NEK7 INHIBITORS

BACKGROUND

Technical Field

Embodiments of the present disclosure are generally directed to compounds and methods for their preparation and use as therapeutic or prophylactic agents, for example for treatment of inflammation.

Description of the Related Art

Inflammasomes are multi-protein complexes whose activation plays a central role in innate immunity and inflammation. To date, four inflammasomes have been described: NLRP1, NLRC4, NLRP3, and AIM2. The NLRP3 inflammasome is composed of NLRP3, ASC, and caspase-1. Its activation results in the activation of caspase-1 which promotes the secretion of IL-1β and IL-18, cytokines that mediate inflammation in animal disease models of several autoimmune diseases, myocardial infarction, metabolic syndromes, inflammatory bowel disease, and macrophage activation syndrome.

NEK7 is a member of the family of NIMA-related kinases (NEKs) that act as NLRP3-binding proteins to regulate its oligomerization and activation. NEK7 is a serine/threonine kinase essential for mitotic entry, cell cycle progression, cell division, and mitotic progression. It is expressed in a variety of tissues such as the brain, heart, lung, liver, and spleen. Overexpression of NEK7 induces the production of abnormal cells, which has an intimate connection to tumors, such as retinoblastoma, gallbladder cancer and carcinoma of the head and neck.

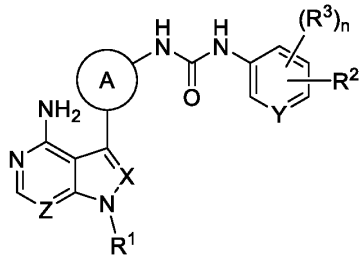
A great number of inhibitors have been widely used to disturb effector signaling pathways, involving IL-1β or IL-18 without abolishing the inflammation response. Inhibitors of NLRP3 inflammasome activation that block the NLRP3-NEK7 interaction can have therapeutic or prophylactic activity in several human diseases, such as type 2 diabetes (T2D), atherosclerosis, gout, and neurodegenerative diseases. However, the exact mechanism of the NLRP-3-NEK7 interaction is not well understood.

Accordingly, there is a need to develop inhibitors that will directly target NEK7 to affect the inflammatory response modulated by the NLRP3 inflammasome in several pathological diseases, such as gout, atherosclerosis, Type 2 diabetes, metabolic syndrome, macular degeneration, Alzheimer's disease, multiple sclerosis, and inflammatory bowel disease. Embodiments of the present disclosure fulfill this need and provide further related advantages.

BRIEF SUMMARY

In brief, embodiments of the present disclosure provide compounds, including pharmaceutically acceptable salts, stereoisomers, and prodrugs thereof, which are capable of modulating the activity the NLRP3 inflammasome.

One embodiment provides compounds of Structure (I):



(I)

or pharmaceutically acceptable salts, stereoisomers or prodrug thereof, wherein each of A, X, Y, Z, R^1, R^2, R^3, and n are as defined herein.

In another embodiment, pharmaceutical compositions comprising the disclosed compounds, and methods of use of the same for treatment of inflammation are also provided.

DETAILED DESCRIPTION

In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments of the disclosure. However, one skilled in the art will understand that the disclosure may be practiced without these details.

Unless the context requires otherwise, throughout the present specification and claims, the word "comprise" and variations thereof, such as, "comprises" and

"comprising" are to be construed in an open, inclusive sense, that is, as "including, but not limited to".

In the present description, any concentration range, percentage range, ratio range, or integer range is to be understood to include the value of any integer within the recited range and, when appropriate, fractions thereof (such as one tenth and one hundredth of an integer), unless otherwise indicated. As used herein, the terms "about" and "approximately" mean ± 20%, ± 10%, ± 5%, or ± 1% of the indicated range, value, or structure, unless otherwise indicated. It should be understood that the terms "a" and "an" as used herein refer to "one or more" of the enumerated components. The use of the alternative (*e.g.*, "or") should be understood to mean either one, both, or any combination thereof of the alternatives.

Reference throughout this specification to "one embodiment" or "an embodiment" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment of the present disclosure. Thus, the appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this disclosure belongs. As used in the specification and claims, the singular form "a", "an" and "the" include plural references unless the context clearly dictates otherwise.

"Amino" refers to the $-NH_2$ radical.

"Carboxy" or "carboxyl" refers to the $-CO_2H$ radical.

"Cyano" refers to the −CN radical.

"Hydroxy" or "hydroxyl" refers to the −OH radical.

"Nitro" refers to the $-NO_2$ radical.

"Oxo" refers to the =O substituent.

"Thiol" refers to the −SH substituent.

"Thioxo" refers to the =S substituent.

"Alkyl" refers to a saturated, straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, having, for example, from one to twelve carbon atoms (C_1-C_{12} alkyl), one to eight carbon atoms (C_1-C_8 alkyl) or one to six carbon atoms (C_1-C_6 alkyl), or any value within these ranges, such as C_4-C_6 alkyl and the like, and which is attached to the rest of the molecule by a single bond, *e.g.*, methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), 3-methylhexyl, 2-methylhexyl and the like. The number of carbons referred to relates to the carbon backbone and carbon branching, but does not include carbon atoms belonging to any substituents. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted.

"Alkenyl" refers to an unsaturated, straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, which contains one or more carbon-carbon double bonds, having from two to twelve carbon atoms (C_2-C_{12} alkenyl), two to eight carbon atoms (C_2-C_8 alkenyl) or two to six carbon atoms (C_2-C_6 alkenyl), or any value within these ranges, and which is attached to the rest of the molecule by a single bond, *e.g.*, ethenyl, prop-1-enyl, but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. The number of carbons referred to relates to the carbon backbone and carbon branching, but does not include carbon atoms belonging to any substituents. Unless stated otherwise specifically in the specification, an alkenyl group is optionally substituted.

The term "alkynyl" refers to unsaturated straight or branched hydrocarbon radical, having 2 to 12 carbon atoms (C_2-C_{12} alkynyl), two to nine carbon atoms (C_2-C_9 alkynyl), or two to six carbon atoms (C_2-C_6 alkynyl), or any value within these ranges, and having at least one carbon- carbon triple bond. Examples of alkynyl groups may be selected from the group consisting of ethynyl, propargyl, but-1 -ynyl, but-2-ynyl and the like. The number of carbons referred to relates to the carbon backbone and carbon branching, but does not include carbon atoms belonging to any substituents. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted.

"Alkoxy" refers to a radical of the formula $-OR_a$ where R_a is an alkyl radical as defined above containing one to twelve carbon atoms (C_1-C_{12} alkoxy), one to eight

carbon atoms (C_1-C_8 alkoxy) or one to six carbon atoms (C_1-C_6 alkoxy), or any value within these ranges. Unless stated otherwise specifically in the specification, an alkoxy group is optionally substituted.

"Aminyl" refers to a radical of the formula $-NR_aR_b$, where R_a and Rb are each independently H or C_1-C_6 alkyl as defined above. When both of R_a and R_b are H, an "aminyl" group is the same as an "amino" group as defined above. The C_1-C_6 alkyl portion of an aminyl group is optionally substituted unless stated otherwise.

"Aromatic ring" refers to a cyclic planar molecule or portion of a molecule (*i.e.*, a radical) with a ring of resonance bonds that exhibits increased stability relative to other connective arrangements with the same sets of atoms. Generally, aromatic rings contain a set of covalently bound co-planar atoms and comprises a number of π-electrons (for example, alternating double and single bonds) that is even but not a multiple of 4 (*i.e.*, 4n + 2 π-electrons, where n = 0, 1, 2, 3, etc.). Aromatic rings include, but are not limited to, phenyl, naphthenyl, imidazolyl, pyrrolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridonyl, pyridazinyl, pyrimidonyl. Unless stated otherwise specifically in the specification, an "aromatic ring" includes all radicals that are optionally substituted.

"Aryl" refers to a carbocyclic ring system radical comprising 6 to 18 carbon atoms, for example 6 to 10 carbon atoms (C_6-C_{10} aryl) and at least one carbocyclic aromatic ring. For purposes of embodiments of this disclosure, the aryl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems. Aryl radicals include, but are not limited to, aryl radicals derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless stated otherwise specifically in the specification, an aryl group is optionally substituted.

"Carbocyclic" or "carbocycle" refers to a ring system, wherein each of the ring atoms are carbon.

"Cycloalkyl" refers to a non-aromatic monocyclic or polycyclic carbocyclic radical consisting solely of carbon and hydrogen atoms, which may include fused or bridged ring systems, having from three to fifteen ring carbon atoms (C_3-C_{15}

cycloalkyl), from three to ten ring carbon atoms (C_3-C_{10} cycloalkyl), or from three to eight ring carbon atoms (C_3-C_8 cycloalkyl), or any value within these ranges such as three to four carbon atoms (C_3-C_4 cycloalkyl), and which is saturated or partially unsaturated and attached to the rest of the molecule by a single bond. Monocyclic radicals include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic radicals include, for example, adamantyl, norbornyl, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Unless otherwise stated specifically in the specification, a cycloalkyl group is optionally substituted.

"Fused" refers to any ring structure described herein which is fused to another ring structure.

"Halo" refers to bromo, chloro, fluoro, or iodo.

"Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like. Unless stated otherwise specifically in the specification, a haloalkyl group is optionally substituted.

"Halocycloalkyl" refers to a cycloalkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like. Unless stated otherwise specifically in the specification, a halocycloalkyl group is optionally substituted.

"Hydroxylalkyl" or "hydroxyalkyl" refers to an alkyl radical, as defined above that is substituted by one or more hydroxyl radical. The hydroxyalkyl radical is joined at the main chain through the alkyl carbon atom. Unless stated otherwise specifically in the specification, a hydroxyalkyl group is optionally substituted.

"Heterocyclyl" refers to a 3- to 18-membered, for example 3- to 10-membered or 3- to 8-membered, non-aromatic ring radical having one to ten ring carbon atoms (*e.g.*, two to ten) and from one to six ring heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. Unless stated otherwise specifically in the specification, the heterocyclyl radical is partially or fully saturated and is a monocyclic,

bicyclic, tricyclic or tetracyclic ring system, which may include fused, spirocyclic and/or bridged ring systems. Nitrogen, carbon and sulfur atoms in a heterocyclyl radical are optionally oxidized, and nitrogen atoms may be optionally quaternized. Examples of such heterocyclyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, furanonyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, hexahydro-1H-pyrrolizine, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, oxiranyl, piperidinyl, piperazinyl, 4-piperidonyl, azetidinyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. Unless stated otherwise specifically in the specification, a heterocyclyl group is optionally substituted.

"Heterocyclylalkyl" refers to a radical comprising a heterocyclyl group as defined above that is connected to the remainder of the molecule by an alkylene linker. Unless stated otherwise specifically in the specification, a heterocyclylalkyl group is optionally substituted.

"Heterocyclylcarbonyl" refers to a radical group of the formula $–C(C=O)R^a$ where R^a is a heterocyclyl group as defined above. Unless stated otherwise specifically in the specification, a heterocyclylcarbonyl group is optionally substituted.

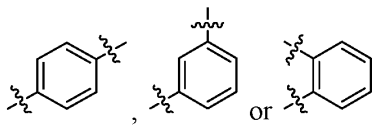
"Heterocyclyloxy" refers to a radical group of the formula $–OR^a$ where R^a is a heterocyclyl group as defined above. Unless stated otherwise specifically in the specification, a heterocyclyloxy group is optionally substituted.

"Heterocyclylalkenyl" refers to a radical group of the formula $–R^aR^b$ where R^a is alkenylene and R^b is a heterocyclyl group as defined above. Unless stated otherwise specifically in the specification, a heteroyclylalkenyl group is optionally substituted.

"Heteroaryl" refers to a 5- to 18-membered, for example 5- to 6-membered, ring system radical comprising one to thirteen ring carbon atoms, one to six ring heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and at least one aromatic ring. Heteroaryl radicals may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl radical may be optionally oxidized;

the nitrogen atom may be optionally quaternized. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (*i.e.*, thienyl). Unless stated otherwise specifically in the specification, a heteroaryl group is optionally substituted.

The suffix "-ene" refers to a particular structural feature (*e.g.*, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 3-10 membered heterocyclyl, or 5-6 membered heteroaryl) attached to the rest of the molecule through a single or double bond and attached to a radical group through a single or double bond. In other words, the suffix "-ene" refers to a linker having the structural features of the moiety to which it is attached. The points of attachment of the "-ene" group to the rest of the molecule and to the radical group can be through one atom of or any two atoms (carbon or heteroatom) within the group. For example, an unsubstituted phenylene group (*i.e.*, a representative C_6-C_{10} arylene) may have one of the following structures:



In some embodiments, the C_6-C_{10} arylene (*e.g.*, phenylene), C_3-C_{10} cycloalkylene (*e.g.*, cyclohexylene), 3-10 membered heterocyclylene (*e.g.*, piperidinylene), or 5-6 membered heteroarylene (*e.g.*, pyridinylene) are divalent.

The term "substituted" as used herein means any of the above groups (*e.g.*, alkyl, alkenyl, alkylene, alkylcarbonyl, alkoxy, alkoxyalkyl, aminylalkyl, aryl, cyanoalkyl, cycloalkyl, haloalkyl, heterocyclyl, heterocyclene, heterocyclylalkyl, heteroaryl, heteroarylalkyl and/or hydroxylalkyl) wherein at least one hydrogen atom (*e.g.*, 1, 2, 3 or all hydrogen atoms) is replaced by a bond to a non-hydrogen substituent. Examples of non-hydrogen substituents include, but are not limited to: amino, carboxyl, cyano, hydroxyl, halo, nitro, oxo, thiol, thioxo, alkyl, alkenyl, alkylcarbonyl, alkoxy, aryl, cyanoalkyl, cycloalkyl, haloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl and/or hydroxylalkyl substituents, each of which may also be optionally substituted with one or more of the above substituents.

In some specific embodiments, the optional substitutions are independently selected from the group consisting of halo, hydroxyl, cyano, aminyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, C_3-C_8 halocycloalkyl, C_6-C_{10} aryl, 5- or 6-membered heteroaryl, C_1-C_6 alkoxy and 3-8 membered heterocyclyl.

The term "effective amount" or "therapeutically effective amount" refers to that amount of a compound described herein that is sufficient to effect the intended application including but not limited to disease treatment, as defined below. The therapeutically effective amount may vary depending upon the intended treatment application (*in vivo*), or the subject and disease condition being treated, *e.g.*, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells, *e.g.*, reduction of platelet adhesion and/or cell migration. The specific dose will vary depending on the particular compounds chosen, the dosing regimen to be followed, whether it is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried.

As used herein, "treatment" or "treating" refer to an approach for obtaining beneficial or desired results with respect to a disease, disorder or medical condition including but not limited to a therapeutic effect and/or a prophylactic effect. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being

treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the subject, notwithstanding that the subject may still be afflicted with the underlying disorder. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof. In certain embodiments, for prophylactic benefit, the compositions are administered to a subject at risk of developing a particular disease, or to a subject reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made.

The term "co-administration," "administered in combination with," and their grammatical equivalents, as used herein, encompass administration of two or more agents to an animal, including humans, so that both agents and/or their metabolites are present in the subject at the same time. Co-administration includes simultaneous administration in separate compositions, administration at different times in separate compositions, or administration in a composition in which both agents are present.

"Pharmaceutically acceptable salt" includes both acid and base addition salts.

"Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness of the free bases, which are biologically tolerable, or otherwise biologically suitable for administration to the subject. See, generally, S.M. Berge, *et al.*, "Pharmaceutical Salts", J. Pharm. Sci., 1977, 66:1-19, and *Handbook of Pharmaceutical Salts, Properties, Selection, and Use,* Stahl and Wermuth, Eds., Wiley-VCH and VHCA, Zurich, 2002. Preferred pharmaceutically acceptable acid addition salts are those that are pharmacologically effective and suitable for contact with the tissues of patients without undue toxicity, irritation, or allergic response. Pharmaceutically acceptable acid addition salts which are formed with inorganic acids such as, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as, but not limited to, acetic acid, 2,2-dichloroacetic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, camphoric acid,

camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, mucic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, propionic acid, pyroglutamic acid, pyruvic acid, salicylic acid, 4-aminosalicylic acid, sebacic acid, stearic acid, succinic acid, tartaric acid, thiocyanic acid, *p*-toluenesulfonic acid, trifluoroacetic acid, undecylenic acid, and the like.

"Pharmaceutically acceptable base addition salt" refers to those salts which retain the biological effectiveness of the free acids, which are biologically tolerable, or otherwise biologically suitable for administration to the subject. *See*, generally, S.M. Berge, *et al.*, "Pharmaceutical Salts", J. Pharm. Sci., 1977, 66:1-19, and *Handbook of Pharmaceutical Salts, Properties, Selection, and Use,* Stahl and Wermuth, Eds., Wiley-VCH and VHCA, Zurich, 2002. Preferred pharmaceutically acceptable base addition salts are those that are pharmacologically effective and suitable for contact with the tissues of patients without undue toxicity, irritation, or allergic response. Pharmaceutically acceptable base addition salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as ammonia, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, diethanolamine, ethanolamine, deanol, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine,

procaine, hydrabamine, choline, betaine, benethamine, benzathine, ethylenediamine, glucosamine, methylglucamine, theobromine, triethanolamine, tromethamine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine.

In some embodiments, pharmaceutically acceptable salts include quaternary ammonium salts such as quaternary amine alkyl halide salts (*e.g.*, methyl bromide).

The terms "antagonist" and "inhibitor" are used interchangeably, and they refer to a compound having the ability to inhibit a biological function of a target protein, whether by inhibiting the activity or expression of the protein, such as NLRP3 inflammasome or NEK7 or the association of NLRP3 inflammasome – NEK7. Accordingly, the terms "antagonist" and "inhibitors" are defined in the context of the biological role of the target protein. While preferred antagonists herein specifically interact with (*e.g.*, bind to) the target, compounds that inhibit a biological activity of the target protein by interacting with other members of the signal transduction pathway of which the target protein is a member are also specifically included within this definition. A preferred biological activity inhibited by an antagonist is associated with the development, growth, or spread of a tumor.

The term "agonist" as used herein refers to a compound having the ability to initiate or enhance a biological function of a target protein, whether by inhibiting the activity or expression of the target protein. Accordingly, the term "agonist" is defined in the context of the biological role of the target polypeptide. While preferred agonists herein specifically interact with (*e.g.*, bind to) the target, compounds that initiate or enhance a biological activity of the target polypeptide by interacting with other members of the signal transduction pathway of which the target polypeptide is a member are also specifically included within this definition.

"Signal transduction" is a process during which stimulatory or inhibitory signals are transmitted into and within a cell to elicit an intracellular response.

The term "selective inhibition" or "selectively inhibit" refers to a biologically active agent refers to the agent's ability to preferentially reduce the target signaling

activity as compared to off-target signaling activity, via direct or indirect interaction with the target.

"Subject" refers to an animal, such as a mammal, for example a human. The methods described herein can be useful in both human therapeutics and veterinary applications. In some embodiments, the subject is a mammal, and in some embodiments, the subject is human.

"Mammal" includes humans and both domestic animals such as laboratory animals and household pets (*e.g.*, cats, dogs, swine, cattle, sheep, goats, horses, rabbits), and non-domestic animals such as wildlife and the like.

"Prodrug" is meant to indicate a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound described herein (*e.g.*, compounds of Structure (I)). Thus, the term "prodrug" refers to a precursor of a biologically active compound that is pharmaceutically acceptable. In some aspects, a prodrug is inactive when administered to a subject, but is converted *in vivo* to an active compound, for example, by hydrolysis. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, *e.g.*, Bundgard, H., Design of Prodrugs (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam). A discussion of prodrugs is provided in Higuchi, T., et al., "Pro-drugs as Novel Delivery Systems," A.C.S. Symposium Series, Vol. 14, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein. The term "prodrug" is also meant to include any covalently bonded carriers, which release the active compound *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of an active compound, as described herein, are typically prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent active compound. Prodrugs include compounds wherein a hydroxy, amino or thiol group is bonded to any group that, when the prodrug of the active compound is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of a hydroxy functional group, or acetamide, formamide and

benzamide derivatives of an amine functional group in the active compound and the like.

The term "*in vivo*" refers to an event that takes place in a subject's body.

Embodiments disclosed herein are also meant to encompass all pharmaceutically acceptable compounds of Structure (I), including salts, stereoisomers, tautomers, polymorphs, solvates, hydrates, and prodrugs thereof.

Certain embodiments are also meant to encompass the *in vivo* metabolic products of the disclosed compounds. Such products may result from, for example, the oxidation, reduction, hydrolysis, amidation, esterification, and the like of the administered compound, primarily due to enzymatic processes. Accordingly, embodiments include compounds produced by a process comprising administering a compound of this disclosure to a mammal for a period of time sufficient to yield a metabolic product thereof. Such products are typically identified by administering a radiolabeled compound of the disclosure in a detectable dose to an animal, such as rat, mouse, guinea pig, monkey, or to human, allowing sufficient time for metabolism to occur, and isolating its conversion products from the urine, blood or other biological samples.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

Often crystallizations produce a solvate of the compounds disclosed herein. As used herein, the term "solvate" refers to an aggregate that comprises one or more compounds of the disclosure with one or more molecules of solvent. In some embodiments, the solvent is water, in which case the solvate is a hydrate. Alternatively, in other embodiments, the solvent is an organic solvent. Thus, the compounds of the present disclosure may exist as a hydrate, including a monohydrate, dihydrate, hemihydrate, sesquihydrate, trihydrate, tetrahydrate and the like, as well as the corresponding solvated forms. In some aspects, the compounds of the disclosure are a true solvate, while in other cases, the compounds of the disclosure merely retain adventitious water or is a mixture of water plus some adventitious solvent.

"Optional" or "optionally" means that the subsequently described event of circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

A "pharmaceutical composition" refers to formulations of compounds of the disclosure and a medium generally accepted in the art for the delivery of compounds of the disclosure to mammals, *e.g.*, humans. Such a medium includes all pharmaceutically acceptable carriers, diluents or excipients therefor.

"Pharmaceutically acceptable carrier, diluent or excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier.

A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present disclosure contemplates various stereoisomers and mixtures thereof and includes "enantiomers", which refers to two stereoisomers whose molecules are non-superimposable mirror images of one another.

The compounds of the disclosure (*i.e.*, compounds of Structure (I)) or their pharmaceutically acceptable salts may contain one or more centers of geometric asymmetry and may thus give rise to stereoisomers such as enantiomers, diastereomers, and other stereoisomeric forms that are defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (D)- or (L)- for amino acids. Embodiments thus include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (*R*)- and (*S*)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

Embodiments of the present disclosure include all manner of rotamers and conformationally restricted states of a compound of the disclosure. Atropisomers, which are stereoisomers arising because of hindered rotation about a single bond, where energy differences due to steric strain or other contributors create a barrier to rotation that is high enough to allow for isolation of individual conformers, are also included. As an example, certain compounds of the disclosure may exist as mixtures of atropisomers or purified or enriched for the presence of one atropisomer.

In some embodiments, the compounds of Structure (I) are a mixture of enantiomers or diastereomers. In other embodiments, the compounds of Structure (I) are substantially one enantiomer or diastereomer.

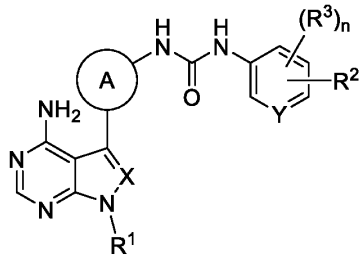
A "tautomer" refers to a proton shift from one atom of a molecule to another atom of the same molecule. Embodiments thus include tautomers of the disclosed compounds.

The chemical naming protocol and structure diagrams used herein are a modified form of the I.U.P.A.C. nomenclature system, using the ACD/Name Version 9.07 software program and/or ChemDraw Professional Version 17.0.0.206 software naming program (CambridgeSoft). For complex chemical names employed herein, a substituent group is typically named before the group to which it attaches. For example, cyclopropylethyl comprises an ethyl backbone with a cyclopropyl substituent. Except as described below, all bonds are identified in the chemical structure diagrams herein, except for all bonds on some carbon atoms, which are assumed to be bonded to sufficient hydrogen atoms to complete the valency.

Compounds

The disclosure provides compounds including pharmaceutically acceptable salts, stereoisomers and prodrugs thereof, which are capable of modulating the activity of NLRP3 inflammasome.

