

INHIBITORS OF CYCLIN-DEPENDENT KINASE 7 (CDK7)

BACKGROUND OF THE INVENTION

[1] The members of the cyclin-dependent kinase (CDK) family play critical regulatory roles in proliferation. Unique among the mammalian CDKs, CDK7 has consolidated kinase activities, regulating both the cell cycle and transcription. In the cytosol, CDK7 exists as a heterotrimeric complex and is believed to function as a CDK1/2-activating kinase (CAK), whereby phosphorylation of conserved residues in CDK1/2 by CDK7 is required for full catalytic CDK activity and cell cycle progression. In the nucleus, CDK7 forms the kinase core of the RNA polymerase (RNAP) II general transcription factor complex and is charged with phosphorylating the C-terminal domain (CTD) of RNAP II, a requisite step in gene transcriptional initiation. Together, the two functions of CDK7, *i.e.*, CAK and CTD phosphorylation, support critical facets of cellular proliferation, cell cycling, and transcription.

[2] Disruption of RNAP II CTD phosphorylation has been shown to preferentially affect proteins with short half-lives, including those of the anti-apoptotic BCL-2 family. Cancer cells have demonstrated ability to circumvent pro-cell death signaling through upregulation of BCL-2 family members. Therefore, inhibition of human CDK7 kinase activity is likely to result in anti-proliferative activity.

[3] The discovery of selective inhibitors of CDK7 has been hampered by the high sequence and structural similarities of the kinase domain of CDK family members. Therefore, there is a need for the discovery and development of selective CDK7 inhibitors. Such CDK7 inhibitors hold promise as a therapeutic agent for the treatment of CLL and other cancers.

BRIEF DESCRIPTION OF THE DRAWINGS

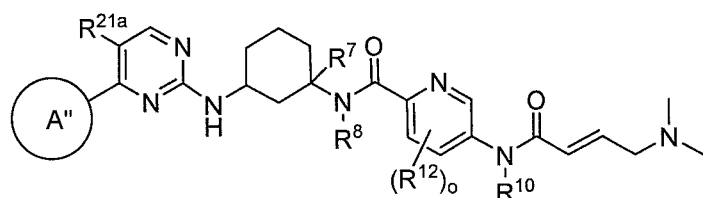
[4] Fig. 1 is a table of exemplary compounds of Formula I.

SUMMARY OF THE INVENTION

[5] The present disclosure provides inhibitors of one or more of the family of CDK proteins. The present disclosure further provides CDK7 inhibitors, in particular selective CDK7 inhibitors of Formula (I) or Formula (II), and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, isotopically labeled derivatives, and compositions thereof. The present

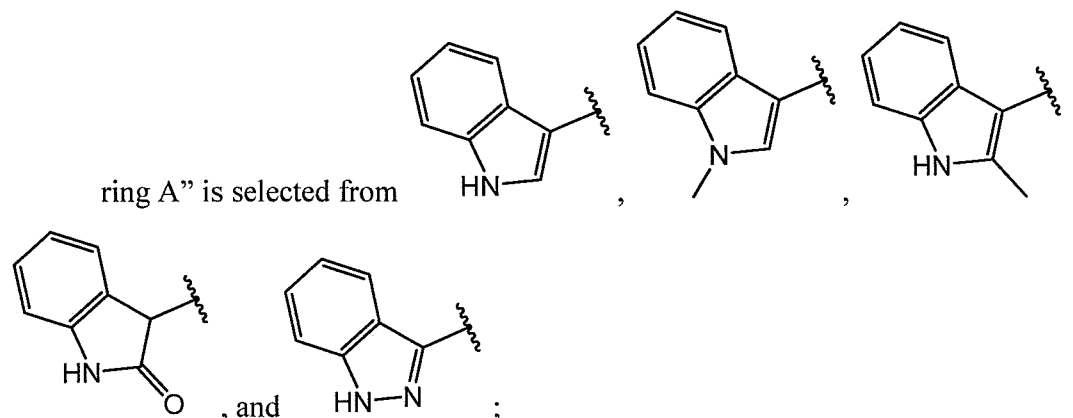
disclosure additionally provides methods of using the compounds of the present disclosure, and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, isotopically labeled derivatives, and compositions thereof, to study the inhibition of CDK7 and CDK12 and/or CDK13 and as therapeutics for the prevention and/or treatment of diseases associated with overexpression and/or aberrant activity of CDK7 and/or CDK12 and/or CDK13. In certain embodiments, the disclosed compounds are used for the prevention and/or treatment of proliferative diseases (*e.g.*, cancers (*e.g.*, leukemia, melanoma, multiple myeloma), benign neoplasms, angiogenesis, inflammatory diseases, autoinflammatory diseases, and autoimmune diseases) in a subject.

In one aspect, there is provided a compound having structural Formula (Ic):



(Ic); or a pharmaceutically acceptable

salt thereof, solvate, hydrate, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein:



each of R^7 , R^8 and R^{10} is independently selected from hydrogen and methyl;

R^{21a} is selected from -Cl, -CN, -CF₃, -CH₃, and -CH₂CH₃; and

each R^{12} if present is halo; and

o is 0, 1, 2, or 3.

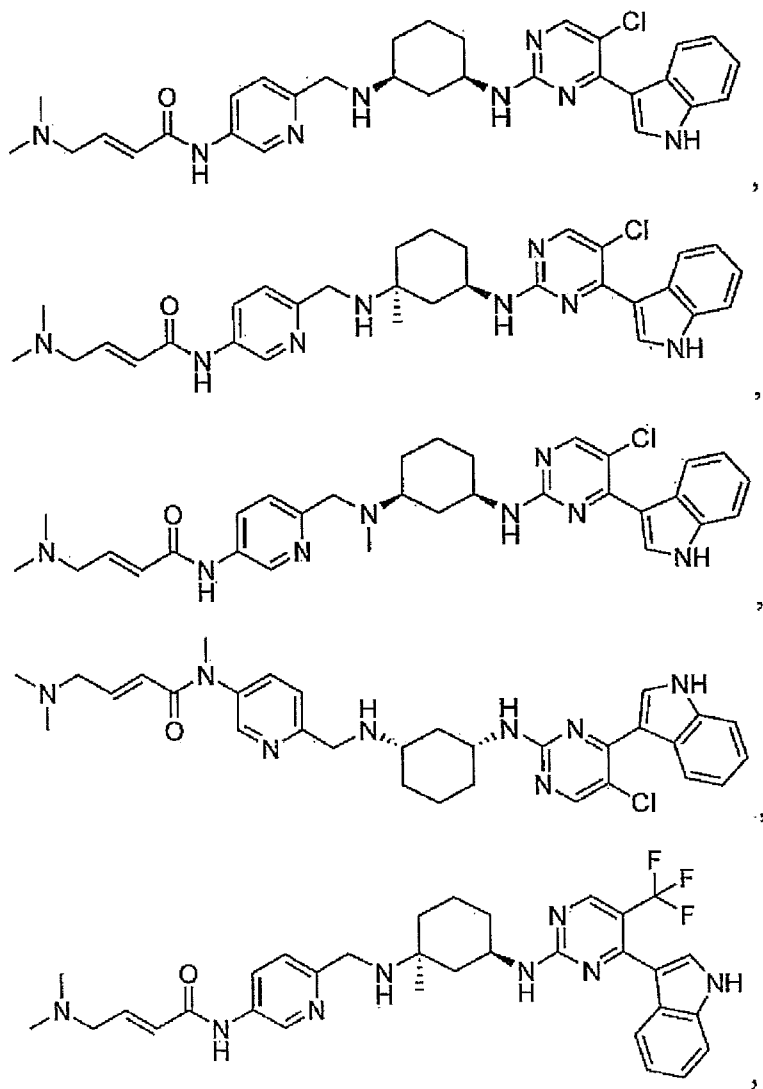
In another aspect, there is provided a pharmaceutical composition comprising a compound as disclosed herein and a pharmaceutically acceptable excipient.

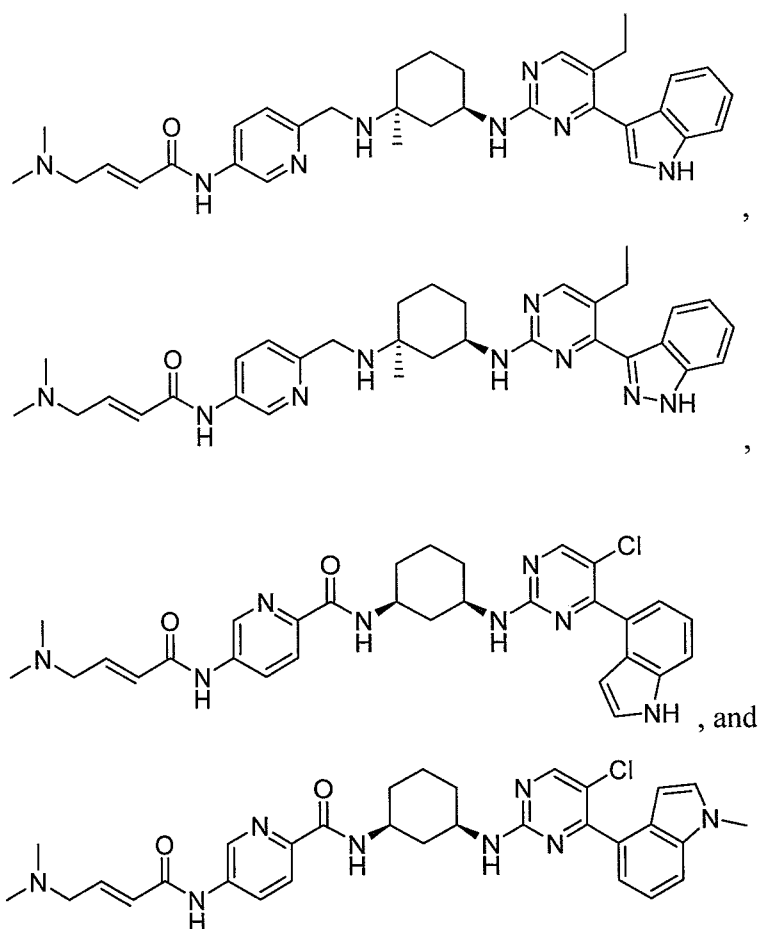
In another aspect, there is provided the use of the composition as disclosed herein in the

manufacture of a medicament, for treating a subject suffering from a disease or condition associated with aberrant activity of a CDK, wherein the disease or condition is selected from the group consisting of cancer, benign neoplasm, angiogenesis, inflammatory disease, autoinflammatory disease, autoimmune disease, and an infectious disease.

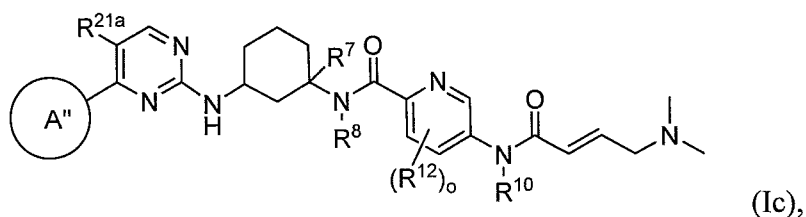
In an embodiment, there is provided the use of the composition as disclosed herein in the manufacture of a medicament, for treating a disease or condition selected from cancer, benign neoplasm, angiogenesis, inflammatory disease, autoinflammatory disease, autoimmune disease, or an infectious disease.

In a further aspect, there is provided a compound selected from any one of the compounds set forth below:





[6] In an embodiment, the present disclosure provides compounds of structural formula (Ic):



and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, and isotopically labeled derivatives thereof, wherein Ring A'', R⁷, R⁸, R¹⁰, R¹², R^{21a}, o and subvariables thereof are as defined herein.

[7] In an embodiment, the present disclosure provides pharmaceutical compositions comprising a compound of Formula (Ic) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, or isotopically labeled derivative thereof, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the

pharmaceutical compositions described herein include a therapeutically effective amount of a compound of Formula (Ic) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, or isotopically labeled derivative thereof. The pharmaceutical composition may be useful for treating and/or preventing a proliferative or infectious disease.

[8] In another embodiment, the present disclosure provides methods for treating and/or preventing proliferative diseases. Exemplary proliferative diseases include cancer (*e.g.*, leukemia, melanoma, multiple myeloma), benign neoplasm, angiogenesis, inflammatory diseases, autoinflammatory diseases, and autoimmune diseases. In other embodiments, the present disclosure provides methods for treating and/or preventing an infectious disease (*e.g.*, a viral infection).

[9] In still another embodiment, the present disclosure provides methods of down-regulating the expression of CDK7 in a biological sample or subject.

[10] Another embodiment of the disclosure relates to methods of inhibiting the activity of CDK7 in a biological sample or subject.

[11] The present disclosure also provides methods of inhibiting cell growth in a biological sample or subject.

[12] In still another embodiment, the present disclosure provides methods of inducing apoptosis of a cell in a biological sample or a subject.

[13] In yet another embodiment, the present disclosure provides compounds of Formula (Ic), and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, isotopically labeled derivatives, and compositions thereof, for use in the treatment of a proliferative disease in a subject.

[14] In yet another embodiment, the present disclosure provides compounds of Formula (Ic), and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, isotopically labeled derivatives, and compositions thereof, for use in the treatment or prevention of an infectious disease in a subject. In certain embodiments, the infectious disease is a viral infection.

[15] Another embodiment of the present disclosure relates to kits comprising a container with a compound of Formula (Ic), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, or isotopically labeled derivative thereof, or a pharmaceutical composition thereof. In certain embodiments, the kits described herein further include instructions for administering the compound of Formula (Ic), or the pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, or isotopically labeled derivative thereof, or the pharmaceutical composition thereof.

[16] In still another embodiment, the present disclosure provides methods of inhibiting other CDKs, specifically CDK12 and/or CDK13, with a compound of Formula (Ic).

[17] The details of one or more embodiments of the present disclosure are set forth herein. Other features, objects, and advantages of the present disclosure will be apparent from the Detailed Description, the Figures, the Examples, and the Claims.

DEFINITIONS

[18] Definitions of specific functional groups and chemical terms are described in more detail

below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[19] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ¹³C- or ¹⁴C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention.

[20] Where a particular enantiomer is preferred, it may, in some embodiments be provided substantially free of the corresponding enantiomer, and may also be referred to as "optically enriched." "Optically-enriched," as used herein, means that the compound is made up of a significantly greater proportion of one enantiomer. In certain embodiments the compound is made up of at least about 90% by weight of a preferred enantiomer. In other embodiments the compound is made up of at least about 95%, 98%, or 99% by weight of a preferred enantiomer. Preferred enantiomers may be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts or prepared by asymmetric syntheses. See, for

example, Jacques et al., *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen, et al., *Tetrahedron* 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972).

[21] “Halo” or “halogen” refers to fluorine (fluoro, –F), chlorine (chloro, –Cl), bromine (bromo, –Br), or iodine (iodo, –I).

[22] These and other exemplary substituents are described in more detail in the Detailed Description, Figures, Examples, and Claims. The invention is not intended to be limited in any manner by the above exemplary listing of substituents.

Other definitions

[23] The following definitions are more general terms used throughout the present application:

[24] As used herein, the term “pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.*, describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1–19, incorporated herein by reference.

Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods known in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate,

propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4} \text{ alkyl})_4^-$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[25] The term “solvate” refers to forms of the compound that are associated with a solvent, usually by a solvolysis reaction. This physical association may include hydrogen bonding. Conventional solvents include water, methanol, ethanol, acetic acid, DMSO, THF, diethyl ether, and the like. The compounds of Formula (I) or Formula (II) may be prepared, *e.g.*, in crystalline form, and may be solvated. Suitable solvates include pharmaceutically acceptable solvates and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances, the solvate will be capable of isolation, for example, when one or more solvent molecules are incorporated in the crystal lattice of a crystalline solid. “Solvate” encompasses both solution-phase and isolable solvates. Representative solvates include hydrates, ethanolates, and methanolates.

[26] The term “hydrate” refers to a compound which is associated with water. Typically, the number of the water molecules contained in a hydrate of a compound is in a definite ratio to the number of the compound molecules in the hydrate. Therefore, a hydrate of a compound may be represented, for example, by the general formula $R \cdot x \text{ H}_2\text{O}$, wherein R is the compound and wherein x is a number greater than 0. A given compound may form more than one type of hydrates, including, *e.g.*, monohydrates (x is 1), lower hydrates (x is a number greater than 0 and smaller than 1, *e.g.*, hemihydrates ($R \cdot 0.5 \text{ H}_2\text{O}$)), and polyhydrates (x is a number greater than 1, *e.g.*, dihydrates ($R \cdot 2 \text{ H}_2\text{O}$) and hexahydrates ($R \cdot 6 \text{ H}_2\text{O}$)).

[27] The term “tautomers” refer to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of π electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. Another example of tautomerism is the aci- and nitro- forms of phenylnitromethane that are likewise formed by treatment with acid or base.

[28] Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest.

[29] It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed “isomers”. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers”.

[30] Stereoisomers that are not mirror images of one another are termed “diastereomers” and those that are non-superimposable mirror images of each other are termed “enantiomers”. When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (*i.e.*, as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a “racemic mixture”.

[31] A “subject” to which administration is contemplated includes, but is not limited to, humans (*i.e.*, a male or female of any age group, *e.g.*, a pediatric subject (*e.g.*, infant, child, adolescent) or adult subject (*e.g.*, young adult, middle-aged adult, or senior adult)) and/or other non-human animals, for example, mammals (*e.g.*, primates (*e.g.*, cynomolgus monkeys, rhesus monkeys); commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs) and birds (*e.g.*, commercially relevant birds such as chickens, ducks, geese, and/or turkeys). In certain embodiments, the animal is a mammal. The animal may be a male or female and at any stage of development. A non-human animal may be a transgenic animal.

[32] The terms “administer,” “administering,” or “administration,” as used herein refers to implanting, absorbing, ingesting, injecting, inhaling, or otherwise introducing an inventive compound, or a pharmaceutical composition thereof.

[33] As used herein, the terms “treatment,” “treat,” and “treating” refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a “pathological condition” (*e.g.*, a disease, disorder, or condition, or one or more signs or symptoms thereof) described herein. In some embodiments, “treatment,” “treat,” and “treating” require that signs or symptoms of the disease disorder or condition have developed or have been observed. In other embodiments,

treatment may be administered in the absence of signs or symptoms of the disease or condition. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (*e.g.*, in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence.

[34] As used herein, the terms “condition,” “disease,” and “disorder” are used interchangeably.

[35] An “effective amount” of a compound of Formula (I) or Formula (II) refers to an amount sufficient to elicit the desired biological response, *i.e.*, treating the condition. As will be appreciated by those of ordinary skill in this art, the effective amount of a compound of Formula (I) or Formula (II) may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the condition being treated, the mode of administration, and the age and health of the subject. An effective amount encompasses therapeutic and prophylactic treatment. For example, in treating cancer, an effective amount of an inventive compound may reduce the tumor burden or stop the growth or spread of a tumor.

[36] A “therapeutically effective amount” of a compound of Formula (I) or Formula (II) is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to delay or minimize one or more symptoms associated with the condition. In some embodiments, a therapeutically effective amount is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to minimize one or more symptoms associated with the condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the condition. The term “therapeutically effective amount” can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of the condition, or enhances the therapeutic efficacy of another therapeutic agent.

[37] A “prophylactically effective amount” of a compound of Formula (I) or Formula (II) is an amount sufficient to prevent a condition, or one or more symptoms associated with the condition or prevent its recurrence. A prophylactically effective amount of a compound means an amount of a therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the condition. The term “prophylactically effective amount” can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of

another prophylactic agent.

[38] The terms “neoplasm” and “tumor” are used herein interchangeably and refer to an abnormal mass of tissue wherein the growth of the mass surpasses and is not coordinated with the growth of a normal tissue. A neoplasm or tumor may be “benign” or “malignant,” depending on the following characteristics: degree of cellular differentiation (including morphology and functionality), rate of growth, local invasion, and metastasis. A “benign neoplasm” is generally well differentiated, has characteristically slower growth than a malignant neoplasm, and remains localized to the site of origin. In addition, a benign neoplasm does not have the capacity to infiltrate, invade, or metastasize to distant sites. Exemplary benign neoplasms include, but are not limited to, lipoma, chondroma, adenomas, acrochordon, senile angiomas, seborrheic keratoses, lentigos, and sebaceous hyperplasias. In some cases, certain “benign” tumors may later give rise to malignant neoplasms, which may result from additional genetic changes in a subpopulation of the tumor’s neoplastic cells, and these tumors are referred to as “pre-malignant neoplasms.” An exemplary pre-malignant neoplasm is a teratoma. In contrast, a “malignant neoplasm” is generally poorly differentiated (anaplasia) and has characteristically rapid growth accompanied by progressive infiltration, invasion, and destruction of the surrounding tissue. Furthermore, a malignant neoplasm generally has the capacity to metastasize to distant sites.

[39] As used herein, the term “cancer” refers to a malignant neoplasm (*Stedman’s Medical Dictionary*, 25th ed.; Hensyl ed.; Williams & Wilkins: Philadelphia, 1990). Exemplary cancers include, but are not limited to, acoustic neuroma; adenocarcinoma; adrenal gland cancer; anal cancer; angiosarcoma (*e.g.*, lymphangiosarcoma, lymphangioendotheliosarcoma, hemangiosarcoma); appendix cancer; benign monoclonal gammopathy; biliary cancer (*e.g.*, cholangiocarcinoma); bladder cancer; breast cancer (*e.g.*, adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer, medullary carcinoma of the breast); brain cancer (*e.g.*, meningioma, glioblastomas, glioma (*e.g.*, astrocytoma, oligodendroglioma), medulloblastoma); bronchus cancer; carcinoid tumor; cervical cancer (*e.g.*, cervical adenocarcinoma); choriocarcinoma; chordoma; craniopharyngioma; colorectal cancer (*e.g.*, colon cancer, rectal cancer, colorectal adenocarcinoma); connective tissue cancer; epithelial carcinoma; ependymoma; endotheliosarcoma (*e.g.*, Kaposi’s sarcoma, multiple idiopathic hemorrhagic sarcoma); endometrial cancer (*e.g.*, uterine cancer, uterine sarcoma); esophageal cancer (*e.g.*, adenocarcinoma of the esophagus, Barrett’s adenocarcinoma); Ewing’s sarcoma; eye cancer

(*e.g.*, intraocular melanoma, retinoblastoma); familial hypereosinophilia; gall bladder cancer; gastric cancer (*e.g.*, stomach adenocarcinoma); gastrointestinal stromal tumor (GIST); germ cell cancer; head and neck cancer (*e.g.*, head and neck squamous cell carcinoma, oral cancer (*e.g.*, oral squamous cell carcinoma), throat cancer (*e.g.*, laryngeal cancer, pharyngeal cancer, nasopharyngeal cancer, oropharyngeal cancer)); hematopoietic cancers (*e.g.*, leukemia such as acute lymphocytic leukemia (ALL) (*e.g.*, B-cell ALL, T-cell ALL), acute myelocytic leukemia (AML) (*e.g.*, B-cell AML, T-cell AML), chronic myelocytic leukemia (CML) (*e.g.*, B-cell CML, T-cell CML), and chronic lymphocytic leukemia (CLL) (*e.g.*, B-cell CLL, T-cell CLL)); lymphoma such as Hodgkin lymphoma (HL) (*e.g.*, B-cell HL, T-cell HL) and non-Hodgkin lymphoma (NHL) (*e.g.*, B-cell NHL such as diffuse large cell lymphoma (DLCL) (*e.g.*, diffuse large B-cell lymphoma), follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), marginal zone B-cell lymphomas (*e.g.*, mucosa-associated lymphoid tissue (MALT) lymphomas, nodal marginal zone B-cell lymphoma, splenic marginal zone B-cell lymphoma), primary mediastinal B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma (*i.e.*, Waldenström's macroglobulinemia), hairy cell leukemia (HCL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma and primary central nervous system (CNS) lymphoma; and T-cell NHL such as precursor T-lymphoblastic lymphoma/leukemia, peripheral T-cell lymphoma (PTCL) (*e.g.*, cutaneous T-cell lymphoma (CTCL) (*e.g.*, mycosis fungoides, Sezary syndrome), angioimmunoblastic T-cell lymphoma, extranodal natural killer T-cell lymphoma, enteropathy type T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, and anaplastic large cell lymphoma); a mixture of one or more leukemia/lymphoma as described above; and multiple myeloma (MM), heavy chain disease (*e.g.*, alpha chain disease, gamma chain disease, mu chain disease); hemangioblastoma; hypopharynx cancer; inflammatory myofibroblastic tumors; immunocytic amyloidosis; kidney cancer (*e.g.*, nephroblastoma *a.k.a.* Wilms' tumor, renal cell carcinoma); liver cancer (*e.g.*, hepatocellular cancer (HCC), malignant hepatoma); lung cancer (*e.g.*, bronchogenic carcinoma, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), adenocarcinoma of the lung); leiomyosarcoma (LMS); mastocytosis (*e.g.*, systemic mastocytosis); muscle cancer; myelodysplastic syndrome (MDS); mesothelioma; myeloproliferative disorder (MPD) (*e.g.*, polycythemia vera (PV), essential thrombocytosis (ET), agnogenic myeloid metaplasia (AMM) *a.k.a.* myelofibrosis (MF), chronic idiopathic

myelofibrosis, chronic myelocytic leukemia (CML), chronic neutrophilic leukemia (CNL), hypereosinophilic syndrome (HES)); neuroblastoma; neurofibroma (*e.g.*, neurofibromatosis (NF) type 1 or type 2, schwannomatosis); neuroendocrine cancer (*e.g.*, gastroenteropancreatic neuroendocrine tumor (GEP-NET), carcinoid tumor); osteosarcoma (*e.g.*, bone cancer); ovarian cancer (*e.g.*, cystadenocarcinoma, ovarian embryonal carcinoma, ovarian adenocarcinoma); papillary adenocarcinoma; pancreatic cancer (*e.g.*, pancreatic adenocarcinoma, intraductal papillary mucinous neoplasm (IPMN), Islet cell tumors); penile cancer (*e.g.*, Paget's disease of the penis and scrotum); pinealoma; primitive neuroectodermal tumor (PNT); plasma cell neoplasia; paraneoplastic syndromes; intraepithelial neoplasms; prostate cancer (*e.g.*, prostate adenocarcinoma); rectal cancer; rhabdomyosarcoma; salivary gland cancer; skin cancer (*e.g.*, squamous cell carcinoma (SCC), keratoacanthoma (KA), melanoma, basal cell carcinoma (BCC)); small bowel cancer (*e.g.*, appendix cancer); soft tissue sarcoma (*e.g.*, malignant fibrous histiocytoma (MFH), liposarcoma, malignant peripheral nerve sheath tumor (MPNST), chondrosarcoma, fibrosarcoma, myxosarcoma); sebaceous gland carcinoma; small intestine cancer; sweat gland carcinoma; synovioma; testicular cancer (*e.g.*, seminoma, testicular embryonal carcinoma); thyroid cancer (*e.g.*, papillary carcinoma of the thyroid, papillary thyroid carcinoma (PTC), medullary thyroid cancer); urethral cancer; vaginal cancer; and vulvar cancer (*e.g.*, Paget's disease of the vulva).

[40] The term “angiogenesis” refers to the formation and the growth of new blood vessels. Normal angiogenesis occurs in the healthy body of a subject for healing wounds and for restoring blood flow to tissues after injury. The healthy body controls angiogenesis through a number of means, *e.g.*, angiogenesis-stimulating growth factors and angiogenesis inhibitors. Many disease states, such as cancer, diabetic blindness, age-related macular degeneration, rheumatoid arthritis, and psoriasis, are characterized by abnormal (*i.e.*, increased or excessive) angiogenesis. Abnormal angiogenesis refers to angiogenesis greater than that in a normal body, especially angiogenesis in an adult not related to normal angiogenesis (*e.g.*, menstruation or wound healing). Abnormal angiogenesis can provide new blood vessels that feed diseased tissues and/or destroy normal tissues, and in the case of cancer, the new vessels can allow tumor cells to escape into the circulation and lodge in other organs (tumor metastases).

[41] As used herein, an “inflammatory disease” refers to a disease caused by, resulting from, or resulting in inflammation. The term “inflammatory disease” may also refer to a dysregulated

inflammatory reaction that causes an exaggerated response by macrophages, granulocytes, and/or T-lymphocytes leading to abnormal tissue damage and/or cell death. An inflammatory disease can be either an acute or chronic inflammatory condition and can result from infections or non-infectious causes. Inflammatory diseases include, without limitation, atherosclerosis, arteriosclerosis, autoimmune disorders, multiple sclerosis, systemic lupus erythematosus, polymyalgia rheumatica (PMR), gouty arthritis, degenerative arthritis, tendonitis, bursitis, psoriasis, cystic fibrosis, arthroseitis, rheumatoid arthritis, inflammatory arthritis, Sjogren's syndrome, giant cell arteritis, progressive systemic sclerosis (scleroderma), ankylosing spondylitis, polymyositis, dermatomyositis, pemphigus, pemphigoid, diabetes (*e.g.*, Type I), myasthenia gravis, Hashimoto's thyroiditis, Graves' disease, Goodpasture's disease, mixed connective tissue disease, sclerosing cholangitis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, pernicious anemia, inflammatory dermatoses, usual interstitial pneumonitis (UIP), asbestosis, silicosis, bronchiectasis, berylliosis, talcosis, pneumoconiosis, sarcoidosis, desquamative interstitial pneumonia, lymphoid interstitial pneumonia, giant cell interstitial pneumonia, cellular interstitial pneumonia, extrinsic allergic alveolitis, Wegener's granulomatosis and related forms of angiitis (temporal arteritis and polyarteritis nodosa), inflammatory dermatoses, hepatitis, delayed-type hypersensitivity reactions (*e.g.*, poison ivy dermatitis), pneumonia, respiratory tract inflammation, Adult Respiratory Distress Syndrome (ARDS), encephalitis, immediate hypersensitivity reactions, asthma, hayfever, allergies, acute anaphylaxis, rheumatic fever, glomerulonephritis, pyelonephritis, cellulitis, cystitis, chronic cholecystitis, ischemia (ischemic injury), reperfusion injury, allograft rejection, host-versus-graft rejection, appendicitis, arteritis, blepharitis, bronchiolitis, bronchitis, cervicitis, cholangitis, chorioamnionitis, conjunctivitis, dacryoadenitis, dermatomyositis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, gingivitis, ileitis, iritis, laryngitis, myelitis, myocarditis, nephritis, omphalitis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, pharyngitis, pleuritis, phlebitis, pneumonitis, proctitis, prostatitis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, testitis, tonsillitis, urethritis, urocystitis, uveitis, vaginitis, vasculitis, vulvitis, vulvovaginitis, angitis, chronic bronchitis, osteomyelitis, optic neuritis, temporal arteritis, transverse myelitis, necrotizing fasciitis, and necrotizing enterocolitis.

[42] As used herein, an "autoimmune disease" refers to a disease arising from an inappropriate

immune response of the body of a subject against substances and tissues normally present in the body. In other words, the immune system mistakes some part of the body as a pathogen and attacks its own cells. This may be restricted to certain organs (*e.g.*, in autoimmune thyroiditis) or involve a particular tissue in different places (*e.g.*, Goodpasture's disease which may affect the basement membrane in both the lung and kidney). The treatment of autoimmune diseases is typically with immunosuppression, *e.g.*, medications which decrease the immune response. Exemplary autoimmune diseases include, but are not limited to, glomerulonephritis, Goodpasture's syndrome, necrotizing vasculitis, lymphadenitis, peri-arteritis nodosa, systemic lupus erythematosus, rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, psoriasis, ulcerative colitis, systemic sclerosis, dermatomyositis/polymyositis, anti-phospholipid antibody syndrome, scleroderma, pemphigus vulgaris, ANCA-associated vasculitis (*e.g.*, Wegener's granulomatosis, microscopic polyangiitis), uveitis, Sjogren's syndrome, Crohn's disease, Reiter's syndrome, ankylosing spondylitis, Lyme arthritis, Guillain-Barré syndrome, Hashimoto's thyroiditis, and cardiomyopathy.

