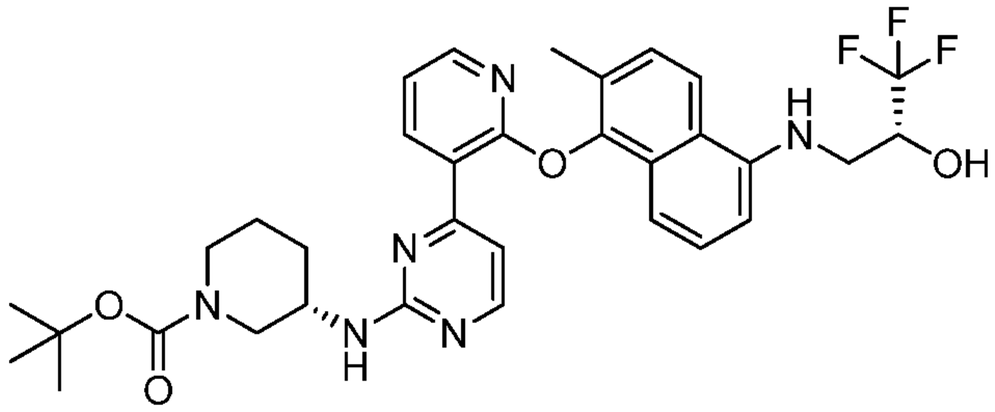
[1069] Step 2: (*S*)-5-(6-Methyl-5-((3-(2-(piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)-5-azaspiro[2.4]heptan-4-one hydrochloride



[1070] The General Procedure B was followed, *tert*-butyl (*S*)-3-((4-(2-((2-methyl-5-(4-oxo-5-azaspiro[2.4]heptan-5-yl)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (80 mg, 0.13 mmol), DCM (4 mL) and hydrochloric acid (4 M in dioxane, 3 mL, 12 mmol). After 3 h, the mixture was concentrated *in vacuo* and the crude solid was washed with ethyl acetate (3 x 3 mL) then with ACN (3 x 3 mL). The solid product was sonicated and concentrated *in vacuo* with ACN (3 x 3 mL) and then dissolved in water and acetonitrile. Lyophilization provided 58 mg (86% yield) of **297** as its hydrochloride salt. LCMS (ESI): $[M+H]^+ = 521.2$; ^{1}H-NMR : (400 MHz, DMSO-d_6) δ 9.05-8.87 (m, 2H), 8.74-8.54 (m,1H), 8.48 (d, J = 5.2 Hz, 1H), 8.09 (dd, J = 4.8, 2.0 Hz, 1H), 7.67-7.44 (m, 7H), 7.28 (dd, J = 7.6, 4.8 Hz, 1H), 4.33-4.22 (m, 1H), 3.98-3.87 (m, 2H), 3.52-3.45 (m, 1H), 3.24-3.15 (m, 1H), 2.92-2.79 (m, 2H), 2.39 (t, J = 7.1 Hz, 2H), 2.22 (s, 3H), 2.05-1.99 (m, 1H), 1.94-1.88 (m, 1H), 1.81-1.59 (m, 2H), 1.08- 0.91 (m, 4H).

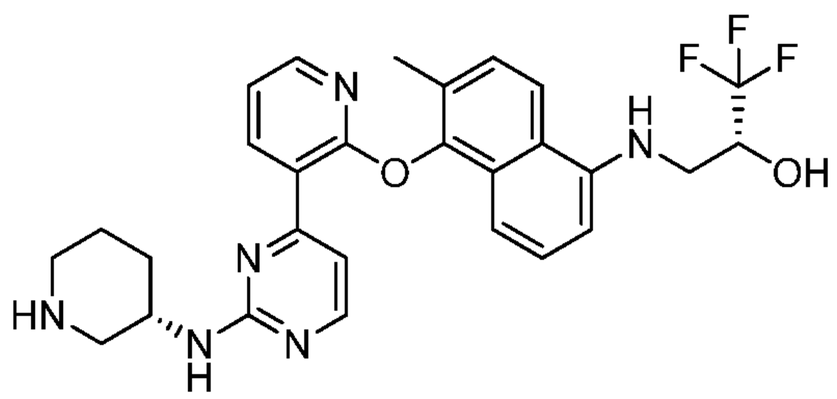
Example 298 *(R)-1,1,1-Trifluoro-3-((6-methyl-5-((3-(2-((S)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)propan-2-ol* ***298***

[1071] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-5-(((*R*)-3,3,3-trifluoro-2-hydroxypropyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[1072] Prepared using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (30 mg, 0.06 mmol), (2*R*)-2-(trifluoromethyl)oxirane (13 mg, 0.11 mmol) and acetic acid (0.30 mL) and heating at 75 °C. After 3 h, acetic acid was evaporated under vacuum. The residue was purified by prep TLC (MTBE (methyl t-butyl ether)/hexanes : 1/1). The product containing band was scratched off and stirred in EtOAc (20 mL) for 10 min. The mixture was filtered through celite and the solvent evaporated to provide 20 mg (55% yield) of the title compound. LCMS (ESI) $[M+H]^+$ = 639.7, rt = 1.97 min.

[1073] Step 2: (*R*)-1,1,1-Trifluoro-3-((6-methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)propan-2-ol

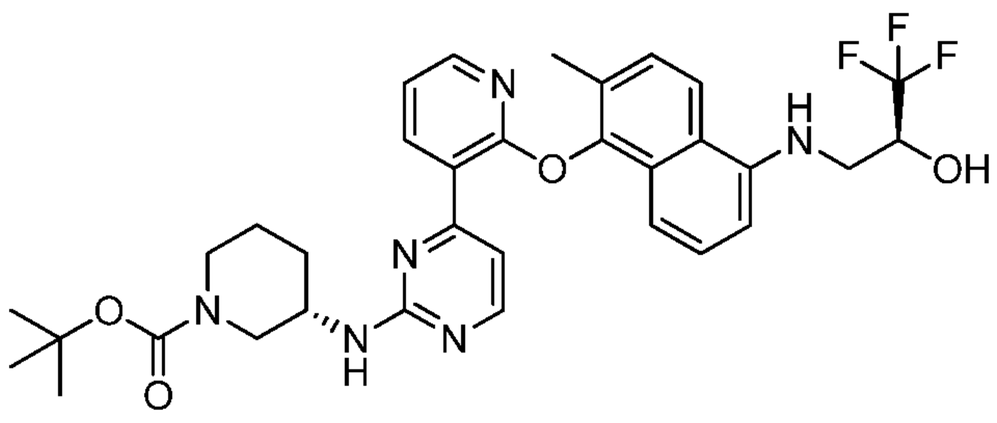


[1074] Prepared according to General Procedure B using (*S*)-*tert*-butyl 3-[[4-[2-[[2-methyl-5-[[(2*R*)-3,3,3-trifluoro-2-hydroxy-propyl]amino]-1-naphthyl]oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (20 mg, 0.03 mmol), 1,4-dioxane (1.0 mL), and hydrochloric acid (4 M in dioxane, 1.0 mL, 4.0 mmol). After 30 min, MTBE, methyl t-butyl ether (15 mL) was added to the suspension to further precipitate out the product. The suspension was stirred at rt overnight and the resulting solids collected by filtration and then dissolved in water and MeCN and lyophilized to provide 17 mg (94% yield) of **298**. LCMS (ESI) $[M+H]^+$ = 539.5, rt = 1.41 min; ^{1}H NMR (400 MHz, d6-DMSO) δ 8.75 (s, 1H), 8.45 (d,

J = 5.2 Hz, 1H), 8.04 – 7.96 (m, 2H), 7.59 – 7.47 (m, 2H), 7.36 (d, J = 9.0 Hz, 1H), 7.25 – 7.13 (m, 2H), 6.85 (d, J = 8.3 Hz, 1H), 6.47 (d, J = 7.5 Hz, 1H), 4.29 (s, 1H), 3.18 (s, 1H), 2.82 (s, 2H), 2.17 (s, 3H), 2.01 (m, 1H), 1.89 (s, 1H), 1.63 (s, 1H)