Embodiments of the present disclosure provide a compound having the following Structure (I):



(I)

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

A is C_6-C_{10} arylene, C_3-C_{10} cycloalkylene, 3-10 membered heterocyclylene, or 5-6 membered heteroarylene;

X is N or CR^4;

Y is N or CH;

R^1 is C_1-C_6 alkyl, C_1-C_6 hydroxylalkyl, C_3-C_{10} cycloalkyl, or 3-10 membered heterocyclyl;

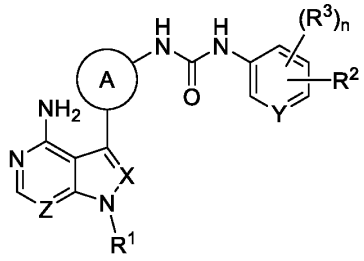
R^2 is a 3-10 membered heterocyclyl, 3-10 membered heterocyclylalkyl, 3-10 membered heterocyclylalkenyl, 3-10 membered heterocyclylcarbonyl, 3-10 membered heterocyclyloxy, or 5-6 membered heteroaryl;

R^3 is, at each occurrence, independently halo, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, or C_3-C_8 cycloalkyl;

R^4 is H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_3-C_8 cycloalkyl; and

n is 0, 1, 2, 3, or 4.

Another embodiment provides a compound having the following Structure (I):



(I)

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

A is C_6-C_{10} arylene, C_3-C_{10} cycloalkylene, 3-10 membered heterocyclylene, or 5-6 membered heteroarylene;

X is N or CR^4;

Y is N or CH;

Z is N or CH;

R^1 is C_1-C_6 alkyl, C_1-C_6 alkynyl, C_1-C_6 hydroxylalkyl, C_1-C_6 carboxyalkyl, C_1-C_6 alkoxyalkyl, C_3-C_{10} cycloalkyl, or 3-10 membered heterocyclyl;

R^2 is a 3-10 membered heterocyclyl, 3-10 membered heterocyclylalkyl, 3-10 membered heterocyclylalkenyl, 3-10 membered heterocyclylcarbonyl, 3-10 membered heterocyclyloxy, or 5-6 membered heteroaryl, or

R^2 joins with an occurrence of R^3 attached to a carbon adjacent to a carbon to which R^2 is attached to form a C_3-C_8 cycloalkyl;

R^3 is, at each occurrence, independently halo, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, or C_3-C_8 cycloalkyl;

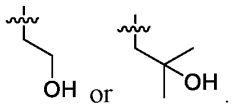
R^4 is H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_3-C_8 cycloalkyl; and

n is 0, 1, 2, 3, or 4.

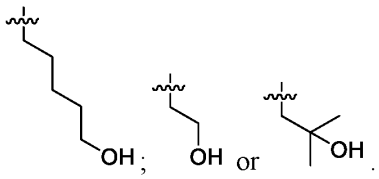
In some embodiments, A is C_6-C_{10} arylene. In some specific embodiments, A is phenylene. In certain embodiments, A is 5-6 membered heteroarylene. In certain specific embodiments, A is pyridinylene. In some embodiments, A is C_3-C_{10} cycloalkylene or 3-10 membered heterocyclylene. In more specific embodiments, A is substituted with one or more substituents selected from halo, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, or C_3-C_8 cycloalkyl. In certain more specific embodiments, A is substituted with one or more halo substituents. In other embodiments, A is unsubstituted.

In certain embodiments, X is CR^4. In more specific embodiments, R^4 is H or C_1-C_6 alkyl. In some embodiments, R^4 is H. In certain specific embodiments, X is N.

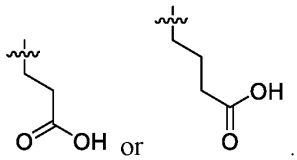
In some embodiments, R^1 is C_1-C_6 alkyl. In some more specific embodiments, R^1 is methyl or iso-propyl. In certain embodiments, R^1 is C_1-C_6 hydroxylalkyl. In certain more specific embodiments, R^1 has one of the following structures:



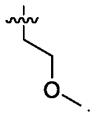
In some embodiments, R^1 has one of the following structures:



In certain embodiments, R^1 is C_1-C_6 carboxyalkyl. In more specific embodiments, R^1 has one of the following structures:

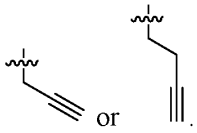


In some embodiments, R^1 is C_1-C_6 alkoxyalkyl. In some embodiments, R^1 has the following structure:



In some embodiments, R^1 is C_3-C_{10} cycloalkyl. In more specific embodiments, R^1 is cyclopropyl or cyclobutyl. In certain embodiments, R^1 is 3-10 membered heterocyclyl. In certain embodiments, R^1 is oxetanyl, pyrrolidinyl, or piperidinyl. In certain embodiments, R^1 is oxetanyl, pyrrolidinyl, azetidinyl, or piperidinyl.

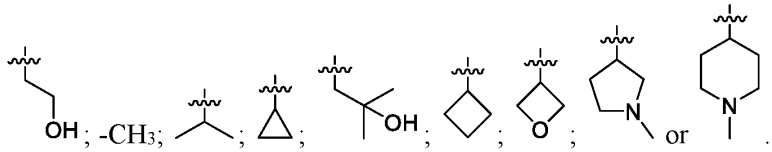
In some embodiments, R^1 is C_1-C_6 alkynyl. In certain embodiments, R^1 has one of the following structures:



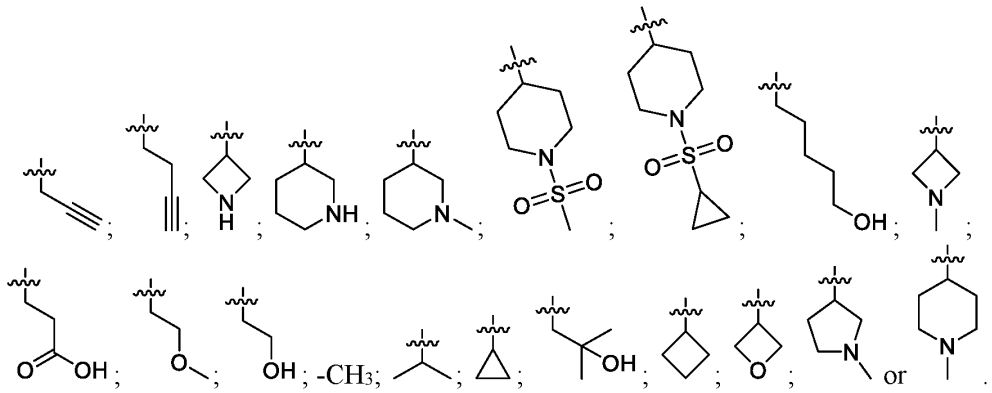
In some embodiments, R^1 is substituted with one or more substituents selected from halo, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, or C_3-C_8 cycloalkyl. In some embodiments, R^1 is substituted with one or more substituents selected from halo, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6

haloalkoxy, -S(O)$_2$CH$_3$, -S(O)$_2$cyclopropyl, or C$_3$-C$_8$ cycloalkyl. In more specific embodiments, R^1 is substituted with one or more C$_1$-C$_6$ alkyl substituents. In other embodiments, R^1 is unsubstituted.

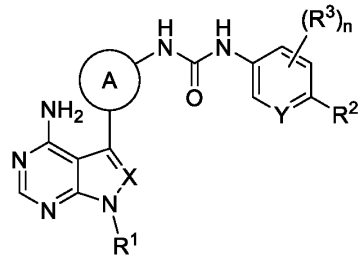
In certain specific embodiments, R^1 has one of the following structures:



In some embodiments, R^1 has one of the following structures:



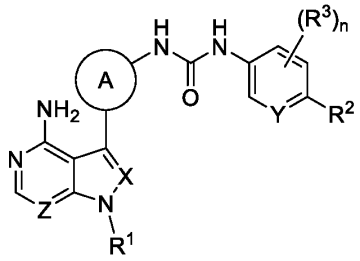
In some specific embodiments, the compound has the following Structure (Ia):



(Ia)

or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof.

In some specific embodiments, the compound has the following Structure (Ia):

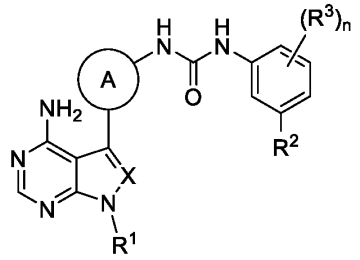


(Ia)

or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof.

In some embodiments, Y is N. In other embodiments, Y is CH.

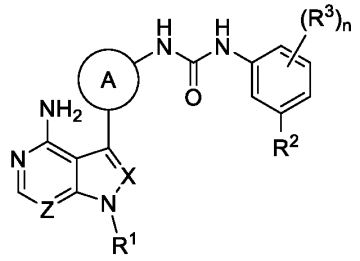
In certain specific embodiments, the compound has the following Structure (Ib):



(Ib)

or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof.

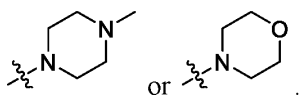
In certain specific embodiments, the compound has the following Structure (Ib):



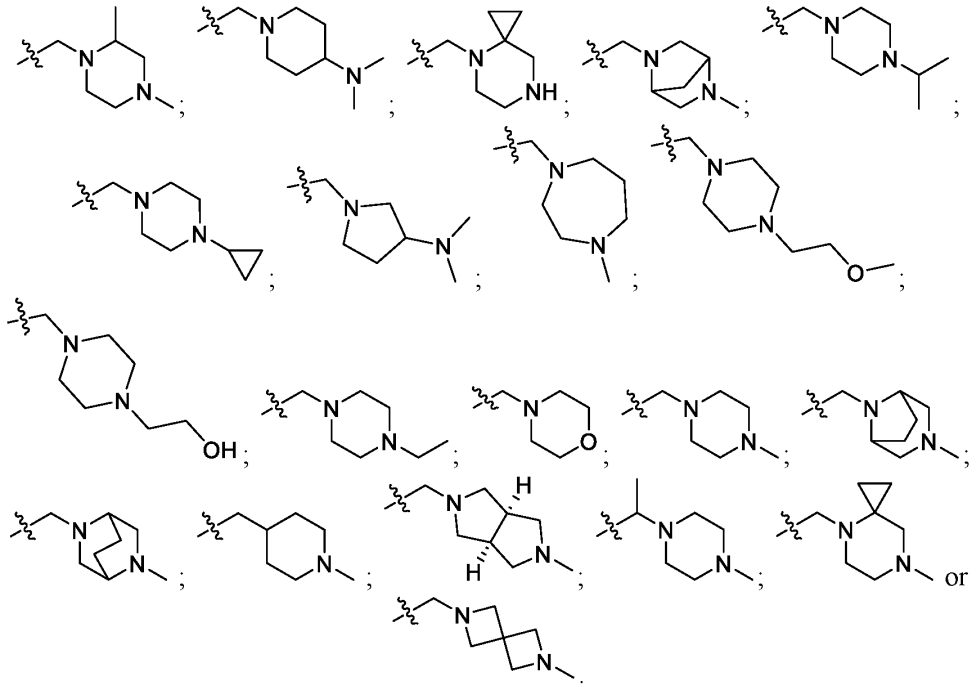
(Ib)

or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof.

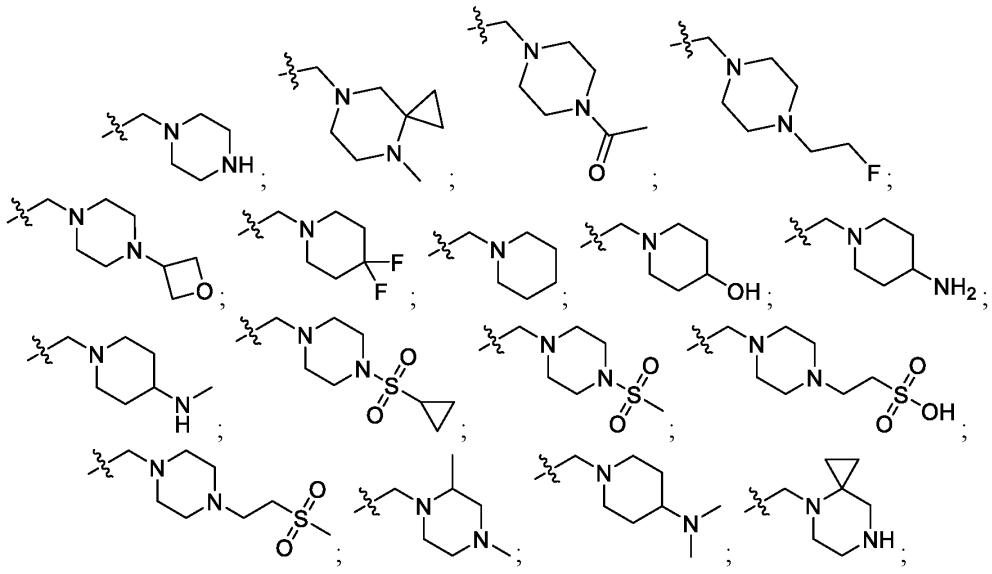
In some embodiments, R^2 is a 3-10 membered heterocyclyl. In some specific embodiments, R^2 is morpholino. In other specific embodiments, R^2 is piperazinyl. In some more specific embodiments, R^2 has one of the following structures:

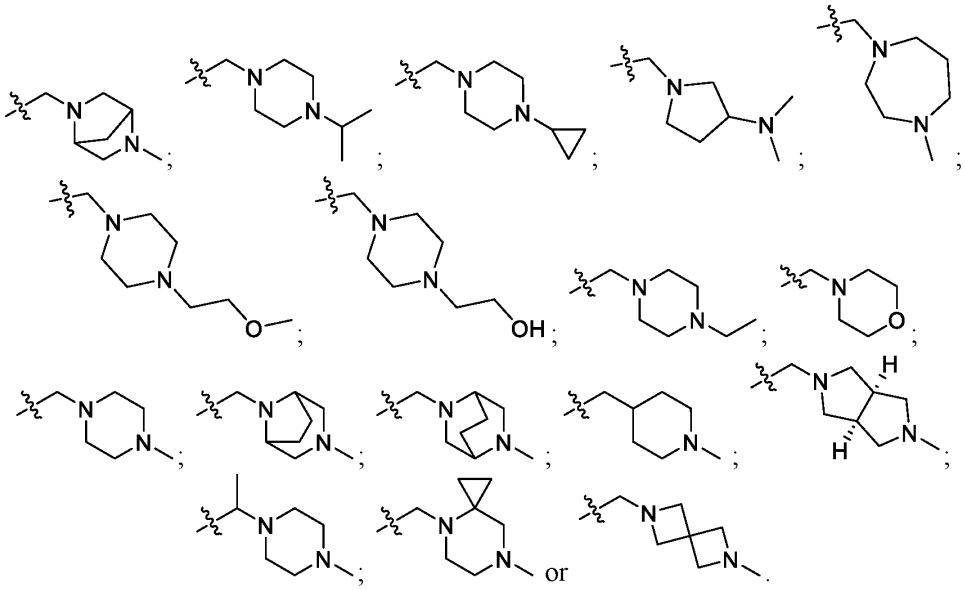


In some embodiments, R^2 is a 3-10 membered heterocyclylalkyl. In certain more specific embodiments, R^2 has one of the following structures:

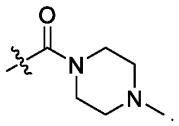


In some more specific embodiments, R^2 has one of the following structures:

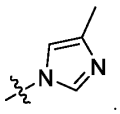




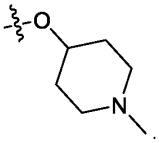
In some embodiments, R^2 is 3-10 membered heterocyclylcarbonyl. In certain more specific embodiments, R^2 has the following structure:



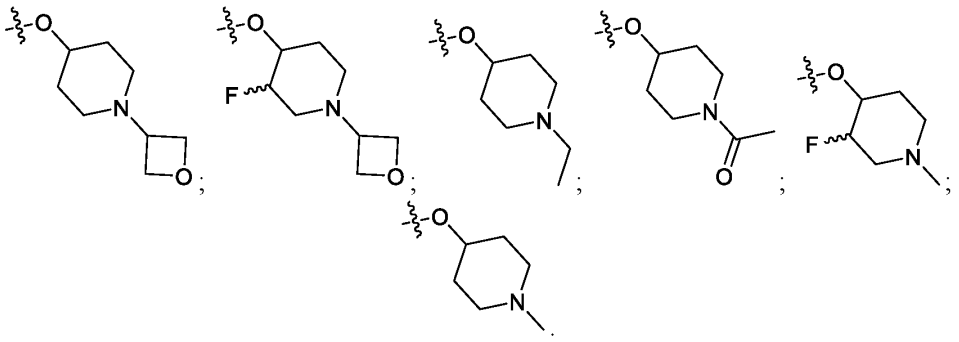
In some embodiments, R^2 is a 5-6 membered heteroaryl. In some more specific embodiments, R^2 has the following structure:



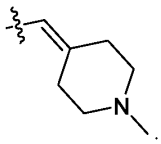
In some embodiments, R^2 is 3-10 membered heterocyclyloxy. In certain more specific embodiments, R^2 has the following structure:



In some embodiments, R^2 has one of the following structures:

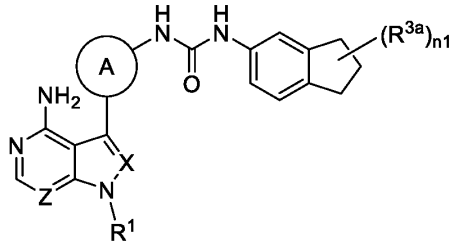


In some more specific embodiments, R^2 has the following structure:



In some embodiments, n is 0. In some embodiments, n is 1 or 2. In certain embodiments, n is 1. In some embodiments, R^3 is halo, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, or C_3-C_8 cycloalkyl. In certain specific embodiments, R^3 is methyl, chloro, fluoro, cyano, difluoromethyl, trifluoromethyl, methoxy, trifluoromethoxy, or cyclopropyl. In some specific embodiments, n is 1 or 2 and R^3 is halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, or C_3-C_8 cycloalkyl. In some embodiments, n is 1 and R^3 is halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, or C_3-C_8 cycloalkyl. In some embodiments, n is 1 and R^3 is methyl, chloro, fluoro, trifluoromethyl, methoxy, trifluoromethoxy, or cyclopropyl.

In some embodiments, the compound has the following Structure (Ic):



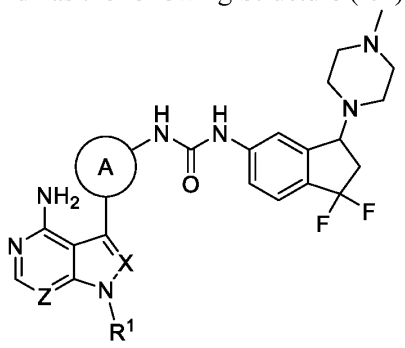
(Ic)

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

R^{3a} is halo or 3-10 membered heterocyclyl; and

n1 is 1, 2, or 3.

In some embodiments, R^{3a} is fluoro or piperazinyl. In more specific embodiments, the compound has the following Structure (Ic1):



(Ic1)

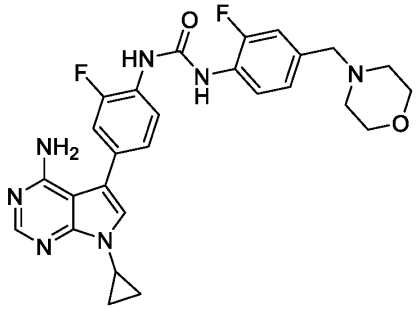
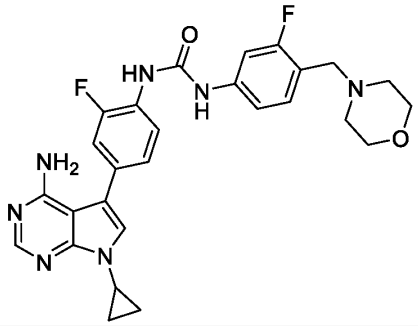
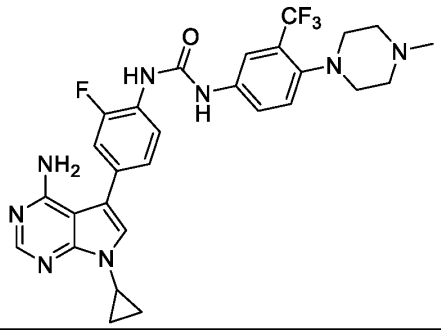
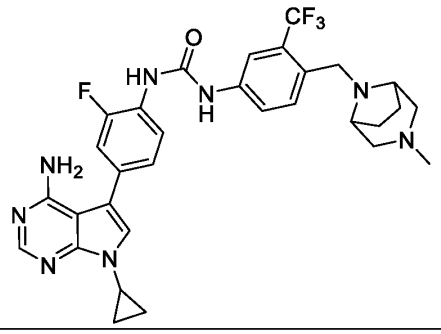
or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof.

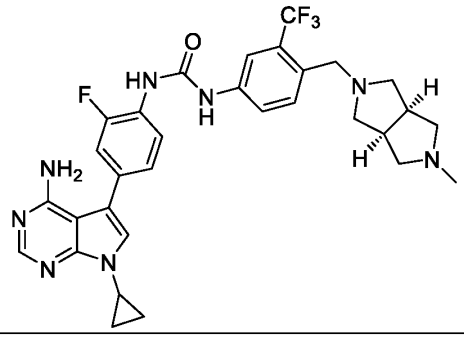
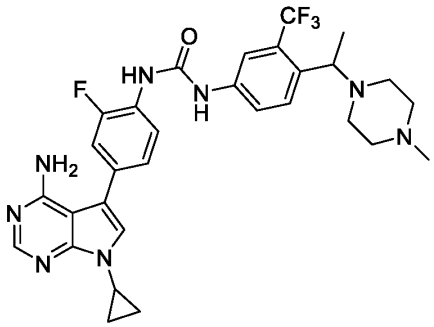
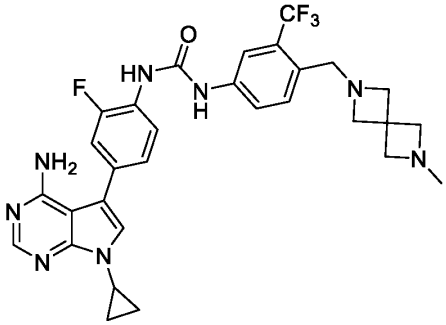
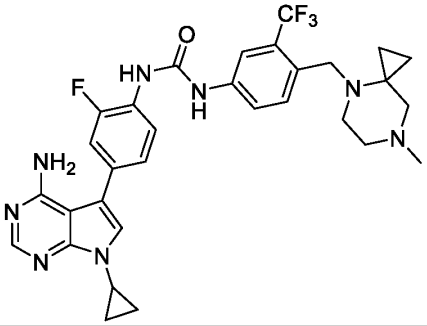
In a certain embodiment, the compound of Structure (I) is a modulator of the NLRP3 inflammasome. In some embodiments, the compound of Structure (I) is a modulator of the NLRP3 inflammasome in a patient or in a biological sample.

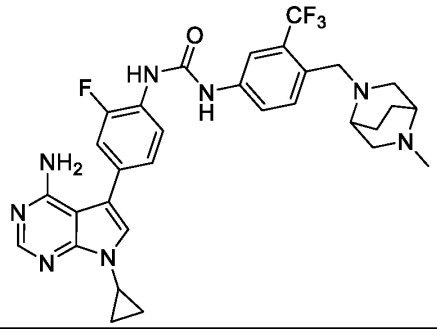
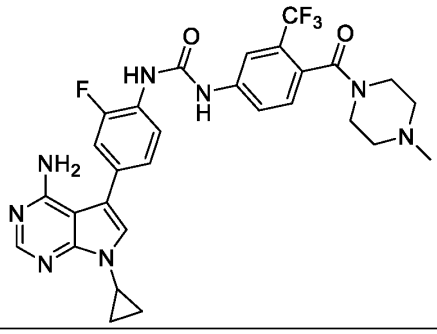
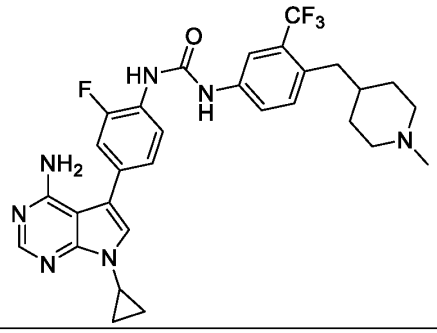
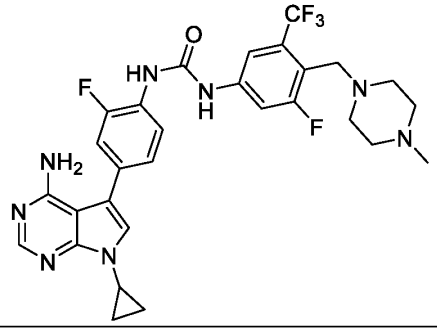
In a specific embodiment, the compound of Structure (I) is an inhibitor of NEK7. In some embodiments, the compound of Structure (I) is an inhibitor of NEK7 in a patient or in a biological sample.