[43] The term "autoinflammatory disease" refers to a category of diseases that are similar but different from autoimmune diseases. Autoinflammatory and autoimmune diseases share common characteristics in that both groups of disorders result from the immune system attacking a subject's own tissues and result in increased inflammation. In autoinflammatory diseases, a subject's innate immune system causes inflammation for unknown reasons. The innate immune system reacts even though it has never encountered autoantibodies or antigens in the subject. Autoinflammatory disorders are characterized by intense episodes of inflammation that result in such symptoms as fever, rash, or joint swelling. These diseases also carry the risk of amyloidosis, a potentially fatal buildup of a blood protein in vital organs. Autoinflammatory diseases include, but are not limited to, familial Mediterranean fever (FMF), neonatal onset multisystem inflammatory disease (NOMID), tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), deficiency of the interleukin-1 receptor antagonist (DIRA), and Behçet's disease.

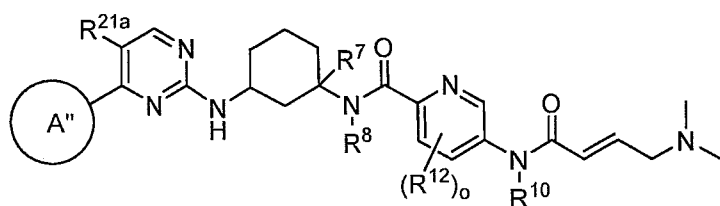
[44] The term "biological sample" refers to any sample including tissue samples (such as tissue sections and needle biopsies of a tissue); cell samples (*e.g.*, cytological smears (such as Pap or blood smears) or samples of cells obtained by microdissection); samples of whole organisms (such as samples of yeasts or bacteria); or cell fractions, fragments or organelles (such

as obtained by lysing cells and separating the components thereof by centrifugation or otherwise). Other examples of biological samples include blood, serum, urine, semen, fecal matter, cerebrospinal fluid, interstitial fluid, mucus, tears, sweat, pus, biopsied tissue (*e.g.*, obtained by a surgical biopsy or needle biopsy), nipple aspirates, milk, vaginal fluid, saliva, swabs (such as buccal swabs), or any material containing biomolecules that is derived from a first biological sample. Biological samples also include those biological samples that are transgenic, such as transgenic oocyte, sperm cell, blastocyst, embryo, fetus, donor cell, or cell nucleus.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS OF THE INVENTION

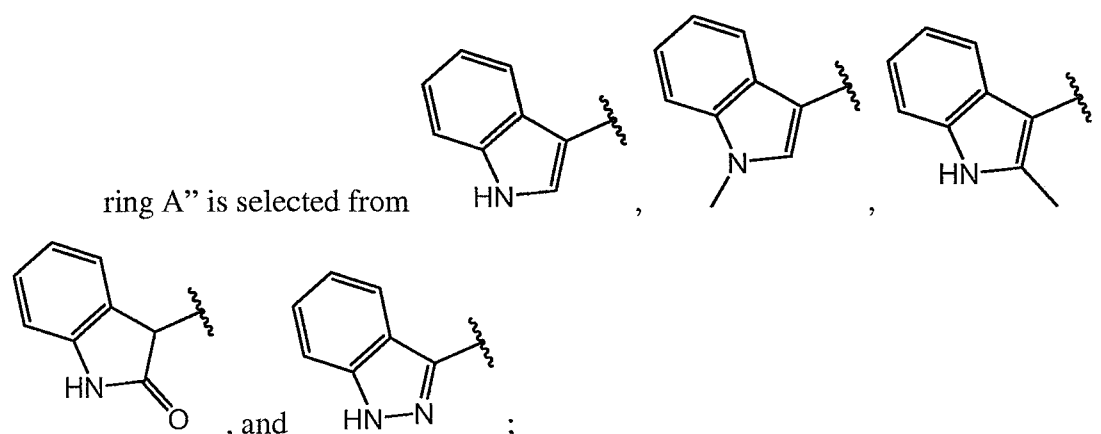
Compounds

[45] In one aspect of the present invention, provided are compounds having structural formula (Ic):



(Ic); or a pharmaceutically acceptable

salt thereof, solvate, hydrate, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein:



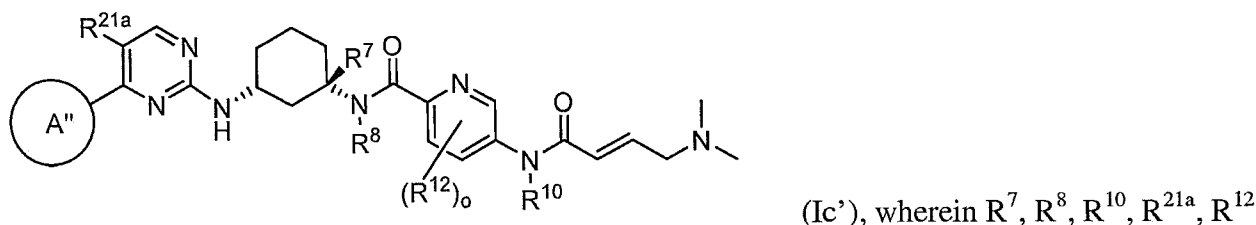
each of R^7 , R^8 and R^{10} is independently selected from hydrogen and methyl;

R^{21a} is selected from -Cl, -CN, -CF₃, -CH₃, and -CH₂CH₃; and

each R^{12} if present is halo; and

o is 0, 1, 2, or 3.

[46] In some embodiments of Formula Ic, the compound has the particular stereochemistry depicted in structural formula Ic':



and o are as defined above from Formula (Ic).

[47] In some embodiments of Formula (Ic) or (Ic'), each R^{12} , if present, is fluoro.

[48] In some embodiments of Formula (Ic) or (Ic') o is 0.

[49] In certain embodiments, the compound of Formula (Ic) is selected from the group consisting of any one of the compounds in Figure 1 and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, and isotopically labeled derivatives thereof.

Pharmaceutical Compositions, Kits, and Administration

[50] The present invention provides pharmaceutical compositions comprising a compound of Formula (Ic), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, or isotopically labeled derivative thereof, as described herein, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition of the invention comprises a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the compound of Formula (Ic), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, or isotopically labeled derivative thereof, is provided in an effective amount in the pharmaceutical composition. In certain embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, the effective amount is a prophylactically effective amount.

[51] Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include the steps of bringing the compound of Formula (Ic) (the "active ingredient") into association with a carrier and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping and/or packaging the product into a desired single- or multi-dose unit.

[52] Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a “unit dose” is a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

[53] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition of the invention will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) active ingredient.

[54] The term “pharmaceutically acceptable excipient” refers to a non-toxic carrier, adjuvant, diluent, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable excipients useful in the manufacture of the pharmaceutical compositions of the invention are any of those that are well known in the art of pharmaceutical formulation and include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Pharmaceutically acceptable excipients useful in the manufacture of the pharmaceutical compositions of the invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[55] Compositions of the present invention may be administered orally, parenterally (including subcutaneous, intramuscular, intravenous and intradermal), by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. In some embodiments, provided compounds or compositions are administrable intravenously and/or orally.

[56] The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intraocular, intravitreal, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intraperitoneal intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, subcutaneously, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. 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 are conventionally employed as a solvent or suspending medium.

[57] Pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added. In some embodiments, a provided oral formulation is formulated for immediate release or sustained/delayed release. In some embodiments, the composition is suitable for buccal or sublingual administration, including tablets, lozenges and pastilles. A provided compound can also be in micro-encapsulated form.

[58] Alternatively, pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. Pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[59] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

[60] For ophthalmic use, provided pharmaceutically acceptable compositions may be formulated as micronized suspensions or in an ointment such as petrolatum.

[61] Pharmaceutically acceptable compositions of this invention may also be administered by nasal aerosol or inhalation.

[62] In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[63] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation.

[64] Compounds provided herein are typically formulated in dosage unit form, e.g., single unit dosage form, for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject or organism will depend upon a variety of factors including the disease being treated and the severity of the disorder; the activity of the specific active ingredient employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific active ingredient employed; the duration of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

[65] The exact amount of a compound required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular compound(s), mode of

administration, and the like. The desired dosage can be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage can be delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

[66] In certain embodiments, an effective amount of a compound for administration one or more times a day to a 70 kg adult human may comprise about 0.0001 mg to about 3000 mg, about 0.0001 mg to about 2000 mg, about 0.0001 mg to about 1000 mg, about 0.001 mg to about 1000 mg, about 0.01 mg to about 1000 mg, about 0.1 mg to about 1000 mg, about 1 mg to about 1000 mg, about 1 mg to about 100 mg, about 10 mg to about 1000 mg, or about 100 mg to about 1000 mg, of a compound per unit dosage form.

[67] In certain embodiments, the compounds of Formula (Ic) may be at dosage levels sufficient to deliver from about 0.001 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, preferably from about 0.1 mg/kg to about 40 mg/kg, preferably from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, and more preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[68] It will be appreciated that dose ranges as described herein provide guidance for the administration of provided pharmaceutical compositions to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult.

[69] It will be also appreciated that a compound or composition, as described herein, can be administered in combination with one or more additional pharmaceutical agents. The compounds or compositions can be administered in combination with additional pharmaceutical agents that improve their bioavailability, reduce and/or modify their metabolism, inhibit their excretion, and/or modify their distribution within the body. It will also be appreciated that the therapy employed may achieve a desired effect for the same disorder, and/or it may achieve different effects.

[70] The compound or composition can be administered concurrently with, prior to, or subsequent to, one or more additional pharmaceutical agents, which may be useful as, *e.g.*,

combination therapies. Pharmaceutical agents include therapeutically active agents. Pharmaceutical agents also include prophylactically active agents. Each additional pharmaceutical agent may be administered at a dose and/or on a time schedule determined for that pharmaceutical agent. The additional pharmaceutical agents may also be administered together with each other and/or with the compound or composition described herein in a single dose or administered separately in different doses. The particular combination to employ in a regimen will take into account compatibility of the inventive compound with the additional pharmaceutical agents and/or the desired therapeutic and/or prophylactic effect to be achieved. In general, it is expected that the additional pharmaceutical agents utilized in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

[71] Exemplary additional pharmaceutical agents include, but are not limited to, anti-proliferative agents, anti-cancer agents, anti-diabetic agents, anti-inflammatory agents, immunosuppressant agents, and a pain-relieving agent. Pharmaceutical agents include small organic molecules such as drug compounds (*e.g.*, compounds approved by the U.S. Food and Drug Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins, and cells.

[72] Also encompassed by the invention are kits (*e.g.*, pharmaceutical packs). The inventive kits may be useful for preventing and/or treating a proliferative disease (*e.g.*, cancer (*e.g.*, leukemia, melanoma, multiple myeloma), benign neoplasm, angiogenesis, inflammatory disease, autoinflammatory disease, or autoimmune disease). The kits provided may comprise an inventive pharmaceutical composition or compound and a container (*e.g.*, a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable container). In some embodiments, provided kits may optionally further include a second container comprising a pharmaceutical excipient for dilution or suspension of an inventive pharmaceutical composition or compound. In some embodiments, the inventive pharmaceutical composition or compound provided in the container and the second container are combined to form one unit dosage form.

[73] Thus, in one aspect, provided are kits including a first container comprising a compound

described herein, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, and isotopically labeled derivative, or a pharmaceutical composition thereof. In certain embodiments, the kit of the invention includes a first container comprising a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In certain embodiments, the kits are useful in preventing and/or treating a proliferative disease in a subject. In certain embodiments, the kits further include instructions for administering the compound, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, isotopically and labeled derivative thereof, or a pharmaceutical composition thereof, to a subject to prevent and/or treat a proliferative disease.

Methods of Treatment and Uses

[74] The present invention also provides methods for the treatment or prevention of a proliferative disease (*e.g.*, cancer, benign neoplasm, angiogenesis, inflammatory disease, autoinflammatory disease, or autoimmune disease) or an infectious disease (*e.g.*, a viral disease) in a subject. Such methods comprise the step of administering to the subject in need thereof an effective amount of a compound of Formula (Ic), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, or isotopically labeled derivative thereof, or a pharmaceutical composition thereof. In certain embodiments, the methods described herein include administering to a subject an effective amount of a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

[75] In certain embodiments, the subject being treated is a mammal. In certain embodiments, the subject is a human. In certain embodiments, the subject is a domesticated animal, such as a dog, cat, cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a companion animal such as a dog or cat. In certain embodiments, the subject is a livestock animal such as a cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a zoo animal. In another embodiment, the subject is a research animal such as a rodent, dog, or non-human primate. In certain embodiments, the subject is a non-human transgenic animal such as a transgenic mouse or transgenic pig.

[76] The proliferative disease to be treated or prevented using the compounds of Formula (Ic) will typically be associated with aberrant activity of CDK7. Aberrant activity of CDK7 may be an elevated and/or an inappropriate (*e.g.*, abnormal) activity of CDK7. In certain embodiments,

CDK7 is not overexpressed, and the activity of CDK7 is elevated and/or inappropriate. In certain other embodiments, CDK7 is overexpressed, and the activity of CDK7 is elevated and/or inappropriate. The compounds of Formula (Ic), and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, isotopically labeled derivatives, and compositions thereof, may inhibit the activity of CDK7 and be useful in treating and/or preventing proliferative diseases.

[77] In other embodiments, the proliferative disease to be treated or prevented using the compounds of Formula (Ic) will typically be associated with aberrant activity of CDK12 and/or CDK13. Aberrant activity of CDK12 and/or CDK13 may be an elevated and/or an inappropriate (e.g., abnormal) activity of CDK12 and/or CDK13. In certain embodiments, CDK12 and/or CDK13 is not overexpressed, and the activity of CDK12 and/or CDK13 is elevated and/or inappropriate. In certain other embodiments, CDK12 and/or CDK13 is overexpressed, and the activity of CDK12 and/or CDK13 is elevated and/or inappropriate. The compounds of Formula (Ic), and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, isotopically labeled derivatives, and compositions thereof, may inhibit the activity of CDK12 and/or CDK13 and be useful in treating and/or preventing proliferative diseases.

[78] A proliferative disease may also be associated with inhibition of apoptosis of a cell in a biological sample or subject. All types of biological samples described herein or known in the art are contemplated as being within the scope of the invention. Inhibition of the activity of CDK7 is expected to cause cytotoxicity via induction of apoptosis. The compounds of Formula (Ic), and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, isotopically labeled derivatives, and compositions thereof, may induce apoptosis, and therefore, be useful in treating and/or preventing proliferative diseases.

[79] In certain embodiments, the proliferative disease to be treated or prevented using the compounds of Formula (Ic) is cancer. All types of cancers disclosed herein or known in the art are contemplated as being within the scope of the invention. In certain embodiments, the proliferative disease is a cancer associated with dependence on BCL-2 anti-apoptotic proteins (e.g., MCL-1 and/or XIAP). In certain embodiments, the proliferative disease is a cancer associated with overexpression of MYC (a gene that codes for a transcription factor). In certain embodiments, the proliferative disease is a hematological malignancy. In certain embodiments, the proliferative disease is a blood cancer. In certain embodiments, the proliferative disease is

leukemia. In certain embodiments, the proliferative disease is chronic lymphocytic leukemia (CLL). In certain embodiments, the proliferative disease is acute lymphoblastic leukemia (ALL). In certain embodiments, the proliferative disease is T-cell acute lymphoblastic leukemia (T-ALL). In certain embodiments, the proliferative disease is chronic myelogenous leukemia (CML). In certain embodiments, the proliferative disease is acute myelogenous leukemia (AML). In certain embodiments, the proliferative disease is lymphoma. In certain embodiments, the proliferative disease is melanoma. In certain embodiments, the proliferative disease is multiple myeloma. In certain embodiments, the proliferative disease is a bone cancer. In certain embodiments, the proliferative disease is osteosarcoma. In some embodiments, the proliferative disease is Ewing's sarcoma. In some embodiments, the proliferative disease is triple-negative breast cancer (TNBC). In some embodiments, the proliferative disease is a brain cancer. In some embodiments, the proliferative disease is neuroblastoma. In some embodiments, the proliferative disease is a lung cancer. In some embodiments, the proliferative disease is small cell lung cancer (SCLC). In some embodiments, the proliferative disease is large cell lung cancer. In some embodiments, the proliferative disease is a benign neoplasm. All types of benign neoplasms disclosed herein or known in the art are contemplated as being within the scope of the invention.

[80] In some embodiments, the proliferative disease is associated with angiogenesis. All types of angiogenesis disclosed herein or known in the art are contemplated as being within the scope of the invention.

[81] In certain embodiments, the proliferative disease is an inflammatory disease. All types of inflammatory diseases disclosed herein or known in the art are contemplated as being within the scope of the invention. In certain embodiments, the inflammatory disease is rheumatoid arthritis. In some embodiments, the proliferative disease is an autoinflammatory disease. All types of autoinflammatory diseases disclosed herein or known in the art are contemplated as being within the scope of the invention. In some embodiments, the proliferative disease is an autoimmune disease. All types of autoimmune diseases disclosed herein or known in the art are contemplated as being within the scope of the invention.

[82] The cell described herein may be an abnormal cell. The cell may be *in vitro* or *in vivo*. In certain embodiments, the cell is a proliferative cell. In certain embodiments, the cell is a blood cell. In certain embodiments, the cell is a lymphocyte. In certain embodiments, the cell is a

cancer cell. In certain embodiments, the cell is a leukemia cell. In certain embodiments, the cell is a CLL cell. In certain embodiments, the cell is a melanoma cell. In certain embodiments, the cell is a multiple myeloma cell. In certain embodiments, the cell is a benign neoplastic cell. In certain embodiments, the cell is an endothelial cell. In certain embodiments, the cell is an immune cell.

[83] In another aspect, the present invention provides methods of down-regulating the expression of CDK7 in a biological sample or subject.

[84] In certain embodiments, the methods described herein comprise the additional step of administering one or more additional pharmaceutical agents in combination with the compound of Formula (Ic), a pharmaceutically acceptable salt thereof, or compositions comprising such compound or pharmaceutically acceptable salt thereof. Such additional pharmaceutical agents include, but are not limited to, anti-proliferative agents, anti-cancer agents, anti-diabetic agents, anti-inflammatory agents, immunosuppressant agents, and a pain-relieving agent. The additional pharmaceutical agent(s) may synergistically augment inhibition of CDK7 or CDK12 and/or CDK13 induced by the inventive compounds or compositions of this invention in the biological sample or subject. Thus, the combination of the inventive compounds or compositions and the additional pharmaceutical agent(s) may be useful in treating proliferative diseases resistant to a treatment using the additional pharmaceutical agent(s) without the inventive compounds or compositions.

[85] In yet another aspect, the present invention provides the compounds of Formula (Ic), and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, isotopically labeled derivatives, and compositions thereof, for use in the treatment of a proliferative disease in a subject. In certain embodiments, provided by the invention are the compounds described herein, and pharmaceutically acceptable salts and compositions thereof, for use in the treatment of a proliferative disease in a subject. In certain embodiments, provided by the invention are the compounds described herein, and pharmaceutically acceptable salts and compositions thereof, for use in inhibiting cell growth. In certain embodiments, provided by the invention are the compounds described herein, and pharmaceutically acceptable salts and compositions thereof, for use in inducing apoptosis in a cell. In certain embodiments, provided by the invention are the compounds described herein, and pharmaceutically acceptable salts and compositions thereof, for use in inhibiting transcription.

EXAMPLES

[86] In order that the invention described herein may be more fully understood, the following examples are set forth. The synthetic and biological examples described in this application are offered to illustrate the compounds, pharmaceutical compositions, and methods provided herein and are not to be construed in any way as limiting their scope.

[87] The compounds provided herein can be prepared from readily available starting materials using modifications to the specific synthesis protocols set forth below that would be well known to those of skill in the art. It will be appreciated that where typical or preferred process conditions (*i.e.*, reaction temperatures, times, mole ratios of reactants, solvents, pressures, *etc.*) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by those skilled in the art by routine optimization procedures.

[88] Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups, and their introduction and removal, are described in Greene *et al.*, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

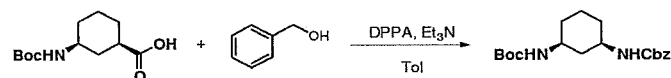
[89] ABBREVIATIONS

Ac	acetyl
ACN	acetonitrile
aq.	aqueous
atm	atmospheres
Boc	<i>tert</i> -butoxy carbonyl
Boc ₂ O	Di- <i>t</i> -butyl dicarbonate
CDI	1,1'-Carbonyldiimidazole
DBU	1-8-Diazabicyclo[5.4.0]undec-7-ene
DCC	N,N'-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DIPEA	N,N-Diisopropyl ethylamine
DMA	Dimethyl adipate
DMF	Dimethylformamide

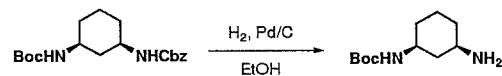
DMSO	Dimethylsulfoxide
DPPA	Diphenoxyphosphoryl azide
EDTA	Ethylenediamine tetraacetic acid
eq(s).	equivalent(s)
EtOAc	Ethyl acetate
Et	Ethyl
EtOH	Ethanol
Et ₃ N	Triethylamine
g	gram(s)
h	hour(s)
HATU	(Dimethylamino)- <i>N,N</i> -dimethyl(3 <i>H</i> -[1,2,3]triazolo[4,5- <i>b</i>]pyridin-3-yloxy)methaniminium hexafluorophosphate
HBTU	O-Benzotriazole- <i>N,N,N',N'</i> -tetramethyl-uronium-hexafluoro-phosphate
Hex	Hexanes
HOBt	1-Hydroxybenzotriazole
HPLC	High pressure liquid chromatography
IPA	Isopropanol
LCMS; LC-MS	liquid chromatography mass spectrometry
MeOH	Methanol
mg	milligram(s)
min	Minute(s)
mL; ml	milliliter(s)
MS	mass spectrometry
MTBE	Methyl <i>tert</i> -butyl ether
mW	megawatt
NMe	N-methyl
NMP	N-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
Pd ₂ dba ₃	Tris(dibenzylideneacetone) dipalladium(0)
Ph	phenyl
r.t.; rt; RT	Room temperature
S., sat.	saturated
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMSI	Trimethylsilyl iodide
X-Phos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

[90] **Example 1. Synthesis of N-((1*S*,3*R*)-3-(5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-ylamino)cyclohexyl)-5-((*E*)-4-(dimethylamino)but-2-enamido)picolinamide (Compound**

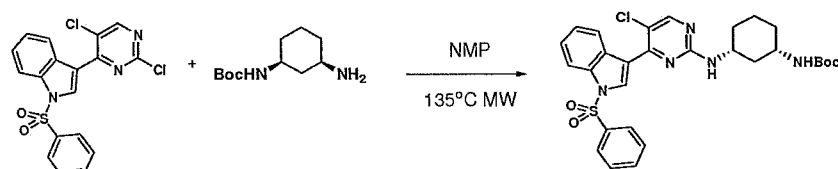
106)

[91] (1S,3R)-3-(Benzyloxycarbonylamino)cyclohexylamino 2,2-dimethylpropionate

[92] To a solution of (1R,3S)-3-(tert-butoxycarbonylamino)cyclohexanecarboxylic acid (prepared following Tetrahedron: *Asymmetry* 2010 (21), 864-866) (8.77 g, 36.1 mmol) was added Et₃N (5.53 mL, 39.7 mmol) and DPPA (7.7 mL, 36.1 mmol). The resulting solution was stirred 2h at 110°C then cooled to 80°C. Benzyl alcohol (4.66mL, 45.1mmol) and triethylamine (5.53 mL, 39.7 mmol) were added and the mixture was stirred for 20h at 80°C. The cooled solution was diluted with EtOAc (100 mL) and water (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 50mL). The combined organics were dried (MgSO₄), filtered, and evaporated to dryness. The residue was purified by SiO₂ chromatography (Hex/EtOAc 1 to 100% gradient), and afforded the title compound (9.89 g, 28.4 mmol, 79%) as a white solid.

[93] tert-butyl (1S,3R)-3-aminocyclohexylcarbamate

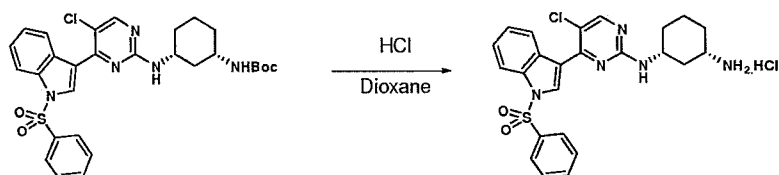
[94] To a degassed solution of (1S,3R)-3-(Benzyloxycarbonylamino)cyclohexylamino 2,2-dimethylpropionate (10 g, 28.4 mmol) in EtOH (473 mL) was added 10% w/w Pd/C (450 mg). The reaction mixture was stirred 5h under H₂ (1 atm). The reaction mixture was filtered through a pad of celite (EtOH), then the filtrate was evaporated to dryness to afford the title compound (6.08 g, 28.4 mmol, 100%) as a white solid.

[95] tert-butyl (1S,3R)-3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexylcarbamate

[96] A solution of 3-(2,5-dichloropyrimidin-4-yl)-1-(phenylsulfonyl)-1H-indole (2.91g, 7.20mmol), tert-butyl (1S,3R)-3-aminocyclohexylcarbamate (1.24 g, 5.76 mmol) and diisopropylethylamine (1.05 mL, 6.05 mmol) in NMP (14.5 mL) was heated 1.5h at 135°C (mW). The mixture was diluted with EtOAc (200 mL), washed with water (50 mL), brine (50

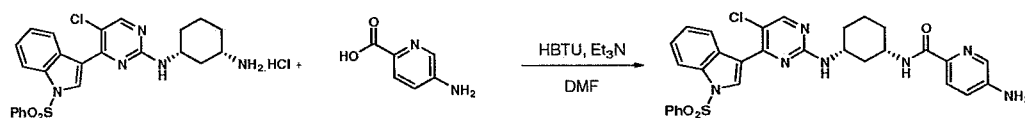
mL), dried (MgSO₄), then filtered and evaporated to dryness. The residue was purified by SiO₂ chromatography (DCM/EtOAc 0 to 30% gradient) and afforded the title compound (1.88 g, 3.23 mmol, 56%) as a light yellow foam.

[97] (1R,3S)-N1-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-yl)cyclohexane-1,3-diamine·HCl



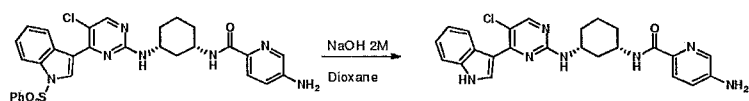
[98] To a solution of tert-butyl (1S,3R)-3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexylcarbamate (1.88 g, 3.23 mmol) in DCM (16.1 mL) was added a solution of 4 N HCl in dioxane (12.11 mL, 48.44 mmol). The resulting mixture was stirred 1.5h at rt before being evaporated to dryness and afforded the title compound (1.72 g, 3.10 mmol, 96%) as a light yellow solid which was used in the next step without further purification.

[99] 5-amino-N-((1S,3R)-3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexyl)picolinamide



[100] To a solution of (1R,3S)-N1-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-yl)cyclohexane-1,3-diamine·HCl (300 mg, 0.579 mmol) in DMF (4 mL) was added Et₃N (322 μL, 2.315 mmol), 5-amino-2-pyridinecarboxylic acid (96 mg, 0.694 mmol), and HBTU (329 mg, 0.868 mmol). The mixture was stirred overnight at rt and then diluted with EtOAc (20 mL). The mixture was then washed twice with a saturated solution of NaHCO₃ (10 mL) followed by brine (5 mL), then dried (MgSO₄), filtered, and evaporated to dryness. The residue was triturated with MTBE and filtered, and the filtrate was evaporated to dryness which afforded the title compound (282 mg, 0.468 mmol, 81%) as a yellow solid.

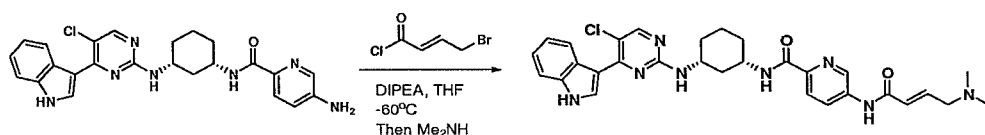
[101] 5-amino-N-((1S,3R)-3-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexyl)picolinamide



[102] A solution of 5-amino-N-((1S,3R)-3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-

yl)pyrimidin-2-ylamino)cyclohexyl)picolinamide in dioxane (5 mL) was treated with a 2M solution of NaOH (3.5 mL, 7.02 mmol) and heated at 75°C for 3h and overnight at rt. The formed solid was filtered and washed several times with water. The solid was dissolved in THF (10 mL) and the resulting solution was evaporated to dryness which afforded the title compound (188 mg, 0.407 mmol, 87%) as a white solid which was used in the next step without further purification.

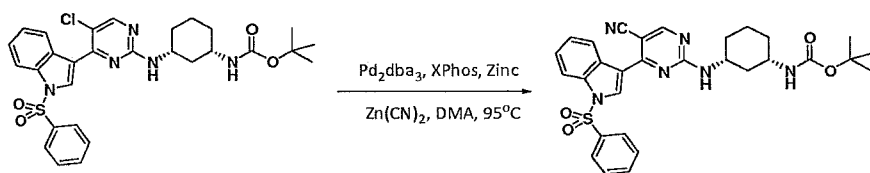
[103] N-((1S,3R)-3-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexyl)-5-((E)-4-(dimethylamino)but-2-enamido)picolinamide



[104] To a -60°C solution of 5-amino-N-((1S,3R)-3-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexyl)picolinamide (188 mg, 0.407mmol) and DIPEA (212 µL, 1.22 mmol) in 3/1 THF/NMP (3.7 mL) was slowly added a 54mg/mL of (E)-4-bromobut-2-enoyl chloride in THF (1.37 mL, 0.407mmol). The mixture was stirred 1h at -60°C and 1h at -20° for 1h before addition of a 2M solution of dimethylamine in THF (814 µL, 1.63 mmol). The mixture was stirred 2h at rt and evaporated to dryness. The residue was purified by reverse phase chromatography (C18, water/ACN 0 to 50% gradient) and afforded the title compound (60 mg, 0.105 mmol, 25%) as a white solid after lyophilisation. ¹H NMR (500 MHz, DMSO) δ 11.82 (s, 1H), 10.54 (s, 1H), 8.87 (d, *J* = 2.1 Hz, 1H), 8.61 (bs, 1H), 8.53 – 8.40 (m, 2H), 8.32 – 8.14 (m, 2H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.48 (d, *J* = 8.6 Hz, 1H), 7.39 – 7.08 (m, 3H), 6.80 (dt, *J* = 15.4, 5.8 Hz, 1H), 6.29 (d, *J* = 15.4 Hz, 1H), 3.94 (s, 2H), 3.08 (d, *J* = 5.1 Hz, 2H), 2.18 (s, 6H), 2.10 – 1.69 (m, 3H), 1.69 – 1.35 (m, 3H), 1.35 – 1.18 (m, 1H).