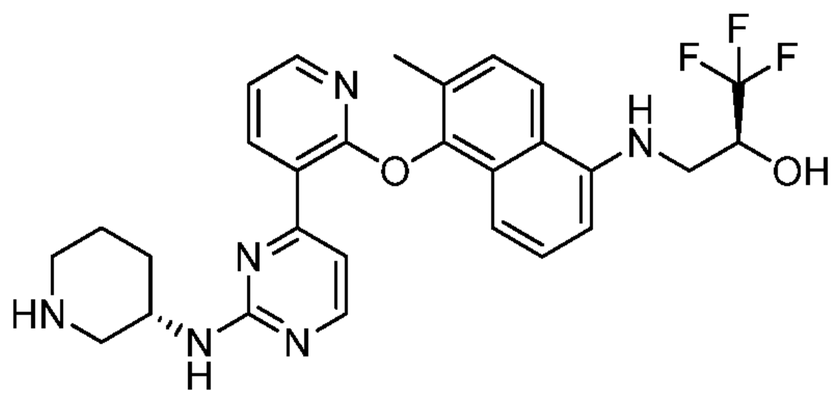
Example 299 *((S)-1,1,1-Trifluoro-3-((6-methyl-5-((3-(2-((S)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)propan-2-ol* ***299***

[1075] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((2-methyl-5-(((S)-3,3,3-trifluoro-2-hydroxypropyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[1076] Prepared using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (50 mg, 0.09 mmol), (2*S*)-2-(trifluoromethyl)oxirane (21 mg, 0.19 mmol), acetic acid (0.30 mL) and heating at 75 °C. After 3 h, acetic acid was evaporated under vacuum. The residue was purified by prep TLC (MTBE/Hexanes : 1/1). The product containing band was scratched off and stirred in EtOAc (20 mL) for 10 min. The mixture was filtered through celite and the solvent evaporated to provide 42 mg (69% yield) of the title compound. LCMS (ESI) $[M+H]^+$ = 639.7, rt = 1.97 min.

[1077] Step 2: ((*S*)-1,1,1-Trifluoro-3-((6-methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)propan-2-ol

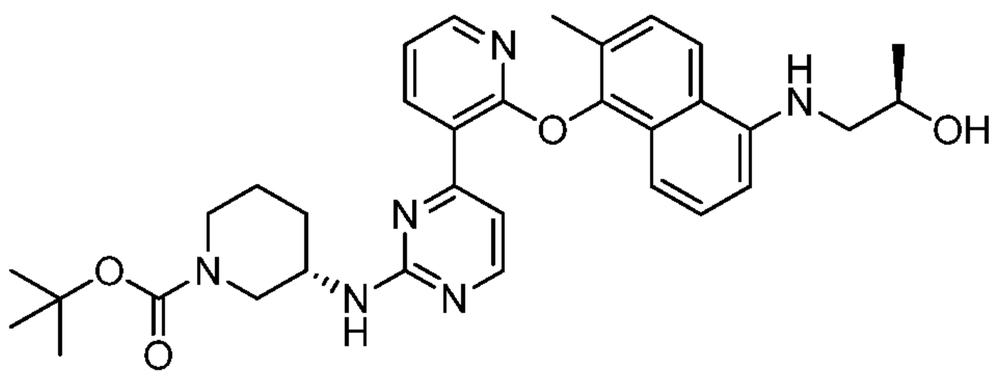


[1078] Prepared according to General Procedure B using (*S*)-*tert*-butyl 3-((4-(2-((2-methyl-5-(((*S*)-3,3,3-trifluoro-2-hydroxypropyl)amino)naphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (42 mg, 0.07 mmol), 1,4-dioxane (1.0 mL), and hydrochloric acid (4 M in dioxane, 1.0 mL, 4.0 mmol). After 30 min, MTBE (15 mL) was added to the suspension to further precipitate out the product and the suspension was stirred at

rt overnight. The resulting solids were collected by filtration and dissolved in water and MeCN and lyophilized to provide 35 mg (93% yield) of **299**. LCMS (ESI) $[M+H]^+$ = 539.5, rt = 1.41 min; ^{1}H NMR (400 MHz, *d*$_6$-DMSO) δ 9.06 (s, 2H), 8.46 (t, J = 5.2 Hz, 1H), 8.16 – 7.95 (m, 2H), 7.62 (s, 2H), 7.36 (d, J = 8.9 Hz, 1H), 7.27 – 7.15 (m, 2H), 6.86 (d, J = 8.4 Hz, 1H), 6.47 (d, J = 7.5 Hz, 1H), 3.55 (d, J = 14.1 Hz, 1H), 3.45 – 3.30 (m, 2H), 3.17 (s, 1H), 2.94 – 2.76 (m, 2H), 2.17 (s, 3H), 2.01 (s, 1H), 1.88 (s, 1H), 1.70 (d, J = 55.3 Hz, 2H).

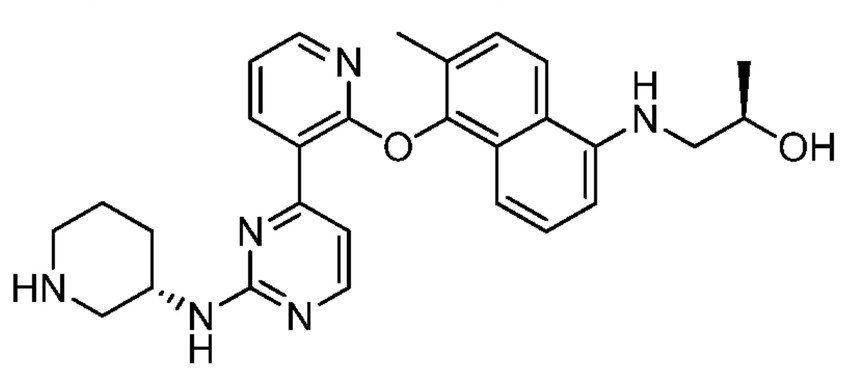
Example 300 *(R)-1-((6-Methyl-5-((3-(2-((S)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)propan-2-ol* ***300***

[1079] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-(((*R*)-2-hydroxypropyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[1080] Prepared using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (50 mg, 0.09 mmol), (*R*)-(+)-propylene oxide (0.01 mL, 0.09 mmol), acetic acid (0.30 mL) and stirring at rt. After 16 h, acetic acid was evaporated under vacuum. The residue was purified by flash chromatography through silica gel (EtOAc/Hexanes) to provide 25 mg (45% yield) of the title compound. LCMS (ESI) $[M+H]^+$ = 585.3, rt = 1.83 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.36 (d, J = 5.2 Hz, 1H), 8.04 (dd, J = 4.8, 2.0 Hz, 1H), 7.72 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.7 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.16 (d, J = 8.3 Hz, 1H), 7.08 (dd, J = 7.6, 4.8 Hz, 1H), 6.61 (dd, J = 29.6, 7.1 Hz, 1H), 5.35 (s, 1H), 4.18 (s, 1H), 3.58 (s, 1H), 3.42 – 3.36 (m, 1H), 3.15 (dd, J = 12.6, 8.6 Hz, 1H), 2.26 (s, 4H), 1.79 (s, 2H), 1.75 – 1.57 (m, 4H), 1.34 (d, J = 6.3 Hz, 4H).