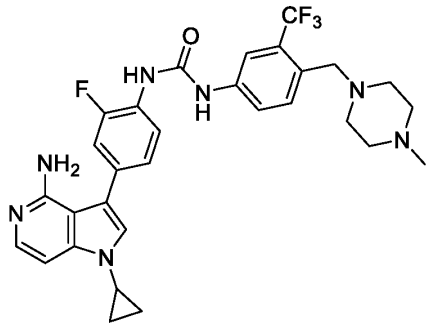
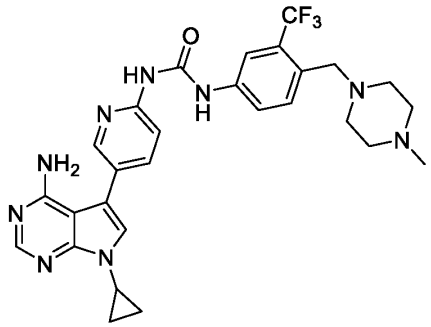
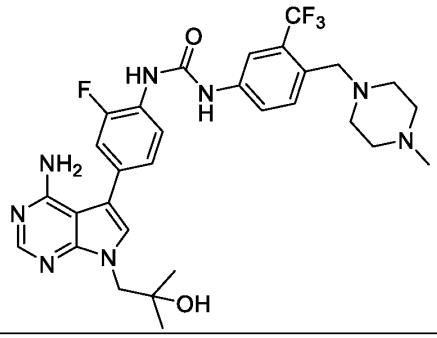
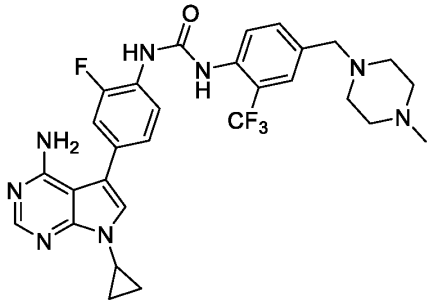
In various different embodiments, the compound has one of the structures set forth in Table 1 below, or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof. Compounds in Table 1 were prepared as described in the Examples or methods known in the art and analyzed by mass spectrometry and/or ^{1}H NMR.

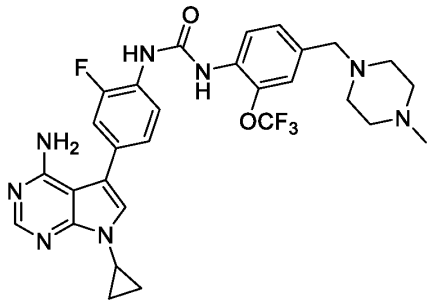
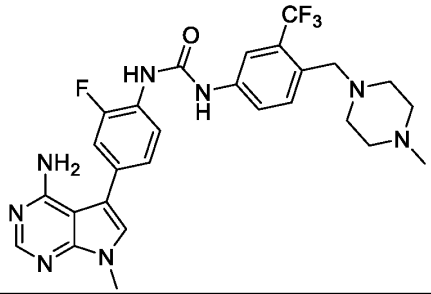
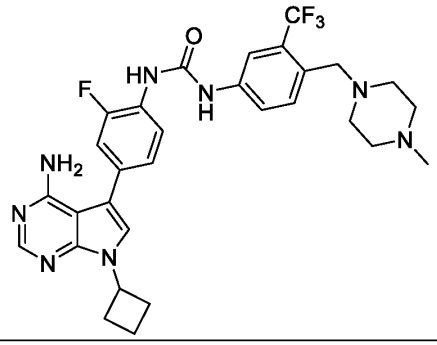
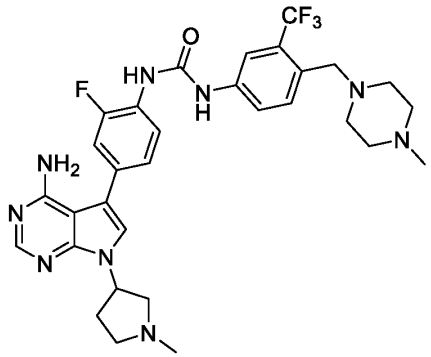
Table 1: Representative compounds of Structure (I)

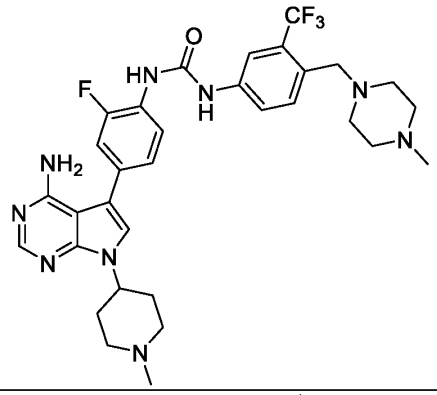
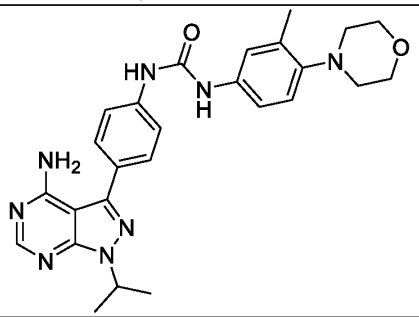
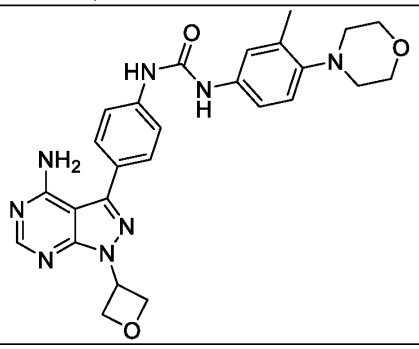
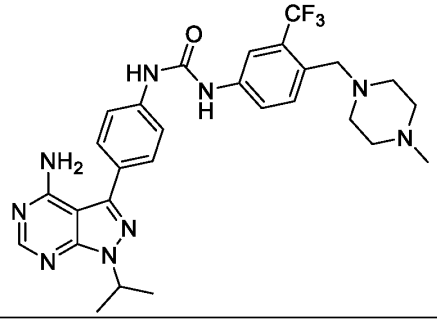
Cmp	Structure	Name
I-1		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(2-fluoro-4-(morpholinomethyl)phenyl)urea
I-2		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(3-fluoro-4-(morpholinomethyl)phenyl)urea
I-3		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-(4-methylpiperazin-1-yl)-3-(trifluoromethyl)phenyl)urea
I-4		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)methyl)-3-(trifluoromethyl)phenyl)urea

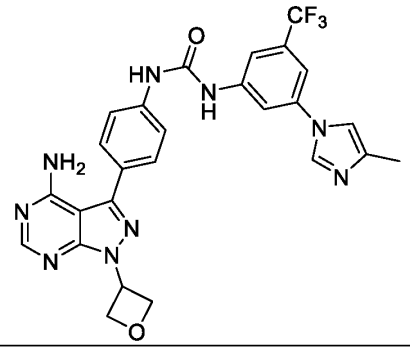
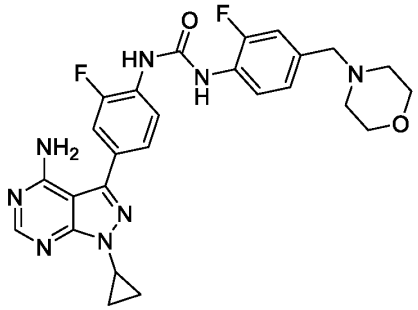
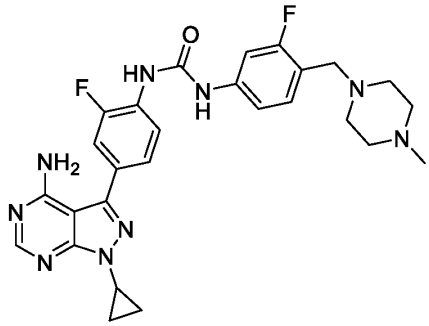
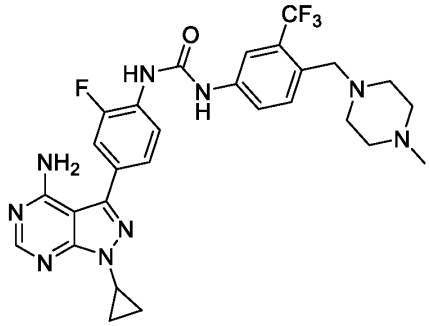
Cmp	Structure	Name
I-5		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-(((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-6		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-(1-(4-methylpiperazin-1-yl)ethyl)-3-(trifluoromethyl)phenyl)urea
I-7		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-8		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((7-methyl-4,7-diazaspiro[2.5]octan-4-yl)methyl)-3-(trifluoromethyl)phenyl)urea

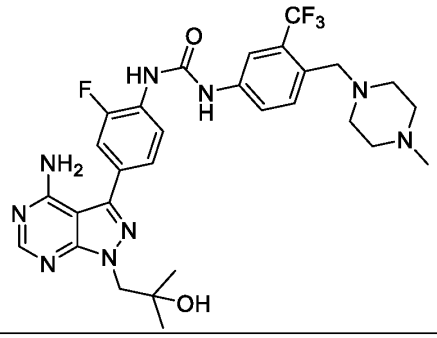
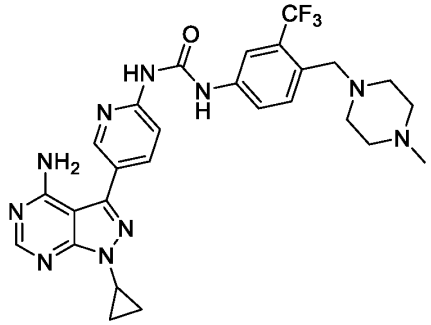
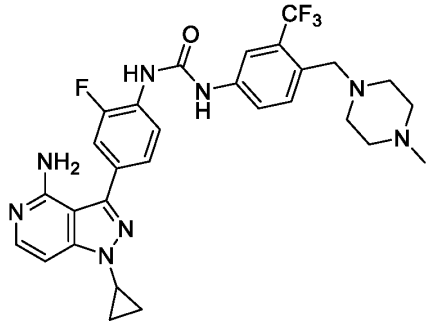
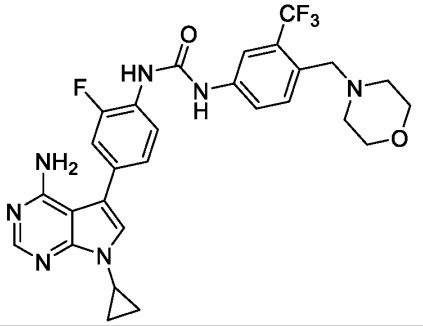
Cmp	Structure	Name
I-9		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((5-methyl-2,5-diazabicyclo[2.2.2]octan-2-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-10		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-(4-methylpiperazine-1-carbonyl)-3-(trifluoromethyl)phenyl)urea
I-11		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((1-methylpiperidin-4-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-12		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(3-fluoro-4-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)urea

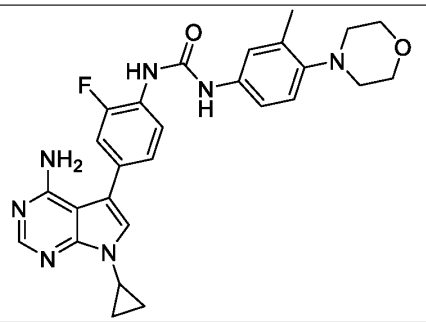
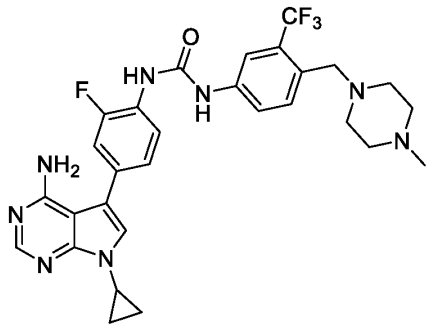
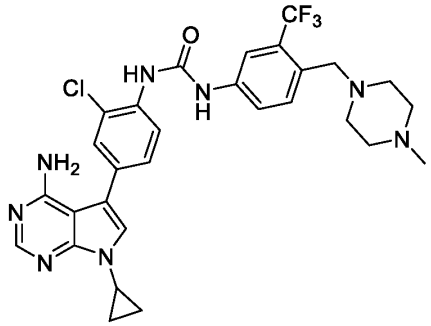
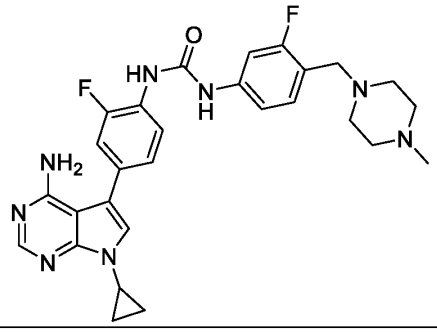
Cmp	Structure	Name
I-13		1-(4-(4-amino-1-cyclopropyl-1H-pyrrolo[3,2-c]pyridin-3-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-14		1-(5-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-15		1-(4-(4-amino-7-(2-hydroxy-2-methylpropyl)-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-16		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-2-(trifluoromethyl)phenyl)urea

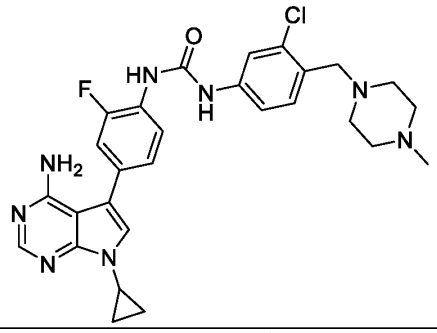
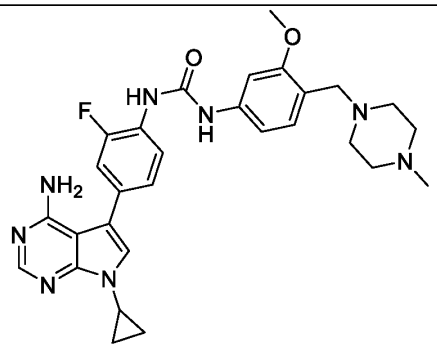
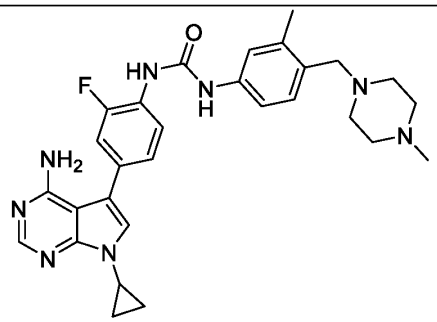
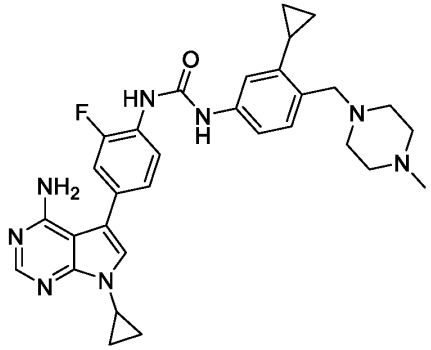
Cmp	Structure	Name
I-17		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-2-(trifluoromethoxy)phenyl)urea
I-18		1-(4-(4-amino-7-methyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-19		1-(4-(4-amino-7-cyclobutyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-20		1-(4-(4-amino-7-(1-methylpyrrolidin-3-yl)-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

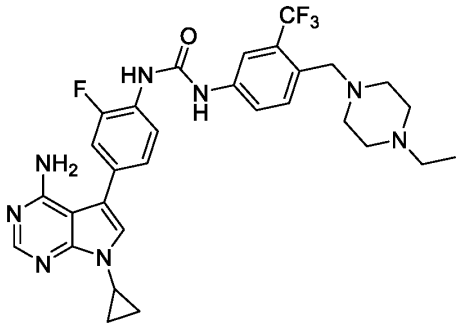
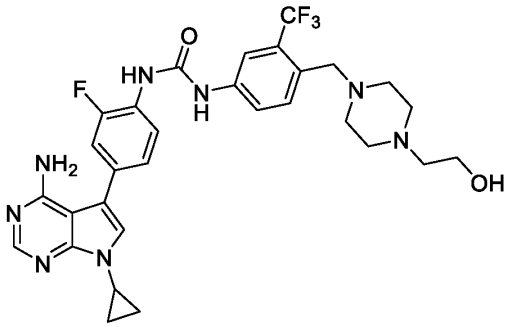
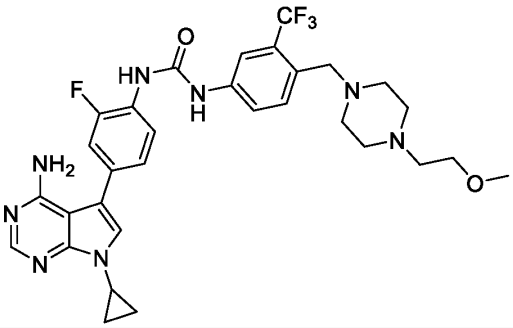
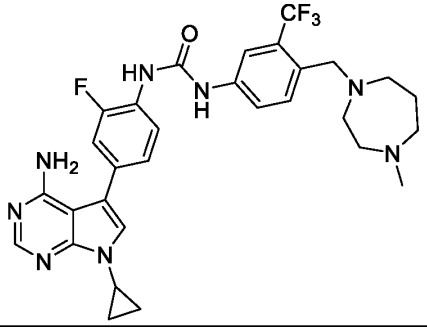
Cmp	Structure	Name
I-21		1-(4-(4-amino-7-(1-methylpiperidin-4-yl)-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-22		1-(4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)-3-(3-methyl-4-morpholinophenyl)urea
I-23		1-(4-(4-amino-1-(oxetan-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)-3-(3-methyl-4-morpholinophenyl)urea
I-24		1-(4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

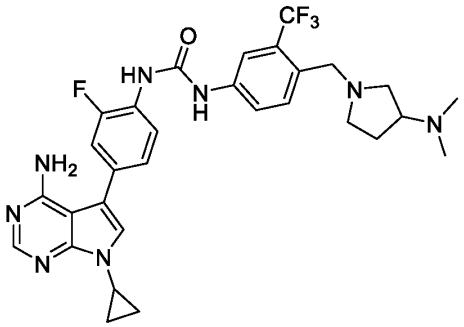
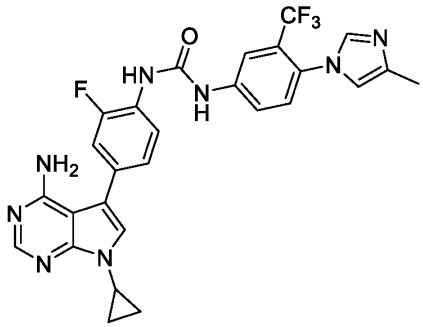
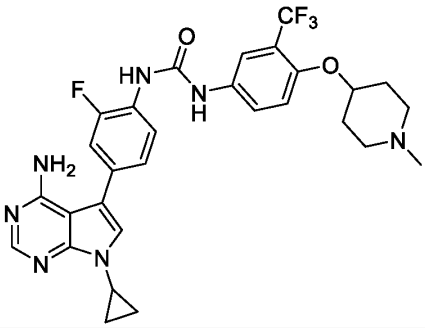
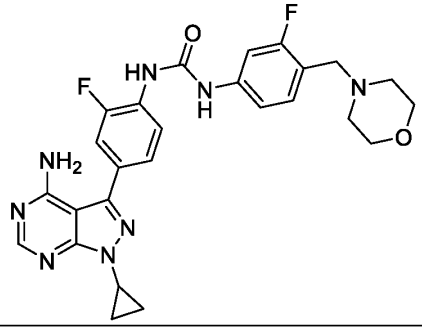
Cmp	Structure	Name
I-25		1-(4-(4-amino-1-(oxetan-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)-3-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)urea
I-26		1-(4-(4-amino-1-cyclopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(2-fluoro-4-(morpholinomethyl)phenyl)urea
I-27		1-(4-(4-amino-1-cyclopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-fluoro-4-((4-methylpiperazin-1-yl)methyl)phenyl)urea
I-28		1-(4-(4-amino-1-cyclopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

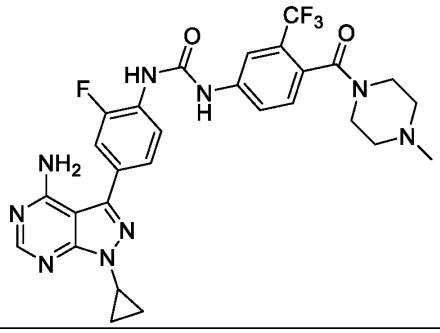
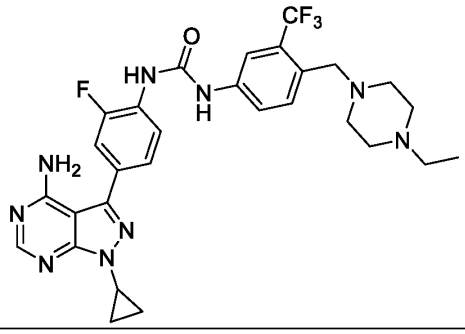
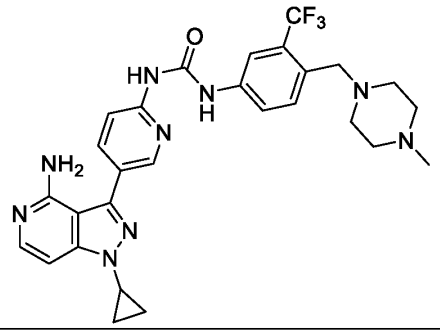
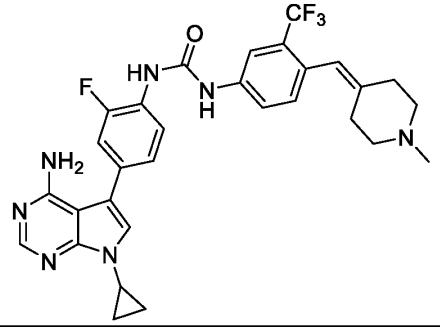
Cmp	Structure	Name
I-29		1-(4-(4-amino-1-(2-hydroxy-2-methylpropyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-30		1-(5-(4-amino-1-cyclopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-31		1-(4-(4-amino-1-cyclopropyl-1H-pyrazolo[4,3-c]pyridin-3-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-32		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-(morpholinomethyl)-3-(trifluoromethyl)phenyl)urea

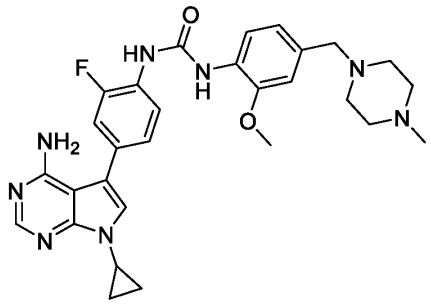
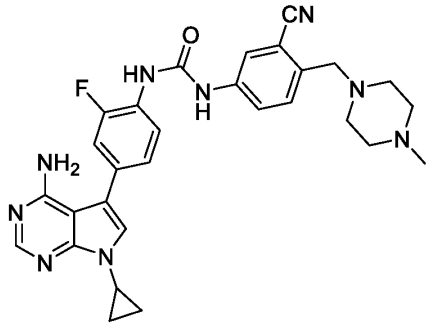
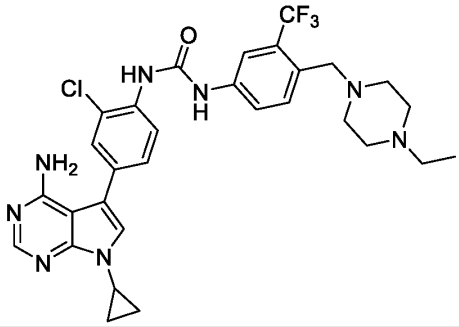
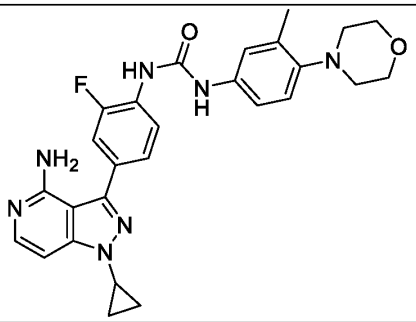
Cmp	Structure	Name
I-33		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(3-methyl-4-morpholinophenyl)urea
I-34		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-35		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-chlorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-36		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(3-fluoro-4-((4-methylpiperazin-1-yl)methyl)phenyl)urea