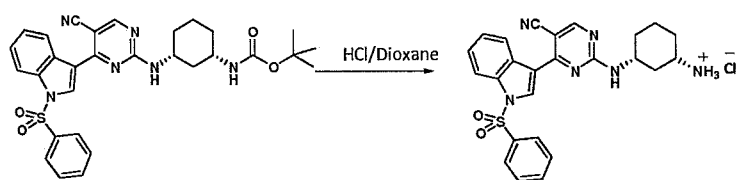
[105] Example 2. Synthesis of N-((1S,3R)-3-(5-cyano-4-(1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexyl)-5-((E)-4-(dimethylamino)but-2-enamido)picolinamide (Compound 110)

[106] tert-butyl (1S,3R)-3-(5-cyano-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexylcarbamate



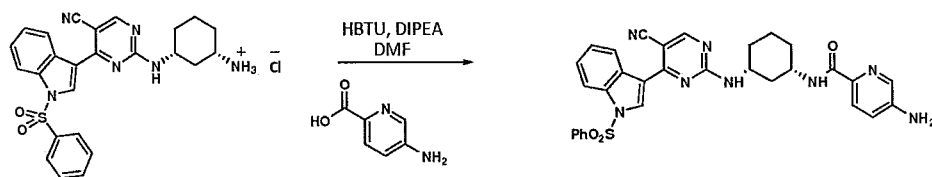
[107] A degassed solution of tert-butyl (1S,3R)-3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexylcarbamate prepared as in Example 1 (250 mg, 0.429 mmol), Zn (2.8 mg, 0.04 mmol), Pd₂dba₃ (39.3 mg, 0.04 mmol), X-Phos (41 mg, 0.09 mmol) and Zn(CN)₂ (30.3 mg, 0.26 mmol) in DMA (8.6 mL) was heated at 95°C for 18h. The cooled solution was diluted with EtOAc (20 mL) and washed with water (3 x 5 mL), brine (5 mL), dried (MgSO₄) and evaporated to dryness. The residue was purified by SiO₂ chromatography (DCM/EtOAc 0 to 70% gradient) and afforded the title compound (180 mg, 0.314 mmol, 73%) as a bright yellow foam.

[108] 2-((1R,3S)-3-aminocyclohexylamino)-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidine-5-carbonitrile·HCl



[109] To a solution of tert-butyl (1S,3R)-3-(5-cyano-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexylcarbamate (180 mg, 0.314 mmol) in DCM (3.1 mL) was added a 4M solution of HCl in dioxane (0.79 mL, 3.14 mmol). The mixture was stirred 3h at rt and evaporated to dryness to afford the title compound (160 mg, 0.314 mmol, 100%) as a white solid which was used in the next step without further purification.

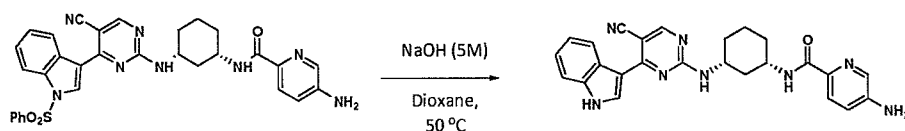
[110] 5-amino-N-((1S,3R)-3-(5-cyano-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexyl)picolinamide



[111] To a solution of 2-((1R,3S)-3-aminocyclohexylamino)-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidine-5-carbonitrile·HCl (160 mg, 0.338 mmol), 5-amino-2-pyridinecarboxylic acid (56 mg, 0.406 mmol) and DIPEA (236 µL, 1.35 mmol) in DMF (3.4 mL) was added, followed by HBTU (174 mg, 1.352 mmol). The mixture was stirred 16h at rt then diluted with EtOAc (30 mL) and a saturated solution of NaHCO₃ (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 10 ML). The combined organic layers were dried (MgSO₄), filtered, and evaporated to dryness. The residue was purified by SiO₂ chromatography

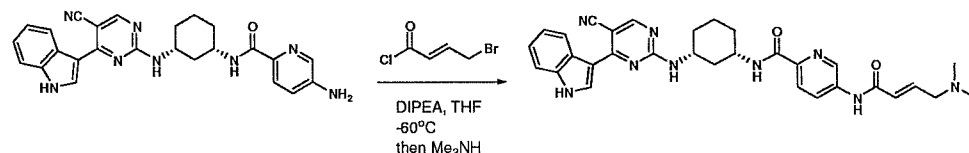
(EtOAc/DCM 1 to 100% gradient) and afforded the title compound (123 mg, 0.207 mmol, 61%) as a white solid.

[112] 5-amino-N-((1S,3R)-3-(5-cyano-4-(1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexyl)picolinamide



[113] A solution of 5-amino-N-((1S,3R)-3-(5-cyano-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexyl)picolinamide (123 mg, 0.208 mmol) in dioxane (4 mL) was treated with a 5M solution of NaOH (0.210 mL, 1.04 mmol) and heated at 50 °C for 7h. The cooled solution was diluted with water (5 mL) and the aqueous layer was extracted with methyl-THF (3 x 10 mL). The combined organic layers were dried (MgSO₄), filtered and evaporated to dryness. The residue was purified by reverse phase chromatography (C18, water/ACN 0 to 100% gradient) and afforded the title compound (54 mg, 0.119 mmol, 58%) as a white solid.

[114] N-((1S,3R)-3-(5-cyano-4-(1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexyl)-5-((E)-4-(dimethylamino)but-2-enamido)picolinamide

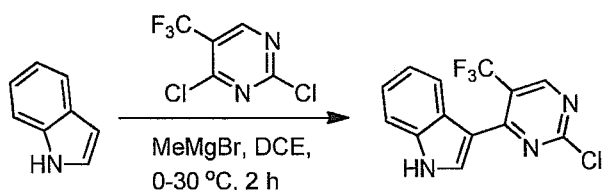


[115] To a -60 °C solution of 5-amino-N-((1S,3R)-3-(5-cyano-4-(1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexyl)picolinamide (50 mg, 0.111 mmol) and DIPEA (58 µL, 0.334 mmol) in 3/1 THF/NMP (4.0 mL) was slowly added a 54mg/mL of (E)-4-bromobut-2-enoyl chloride in THF (239 µL, 0.117 mmol). The mixture was stirred 4h at -60 °C before addition of a 2M solution of dimethylamine in THF (333 µL, 0.667 mmol). The mixture was stirred 2h at rt and evaporated to dryness. The residue was purified by reverse phase chromatography (C18, water/ACN +0.1% HCO₂H 0 to 100% gradient) and afforded the title compound (35 mg, 0.062 mmol, 56%) as a white solid after lyophilisation. ¹H NMR (500 MHz, DMSO) indicated the presence of rotamers. Rotamer 1: δ 12.00 (s, 1H), 10.53 (s, 1H), 8.88 (dd, *J* = 8.6, 2.4 Hz, 1H), 8.57 (s, 1H) 8.57 – 8.42 (m, 2H), 8.20 (ddd, *J* = 20.8, 8.4, 3.3 Hz, 2H), 8.01 (d, *J* = 8.7 Hz, 1H), 7.52 (dd, *J* = 14.0, 8.0 Hz, 1H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.24 (m, 1H), 6.80 (dt, *J* = 15.4, 5.8 Hz, 1H), 6.29 (d, *J* = 15.5 Hz, 1H), 4.10-3.87 (m, 2H), 3.07 (d, *J* = 5.8 Hz, 2H), 2.27 – 2.06 (m, 2H), 2.18 (s, 6H), 2.04 (d,

$J = 8.2$ Hz, 1H), 1.94-1.79 (m, 2H), 1.64 – 1.28 (m, 3H). Rotamer 2: δ 11.95 (s, 1H), 10.54 (s, 2H), 8.72 (d, $J = 7.7$ Hz, 1H), 8.65 (s, 1H), 8.57 – 8.42 (m, 2H), 8.20 (ddd, $J = 20.8, 8.4, 3.3$ Hz, 2H), 8.01 (d, $J = 8.7$ Hz, 2H), 7.52 (dd, $J = 14.0, 8.0$ Hz, 1H), 7.31 (t, $J = 7.3$ Hz, 1H), 7.24 (m, 1H), 6.80 (dt, $J = 15.4, 5.8$ Hz, 1H), 6.29 (d, $J = 15.5$ Hz, 1H), 4.10-3.87 (m, 2H), 3.07 (d, $J = 5.8$ Hz, 2H), 2.27 – 2.06 (m, 2H), 2.18 (s, 6H), 2.04 (d, $J = 8.2$ Hz, 1H), 1.94-1.79 (m, 2H), 1.64 – 1.28 (m, 3H); MS (m/z): 563.64 $[M+1]^+$.

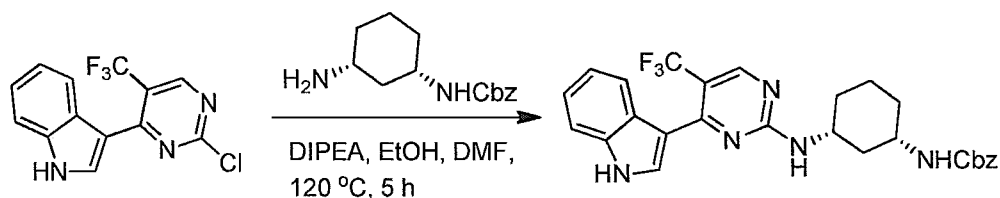
[116] Example 3. Synthesis of N-((1S,3R)-3-((4-(1H-indol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-5-((E)-4-(dimethylamino)but-2-enamido)picolinamide (Compound 248).

[117] 3-(2-chloro-5-(trifluoromethyl)pyrimidin-4-yl)-1H-indole



[118] To a mixture of indole (3.0 g, 25.61 mmol) in DCE (40 mL) was added MeMgBr (38.4 mL, 38.42 mmol) at 0 °C, the mixture was stirred at 0 °C for 0.5 h. Then 2,4-dichloro-5-(trifluoromethyl)pyrimidine (5.56 g, 25.61 mmol) was added at 0 °C, the mixture was stirred at 30 °C for 1.5 h. The mixture was poured into water, extracted with EA, and the organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate = 50:1 ~ 20:1) to afford title compound (5.4 g, 70.8%) as yellow solid.

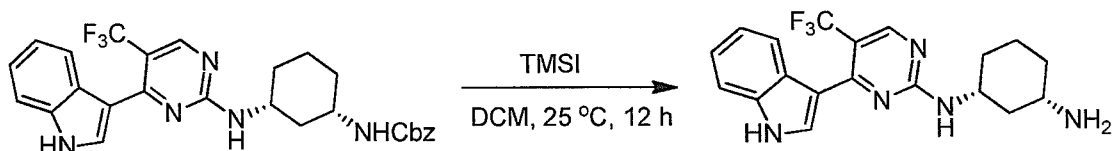
[119] Benzyl((1S,3R)-3-((4-(1H-indol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)carbamate



To a mixture of 3-[2-chloro-5-(trifluoromethyl)pyrimidin-4-yl]-1H-indole (1.0 g, 3.36 mmol) and benzyl ((1S,3R)-3-aminocyclohexyl)carbamate (1.0 g, 4.03 mmol) in DMF (10 mL) was added DIPEA (2.2 g, 16.8 mmol) at 25 °C, the mixture was heated to 120 °C and stirred for 5 h. The mixture was poured into water (50 mL), extracted with EA (20 mL*2), and the

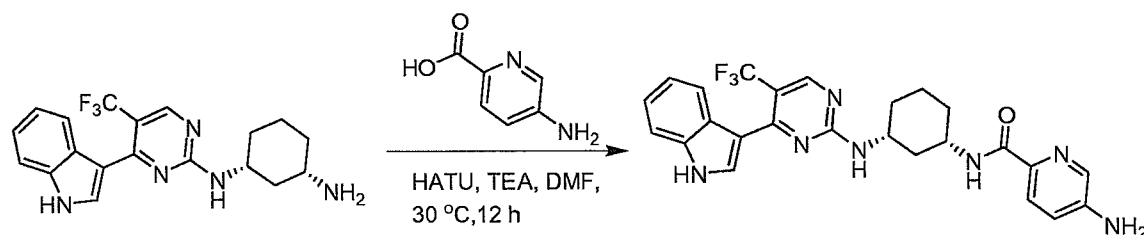
organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash column (DCM/MeOH = 100:1~50:1) to afford title compound (1.3 g, 76.4%) as yellow solid.

[120] (1R,3S)-N1-(4-(1H-indol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)cyclohexane-1,3-diamine



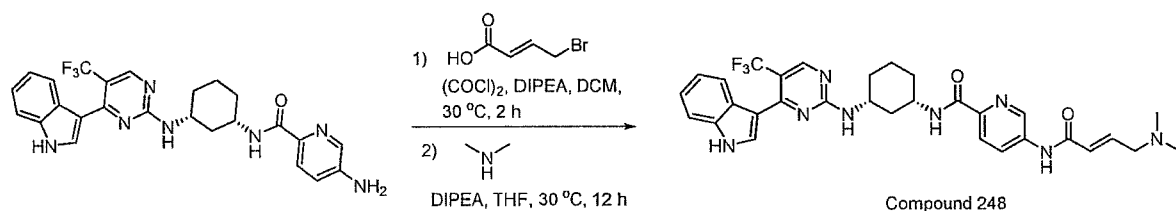
[121] To a mixture of benzyl((1S,3R)-3-((4-(1H-indol-3-yl)-5-(trifluoromethyl) pyrimidin-2-yl) amino)cyclohexyl)carbamate (1.0 g, 2.1 mmol) in DCM (20 mL) was added TMSI (2.1 g, 10.5 mmol) at 30 °C, the mixture was stirred for 12 h. The mixture was concentrated, and the residue was purified by flash column to afford title compound (600 mg, 90.9 %) as a yellow solid.

[122] N-((1S,3R)-3-((4-(1H-indol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-5-aminopicolinamide



[123] To a mixture of (1R,3S)-N1-[4-(1H-indol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl] cyclohexane-1,3-diamine (400 mg, 0.97 mmol) and 5-aminopyridine-2-carboxylic acid (147.6 mg, 1.07 mmol) in DMF (10 mL) was added TEA (196 mg, 1.96 mmol) and HATU (406.8 mg, 1.07 mmol) at 30 °C and the mixture was stirred for 12 h. The mixture poured into water, extracted with EA, and the organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography to afford title compound (400 mg, 83.1%) as yellow solid. **LCMS:** ($\text{M}+\text{H}^+$): 496.3 @ 0.813 min (5-95% ACN in H_2O , 1.5 min)

[124] N-((1S,3R)-3-((4-(1H-indol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexyl)-5-((E)-4-(dimethylamino)but-2-enamido)picolinamide

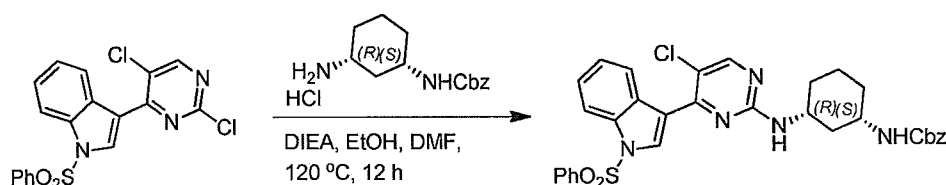


[125] To a mixture of (E)-4-bromobut-2-enoic acid (99.9 mg, 0.6 mmol) in DCM (5 mL) was added (COCl)₂ (256.2 mg, 2.0 mmol) at 30 °C under N₂, the mixture was stirred for 1 h. Then this mixture was added to a solution of 5-amino-N-[(1S, 3R)-3-[[4-(1H-indol-3-yl)-5-

[126] (trifluoromethyl)pyrimidin-2-yl]amino]cyclohexyl]pyridine-2-carboxamide (200 mg, 0.4 mmol) and DIPEA (156.4 mg, 1.2 mmol) in DCM (5 mL), the mixture was stirred at 30 °C for 1 h. Then dimethylamine (27.3 mg, 0.6 mmol) was added, the mixture was stirred for 12 h. The mixture was concentrated, and the residue was purified by pre-HPLC (HCl condition) to afford title compound (25 mg, 10.2%) as yellow solid. **LCMS:** ET1741-66-P1A (M+H⁺): 304.2 @ 2.448 min (10-80% ACN in H₂O, 4.5 min). **¹H NMR:** ET1741-66-P1A (MeOD, 400 MHz) δ 8.91 (br. s., 1 H), 8.49 (br. s., 1 H), 8.39 (br. s., 1 H), 8.25 (d, *J* = 8.28 Hz, 1 H), 8.08 (d, *J* = 8.78 Hz, 1 H), 7.87 (br. s., 1 H), 7.47 (br. s., 1 H), 7.24 (br. s., 2 H), 6.99 (d, *J* = 15.31 Hz, 1 H), 6.32 (d, *J* = 15.56 Hz, 1 H), 3.22 (d, *J* = 5.77 Hz, 2 H), 2.44-2.54 (m, 1 H), 2.23-2.26 (m, 1 H), 2.23-2.43 (m, 6 H), 2.18 (br. s., 1 H), 2.05 (br. s., 1 H), 1.97 (d, *J* = 11.54 Hz, 1 H), 1.59 (br. s., 3 H), 1.28-1.46 (m, 3 H).

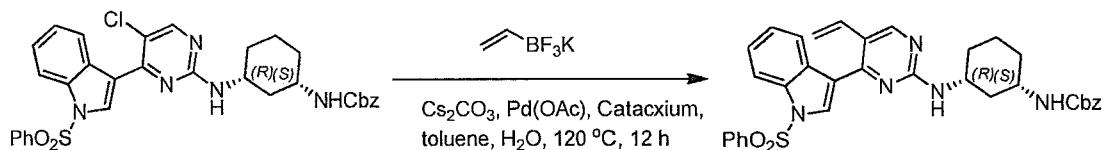
[127] **Example 4. Synthesis of 5-[(E)-4-(dimethylamino)but-2-enoyl]amino]-N-[(1S,3R)-3-[[5-ethyl-4-(1H-indol-3-yl)pyrimidin-2-yl]amino]cyclohexyl]pyridine-2-carboxamide (Compound 262).**

[128] **Benzyl N-[(1S,3R)-3-[[4-[1-(benzenesulfonyl)indol-3-yl]-5-chloro-pyrimidin-2-yl]amino]cyclohexyl]carbamate**



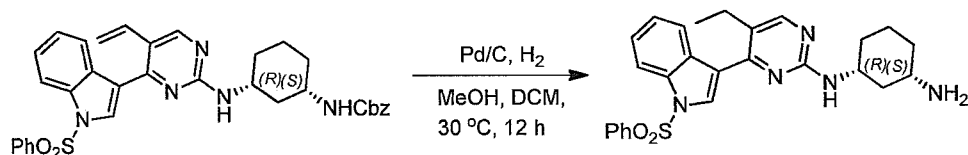
[129] A mixture of benzyl N-[(1S,3R)-3-aminocyclohexyl]carbamate hydrochloride (5 g, 17.56 mmol), 1-(benzenesulfonyl)-3-(2,5-dichloropyrimidin-4-yl)indole (6.4 g, 15.80 mmol) and DIEA (11.4 g, 87.79 mmol) in DMF (50 mL) and EtOH (50 mL) was heated to 120 °C and stirred for 12 h under N₂. The mixture was poured into water (300 mL), extracted with EA (150 mL*3), and the organic phase was dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by column to afford title compound (4 g, 37%) as yellow solid.

[130] Benzyl N-[(1S,3R)-3-[[4-[1-(benzenesulfonyl)indol-3-yl]-5-vinyl-pyrimidin-2-yl]amino]cyclohexyl]carbamate



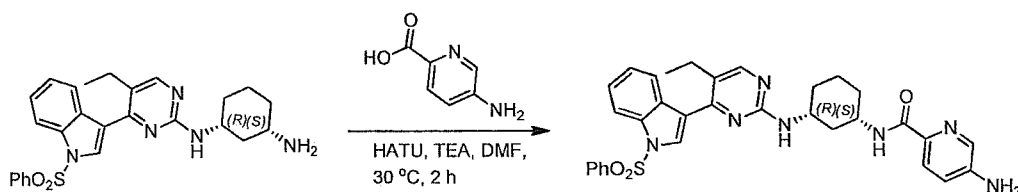
[131] To a mixture of benzyl N-[(1S,3R)-3-[[4-[1-(benzenesulfonyl)indol-3-yl]-5-chloro-pyrimidin-2-yl]amino]cyclohexyl]carbamate (1.5 g, 2.43 mmol), potassium hydride trifluoro(vinyl) boron (1.63 g, 12.17 mmol) and Cs_2CO_3 (2.38 g, 7.30 mmol) in toluene (30 mL) and H_2O (6 mL) was added Catacixium (2.28 g, 2.43 mmol) and $\text{Pd}(\text{OAc})_2$ (273.29 mg, 1.22 mmol) under N_2 protection, the mixture was heated to 120 °C, and stirred for 12 h. The mixture was added water (50 mL), extracted with EA (50 mL*3), and the organic phase was dried over N_2SO_4 and concentrated. The residue was purified by column to afford title compound (1.60 g, 86.7%) as yellow solid.

[132] (1R,3S)-N1-[4-[1-(benzenesulfonyl)indol-3-yl]-5-ethyl-pyrimidin-2-yl]cyclohexane-1,3-diamine



[133] A solution of benzyl N-[(1S,3R)-3-[[4-[1-(benzenesulfonyl)indol-3-yl]-5-vinyl-pyrimidin-2-yl]amino]cyclohexyl]carbamate (1.5 g, 2.47 mmol) and Pd/C (1g, 2.47 mmol) in MeOH (200 mL) and DCM (20 mL) was stirred at 30 °C for 12 h under H_2 (50 Psi) protection. The mixture was filtrated, and the filtrate was concentrated under vacuum to give title compound (1.2 g, 81.7%) as yellow solid.

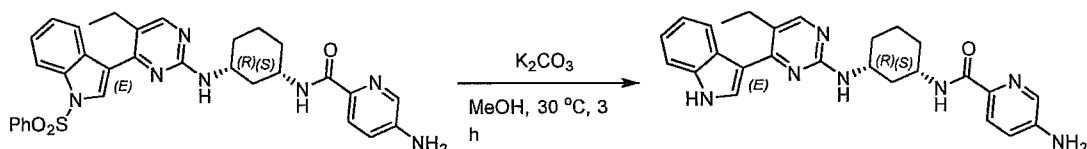
[134] 5-amino-N-[(1S,3R)-3-[[4-[1-(benzenesulfonyl)indol-3-yl]-5-ethyl-pyrimidin-2-yl]amino]cyclohexyl]pyridine-2-carboxamide



[135] To a mixture of (1R,3S)-N1-[4-[1-(benzenesulfonyl)indol-3-yl]-5-ethyl-pyrimidin-2-yl]cyclohexane-1,3-diamine (400 mg, 0.84 mmol) and 5-aminopyridine-2-carboxylic acid (128

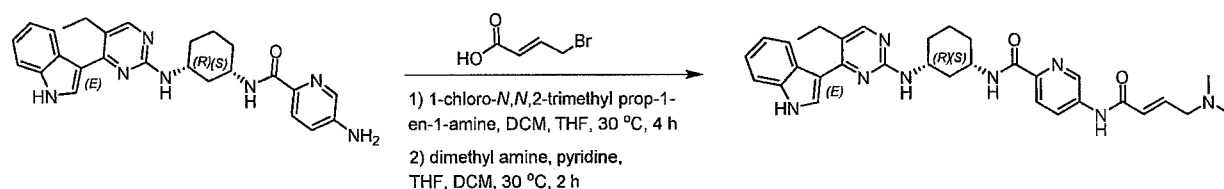
mg, 0.93 mmol) in DCM (20 mL) was added TEA (170 mg, 1.68 mmol) and HATU (480 mg, 1.26 mmol) at 30 °C and the mixture was stirred for 2 h. The mixture was poured into water (30 mL), extracted with EA (20 mL*3), the organic phase was concentrated, and the residue was purified by pre-HPLC to afford title compound (100 mg, 10%) as yellow solid.

[136] 5-amino-N-[(1S,3R)-3-[[5-ethyl-4-(1H-indol-3-yl)pyrimidin-2-yl]amino]cyclohexyl]pyridine-2-carboxamide



[137] A solution of 5-amino-N-[(1S,3R)-3-[[4-[1-(benzenesulfonyl)indol-3-yl]-5-ethylpyrimidin-2-yl]amino]cyclohexyl]pyridine-2-carboxamide (120 mg, 0.2 mmol) and K₂CO₃ (56 mg, 0.40 mmol) in MeOH (10 mL) was stirred at 30 °C for 3 h. The mixture was poured into water (20 mL), extracted with EA (20 mL*2), and the organic phase was dried over Na₂SO₄ and concentrated to give title compound (90 mg, 78.5%) as white solid. **LCMS:** (M+H⁺): 456.2 @ 0.743 min (5-95% ACN in H₂O, 1.5 min)

[138] 5-[[*(E)*-4-(dimethylamino)but-2-enoyl]amino]-N-[(1S,3R)-3-[[5-ethyl-4-(1H-indol-3-yl)pyrimidin-2-yl]amino]cyclohexyl]pyridine-2-carboxamide (Compound 262)

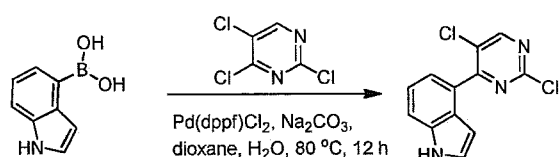


[139] To a solution of (E)-4-bromobut-2-enoic acid (38 mg, 0.21 mmol) in DCM (5 mL) was added 1-chloro-N,N,2-trimethyl-prop-1-en-1-amine (35 mg, 0.26 mmol) at 0 °C and the mixture was stirred at 30 °C for 2 h. This mixture solution was added to a solution of 5-amino-N-[(1S,3R)-3-[[5-ethyl-4-(1H-indol-3-yl)pyrimidin-2-yl]amino]cyclohexyl]pyridine-2-carboxamide (80 mg, 0.175 mmol) and pyridine (21 mg, 0.26 mmol) in THF (5 mL) and the reaction mixture was stirred at 30 °C for 2 h. Then N-methylmethane amine (8 mg, 0.18 mmol) was added and the mixture was stirred at 30 °C for 2 h. The mixture was concentrated, and the residue mixture was purified by pre-HPLC to afford title compound (20 mg, 20%) as white solid. **LCMS:** (M+H⁺): 567.4 @ 2.077 min (10-80% ACN in H₂O, 4.5 min). **¹H NMR:** (MeOD-d₆, 400 MHz) δ 8.86-8.89 (m, 1H), 8.27 (d, *J* = 7.06 Hz, 1H), 8.23 (dd, *J* = 8.60, 2.43 Hz, 1H), 8.10 (s, 1H), 8.03-8.07

(m, 1H), 7.73 (s, 1H), 7.43-7.46 (m, 1H), 7.18 (tt, $J = 7.44, 5.57$ Hz, 2H), 6.93-6.99 (m, 1H), 6.28-6.32 (d, $J = 17.2$ Hz, 1H), 4.04-4.12 (m, 2H), 3.20 (dd, $J = 6.39, 1.54$ Hz, 2H), 2.73-2.79 (m, 2H), 2.40 (d, $J = 11.47$ Hz, 1H), 2.30 (s, 6H), 2.15 (d, $J = 11.91$ Hz, 1H), 2.03 (d, $J = 10.58$ Hz, 1H), 1.91 (d, $J = 13.67$ Hz, 1H), 1.58 (d, $J = 13.23$ Hz, 1H), 1.45 (d, $J = 11.91$ Hz, 1H), 1.28-1.39 (m, 2H), 1.20 (t, $J = 7.28$ Hz, 3H).

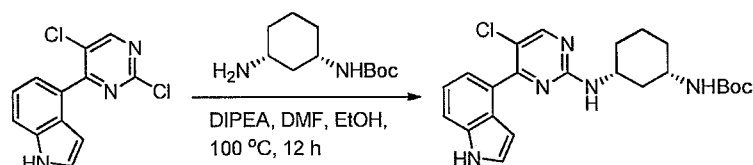
[140] Example 5. Synthesis of N-((1S,3R)-3-((5-chloro-4-(1H-indol-4-yl)pyrimidin-2-yl)amino)cyclohexyl)-5-((E)-4-(dimethylamino)but-2-enamido)picolinamide (Compound 264)

[141] 4-(2,5-dichloropyrimidin-4-yl)-1H-indole



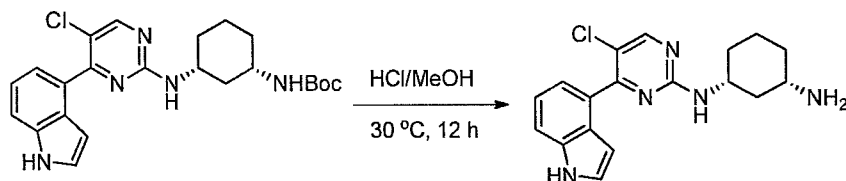
[142] To a mixture of 1H-indol-4-ylboronic acid (20 g, 124.2 mmol) and 2,4,5-trichloropyrimidine (34.2 g, 186.4 mmol) in dioxane (400 mL) and H₂O (100 mL) was added Pd(dppf)Cl₂ (9.1 g, 12.4 mmol) and Na₂CO₃ (26.3 g, 248.5 mmol) under N₂, the mixture was heated to 80 °C, and stirred for 12 h. The mixture was concentrated in vacuum, and the residue was purified by column (PE/EA = 50/1, 10/1) to afford title compound (13.0 g, 39.6%).

[143] tert-benzyl((1S,3R)-3-((5-chloro-4-(1H-indol-4-yl)pyrimidin-2-yl)amino)cyclohexyl)carbamate



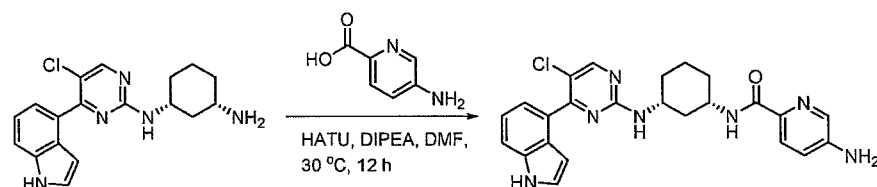
[144] To a mixture of 4-(2,5-dichloropyrimidin-4-yl)-1H-indole (3 g, 11.3 mmol) and tert-butyl((1S,3R)-3-aminocyclohexyl)carbamate (3.6 g, 17.0 mmol) in DMF (20 mL) and EtOH (20 mL) was added DIPEA (2.9 g, 22.7 mmol) under N₂, the mixture was heated to 100 °C, and stirred for 12 h. The mixture was purified by pre-HPLC (TFA condition) to afford title compound (2.8 g, 55.8%) as yellow solid.

[145] (1R,3S)-N1-(5-chloro-4-(1H-indol-4-yl)pyrimidin-2-yl)cyclohexane-1,3-diamine



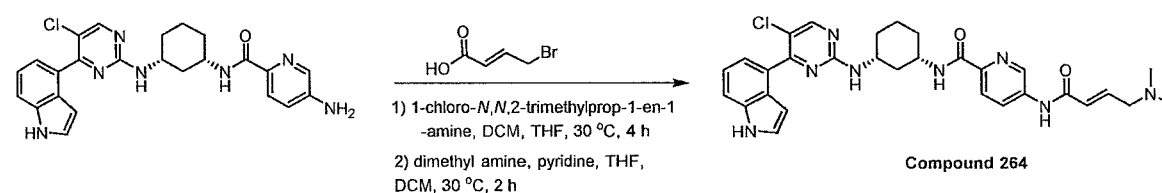
[146] A mixture of tert-butyl N-[(1S,3R)-3-[[5-chloro-4-(1H-indol-4-yl)pyrimidin-2-yl]amino]cyclohexyl]carbamate (2 g, 4.5 mmol) was stirred at 30 °C for 12 h in 100 mL HCl in MeOH. The mixture was concentrated in vacuum to give title compound (1.5 g, crude) as a brown solid, which was used for next step directly.

[147] 5-amino-N-((1S,3R)-3-((5-chloro-4-(1H-indol-4-yl)pyrimidin-2-yl)amino)cyclohexyl)picolinamide



[148] To a mixture of (1R,3S)-N1-[5-chloro-4-(1H-indol-4-yl)pyrimidin-2-yl]cyclohexane-1,3-diamine (0.8 g, 2.3 mmol) and 5-aminopyridine-2-carboxylic acid (0.36 g, 2.6 mmol) in DMF (20 mL) was added HATU (1.1 g, 2.8 mmol) and DIPEA (0.45 g, 3.5 mmol) under N₂ and the mixture was stirred at 30 °C for 12 h. The mixture was poured into water (100 mL), extracted with EA (50 mL*3), and the organic layer was concentrated. The residue was purified by pre-HPLC (TFA condition) to afford title compound (0.3 g, 27.7%) as brown solid.