[1081] Step 2: (((*R*)-1-((6-Methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)propan-2-ol

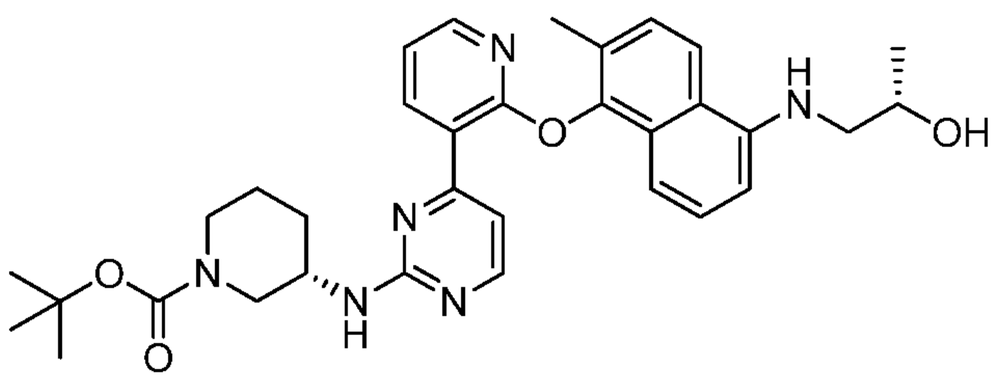


[1082] Prepared according to General Procedure B using (*S*)-*tert*-butyl 3-((4-(2-((5-(((*R*)-2-hydroxypropyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-

yl)amino)piperidine-1-carboxylate (43 mg, 0.070 mmol), 1,4-dioxane (1.0 mL), and hydrochloric acid (4 M in dioxane, 1.0 mL, 4.0 mmol). After 30 min, MTBE (15 mL) was added to the suspension to further precipitate out the product and the suspension was stirred at rt overnight. The resulting solids were collected by filtration, dissolved in water and MeCN and lyophilized to provide 35 mg (91% yield) of **300**. LCMS (ESI) $[M+H]^+$ = 485.5, rt = 1.25 min; ^{1}H NMR (400 MHz, d6-dmso) δ 9.04 (s, 2H), 8.46 (s, 1H), 8.02 (d, J = 8.8 Hz, 2H), 7.62 (s, 2H), 7.39 (d, J = 8.8 Hz, 1H), 7.23 (ddd, J = 16.0, 12.2, 6.9 Hz, 2H), 6.95 (d, J = 8.4 Hz, 1H), 6.67 (s, 1H), 3.99 (d, J = 6.0 Hz, 2H), 3.40 (s, 1H), 3.17 (s, 3H), 2.81 (d, J = 10.3 Hz, 2H), 2.18 (s, 3H), 2.01 (s, 1H), 1.88 (s, 1H), 1.70 (d, J = 52.3 Hz, 2H), 1.15 (d, J = 6.2 Hz, 3H).

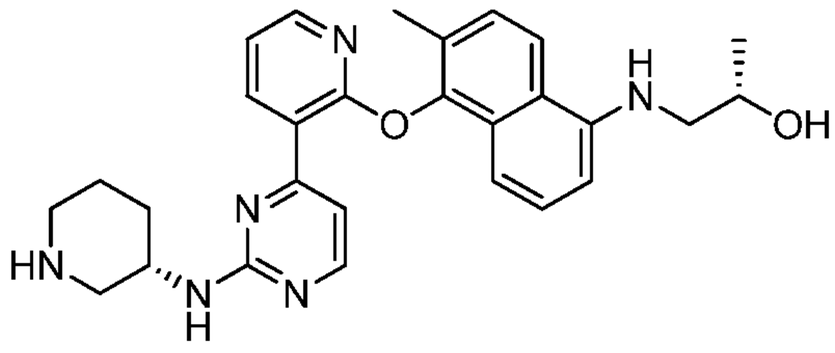
Example 301 *(S)-1-((6-Methyl-5-((3-(2-((S)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)propan-2-ol* ***301***

[1083] Step 1: (*S*)-*tert*-Butyl 3-((4-(2-((5-(((*S*)-2-hydroxypropyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate



[1084] Prepared using *tert*-butyl (3*S*)-3-[[4-[2-[(5-amino-2-methyl-1-naphthyl)oxy]-3-pyridyl]pyrimidin-2-yl]amino]piperidine-1-carboxylate (50 mg, 0.09 mmol), (*R*)-(+)-propylene oxide (0.01mL, 0.09 mmol), acetic acid (0.30 mL) and stirring at rt. After 16 h, acetic acid was evaporated under vacuum. The residue was purified by flash chromatography through silica gel (EtOAc/Hexanes) to provide 25 mg (45% yield) of the title compound. LCMS (ESI) [M+H]+ = 585.3, rt = 1.83 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.36 (d, J = 5.2 Hz, 1H), 8.04 (dd, J = 4.8, 2.0 Hz, 1H), 7.72 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.7 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.16 (d, J = 8.3 Hz, 1H), 7.08 (dd, J = 7.6, 4.8 Hz, 1H), 6.61 (dd, J = 29.6, 7.1 Hz, 1H), 5.35 (s, 1H), 4.18 (s, 1H), 3.58 (s, 1H), 3.42 – 3.36 (m, 1H), 3.15 (dd, J = 12.6, 8.6 Hz, 1H), 2.26 (s, 4H), 1.79 (s, 2H), 1.75 – 1.57 (m, 4H), 1.34 (d, J = 6.3 Hz, 4H).

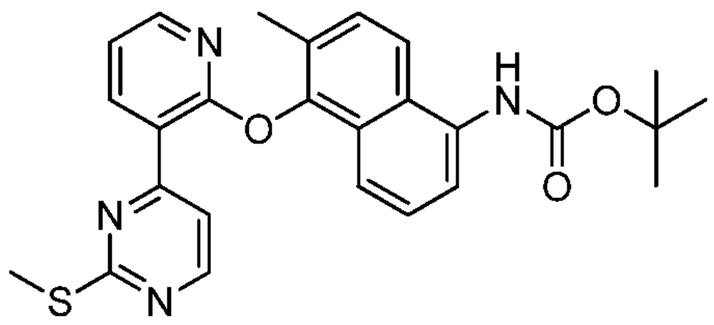
[1085] Step 2: (*S*)-1-((6-Methyl-5-((3-(2-((*S*)-piperidin-3-ylamino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)amino)propan-2-ol



[1086] Prepared according to General Procedure B using (*S*)-*tert*-butyl 3-((4-(2-((5-(((*S*)-2-hydroxypropyl)amino)-2-methylnaphthalen-1-yl)oxy)pyridin-3-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (23 mg, 0.04 mmol), 1,4-dioxane (1.0 mL), and hydrochloric acid (4 M in dioxane, 1.0 mL, 4.0 mmol). After 30 min, MTBE (15 mL) was added to the suspension to further precipitate out the product and the suspension was stirred at rt overnight. The resulting solids were collected by filtration, dissolved in water and MeCN and lyophilized to provide 17 mg (83% yield) of **301**. LCMS (ESI) $[M+H]^+$ = 485.5, rt = 1.25 min; ^{1}H NMR (400 MHz, d6-dmso) δ 8.88 (s, 2H), 8.46 (d, J = 5.3 Hz, 1H), 8.06 – 7.96 (m, 2H), 7.58 (s, 3H), 7.36 (d, J = 8.8 Hz, 1H), 7.24 – 7.14 (m, 2H), 6.86 (d, J = 8.5 Hz, 1H), 6.53 (d, J = 7.8 Hz, 1H), 3.97 (d, J = 6.1 Hz, 2H), 3.47 – 3.38 (m, 2H), 3.15 (d, J = 17.8 Hz, 3H), 2.82 (s, 2H), 2.17 (s, 3H), 1.94 (d, J = 51.6 Hz, 2H), 1.62 (s, 2H), 1.15 (d, J = 6.2 Hz, 3H).

Example 302 *3,3-Dimethyl-N-(6-methyl-5-((3-(2-(((3S,5R)-5-methylpiperidin-3-yl)amino)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)butanamide* ***302***

[1087] Step 1: *tert*-Butyl (6-methyl-5-((3-(2-(methylthio)pyrimidin-4-yl)pyridin-2-yl)oxy)naphthalen-1-yl)carbamate



[1088] To a suspension of 6-methyl-5-[[3-(2-methylsulfanylpyrimidin-4-yl)-2-pyridyl]oxy]naphthalen-1-amine (1.00 g, 2.67 mmol) in 1,4-dioxane (8 mL) was added di-tert-butyl dicarbonate (0.73 g, 3.34 mmol) followed by triethylamine (0.41 mL, 2.94 mmol) and the mixture was heated at 60 °C. After 16 h, EtOAc (16 mL) and brine (32 mL) were added and the phases were separated. The organic extract was washed with saturated NH_4Cl(aq) (50 mL), dried ($MgSO_4$), filtered and concentrated under vacuum. The residue was purified by flash chromatography through silica gel (0 – 10% EtOAc/DCM) to provide 640 mg (50% yield) of the title compound. LCMS (ESI) $[M+H]^+$ = 475.2, rt = 2.06 min.