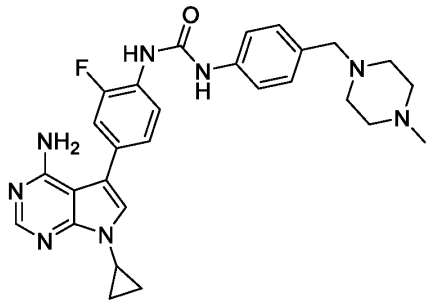
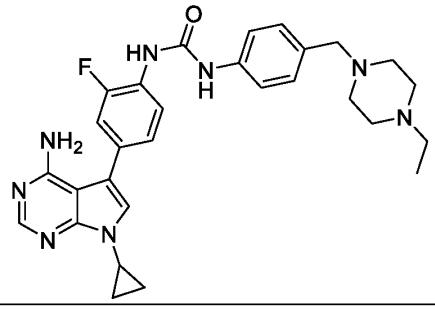
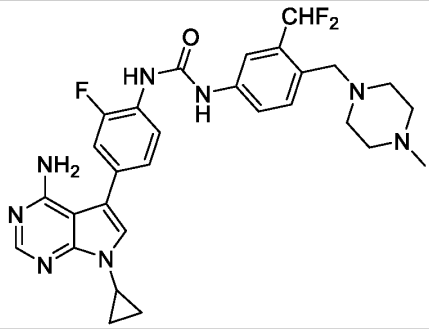
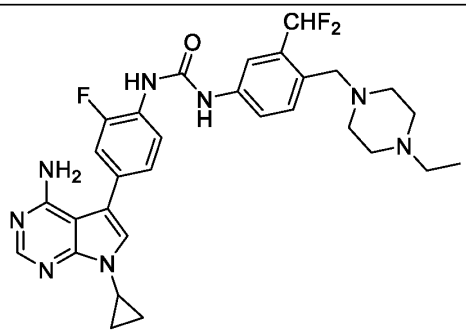
Cmp	Structure	Name
I-37		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(3-chloro-4-((4-methylpiperazin-1-yl)methyl)phenyl)urea
I-38		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(3-methoxy-4-((4-methylpiperazin-1-yl)methyl)phenyl)urea
I-39		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(3-methyl-4-((4-methylpiperazin-1-yl)methyl)phenyl)urea
I-40		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(3-cyclopropyl-4-((4-methylpiperazin-1-yl)methyl)phenyl)urea

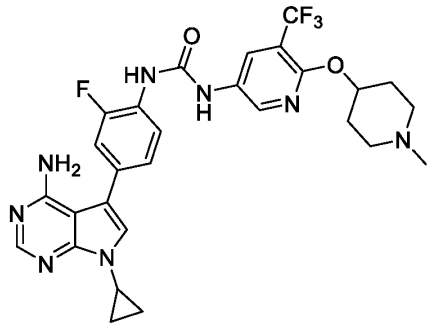
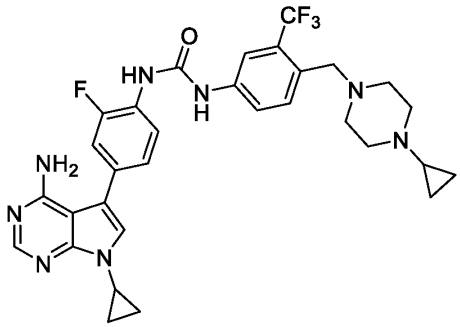
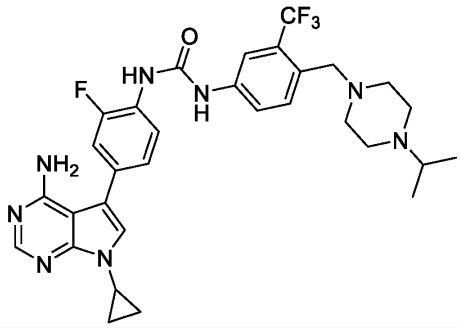
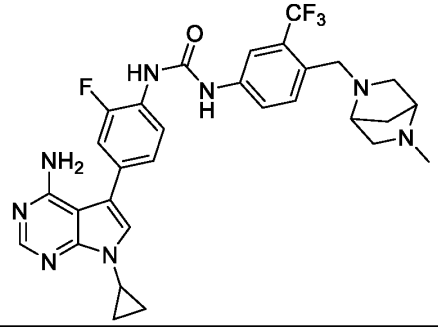
Cmp	Structure	Name
I-41		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-42		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-(2-hydroxyethyl)piperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-43		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-(2-methoxyethyl)piperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-44		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-methyl-1,4-diazepan-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

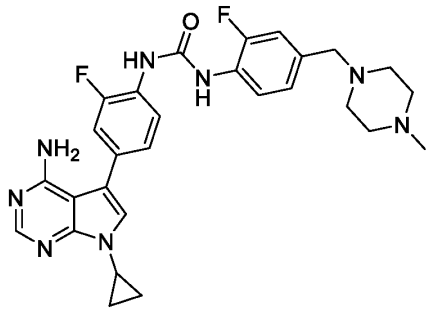
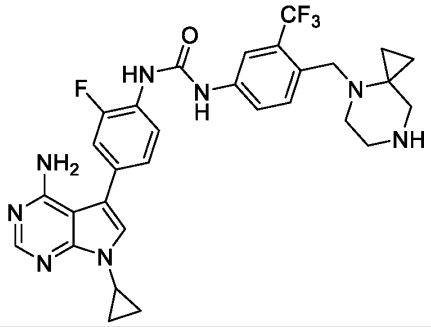
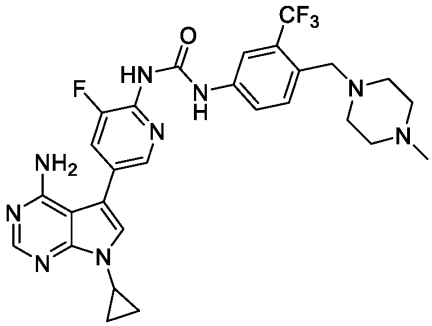
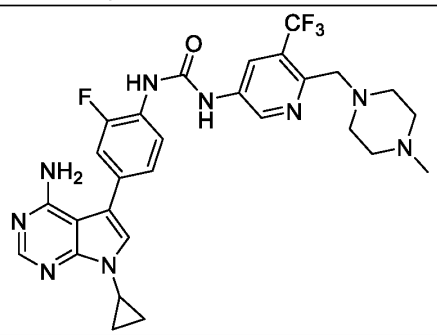
Cmp	Structure	Name
I-45		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((3-(dimethylamino)pyrrolidin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-46		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-(4-methyl-1H-imidazol-1-yl)-3-(trifluoromethyl)phenyl)urea
I-47		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((1-methylpiperidin-4-yl)oxy)-3-(trifluoromethyl)phenyl)urea
I-48		1-(4-(4-amino-1-cyclopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-fluoro-4-(morpholinomethyl)phenyl)urea

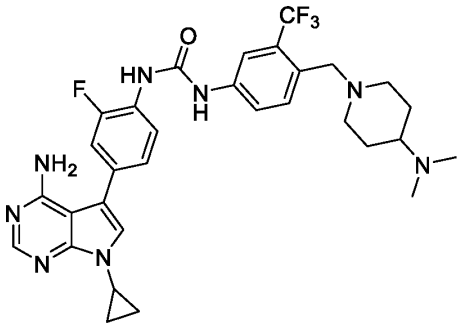
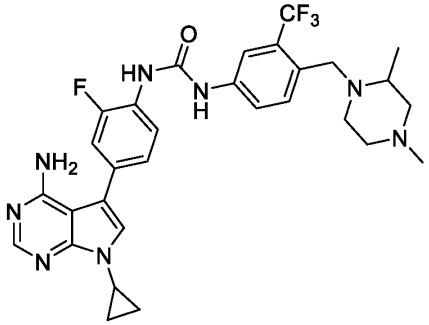
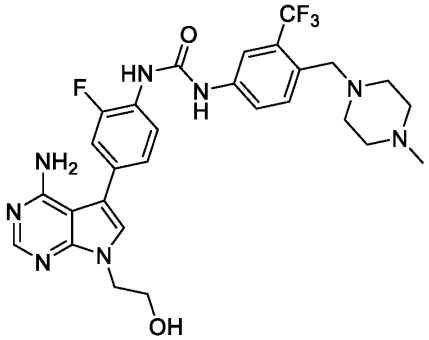
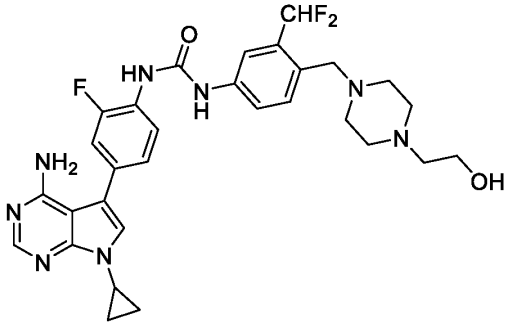
Cmp	Structure	Name
I-49		1-(4-(4-amino-1-cyclopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(4-(4-methylpiperazine-1-carbonyl)-3-(trifluoromethyl)phenyl)urea
I-50		1-(4-(4-amino-1-cyclopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-51		1-(5-(4-amino-1-cyclopropyl-1H-pyrazolo[4,3-c]pyridin-3-yl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-52		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((1-methylpiperidin-4-ylidene)methyl)-3-(trifluoromethyl)phenyl)urea

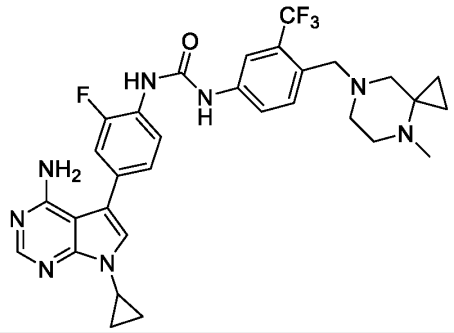
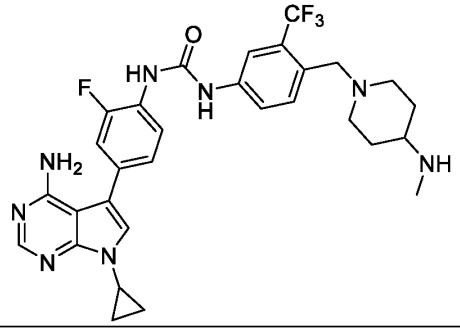
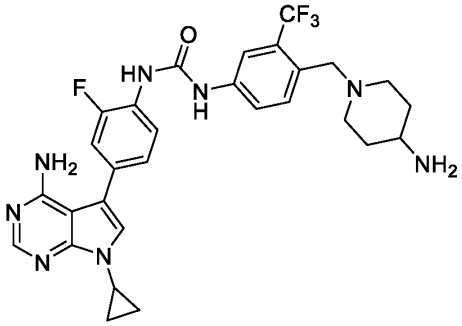
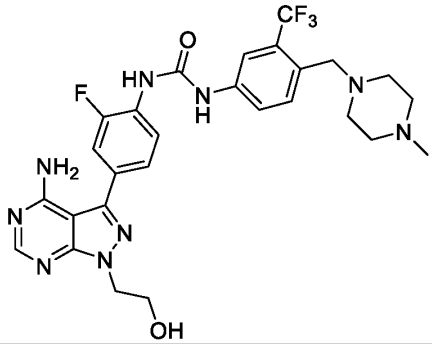
Cmp	Structure	Name
I-53		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(2-methoxy-4-((4-methylpiperazin-1-yl)methyl)phenyl)urea
I-54		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(3-cyano-4-((4-methylpiperazin-1-yl)methyl)phenyl)urea
I-55		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-chlorophenyl)-3-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-56		1-(4-(4-amino-1-cyclopropyl-1H-pyrazolo[4,3-c]pyridin-3-yl)-2-fluorophenyl)-3-(3-methyl-4-morpholinophenyl)urea

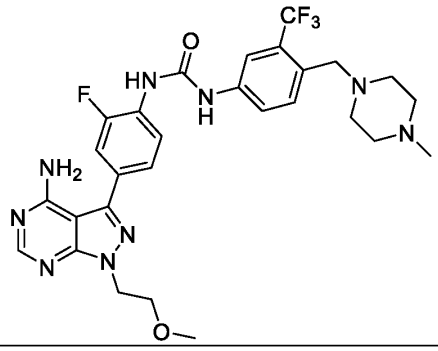
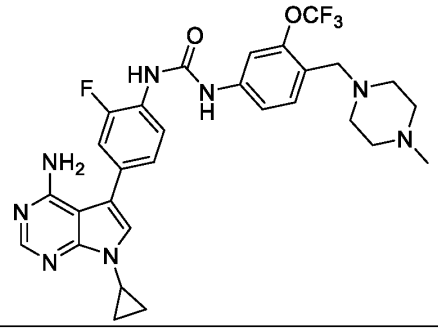
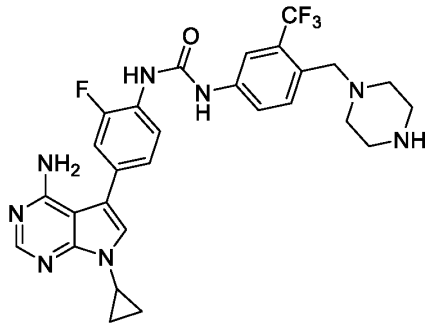
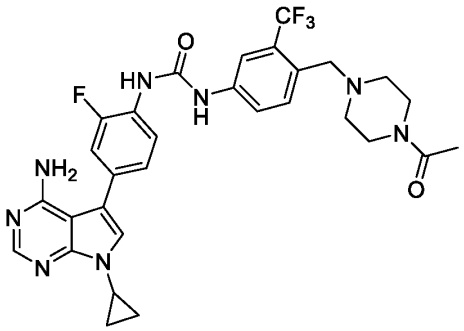
Cmp	Structure	Name
I-57		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)phenyl)urea
I-58		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-ethylpiperazin-1-yl)methyl)phenyl)urea
I-59		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(3-(difluoromethyl)-4-((4-methylpiperazin-1-yl)methyl)phenyl)urea
I-60		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(3-(difluoromethyl)-4-((4-ethylpiperazin-1-yl)methyl)phenyl)urea

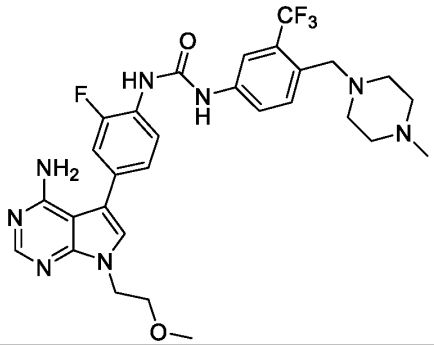
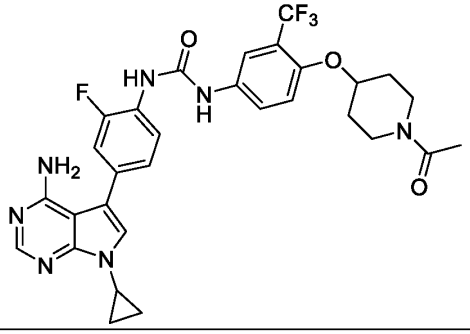
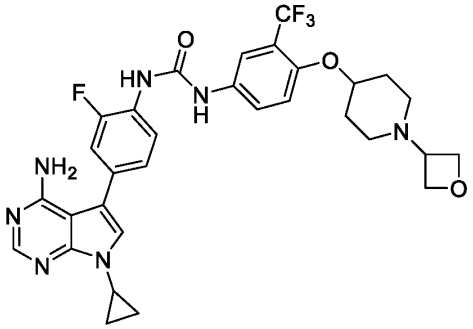
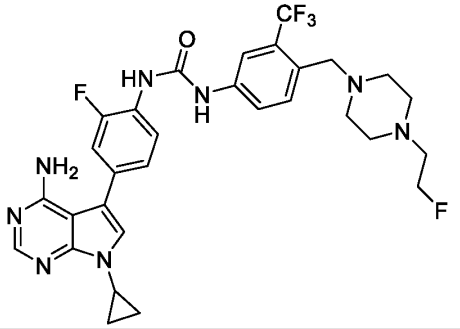
Cmp	Structure	Name
I-61		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(6-((1-methylpiperidin-4-yl)oxy)-5-(trifluoromethyl)pyridin-3-yl)urea
I-62		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-cyclopropylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-63		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-isopropylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-64		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)methyl)-3-(trifluoromethyl)phenyl)urea

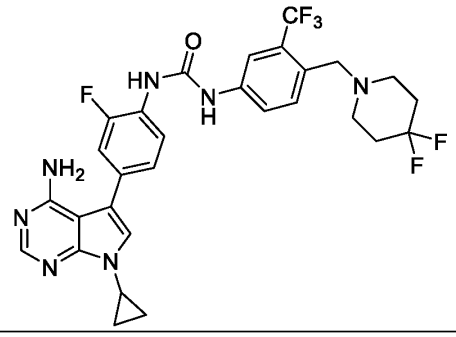
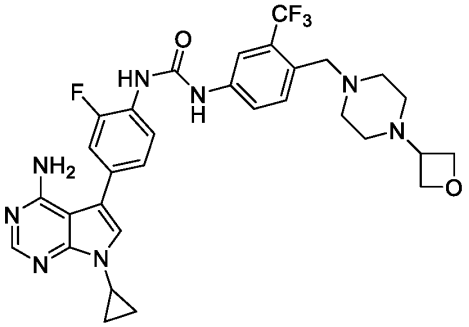
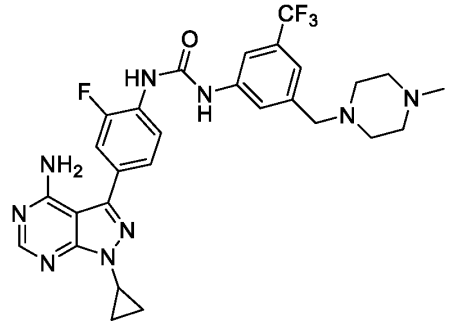
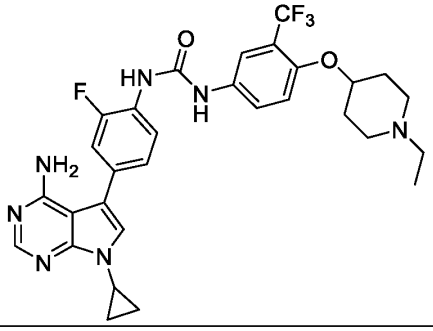
Cmp	Structure	Name
I-65		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(2-fluoro-4-((4-methylpiperazin-1-yl)methyl)phenyl)urea
I-66		1-(4-((4,7-diazaspiro[2.5]octan-4-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)urea
I-67		1-(5-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-3-fluoropyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-68		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(6-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)pyridin-3-yl)urea

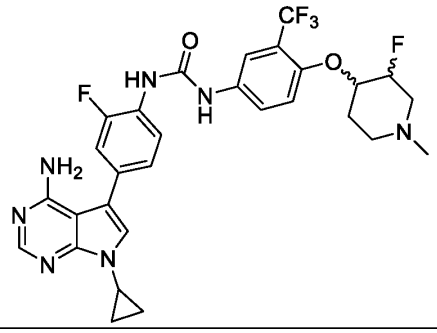
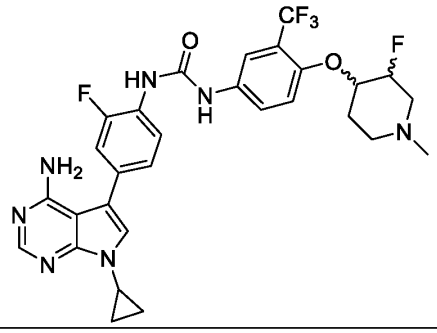
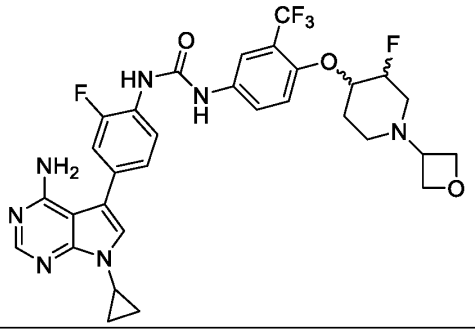
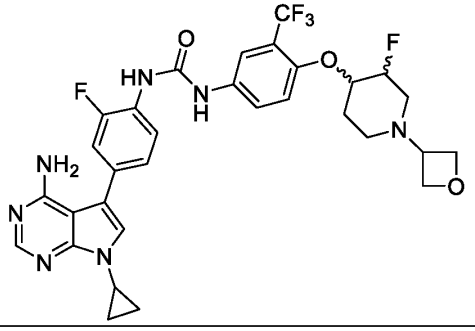
Cmp	Structure	Name
I-69		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-(dimethylamino)piperidin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-70		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((2,4-dimethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-71		1-(4-(4-amino-7-(2-hydroxyethyl)-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-72		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(3-(difluoromethyl)-4-((4-(2-hydroxyethyl)piperazin-1-yl)methyl)phenyl)urea

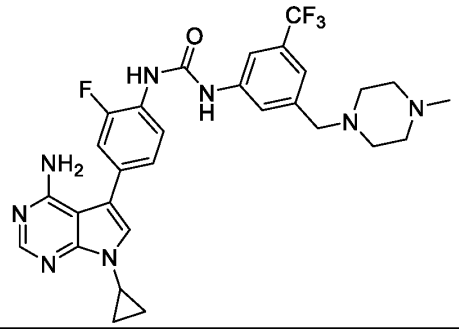
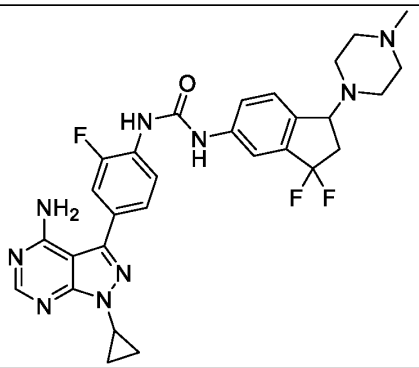
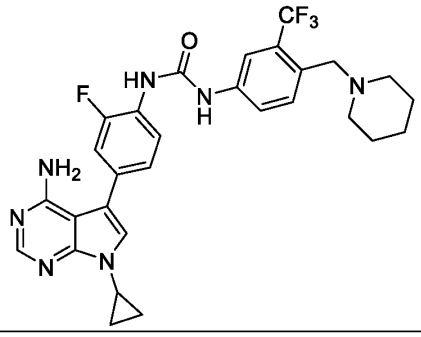
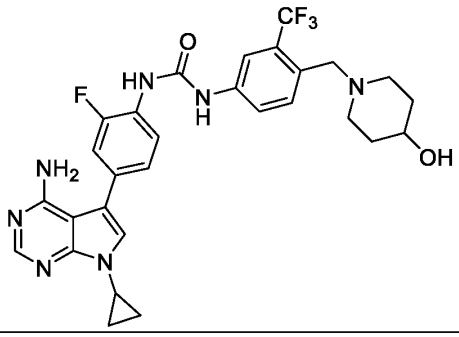
Cmp	Structure	Name
I-73		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-methyl-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-74		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-(methylamino)piperidin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-75		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-aminopiperidin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-76		1-(4-(4-amino-1-(2-hydroxyethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