[149] N-((1S,3R)-3-((5-chloro-4-(1H-indol-4-yl)pyrimidin-2-yl)amino)cyclohexyl)-5-((E)-4-(dimethylamino)but-2-enamido)picolinamide (Compound 264)

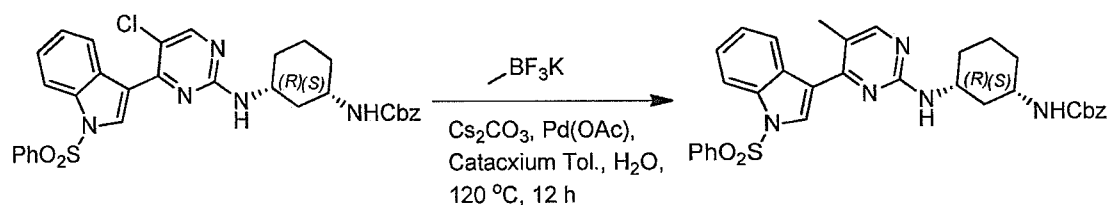


To a mixture of (E)-4-bromobut-2-enoic acid (35 mg, 0.22 mmol) in THF (3 mL) was added 1-chloro-N,N,2-trimethylprop-1-en-1-amine (29 mg, 0.22 mmol) at 30 °C and the mixture was stirred for 2 h. Then this solution was added to a solution of 5-amino-N-[(1S,3R)-3-[[5-chloro-4-(1H-indol-4-yl)pyrimidin-2-yl]amino]cyclohexyl]pyridine-2-carboxamide (100 mg, 0.22 mmol) and pyridine (25 mg, 0.32 mmol) in DCM (3 mL) and the mixture was stirred at 30 °C for 2 h.

Finally, dimethyl amine (19 mg, 0.43 mmol) was added into the mixture and the mixture was stirred at 30°C for 2 h. The mixture was concentrated, and the residue was purified by pre-HPLC to afford title compound (10 mg, 8.1%) as brown solid. **LCMS:** $M+H^+$: 573.3 @ 2.387 min (10-80% ACN in H_2O , 4.5 min). **^1H NMR** (MeOH, 400 MHz); δ 9.08 (br. s., 1H), 8.68 (br. s., 1H), 8.39 (br. s., 1H), 8.22 (br. s., 1H), 7.70 (d, J = 8.03 Hz, 1H), 7.42-7.57 (m, 2H), 7.31 (br. s., 1H), 6.92-7.03 (m, 1H), 6.65 (d, J = 14.81 Hz, 2H), 4.06 (d, J = 6.53 Hz, 3H), 2.96 (s, 6H), 2.72 (br. s., 1H), 2.41 (br. s., 1H), 2.14 (br. s., 1H), 2.00 (br. s., 2H), 1.41-1.66 (m, 4H).

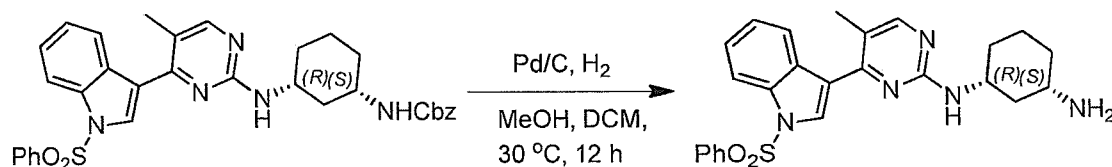
[150] Example 6. Synthesis of N-((1S,3R)-3-((4-(1H-indol-3-yl)-5-methylpyrimidin-2-yl)amino)cyclohexyl)-5-((E)-4-(dimethylamino)but-2-enamido)picolinamide (Compound 265)

[151] Benzyl-N-[(1S,3R)-3-[[4-[1-(benzenesulfonyl)indol-3-yl]-5-methyl-pyrimidin-2-yl]amino]cyclohexyl]carbamate



[152] To a mixture of benzyl-N-[(1S,3R)-3-[[4-[1-(benzenesulfonyl)indol-3-yl]-5-chloro-pyrimidin-2-yl]amino]cyclohexyl]carbamate (1.5 g, 2.43 mmol), potassium hydride trifluoro(methyl) boron (1.48 g, 12.15 mmol), Cs_2CO_3 (2.38 g, 7.29 mmol) in toluene (50 mL) and H_2O (10 mL) was added Cataxium (2.28 g, 2.43 mmol) and $Pd(OAc)_2$ (273 mg, 1.22 mmol) under N_2 protection, the mixture was heated to 120 °C, and stirred for 12 h. The mixture was concentrated, and the residue was purified by flash column to afford title compound (1.5 g, 92%) as yellow solid.

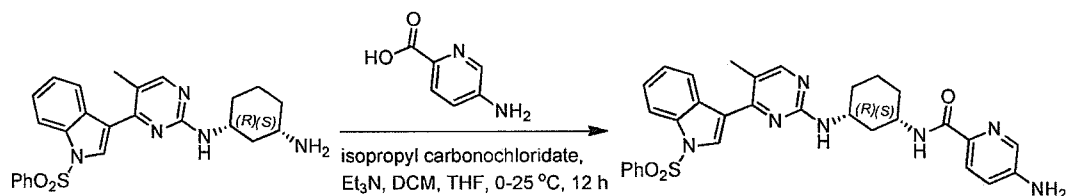
[153] (1R,3S)-N1-[4-[1-(benzenesulfonyl)indol-3-yl]-5-methyl-pyrimidin-2-yl]cyclohexane-1,3-diamine



[154] A mixture of benzyl N-[(1S,3R)-3-[[4-[1-(benzenesulfonyl)indol-3-yl]-5-methyl-pyrimidin-2-yl]amino]cyclohexyl]carbamate (1.5 g, 2.52 mmol) and Pd/C (1 g, 2.52 mmol) in MeOH (200 mL) and DCM (20 mL) was stirred at 30 °C for 12 h under H_2 (50 Psi). The mixture

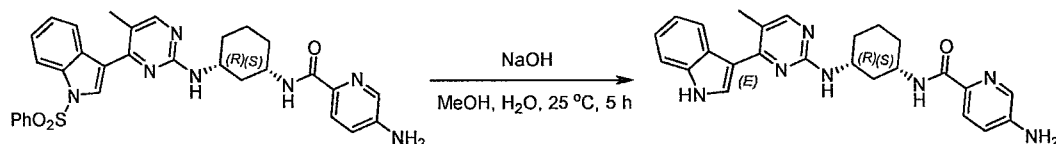
was filtrated, and the filtrate was concentrated to give title compound (1.2 g, 86.7%) as yellow solid.

[155] 5-amino-N-[(1S,3R)-3-[[4-[1-(benzenesulfonyl)indol-3-yl]-5-methyl-pyrimidin-2-yl]amino]cyclohexyl]pyridine-2-carboxamide



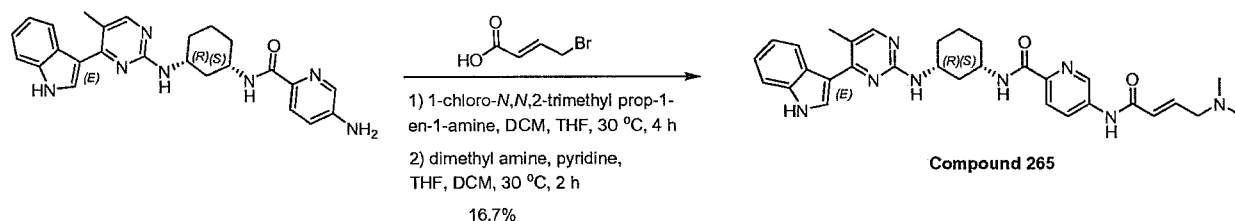
[156] To a mixture of 5-aminopyridine-2-carboxylic acid (179 mg, 1.30 mmol) and Et₃N (131.54 mg, 1.30 mmol) in THF (2 mL) was added isopropyl carbonochloridate (159 mg, 1.30 mmol) at 0 °C, the mixture was stirred at 0 °C for 0.5 h. Then the mixture solution was added to a solution of (1R,3S)-N1-[4-[1-(benzenesulfonyl)indol-3-yl]-5-methyl-pyrimidin-2-yl]cyclohexane-1,3-diamine (300 mg, 0.65 mmol) and Et₃N (131.54 mg, 1.30 mmol) in DCM (3 mL) at 25 °C and the mixture was stirred for 11.5 h. The mixture was poured into water (20 mL), extracted with EA (20 mL*3), and the organic layer was dried over Na₂SO₄ and concentrated to give title compound (300 mg, crude) as a yellow solid.

[157] N-((1S,3R)-3-((4-(1H-indol-3-yl)-5-methylpyrimidin-2-yl)amino)cyclohexyl)-5-aminopicolinamide



[158] A mixture of 5-amino-N-[(1S,3R)-3-[[4-[1-(benzenesulfonyl)indol-3-yl]-5-methyl-pyrimidin-2-yl]amino]cyclohexyl]pyridine-2-carboxamide (300 mg, 0.51 mmol) in NaOH solution (2 mL) and MeOH (10 mL) was stirred at 25 °C for 5 h. The mixture was poured into water (20 mL), extracted with EA (30 mL*3), and the organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by pre-HPLC (acid condition) to afford title compound (100 mg, 43.9%) as a white solid.

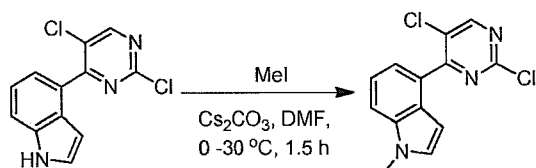
[159] N-((1S,3R)-3-((4-(1H-indol-3-yl)-5-methylpyrimidin-2-yl)amino)cyclohexyl)-5-((E)-4-(dimethylamino)but-2-enamido)picolinamide (Compound 265)



[160] To a solution of (E)-4-bromobut-2-enoic acid (38 mg, 0.21 mmol) in DCM (5 mL) was added 1-chloro-*N,N*,2-trimethyl-prop-1-en-1-amine (35 mg, 0.26 mmol) at 0 °C and the mixture was stirred at 30 °C for 2 h. This mixture solution was added to a solution of 5-amino-*N*-[(1*S*,3*R*)-3-[[4-(1*H*-indol-3-yl)-5-methylpyrimidin-2-yl]amino]cyclohexyl]pyridine-2-carboxamide (50 mg, 0.11 mmol) and pyridine (21 mg, 0.26 mmol) in THF (5 mL) and the reaction mixture was stirred at 30 °C for 2 h. Then *N*-methylmethanamine (16 mg, 0.36 mmol, 0.36 mL, 1 mmol/L in THF) was added and the mixture was stirred at 30 °C for 2 h. The mixture was concentrated, and the residue mixture was purified by pre-HPLC to afford title compound (10.5 mg, 16.7%) as white solid. **LCMS:** ($M+H^+$): 553.4 @ 3.007 min (10-80% ACN in H_2O , 4.5 min). **^1H NMR:** ($DMSO-d_6$, 400 MHz), δ 8.88 (br. s., 1H), 8.61 (br. s., 1H), 8.47 (d, $J = 8.53$ Hz, 1H), 8.24 (d, $J = 8.78$ Hz, 1H), 8.07 (s, 1H), 8.02 (d, $J = 8.53$ Hz, 1H), 7.94 (br. s., 1H), 7.46 (d, $J = 7.03$ Hz, 1H), 7.19 (br. s., 2H), 6.82 (d, $J = 15.31$ Hz, 1H), 6.70 (d, $J = 7.53$ Hz, 1H), 6.30 (d, $J = 15.56$ Hz, 1H), 3.95 (br. s., 3H), 3.08 (d, $J = 5.02$ Hz, 2H), 2.30 (br. s., 3H), 2.19 (s, 6H), 2.02 (br. s., 1H), 1.84 (br. s., 2H), 1.35-1.59 (m, 3H), 1.26 (d, $J = 11.80$ Hz, 1H).

[161] **Example 7. Synthesis of *N*-((1*S*,3*R*)-3-((5-chloro-4-(1-methyl-1*H*-indol-4-yl)pyrimidin-2-yl)amino)cyclohexyl)-5-((E)-4-(dimethylamino)but-2-enamido)picolinamide (Compound 269).**

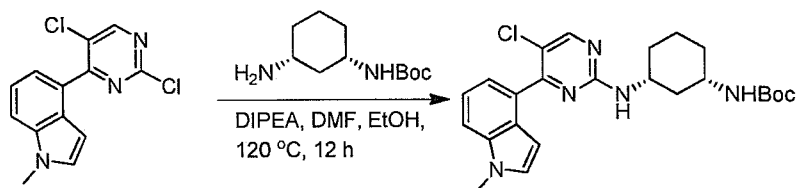
[162] **4-(2,5-dichloropyrimidin-4-yl)-1-methyl-1*H*-indole**



[163] To a mixture of 4-(2,5-dichloropyrimidin-4-yl)-1*H*-indole (4.00 g, 15.15 mmol) in DMF (50 mL) was added CS_2CO_3 (9.87 g, 30.29 mmol) at 0 °C under N_2 and the mixture was stirred for 0.5 h. Then iodomethane (2.15 g, 15.15 mmol) was added and the mixture was stirred for 1 h. The mixture was poured into water (100 mL), extracted with ethyl acetate (40 mL*3), and the combined organic phase was washed with saturated brine (40 mL*2), dried with anhydrous

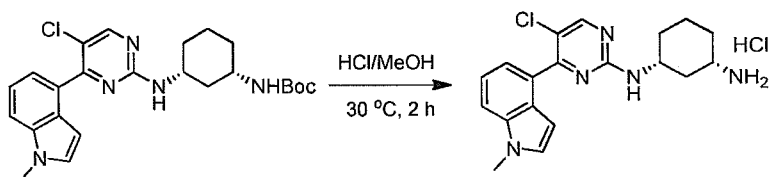
Na₂SO₄, filtered, and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=40/1, 5/1) to afford title compound (3.10 g, 73.6%) as yellow solid.

[164] Benzyl ((1S,3R)-3-((5-chloro-4-(1-methyl-1H-indol-4-yl)pyrimidin-2-yl)amino)cyclohexyl)carbamate



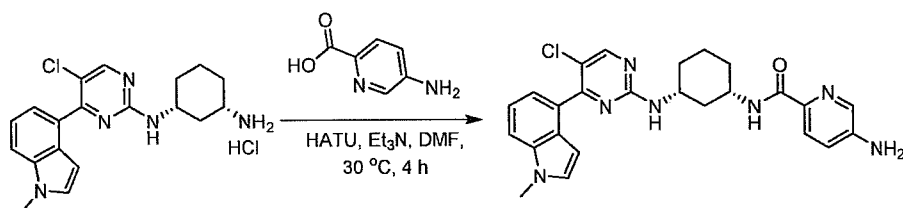
[165] A mixture of 4-(2,5-dichloropyrimidin-4-yl)-1-methyl-indole (2.7 g, 9.71 mmol), tert-butyl N-[(1S,3R)-3-aminocyclohexyl]carbamate (2.08 g, 9.71 mmol) and DIPEA (3.75 g, 29.12 mmol) in DMF (20 mL) and EtOH (20 mL) was heated to 120 °C and stirred for 12 h. The mixture was poured into water (50 mL), extracted with ethyl acetate (50 mL*3), and the combined organic phase was washed with saturated brine (50 mL*2), dried over anhydrous Na₂SO₄, and filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=8/1, 1/1) to afford title compound (2.9 g, 65.5%) as yellow solid.

[166] (1R,3S)-N1-(5-chloro-4-(1-methyl-1H-indol-4-yl)pyrimidin-2-yl)cyclohexane-1,3-diamine



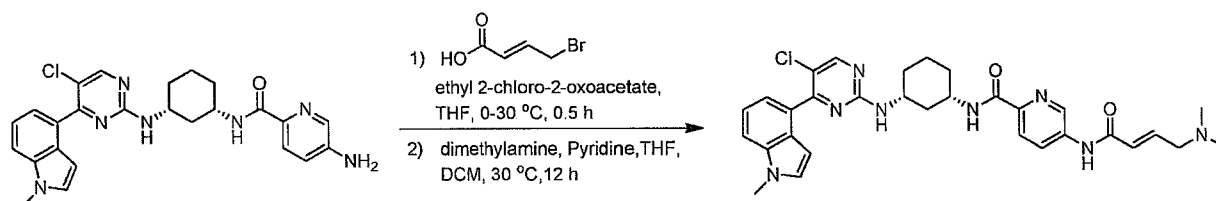
[167] A mixture of tert-butyl N-[(1S,3R)-3-[[5-chloro-4-(1-methylindol-4-yl)pyrimidin-2-yl]amino] cyclohexyl]carbamate (2.9 g, 6.36 mmol) in HCl/MeOH (80 mL) was stirred at 30 °C for 2 h. The mixture was concentrated to give title compound (2.40 g, 96.2%).

[168] 5-amino-N-((1S,3R)-3-((5-chloro-4-(1-methyl-1H-indol-4-yl)pyrimidin-2-yl)amino)cyclohexyl)picolinamide



[169] To a mixture of (1R,3S)-N1-(5-chloro-4-(1-methyl-1H-indol-4-yl)pyrimidin-2-yl)cyclohexane-1,3-diamine (1.00 g, 2.55 mmol), 5-aminopicolinic acid (0.39 g, 2.80 mmol) and Et₃N (0.77 g, 7.65 mmol) in DMF (10 mL) was added HATU (1.45 g, 3.82 mmol) at 30 °C under N₂ and the mixture was stirred for 4 h. The mixture was poured into water (50 mL), extracted with EA (20 mL*3), the combined organic phase was dried over anhydrous Na₂SO₄, and filtered and concentrated in vacuum. The residue was purified by pre-HPLC (TFA condition) to afford title compound (0.34 g, 18.2%) as yellow solid. **LCMS:** (M+H⁺): 476.0 @ 0.800 min (5-95% ACN in H₂O, 1.5 min)

[170] N-((1S,3R)-3-((5-chloro-4-(1-methyl-1H-indol-4-yl)pyrimidin-2-yl)amino)cyclohexyl)-5-((E)-4-(dimethylamino)but-2-enamido)picolinamide (Compound 269)

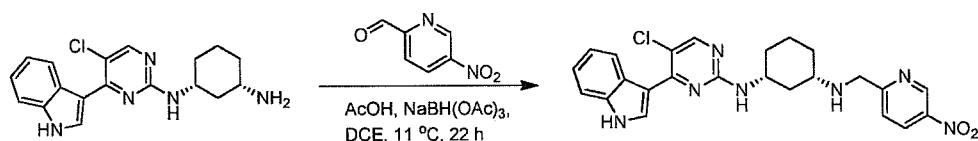


[171] To a solution of (E)-4-bromobut-2-enoic acid (45.1 mg, 0.27 mmol) in DCM (5.0 mL) was added 1-chloro-N,N,2-trimethyl-prop-1-en-1-amine (42.1 mg, 0.32 mmol) and the mixture was stirred at 30 °C for 0.5 h. Then this mixture was added to a solution of 5-amino-N-[(1S,3R)-3-[[5-chloro-4-(1-methylindol-4-yl)pyrimidin-2-yl]amino]cyclohexyl] pyridine-2-carboxamide (100.0 mg, 0.21 mmol) and pyridine (49.9 mg, 0.63 mmol) in THF (10.0 mL) and the mixture was stirred at 30 °C for 0.5 h. Then dimethylamine hydrochloride (47.4 mg, 1.05 mmol) was added and the mixture was stirred at 30 °C for 12 h. The mixture was concentrated in reduced pressure, and the residue was purified by pre-HPLC (basic condition) to afford title compound (4.0 mg, 3.24%) as white solid. **LCMS:** (M+H⁺): 587.3 @ 2.531 min (10-80% ACN in H₂O, 4.5 min). **¹H NMR:** (MeOD, 400 MHz), δ 8.87 (d, *J* = 2.01 Hz, 1H), 8.33 (s, 1H), 8.22 (dd, *J* = 8.53, 2.26 Hz, 1H), 8.03 (d, *J* = 8.66 Hz, 1H), 7.45-7.55 (m, 1H), 7.18-7.32 (m, 3H), 6.91-7.01

(m, 1H), 6.42 (d, $J = 2.89$ Hz, 1H), 6.29 (d, $J = 15.43$ Hz, 1H), 3.97 (br. s., 2H), 3.85 (s, 3H), 3.19 (d, $J = 6.53$ Hz, 2H), 2.29 (s, 7H), 2.08 (d, $J = 12.30$ Hz, 1H), 1.97 (d, $J = 10.04$ Hz, 1H), 1.87 (d, $J = 13.18$ Hz, 1H), 1.23-1.54 (m, 4H).

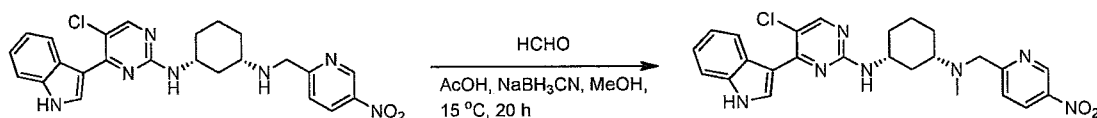
[172] **Example 8. Synthesis of (E)-N-(6-((((1S,3R)-3-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl)amino)cyclohexyl)(methyl)amino)methyl)pyridin-3-yl)-4-(dimethylamino)but-2-enamide (Compound 377).**

[173] **(1R,3S)-N1-[5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl]-N3-[(5-nitro-2-pyridyl)methyl]cyclohexane-1,3-diamine**



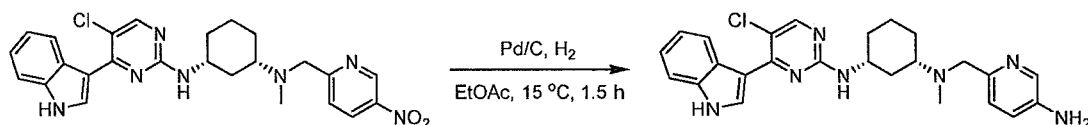
[174] To a stirred solution of (1R,3S)-N1-[5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl]cyclohexane-1,3-diamine (2.5 g, 7.31 mmol) and 5-nitropyridine-2-carbaldehyde (1.22 g, 8.04 mmol) in DCE (30 mL) was added AcOH (0.44 g, 7.31 mmol) at 11 °C. Then the mixture was stirred at 11 °C for 16 h. Then NaBH(OAc)₃ (2.32 g, 10.97 mmol) was added, the reaction mixture was stirred at 11 °C for 6 h. The mixture was added to NaHCO₃ solution (50 mL), extracted with DCM (50 mL*5), and the organic layer was washed with brine (100 mL), dried over Na₂SO₄, filtered and evaporated. The residue was purified by silica gel chromatography (PE/EA = 1:1 to DCM/MeOH = 50:1) to give title compound (1.6 g, 46%) as brown solid.

[175] **(1S,3R)-N3-[5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl]-N1-methyl-N1-[(5-nitro-2-pyridyl)methyl]cyclohexane-1,3-diamine**



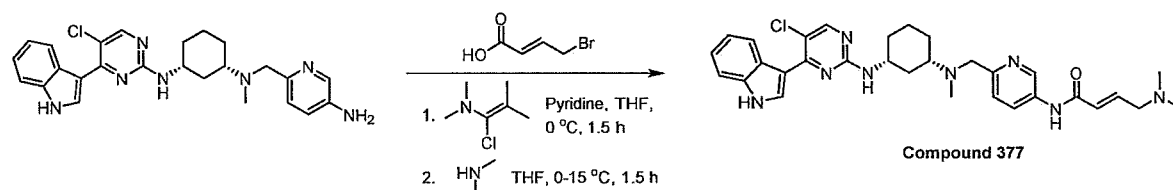
[176] A mixture of (1R,3S)-N1-[5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl]-N3-[(5-nitro-2-pyridyl)methyl]cyclohexane-1,3-diamine (450 mg, 0.94 mmol), AcOH (56.54 mg, 0.94 mmol) and formaldehyde (76.42 mg, 0.94 mmol) in MeOH (10 mL) was stirred at 15 °C for 4 h. Then NaBH₃CN (88.75 mg, 1.41 mmol) was added and the mixture was stirred at 15 °C for 16 h. The mixture was added to NaHCO₃ solution (20 mL), extracted with DCM (40 mL*4), and the organic layer was washed with brine (100 mL), dried over Na₂SO₄, and evaporated. The residue was purified by silica gel column chromatography (DCM/MeOH = 150:1 to 100:1 to 50:1) to give title compound (420 mg, 90.6%) as a yellow solid.

[177] (1S,3R)-N1-[(5-amino-2-pyridyl)methyl]-N3-[5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl]-N1-methyl-cyclohexane-1,3-diamine



[178] To a solution of (1S,3R)-N3-[5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl]-N1-methyl-N1-[(5-nitro-2-pyridyl)methyl]cyclohexane-1,3-diamine (370 mg, 752.08 μmol) in EtOAc (5 mL) was added Pd/C (10%, 200 mg) under N_2 . The suspension was degassed under vacuum and purged with H_2 three times. The mixture was stirred at 15 °C for 1.5 h under H_2 (15 psi). The reaction mixture was filtered through a pad of Celite filter cake which was washed with DCM (30 mL $\times$ 4) and MeOH (10 mL $\times$ 4). The filtrate was concentrated to give title compound (350 mg, crude) as a yellow solid. **LCMS:** $\text{M}+\text{H}^+$: 462.2 @ 0.648 min (5-95% ACN in H_2O , 1.5 min)

[179] (E)-N-[6-[[[(1S,3R)-3-[[5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl]amino]cyclohexyl]-methyl-amino]methyl]-3-pyridyl]-4-(dimethylamino)but-2-enamide (Compound 377)

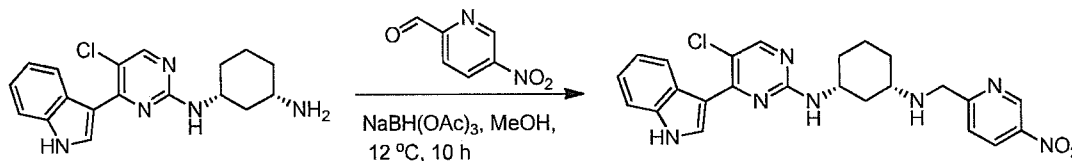


[180] To a mixture of (E)-4-bromobut-2-enoic acid (64.28 mg, 389.62 μmol) in DCM (5 mL) was added 1-chloro-N,N,2-trimethyl-prop-1-en-1-amine (52.06 mg, 389.62 μmol) at 0 °C under N_2 and the mixture was stirred at 0 °C for 1 h. Then the mixture was added to a solution of (1S,3R)-N1-[(5-amino-2-pyridyl)methyl]-N3-[5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl]-N1-methyl-cyclohexane-1,3-diamine (150 mg, 324.68 μmol) and pyridine (77.05 mg, 974.04 μmol) in THF (5 mL) at 0 °C and the reaction mixture was stirred at 0 °C for 0.5 h. N-methylmethanamine (2 M, 1.62 mL, 3250 μmol) was added at 0 °C and the mixture was stirred at 15 °C for 1.5 h. The reaction mixture was concentrated, and the residue was purified by prep-HPLC (TFA). The solution of the prep-HPLC was adjusted with NaHCO_3 to pH = 8, extracted with EtOAc/THF (2:1, 30 mL $\times$ 3). The organic layer was dried over Na_2SO_4 , filtered and the filtrate was concentrated to give title compound (31.2 mg, 16.7%) as white solid. **LCMS:** ET3422-94-P1B $\text{M}+\text{H}^+$: 573.3 @ 1.977 min (10-80% ACN in H_2O , 4.5 min). **^1H NMR:** ET3422-94-P1B (MeOD, 400 MHz), δ 8.72 (br. s., 1H), 8.60 (d, J = 7.91 Hz, 1H), 8.47 (br. s., 1H), 8.15 (s, 1H), 8.08 (d, J = 6.78 Hz, 1H), 7.45 (t, J = 8.78 Hz, 2H), 7.19 (t, J = 7.53 Hz, 1H), 7.08 (br.

s., 1H), 6.86-6.99 (m, 1H), 6.28 (d, $J = 15.56$ Hz, 1H), 3.97 (br. s., 1H), 3.69-3.90 (m, 2H), 3.21 (d, $J = 6.15$ Hz, 2H), 2.79 (br. s., 1H), 2.39 (br. s., 2H), 2.32 (s, 6H), 2.11 (d, $J = 9.79$ Hz, 1H), 1.89-2.05 (m, 2H), 1.36-1.51 (m, 3H), 1.29 (br. s., 2H), 0.89 (d, $J = 7.40$ Hz, 1H).

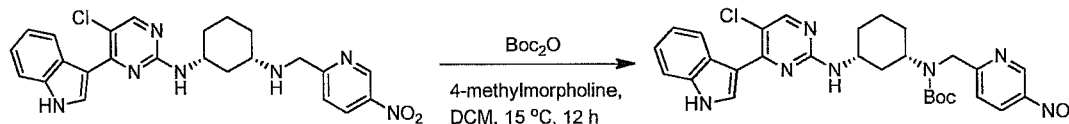
[181] **Example 9. Synthesis of (E)-N-(6-((((1S,3R)-3-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl)amino)cyclohexyl)amino)methyl)pyridin-3-yl)-4-(dimethylamino)-N-methylbut-2-enamide (Compound 390).**

[182] **(1R,3S)-N1-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl)-N3-((5-nitropyridin-2-yl)methyl)cyclohexane-1,3-diamine**



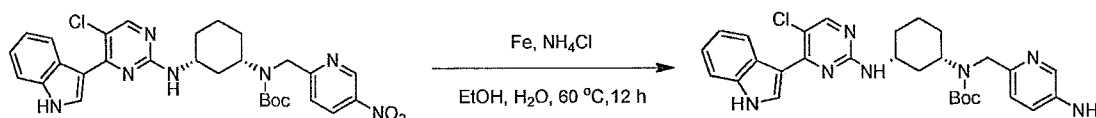
[183] To a solution of (1R,3S)-N1-[5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl]cyclohexane-1,3-diamine (3.0 g, 8.78 mmol) and 5-nitropyridine-2-carbaldehyde (1.6 g, 10.53 mmol) in MeOH (15 mL) was stirred for 2 h. Then NaBH(OAc)₃ (3.7 g, 17.55 mmol) was added to the reaction. The mixture was stirred at 12 °C for 10 h. The mixture was concentrated under vacuum to afford a residue. The residue was purified by column chromatography to give title compound (3.0 g, 71.5%) as orange solid.

[184] **Tert-butyl((1S,3R)-3-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl)amino)cyclohexyl)((5-nitropyridin-2-yl)methyl)carbamate**



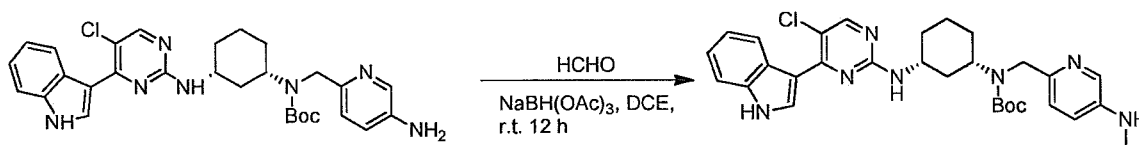
[185] To a solution of (1R,3S)-N1-[5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl]-N3-[(5-nitro-2-pyridyl)methyl]cyclohexane-1,3-diamine (2.0 g, 4.18 mmol) and TEA (846.9 mg, 8.37 mmol) in DCM (20 mL) was added Boc₂O (1.1 g, 5.02 mmol). The mixture was stirred at 20 °C for 12 h. The mixture was concentrated to get the crude product. The crude product was purified by column to give title compound (1.5 g, 62.1%) as yellow solid.