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

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 364

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JUMBO APPLICATIONS/PATENTS

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CONTAINING PAGES 1 TO 364

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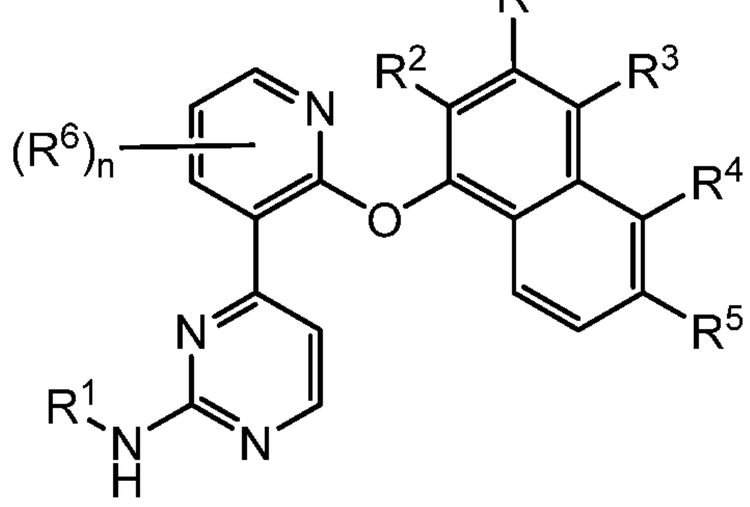
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NOTE POUR LE TOME / VOLUME NOTE:

CLAIMS

We claim:

1. A compound of the Formula I′:



I′ ,

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein:

R^1 is C_3–C_{12} cycloalkyl, C_3-C_{12} heterocyclyl, C_1–C_{12} heteroaryl, C_6–C_{20} aryl, -(C_1–C_6 alkyldiyl)–(C_3–C_{12} cycloalkyl), or –(C_1–C_6 alkyldiyl)–(C_3-C_{12} heterocyclyl);

R^2 is H, F, Cl, –CN, –OCH_3, –OCH_2CH_3, or C_1–C_6 alkyl;

R^3 is H, –CN, C_3-C_{12} cycloalkyl, C_3-C_{12} heterocyclyl, C_1–C_{12} heteroaryl, C_6–C_{20} aryl, -O–(C_1–C_{12} heteroaryl), -O–(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl), -N(R^8)(C_1–C_6 alkyl), -$NR^8C(O)R^9$, -$NR^8C(O)OR^9$, -$NR^8C(O)NHR^9$, -NR^8SO_2–(C_1–C_6 alkyl), -NR^8SO_2–(C_1–C_6 alkenyl), -NR^8SO_2–(C_3–C_{12} cycloalkyl), -NR^8SO_2–(C_1–C_{12} heteroaryl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_3–C_{12} cycloalkyl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_3-C_{12} heterocyclyl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_1–C_{12} heteroaryl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl), -$NR^8SO_2NR^8R^9$, or -$SO_2NR^8R^9$;

R^4 is H, –CN, C_3-C_{12} cycloalkyl, C_3-C_{12} heterocyclyl, C_1–C_{12} heteroaryl, C_6–C_{20} aryl, -O–(C_1–C_{12} heteroaryl), -O–(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl), -NR^8R^9, -$NR^8C(O)R^9$, -$NR^8C(O)OR^9$, -$NR^8C(O)NHR^9$, -NR^8SO_2–(C_1–C_6 alkyl), -NR^8SO_2–(C_1–C_6 alkenyl), -NR^8SO_2–(C_1–C_{12} heteroaryl), -NR^8SO_2–(C_3–C_{12} cycloalkyl), -NR^8SO_2–(C_3-C_{12} heterocyclyl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_3–C_{12} cycloalkyl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_3-C_{12} heterocyclyl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_1–C_{12} heteroaryl), -NR^8SO_2–(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl), -$NR^8SO_2NR^8R^9$, or -$SO_2NR^8R^9$;

each R^5 and R^7 are independently H, F, Cl, –CN, –CH_2OH, –$C(O)NH_2$, –OH, -OCH_3, -OCH_2CH_3, or C_1–C_6 alkyl;

n is 0, 1, 2, or 3;

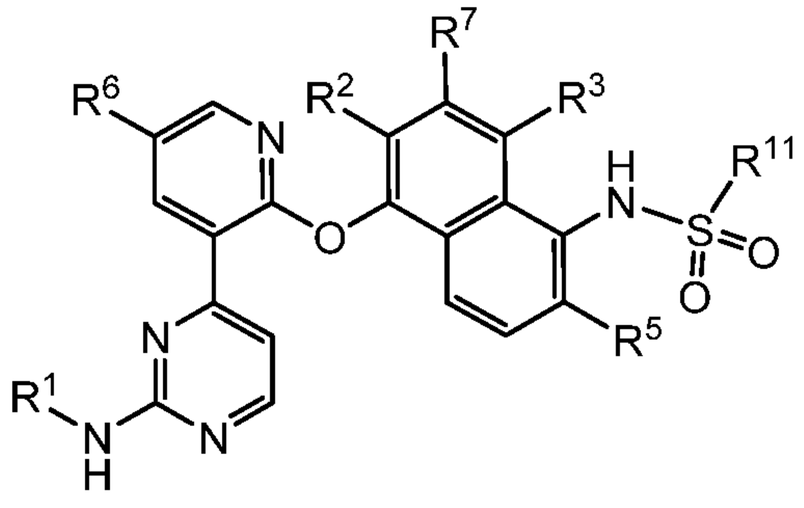
each R^6 is independently H, F, Cl, Br, I, –CN, –NO_2, -O-(C_1–C_6 alkyl) or C_1–C_6 alkyl;

each R^8 is independently H, or C_1–C_6 alkyl;

each R^9 is independently C_1–C_6 alkyl, C_2–C_6 alkenyl, C_3–C_{12} cycloalkyl, C_3-C_{12} heterocyclyl, C_1–C_{12} heteroaryl, C_6–C_{20} aryl; –(C_1–C_6 alkyldiyl)–(C_3–C_{12} cycloalkyl), –(C_1–C_6 alkyldiyl)–(C_3-C_{12} heterocyclyl), –(C_1–C_6 alkyldiyl)–(C_1–C_6 heteroaryl), –(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl), or –(C_1–C_6 alkyldiyl)–O–(C_6–C_{20} aryl); and