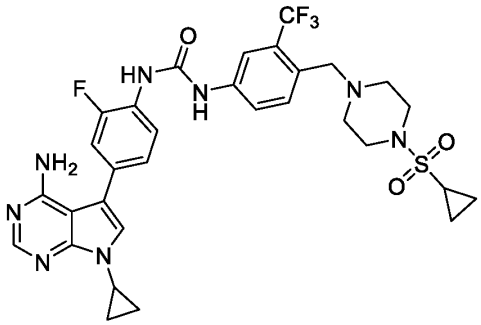
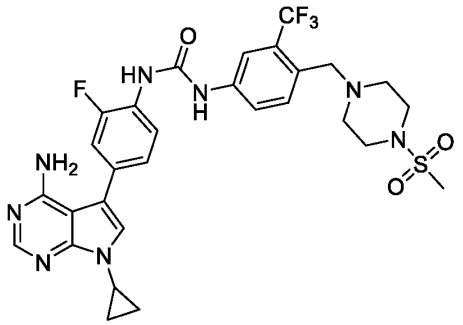
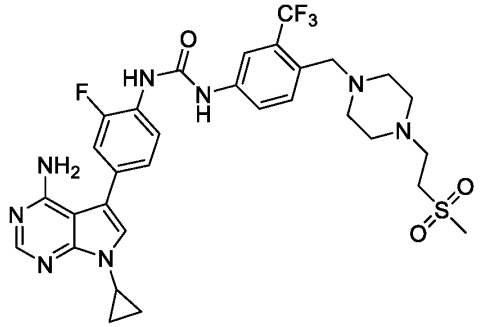
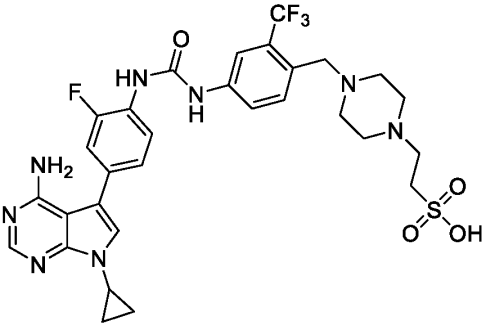
Cmp	Structure	Name
I-77		1-(4-(4-amino-1-(2-methoxyethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-78		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethoxy)phenyl)urea
I-79		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)urea
I-80		1-(4-((4-acetylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)urea

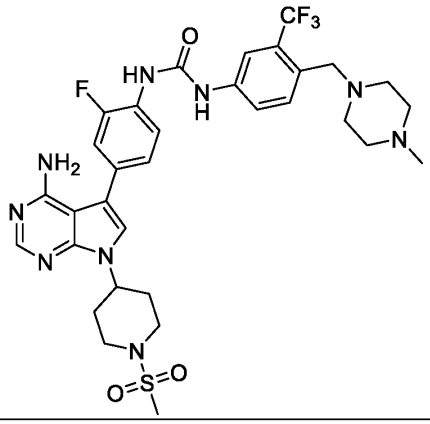
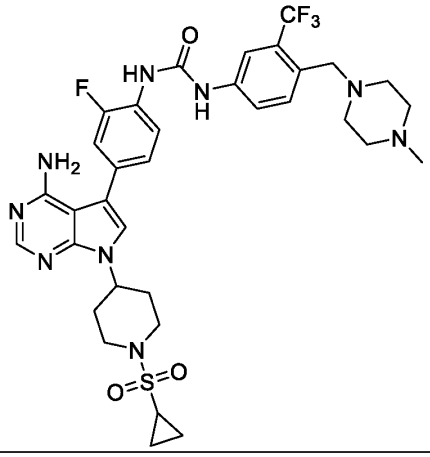
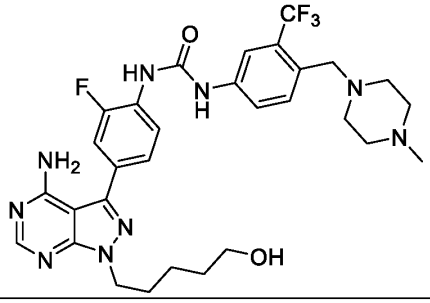
Cmp	Structure	Name
I-81		1-(4-(4-amino-7-(2-methoxyethyl)-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-82		1-(4-((1-acetylpiperidin-4-yl)oxy)-3-(trifluoromethyl)phenyl)-3-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)urea
I-83		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((1-(oxetan-3-yl)piperidin-4-yl)oxy)-3-(trifluoromethyl)phenyl)urea
I-84		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-(2-fluoroethyl)piperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

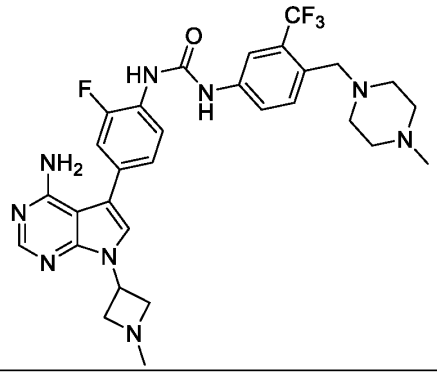
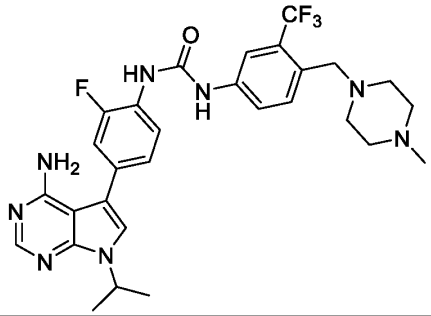
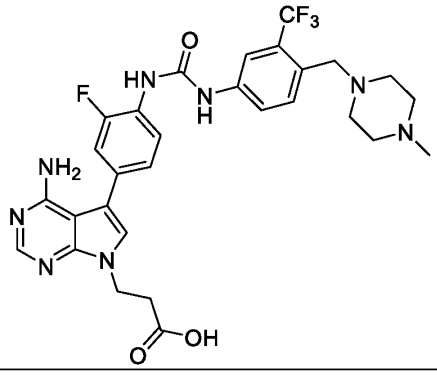
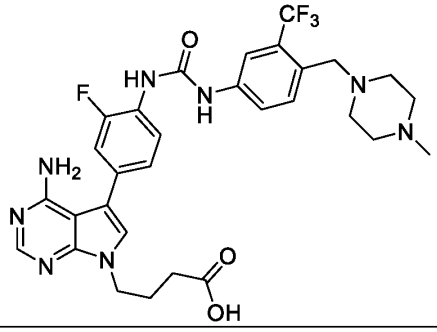
Cmp	Structure	Name
I-85		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4,4-difluoropiperidin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-86		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-(oxetan-3-yl)piperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-87		1-(4-(4-amino-1-cyclopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)urea
I-88		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((1-ethylpiperidin-4-yl)oxy)-3-(trifluoromethyl)phenyl)urea

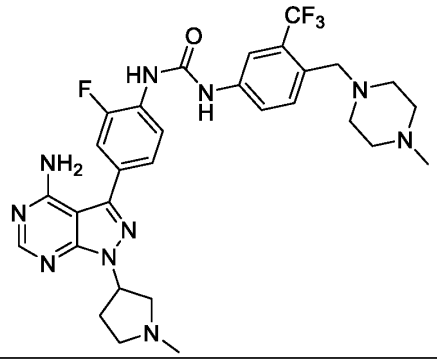
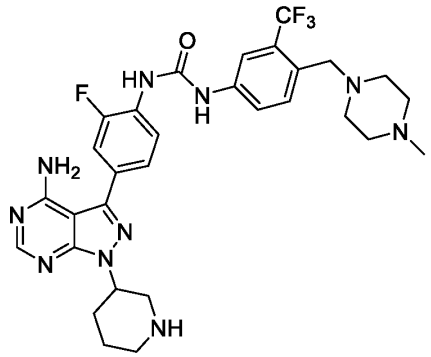
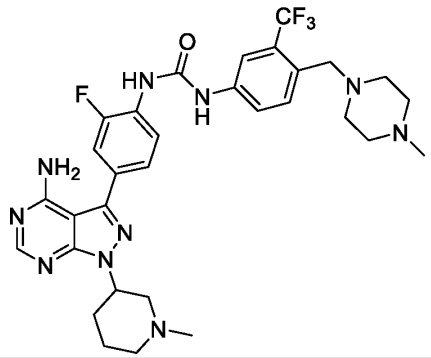
Cmp	Structure	Name
I-89		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((3-fluoro-1-methylpiperidin-4-yl)oxy)-3-(trifluoromethyl)phenyl)urea (diastereomer #1)
I-90		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((3-fluoro-1-methylpiperidin-4-yl)oxy)-3-(trifluoromethyl)phenyl)urea (diastereomer #2)
I-91		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((3-fluoro-1-(oxetan-3-yl)piperidin-4-yl)oxy)-3-(trifluoromethyl)phenyl)urea (diastereomer #1)
I-92		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((3-fluoro-1-(oxetan-3-yl)piperidin-4-yl)oxy)-3-(trifluoromethyl)phenyl)urea (diastereomer #2)

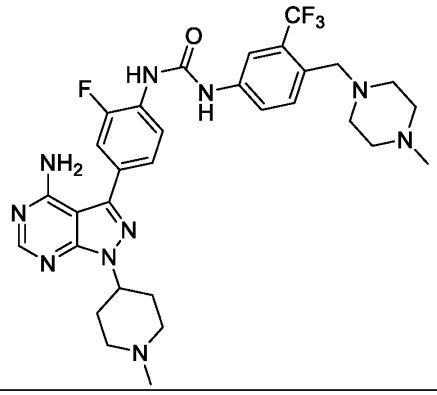
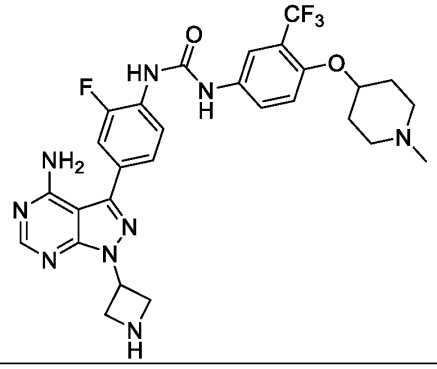
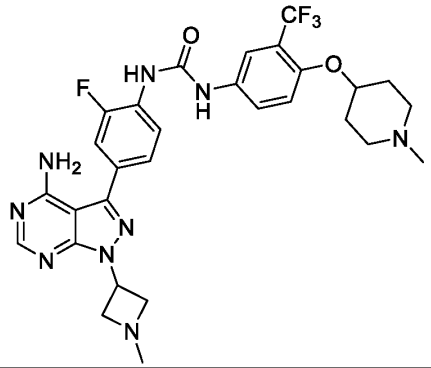
Cmp	Structure	Name
I-93		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)urea
I-94		1-(4-(4-amino-1-cyclopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(3,3-difluoro-1-(4-methylpiperazin-1-yl)-2,3-dihydro-1H-inden-5-yl)urea
I-95		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-(piperidin-1-ylmethyl)-3-(trifluoromethyl)phenyl)urea
I-96		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-hydroxypiperidin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

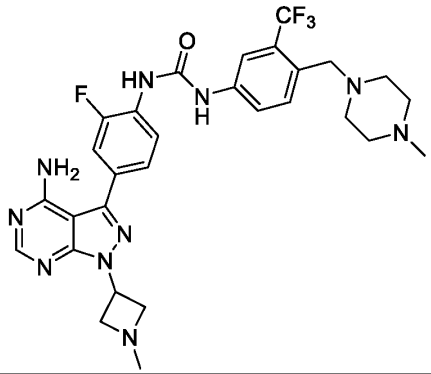
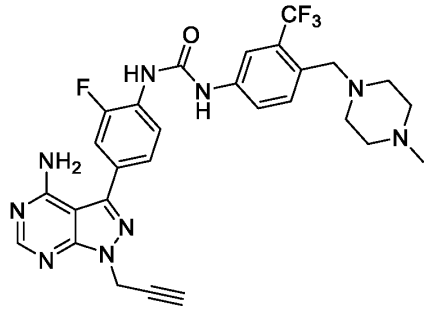
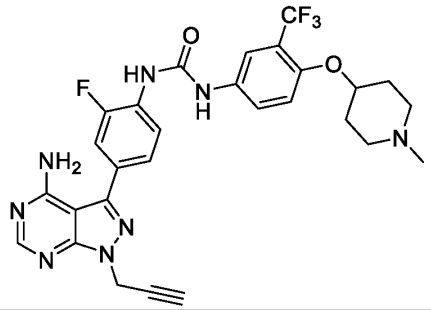
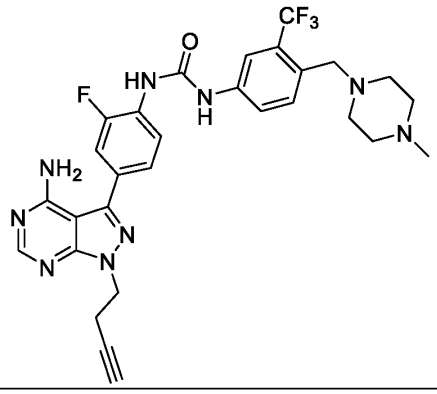
Cmp	Structure	Name
I-97		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-(cyclopropylsulfonyl)piperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-98		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-(methylsulfonyl)piperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-99		1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-(2-(methylsulfonyl)ethyl)piperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-100		2-(4-(4-(3-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)ureido)-2-(trifluoromethyl)benzyl)piperazin-1-yl)ethane-1-sulfonic acid

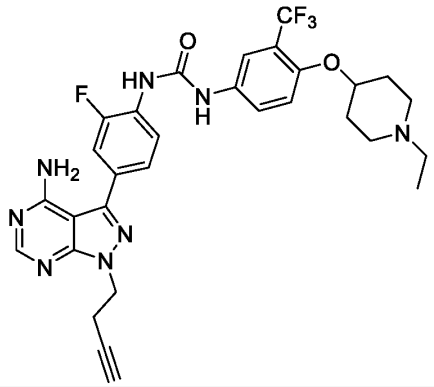
Cmp	Structure	Name
I-101		1-(4-(4-amino-7-(1-(methylsulfonyl)piperidin-4-yl)-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-102		1-(4-(4-amino-7-(1-(cyclopropylsulfonyl)piperidin-4-yl)-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-103		1-(4-(4-amino-1-(5-hydroxypentyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

Cmp	Structure	Name
I-104		1-(4-(4-amino-7-(1-methylazetidin-3-yl)-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-105		1-(4-(4-amino-7-isopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-106		3-(4-amino-5-(3-fluoro-4-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)phenyl)-7*H*-pyrrolo[2,3-d]pyrimidin-7-yl)propanoic acid
I-107		4-(4-amino-5-(3-fluoro-4-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)phenyl)-7*H*-pyrrolo[2,3-d]pyrimidin-7-yl)butanoic acid

Cmp	Structure	Name
I-108		1-(4-(4-amino-1-(1-methylpyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-109		1-(4-(4-amino-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-110		1-(4-(4-amino-1-(1-methylpiperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

Cmp	Structure	Name
I-111		1-(4-(4-amino-1-(1-methylpiperidin-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-112		1-(4-(4-amino-1-(azetidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(4-((1-methylpiperidin-4-yl)oxy)-3-(trifluoromethyl)phenyl)urea
I-113		1-(4-(4-amino-1-(1-methylazetidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(4-((1-methylpiperidin-4-yl)oxy)-3-(trifluoromethyl)phenyl)urea

Cmp	Structure	Name
I-114		1-(4-(4-amino-1-(1-methylazetidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-115		1-(4-(4-amino-1-(prop-2-yn-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea
I-116		1-(4-(4-amino-1-(prop-2-yn-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(4-((1-methylpiperidin-4-yl)oxy)-3-(trifluoromethyl)phenyl)urea
I-117		1-(4-(4-amino-1-(but-3-yn-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

Cmp	Structure	Name
I-118		1-(4-(4-amino-1-(but-3-yn-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(4-((1-ethylpiperidin-4-yl)oxy)-3-(trifluoromethyl)phenyl)urea

It is understood that in the present description, combinations of substituents and/or variables of the depicted formulae are permissible only if such contributions result in stable compounds.

In an additional embodiment, various compounds of the disclosure which exist in free base or acid form can be converted to their pharmaceutically acceptable salts by treatment with the appropriate inorganic or organic base or acid by methods known to one skilled in the art. Salts of the compounds of the disclosure can be converted to their free base or acid form by standard techniques.

Pharmaceutical Compositions

Other embodiments are directed to pharmaceutical compositions. The pharmaceutical composition comprises any one (or more) of the foregoing compounds and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition is formulated for oral administration. In other embodiments, the pharmaceutical composition is formulated for injection. In still more embodiments, the pharmaceutical compositions comprise a compound as disclosed herein and an additional therapeutic agent (*e.g.*, anticancer agent). Non-limiting examples of such therapeutic agents are described herein below.

Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal,

transdermal, vaginal, otic, nasal, and topical administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

In certain embodiments, a compound as described herein is administered in a local rather than systemic manner, for example, via injection of the compound directly into an organ, often in a depot preparation or sustained release formulation. In specific embodiments, long acting formulations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Furthermore, in other embodiments, the compound is delivered in a targeted drug delivery system, for example, in a liposome coated with and organ-specific antibody. In such embodiments, the liposomes are targeted to and taken up selectively by the organ. In yet other embodiments, the compound as described herein is provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation. In yet other embodiments, the compound described herein is administered topically.

In treatment methods according to embodiments of the disclosure, an effective amount of at least one compound of Structure (I) is administered to a subject suffering from or diagnosed as having such a disease, disorder, or medical condition. Effective amounts or doses may be ascertained by methods such as modeling, dose escalation studies or clinical trials, *e.g.*, the mode or route of administration or drug delivery, the pharmacokinetics of the agent, the severity and course of the disease, disorder, or condition, the subject's previous or ongoing therapy, the subject's health status and response to drugs, and the judgment of the treating physician.

The compounds according to the disclosure are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from 10 to 5000 mg, from 100 to 5000 mg, from 1000 mg to 4000 mg per day, and from 1000 to 3000 mg per day are examples of dosages that are used in some embodiments. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

In some embodiments, compounds of the disclosure are administered in a single dose. Typically, such administration will be by injection, *e.g.*, intravenous injection, in order to introduce the agent quickly. However, other routes are used as appropriate. A single dose of a compound of the disclosure may also be used for treatment of an acute condition.

In some embodiments, compounds of the disclosure are administered in multiple doses. In some embodiments, dosing is about once, twice, three times, four times, five times, six times, or more than six times per day. In other embodiments, dosing is about once a month, once every two weeks, once a week, or once every other day. In another embodiment compounds of the disclosure and another agent (*e.g.*, anti-cancer agent) are administered together about once per day to about 6 times per day. In another embodiment the administration of compounds of the disclosure and an agent continues for less than about 7 days. In yet another embodiment the administration continues for more than about 6, 10, 14, 28 days, two months, six months, or one year. In some cases, continuous dosing is achieved and maintained as long as necessary.

Administration of compounds of the disclosure may continue as long as necessary. In some embodiments, compounds of the disclosure are administered for more than 1, 2, 3, 4, 5, 6, 7, 14, or 28 days. In some embodiments, compounds of the disclosure are administered for less than 28, 14, 7, 6, 5, 4, 3, 2, or 1 day. In some embodiments, compounds of the disclosure are administered chronically on an ongoing basis, *e.g.*, for the treatment of chronic effects.

In some embodiments, the compounds of the disclosure are administered in individual dosage forms. It is known in the art that due to inter-subject variability in compound pharmacokinetics, individualization of dosing regimen is necessary for optimal therapy.

In some embodiments, the compounds described herein are formulated into pharmaceutical compositions. In specific embodiments, pharmaceutical compositions are formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the disclosed compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any

pharmaceutically acceptable techniques, carriers, and excipients are used as suitable to formulate the pharmaceutical compositions described herein: Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999).

Provided herein are pharmaceutical compositions comprising one or more compounds of Structure (I), and a pharmaceutically acceptable carrier.

Provided herein are pharmaceutical compositions comprising one or more compounds selected from compounds of Structure (I) and pharmaceutically acceptable diluent(s), excipient(s), and carrier(s). In certain embodiments, the compounds described are administered as pharmaceutical compositions in which one or more compounds selected from compounds of Structure (I) are mixed with other active ingredients, as in combination therapy. Encompassed herein are all combinations of actives set forth in the combination therapies section below and throughout this disclosure. In specific embodiments, the pharmaceutical compositions include one or more compounds of Structure (I).

In a certain embodiment, pharmaceutical compositions of the compounds of Structure (I) are modulators of the NLRP3 inflammasome.

In a specific embodiment, pharmaceutical compositions of the compounds of Structure (I) inhibit NEK7 when administered to a patient or a biological sample.

A pharmaceutical composition, as used herein, refers to a mixture of one or more compounds selected from compounds of Structure (I) with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. In certain embodiments, the pharmaceutical composition facilitates administration of the compound to an organism. In some embodiments, therapeutically effective amounts of one or more compounds selected from compounds of Structure (I) provided herein are administered in a pharmaceutical composition to a mammal having a disease, disorder or medical condition to be treated. In specific embodiments, the mammal is a human. In certain embodiments,

therapeutically effective amounts vary depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. The compounds described herein are used singly or in combination with one or more therapeutic agents as components of mixtures.

In one embodiment, one or more compounds selected from compounds of Structure (I) are formulated in aqueous solutions. In specific embodiments, the aqueous solution is selected from, by way of example only, a physiologically compatible buffer, such as Hank's solution, Ringer's solution, or physiological saline buffer. In other embodiments, one or more compounds selected from compounds of Structure (I) are formulated for trans-mucosal administration. In specific embodiments, trans-mucosal formulations include penetrants that are appropriate to the barrier to be permeated. In still other embodiments wherein the compounds described herein are formulated for other parenteral injections, appropriate formulations include aqueous or non-aqueous solutions. In specific embodiments, such solutions include physiologically compatible buffers and/or excipients.

In another embodiment, compounds described herein are formulated for oral administration. Compounds described herein are formulated by combining the active compounds with, *e.g.*, pharmaceutically acceptable carriers or excipients. In various embodiments, the compounds described herein are formulated in oral dosage forms that include, by way of example only, tablets, powders, pills, dragees, capsules, liquids, gels, syrups, elixirs, slurries, suspensions and the like.

In certain embodiments, pharmaceutical preparations for oral use are obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as: for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. In specific embodiments, disintegrating agents are optionally added.

Disintegrating agents include, by way of example only, cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

In one embodiment, dosage forms, such as dragee cores and tablets, are provided with one or more suitable coating. In specific embodiments, concentrated sugar solutions are used for coating the dosage form. The sugar solutions, optionally contain additional components, such as by way of example only, gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs and/or pigments are also optionally added to the coatings for identification purposes. Additionally, the dyestuffs and/or pigments are optionally utilized to characterize different combinations of active compound doses.

In certain embodiments, therapeutically effective amounts of at least one of the compounds described herein are formulated into other oral dosage forms. Oral dosage forms include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. In specific embodiments, push-fit capsules contain the active ingredients in admixture with one or more filler. Fillers include, by way of example only, lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In other embodiments, soft capsules, contain one or more active compound that is dissolved or suspended in a suitable liquid. Suitable liquids include, by way of example only, one or more fatty oil, liquid paraffin, or liquid polyethylene glycol. In addition, stabilizers are optionally added.

In still other embodiments, the compounds described herein are formulated for parental injection, including formulations suitable for bolus injection or continuous infusion. In specific embodiments, formulations for injection are presented in unit dosage form (*e.g.*, in ampoules) or in multi-dose containers. Preservatives are, optionally, added to the injection formulations. In still other embodiments, the pharmaceutical compositions are formulated in a form suitable for parenteral injection as sterile suspensions, solutions or emulsions in oily or aqueous vehicles. Parenteral injection formulations optionally contain formulatory agents such as suspending,

stabilizing and/or dispersing agents. In specific embodiments, pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. In additional embodiments, suspensions of one or more compounds selected from compounds of Structure (I) are prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles for use in the pharmaceutical compositions described herein include, by way of example only, fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. In certain specific embodiments, aqueous injection suspensions contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension contains suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, in other embodiments, the active ingredient is in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

Pharmaceutical compositions include at least one pharmaceutically acceptable carrier, diluent, or excipient, and one or more compounds selected from compounds of Structure (I), described herein as an active ingredient. The active ingredient is in free-acid or free-base form, or in a pharmaceutically acceptable salt form. In addition, the methods and pharmaceutical compositions described herein include the use of N-oxides, crystalline forms (also known as polymorphs), as well as active metabolites of these compounds having the same type of activity. All tautomers of the compounds described herein are included within the scope of the compounds presented herein. Additionally, the compounds described herein encompass un-solvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein. In addition, the pharmaceutical compositions optionally include other medicinal or pharmaceutical agents, carriers, adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure, buffers, and/or other therapeutically valuable substances.

Methods for the preparation of compositions comprising the compounds described herein include formulating the compounds with one or more inert,

pharmaceutically acceptable excipients or carriers to form a solid, semi-solid or liquid. Solid compositions include, but are not limited to, powders, tablets, dispersible granules, capsules, cachets, and suppositories. Liquid compositions include solutions in which a compound is dissolved, emulsions comprising a compound, or a solution containing liposomes, micelles, or nanoparticles comprising a compound as disclosed herein. Semi-solid compositions include, but are not limited to, gels, suspensions and creams. The form of the pharmaceutical compositions described herein include liquid solutions or suspensions, solid forms suitable for solution or suspension in a liquid prior to use, or as emulsions. These compositions also optionally contain minor amounts of nontoxic, auxiliary substances, such as wetting or emulsifying agents, pH buffering agents, and so forth.