[186] **Tert-butyl((5-aminopyridin-2-yl)methyl)((1S,3R)-3-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl)amino)cyclohexyl)carbamate**



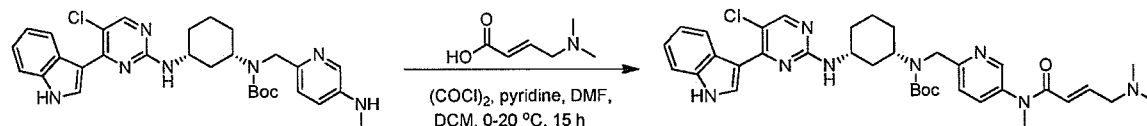
[187] To a solution of tert-butyl N-[(1S,3R)-3-[[5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl]amino] cyclohexyl]-N-[(5-nitropyridin-2-yl)methyl]carbamate (1.5 g, 2.59 mmol) in EtOH (20.0 mL) and H₂O (4.00 mL) was added Fe (723.3 mg, 12.95 mmol) and NH₄Cl (138.5 mg, 2.59 mmol). The reaction was stirred at 60 °C for 12 h. The suspension was filtered and the filtrate was concentrated to give title compound (1.0 g, 70.3%) as light yellow solid without further purification.

[188] *Tert-butyl ((1S,3R)-3-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl)amino)cyclohexyl)((5-(methylamino)pyridin-2-yl)methyl)carbamate*



[189] To a solution of tert-butyl((5-aminopyridin-2-yl)methyl)((1S,3R)-3-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl)amino)cyclohexyl)carbamate (500 mg, 0.91 mmol) and HCHO (88.9 mg, 1.1 mmol) in DCE (10 mL) was added NaBH(OAc)₃ (386.7 mg, 1.8 mmol). The reaction was stirred at 15 °C for 12 h. The reaction was concentrated to give the residue. The residue was purified by column to obtain title compound (150 mg, 27.8%) as light yellow solid.

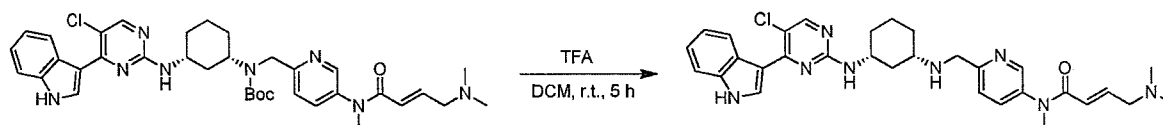
[190] *Tert-butyl((1S,3R)-3-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl)amino)cyclohexyl)((5-(E)-4-(dimethylamino)-N-methylbut-2-enamido)pyridin-2-yl)methyl)carbamate*



[191] To a solution of (E)-4-(dimethylamino)but-2-enoic acid (66.3 mg, 0.4 mmol, HCl) in THF (5 mL) was added oxalyl dichloride (50.8 mg, 0.4 mmol) and DMF (1.03 μ L, 0.013 mmol) at 0 °C. The reaction mixture was stirred at 15 °C for 3 h. Then the mixture was added into a solution of tert-butyl ((1S,3R)-3-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl)amino)

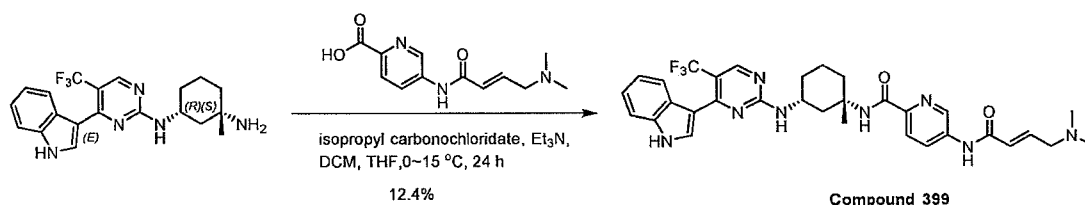
[192] cyclohexyl)((5-(methylamino)pyridin-2-yl)methyl)carbamate (150 mg, 0.27 mmol) and pyridine (63.33 mg, 0.8 mmol) in DCM (5 mL) at 0 °C. The reaction was stirred at 15 °C. The reaction was concentrated. The residue was purified by the prep-TLC to give title compound (100 mg, 55.7%) as yellow solid.

[193] *(E)-N-(6-(((1S,3R)-3-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl)amino)cyclohexyl)amino)methyl)pyridin-3-yl)-4-(dimethylamino)-N-methylbut-2-enamide*

(Compound 390)

[194] To a solution of tert-butyl((1S,3R)-3-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl)amino)cyclohexyl)((5-((E)-4-(dimethylamino)-N-methylbut-2-enamido)pyridin-2-yl)methyl)carbamate (100 mg, 0.15 mmol) in DCM (20 mL) was added TFA (4.0 mL) at 0 °C. The reaction was stirred at 15 °C for 9 h. The mixture was concentrated to give a residue. The residue was purified by pre-HPLC (HCl condition) to give title compound (24.0 mg, 26%, HCl salt) as yellow solid. **LCMS:** (M+H⁺): 573.4 @ 1.959 min (10-80% ACN in H₂O, 4.5 min). **¹H NMR** (MeOD, 400 MHz), δ 8.98 (br. s., 1H), 8.56 (br. s., 2H), 8.22 (br. s., 1H), 7.85 (br. s., 1H), 7.58 (br. s., 2H), 7.34 (br. s., 2H), 6.79 (br. s., 1H), 6.43 (br. s., 1H), 4.53 (br. s., 2H), 3.88 (br. s., 2H), 3.57 (br. s., 1H), 3.40 (br. s., 3H), 3.01-2.62 (m, 8H), 2.38 (br. s., 1H), 2.26 (br. s., 1H), 2.09 (br. s., 1H), 1.78 (d, J = 9.29 Hz, 1H), 1.70-1.52 (m, 3H).

[195] **Example 10. Synthesis of 5-[[*(E)*-4-(dimethylamino)but-2-enoyl]amino]-N-[(1S,3R)-3-[[4-(1H-indol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl]amino]-1-methylcyclohexyl]pyridine-2-carboxamide (Compound 399).**



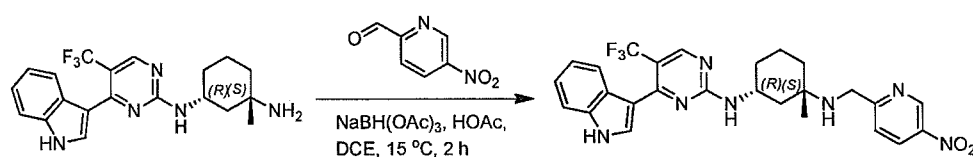
[196] To a solution of 5-[[*(E)*-4-(dimethylamino)but-2-enoyl]amino]pyridine-2-carboxylic acid (192.03 mg, 528.99 μmol, TFA salt) in THF (5 mL) and DCM (5 mL) was added Et₃N (129.92 mg, 1.28 mmol) and isopropyl carbonochloridate (94.41 mg, 770.37 μmol) at 0 °C. The reaction was stirred at 15 °C for 3 h. Then the mixture was added into (1S,3R)-N3-[4-(1H-indol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl]-1-methylcyclohexane-1,3-diamine (100 mg, 256.79 μmol) in DCM (5 mL). The reaction was stirred at 15 °C for 21 h. The reaction was concentrated to give the residue. The residue was purified by prep-HPLC (HCl condition) to give title compound (22.0 mg, 12.4%, HCl salt) as a brown solid.

[197] **LCMS:** (M+H⁺): 621.4 @ 2.457 min (10-80% ACN in H₂O, 4.5 min). **¹H NMR:** (MeOD, 400 MHz); δ 9.12 (br. s., 1H), 9.17-7.99 (m, 5H), 7.57 (br. s., 1H), 7.13-7.61 (m, 2H), 6.98 (dt, J = 14.93, 7.34 Hz, 1H), 6.66 (d, J = 14.56 Hz, 1H), 4.66-4.51 (m, 1H), 4.06 (br. s., 2

H), 2.95 (br. s., 6H), 2.72-2.55 (m, 1H), 2.21 (d, $J = 11.29$ Hz, 2H), 2.10-1.89 (m, 3H), 1.78 (br. s., 1H), 1.67 (d, $J = 6.78$ Hz, 3H), 1.52 (d, $J = 8.03$ Hz, 1H).

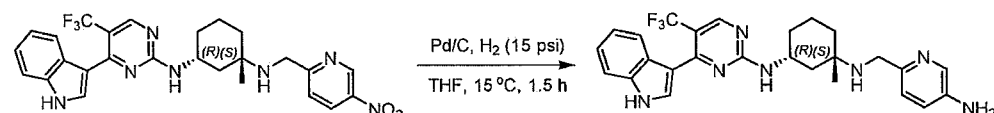
[198] **Example 11. Synthesis of (E)-4-(dimethylamino)-N-[6-[[[(1S,3R)-3-[[4-(1H-indol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl]amino]-1-methylcyclohexyl]amino]methyl]-3-pyridyl]but-2-enamide (Compound 403).**

[199] **(1S,3R)-N3-[4-(1H-indol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl]-1-methyl-N1-[(5-nitro-2-pyridyl)methyl]cyclohexane-1,3-diamine**



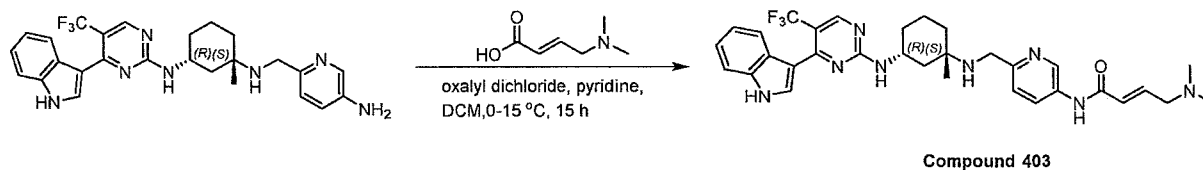
[200] To a solution of (1S,3R)-N3-[4-(1H-indol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl]-1-methylcyclohexane-1,3-diamine (300 mg, 0.77 mmol) and 5-nitropyridine-2-carbaldehyde (152.34 mg, 1.0 mmol) in DCE (10 mL) was added HOAc (46.26 mg, 0.77 mmol) at 0 °C and the mixture was stirred at 15 °C for 1 h. Then NaBH(OAc)₃ (489.82 mg, 2.31 mmol) was added at 0 °C and the mixture was stirred at 15 °C for 1 h. The mixture was concentrated, and the residue was purified by column to give title compound (200 mg, 42%) as yellow solid.

[201] **(1S,3R)-N1-[(5-amino-2-pyridyl)methyl]-N3-[4-(1H-indol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl]-1-methylcyclohexane-1,3-diamine**



[202] To a solution of (1S,3R)-N3-[4-(1H-indol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl]-1-methyl-N1-[(5-nitro-2-pyridyl)methyl]cyclohexane-1,3-diamine (100 mg, 190.29 μmol) in THF (10 mL) was added Pd-C (5%, 100 mg) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred at 15 °C for 1.5 h under H₂ (15 psi). The reaction mixture was filtered, and the filtrate was concentrated to give title compound (70 mg, 66.8%) was used into the next step without further purification as a yellow solid. **LCMS:** (M+H⁺): 496.2 @ 1.643 min (10-80% ACN in H₂O, 4.5 min)

[203] **(E)-4-(dimethylamino)-N-[6-[[[(1S,3R)-3-[[4-(1H-indol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl]amino]-1-methylcyclohexyl]amino]methyl]-3-pyridyl]but-2-**

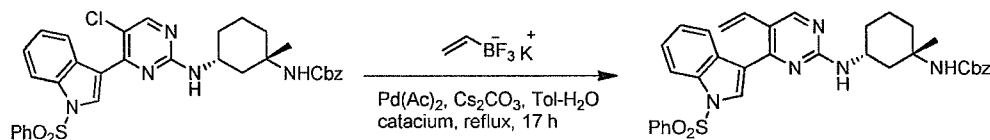
enamide (Compound 403)

[204] To a solution of (E)-4-(dimethylamino)but-2-enoic acid (46.79 mg, 282.52 μmol) in DCM (5 mL) was added oxalyl dichloride (35.86 mg, 282.52 μmol) and DMF (0.52 mg, 7.06 μmol) at 0 °C for 3 h. Then the mixture was added to a solution of (1S,3R)-N1-[(5-amino-2-pyridyl)methyl]-N3-[4-(1H-indol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl]-1-methyl-cyclohexane-1,3-diamine (70 mg, 141.26 μmol) in DCM (5 mL) at 0 °C and the reaction was stirred at 15 °C for 12 h. The mixture was concentrated under reduced pressure, and the residue was purified by prep-HPLC to give title compound (36.2 mg, 38%, HCl salt) as yellow solid.

LCMS: ($M+H^+$): 607.4 @ 2.148 min (10-80% ACN in H_2O , 4.5 min). **^1H NMR:** (MeOD, 400 MHz), δ 9.17 (br. s., 1H), 8.61-8.47 (m, 2H), 8.41-8.27 (m, 2H), 7.84 (d, J = 8.28 Hz, 1H), 7.58 (br. s., 1H), 7.36 (d, J = 3.51 Hz, 2H), 6.96 (dt, J = 15.06, 7.28 Hz, 1H), 6.65 (d, J = 15.31 Hz, 1H), 4.62 (br. s., 1H), 4.50 (br. s., 2H), 4.04 (d, J = 7.03 Hz, 2H), 2.94 (s, 6H), 2.50 (d, J = 10.29 Hz, 1H), 2.27 (d, J = 11.54 Hz, 1H), 2.11-1.96 (m, 3H), 1.91-1.76 (m, 2H), 1.72-1.66 (m, 3H), 1.59 (d, J = 10.79 Hz, 1H).

[205] **Example 12. Synthesis of 5-[[*(E)*-4-(dimethylamino)but-2-enoyl]amino]-N-[(1S,3R)-3-[[5-ethyl-4-(1H-indol-3-yl)pyrimidin-2-yl]amino]-1-methyl-cyclohexyl]pyridine-2-carboxamide (Compound 407).**

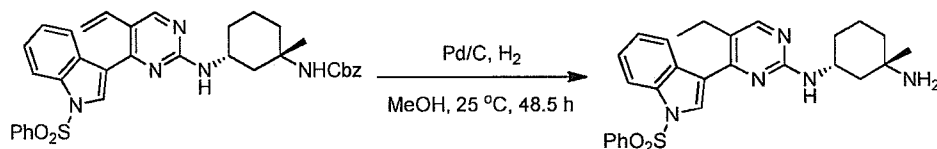
[206] **Benzyl-N-[(1S,3R)-3-[[4-[1-(benzenesulfonyl)indol-3-yl]-5-vinyl-pyrimidin-2-yl]amino]-1-methyl-cyclohexyl]carbamate**



[207] Benzyl-N-[(1S,3R)-3-[[4-[1-(benzenesulfonyl)indol-3-yl]-5-chloro-pyrimidin-2-yl]amino]-1-methyl-cyclohexyl]carbamate (11 g, 17.46 mmol), potassium trifluoro(vinyl)boranuide (11.69 g, 87.28 mmol), CS_2CO_3 (17.06 g, 52.37 mmol), $Pd(OAc)_2$ (1.96 g, 8.73 mmol) and bis(1-adamantyl)-butyl-phosphane (6.26 g, 17.46 mmol) in toluene (100 mL) and H_2O (20 mL) was degassed under vacuum and purged with N_2 three times. The reaction was heated to 120 °C and stirred for 17 h. The mixture was poured into water (100 mL), extracted

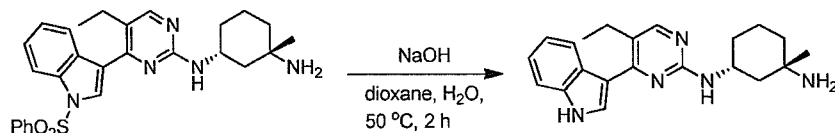
with EtOAc (50 mL*3), and the organic layer was washed with brine (100 mL), dried over Na₂SO₄, concentrate. The residue was purified by silica gel chromatography (DCM/Ethyl acetate = 80/1, 20/1) to give title compound (6 g, 55.2%) as brown solid.

[208] (1S,3R)-N3-[4-[1-(benzenesulfonyl)indol-3-yl]-5-ethyl-pyrimidin-2-yl]-1-methyl-cyclohexane-1,3-diamine



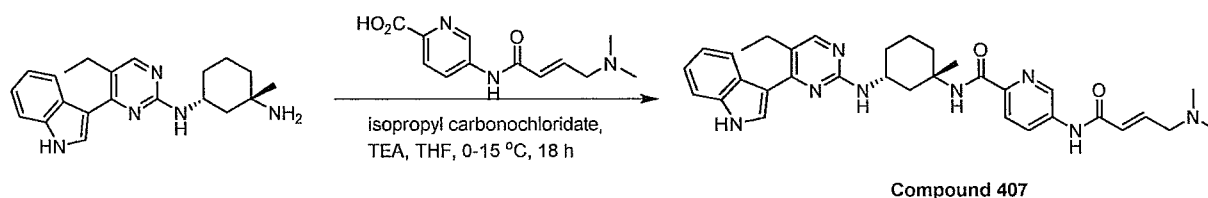
[209] To a solution of benzyl N-[(1S,3R)-3-[[4-[1-(benzenesulfonyl)indol-3-yl]-5-vinyl-pyrimidin-2-yl]amino]-1-methyl-cyclohexyl]carbamate (6 g, 9.65 mmol) in MeOH (50 mL) and DCM (20 mL) was added Pd/C (3 g) under N₂. The suspension was degassed under vacuum and purged with H₂ three times. The mixture was stirred at 25 °C for 48.5 h under H₂ (50 psi). The mixture was filtered through a pad of Celite filter cake and the filtrate was concentrated to give title compound (4 g, crude) as brown solid.

[210] (1S,3R)-N3-[5-ethyl-4-(1H-indol-3-yl)pyrimidin-2-yl]-1-methyl-cyclohexane-1,3-diamine



[211] A mixture of (1S,3R)-N3-[4-[1-(benzenesulfonyl)indol-3-yl]-5-ethyl-pyrimidin-2-yl]-1-methyl-cyclohexane-1,3-diamine (1.00 g, 2.04 mmol) and NaOH (0.41 g, 10.2 mmol) in dioxane (10 mL) and H₂O (1 mL) was stirred at 50 °C for 2 h. The reaction mixture was added to water (40 mL) and extracted with DCM (30 mL*5). The organic layer was wash with brine (50 mL), dried over Na₂SO₄, evaporated to give title compound (0.7 g, crude) as yellow solid.

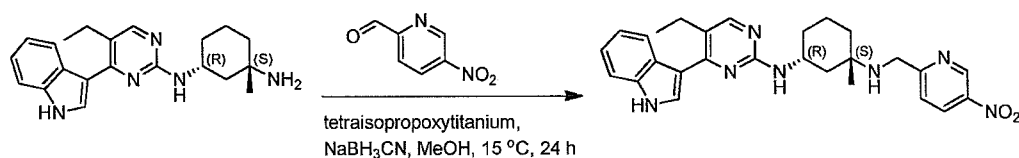
[212] 5-[[[E]-4-(dimethylamino)but-2-enoyl]amino]-N-[(1S,3R)-3-[[5-ethyl-4-(1H-indol-3-yl)pyrimidin-2-yl]amino]-1-methyl-cyclohexyl]pyridine-2-carboxamide



[213] To a mixture of 5-[[*(E)*-4-(dimethylamino)but-2-enoyl]amino]pyridine-2-carboxylic acid (142.7 mg, 572.30 μ mol) and TEA (173.7 mg, 1720 μ mol) in THF (15 mL) was added isopropyl carbonochloridate (70.13 mg, 572.30 μ mol) at 0 °C and the mixture was stirred for 2 h. Then (1*S*,3*R*)-*N*3-[5-ethyl-4-(1*H*-indol-3-yl)pyrimidin-2-yl]-1-methyl-cyclohexane-1,3-diamine (200 mg, 572.30 μ mol) was added and the mixture was stirred at 15 °C for 16 h. The mixture was added to H₂O (20 mL) and extract with EA:THF (3:1, 20mL*3). The organic layer was combined and evaporated, and the residue was purified by prep-HPLC to afford title compound (87 mg, 26.1% yield) as yellow solid. **LCMS:** $M+H^+$: 581.4/291.4 @ 2.174 min (10-80% ACN in H₂O, 4.5 min). **¹H NMR:** (MeOD, 400 MHz); δ 9.17 (br. s., 1H), 8.67-8.25 (m, 4H), 7.92 (s, 1H), 7.52 (br. s., 1H), 7.32 (br. s., 2H), 7.08-6.96 (m, 1H), 6.65 (d, J = 15.31 Hz, 1H), 4.52 (br. s., 1H), 4.08 (d, J = 7.03 Hz, 2H), 3.00-2.93 (m, 8H), 2.62 (br. s., 1H), 2.23-1.95 (m, 5H), 1.83-1.58 (m, 5H), 1.38 (t, J = 7.28 Hz, 3H).

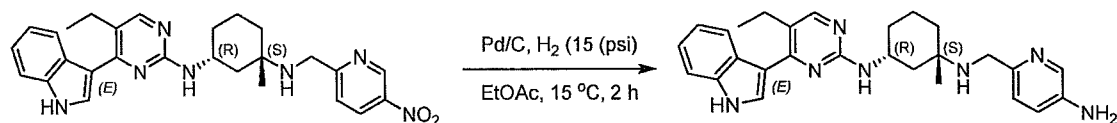
[214] **Example 13. Synthesis of (*E*)-4-(dimethylamino)-*N*-[6-[[[(1*S*,3*R*)-3-[[5-ethyl-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino]-1-methylcyclohexyl]amino]methyl]-3-pyridyl]but-2-enamide (Compound 411).**

[215] **(1*S*,3*R*)-*N*3-[5-ethyl-4-(1*H*-indol-3-yl)pyrimidin-2-yl]-1-methyl-*N*1-[(5-nitro-2-pyridyl)methyl]cyclohexane-1,3-diamine**



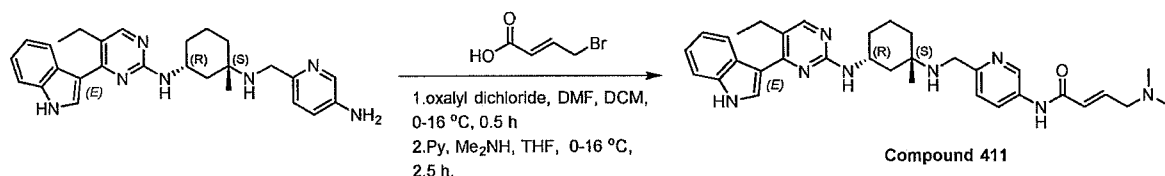
[216] A mixture of (1*S*,3*R*)-*N*3-[5-ethyl-4-(1*H*-indol-3-yl)pyrimidin-2-yl]-1-methyl-cyclohexane-1,3-diamine (550 mg, 1.57 mmol), 5-nitropyridine-2-carbaldehyde (263.3 mg, 1.73 mmol) and tetrakisopropoxytitanium (447.3 mg, 1.57 mmol) in MeOH (10 mL) was stirred at 15 °C for 17 h. Then NaBH₃CN (148.3 mg, 2.36 mmol) was added and the mixture was stirred at 15 °C for 7 h. The reaction mixture was poured into water (50 mL), extracted with DCM (20 mL*4), the organic layer was washed with brine (50 mL), dried over Na₂SO₄, and concentrated. The residue was purified by silica gel chromatography (DCM/MeOH = 80/1~30/1) to give title compound (320 mg, 41.9%) as yellow solid..

[217] (1S,3R)-N1-[(5-amino-2-pyridyl)methyl]-N3-[5-ethyl-4-(1H-indol-3-yl)pyrimidin-2-yl]-1-methylcyclohexane-1,3-diamine (Compound 1059)



[218] To a mixture of (1S,3R)-N3-[5-ethyl-4-(1H-indol-3-yl)pyrimidin-2-yl]-1-methyl-N1-[(5-nitro-2-pyridyl)methyl]cyclohexane-1,3-diamine (300 mg, 617.82 μmol) in EtOAc (20 mL) was added Pd/C (200 mg) under N_2 . The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred at 15 °C for 2 h under H_2 ball (15 psi). The reaction solution was filtered and the filter was concentrated to give title compound (280 mg, 99.4%) as light yellow solid. **LCMS:** $\text{M}+\text{H}^+$: 456.1 @ 0.739 min (5-95% ACN in H_2O , 1.5 min).

[219] (E)-4-(dimethylamino)-N-[6-[[[(1S,3R)-3-[[5-ethyl-4-(1H-indol-3-yl)pyrimidin-2-yl]amino]-1-methylcyclohexyl]amino]methyl]-3-pyridyl]but-2-enamide (Compound 411)



[220] To a stirred solution of (E)-4-bromobut-2-enoic acid (36.21 mg, 219.49 μmol) in DCM (5 mL) was added oxalyl dichloride (27.86 mg, 219.49 μmol) dropwise at 0 °C, followed by DMF (1.60 mg, 21.95 μmol), and the mixture was stirred at 16 °C for 0.5 h. This mixture was added to a solution of (1S,3R)-N1-[(5-amino-2-pyridyl)methyl]-N3-[5-ethyl-4-(1H-indol-3-yl)

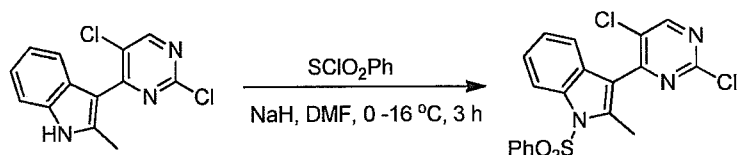
[221] pyrimidin-2-yl]-1-methyl-cyclohexane-1,3-diamine (100 mg, 219.49 μmol) and pyridine (52.1 mg, 658.47 μmol) in DCM (5 mL) at 0 °C dropwise and the mixture was stirred at 0 °C for 0.5 h. Then N-methylmethanamine (98.95 mg, 2.19 mmol) was added at 0 °C, the reaction mixture was allowed to warm to 16 °C, and stirred for 2 h. The mixture was concentrated, and the residue was purified by acidic prep-HPLC (HCl) to afford title compound (15.70 mg, 11.8%, HCl) as dark yellow solid.

[222] **LCMS:** $\text{M}+\text{H}^+$: 567.4 @ 1.860 min (10-80% ACN in H_2O , 4.5 min). **^1H NMR:** (MeOD, 400 MHz); δ 9.10 (br. s., 1H), 8.59 (d, $J = 7.28$ Hz, 1H), 8.38-8.25 (m, 2H), 7.99 (s, 1H), 7.72 (d, $J = 8.28$ Hz, 1H), 7.56 (d, $J = 7.53$ Hz, 1H), 7.38-7.23 (m, 2H), 6.94 (dt, $J = 15.00, 7.18$ Hz, 1H), 6.63 (d, $J = 15.06$ Hz, 1H), 4.46 (br. s., 3H), 4.03 (d, $J = 7.03$ Hz, 2H), 3.03-2.88 (m, 8H), 2.49

(d, $J = 11.29$ Hz, 1H), 2.26 (d, $J = 11.04$ Hz, 1H), 2.06 (br. s., 2H), 1.96-1.77 (m, 3H), 1.68 (s, 3H), 1.54 (d, $J = 12.80$ Hz, 1H), 1.36 (t, $J = 7.28$ Hz, 3H).

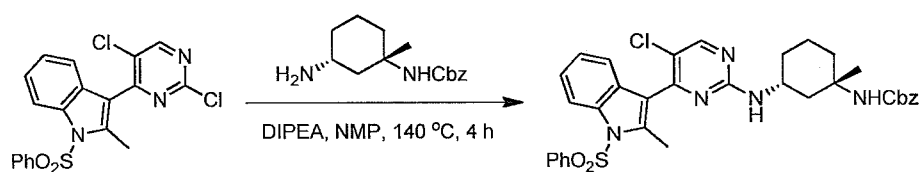
[223] **Example 14. Synthesis of 5-[[*(E)*-4-(dimethylamino)but-2-enoyl]amino]-*N*-[(1*S*,3*R*)-3-[[5-ethyl-4-(2-methyl-1*H*-indol-3-yl)pyrimidin-2-yl]amino]-1-methyl-cyclohexyl]pyridine-2-carboxamide (Compound 412).**

[224] ***1*-(benzenesulfonyl)-3-(2,5-dichloropyrimidin-4-yl)-2-methyl-indole**



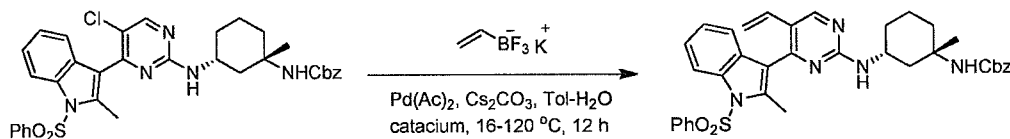
[225] To a stirred solution of 3-(2,5-dichloropyrimidin-4-yl)-2-methyl-1*H*-indole (5.00 g, 17.98 mmol) in DMF (50 mL) was added NaH (1.44 g, 35.96 mmol) at 0 °C under N₂ and the mixture was stirred at 0 °C for 0.5 h. Then benzenesulfonyl chloride (4.76 g, 26.97 mmol) was added at 0 °C and the mixture was allowed to warm to 16 °C and stirred for 3 h. The mixture was poured into water (100 mL), extracted by EtOAc (40 mL*3), and the organic layer was washed with water (100 mL *2) and brine (100 mL), dried over Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate = 8/1, 5/1) to give title compound (6.50 g, 86.4%) as light yellow solid.

[226] ***Benzyl N*-[(1*S*,3*R*)-3-[[4-[1-(benzenesulfonyl)-2-methyl-indol-3-yl]-5-chloro-pyrimidin-2-yl]amino]-1-methyl-cyclohexyl]carbamate**



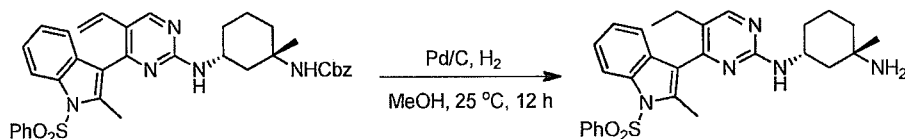
[227] A mixture of 1-(benzenesulfonyl)-3-(2,5-dichloropyrimidin-4-yl)-2-methyl-indole (6.50 g, 15.54 mmol), benzyl *N*-[(1*S*,3*R*)-3-amino-1-methyl-cyclohexyl]carbamate (4.89 g, 18.65 mmol) and DIPEA (6.02 g, 46.62 mmol) in NMP (80 mL) was heated to 140 °C and stirred for 4 h. The reaction mixture was cooled to r.t., diluted with EtOAc (80 mL), washed with water (100 mL*3) and brine (100 mL), dried over Na₂SO₄, filtered, and concentrated. The residue was purified by silica gel chromatography eluted with Petroleum ether/Ethyl acetate = 8:1~4:1) to give title compound (9.00 g, 89.9%) as light yellow solid.

[228] Benzyl N-[(1S,3R)-3-[[4-[1-(benzenesulfonyl)-2-methyl-indol-3-yl]-5-vinyl-pyrimidin-2-yl]amino]-1-methylcyclohexyl]carbamate



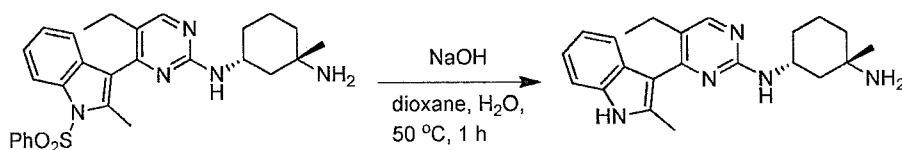
[229] A mixture of benzyl N-[(1S,3R)-3-[[4-[1-(benzenesulfonyl)-2-methyl-indol-3-yl]-5-chloro-pyrimidin-2-yl]amino]-1-methylcyclohexyl]carbamate (4.00 g, 6.21 mmol), potassium trifluoro(vinyl)boranuide (4.16 g, 31.05 mmol), Cs_2CO_3 (6.07 g, 18.63 mmol) and $\text{Pd}(\text{OAc})_2$ (697.04 mg, 3.11 mmol), bis(1-adamantyl)-butyl-phosphane (2.23 g, 6.21 mmol) in toluene (40 mL) and H_2O (8 mL) was degassed under vacuum and purged with N_2 three times at 16 °C. Then the mixture was stirred at 120 °C under N_2 for 12 h. The reaction mixture was poured into water (100 mL), extracted with EtOAc (40 mL*4), and the organic layer was dried over Na_2SO_4 , and evaporated. The residue was purified by silica gel chromatography (100-200 mesh silica gel, Petroleum ether/Ethyl acetate=6/1, 3/1) to give title compound (560.00 mg, 14.1%) as brown solid.