wherein cycloalkyl, heterocyclyl, heteroaryl, aryl, alkyl, alkyldiyl, and alkenyl are optionally and independently substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, –CN, –CH_3, –CH_2CH_3, –$CH_2CH_2CH_3$, –$CH(CH_3)_2$, –$CH_2CH(CH_3)_2$, -$CH(CH_3)CH_2CH_3$, –$CH_2C(CH_3)_3$, –CH_2OH, –CH_2OCH_3, –CH_2CH_2OH, –$C(CH_3)_2OH$, -$CH(OH)CH(CH_3)_2$, –$C(CH_3)_2CH_2OH$, –$CH_2CH_2CH_2OH$, –$CH_2CH_2C(CH_3)_2OH$, -$CH_2CH_2OCH_3$, –$CH_2CH(CH_3)OCH_3$, –$CH_2CH_2CH_2OCH_3$, –$CH_2CH_2C(CH_3)_2OCH_3$, -$CH_2CH_2SO_2CH_3$, –$CH_2OP(O)(OH)_2$, –CH_2F, –CHF_2, –CH_2NH_2, –$CH_2NHSO_2CH_3$, -CH_2NHCH_3, –$CH_2N(CH_3)_2$, –CF_3, –CH_2CF_3, –CH_2CHF_2, –$CH_2CH_2CHF_2$, –$CH_2CH_2CF_3$, -$CH(CH_3)CN$, –$C(CH_3)_2CN$, –CH_2CN, –CO_2H, –$COCH_3$, –CO_2CH_3, –$CO_2C(CH_3)_3$, -$COCH(OH)CH_3$, –$CONH_2$, –$CONHCH_3$, –$CONHCH_2CH_3$, –$CONHCH(CH_3)_2$, –$CON(CH_3)_2$, -$C(CH_3)_2CONH_2$, –NH_2, –$NHCH_3$, –$N(CH_3)_2$, -$N(CH_3)CH_2CH_3$, -$NHCOCH_3$, -$N(CH_3)COCH_3$, -$NHS(O)_2CH_3$, –$N(CH_3)C(CH_3)_2CONH_2$, –$N(CH_3)CH_2CH_2S(O)_2CH_3$, –$NO_2$, =O, –OH, -$OCH_3$, -$OCH_2CH_3$, –$OCH_2CH_2OCH_3$, –$OCH_2CH_2OH$, –$OCH_2CH_2N(CH_3)_2$, –$OP(O)(OH)_2$, -$S(O)_2N(CH_3)_2$, –$SCH_3$, –$S(O)_2CH_3$, –$S(O)_3H$, cyclopropyl, cyclopropylamide, cyclobutyl, oxetanyl, azetidinyl, 1-methylazetidin-3-yl)oxy, *N*-methyl-N-oxetan-3-ylamino, azetidin-1-ylmethyl, benzyloxyphenyl, pyrrolidin-1-yl, pyrrolidin-1-yl-methanone, phenyl, piperazin-1-yl, piperidin-1-yl, morpholinomethyl, morpholino-methanone, and morpholino.

2. The compound of claim 1, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein the compound is of the Formula Ij:



Ij ,

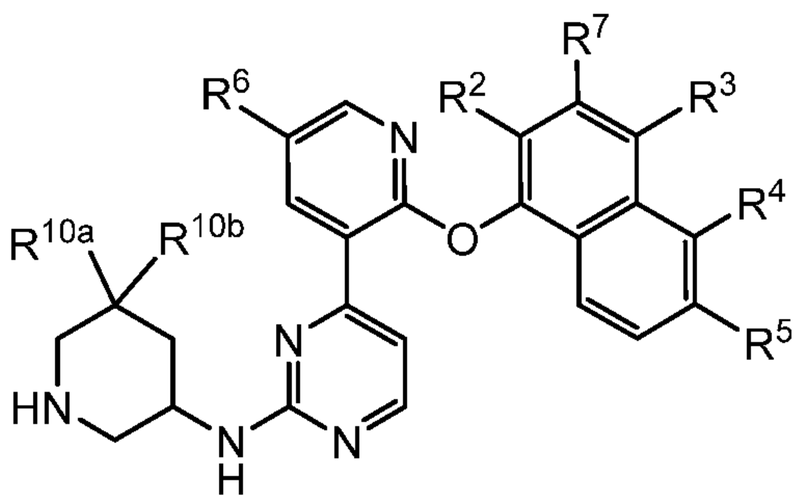
wherein R^{11} is C_1–C_6 alkyl, C_1–C_6 alkenyl, C_1–C_{12} heteroaryl, C_3-C_{12} cycloalkyl, C_3-C_{12} heterocyclyl, -(C_1–C_6 alkyldiyl)–(C_3–C_{12} cycloalkyl), -(C_1–C_6 alkyldiyl)–(C_3-C_{12} heterocyclyl), -(C_1–C_6 alkyldiyl)–(C_1–C_{12} heteroaryl), -(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl), -NR^8–(C_1–C_{12} heteroaryl), -NR^8–(C_1–C_6 alkyl), or -NR^8–(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl); and wherein cycloalkyl, heterocyclyl, heteroaryl, aryl, alkyl, alkyldiyl, and alkenyl are optionally and independently substituted as defined in claim 1.

3. The compound of claim 1 or 2, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^1 is optionally substituted C_3–C_{12} cycloalkyl or optionally substituted C_3-C_{12} heterocyclyl.

4. The compound of claim 3, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^1 is cyclohexyl or piperidinyl, optionally substituted with one or more substituents selected from the group consisting of F, –CH_3, and –NH_2.

5. The compound of claim 3, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^1 is selected from the group consisting of piperidin-3-yl, 5-fluoropiperidin-3-yl, 5-methylpiperidin-3-yl and 5-fluro-5-methylpiperidin-3-yl.

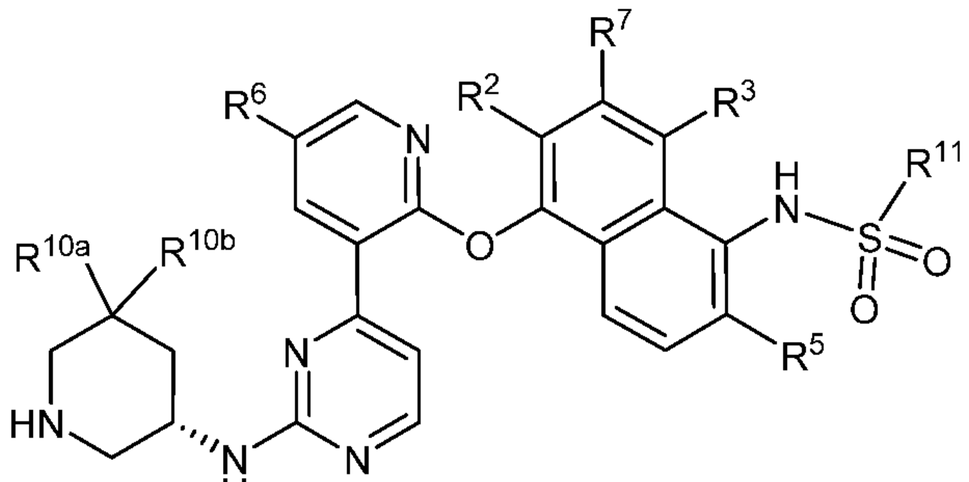
6. The compound of claim 1, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein the compound is of the Formula Ih:



Ih ,

wherein R^{10a} and R^{10b} are independently H, F, –CH_3 or –NH_2.

7. The compound of claim 2, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein the compound is of the Formula Ik:

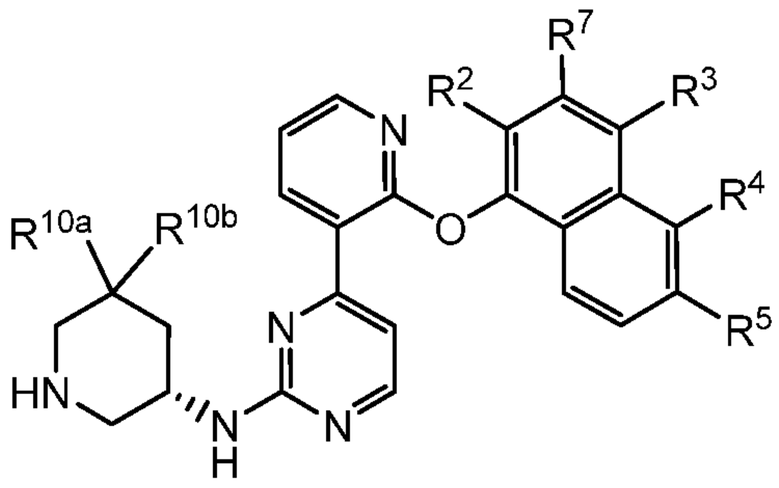


Ik ,

wherein R^{10a} and R^{10b} are independently H, F or -CH_3.

8. The compound of any one of claims 1 to 7, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^6 is H, F, Cl, Br, -OCH_3, or C_1–C_6 alkyl.

9. The compound of claim 6, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein the compound is of the Formula Ii:



Ii .

10. The compound of any one of claims 1 to 9, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^2 is H, F, Cl or C_1–C_6 alkyl.