In some embodiments, pharmaceutical compositions comprising one or more compounds selected from compounds of Structure (I) illustratively takes the form of a liquid where the agents are present in solution, in suspension or both. Typically when the composition is administered as a suspension, a first portion of the agent is present in solution and a second portion of the agent is present in particulate form, in suspension in a liquid matrix. In some embodiments, a liquid composition includes a gel formulation. In other embodiments, the liquid composition is aqueous.

In certain embodiments, aqueous suspensions contain one or more polymers as suspending agents. Polymers include water-soluble polymers such as cellulosic polymers, *e.g.*, hydroxypropyl methylcellulose, and water-insoluble polymers such as cross-linked carboxyl-containing polymers. Certain pharmaceutical compositions described herein comprise a mucoadhesive polymer, selected for example from carboxymethylcellulose, carbomer (acrylic acid polymer), poly(methylmethacrylate), polyacrylamide, polycarbophil, acrylic acid/butyl acrylate copolymer, sodium alginate and dextran.

Pharmaceutical compositions also, optionally, include solubilizing agents to aid in the solubility of one or more compounds selected from compounds of Structure (I). The term "solubilizing agent" generally includes agents that result in formation of a micellar solution or a true solution of the agent. Certain acceptable nonionic surfactants,

for example polysorbate 80, are useful as solubilizing agents, as can ophthalmically acceptable glycols, polyglycols, *e.g.*, polyethylene glycol 400, and glycol ethers.

Furthermore, pharmaceutical compositions optionally include one or more pH adjusting agents or buffering agents, including acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymethylaminomethane; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases and buffers are included in an amount required to maintain pH of the composition in an acceptable range.

Compositions also, optionally, include one or more salts in an amount required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate.

Other pharmaceutical compositions optionally include one or more preservatives to inhibit microbial activity. Suitable preservatives include mercury-containing substances such as merfen and thiomersal; stabilized chlorine dioxide; and quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium bromide and cetylpyridinium chloride.

Compositions may include one or more surfactants to enhance physical stability or for other purposes. Suitable nonionic surfactants include polyoxyethylene fatty acid glycerides and vegetable oils, *e.g.*, polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, *e.g.*, octoxynol 10, octoxynol 40.

Compositions may include one or more antioxidants to enhance chemical stability where required. Suitable antioxidants include, by way of example only, ascorbic acid and sodium metabisulfite.

In certain embodiments, aqueous suspension compositions are packaged in single-dose non-re-closable containers. Alternatively, multiple-dose re-closable containers are used, in which case it is typical to include a preservative in the composition.

In alternative embodiments, other delivery systems for hydrophobic pharmaceutical compounds are employed. Liposomes and emulsions are examples of delivery vehicles or carriers useful herein. In certain embodiments, organic solvents such as N-methylpyrrolidone are also employed. In additional embodiments, the compounds described herein are delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials are useful herein. In some embodiments, sustained-release capsules release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization are employed.

In certain embodiments, the formulations described herein comprise one or more antioxidants, metal chelating agents, thiol containing compounds and/or other general stabilizing agents. Examples of such stabilizing agents, include, but are not limited to: (a) about 0.5% to about 2% w/v glycerol, (b) about 0.1% to about 1% w/v methionine, (c) about 0.1% to about 2% w/v monothioglycerol, (d) about 1 mM to about 10 mM EDTA, (e) about 0.01% to about 2% w/v ascorbic acid, (f) 0.003% to about 0.02% w/v polysorbate 80, (g) 0.001% to about 0.05% w/v. polysorbate 20, (h) arginine, (i) heparin, (j) dextran sulfate, (k) cyclodextrins, (l) pentosan polysulfate and other heparinoids, (m) divalent cations such as magnesium and zinc; or (n) combinations thereof.

In some embodiments, the concentration of one or more compounds selected from compounds of Structure (I) provided in the pharmaceutical compositions of the present disclosure is greater than 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19.75%, 19.50%, 19.25% 19%, 18.75%, 18.50%, 18.25% 18%, 17.75%, 17.50%, 17.25% 17%, 16.75%, 16.50%, 16.25% 16%, 15.75%, 15.50%, 15.25% 15%, 14.75%, 14.50%, 14.25% 14%, 13.75%, 13.50%, 13.25% 13%, 12.75%, 12.50%, 12.25% 12%, 11.75%, 11.50%, 11.25% 11%, 10.75%, 10.50%, 10.25% 10%, 9.75%, 9.50%, 9.25% 9%, 8.75%, 8.50%, 8.25% 8%, 7.75%, 7.50%, 7.25% 7%, 6.75%, 6.50%, 6.25% 6%, 5.75%, 5.50%, 5.25% 5%, 4.75%, 4.50%, 4.25%, 4%, 3.75%, 3.50%, 3.25%, 3%, 2.75%, 2.50%, 2.25%, 2%, 1.75%, 1.50%, 125% , 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%,

0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002%, or 0.0001% w/w, w/v, or v/v.

In some embodiments, the concentration of one or more compounds selected from compounds of Structure (I) provided in the pharmaceutical compositions of the present disclosure is in the range from approximately 0.0001% to approximately 50%, approximately 0.001% to approximately 40 %, approximately 0.01% to approximately 30%, approximately 0.02% to approximately 29%, approximately 0.03% to approximately 28%, approximately 0.04% to approximately 27%, approximately 0.05% to approximately 26%, approximately 0.06% to approximately 25%, approximately 0.07% to approximately 24%, approximately 0.08% to approximately 23%, approximately 0.09% to approximately 22%, approximately 0.1% to approximately 21%, approximately 0.2% to approximately 20%, approximately 0.3% to approximately 19%, approximately 0.4% to approximately 18%, approximately 0.5% to approximately 17%, approximately 0.6% to approximately 16%, approximately 0.7% to approximately 15%, approximately 0.8% to approximately 14%, approximately 0.9% to approximately 12%, approximately 1% to approximately 10% w/w, w/v or v/v.

In some embodiments, the amount the one or more compounds selected from compounds of Structure (I) provided in the pharmaceutical compositions of the present disclosure is equal to or less than 10 g, 9.5 g, 9.0 g, 8.5 g, 8.0 g, 7.5 g, 7.0 g, 6.5 g, 6.0 g, 5.5 g, 5.0 g, 4.5 g, 4.0 g, 3.5 g, 3.0 g, 2.5 g, 2.0 g, 1.5 g, 1.0 g, 0.95 g, 0.9 g, 0.85 g, 0.8 g, 0.75 g, 0.7 g, 0.65 g, 0.6 g, 0.55 g, 0.5 g, 0.45 g, 0.4 g, 0.35 g, 0.3 g, 0.25 g, 0.2 g, 0.15 g, 0.1 g, 0.09 g, 0.08 g, 0.07 g, 0.06 g, 0.05 g, 0.04 g, 0.03 g, 0.02 g, 0.01 g, 0.009 g, 0.008 g, 0.007 g, 0.006 g, 0.005 g, 0.004 g, 0.003 g, 0.002 g, 0.001 g, 0.0009 g, 0.0008 g, 0.0007 g, 0.0006 g, 0.0005 g, 0.0004 g, 0.0003 g, 0.0002 g, or 0.0001 g.

In some embodiments, the amount of the one or more compounds selected from compounds of Structure (I) provided in the pharmaceutical compositions of the present disclosure is in the range of 0.0001-10 g, 0.0005-9 g, 0.001-8 g, 0.005-7 g, 0.01-6 g, 0.05-5 g, 0.1-4 g, 0.5-4 g, or 1-3 g.

Packaging materials for use in packaging pharmaceutical compositions described herein include those found in, *e.g.*, U.S. Pat. Nos. 5,323,907, 5,052,558 and

5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. For example, the container(s) includes one or more compounds described herein, optionally in a composition or in combination with another agent as disclosed herein. The container(s) optionally have a sterile access port (for example the container is an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). Such kits optionally comprise a compound with an identifying description or label or instructions relating to its use in the methods described herein.

For example, a kit typically includes one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for use of a compound described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also typically be included. A label is optionally on or associated with the container. For example, a label is on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself, a label is associated with a container when it is present within a receptacle or carrier that also holds the container, *e.g.*, as a package insert. In addition, a label is used to indicate that the contents are to be used for a specific therapeutic application. In addition, the label indicates directions for use of the contents, such as in the methods described herein. In certain embodiments, the pharmaceutical compositions are presented in a pack or dispenser device which contains one or more unit dosage forms containing a compound provided herein. The pack for example contains metal or plastic foil, such as a blister pack. Or, the pack or dispenser device is accompanied by instructions for administration. Or, the pack or dispenser is accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human

or veterinary administration. Such notice, for example, is the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. In some embodiments, compositions containing a compound provided herein formulated in a compatible pharmaceutical carrier are prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

Methods

Embodiments of the present disclosure are useful as modulators of the NLRP3 inflammasome via the inhibition of NEK7 in a host species. Therefore, the compounds of Structure (I) are also useful in the treatment of conditions mediated by effector signaling molecules like IL-1β and IL-18.

The host or patient can belong to any mammalian species, for example a primate species, particularly humans; rodents, including mice, rats and hamsters; rabbits; horses, cows, dogs, cats, *etc*. Animal models are of interest for experimental investigations, providing a model for treatment of human disease.

In one embodiment, the present disclosure is useful as an inhibitor of the NLRP3 inflammasome activation mechanism. Therefore, the compounds of Structure (I) are also useful in the treatment of conditions resulting from that activation in a host species.

In another embodiment, the compounds of Structure (I) are useful as inhibitors of the NLRP3 (protein) -NEK7 (protein) interaction. Therefore, the compounds are also useful in the treatment of conditions resulting from the association of NLRP3-NEK7 in a host species.

In certain embodiments, the compounds of Structure (I) are useful in treating human conditions mediated by effectors selected from the group consisting of IL-1β, IL-18, and caspase-1.

Embodiments of the disclosure also relate to the use of compounds according to Structure (I) and/or physiologically acceptable salts thereof for the prophylactic or therapeutic treatment and/or monitoring of diseases that are caused, mediated and/or modulated by the NLRP3 inflammasome activity. Furthermore, embodiments of the disclosure relate to the use of compounds according to Structure (I) and/or

physiologically acceptable salts thereof for the production of a medicament for the prophylactic or therapeutic treatment and/or monitoring of diseases that are caused, mediated and/or modulated by NLRP3 inflammasome activity. In certain embodiments, the disclosure provides the use of a compound according to Structure I or physiologically acceptable salts thereof, for the production of a medicament for the prophylactic or therapeutic treatment of a NLRP3 -mediated disorder.

In another embodiment, the present disclosure relates to a method of treating inflammatory diseases or conditions mediated by NLRP3 inflammasome by administering to a patient in need thereof a therapeutically effective amount of the compound of Structure (I).

In certain embodiments, the diseases which can be treated with a compound of Structure (I) include type II diabetes, atherosclerosis, Alzheimer's disease, aging, fatty liver, metabolic syndrome, asthma, psoriasis, obesity, acute and chronic tissue damage caused by infection, gout, arthritis, enteritis, hepatitis, peritonitis, silicosis, UV-induced skin sunburn, contact hypersensitivity, sepsis, cancer, neurodegenerative disease, multiple sclerosis, Muckle-Wells syndrome, and combinations thereof.

In certain other embodiments, the compounds of Structure (I) are used in methods for treatment of disorders or diseases selected from auto-immune, inflammatory disorders, cardiovascular diseases, neurodegenerative disorders, bacterial and viral infections, allergy, asthma, pancreatitis, multi-organ failure, kidney diseases, platelet aggregation, cancer, transplantation, sperm motility, erythrocyte deficiency, graft rejection, lung injuries, respiratory diseases, ischemic conditions, cancer, and combinations thereof.

In some embodiments, the disorders associated with NEK7 which are treatable with a compound of Structure (I) are selected from rheumatoid arthritis, psoriatic arthritis, osteoarthritis, systemic lupus erythematosus, lupus nephritis, ankylosing spondylitis, osteoporosis, systemic sclerosis, multiple sclerosis, psoriasis, type I diabetes, type II diabetes, inflammatory bowel disease (Crohn's Disease and ulcerative colitis), hyperimmunoglobulinemia D and periodic fever syndrome, cryopyrin associated periodic syndromes, Schnitzler's syndrome, systemic juvenile idiopathic arthritis, adult's onset Still's disease, gout, pseudogout, SAPHO syndrome, Castleman's

disease, sepsis, stroke, atherosclerosis, celiac disease, DIRA (Deficiency of IL-l Receptor Antagonist), Alzheimer's disease, Parkinson's disease, cancer, and combinations thereof.

Also included herein are methods of treatment in which at least one compound of Structure (I) is administered in combination with an anti-inflammatory or a therapeutic agent. Anti-inflammatory agents include but are not limited to NSAIDs, non-specific and COX-2 specific cyclooxygenase enzyme inhibitors, gold compounds, corticosteroids, methotrexate, tumor necrosis factor (TNF) antagonists, immunosuppressants and methotrexate. Examples of NSAIDs include, but are not limited to, ibuprofen, flurbiprofen, naproxen and naproxen sodium, diclofenac, combinations of diclofenac sodium and misoprostol, sulindac, oxaprozin, diflunisal, piroxicam, indomethacin, etodolac, fenoprofen calcium, ketoprofen, sodium nabumetone, sulfasalazine, tolmetin sodium, hydroxychloroquine, and combinations thereof.

Examples of NSAIDs also include COX-2 specific inhibitors such as celecoxib, valdecoxib, lumiracoxib, and/or etoricoxib.

In some embodiments, the anti-inflammatory agent is a salicylate. Salicylates include by are not limited to acetylsalicylic acid or aspirin, sodium salicylate, and choline and magnesium salicylates.

The anti-inflammatory agent may also be a corticosteroid. For example, the corticosteroid may be cortisone, dexamethasone, methylprednisolone, prednisolone, prednisolone sodium phosphate, or prednisone.

In additional embodiments the anti-inflammatory agent is a gold compound such as gold sodium thiomalate or auranofin.

The disclosure also includes embodiments in which the anti-inflammatory agent is a metabolic inhibitor such as a dihydrofolate reductase inhibitor, such as methotrexate or a dihydroorotate dehydrogenase inhibitor, such as leflunomide.

Therapeutic agents can also include agents for pain and inflammation such as histamine and histamine antagonists, bradykinin and bradykinin antagonists, 5-hydroxytryptamine (serotonin), lipid substances that are generated by biotransformation of the products of the selective hydrolysis of membrane phospholipids, eicosanoids,

prostaglandins, thromboxanes, leukotrienes, aspirin, nonsteroidal anti-inflammatory agents, analgesic-antipyretic agents, agents that inhibit the synthesis of prostaglandins and thromboxanes, selective inhibitors of the inducible cyclooxygenase, selective inhibitors of the inducible cyclooxygenase-2, autacoids, paracrine hormones, somatostatin, gastrin, cytokines that mediate interactions involved in humoral and cellular immune responses, lipid-derived autacoids, eicosanoids, β-adrenergic agonists, ipratropium, glucocorticoids, methylxanthines, sodium channel blockers, opioid receptor agonists, calcium channel blockers, membrane stabilizers and leukotriene inhibitors.

Other embodiments of the disclosure pertain to combinations in which at least one anti-inflammatory compound is an anti-monoclonal antibody (such as eculizumab or pexelizumab), a TNF antagonist, such as entanercept, or infliximab, which is an anti-TNF alpha monoclonal antibody.

Therapeutic agents used in combination with the compounds of Structure (I) can also include small molecule compounds that inhibit the activation of NLRP3 inflammasomes, such as MCC950, sulforaphane, iisoliquiritigenin, β-hydroxybutyrate, flufenamic acid, mefenamic acid, 3,4-methylenedioxy-β-nitrostyrene (MNS), and parthenolide.

Still other embodiments of the disclosure pertain to combinations in which at least one active agent is an immunosuppressant compound such as an immunosuppressant compound chosen from methotrexate, leflunomide, cyclosporine, tacrolimus, azathioprine, and mycophenolate mofetil.

The disclosed compounds of Structure (I) can be administered in combination with other known therapeutic agents, including anticancer agents. As used here, the term "anticancer agent" relates to any agent which is administered to a patient with cancer for the purposes of treating the cancer.

In some embodiments the anti-cancer agents belong to the following categories –

Alkylating agents: such as altretamine, bendamustine, busulfan, carmustine, chlorambucil, chlormethine, cyclophosphamide, dacarbazine, ifosfamide, improsulfan, tosilate, lomustine, melphalan, mitobronitol, mitolactol, nimustine, ranimustine,

temozolomide, thiotepa, treosulfan, mechloretamine, carboquone; apaziquone, fotemustine, glufosfamide, palifosfamide, pipobroman, trofosfamide, uramustine, TH-3024, VAL-0834;

Platinum Compounds: such as carboplatin, cisplatin, eptaplatin, miriplatine hydrate, oxaliplatin, lobaplatin, nedaplatin, picoplatin, satraplatin; lobaplatin, nedaplatin, picoplatin, satraplatin;

DNA altering agents: such as amrubicin, bisantrene, decitabine, mitoxantrone, procarbazine, trabectedin, clofarabine; amsacrine, brostallicin, pixantrone, laromustine;

Topoisomerase Inhibitors: such as etoposide, irinotecan, razoxane, sobuzoxane, teniposide, topotecan; amonafide, belotecan, elliptinium acetate, voreloxin;

Microtubule modifiers: such as cabazitaxel, docetaxel, eribulin, ixabepilone, paclitaxel, vinblastine, vincristine, vinorelbine, vindesine, vinflunine; fosbretabulin, tesetaxel;

Antimetabolites: such as asparaginase3, azacitidine, calcium levofolinate, capecitabine, cladribine, cytarabine, enocitabine, floxuridine, fludarabine, fluorouracil, gemcitabine, mercaptopurine, methotrexate, nelarabine, pemetrexed, pralatrexate, azathioprine, thioguanine, carmofur; doxifluridine, elacytarabine, raltitrexed, sapacitabine, tegafur, trimetrexate;

Anticancer antibiotics: such as bleomycin, dactinomycin, doxorubicin, epirubicin, idarubicin, levamisole, miltefosine, mitomycin C, romidepsin, streptozocin, valrubicin, zinostatin, zorubicin, daunurobicin, plicamycin; aclarubicin, peplomycin, pirarubicin;

Hormones/Antagonists: such as abarelix, abiraterone, bicalutamide, buserelin, calusterone, chlorotrianisene, degarelix, dexamethasone, estradiol, fluocortolone fluoxymesterone, flutamide, fulvestrant, goserelin, histrelin, leuprorelin, megestrol, mitotane, nafarelin, nandrolone, nilutamide, octreotide, prednisolone, raloxifene, tamoxifen, thyrotropin alfa, toremifene, trilostane, triptorelin, diethylstilbestrol; acolbifene, danazol, deslorelin, epitiostanol, orteronel, enzalutamide;

Aromatase inhibitors: such as aminoglutethimide, anastrozole, exemestane, fadrozole, letrozole, testolactone; formestane;

Small molecule kinase inhibitors: such as crizotinib, dasatinib, erlotinib, imatinib, lapatinib, nilotinib, pazopanib, regorafenib, ruxolitinib, sorafenib, sunitinib, vandetanib, vemurafenib, bosutinib, gefitinib, axitinib; afatinib, alisertib, dabrafenib, dacomitinib, dinaciclib, dovitinib, enzastaurin, nintedanib, lenvatinib, linifanib, linsitinib, masitinib, midostaurin, motesanib, neratinib, orantinib, perifosine, ponatinib, radotinib, rigosertib, tipifamib, tivantinib, tivozanib, trametinib, pimasertib, brivanib alaninate, cediranib.

In some embodiments, medicaments which are administered in conjunction with the compounds described herein include any suitable drugs usefully delivered by inhalation for example, analgesics, *e.g.* codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, *e.g.* diltiazem; antiallergics, *e.g.* cromoglycate, ketotifen or nedocromil; anti-infectives, *e.g.* cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines or pentamidine; antihistamines, *e.g.* methapyrilene; anti-inflammatories, *e.g.* beclomethasone, flunisolide, budesonide, tipredane, triamcinolone acetonide or fluticasone; antitussives, *e.g.* noscapine; bronchodilators, *e.g.* ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, salbutamol, salmeterol, terbutalin, isoetharine, tulobuterol, orciprenaline or (-)-4-amino-3,5-dichloro-α-[[[6-[2-(2-pyridinyl)ethoxy]hexyl]-amino]methyl]benzenemethanol; diuretics, *e.g.*, amiloride; anticholinergics, *e.g.*, ipratropium, atropine or oxitropium; hormones, *e.g.*, cortisone, hydrocortisone or prednisolone; xanthines, *e.g.*, aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; and therapeutic proteins and peptides, *e.g.*, insulin or glucagon. It will be clear to a person skilled in the art that, where appropriate, the medicaments are used in the form of salts (*e.g.*, as alkali metal or amine salts or as acid addition salts) or as esters (*e.g.*, lower alkyl esters) or as solvates (*e.g.*, hydrates) to optimize the activity and/or stability of the medicament.

The agents disclosed herein or other suitable agents are administered depending on the condition being treated. Hence, in some embodiments the one or more compounds of the disclosure will be co-administered with other agents as described above. When used in combination therapy, the compounds described herein are administered with the second agent simultaneously or separately. This administration in

combination can include simultaneous administration of the two agents in the same dosage form, simultaneous administration in separate dosage forms, and separate administration. That is, a compound described herein and any of the agents described above can be formulated together in the same dosage form and administered simultaneously. Alternatively, a compound of the disclosure and any of the agents described above can be simultaneously administered, wherein both the agents are present in separate formulations. In another alternative, a compound of the present disclosure can be administered just followed by and any of the agents described above, or vice versa. In some embodiments of the separate administration protocol, a compound of the disclosure and any of the agents described above are administered a few minutes apart, or a few hours apart, or a few days apart.

In some embodiments, the compounds of Structure (I) are administered as a mono-therapy.

For identification of a signal transduction or a mechanistic pathway and for detection of interactions between various signal transduction pathways, various scientists have developed suitable models or model systems, for example cell culture models and models of transgenic animals. For the determination of certain stages in the signal transduction cascade, interacting compounds can be utilized in order to modulate the signal. The compounds of embodiments of the disclosure can also be used as reagents for testing NEK7-dependent signal transduction pathways in animals and/or cell culture models or in the clinical diseases mentioned in this application.

The methods of embodiments of embodiments of the disclosure can be performed either *in vitro* or *in vivo*. The susceptibility of a particular cell to treatment with the compounds of Structure (I) can be particularly determined by *in vitro* tests, whether in the course of research or clinical application. Typically, a culture of the cell is combined with a compound at various concentrations for a period of time which is sufficient to allow the active agents to inhibit NEK7 activity, usually between about one hour and one week. In-vitro treatment can be carried out using cultivated cells from a biopsy sample or cell line.

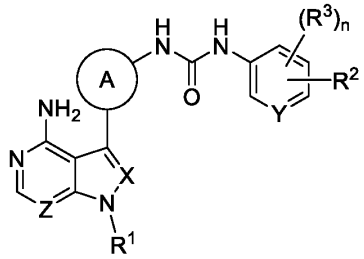
In some embodiments, the IC_{50} of the compounds of Structure (I) to inhibit NEK7 was determined by the concentration of the compound required to inhibit 50% of

the activity of the NEK kinase. The compounds of Structure (I) exhibited potency values of IC_{50} of less than about 5 mM, preferably less than about 1 mM and even more preferably less than about 0.100 mM as described in further detail in the Examples.

The examples and preparations provided below further illustrate and exemplify the compounds of the present disclosure and methods of preparing and testing such compounds. It is to be understood that the scope of the present disclosure is not limited in any way by the scope of the following examples and preparations. In the following examples, and throughout the specification and claims, molecules with a single stereocenter, unless otherwise noted, exist as a racemic mixture. Those molecules with two or more stereocenters, unless otherwise noted, exist as a racemic mixture of diastereomers. Single enantiomers/diastereomers may be obtained by methods known to those skilled in the art.

Methods for producing the compounds described herein is provided below. In general, starting components may be obtained from sources such as Sigma Aldrich, Lancaster Synthesis, Inc., Maybridge, Matrix Scientific, TCI, and Fluorochem USA, etc. or synthesized according to sources known to those skilled in the art (see, for example, Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 5th edition (Wiley, December 2000)) or prepared as described herein.