[230] Benzyl N-[(1S,3R)-3-[[4-[1-(benzenesulfonyl)-2-methyl-indol-3-yl]-5-vinyl-pyrimidin-2-yl]amino]-1-methylcyclohexyl]carbamate



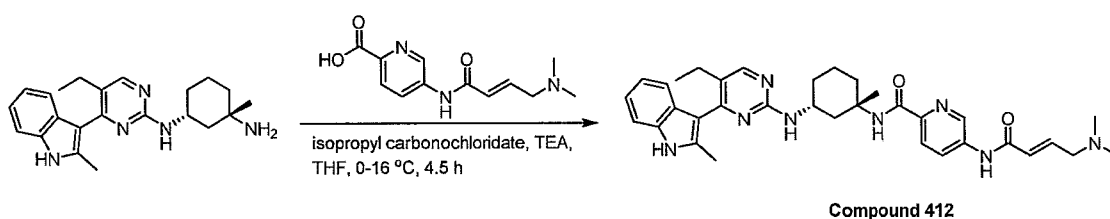
[231] To a solution of benzyl N-[(1S,3R)-3-[[4-[1-(benzenesulfonyl)-2-methyl-indol-3-yl]-5-vinyl-pyrimidin-2-yl]amino]-1-methylcyclohexyl]carbamate (730 mg, 1.15 mmol) in MeOH (10 mL) and DCM (2 mL) was added Pd/C (500 mg) under N_2 . The suspension was degassed under vacuum and purged with H_2 three times. The mixture was stirred at 25 °C for 24 h under H_2 (50 psi). The reaction mixture was filtered through a pad of Celite. The filter cake was washed with MeOH (10 mL*2) and DCM (10 mL*4), and the filtrate was concentrated to give title compound (250 mg, crude) as brown solid.

[232] (1S,3R)-N3-[5-ethyl-4-(2-methyl-1H-indol-3-yl)pyrimidin-2-yl]-1-methyl-cyclohexane-1,3-diamine



[233] A mixture of (1S,3R)-N3-[4-[1-(benzenesulfonyl)-2-methyl-indol-3-yl]-5-ethyl-pyrimidin-2-yl]-1-methyl-cyclohexane-1,3-diamine (260 mg, 516.22 μmol) and NaOH (62.4 mg, 1.56 mmol) in MeOH (5 mL) and H₂O (1 mL) was heated to 70 °C and stirred for 1 h. The mixture was poured into water (30 mL), extracted with DCM (10 mL*5), and the organic layer was washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated to give title compound (160 mg, crude) as light yellow solid.

[234] 5-[[*(E)*-4-(dimethylamino)but-2-enoyl]amino]-N-[(1S,3R)-3-[[5-ethyl-4-(2-methyl-1H-indol-3-yl)pyrimidin-2-yl]amino]-1-methyl-cyclohexyl]pyridine-2-carboxamide (Compound 412)

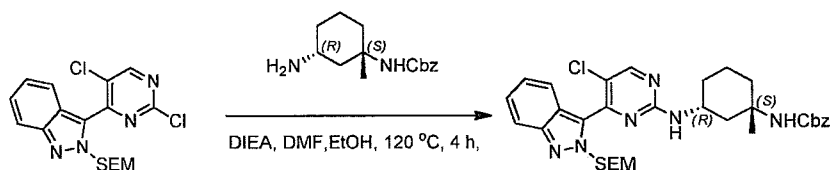


[235] To a stirred solution of 5-[[*(E)*-4-(dimethylamino)but-2-enoyl]amino]pyridine-2-carboxylic acid (68.5 mg, 275.10 μmol) and TEA (83.5 mg, 825.3 μmol) in THF (3 mL) was added isopropyl carbonochloridate (33.7 mg, 275.10 μmol) at 0 °C slowly. The reaction mixture was stirred at 16 °C for 3 h. Then this mixture was added to a stirred solution of (1S,3R)-N3-[5-ethyl-4-(2-methyl-1H-indol-3-yl)pyrimidin-2-yl]-1-methyl-cyclohexane-1,3-diamine (100 mg, 275.10 μmol) and TEA (55.6 mg, 550.20 μmol) in THF (5 mL) at 0 °C and the mixture was allowed to warm to 16 °C and stirred for 1.5 h. The reaction mixture was concentrated, the residue was purified by acidic prep-HPLC (HCl) to give title compound (72.70 mg, 41.8%, HCl) as dark yellow solid. LCMS: $M+H^+$: 595.4 @2.216 min (10-80% ACN in H₂O, 4.5 min).

¹HNMR (MeOD, 400 MHz); δ 9.17 (br. s., 1H), 8.61-8.20 (m, 3H), 7.40 (d, J = 7.78 Hz, 2H), 7.23-7.10 (m, 2H), 7.05-6.94 (m, 1H), 6.65 (d, J = 15.31 Hz, 1H), 4.29 (t, J = 6.53 Hz, 1H), 4.06 (d, J = 7.03 Hz, 2H), 2.95 (s, 6H), 2.66 (d, J = 6.27 Hz, 2H), 2.55 (br. s., 4H), 2.14-2.05 (m, 1H), 1.95 (br. s., 3H), 1.79-1.61 (m, 2H), 1.57 (s, 3H), 1.46 (dd, J = 14.93, 7.40 Hz, 1H), 1.07-0.95 (m, 3H).

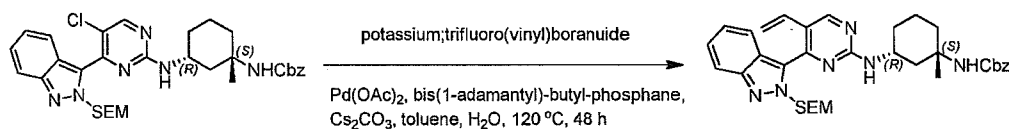
[236] Example 15. Synthesis of (*E*)-4-(dimethylamino)-N-[6-[[[(1S,3R)-3-[[5-ethyl-4-(1H-indazol-3-yl)pyrimidin-2-yl]amino]-1-methyl-cyclohexyl]amino]methyl]-3-pyridyl]but-2-enamide (Compound 413).

[237] Benzyl N-[(1S,3R)-3-[[5-chloro-4-[2-(2-trimethylsilylethoxymethyl)indazol-3-yl]pyrimidin-2-yl]amino]-1-methyl-cyclohexyl]carbamate



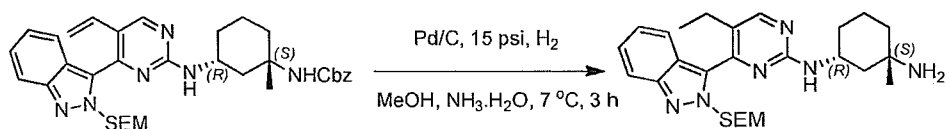
[238] A solution of 2-[[3-(2,5-dichloropyrimidin-4-yl)indazol-2-yl]methoxy]ethyl-trimethylsilane (5 g, 12.65 mmol), Benzyl N-[(1S,3R)-3-amino-1-methyl-cyclohexyl]carbamate (3.98 g, 15.18 mmol) and DIEA (8.17 g, 63.25 mmol) in DMF (20 mL) and EtOH (20 mL) was added and stirred at 120 °C for 4 h. The mixture was washed with water (30 mL) and extracted by EA (50 mL* 3). The organic layer was combined, dried over Na₂SO₄, and evaporated under reduced pressure to dryness. The residue was purified by column PE/EA = (10:1~8:1~5:1~4:1) to give title compound (7 g, 89.07%) as yellow solid.

[239] Benzyl N-[(1S,3R)-1-methyl-3-[[4-[2-(2-trimethylsilylethoxymethyl)indazol-3-yl]-5-vinyl-pyrimidin-2-yl]amino]cyclohexyl]carbamate



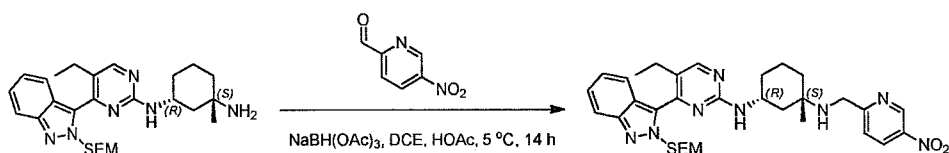
[240] A flask was fitted with benzyl N-[(1S,3R)-3-[[5-chloro-4-[2-(2-trimethylsilylethoxymethyl)indazol-3-yl]pyrimidin-2-yl]amino]-1-methyl-cyclohexyl]carbamate (2 g, 3.22 mmol), potassium trifluoro(vinyl)boranuide (2.16 g, 16.10 mmol), Pd(OAc)₂ (361.39 mg, 1.61 mmol), Cs₂CO₃ (3.15 g, 9.66 mmol) and bis(1-adamantyl)-butyl-phosphane (1.15 g, 3.22 mmol) in toluene (30 mL) and H₂O (6 mL). The reaction mixture was stirred at 120 °C under N₂ for 48 h. The mixture was filtered and extracted by EA (50 mL*3). The organic layer was combined, dried over Na₂SO₄ and evaporated under reduce pressure to dryness. The residue was purified by column PE/EA = (10:1-5:1-3:1) to give title compound (700 mg, 35.47%) as brown solid.

[241] (1S,3R)-N3-[5-ethyl-4-[2-(2-trimethylsilylethoxymethyl)indazol-3-yl]pyrimidin-2-yl]-1-methyl-cyclohexane-1,3-diamine



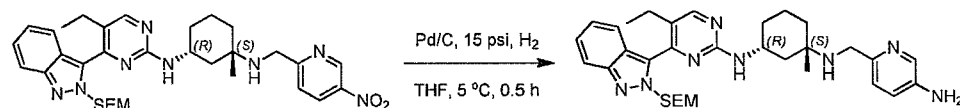
[242] To a solution of benzyl N-[(1S,3R)-1-methyl-3-[[4-[2-(2-trimethylsilylethoxymethyl)indazol-3-yl]-5-vinyl-pyrimidin-2-yl]amino]cyclohexyl]carbamate (500 mg, 815.87 μ mol) in MeOH (30 mL) and $\text{NH}_3 \cdot \text{H}_2\text{O}$ (3 mL) was added Pd/C (200 mg, 10%). The mixture was stirred at 7 °C under H_2 (15 psi) for 3 h. The mixture was filtered and the filtrate was evaporated to give title compound (400 mg, crude) as brown oil.

[243] *(1S,3R)-N3-[5-ethyl-4-[2-(2-trimethylsilylethoxymethyl)indazol-3-yl]pyrimidin-2-yl]-1-methyl-N1-[(5-nitro-2-pyridyl)methyl]cyclohexane-1,3-diamine*



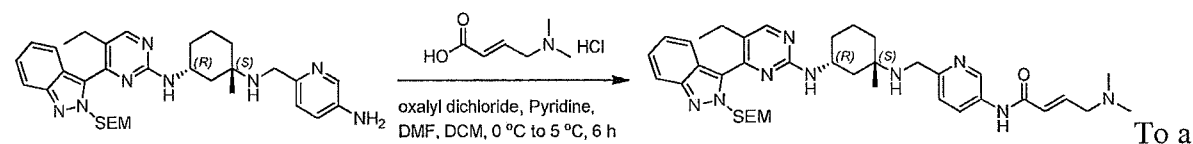
[244] A solution of (1S,3R)-N3-[5-ethyl-4-[2-(2-trimethylsilylethoxymethyl)indazol-3-yl]pyrimidin-2-yl]-1-methyl-cyclohexane-1,3-diamine (500 mg, 1.04 mmol) in DCE (30 mL) was added 5-nitropyridine-2-carbaldehyde (158.21 mg, 1.04 mmol) and HOAc (62.46 mg, 1.04 mmol). The reaction mixture was stirred at 5 °C for 12 h. Then $\text{NaBH}(\text{OAc})_3$ (440.88 mg, 2.08 mmol) was added and the mixture was stirred at 5 °C for another 2 h. The mixture was evaporated and the residue was purified by column (DCM/MeOH = 80:1-60:1-50:1) to give title compound (200 mg, 31.18%) as yellow oil.

[245] *1-[(1S,3R)-3-[[5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl]amino]cyclohexyl]-4-prop-2-enoyl-piperazin-2-one*



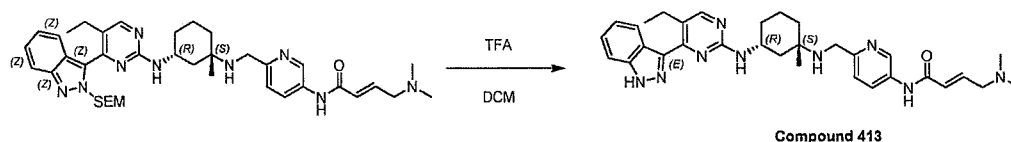
[246] To a solution of (1S,3R)-N3-[5-ethyl-4-[2-(2-trimethylsilylethoxymethyl)indazol-3-yl]pyrimidin-2-yl]-1-methyl-N1-[(5-nitro-2-pyridyl)methyl]cyclohexane-1,3-diamine (170 mg, 275.60 μ mol) in THF (30 mL) was added Pd/C (10%, 70 mg) and the mixture was stirred at 5 °C under H_2 (15 psi) for 0.5 h. The mixture was filtered and the solvent was evaporated under reduced pressure to dryness to give title compound (170 mg, crude) as brown solid.

[247] *(E)-4-(dimethylamino)-N-[6-[[[(1S,3R)-3-[[5-ethyl-4-(1H-indazol-3-yl)pyrimidin-2-yl]amino]-1-methyl-cyclohexyl]amino]methyl]-3-pyridyl]but-2-enamide*



solution of (E)-4-(dimethylamino)but-2-enoic acid (47.98 mg, 289.69 μmol , HCl salt) in DCM (1 mL) was added oxalyl dichloride (36.77 mg, 289.69 μmol) and DMF (10.59 mg, 144.85 μmol), the mixture was stirred at 0 °C for 2 h. Then the mixture was added to a solution of (1S,3R)-N1-[(5-amino-2-pyridyl)methyl]-N3-[5-ethyl-4-[2-(2-trimethylsilylethoxymethyl)indazol-3-yl]pyrimidin-2-yl]-1-methyl-cyclohexane-1,3-diamine (170 mg, 289.69 μmol) and pyridine (45.83 mg, 579.38 μmol) in DCM (14 mL) at 0 °C. The mixture was then slowly warmed to 5 °C for 12 h. The mixture was evaporated and the residue was purified by column (DCM/MeOH = 70:1-50:1-30:1-10:1) to afford title compound (100 mg, 34.4%).

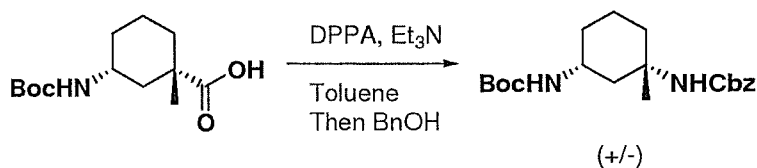
[248] (E)-4-(dimethylamino)-N-[6-[[[(1S,3R)-3-[[5-ethyl-4-(1H-indazol-3-yl)pyrimidin-2-yl]amino]-1-methyl-cyclohexyl]amino]methyl]-3-pyridyl]but-2-enamide (Compound 413)



[249] (E)-4-(dimethylamino)-N-[6-[[[(1S,3R)-3-[[5-ethyl-4-(1H-indazol-3-yl)pyrimidin-2-yl]amino]-1-methyl-cyclohexyl]amino]methyl]-3-pyridyl]but-2-enamide (100 mg, 123.3 μmol) was purified by prep-HPLC(TFA) to give (E)-4-(dimethylamino)-N-[6-[[[(1S,3R)-3-[[5-ethyl-4-(1H-indazol-3-yl)pyrimidin-2-yl]amino]-1-methyl-cyclohexyl]amino]methyl]-3-pyridyl]but-2-enamide (30 mg, TFA salt). Then the final product was purified by prep-HPLC (Neutral) to give title compound (4.4 mg, 4.4%). **LCMS:** $M+H^+$: 568.5@ 1.947 min (10-80% ACN in H_2O , 4.5 min). **^1H NMR** (MeOD, 400 MHz); δ 8.76 (s, 1H), 8.45 (d, $J = 7.6$ Hz, 1H), 8.19 (s, 1H), 8.07 (d, $J = 8.4$ Hz, 1H), 7.58 (d, $J = 8.4$ Hz, 1H), 7.45-7.39 (m, 2H), 7.22-7.18 (m, 1H), 6.95-6.91 (m, 1H), 6.27 (d, $J = 15.2$ Hz, 1H), 4.22 (s, 1H), 3.96 (s, 2H), 3.19 (d, $J = 5.2$ Hz, 2H), 3.04-2.99 (m, 2H), 2.30 (s, 6H), 2.17-2.15 (m, 2H), 1.84-1.77 (m, 1H), 1.74-1.66 (m, 1H), 1.63-1.57 (m, 1H), 1.54-1.51 (m, 2H), 1.37 (s, 4H), 1.20-1.16 (m, 3H).

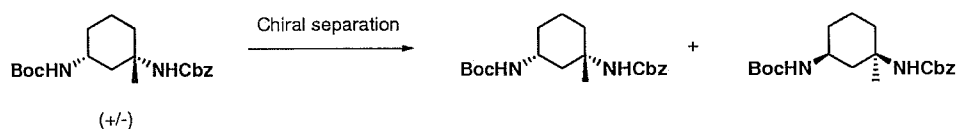
[250] Example 16. Synthesis of N-((1S,3R)-3-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)-1-methylcyclohexyl)-5-((E)-4-(dimethylamino)but-2-enamido)picolinamide (Compound 267).

[251] (+/-) Benzyl tert-butyl ((1S,3R)-1-methylcyclohexane-1,3-diyl)dicarbamate



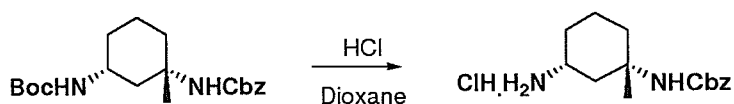
[252] A solution of (+/-)-(1S,3R)-3-((tert-butoxycarbonyl)amino)-1-methylcyclohexanecarboxylic acid prepared as in WO2010/148197 (4.00 g, 15.5 mmol) in toluene (155 mL) was treated with Et₃N (2.4 mL, 17.1 mmol) and DPPA (3.68 mL, 17.1 mmol) and heated at reflux for 1h. Benzyl alcohol (8.0 mL, 77.7 mmol) and Et₃N (4.4 mL, 31.4 mmol) were added to the reaction mixture and the solution was heated at 100 °C for 72h. The mixture was cooled to room temperature and then diluted with EtOAc (300 mL) and H₂O (300 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 200 mL). The combined organics layers were washed with brine (100 mL), filtered and evaporated to dryness. The residue was purified by SiO₂ chromatography (EtOAc in hexanes, 0 to 50% gradient) and afforded the title compound (3.40 g, 9.38 mmol, 60%) as a white solid.

[253] **Benzyl tert-butyl ((1S,3R)-1-methylcyclohexane-1,3-diyl)dicarbamate and benzyl tert-butyl ((1R,3S)-1-methylcyclohexane-1,3-diyl)dicarbamate**



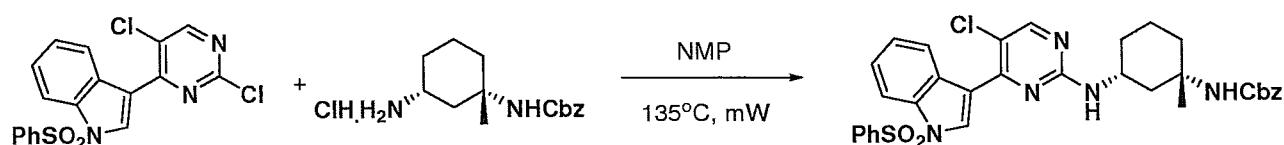
[254] Both enantiomers of (+/-)-Benzyl tert-butyl ((1S,3R)-1-methylcyclohexane-1,3-diyl)dicarbamate (3.40 g, 9.38 mmol) were separated using preparative chiral HPLC (Chiralpak IA, 5 μ m, 20x250 mm; hex/MeOH/DCM = 90/5/5) to yield both compounds benzyl tert-butyl ((1S,3R)-1-methylcyclohexane-1,3-diyl)dicarbamate (1.20 g, 3.31 mmol) and benzyl tert-butyl ((1R,3S)-1-methylcyclohexane-1,3-diyl)dicarbamate (1.15 g, 3.17 mmol) as white solids.

[255] **Benzyl ((1S,3R)-3-amino-1-methylcyclohexyl)carbamate hydrochloride**



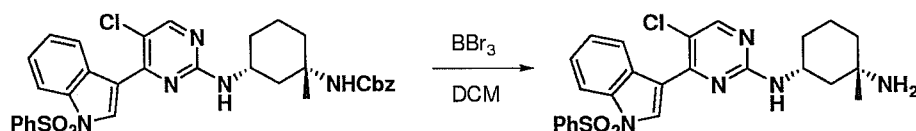
[256] A solution of benzyl tert-butyl ((1S,3R)-1-methylcyclohexane-1,3-diyl)dicarbamate (700 mg, 1.93 mmol) in DCM (19 mL) was treated with a 4M solution of HCl in dioxane (9.66 mL, 38.6 mmol) and stirred 16h at rt. The mixture was evaporated to dryness and afforded the title compound (577 mg, 1.93 mmol, 100%) as a white solid which was used in the next step without further purification.

[257] **(1S,3R)-Benzyl-3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)-1-methylcyclohexylcarbamate**



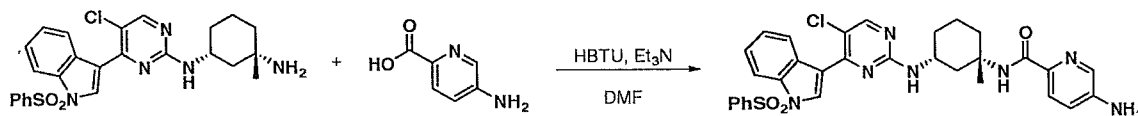
[258] A solution of 3-(2,5-dichloropyrimidin-4-yl)-1-(phenylsulfonyl)-1H-indole (1.02 g, 2.53 mmol), benzyl ((1S,3R)-3-amino-1-methylcyclohexyl)carbamate hydrochloride (577 mg, 1.93 mmol) and DIPEA (1.15 mL, 6.60 mmol) in NMP (11 mL) was heated at 135 °C (microwave) for 60 min. The cooled mixture was diluted with EtOAc (250 mL), washed with H₂O (100 mL), brine (100 mL), dried over MgSO₄, filtered and evaporated to dryness. The residue was purified by SiO₂ chromatography (EtOAc in DCM, 0 to 50% gradient) and afforded the title compound (747 mg, 1.19 mmol, 54%) as a yellow foam.

[259] (1S,3R)-N-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-yl)-3-methylcyclohexane-1,3-diamine



[260] A cooled (-78°C) solution of (1S,3R)-benzyl-3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)-1-methylcyclohexylcarbamate (747 mg, 1.19 mmol) in DCM (39 mL) was treated with a 1M solution of BBr₃ in DCM (2.83 mL, 2.83 mmol) and was slowly warmed up to rt. MeOH (10 mL) was added to the mixture and the resulting solution was stirred 1h at rt. The resulting mixture was evaporated to dryness. The residue was purified by reverse phase chromatography (C₁₈, H₂O/ACN +0.1% HCO₂H, 0 to 60% gradient) and afforded the title compound (485 mg, 0.978 mmol, 83%) as a yellow solid.

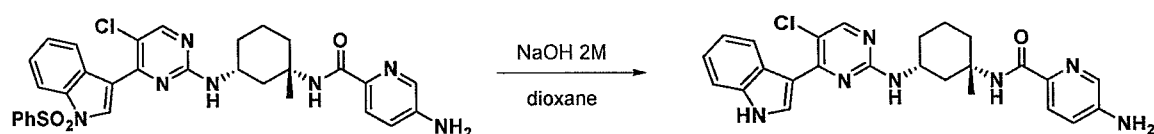
[261] 5-amino-N-((1S,3R)-3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)-1-methylcyclohexyl)picolinamide



[262] A solution of (1R,3S)-N-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-yl)-3-methylcyclohexane-1,3-diamine (75.0 mg, 0.150 mmol) and 5-aminopicolinic acid (25.0 mg, 0.180 mmol) in DMF (5.0 mL) was treated with HBTU (86.0 mg, 0.230 mmol) and DIPEA (79 µL, 0.45 mmol). The resulting mixture was stirred 5h at rt and diluted with MeTHF (50 mL) and

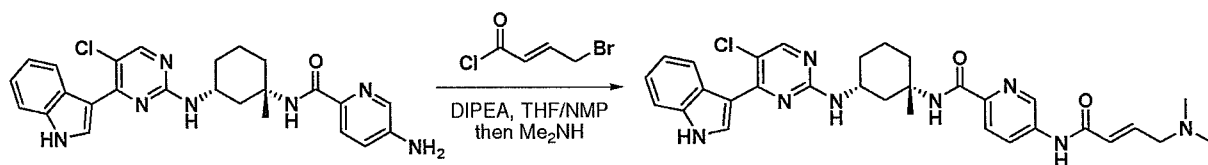
saturated NaHCO_3 (50 mL). The layers were separated and the aqueous layer was extracted with MeTHF (2 x 50 mL). The combined organic layers were dried over MgSO_4 , filtered and evaporated to dryness. The residue was purified by SiO_2 chromatography (EtOAc in DCM, 0 to 50% gradient) and afforded the title compound (74.0 mg, 0.120 mmol, 79%) as a light yellow oil.

[263] 5-amino-N-((1S,3R)-3-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)-1-methylcyclohexyl)picolinamide



[264] A solution of 5-amino-N-((1S,3R)-3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)-1-methylcyclohexyl)picolinamide (74.0 mg, 0.120 mmol) in 1,4-dioxane (4.0 mL) was treated with a 2M solution of NaOH in H_2O (960 μL , 4.78 mmol) and heated at 60°C for 1h. The cooled mixture was diluted with MeTHF (30 mL) and H_2O (30 mL). The layers were separated and the aqueous layer was extracted with MeTHF (3 x 30 mL). The combined organic layers were dried over MgSO_4 , filtered and evaporated to dryness affording the title compound (57.0 mg, 0.120 mmol, 100%) as a light yellow oil which was used in the next step without further purification.

[265] N-((1S,3R)-3-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)-1-methylcyclohexyl)-5-((E)-4-(dimethylamino)but-2-enamido)picolinamide (Compound 267)

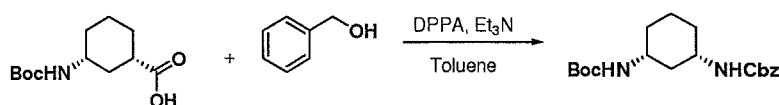


[266] A cooled (-78°C) solution of 5-amino-N-((1S,3R)-3-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)-1-methylcyclohexyl)picolinamide (57.0 mg, 0.120 mmol) and DIPEA (104 μL , 0.598 mmol) in THF/NMP (4.0 mL/1.0 mL) was treated with a 54.2 mg/mL solution of (E)-4-bromobut-2-enoyl chloride in DCM (104 μL , 0.598 mmol). The resulting mixture was stirred 4h at -78°C before addition of a 2M solution of dimethylamine in THF (359 μL , 0.717 mmol). The resulting mixture was warmed up to rt and stirred 45min at this temperature before being evaporated to dryness. The residue was purified by reverse phase chromatography (C_{18} , $\text{H}_2\text{O}/\text{ACN}$ +0.1% HCO_2H , 0 to 50% gradient) and afforded the title compound (15.0 mg, 0.026

mmol, 22%) as a white solid after lyophilization. **LCMS:** Calculated: 587.12; Found ($M+H^+$): 587.39. **^1H NMR** (500 MHz, DMSO) δ 11.84 (s, 1H), 10.54 (s, 1H), 8.82 (d, $J = 2.3$ Hz, 1H), 8.64 (s, 1H), 8.47 (s, 1H), 8.25 (dd, $J = 8.6, 2.4$ Hz, 2H), 7.98 (d, $J = 8.9$ Hz, 2H), 7.50 (d, $J = 7.7$ Hz, 1H), 7.25 – 7.07 (m, 3H), 6.81 (dt, $J = 15.5, 5.8$ Hz, 1H), 6.29 (d, $J = 15.4$ Hz, 1H), 4.23 – 4.08 (m, 1H), 3.08 (dd, $J = 5.7, 1.1$ Hz, 2H), 2.46 – 2.37 (m, 1H), 2.18 (s, 6H), 2.04 – 1.95 (m, 2H), 1.87 – 1.70 (m, 3H), 1.63 – 1.46 (m, 4H), 1.39 – 1.26 (m, 1H).

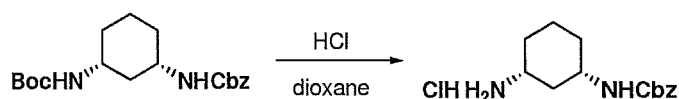
[267] Example 17. Synthesis of N-(6-(((1S,3R)-3-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexylamino)methyl)pyridin-3-yl)acrylamide (Compound 261)

[268] (1S,3R)-3-(Benzyloxycarbonylamino)cyclohexylamino-2,2-dimethylpropionate



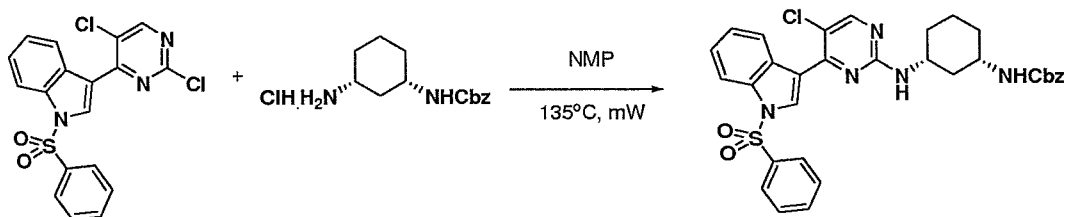
[269] To a solution of (1S,3R)-3-(*tert*-butoxycarbonylamino)cyclohexanecarboxylic acid (8.77 g, 36.1 mmol) (prepared following Tetrahedron: *Asymmetry* 2010 (21), 864-866) in toluene (145 mL) was added Et_3N (5.53 mL, 39.7 mmol) and DPPA (7.7 mL, 36.1 mmol). The resulting solution was stirred for 2 h at 110 °C and cooled down to 80 °C. Benzyl alcohol (4.66 mL, 45.1 mmol) and triethylamine (5.53 mL, 39.7 mmol) were added, and the mixture was stirred for 20 h at 80 °C. The cooled solution was diluted with EtOAc (100 mL) and water (50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 $\times$ 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by SiO_2 chromatography (EtOAc in hexanes, 1 to 100% gradient) to afford the title compound (9.89 g, 28.4 mmol, 79% yield) as a white solid.