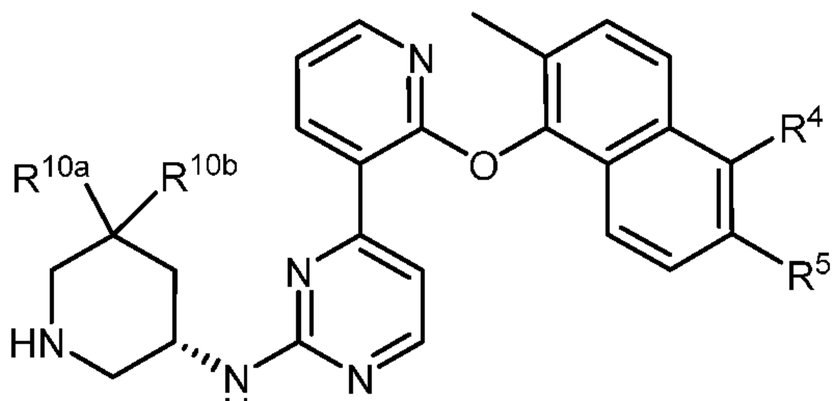
11. The compound of claim 10, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^2 is methyl.

12. The compound of any one of claims 1 to 11, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^7 is hydrogen or fluoro.

13. The compound of any one of claims 1 to 12, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^5 is H, F, Cl or CH_3.

14. The compound of any one of claims 1 to 13, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^3 is H.

15. The compound of claim 9, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein the compound is of the Formula Iq:



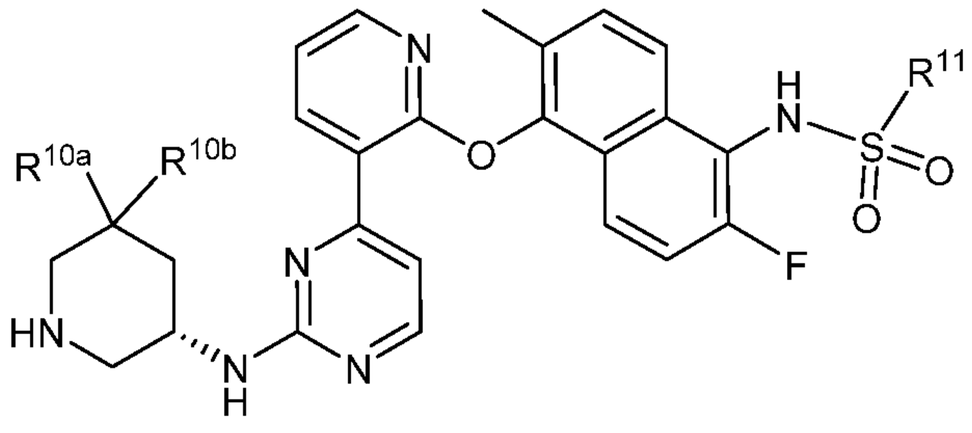
Iq .

16. The compound of claim 15, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^4 is C_3-C_{12} heterocyclyl, C_1–C_{12} heteroaryl, -NR^8R^9, -$NR^8C(O)R^9$, -$NR^8C(O)OR^9$, -$NR^8C(O)NHR^9$ or -$SO_2NR^8R^9$.

17. The compound of claim 15, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^4 is C_3-C_{12} heterocyclyl, C_1–C_{12} heteroaryl, -NR^8R^9 or -$NR^8C(O)R^9$.

18. The compound of any one of claims 1 to 17, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^5 is H.

19. The compound of claim 7, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein the compound is of the Formula II:



II .

20. The compound of claim 7 or 19, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^{11} is C_1–C_6 alkyl, C_1–C_6 alkenyl, C_1–C_{12} heteroaryl, C_3-C_{12} cycloalkyl, C_3-C_{12} heterocyclyl, -(C_1–C_6 alkyldiyl)–(C_3–C_{12} cycloalkyl), -(C_1–C_6 alkyldiyl)–(C_3-C_{12} heterocyclyl), -(C_1–C_6 alkyldiyl)–(C_1–C_{12} heteroaryl), or -(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl); and wherein cycloalkyl, heterocyclyl, heteroaryl, aryl, alkyl, alkyldiyl, and alkenyl are optionally and independently substituted as defined in claim 1.

21. The compound of claim 7 or 19, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^{11} is $-NR^8-(C_1-C_{12}$ heteroaryl), $-NR^8-(C_1-C_6$ alkyl), or $-NR^8-(C_1-C_6$ alkyldiyl$)-(C_6-C_{20}$ aryl); and R^8 is independently H or $-CH_3$; and wherein cycloalkyl, heterocyclyl, heteroaryl, aryl, alkyl, alkyldiyl, and alkenyl are optionally and independently substituted as defined in claim 1.

22. The compound of claim 7 or 19, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^{11} is selected from the group consisting of benzyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentanyl, cyclopentanylmethyl, cyclohexyl, cyclohexylmethyl, pyrrolidin-1-yl, piperidin-1-yl, pyridyl, pyridylmethyl, tetrahydrofuranyl, tetrahydrofuranylmethyl, and tetrahydropyranyl, tetrahydropyranylmethyl, thiazolyl, and thiazolylmethyl; each of which is optionally and independently substituted with one or more substituents selected from fluoro, chloro, bromo, $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, and $-CN$.

23. The compound of claim 7 or 19, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^{11} is selected from the group consisting of $-CH_3$, $-CH_2CH_3$, $-CH{=}CH_2$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2C(CH_3)_3$, $-CH_2CHF_2$, $-CH_2CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2CH_2OCH_3$, $-CH_2CH(CH_3)OCH_3$, $-CH_2F$, $-CH_2Cl$, $-CH_2Br$, $-CH_2CN$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, and $-N(CH_3)CH_2CH_3$.

24. The compound of any one of claims 6 to 23, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^{10a} and R^{10b} are H.

25. The compound of any one of claims 6 to 23, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^{10a} is F and R^{10b} is H.

26. The compound of any one of claims 6 to 23, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^{10a} is H and R^{10b} is $-CH_3$.

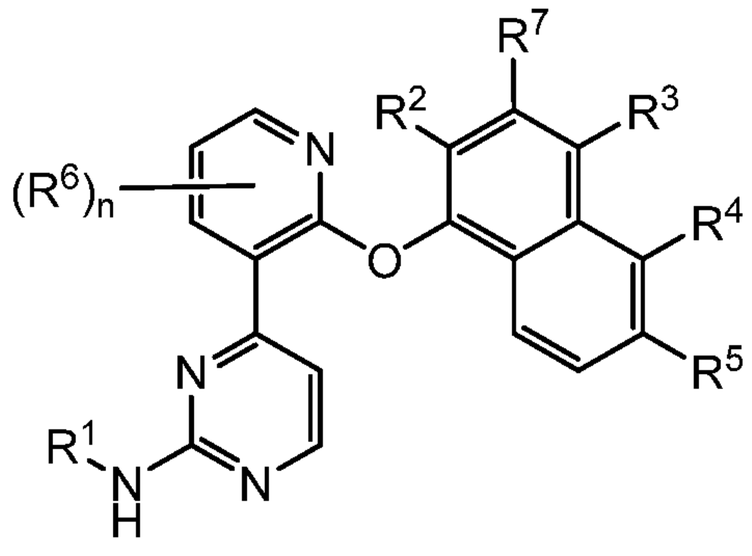
27. The compound of any one of claims 6 to 23, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^{10a} is F and R^{10b} is $-CH_3$.

28. The compound of claim 1, wherein the compound is selected from Table 1, or a pharmaceutically acceptable salt thereof.

29. The compound of claim 1, wherein the compound is selected from Table 2, or a pharmaceutically acceptable salt thereof.

30. The compound of claim 1, wherein the compound is selected from Table 3, or a pharmaceutically acceptable salt thereof.