The following examples illustrate exemplary methods for preparation of compounds of Structure (I):



(I)

or pharmaceutically acceptable salts, stereoisomers, or prodrug thereof, wherein each of A, X, Y, Z, R^1, R^2, R^3, and n are as defined herein.

It will also be appreciated by those skilled in the art that in the processes for preparing the compounds described herein the functional groups of intermediate

compounds may need to be protected by suitable protecting groups. Such functional groups include, but are not limited to, hydroxy, amino, mercapto, and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl or diarylalkylsilyl (for example, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl, benzyl, and the like. Suitable protecting groups for amino, amidino and guanidino include *t*-butoxycarbonyl, benzyloxycarbonyl, and the like. Suitable protecting groups for mercapto include -C(O)-R" (where R" is alkyl, aryl or arylalkyl), *p*-methoxybenzyl, trityl and the like. Suitable protecting groups for carboxylic acid include alkyl, aryl or arylalkyl esters. Protecting groups are optionally added or removed in accordance with standard techniques, which are known to one skilled in the art and as described herein. The use of protecting groups is described in detail in Green, T.W. and P.G.M. Wutz, *Protective Groups in Organic Synthesis* (1999), 3rd Ed., Wiley. As one of skill in the art would appreciate, the protecting group may also be a polymer resin such as a Wang resin, Rink resin or a 2-chlorotrityl-chloride resin.

It will also be appreciated by those skilled in the art, although such protected derivatives of compounds of this disclosure may not possess pharmacological activity as such, they may be administered to a mammal and thereafter metabolized in the body to form compounds of the disclosure which are pharmacologically active. Such derivatives may therefore be described as "prodrugs." Prodrugs of compounds of this disclosure are included within the scope of embodiments of the disclosure.

EXAMPLES

The following examples are provided for exemplary purposes.

General Procedures

All proton NMR experiments were recorded on a Bruker NEO Spectrometer equipped with a BBFO probe at 400 MHz. Deuterated solvents contained less than 0.05% v/v tetramethylsilane which was used as the reference signal (set at 0.00 ppm). When deuterated solvents did not contain tetramethylsilane, the residual nondeuterated solvent peaks were used as a reference signal, as per published guidelines (*J. Org. Chem.* 1997, 62(21), 7512-7515). Chemical shifts are expressed in parts per million

(ppm, δ units). Coupling constants are in hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), qt (quintuplet) or brs (broad signal).

LC/MS analyses were performed on an Agilent Technologies UHPLC 1290 Infinity II with a G6125 MS detector.

Microwave reactions were conducted with a Monowave 300 by Anton Paar GmbH using standard protocols.

NEK7 Enzymatic Assay

Casein substrate (from bovine milk, hydrolyzed and partially dephosphorylated mixture of α, β and κ caseins, obtained from Sigma Aldrich, catalogue # C4765, diluted in distilled water to a final concentration of 1 mg/mL) and full-length recombinant human NEK7 (expressed by baculovirus in Sf9 insect cells using a N-terminal GST tag, obtained from SignalChem, catalogue # N09-10G, 0.1 μg/μL) were mixed in assay buffer (20 mM Hepes pH 7.5, 10 mM $MgCl_2$, 1 mM EGTA, 0.02% Brij35, 0.02 mg/ml BSA, 0.1 mM Na_3VO_4, 2 mM DTT, 1% DMSO). Compounds of interest (serial 3-fold dilution in DMSO from 10 μM to 0.5 nM) or vehicle (1% DMSO) were dispensed into the kinase reaction mixture by Acoustic technology (Echo550; nanoliter range). After incubation at room temperature for 20 minutes, the kinase reaction was initiated by addition of [^{33}P]-ATP (specific activity 10 μCi/μl) and the mixture was incubated at room temperature for 2 hours. The reaction was then stopped by spotting the reaction mixture on strips of phosphocellulose P81 paper. Following washing, the radioactivity of the P81 paper was measured and kinase activity data were expressed as the percent remaining kinase activity in test samples compared to vehicle reactions. IC_{50} values and curve fits were obtained using Prism (GraphPad Software).

IL-1β Release Assay

Approximately 1.5 million THP-1 cells were plated in each well of a 6-well TC plate and incubated with 40 nM PMA in RPMI (10% FBS, 1% Penstrep) for 24 hours. The media was then removed and cells were rested in RPMI (10% FBS, 1% Penstrep) for 24 hours after which time the media was removed and cells were pre-treated for 2

hours with various concentrations of compounds of interest (typically serial 3-fold dilution in RPMI + 5% FBS, concentrations ranging from 1 μM to 0.5 nM) in RPMI (5% FBS). The media was again removed and cells were incubated with 250 ng/mL LPS and compounds of interest (concentrations as above) in RMPI (5% FBS) for 2 hours. The media was removed for a last time and cells were incubated with 20 μM nigericin and compounds of interest (concentrations as above) in Opti-MEM for 30 minutes. Cell media was then collected and the amount of cleaved IL-1β was determined using a JESS instrument (Protein Simple) and standard protocols. Cleaved Il-1β antibody was obtained from Cell Signaling (catalogue #83186S) and was used at 1:20 dilution in antibody diluent 2. Protein Simple 1x anti-Rabbit HRP secondary antibody was used along with Protein Simple luminol and peroxide for chemiluminescent detection. Primary antibody incubation time was increased from 30 minutes to 60 minutes.

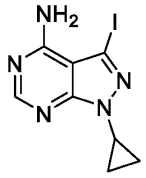
Abbreviations

°C (degree Celsius); ^{1}H NMR (proton Nuclear Magnetic Resonance); ACN (acetonitrile); AIBN (azobisisobutyronitrile); bipy (2,2′-bipyridine); $(Boc)_2O$ (di-*tert*-butyl dicarbonate); $Cu(OAC)_2$ (copper (II) acetate); DCE (dichloroethane); DCM (dichloromethane); DIPEA (*N*,*N*-diisopropylethylamine); DMAP (4-dimethylaminopyridine); DMF (*N*,*N*-dimethylformamide); DMSO-d_6 (deuterated dimethylsulfoxide); eq. (equivalent); EtOAc (ethyl acetate); g (gram); h (hour); HPLC (High Performance Liquid Chromatography); LC-MS (Liquid Chromatography Mass Spectrometry); MeOH (methanol); mg (milligram); min (minute); mL (milliliter); mmol (millimole); MsCl (methanesulfonyl chloride); NBS (N-bromosuccinimide); NIS (N-iodosuccinimide); $Pd_2(dba)_3$ (tris(dibenzylideneacetone)dipalladium(0)); $Pd(PPh_3)_4$ (palladium-tetrakis(triphenylphosphine)); $PdCl_2(dppf)$ ([1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride); STAB (sodium triacetoxyborohydride); TBAF (tetra-*n*-butylammonium fluoride); TEA (triethylamine); TFA (trifluoroacetic acid); THF (tetrahydrofuran); TLC (Thin Layer Chromatography); XPhos (2-sicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl).

Preparation of Synthetic Intermediates

INTERMEDIATE A1

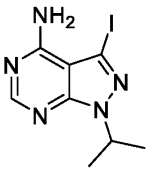
1-CYCLOPROPYL-3-IODO-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-4-AMINE



$Cu(OAc)_2$ (0.348 g, 1.916 mmol), bipy (0.299 g, 1.916 mmol), and $NaHCO_3$ (0.322 g, 3.830 mmol) were added to a stirred solution of 3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.500 g, 1.916 mmol) and cyclopropylboronic acid (0.329 g, 3.830 mmol) in dichloroethane (10 mL). The resulting mixture was stirred at 70 °C under oxygen atmosphere for 12 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was filtered through a pad of Celite® (*i.e.*, diatomaceous earth) which was then rinsed with DCM (2 × 20 mL). The combined filtrates were washed with water (20 mL) and brine (25 mL), the organic layer separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield crude material which was purified by flash chromatography (silica gel 230-400 mesh, eluting with 20% EtOAc in petroleum ether), giving the title compound as an off-white solid (0.24 g, 36% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.21 (s, 1H), 3.74-3.79 (m, 1H), 1.11-1.15 (m, 2H), 1.04-1.09 (m, 2H). LCMS: 301.8 [M+H].

INTERMEDIATE A2

3-IODO-1-ISOPROPYL-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-4-AMINE

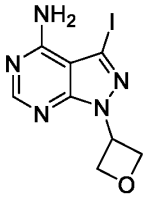


Cs_2CO_3 (12.38 g, 38.31 mmol) and 2-iodopropane (3.60 g, 21.16 mmol) were added to a stirred solution of 3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (5.00 g, 19.15 mmol) in DMF (25 mL). The reaction mixture was stirred at 90 °C for 16 h in a

sealed tube and, following completion of the reaction (as indicated by TLC), was poured into crushed ice (50 g) and stirred for 15 min. The resulting solid was filtered, washed with water (2 × 5 mL), and dried to afford the title compound as an off-white solid (3.25 g, 56% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.18 (s, 1H), 4.93-4.99 (m, 1H), 1.42 (d, *J* = 6.8 Hz, 6H). LCMS: 303.8 [M+H].

INTERMEDIATE A3

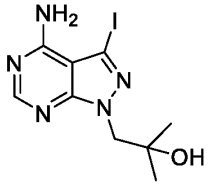
3-IODO-1-(OXETAN-3-YL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-4-AMINE



The title compound was prepared via a similar procedure described for intermediate A2, replacing 2-iodopropane with 3-iodooxetane. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.21 (s, 1H), 5.89-5.93 (m, 1H), 4.93-5.00 (m, 4H). LCMS: 318.0 [M+H].

INTERMEDIATE A4

1-(4-AMINO-3-IODO-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-1-YL)-2-METHYLPROPAN-2-OL



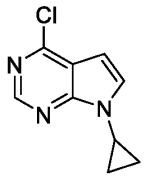
NaH_2PO_4 (0.044 g, 0.372 mmol) was added to a mixture of 3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.100 g, 0.380 mmol), 2,2-dimethyloxirane (0.055 g, 0.760 mmol), and K_2CO_3 (0.050 g, 0.372 mmol) in acetonitrile (3 mL) and water (1 mL) and the resulting solution was subjected to microwave irradiation at 150 °C for 1 h. Following completion of the reaction (as indicated by TLC), the solvents were removed under reduced pressure to yield crude material which was purified by flash chromatography (silica gel 230-400 mesh, eluting with 25% EtOAc in petroleum ether),

giving the title compound as a pale brown solid (0.064 g, 51% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.20 (s, 1H), 4.19 (s, 2H), 1.09 (s, 6H). LCMS: 334.0 [M+H].

INTERMEDIATE A5

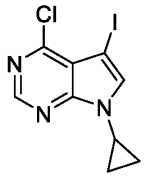
7-CYCLOPROPYL-5-IODO-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-4-AMINE

Step 1: Synthesis of 4-chloro-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidine



$NaHCO_3$ (10.94 g, 130.0 mmol), bipy (10.17 g, 65.1 mmol), and $Cu(OAc)_2$ (11.83 g, 65.1 mmol) were added to a solution of 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (10.00 g, 65.1 mmol) and cyclopropylboronic acid (11.19 g, 130.0 mmol) in DCE (150 mL) and the resulting mixture was stirred at 80 °C for 12 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was filtered through a pad of Celite® (*i.e.*, diatomaceous earth) which was then rinsed with DCM (2 × 100 mL). The combined filtrates were washed with water (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield crude material which was purified by GRACE (silica gel 230-400 mesh, eluting with 6% EtOAc in petroleum ether), giving the title compound as an off-white solid (7.30 g, 58% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.65 (s, 1H), 7.70 (d, *J* = 3.6 Hz, 1H), 6.59 (d, *J* = 4.0 Hz, 1H), 3.62-3.68 (m, 1H), 1.08-1.10 (m, 4H). LCMS: 194.0 [M+H].

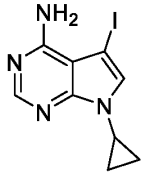
Step 2: Synthesis of 4-chloro-7-cyclopropyl-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine



NIS (8.25 g, 36.7 mmol) was added to a solution of 4-chloro-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (7.10 g, 36.7 mmol) in DMF (50 mL) at 0 °C and the resulting mixture was stirred at 25 °C for 12 h. Following completion of the reaction (as

indicated by TLC), the reaction mixture was poured into ice cold water (600 mL) and stirred at 25 °C for 15 min. The resulting precipitate was filtered, washed with water (2 × 250 mL), and dried under reduced pressure to afford the title product (8.30 g, 70 % yield) as a pale brown solid. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.65 (s, 1H), 7.94 (s, 1H), 3.62-3.68 (m, 1H), 1.05-1.10 (m, 1H). LCMS: 319.9 [M+H].

Step 3: Synthesis of 7-cyclopropyl-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine

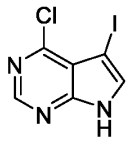


A mixture of 4-chloro-7-cyclopropyl-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine (8.3 g, 26 mmol) and ammonia (25% in water, 25 mL) in 1,4-dioxane (25 mL) was loaded in a tinyclave and stirred at 120 °C for 16 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was cooled to 25 °C and the resulting precipitate was filtered, washed with petroleum ether (2 × 50 mL), and dried to afford the title compound as an off-white solid (6.0 g, 76% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.11 (s, 1H), 7.38 (s, 1H), 6.59 (bs, 2H), 3.48-3.54 (m, 1H), 0.97-0.99 (m, 4H). LCMS: 300.9 [M+H].

INTERMEDIATE A6

5-IODO-7-METHYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-4-AMINE

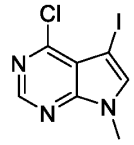
Step 1: Synthesis of 4-chloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine



NIS (7.33 g, 32.6 mmol) was added to a solution of 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (5.00 g, 32.6 mmol) in DMF (20 mL) at 0 °C and the resulting mixture was stirred at 25 °C for 12 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was poured into crushed ice (200 g) and stirred at 25 °C for 30 minutes. The resulting precipitate was filtered, washed with water (2 × 20 mL), and

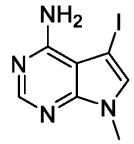
dried to afford the title compound as pale brown solid (8.52 g, 92% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 12.96 (bs, 1H), 8.60 (s, 1H), 7.94 (s, 1H). LCMS: 280.0 [M+H].

Step 2: Synthesis of 4-chloro-5-iodo-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine



A solution of 4-chloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine (0.500 g, 1.789 mmol) in THF (5 mL) was added dropwise to a stirred suspension of NaH (60% in mineral oil, 0.143 g, 3.580 mmol) in THF (15 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 30 min. Iodomethane (0.134 mL, 2.147 mmol) was then added and the resulting mixture was stirred at 25 °C for 4 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was quenched with water (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the title compound as an off-white solid (0.38 g, 71% yield). LCMS: 294.0 [M+H].

Step 3: Synthesis of 5-iodo-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine

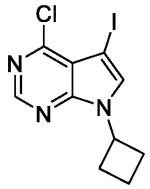


A mixture of 4-chloro-5-iodo-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (0.40 g, 1.363 mmol) and ammonia (25% in water, 4 mL) in 1,4-dioxane (4 mL) was subjected to microwave irradiation at 150 °C for 1 h. Following completion of the reaction (as indicated by LCMS), the reaction mixture was concentrated under reduced pressure to afford crude material which was purified by flash chromatography (silica gel 230-400 mesh, eluting with 10% MeOH in DCM), affording the title compound as an off-white solid (0.12 g, 32% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.10 (s, 1H), 7.42 (s, 1H), 6.59 (bs, 2H), 3.67 (s, 3H). LCMS: 275.0 [M+H].

INTERMEDIATE A7

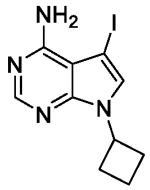
7-CYCLOBUTYL-5-IODO-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-4-AMINE

Step 1: Synthesis of 4-chloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine



Bromocyclobutane (0.580 g, 4.29 mmol) and K_2CO_3 (0.742 g, 5.37 mmol) were added to a solution of 4-chloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine (1.000 g, 3.58 mmol) in DMF (5 mL) and the resulting mixture was stirred at 80 °C for 16 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was poured into crushed ice (25 g). The resulting precipitate was filtered, washed with water (20 mL), and dried to give crude material which was purified by Isolera (silica gel 230-400 mesh, eluting with 20% EtOAc in petroleum), affording the title compound as an off-white solid (0.35 g, 29% yield). LCMS: 333.9 [M+H].

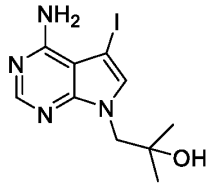
Step 2: Synthesis of 7-cyclobutyl-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine



A mixture of 4-chloro-7-cyclobutyl-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine (0.35 g, 1.049 mmol) and ammonia (25% in water, 4.5 mL) in 1,4-dioxane (4.5 mL) was subjected to microwave irradiation at 150 °C for 1 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was concentrated under reduced pressure to afford the title compound as an off-white solid (0.30 g, 83 % yield) which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.09 (s, 1H), 7.73 (s, 1H), 6.61 (bs, 2H), 5.09-5.16 (m, 1H), 2.50-2.50 (m, 2H), 2.31-2.38 (m, 2H), 1.75-1.83 (m, 2H). LCMS: 315.0 [M+H].

INTERMEDIATE A8

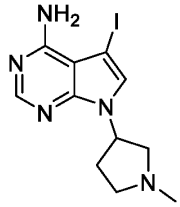
1-(4-AMINO-5-IODO-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-7-YL)-2-METHYLPROPAN-2-OL



The title compound was prepared as reported in PCT Publication No. WO 2021/226547 A2.

INTERMEDIATE A9

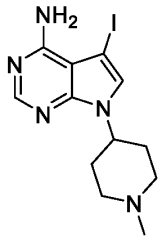
5-IODO-7-(1-METHYLPYRROLIDIN-3-YL)-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-4-AMINE



The title compound was prepared as reported in PCT Publication No. WO 2014/184069 A1.

INTERMEDIATE A10

5-IODO-7-(1-METHYLPIPERIDIN-4-YL)-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-4-AMINE

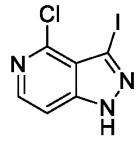


The title compound was prepared as reported in PCT Publication No. WO 2017/220477 A1.

INTERMEDIATE A11

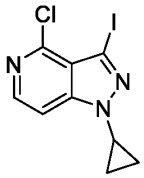
1-CYCLOPROPYL-*N*-(2,4-DIMETHOXYBENZYL)-3-IODO-1H-PYRAZOLO[4,3-*C*]PYRIDIN-4-AMINE

Step 1: Synthesis of 4-chloro-3-iodo-1H-pyrazolo[4,3-*c*]pyridine



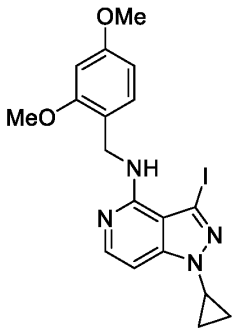
KOH (1.32 g, 23.0 mmol) and iodine (1.62 g, 12.8 mmol) were added to a solution of 4-chloro-1H-pyrazolo[4,3-*c*]pyridine (1.00 g, 6.4 mmol) in 1,4-dioxane (10 mL) and the resulting mixture was stirred at 75 °C for 4 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was filtered over a pad of Celite® (*i.e.*, diatomaceous earth). The resulting filtrate was concentrated under reduced pressure to give crude material which was purified by reverse-phase column chromatography, giving the title compound as a white solid (0.633 g, 63% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 14.12 (bs, 1H), 8.14 (d, *J* = 6.0 Hz, 1H), 7.66 (d, *J* = 5.6 Hz, 1H). LCMS: 279.9 [M+H].

Step 2: Synthesis of 4-chloro-1-cyclopropyl-3-iodo-1H-pyrazolo[4,3-*c*]pyridine



The title compound was prepared via a similar procedure described for intermediate A1, starting from 4-chloro-3-iodo-1H-pyrazolo[4,3-*c*]pyridine (0.630 g, 2.20 mmol) and cyclopropylboronic acid (0.329 g, 3.83 mmol), and was obtained as a white solid (0.430 g, 60% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.21 (d, *J* = 6.0 Hz, 1H), 7.81 (d, *J* = 5.6 Hz, 1H), 3.84-3.89 (m, 1H), 1.14-1.17 (m, 4H). LCMS: 319.7 [M+H].

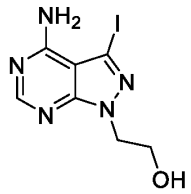
Step 3: Synthesis of 1-cyclopropyl-*N*-(2,4-dimethoxybenzyl)-3-iodo-1H-pyrazolo[4,3-*c*]pyridin-4-amine



A mixture of 4-chloro-1-cyclopropyl-3-iodo-1H-pyrazolo[4,3-*c*]pyridine (0.880 g, 2.75 mmol) and (2,4-dimethoxyphenyl)methanamine (1.245 mL, 8.26 mmol) in *n*BuOH (10 mL) was stirred at 110 °C for 12 h. Following completion of the reaction (as indicated by LCMS), the reaction mixture was concentrated under reduced pressure to afford crude material which was purified by Isolera (silica gel 230-400 mesh, eluting with 40% EtOAc in petroleum ether), giving the title product as a yellow gum (1.0 g, 80 % yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.81 (d, *J* = 6.4 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 6.0 Hz, 1H), 6.60 (d, *J* = 2.4 Hz, 1H), 6.53-6.56 (m, 1H), 6.45-6.47 (m, 1H), 4.62 (d, *J* = 5.6 Hz, 2H), 3.88 (s, 3H), 3.73 (s, 3H), 3.66-3.70 (m, 1H), 1.01-1.10 (m, 4H). LCMS: 451.0 [M+H].

INTERMEDIATE A12

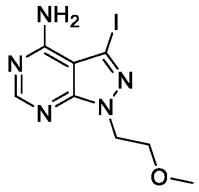
2-(4-AMINO-3-IODO-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-1-YL)ETHAN-1-OL



The title compound was prepared as reported in PCT Publication No. WO 2011/119663 A1.

INTERMEDIATE A13

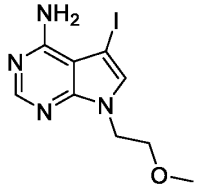
3-IODO-1-(2-METHOXYETHYL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-4-AMINE



K_2CO_3 (0.397 g, 2.870 mmol) and 1-bromo-2-methoxyethane (0.319 g, 2.299 mmol) were added to a solution of 3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.500 g, 1.916 mmol) in DMF (6 mL) and the resulting solution was stirred at 80 °C for 12 h in a sealed tube. Following completion of the reaction (as indicated by TLC), the reaction mixture was poured into crushed ice (25 g) and extracted with EtOAc (2 × 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title product (0.500 g, crude) which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.20 (s, 1H), 4.43 (t, *J* = 5.6 Hz, 2H), 3.75 (t, *J* = 5.6 Hz, 2H), 3.20 (s, 3H). LCMS: 319.8 [M+H].

INTERMEDIATE A14

5-IODO-7-(2-METHOXYETHYL)-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-4-AMINE

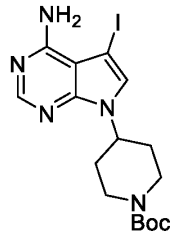


The title compound was prepared as reported in PCT Publication No. WO 2014/184069 A1.

INTERMEDIATE A15

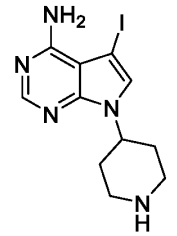
5-IODO-7-(1-(METHYLSULFONYL)PIPERIDIN-4-YL)-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-4-AMINE

Step 1: Synthesis of *tert*-butyl 4-(4-amino-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)piperidine-1-carboxylate



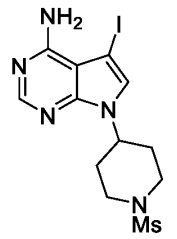
Cs_2CO_3 (3.76 g, 11.54 mmol) and *tert*-butyl 4-(tosyloxy)piperidine-1-carboxylate (synthesized as reported in PCT Publication No. WO 2018/050771 A1, 4.10 g, 11.54 mmol) were added to a solution 5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (1.50 g, 5.77 mmol) in DMF (15 mL) and the resulting mixture was stirred at 90 °C for 12 h. Following completion of the reaction (as indicated by LCMS), the reaction mixture was poured into ice-cold water (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield crude material which was purified by flash chromatography (silica gel 230-400 mesh, eluting with 70% EtOAc in petroleum ether), giving the title compound as a yellow solid (1.2 g, 47% yield). LCMS: 444.1 [M+H].