[270] Benzyl (1S,3R)-3-aminocyclohexylcarbamate hydrochloride



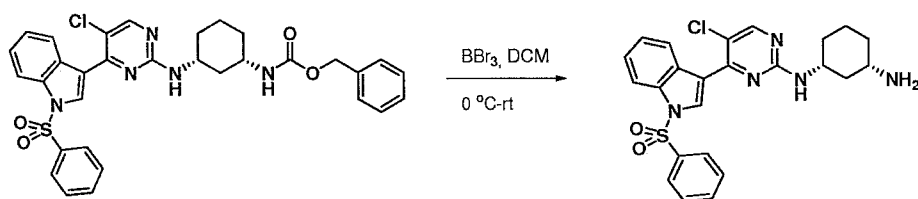
[271] A solution of (1S,3R)-3-(benzyloxycarbonylamino)cyclohexylamino-2,2-dimethylpropionate (1.50 g, 4.31 mmol) in DCM (43 mL) was treated with a 4M solution of HCl in dioxane (16.0 mL, 64.6 mmol) and stirred for 2h at rt. The resulting solution was evaporated to dryness and afforded the title compound (1.23 g, 4.31 mmol, 100%) as a white solid which was used in the next step without further purification.

[272] Benzyl (1S,3R)-3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexylcarbamate



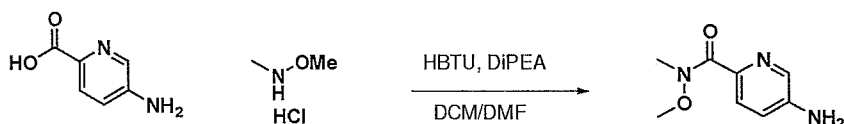
[273] A solution of 3-(2,5-dichloropyrimidin-4-yl)-1-(phenylsulfonyl)-1H-indole (791 mg, 1.96 mmol), benzyl (1S,3R)-3-aminocyclohexylcarbamate hydrochloride (613 mg, 2.15 mmol) and diisopropylethylamine (0.75 mL, 4.31 mmol) in NMP (20 mL) was heated 30 min at 135°C (microwave). The mixture was diluted with EtOAc (100 mL), washed with H₂O (50 mL), brine (50 mL), dried (MgSO₄), filtered and evaporated to dryness. The residue was purified by SiO₂ chromatography (EtOAc in hexanes, 5 to 70% gradient), and afforded the title compound (1.04 g, 1.69 mmol, 40%) as a yellow solid.

[274] *(1R,3S)-N-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-yl)cyclohexane-1,3-diamine*



[275] A solution of 1M BBr₃ in DCM (1.97 mL, 1.97 mmol) was added to a stirring solution of benzyl (1S,3R)-3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexylcarbamate (971 mg, 1.58 mmol) at 0 °C. The reaction mixture was allowed to stir 30 min at this temperature and then allowed to stir at room temperature overnight. The solution was then re-cooled to 0 °C and quenched with MeOH (10 mL). The solution was allowed to stir 30 min and was then concentrated under reduced pressure to a light yellow oil. The oil was purified by reverse phase column (C₁₈, H₂O/ACN +0.1% HCO₂H, 5 to 100% gradient) to yield the title compound as a light yellow solid (762 mg, 1.58 mmol, 100%).

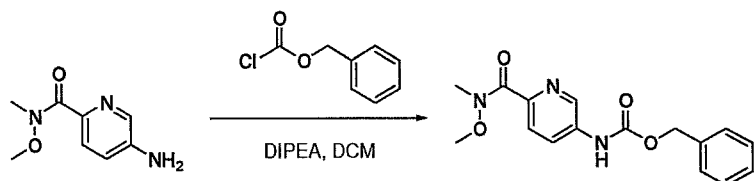
[276] *5-Amino-N-methoxy-N-methylpicolinamide*



[277] N,O-dimethylhydroxylamine hydrochloride (520 mg, 5.33 mmol), 5-aminopyridine-2-carboxylic acid (491 mg, 3.55 mmol), HBTU (2.02 g, 5.33 mmol) and diisopropylethylamine

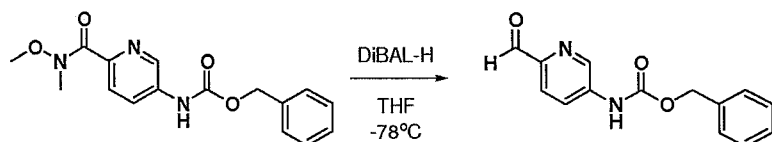
(2.48 mL, 14.2 mmol) were stirred in a mixture of DCM/DMF (5/1, 23.7 mL) at room temperature overnight. The reaction mixture was poured into a saturated solution of NaHCO₃ (50 mL) and the product extracted 4 times with 2-methyltetrahydrofuran (50 mL). Organics were combined, washed with water, brine, dried over MgSO₄, filtered and concentrated under reduced pressure to afford the title compound as an orange foamy solid (643 mg, 3.55 mmol, 100%).

[278] **Benzyl 6-(methoxy(methyl)carbamoyl)pyridin-3-ylcarbamate**



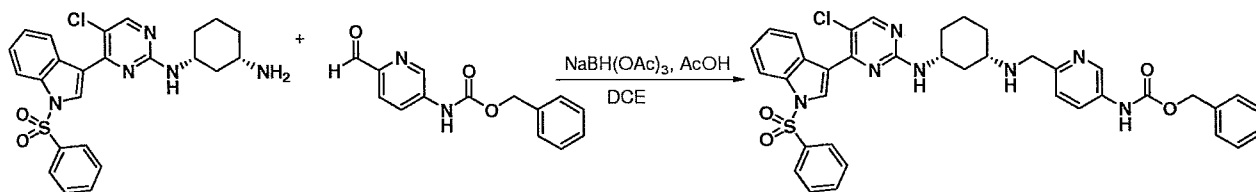
[279] Diisopropylethylamine (1.9 mL, 10.7 mmol) was added to a stirring solution of 5-amino-*N*-methoxy-*N*-methylpicolinamide (643 mg, 3.55 mmol) in DCM (24 mL) and cooled to 0 °C. Benzylchloroformate (0.76 mL, 5.3 mmol) was then added to the solution and the reaction mixture stirred from 0 °C to room temperature overnight. Aqueous sodium bicarbonate (100 mL) was added and the phases were separated. The aqueous phase was extracted twice with dichloromethane (50 mL). Organics were combined, washed with brine, dried over MgSO₄, filtered and concentrated to afford the title compound as a yellow oil (391 mg, 1.24 mmol, 35%).

[280] **Benzyl 6-formylpyridin-3-ylcarbamate**

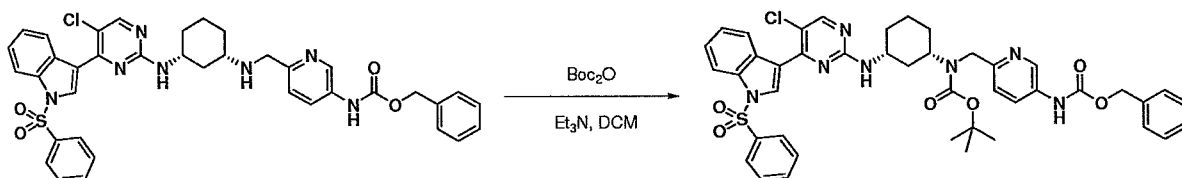


[281] Diisobutylaluminum hydride 1M in DCM (1.90 mL, 1.90 mmol) was added dropwise to a stirring solution of benzyl 6-(methoxy(methyl)carbamoyl)pyridin-3-ylcarbamate (391 mg, 1.24 mmol) in tetrahydrofuran (5 mL) at -78 °C. The resulting solution was allowed to stir at this temperature for 1h30min. The solution was then quenched at -78 °C with 1M HCl (10 mL) and temperature was slowly raised to 0 °C. A saturated aqueous solution of NaHCO₃ (50 mL) was added to the reaction mixture and the solution was extracted 3 times with EtOAc (50 mL). The combined organic layers were dried over MgSO₄, filtered and evaporated to dryness. The residue was purified by SiO₂ chromatography (EtOAc in hexanes, 0 to 100% gradient) and afforded the title compound as a white solid (69 mg, 0.27 mmol, 22%).

[282] **Benzyl 6-(((1*S*,3*R*)-3-(5-chloro-4-(1-(phenylsulfonyl)-1*H*-indol-3-yl)pyrimidin-2-**

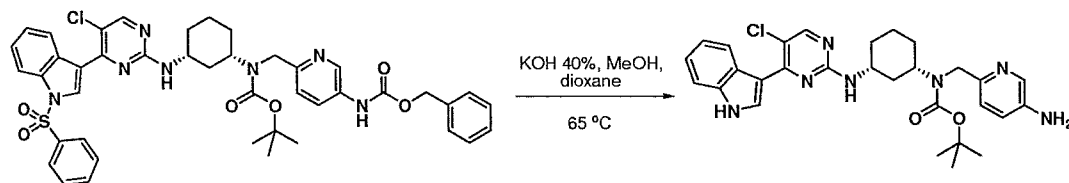
ylamino)cyclohexylamino)methyl)pyridin-3-ylcarbamate

[283] To a DCE solution (3.1 mL) of (1R,3S)-*N*-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-yl)cyclohexane-1,3-diamine (120 mg, 0.25 mmol) was added acetic acid (7.0 μ L, 0.12 mmol) followed by the addition of benzyl 6-formylpyridin-3-ylcarbamate (69 mg, 0.27 mmol). The reaction mixture was stirred at room temperature for 10 minutes. Sodium triacetoxyborohydride (106 mg, 0.50 mmol) was then added in one portion and the resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane (50 mL) and the organic phase was washed with saturated solution of NaHCO_3 (50 mL) and brine (50 mL). The organic layer was dried over MgSO_4 , filtered and concentrated under reduced pressure to afford the title compound as a pale yellow solid (167 mg, 0.231 mmol, 93%).

[284] Benzyl 6-((((1S,3R)-3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexyl)(Boc)amino)methyl)pyridin-3-ylcarbamate

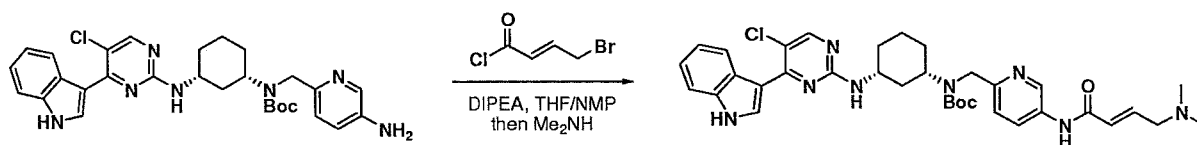
[285] Benzyl 6-((((1S,3R)-3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexylamino)methyl)pyridin-3-ylcarbamate (167 mg, 0.231 mmol) was dissolved in DCM (2 mL) and triethylamine (64 μ L, 0.46 mmol) was added. The solution was cooled to 0 $^{\circ}\text{C}$ and di-*tert*-butyl dicarbonate (53 mg, 0.240 mmol) was added. The reaction mixture was stirred from 0 $^{\circ}\text{C}$ to room temperature overnight. The reaction mixture was then quenched with a saturated solution of NaHCO_3 (50 mL) and extracted 3 times with DCM (50 mL). The combined organic layers were dried over MgSO_4 , filtered and evaporated to dryness. The residue was purified by SiO_2 chromatography (EtOAc in DCM, 10 to 100% gradient) and afforded the title compound as a white solid (139 mg, 0.169 mmol, 73%).

[286] *tert*-Butyl (5-aminopyridin-2-yl)methyl((1S,3R)-3-(5-chloro-4-(1H-indol-3-

yl)pyrimidin-2-ylamino)cyclohexyl)carbamate

[287] Benzyl 6-((((1S,3R)-3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexyl)(Boc)amino)methyl) pyridin-3-ylcarbamate (139 mg, 0.169 mmol) was dissolved in 1,4-dioxane (1.1 mL) and KOH 40% in water (474 μ L, 3.38 mmol) was added. The reaction mixture was stirred at 65 °C overnight. The reaction mixture was then diluted with water (50 mL) and extracted 3 times with EtOAc (50 mL) and 2-methyltetrahydrofuran (50 mL). The combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. The residue was purified by SiO_2 chromatography (THF in DCM, 0 to 100% gradient) and afforded the title compound as a pale yellow solid (45 mg, 0.082 mmol, 49%).

[288] tert-Butyl (1S,3R)-3-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexyl((5-((E)-4-(dimethylamino)but-2-enamido)pyridin-2-yl)methyl)carbamate



[289] A cooled (-78°C) solution of *tert*-butyl (5-aminopyridin-2-yl)methyl((1S,3R)-3-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexyl)carbamate (45 mg, 0.082 mmol) and DIPEA (43 μ L, 0.25 mmol) in NMP/THF (0.3 mL/1.2 mL) was treated with a 54.2 mg/mL solution of (E)-4-bromobut-2-enoyl chloride in DCM (278 μ L, 0.08 mmol). The resulting mixture was stirred 1 h under inert atmosphere at -78°C before addition of a 2M solution of dimethylamine in THF (246 μ L, 0.49 mmol). The resulting mixture was warmed up to rt and stirred 1 h at this temperature before being concentrated. The residue was then re-dissolved in MeTHF (20 mL) and washed twice with water (10 mL). The aqueous layers were extracted twice with MeTHF (20 mL). Organic extracts were combined, washed with brine, dried over MgSO_4 , filtered, concentrated, providing the title compound as a brown oil (54 mg, 0.082 mmol, 100 %).

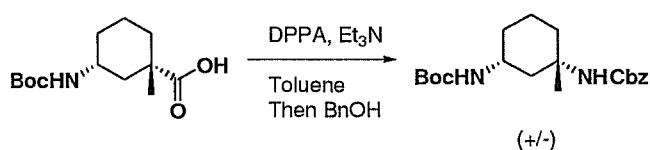
[290] (E)-N-(6-((((1S,3R)-3-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexylamino)methyl)pyridin-3-yl)-4-(dimethylamino)but-2-enamide



[291] *tert*-Butyl (1S,3R)-3-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexyl((5-((E)-4-(dimethylamino)but-2-enamido)pyridin-2-yl)methyl)carbamate (54 mg, 0.082 mmol) was dissolved in DCM (1 mL) and trifluoroacetic acid (83 μ L, 1.23 mmol, 15 eq) was added. The reaction mixture was stirred at room temperature for 5 h. The reaction mixture was then concentrated to remove DCM and excess TFA. Excess triethylamine was added and the residual oil was purified by reverse phase flash chromatography (C₁₈, H₂O/ACN +0.1% HCO₂H, 0 to 50% gradient). Pure fractions were directly lyophilized and afforded the title compound as a white solid (21 mg, 0.038 mmol, 46 %). **LCMS**: Calculated: 559.1; Found (M+H⁺): 559.37. **¹H NMR** (500 MHz, DMSO) δ 11.83 (br s, 1H), 10.26 (s, 1H), 8.74 (br s, 1H), 8.55 (br s, 1H), 8.47 (d, J = 2.8 Hz, 1H), 8.24 (s, 1H), 8.19 (s, 1H), 8.04 (d, J = 6.7 Hz, 1H), 7.48 (d, J = 8.2 Hz, 1H), 7.40 (d, J = 9.0 Hz, 1H), 7.26 (s, 1H), 7.18 (t, J = 7.4 Hz, 1H), 7.05 (br s, 1H), 6.76 (dt, J = 15.4, 5.9 Hz, 1H), 6.27 (dt, J = 15.4, 1.6 Hz, 1H), 3.93 (br s, 3H), 3.07 (dd, J = 5.9, 1.5 Hz, 2H), 2.73 (br s, 1H), 2.35 (br s, 1H), 2.18 (s, 6H), 2.01 (br s, 2H), 1.79 (brs, 1H), 1.40 – 1.20 (m, 3H), 1.15 – 1.05 (m, 1H).

[292] **Example 18. Synthesis of (E)-N-(6-(((1S,3R)-3-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)-1-methylcyclohexylamino)methyl)pyridin-3-yl)-4-(dimethylamino)but-2-enamide (Compound 294).**

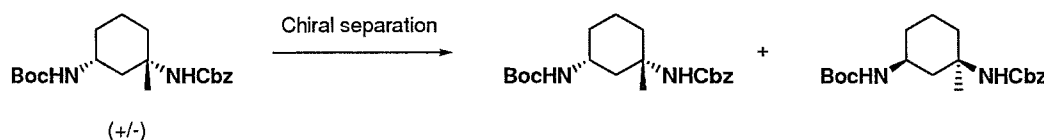
[293] **(+/-) Benzyl *tert*-butyl ((1S,3R)-1-methylcyclohexane-1,3-diyl)dicarbamate**



[294] A solution of (+/-)-(1S,3R)-3-((*tert*-butoxycarbonyl)amino)-1-methylcyclohexanecarboxylic acid prepared as in WO2010/148197 (4.00 g, 15.5 mmol) in toluene (155 mL) was treated with Et₃N (2.4 mL, 17.1 mmol) and DPPA (3.68 mL, 17.1 mmol) and heated at reflux for 1h. Benzyl alcohol (8.0 mL, 77.7 mmol) and Et₃N (4.4 mL, 31.4 mmol) were added to the reaction mixture and the solution was heated at 100 °C for 72h. The mixture was cooled to room temperature and then diluted with EtOAc (300 mL) and H₂O (300 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 200 mL). The combined organics layers were washed with brine (100 mL), filtered and evaporated to dryness.

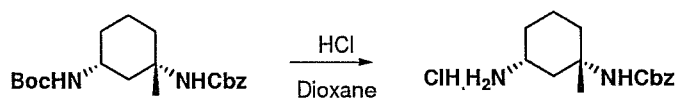
The residue was purified by SiO₂ chromatography (EtOAc in hexanes, 0 to 50% gradient) and afforded the title compound (3.40 g, 9.38 mmol, 60%) as a white solid.

[295] Benzyl tert-butyl ((1S,3R)-1-methylcyclohexane-1,3-diyl)dicarbamate and benzyl tert-butyl ((1R,3S)-1-methylcyclohexane-1,3-diyl)dicarbamate



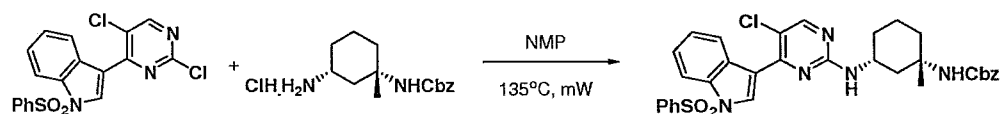
[296] Both enantiomers of (+/-)-Benzyl *tert*-butyl ((1S,3R)-1-methylcyclohexane-1,3-diyl)dicarbamate (3.40 g, 9.38 mmol) were separated using preparative chiral HPLC (Chiralpak IA, 5 μ m, 20x250 mm; hex/MeOH/DCM = 90/5/5) to yield both compounds benzyl *tert*-butyl ((1S,3R)-1-methylcyclohexane-1,3-diyl)dicarbamate (1.20 g, 3.31 mmol) and benzyl *tert*-butyl ((1R,3S)-1-methylcyclohexane-1,3-diyl)dicarbamate (1.15 g, 3.17 mmol) as white solids.

[297] Benzyl ((1S,3R)-3-amino-1-methylcyclohexyl)carbamate hydrochloride



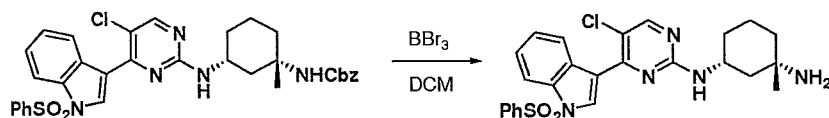
[298] A solution of benzyl *tert*-butyl ((1S,3R)-1-methylcyclohexane-1,3-diyl)dicarbamate (700 mg, 1.93 mmol) in DCM (19 mL) was treated with a 4M solution of HCl in dioxane (9.66 mL, 38.6 mmol) and stirred 16h at rt. The mixture was evaporated to dryness and afforded the title compound (577 mg, 1.93 mmol, 100%) as a white solid which was used in the next step without further purification.

[299] (1S,3R)-Benzyl-3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)-1-methylcyclohexylcarbamate



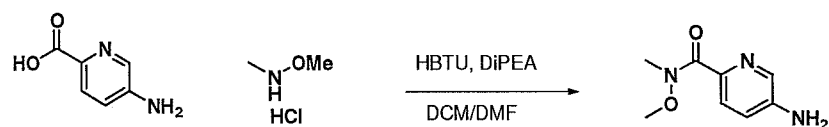
[300] A solution of 3-(2,5-dichloropyrimidin-4-yl)-1-(phenylsulfonyl)-1H-indole (1.02 g, 2.53 mmol), benzyl ((1S,3R)-3-amino-1-methylcyclohexyl)carbamate hydrochloride (577 mg, 1.93 mmol) and DIPEA (1.15 mL, 6.60 mmol) in NMP (11 mL) was heated at 135 °C (microwave) for 60 min. The cooled mixture was diluted with EtOAc (250 mL), washed with H₂O (100 mL), brine (100 mL), dried over MgSO₄, filtered and evaporated to dryness. The residue was purified by SiO₂ chromatography (EtOAc in DCM, 0 to 50% gradient) and afforded the title compound (747 mg, 1.19 mmol, 54%) as a yellow foam.

[301] (1S,3R)-N-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-yl)-3-methylcyclohexane-1,3-diamine



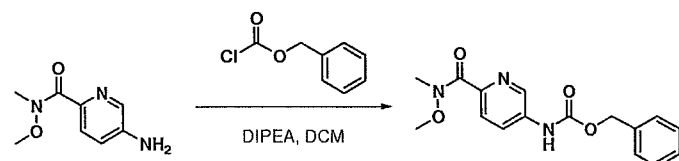
[302] A cooled (-78°C) solution of (1S,3R)-benzyl-3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)-1-methylcyclohexylcarbamate (747 mg, 1.19 mmol) in DCM (39 mL) was treated with a 1M solution of BBr_3 in DCM (2.83 mL, 2.83 mmol) and was slowly warmed up to rt. MeOH (10 mL) was added to the mixture and the resulting solution was stirred 1h at rt. The resulting mixture was evaporated to dryness. The residue was purified by reverse phase chromatography (C_{18} , $\text{H}_2\text{O}/\text{ACN} + 0.1\% \text{HCO}_2\text{H}$, 0 to 60% gradient) and afforded the title compound (485 mg, 0.978 mmol, 83%) as a yellow solid.

[303] 5-Amino-N-methoxy-N-methylpicolinamide



[304] *N,O*-dimethylhydroxylamine hydrochloride (520 mg, 5.33 mmol), 5-aminopyridine-2-carboxylic acid (491 mg, 3.55 mmol), HBTU (2.02 g, 5.33 mmol) and diisopropylethylamine (2.48 mL, 14.2 mmol) were stirred in a mixture of DCM/DMF (5/1, 23.7 mL) at room temperature overnight. The reaction mixture was poured into a saturated solution of NaHCO_3 (50 mL) and the product extracted 4 times with 2-methyltetrahydrofuran (50 mL). Organics were combined, washed with water, brine, dried over MgSO_4 , filtered and concentrated under reduced pressure to afford the title compound as an orange foamy solid (643 mg, 3.55 mmol, 100%).

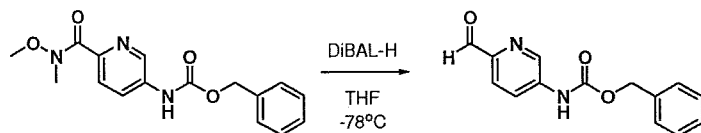
[305] Benzyl 6-(methoxy(methyl)carbamoyl)pyridin-3-ylcarbamate



[306] Diisopropylethylamine (1.9 mL, 10.7 mmol) was added to a stirring solution of 5-amino-*N*-methoxy-*N*-methylpicolinamide (643 mg, 3.55 mmol) in DCM (24 mL) and cooled to 0°C . Benzylchloroformate (0.76 mL, 5.3 mmol) was then added to the solution and the reaction mixture stirred from 0°C to room temperature overnight. Aqueous sodium bicarbonate (100 mL) was added and the phases were separated. The aqueous phase was extracted twice with

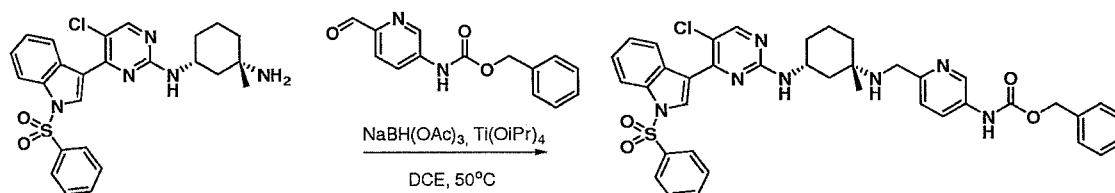
dichloromethane (50 mL). Organics were combined, washed with brine, dried over MgSO_4 , filtered and concentrated to afford the title compound as a yellow oil (391 mg, 1.24 mmol, 35%).

[307] **Benzyl 6-formylpyridin-3-ylcarbamate**



[308] Diisobutylaluminum hydride 1M in DCM (1.90 mL, 1.90 mmol) was added dropwise to a stirring solution of benzyl 6-(methoxy(methyl)carbamoyl)pyridin-3-ylcarbamate (391 mg, 1.24 mmol) in tetrahydrofuran (5 mL) at -78°C . The resulting solution was allowed to stir at this temperature for 1h30min. The solution was then quenched at -78°C with 1M HCl (10 mL) and temperature was slowly raised to 0°C . A saturated aqueous solution of NaHCO_3 (50 mL) was added to the reaction mixture and the solution was extracted 3 times with EtOAc (50 mL). The combined organic layers were dried over MgSO_4 , filtered and evaporated to dryness. The residue was purified by SiO_2 chromatography (EtOAc in hexanes, 0 to 100% gradient) and afforded the title compound as a white solid (69 mg, 0.27 mmol, 22%).

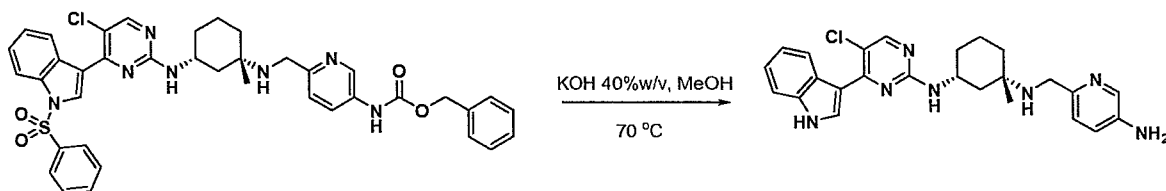
[309] **Benzyl 6-(((1S,3R)-3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)-1-methylcyclohexylamino)methyl)pyridin-3-ylcarbamate**



[310] To a DCE (3.7 mL) solution of (1S,3R)-N-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-yl)-3-methylcyclohexane-1,3-diamine (55 mg, 0.11 mmol) was added benzyl 6-formylpyridin-3-ylcarbamate (31 mg, 0.12 mmol) and titanium isopropoxide (98 μL , 0.33 mmol). The reaction mixture was stirred at room temperature overnight. $\text{NaBH}(\text{OAc})_3$ (71 mg, 0.33 mmol) was then added in one portion and the resulting mixture was stirred at room temperature for 5h. Titanium isopropoxide (49 μL , 0.17 mmol) and $\text{NaBH}(\text{OAc})_3$ (36 mg, 0.17 mmol) were added and the reaction was heated to 50°C overnight. A saturated solution of NaHCO_3 (50 mL) was added and the mixture was stirred for 15 minutes and was then filtrated over Celite and washed with EtOAc (100 mL). The phases were separated and the aqueous phase extracted 2 more times with EtOAc (100 mL). The organic layers were combined, dried over

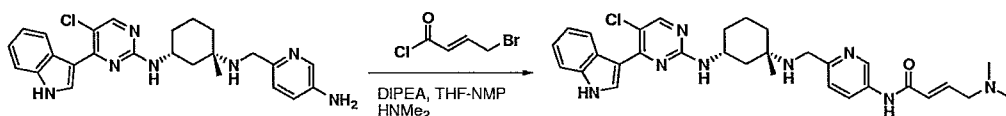
MgSO₄, filtered and evaporated to dryness affording the title compound as a pale yellow solid (82 mg, 0.11 mmol, 100%). Product was used crude for next step.

[311] (1S,3R)-N¹-((5-Aminopyridin-2-yl)methyl)-N³-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl)-1-methylcyclohexane-1,3-diamine



[312] Benzyl 6-(((1S,3R)-3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)-1-methylcyclohexylamino) methyl)pyridin-3-ylcarbamate (82 mg, 0.11 mmol) was dissolved in methanol (2.2 mL) and KOH 40% w/v (0.23 mL, 1.7 mmol) was added. The reaction mixture was stirred at 70 °C for 3 days. The reaction mixture was then diluted with water (50 mL) and extracted 3 times with EtOAc (50 mL) and 2-methyltetrahydrofuran (50 mL). The organic layers were combined, washed with brine (50 mL), dried over MgSO₄, filtered and evaporated to dryness. The residue was purified by SiO₂ chromatography (MeOH in DCM, 0 to 10% gradient) and afforded the title compound as a pale yellow solid (46 mg, 0.099 mmol, 89% over 2 steps).

[313] (E)-N-(6-(((1S,3R)-3-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)-1-methylcyclohexylamino)methyl)pyridin-3-yl)-4-(dimethylamino)but-2-enamide (Compound 294)

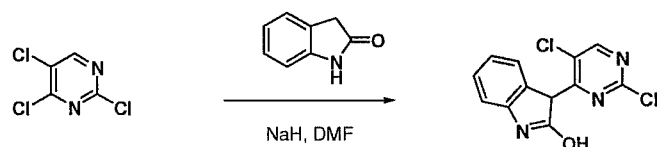


[314] A cooled (-78°C) solution of 5((1S,3R)-N¹-((5-aminopyridin-2-yl)methyl)-N³-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl)-1-methylcyclohexane-1,3-diamine (30 mg, 0.065 mmol), and DIPEA (34 µL, 0.195 mmol) in THF/NMP (1.0 mL/0.3 mL) was treated with a 54.2 mg/mL solution of (E)-4-bromobut-2-enoyl chloride in DCM (220 µL, 0.065 mmol). The resulting mixture was stirred 4h at -78°C before addition of a 2M solution of dimethylamine in THF (97 µL, 0.195 mmol). The resulting mixture was warmed up to -20 °C for 2h and then evaporated to dryness. The residue was purified by reverse phase chromatography (C₁₈, H₂O/ACN +0.1% HCO₂H, 5 to 70% gradient) and afforded the title compound (5.7 mg, 0.0099 mmol, 15%) as a white solid after lyophilization.

[315] LCMS: Calculated: 573.13, Found ($M+H^+$): 573.34. ^1H NMR (500 MHz, DMSO) δ 11.84 (s, 1H), 10.25 (s, 1H), 8.74 (s, 1H), 8.59 (br d, $J = 9.5$ Hz, 1H), 8.50 – 8.41 (m, 1H), 8.28 – 8.16 (m, 2H), 8.03 (dd, $J = 8.8, 2.3$ Hz, 1H), 7.54 – 7.46 (m, 1H), 7.44 (d, $J = 8.3$ Hz, 1H), 7.36 – 7.27 (m, 1H), 7.20 (dd, $J = 13.3, 7.0$ Hz, 1H), 7.16 – 7.04 (m, 1H), 6.76 (dt, $J = 15.5, 5.9$ Hz, 1H), 6.27 (dt, $J = 15.3, 1.6$ Hz, 1H), 4.22 – 4.07 (m, 1H), 3.88 (s, 2H), 3.06 (dd, $J = 5.8, 1.4$ Hz, 2H), 2.18 (s, 6H), 2.01 – 1.85 (m, 2H), 1.77 – 1.68 (m, 1H), 1.64 – 1.42 (m, 4H), 1.37 – 1.28 (m, 1H), 1.26 (br s, 3H).