31. A compound of the Formula I:



I ,

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from C_3–C_{12} cycloalkyl, C_3-C_{12} heterocyclyl, C_1–C_{12} heteroaryl, C_6–C_{20} aryl, –(C_1–C_6 alkyldiyl)–(C_3–C_{12} cycloalkyl), and –(C_1–C_6 alkyldiyl)–(C_3-C_{12} heterocyclyl);

R^2 is selected from H, F, Cl, –CN, $–OCH_3$, $–OCH_2CH_3$, and C_1–C_6 alkyl;

R^3 and R^4 are independently selected from H, –CN, C_3-C_{12} cycloalkyl, C_3-C_{12} heterocyclyl, C_1–C_{12} heteroaryl, C_6–C_{20} aryl, –O–(C_1–C_{12} heteroaryl), –O–(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl), $–NR^8R^9$, $–NR^8C(O)R^9$, $–NR^8C(O)OR^9$, $–NR^8C(O)NHR^9$, $–NR^8SO_2$–(C_1–C_6 alkyl), $–NR^8SO_2$–(C_1–C_6 alkenyl), $–NR^8SO_2$–(C_1–C_{12} heteroaryl), $–NR^8SO_2$–(C_1–C_6 alkyldiyl)–(C_3–C_{12} cycloalkyl), $–NR^8SO_2$–(C_1–C_6 alkyldiyl)–(C_3-C_{12} heterocyclyl), $–NR^8SO_2$–(C_1–C_6 alkyldiyl)–(C_1–C_{12} heteroaryl), $–NR^8SO_2$–(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl), $–NR^8SO_2NR^8R^9$, and $–SO_2NR^8R^9$;

R^5 and R^7 are independently selected from H, F, Cl, –CN, $–CH_2OH$, $–C(O)NH_2$, –OH, $-OCH_3$, $–OCH_2CH_3$, and C_1–C_6 alkyl;

R^6 are independently selected from H, F, Cl, Br, I, –CN, $–NO_2$, and C_1–C_6 alkyl;

R^8 is independently selected from H, and C_1–C_6 alkyl;

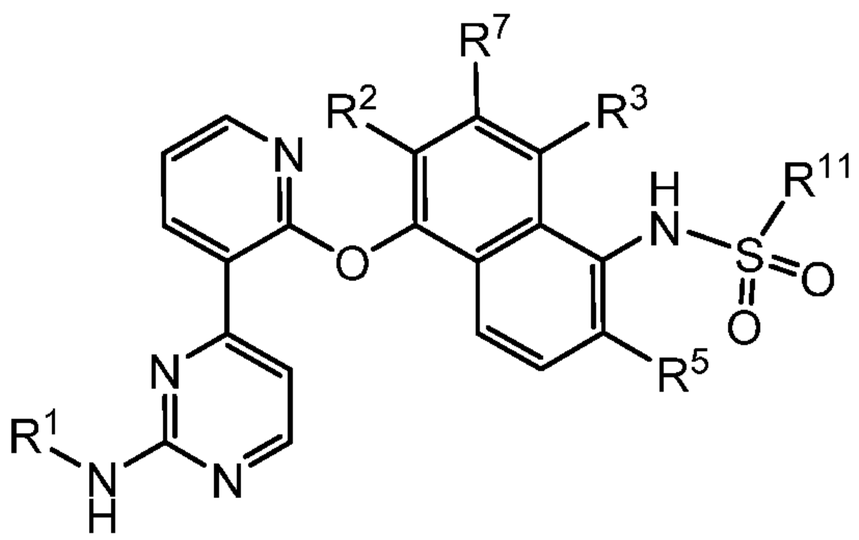
R^9 is independently selected from C_1–C_6 alkyl, C_2–C_6 alkenyl, C_3–C_{12} cycloalkyl, C_3-C_{12} heterocyclyl, C_1–C_{12} heteroaryl, C_6–C_{20} aryl; –(C_1–C_6 alkyldiyl)–(C_3–C_{12} cycloalkyl), –(C_1–C_6 alkyldiyl)–(C_3-C_{12} heterocyclyl), –(C_1–C_6 alkyldiyl)–(C_1–C_6 heteroaryl), –(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl), and –(C_1–C_6 alkyldiyl)–O–(C_6–C_{20} aryl); and

n is 0, 1, 2, or 3;

wherein cycloalkyl, heterocyclyl, heteroaryl, aryl, alkyl, alkyldiyl, and alkenyl are optionally and independently substituted with one or more groups selected from F, Cl, Br, I, -CN, $–CH_3$, $–CH_2CH_3$, $–CH_2CH_2CH_3$, $–CH(CH_3)_2$, $–CH_2CH(CH_3)_2$, $–CH(CH_3)CH_2CH_3$, $-CH_2C(CH_3)_3$, $–CH_2OH$, $–CH_2OCH_3$, $–CH_2CH_2OH$, $–C(CH_3)_2OH$, $–CH(OH)CH(CH_3)_2$, $-C(CH_3)_2CH_2OH$, $–CH_2CH_2CH_2OH$, $–CH_2CH_2C(CH_3)_2OH$, $–CH_2CH_2OCH_3$, $-CH_2CH(CH_3)OCH_3$, $–CH_2CH_2CH_2OCH_3$, $–CH_2CH_2C(CH_3)_2OCH_3$, $–CH_2CH_2SO_2CH_3$, $-CH_2OP(O)(OH)_2$, $–CH_2F$, $–CHF_2$, $–CH_2NH_2$, $–CH_2NHSO_2CH_3$, $–CH_2NHCH_3$, $–CH_2N(CH_3)_2$, $–CF_3$, $–CH_2CF_3$, $–CH_2CHF_2$, $–CH_2CH_2CHF_2$, $–CH_2CH_2CF_3$,$–CH(CH_3)CN$, $–C(CH_3)_2CN$, $-CH_2CN$, $–CO_2H$, $–COCH_3$, $–CO_2CH_3$, $–CO_2C(CH_3)_3$, $–COCH(OH)CH_3$, $–CONH_2$, $-CONHCH_3$, $–CONHCH_2CH_3$, $–CONHCH(CH_3)_2$, $–CON(CH_3)_2$, $–C(CH_3)_2CONH_2$, $–NH_2$, $-NHCH_3$, $–N(CH_3)_2$, $–N(CH_3)CH_2CH_3$, $–NHCOCH_3$, $–N(CH_3)COCH_3$, $–NHS(O)_2CH_3$, $-N(CH_3)C(CH_3)_2CONH_2$, $–N(CH_3)CH_2CH_2S(O)_2CH_3$, $–NO_2$, =O, –OH, $–OCH_3$, $–OCH_2CH_3$, $-OCH_2CH_2OCH_3$, $–OCH_2CH_2OH$, $–OCH_2CH_2N(CH_3)_2$, $–OP(O)(OH)_2$, $–S(O)_2N(CH_3)_2$, $-SCH_3$, $-S(O)_2CH_3$, $–S(O)_3H$, cyclopropyl, cyclopropylamide, cyclobutyl, oxetanyl, azetidinyl, 1-methylazetidin-3-yl)oxy, *N*-methyl-N-oxetan-3-ylamino, azetidin-1-ylmethyl, benzyloxyphenyl, pyrrolidin-1-yl, pyrrolidin-1-yl-methanone, phenyl, piperazin-1-yl, piperidin-1-yl, morpholinomethyl, morpholino-methanone, and morpholino;

provided that the compound is other than a compound of Table 1X.

32. The compound of claim 31, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein the compound is of the Formula Ic:

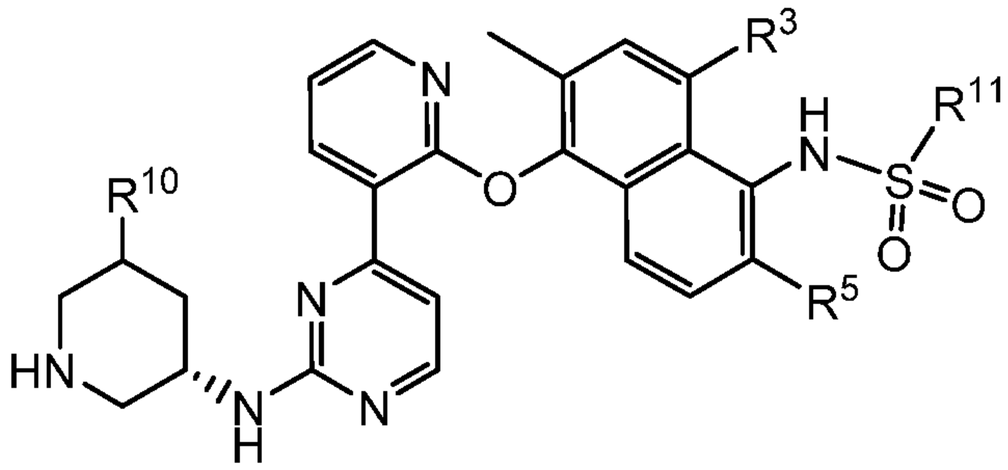


Ic ,

wherein R^{11} is selected from $C_1–C_6$ alkyl, $C_1–C_6$ alkenyl, $C_1–C_{12}$ heteroaryl, ($C_1–C_6$ alkyldiyl)–(C_3-C_{12} heterocyclyl), ($C_1–C_6$ alkyldiyl)–($C_1–C_{12}$ heteroaryl), ($C_1–C_6$ alkyldiyl)–

(C_6–C_{20} aryl), NR^7–(C_1–C_{12} heteroaryl), NR^7–(C_1–C_6 alkyl), and NR^7–(C_1–C_6 alkyldiyl)–(C_6–C_{20} aryl).

33. The compound of claim 32, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein the compound is of the Formula If:



If .

34. A pharmaceutical composition comprising a compound of any of claims 1 to 33, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, glidant, diluent, or excipient.

35. A process for making a pharmaceutical composition which comprises combining a compound of any of claims 1 to 33, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable carrier, glidant, diluent, or excipient.

36. A method of treating an IRE1-related disease or disorder in a patient comprising administering a therapeutically effective amount of the pharmaceutical composition of claim 34 to a patient with an IRE1-related disease or condition.

37. The method of claim 36, wherein the IRE1-related disease or disorder is cancer selected from the group consisting of squamous cell cancer, small-cell lung cancer, non-small cell lung cancer ("NSCLC"), adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, stomach cancer, gastrointestinal cancer, esophageal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, and head and neck cancer.

38. The method of claim 36, wherein the IRE1-related disease or disorder is a hematological malignancy selected from the group consisting of lymphomas, lymphocytic leukemia, myeloma, acute and chronic myelogenous leukemia, myelodysplastic syndrome and myeloproliferative disease.

39. The method of claim 36, wherein the IRE1-related disease or disorder is multiple myeloma.

40. The method of claim 36, wherein the IRE1-related disease or disorder is a triple-negative breast cancer ("TNBC").

41. The method of any one of claims 36 to 40, further comprising administering one or more additional therapeutic agent(s) selected from the group consisting of an anti-inflammatory agent, a corticosteroid, an immunomodulatory agent, chemotherapeutic agent, an apoptosis-enhancer, a neurotropic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, an agent for treating metabolic disorders, an agent for treating autoimmune disorders, and an agent for treating immunodeficiency disorders.

42. The method of claim 41 wherein the additional therapeutic agent is a corticosteroid, a proteasome inhibitor, an IMiD, an antibody, or a combination thereof.

43. The method of claim 42, wherein the additional therapeutic agent is a corticosteroid which is dexamethasone, a proteasome inhibitor selected from the group consisting of carfilzomib, ixazomib and bortezomib; an IMiD selected from the group consisting of lenalidomide and pomalidomide; an antibody selected from the group consisting of an anti-CD38 antibody, an anti-VEGF-A antibody, an anti-PD-1 antibody, an anti-PD-L1 antibody and an anti-interleukin-6 antibody; or a combination thereof.

44. The method of any one of claims 36 to 40, further comprising administering radiotherapy.

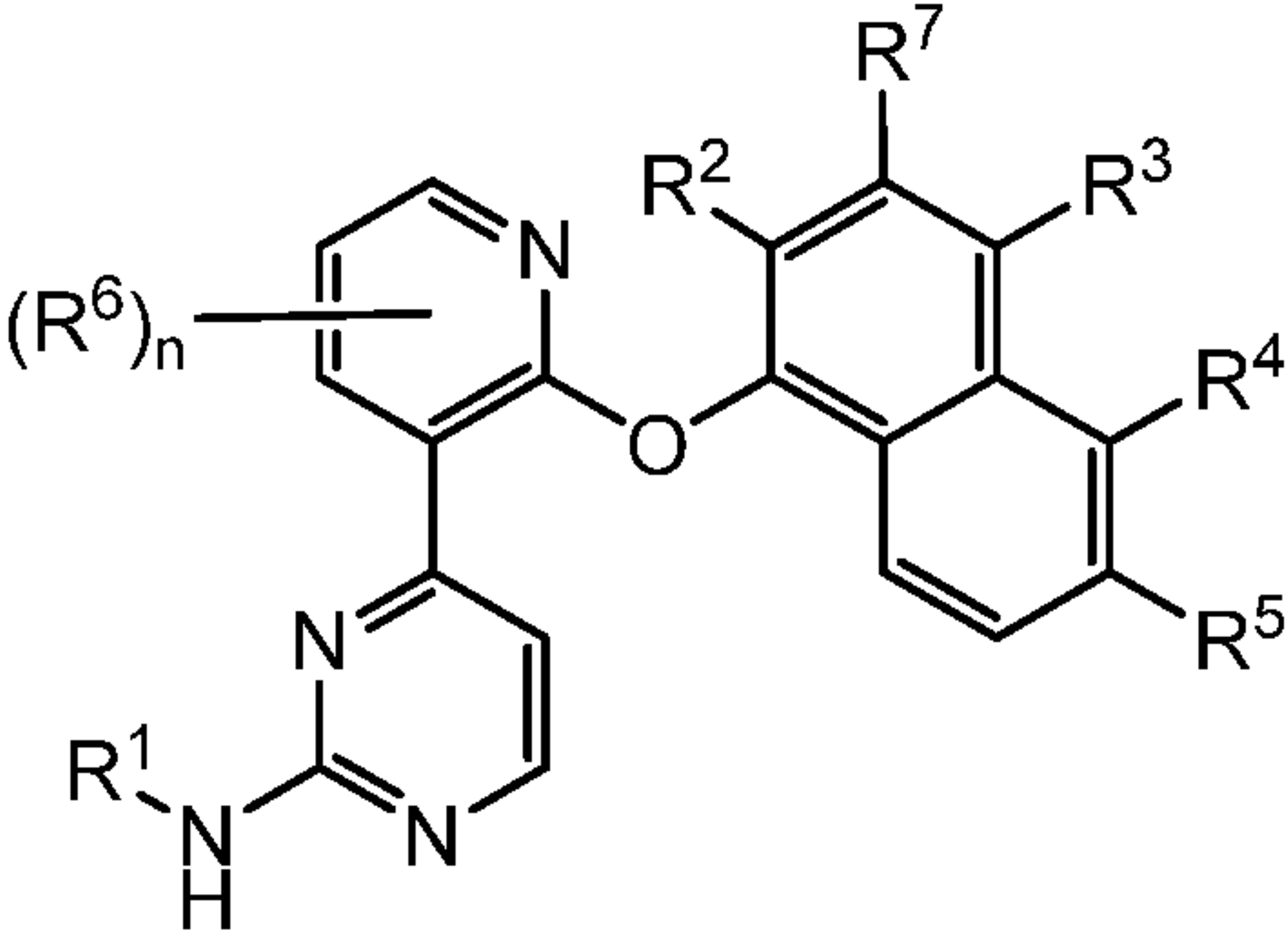
45. Use of a compound according to any of claims 1 to 33, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, or a pharmaceutical compositon according to claim 34, in the manufacture of a medicament for the treatment of an IRE1-related disease or disorder.

46. A compound according to any of claims 1 to 33, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, for use in a method for treating an IRE1-related disease or disorder.

47. A kit for treating a condition mediated by IRE1, comprising:

a) a pharmaceutical composition of claim 34; and

b) instructions for use.



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