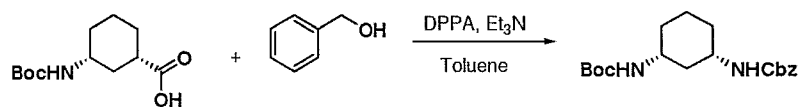
[316] **Example 19. Synthesis of N-((1S,3R)-3-(5-chloro-4-(2-oxoindolin-3-yl)pyrimidin-2-ylamino)cyclohexyl)-5-((E)-4-(dimethylamino)but-2-enamido)picolinamide (Compound 282).**

[317] **3-(2,5-Dichloropyrimidin-4-yl)-3H-indol-2-ol**



[318] 2-Oxindole (239 mg, 1.79 mmol) was dissolved in DMF (15 mL) at room temperature and sodium hydride (144 mg, 3.60 mmol) was added. The reaction mixture stirred at room temperature for 15 minutes. 2,4,5-Trichloropyrimidine (300 mg, 1.63 mmol) was then added dropwise and the resulting solution was stirred at room temperature for 30 minutes. The solution was then quenched with a saturated aqueous solution of NH_4Cl (100 mL) and extracted 3 times with DCM (100 mL). The organic layers were combined, washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and evaporated to dryness. The crude residue was stirred in EtOH (20 mL), filtered, washed with EtOH (5 mL) and hexanes (5 mL) to yield the title compound (379 mg, 1.35 mmol, 83%) as an orange solid.

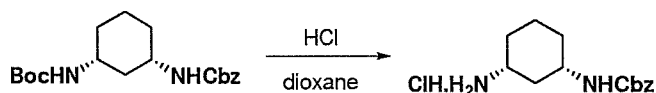
[319] **(1S,3R)-3-(Benzyloxycarbonylamino)cyclohexylamino-2,2-dimethylpropionate**



[320] To a solution of (1S,3R)-3-(tert-butoxycarbonylamino)cyclohexanecarboxylic acid (8.77 g, 36.1 mmol) (prepared following Tetrahedron: *Asymmetry* 2010 (21), 864-866) in toluene (145 mL) was added Et_3N (5.53 mL, 39.7 mmol) and DPPA (7.7 mL, 36.1 mmol). The resulting solution was stirred for 2 h at 110 °C and cooled down to 80 °C. Benzyl alcohol (4.66 mL, 45.1 mmol) and triethylamine (5.53 mL, 39.7 mmol) were added, and the mixture was

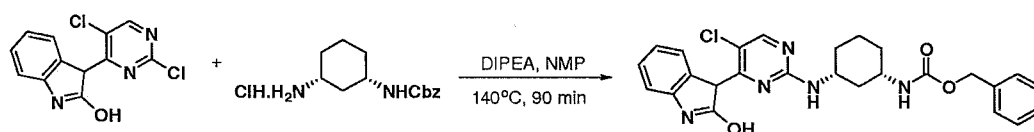
stirred for 20 h at 80 °C. The cooled solution was diluted with EtOAc (100 mL) and water (50 mL). The layers were separated, and the aqueous layer was extracted twice with EtOAc (50 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by SiO₂ chromatography (EtOAc in hexanes, 1 to 100% gradient) to afford the title compound (9.89 g, 28.4 mmol, 79%) as a white solid.

[321] Benzyl (1S,3R)-3-aminocyclohexylcarbamate hydrochloride



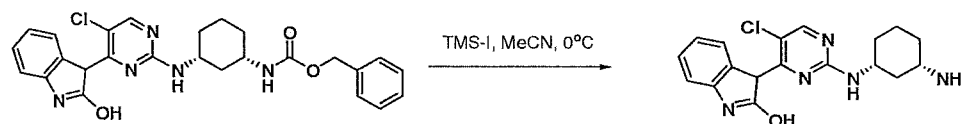
[322] A solution of (1S,3R)-3-(benzyloxycarbonylamino)cyclohexylamino-2,2-dimethylpropionate (1.50 g, 4.31 mmol) in DCM (43 mL) was treated with a 4M solution of HCl in dioxane (16.0 mL, 64.6 mmol) and stirred for 2h at rt. The resulting solution was evaporated to dryness and afforded the title compound (1.23 g, 4.31 mmol, 100%) as a white solid which was used in the next step without further purification.

[323] Benzyl (1S,3R)-3-(5-chloro-4-(2-hydroxy-3H-indol-3-yl)pyrimidin-2-ylamino)cyclohexylcarbamate



[324] 3-(2,5-Dichloropyrimidin-4-yl)-3H-indol-2-ol (79 mg, 0.28 mmol), benzyl (1S,3R)-3-aminocyclohexylcarbamate hydrochloride (88 mg, 0.31 mmol) and diisopropylethylamine (246 μL, 1.41 mmol) were dissolved in NMP (1.9 mL) in a microwave vial. The vial was heated to 140 °C under microwave irradiation and stirred for 90 min. The reaction mixture was poured into water (30 mL) and extracted with dichloromethane (50 mL). The organics were combined, washed with water (50 mL), brine (50 mL), dried with MgSO₄ filtered and concentrated. The residue was purified by SiO₂ chromatography (EtOAc in hexanes:DCM (9:1), 40 to 100% gradient) to afford the title compound (61.3 mg, 0.125 mmol, 48% yield) as a yellow solid.

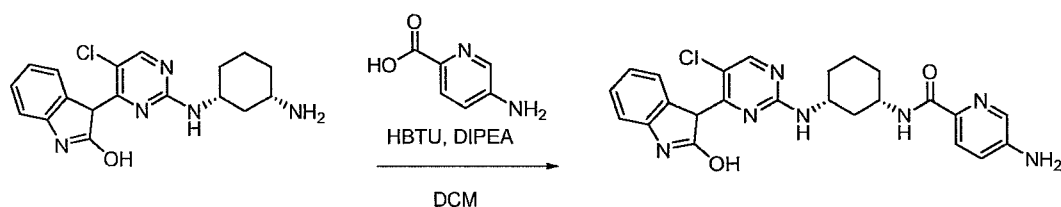
[325] 3-(2-((1R,3S)-3-Aminocyclohexylamino)-5-chloropyrimidin-4-yl)-3H-indol-2-ol



[326] Benzyl (1S,3R)-3-(5-chloro-4-(2-hydroxy-3H-indol-3-yl)pyrimidin-2-ylamino)cyclohexylcarbamate (60.0 mg, 0.122 mmol) was dissolved in acetonitrile (2.4 mL) and

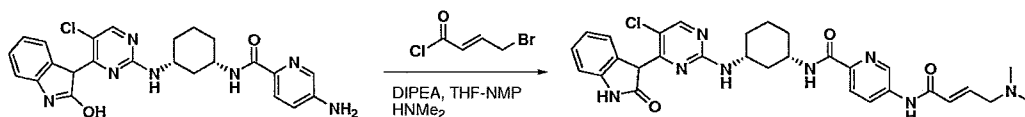
the solution was cooled to 0 °C. Iodotrimethylsilane (174 μ L, 1.22 mmol) was added dropwise at 0 °C, and the mixture was then stirred for 3h. MeOH (3 mL) was added dropwise at 0 °C, the solution was then slowed to warm to room temperature and was concentrated to dryness. The crude residue was purified by reverse phase flash chromatography (from 5 to 70% MeCN-H₂O-0.1% HCOOH buffer). Fractions containing product were concentrated to dryness and the residue was dissolved with 2-methyltetrahydrofuran (20 mL) and stirred for 10 minutes with excess powdered potassium carbonate. The mixture was filtered, washed with 2-methyltetrahydrofuran (30 mL) and evaporated to dryness affording the title compound (22 mg, 0.061 mmol, 50%) as a yellow solid.

[327] 5-Amino-N-((1S,3R)-3-(5-chloro-4-(2-hydroxy-3H-indol-3-yl)pyrimidin-2-ylamino)cyclohexyl)picolinamide (Compound 1065)



[328] 3-(2-((1R,3S)-3-Aminocyclohexylamino)-5-chloropyrimidin-4-yl)-3H-indol-2-ol (22 mg, 0.061 mmol), the 5-amino-2-pyridinecarboxylic acid (8.3 mg, 0.060 mmol), the coupling agent HBTU (34 mg, 0.090 mmol), diisopropylethylamine (42 μ L, 0.24 mmol) were mixed in DCM (0.40 mL) and stirred at room temperature overnight. The reaction mixture was poured into a saturated aqueous solution of NaHCO₃ (30 mL) and the product extracted 4 times with 2-methyltetrahydrofuran (30 mL). The organics were combined, washed with water (30 mL), brine (30 mL), dried over MgSO₄, filtered and evaporated to dryness. The residue was purified by SiO₂ chromatography (MeOH in DCM, 0 to 10% gradient) to afford the title compound (15.5 mg, 0.032 mmol, 54%) as a yellow solid.

[329] N-((1S,3R)-3-(5-Chloro-4-(2-oxoindolin-3-yl)pyrimidin-2-ylamino)cyclohexyl)-5-((E)-4-(dimethylamino)but-2-enamido)picolinamide (Compound 282)



[330] A cooled (-78°C) solution of 5-Amino-N-((1S,3R)-3-(5-chloro-4-(2-hydroxy-3H-indol-3-yl)pyrimidin-2-ylamino)cyclohexyl)picolinamide (15.5 mg, 0.032 mmol), and DIPEA (17.0 μ L,

0.097 mmol) in THF/NMP (0.5 mL/0.2 mL) was treated with a 54.2 mg/mL solution of (E)-4-bromobut-2-enoyl chloride in DCM (115 μ L, 0.034 mmol). The resulting mixture was stirred 8h at -78°C before addition of a 2M solution of dimethylamine in THF (49 μ L, 0.097 mmol). The resulting mixture was warmed up to -20 °C, stirred overnight and then evaporated to dryness. The residue was purified by reverse phase chromatography (C₁₈, H₂O/ACN +0.1% HCO₂H, 5 to 70% gradient) and afforded the title compound (4.3 mg, 0.007 mmol, 23%) as a light yellow solid after lyophilization.

[331] LCMS: Calculated = 589.09; Found [M+H⁺] = 589.30. ¹H NMR (500 MHz, DMSO) Mixture of 2 diastereoisomers δ 10.62 (s, 1H), 10.53 (s, 1H), 8.87 (d, *J* = 2.9 Hz, 1H), 8.40 (d, *J* = 7.9 Hz, 1H), 8.24 – 8.19 (m, 1H), 8.02 – 7.94 (m, 1H), 7.48 (d, *J* = 7.3 Hz, 1H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.02 (d, *J* = 7.0 Hz, 1H), 6.91 (td, *J* = 7.7, 1.0 Hz, 1H), 6.89 – 6.84 (m, 1H), 6.81 (dtd, *J* = 15.3, 5.7, 1.1 Hz, 1H), 6.54 (br s, 1H), 6.29 (dd, *J* = 15.4, 1.6 Hz, 1H), 5.07 – 4.96 (m, 1H), 3.86 – 3.77 (m, 1H), 3.75 – 3.64 (m, 1H), 3.17 (d, *J* = 5.0 Hz, 1H), 3.08 (d, *J* = 5.7 Hz, 2H), 2.18 (s, 6H), 2.08 (d, *J* = 6.3 Hz, 1H), 1.84 – 1.69 (m, 2H), 1.45 – 1.26 (m, 3H), 1.19 – 1.09 (m, 1H).

[332] **Example 20. CDK7 Kinase Activity.** Compounds of the invention were assayed for CDK7 activity at Life TechnologiesTM (Grand Island, New York) using their commercially available Adapta® kinase assay services. Compounds were tested at concentrations ranging from 10 μ M down to 0.514 nM in a series of 3-fold serial dilutions. Details of these assays, including substrates used, are available on the Life Technologies web site (<http://www.lifetechnologies.com/us/en/home/life-science/drug-discovery/target-and-lead-identification-and-validation/kinasebiology/kinase-activity-assays.html>). The results of the assay are shown below in Table 3 where “A” represents a calculated IC₅₀ of less than 100 nM; “B” represents a calculated IC₅₀ of between 100 nM and 1 μ M; and “C” represents a calculated IC₅₀ of greater than 1 μ M.

[333] Table 3. CDK7 Inhibitory Activity of Selected Compounds of the Invention.

Compound No.	CDK7 Inhibition (IC ₅₀)
106	A
110	A
248	A

[334] Compounds of the invention were further assayed for CDK7 activity at Biortus Biosciences (Jiangyin, Jiangsu Province, P.R. of China) using a CDK7 kinase assay developed with a Caliper/LabChip EZ Reader (Perkin Elmer, Waltham, MA). This assay measures the amount of phosphorylated peptide substrate produced as a fraction of the total peptide following an incubation period (30 min.) with the following components: test compounds (variable concentrations from 10 μ M down to 0.514 nM in a series of 3-fold serial dilutions), CDK7/Cyclin H/MAT1 trimeric complex (10 nM), ATP (2 mM), and “FAM-CDK7tide” peptide substrate (2 μ M, synthesized fluorophore-labeled peptide with the following sequence: 5-FAM-YSPTSPSYPTSPSYPTSPSKKKK) in the following buffer: 20 mM MES, pH 6.75, 6 mM MgCl₂, 0.01% Tween 20, 0.05 mg/mL BSA. The incubation period was chosen such that the total fraction of phosphorylated peptide product produced was $\leq$ 20% for the uninhibited kinase. CDK7 kinase inhibition IC₅₀ values were recorded for selected test compounds reported in Table 4, where “A” represents a calculated IC₅₀ of less than 100 nM; “B” represents a calculated IC₅₀ of between 100 nM and 1 μ M; and “C” represents a calculated IC₅₀ of greater than 1 μ M.

[335] Table 4. CDK7 Inhibitory Activity of Selected Compounds of the Invention.

Compound No.	CDK7 Inhibition (IC ₅₀)	Compound No.	CDK7 Inhibition (IC ₅₀)	Compound No.	CDK7 Inhibition (IC ₅₀)
106	A	267	A	399	A
110	A	269	A	403	A
248	A	270	A	407	A
261	A	282	B	411	A
262	A	294	A	412	B
264	A	377	A	413	A
265	A	390	A		

Example 21. Inhibition of Cell Proliferation.

Jurkat Cells. Jurkat cells are a cell line established from a human T cell leukemia.

Representative compounds of the invention were tested at different concentrations (from 10 μ M to 316 pM; 0.5 log serial dilutions) for their ability to inhibit the proliferation of Jurkat cells. Known CDK inhibitors flavopiridol and triptolide were used as positive controls. Cells were grown in RPMI 1640 + 10% FBS + 1% Glutamax. The cells were supplemented with FBS (Life Technologies) and 100 U·mL⁻¹ penicillin, 100 μ g·mL⁻¹ streptomycin (Invitrogen) and cultured at 37 °C in a humidified chamber in the presence of 5% CO₂. Proliferation assays were conducted

over a 72 hour time period. CellTiter-Glo® (Promega Corporation, Madison, WI USA) was used to assess the anti-proliferative effects of the compounds following manufacturer's directions and utilizing the reagents supplied with the CellTiter-Glo® kit. In this table, "A" represents an IC₅₀ of less than 500 nM; "B" an IC₅₀ of between 500 nM and 5 µM; and "C" an IC₅₀ of greater than 5 µM.

[336] Table 5. Inhibition of Proliferation of Jurkat Cells by Compounds of the Invention.

Compound No.	Jurkat IC ₅₀
110	A

[337] **A673 Cells.** A673 cells are a cell line derived from human muscle Ewing's sarcoma. Representative compounds of the invention were tested at different concentrations (from 4 µM to 126.4 pM; 0.5 log serial dilutions) for their ability to inhibit the proliferation of A673 cells. Known CDK inhibitors flavopiridol and triptolide were used as positive controls. Cells were grown in Dulbecco's Modified Eagle's Medium, + 10% FBS + 1mM Sodium Pyruvate. The cells were cultured at 37 °C in a humidified chamber in the presence of 5% CO₂. Proliferation assays were conducted over a 72 hour time period. CyQUANT® (Life Technologies, Chicago, IL USA) was used to assess the anti-proliferative effects of the compounds following manufacturer's directions and utilizing the reagents supplied with the CyQUANT® kit. In this table, "A" represents an IC₅₀ of less than 500 nM; "B" an IC₅₀ of between 500 nM and 5 µM; and "C" an IC₅₀ of greater than 5 µM

[338] Table 6. Inhibition of Proliferation of A673 Cells by Compounds of the Invention.

Compound No.	A673 IC ₅₀ (nM)
106	A
110	A
248	A
261	A
262	A
264	A
265	A

Compound No.	A673 IC ₅₀ (nM)
267	A
269	A
282	A
294	A
377	A
390	A
399	A

Compound No.	A673 IC ₅₀ (nM)
403	A
407	A
411	A
412	A
413	A

Equivalents and Scope

[339] In the claims articles such as "a," "an," and "the" may mean one or more than one unless

indicated to the contrary or otherwise evident from the context. Claims or descriptions that include “or” between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

[340] Furthermore, the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims are introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists, *e.g.*, in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements and/or features, certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth *in haec verba* herein. It is also noted that the terms “comprising” and “containing” are intended to be open and permits the inclusion of additional elements or steps. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub-range within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[341] This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be

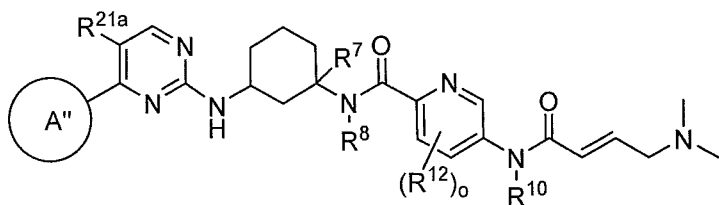
excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the invention can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

[342] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

CLAIMS

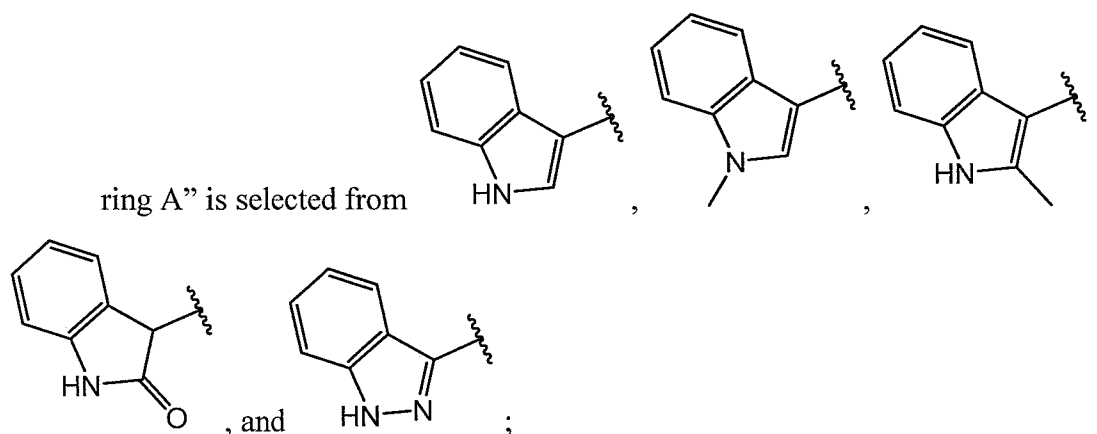
What is claimed is:

1. A compound having structural Formula (Ic):



(Ic); or a pharmaceutically

acceptable salt thereof, solvate, hydrate, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein:



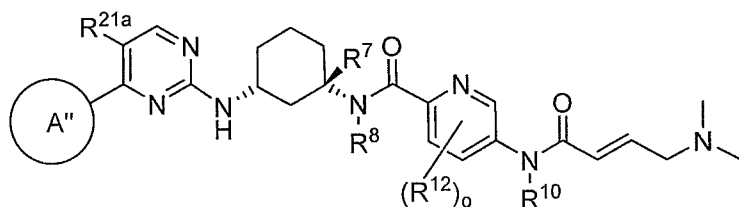
each of R^7 , R^8 and R^{10} is independently selected from hydrogen and methyl;

R^{21a} is selected from -Cl, -CN, -CF₃, -CH₃, and -CH₂CH₃; and

each R^{12} if present is halo; and

o is 0, 1, 2, or 3.

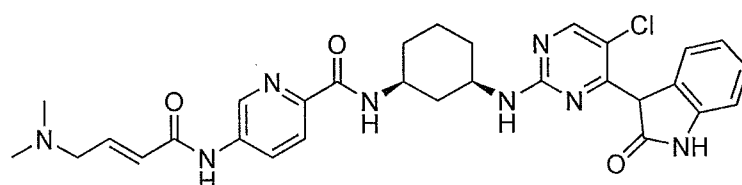
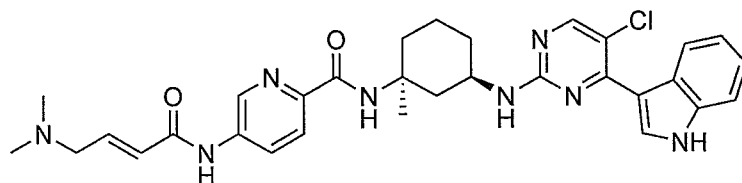
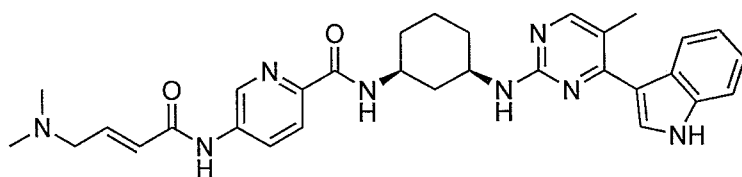
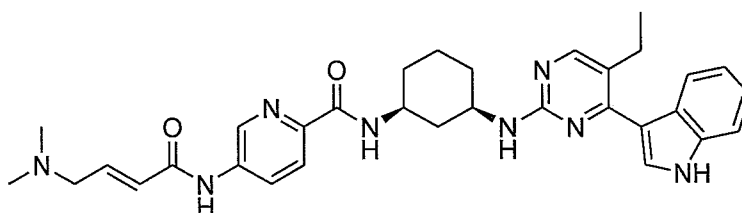
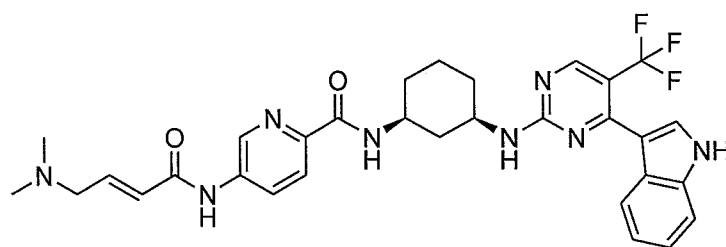
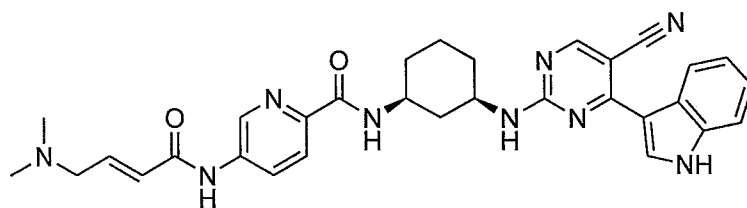
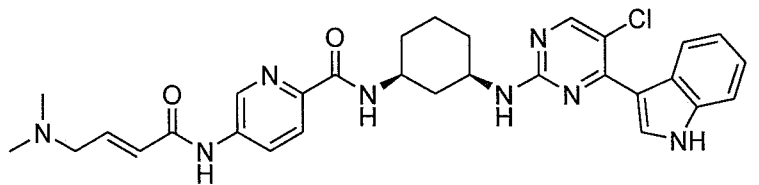
2. The compound of claim 1, having structural Formula (Ic'):

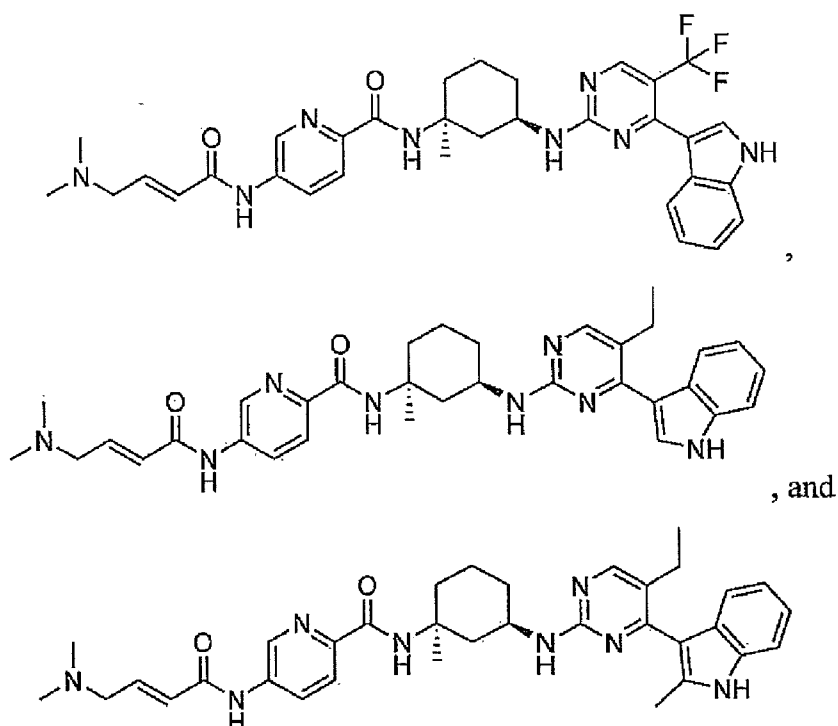


(Ic'), wherein ring A'', R^7 , R^8 ,

R^{10} , R^{21a} , R^{12} and o are as defined in claim 1.

3. The compound of claim 1 or 2, wherein each R¹², if present, is fluoro.
4. The compound of any one of claims 1-3, wherein o is 0.
5. The compound of claim 1, selected from any one of the compounds set forth below:





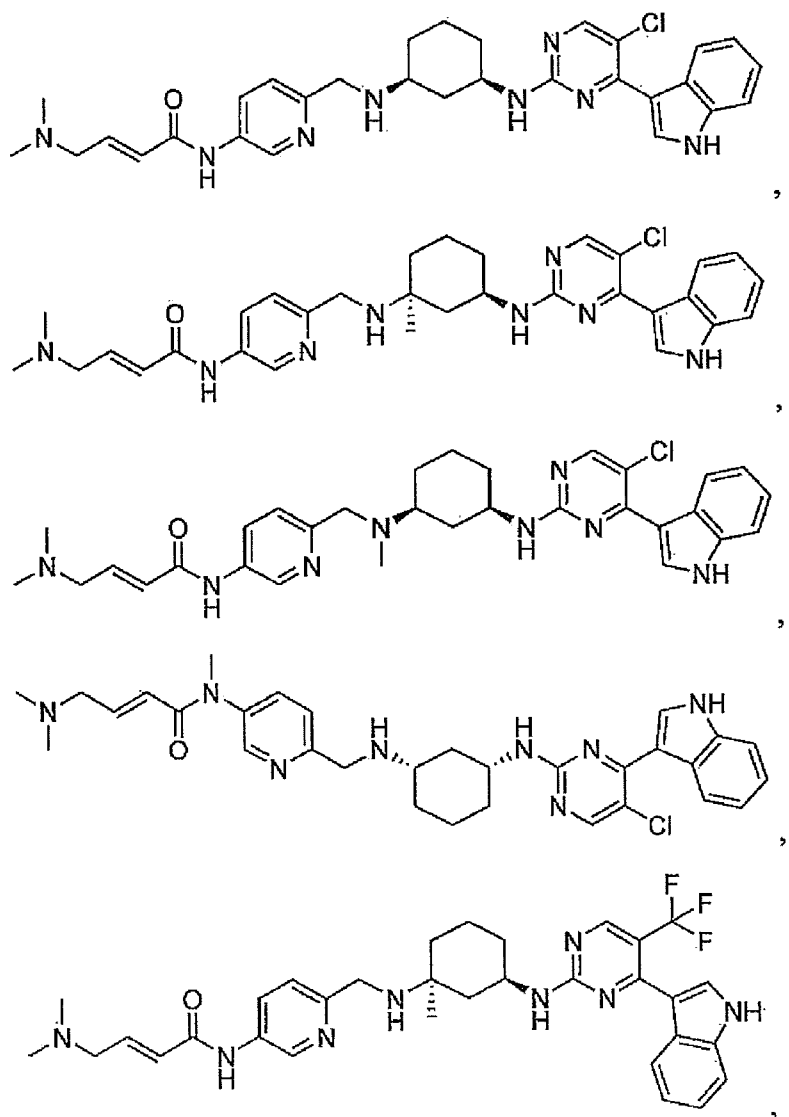
6. A pharmaceutical composition comprising a compound of any one of claims 1-5 and a pharmaceutically acceptable excipient.
7. Use of the composition of claim 6 in the manufacture of a medicament, for treating a subject suffering from a disease or condition associated with aberrant activity of a CDK, wherein the disease or condition is selected from the group consisting of cancer, benign neoplasm, angiogenesis, inflammatory disease, autoinflammatory disease, autoimmune disease, and an infectious disease.
8. The use of claim 7, wherein the disease or condition is suffered by a human subject.
9. The use of any one of claims 7-8, wherein the disease is cancer.
10. The use of claim 9, wherein the cancer is selected from the group consisting of a blood cancer, melanoma, a bone cancer, a breast cancer, a brain cancer, and a lung cancer.
11. The use of claim 10, wherein the cancer is a blood cancer selected from chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), T-cell acute lymphoblastic leukemia (T-ALL), chronic myelogenous leukemia (CML), acute

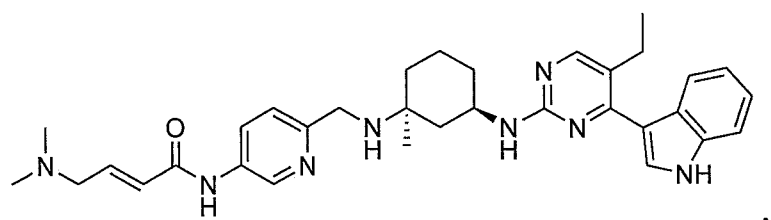
myelogenous leukemia (AML), lymphoma, and multiple myeloma.

12. The use of claim 10, wherein the cancer is selected from osteosarcoma, Ewing's sarcoma, triple-negative breast cancer (TNBC), neuroblastoma, and small cell lung cancer (SCLC).

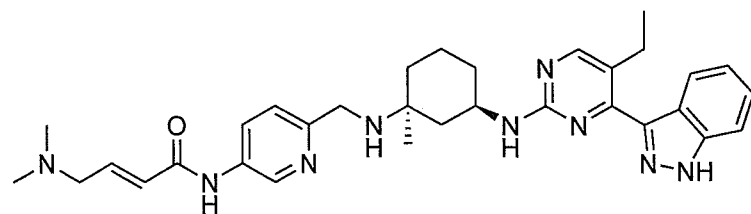
13. The use of any one of claims 7-12, wherein the composition is to be used in conjunction with one or more additional agents independently selected from anti-proliferative agents, anti-cancer agents, immunosuppressant agents, and pain-relieving agents.

14. A compound selected from any one of the compounds set forth below:

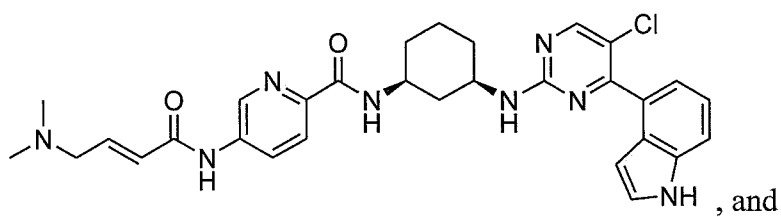




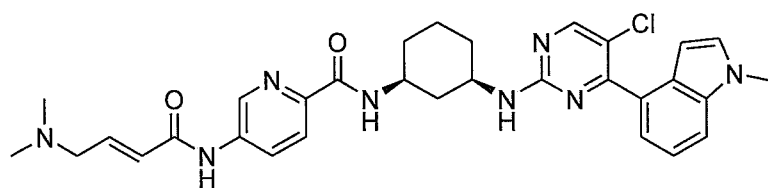
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