Step 2: Synthesis of 5-iodo-7-(piperidin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine



HCl in 1,4-dioxane (4 M, 6 mL) was added to a solution of *tert*-butyl 4-(4-amino-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)piperidine-1-carboxylate (1.20 g, 2.71 mmol) in DCM (15 mL) at 0 °C and the resulting mixture was stirred at 25 °C for 16 h. Following completion of the reaction (as indicated by LCMS), the reaction mixture was concentrated under reduced pressure to give the title compound (0.697g, crude) as an off-white solid which was used without further purification. LCMS: 344.1 [M+H].

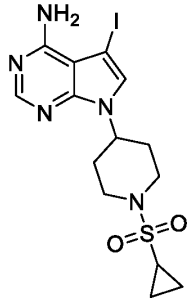
Step 3: Synthesis of 5-iodo-7-(1-(methylsulfonyl)piperidin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine



TEA (0.205 mL, 1.457 mmol) and MsCl (0.057 mL, 0.728 mmol) were added to a solution of 5-iodo-7-(piperidin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (0.250 g, 0.728 mmol) in DCM (5 mL) at 0 °C and the resulting mixture was stirred at 25 °C for 16 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was diluted with DCM (10 mL) and washed with brine (2 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude material which was purified by flash chromatography (silica gel 230-400 mesh, eluting with 10% MeOH in DCM), affording the title compound as a pale brown solid (0.28 g, 91% yield). LCMS: 422.0 [M+H].

INTERMEDIATE A16

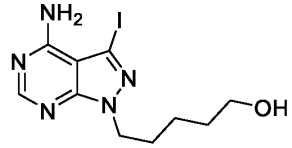
7-(1-(CYCLOPROPYLSULFONYL)PIPERIDIN-4-YL)-5-IODO-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-4-AMINE



The title compound was prepared via a similar procedure described for step 3 of intermediate A15, starting from 5-iodo-7-(piperidin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (0.300 g, 0.874 mmol) and cyclopropanesulfonyl chloride (0.123 g, 0.874 mmol), and was obtained as a pale brown gum (0.101 g, 46% yield). LCMS: 448.0 [M+H].

INTERMEDIATE A17

5-(4-AMINO-3-IODO-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-1-YL)PENTAN-1-OL

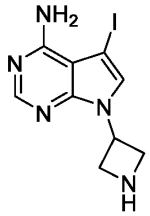


Cs_2CO_3 (0.187 g, 0.383 mmol) and 5-bromopentan-1-ol (0.064 g, 0.383 mmol) were added to a solution 5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (0.100 g, 0.383 mmol) in DMF (2 mL) and the resulting mixture was stirred at 80 °C for 12 h. Following completion of the reaction (as indicated by LCMS), the reaction mixture was poured into ice-cold water (100 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield the title compound as a pale brown gum (0.130 g, crude) which was used without further purification. LCMS: 348.0 [M+H].

INTERMEDIATE A18

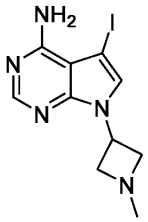
5-IODO-7-(1-METHYLAZETIDIN-3-YL)-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-4-AMINE

Step 1: Synthesis of 7-(azetidin-3-yl)-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine



TFA (2.5 mL) was added to a solution of *tert*-butyl 3-(4-amino-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)azetidine-1-carboxylate (synthesized as reported in PCT Publication No. WO 2017/215485 A1, 0.520 g, 1.252 mmol) in DCM (5 mL) and the resulting mixture was stirred at 25 °C for 12 h. Following completion of the reaction (as indicated by UPLC), the reaction mixture was concentrated under reduced pressure to afford the title compound as an off-white solid (0.4 g, crude) which was used without further purification. LCMS: 316.0 [M+H].

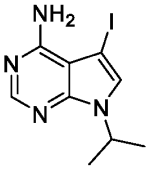
Step 2: Synthesis of 5-iodo-7-(1-methylazetidin-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine



Paraformaldehyde (0.149 g, 4.950 mmol) and acetic acid (4.95 mg, 0.083 mmol) were added to a solution of 7-(azetidin-3-yl)-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (0.520 g, 1.650 mmol) in MeOH (5 mL) and the resulting mixture was stirred at 50 °C for 2 h. $NaBH_3CN$ (0.518 g, 8.25 mmol) was then added and the reaction mixture was stirred at 50 °C for another 12 h. Following completion of the reaction (as indicated by LCMS), the reaction mixture was concentrated under reduced pressure to yield the title compound as an off-white solid (0.30 g, crude) which was used without further purification. LCMS: 330.0 [M+H].

INTERMEDIATE A19

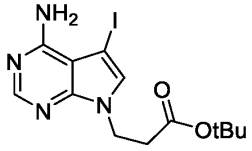
5-IODO-7-ISOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-4-AMINE



The title compound was prepared as reported in PCT Publication No. WO 2017/220477 A1.

INTERMEDIATE A20

TERT-BUTYL 3-(4-AMINO-5-IODO-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-7-YL)PROPANOATE

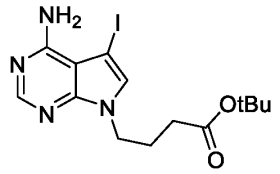


Cs_2CO_3 (2.506 g, 7.69 mmol) and *tert*-butyl 3-bromopropanoate (0.804 g, 3.85 mmol) were added to a solution of 5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (1.000 g, 3.85 mmol) in DMF (5 mL) and the resulting mixture was stirred at 90 °C for 12 h.

Following completion of the reaction (as indicated by LCMS), the reaction mixture was poured into crushed ice (25 g) and extracted with EtOAc (3 × 25 mL). The combined filtrates were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude material which was purified by flash chromatography (silica gel 230-400 mesh, eluting with 40% EtOAc in petroleum ether), giving the title compound as a pale brown solid (0.34 g, 23% yield). LCMS: 389.0 [M+H].

INTERMEDIATE A21

TERT-BUTYL 4-(4-AMINO-5-IODO-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-7-YL)BUTANOATE

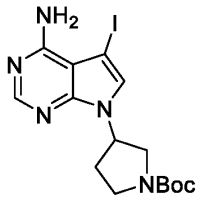


The title compound was prepared via a similar procedure described for intermediate A20, starting from 5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (1.000 g, 3.85 mmol) and *tert*-butyl 4-bromobutanoate (0.858 g, 3.85 mmol), and was obtained as a brown solid (1.28 g, 83% yield). LCMS: 403.1 [M+H].

INTERMEDIATE A22

5-IODO-7-(1-METHYLPYRROLIDIN-3-YL)-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-4-AMINE

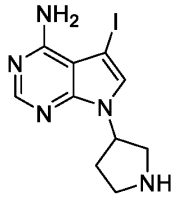
Step 1: Synthesis of *tert*-butyl 3-(4-amino-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)pyrrolidine-1-carboxylate



The title compound was prepared via a similar procedure described for step 1 of intermediate A15, starting from 3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (2.00 g, 7.66 mmol) and *tert*-butyl 3-(tosyloxy)pyrrolidine-1-carboxylate (synthesized as

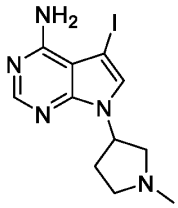
reported in PCT Publication No. WO 2019/238067 A1, 2.62 g, 7.66 mmol), and was obtained as a yellow solid (2.0 g, 61% yield). LCMS: 431.0 [M+H].

Step 2: Synthesis of 5-iodo-7-(pyrrolidin-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine



The title compound was prepared via a similar procedure described for step 2 of intermediate A15, starting from *tert*-butyl 3-(4-amino-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)pyrrolidine-1-carboxylate (1.0 g, 2.324 mmol), and was obtained as an off-white solid (0.70 g, crude) which was used without further purification. LCMS: 331.0 [M+H].

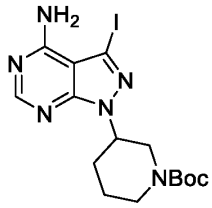
Step 3: Synthesis of 5-iodo-7-(1-methylpyrrolidin-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine



The title compound was prepared via a similar procedure described for step 2 of intermediate A18, starting from 5-iodo-7-(pyrrolidin-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (1.0 g, 3.03 mmol), and was obtained as an off-white solid (0.33 g, 32% yield) following purification by preparative HPLC (eluting with 0.1% HCOOH in water and ACN). LCMS: 345.1 [M+H].

INTERMEDIATE A23

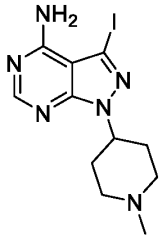
TERT-BUTYL 3-(4-AMINO-3-IODO-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-1-YL)PIPERIDINE-1-CARBOXYLATE



The title compound was prepared as reported in PCT Publication No. WO 2016/112846 A1.

INTERMEDIATE A24

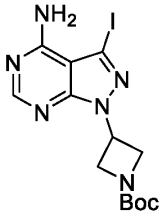
3-IODO-1-(1-METHYLPIPERIDIN-4-YL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-4-AMINE



The title compound was prepared as reported in *J. Med. Chem.* 2016, 59(21), 9788-9805.

INTERMEDIATE A25

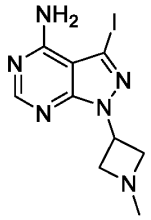
TERT-BUTYL 3-(4-AMINO-3-IODO-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-1-YL)AZETIDINE-1-CARBOXYLATE



The title compound was prepared via a similar procedure described for step 1 of intermediate A15, starting from 3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (1.000 g, 3.83 mmol) and *tert*-butyl 3-iodoazetidine-1-carboxylate (1.085 g, 3.83 mmol), and was obtained as an off-white solid (1.31 g, 82% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.20 (s, 1H), 7.84 (s, 2H), 5.51-5.76 (m, 1H), 4.20-4.35 (m, 4H), 1.42 (s, 9H). LCMS: 417.0 [M+H].

INTERMEDIATE A26

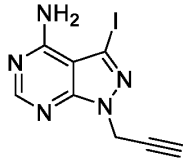
3-IODO-1-(1-METHYLAZETIDIN-3-YL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-4-AMINE



The title compound was prepared as reported in PCT Publication No. WO 2002/076986 A1.

INTERMEDIATE A27

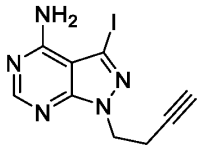
3-IODO-1-(PROP-2-YN-1-YL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-4-AMINE



K_2CO_3 (1.059 g, 7.66 mmol) and 3-bromoprop-1-yne (80% in toluene, 0.38 mL, 3.83 mmol) were added to a solution 3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (1.000 g, 3.83 mmol) in DMF (5 mL) and the resulting mixture was stirred at 70 °C for 12 h. Following completion of the reaction (as indicated by LCMS), the reaction mixture was poured into ice-cold water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude material which was purified by flash chromatography (silica gel 230-400 mesh, eluting with 70% EtOAc in petroleum ether), affording the title compound as a pale brown solid (0.846 g, 74% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.25 (s, 1H), 6.77 (bs, 2H), 5.14 (s, 2H), 3.39 (s, 1H). LCMS: 300.0 [M+H].

INTERMEDIATE A28

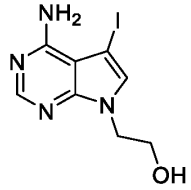
1-(BUT-3-YN-1-YL)-3-IODO-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-4-AMINE



The title compound was prepared via a similar procedure described for intermediate A27, starting from 4-bromobut-1-yne (0.123 g, 0.9589 mmol) and 3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.25 g, 0.958 mmol), and was obtained as a pale brown solid (0.230 g, 77% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.21 (s, 1H), 6.70 (bs, 2H), 4.39 (t, *J* = 6.8 Hz, 2H), 2.72-2.80 (m, 3H). LCMS: 314.0 [M+H].

INTERMEDIATE A29

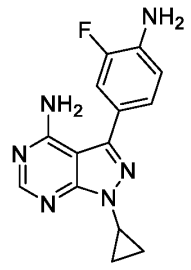
2-(4-AMINO-5-IODO-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-7-YL)ETHAN-1-OL



The title compound was prepared as reported in PCT Publication No. WO 2021/226547 A2.

INTERMEDIATE B1

3-(4-AMINO-3-FLUOROPHENYL)-1-CYCLOPROPYL-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-4-AMINE



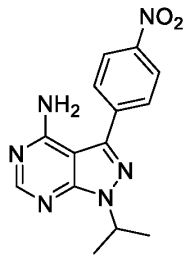
A mixture of 1-cyclopropyl-3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (A1, 0.500 g, 1.66 mmol), 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.433 g, 1.82 mmol), and K_2CO_3 (0.688 g, 4.98 mmol) in 1,4-dioxane (25 mL) and water (2.5 mL) was purged with N_2 for 10 min. $Pd(PPh_3)_4$ (0.092 g, 0.08 mmol) was

then added and the resulting mixture was stirred at 100 °C for 16 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was filtered through a pad of Celite® (*i.e.*, diatomaceous earth) which was then rinsed with EtOAc (2 × 10 mL). The combined filtrates were concentrated under reduced pressure to yield crude material which was purified by flash chromatography (silica gel 230-400 mesh, eluting with 2% MeOH in DCM), affording the title compound as a yellow solid (0.46 g, 98% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.23 (s, 1H), 7.15-7.24 (m, 2H), 6.87-6.91 (m, 1H), 5.47 (bs, 2H), 3.80-3.84 (m, 1H), 1.18-1.19 (m, 2H), 1.05-1.08 (m, 2H). LCMS: 285.0 [M+H].

INTERMEDIATE B2

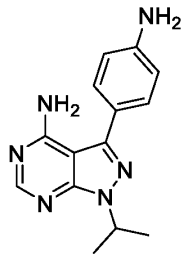
3-(4-AMINOPHENYL)-1-ISOPROPYL-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-4-AMINE

Step 1: Synthesis of 1-isopropyl-3-(4-nitrophenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine



The title compound was prepared via a similar procedure described for intermediate B1, starting from 3-iodo-1-isopropyl-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (A2, 1.887 g, 6.23 mmol) and (4-nitrophenyl)boronic acid (1.560 g, 9.34 mmol), and was obtained as a yellow solid (1.242 g, 67% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.38-8.40 (m, 2H), 8.28 (s, 1H), 7.92-7.95 (m, 2H), 5.07-5.14 (m, 1H), 1.51 (d, *J* = 6.8 Hz, 6H). LCMS: 299.1 [M+H].

Step 2: Synthesis of 3-(4-aminophenyl)-1-isopropyl-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine

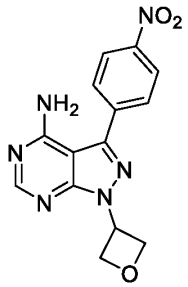


Iron powder (2.320 g, 41.60 mmol) and NH_4Cl (2.220 g, 41.60 mmol) were added to a solution of 1-isopropyl-3-(4-nitrophenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (1.242 g, 4.16 mmol) in ethanol (50 mL) and water (20 mL) and the resulting mixture was stirred at 80 °C for 3 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was filtered through a pad of Celite® (*i.e.*, diatomaceous earth) which was then rinsed with EtOAc (2 × 25 mL). The combined filtrates were concentrated under reduced pressure, the residue was dissolved in EtOAc (100 mL), washed with brine (25 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give the title compound as a pale yellow solid (1.042 g, quantitative yield) which was taken forward without further purification.

INTERMEDIATE B3

3-(4-AMINOPHENYL)-1-(OXETAN-3-YL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-4-AMINE

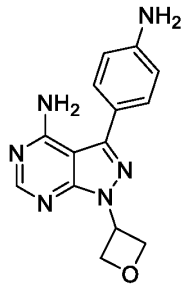
Step 1: Synthesis of 3-(4-nitrophenyl)-1-(oxetan-3-yl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine



The title compound was prepared via a similar procedure described for intermediate B1, starting from 3-iodo-1-(oxetan-3-yl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (A3, 0.800 g, 2.522 mmol) and (4-nitrophenyl)boronic acid (0.632 g, 3.78 mmol), and was obtained as a yellow solid (0.596 g, 76% yield). ^{1}H NMR (400 MHz,

DMSO-d_6) δ = 8.41-8.43 (m, 2H), 8.30 (s, 1H), 7.99-8.01 (m, 2H), 6.05-6.08 (m, 1H), 4.97-5.12 (m, 4H). LCMS: 311.0 [M-H].

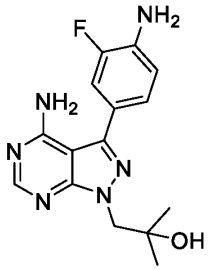
Step 2: Synthesis of 3-(4-aminophenyl)-1-(oxetan-3-yl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine



The title compound was prepared via a similar procedure described for step 2 of intermediate B2, starting from 3-(4-nitrophenyl)-1-(oxetan-3-yl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.596 g, 1.91 mmol), and was obtained as a pale yellow solid (0.42 g, quantitative yield) which was taken forward without further purification. LCMS: 283.0 [M+H].

INTERMEDIATE B4

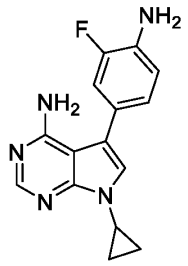
1-(4-AMINO-3-(4-AMINO-3-FLUOROPHENYL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-1-YL)-2-METHYLPROPAN-2-OL



The title compound was prepared via a similar procedure described for intermediate B1, starting from 1-(4-amino-3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)-2-methylpropan-2-ol (A4, 0.110 g, 0.330 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.094 g, 0.396 mmol), and was obtained as a pale yellow solid (0.077 g, 66% yield). LCMS: 317.1 [M+H].

INTERMEDIATE B5

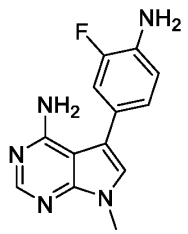
5-(4-AMINO-3-FLUOROPHENYL)-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-4-AMINE



A mixture of 7-cyclopropyl-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (A5, 10.5 g, 35.0 mmol), 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (9.12 g, 38.5 mmol), and K_2CO_3 (9.67 g, 70.0 mmol) in 1,4-dioxane (130 mL), EtOH (60 mL), and water (74.2 mL) was purged with N_2 for 10 min. $PdCl_2$(dppf) (1.280 g, 1.749 mmol) was then added and the resulting mixture was stirred at 80 °C for 3 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was filtered through a pad elite which was then washed with EtOAc (2 × 100 mL). The combined filtrates were concentrated under reduced pressure to give crude material which was purified by GRACE (silica gel 230-400 mesh, eluting with 3% MeOH in DCM), affording the title compound as a yellow solid (5.7 g, 57% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.13 (s, 1H), 7.12 (s, 1H), 7.05-7.09 (m, 1H), 6.95-6.98 (m, 1H), 6.82-6.87 (m, 1H), 6.04 (bs, 2H), 5.22 (bs, 2H), 3.53-3.56 (m, 1H), 1.02-1.04 (m, 4H). LCMS: 284.1 [M+H].

INTERMEDIATE B6

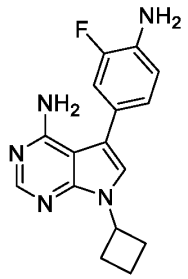
5-(4-AMINO-3-FLUOROPHENYL)-7-METHYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-4-AMINE



The title compound was prepared via a similar procedure described for intermediate B5, starting from 5-iodo-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (A6, 0.120 g, 0.438 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.114 g, 0.482 mmol), and was obtained as a pale yellow solid (0.09 g, 65% yield). LCMS: 258.1 [M+H].

INTERMEDIATE B7

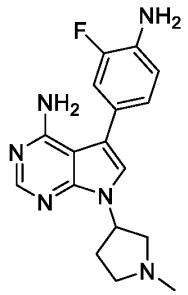
5-(4-AMINO-3-FLUOROPHENYL)-7-CYCLOBUTYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-4-AMINE



The title compound was prepared via a similar procedure described for intermediate B5, starting from 7-cyclobutyl-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (A7, 0.410 g, 1.305 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.309 g, 1.305 mmol), and was obtained as a brown solid (0.18 g, 37% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.13 (s, 1H), 7.51 (s, 1H), 7.09-7.13 (m, 1H), 6.98-7.01 (m, 1H), 6.84-6.88 (m, 1H), 6.21 (bs, 2H), 5.14-5.26 (m, 3H), 2.50-2.51 (m, 2H), 2.34-2.39 (m, 2H), 1.85-1.92 (m, 2H). LCMS: 298.0 [M+H].

INTERMEDIATE B8

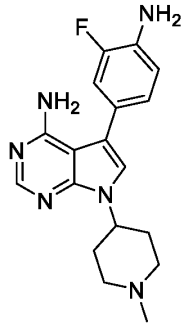
DI-*TERT*-BUTYL (3-(6-AMINOPYRIDIN-3-YL)-1-CYCLOPROPYL-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-4-YL)IMINODICARBONATE



The title compound was prepared via a similar procedure described for intermediate B5, starting from 5-iodo-7-(1-methylpyrrolidin-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (A9, 0.210 g, 0.612 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.145 g, 0.612 mmol), and was obtained as a brown gum (0.048 g, 24% yield) following purification by preparative HPLC (eluting with 0.1% TFA in H_2O and ACN). LCMS: 327.3 [M+H].

INTERMEDIATE B9

5-(4-AMINO-3-FLUOROPHENYL)-7-(1-METHYLPIPERIDIN-4-YL)-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-4-AMINE

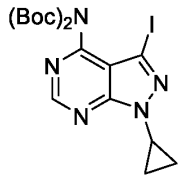


The title compound was prepared via a similar procedure described for intermediate B5, starting from 5-iodo-7-(1-methylpiperidin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (A10, 0.210 g, 0.388 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.095 g, 0.427 mmol), and was obtained as a brown gum (0.08 g, 59% yield) following purification by preparative HPLC (eluting with 10 mM NH_4OAc in H_2O and ACN). LCMS: 341.2 [M+H].

INTERMEDIATE B10

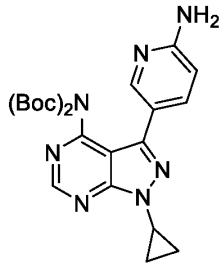
3-(4-AMINOPHENYL)-1-(OXETAN-3-YL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-4-AMINE

Step 1: Synthesis of di-*tert*-butyl (1-cyclopropyl-3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-4-yl)iminodicarbonate



DMAP (0.073 g, 0.598 mmol) and $(Boc)_2O$ (1.631 g, 7.47 mmol) were added to a solution of 1-cyclopropyl-3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (A1, 0.900 g, 2.99 mmol) in THF (10 mL) and the resulting solution was stirred at 25 °C for 12 h. Following completion of the reaction (as indicated by LCMS), the reaction mixture was concentrated under reduced pressure to yield crude material which was purified by flash chromatography (silica gel 230-400 mesh, eluting with 80% EtOAc in petroleum ether) to give the title compound as a pale brown solid (0.40 g, 27% yield). LCMS: 501.8 [M+H].

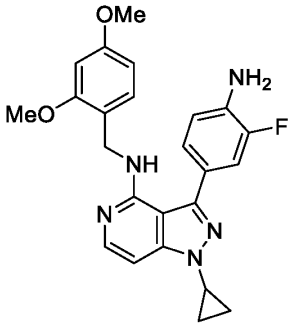
Step 2: Synthesis of di-*tert*-butyl (3-(6-aminopyridin-3-yl)-1-cyclopropyl-1H-pyrazolo[3,4-*d*]pyrimidin-4-yl)iminodicarbonate



The title compound was prepared via a similar procedure described for intermediate B5, starting from di-*tert*-butyl (1-cyclopropyl-3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-4-yl)iminodicarbonate (0.200 g, 0.399 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (0.097 g, 0.439 mmol), and was obtained as a brown gum (0.09 g, 48% yield). LCMS: 468.2 [M+H].

INTERMEDIATE B11

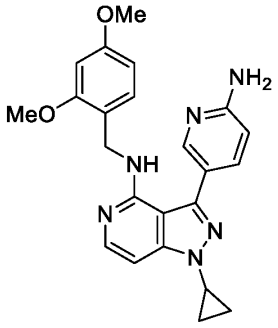
3-(4-AMINO-3-FLUOROPHENYL)-1-CYCLOPROPYL-*N*-(2,4-DIMETHOXYBENZYL)-1H-PYRAZOLO[4,3-*C*]PYRIDIN-4-AMINE



The title compound was prepared via a similar procedure described for intermediate B5, starting from 1-cyclopropyl-*N*-(2,4-dimethoxybenzyl)-3-iodo-1H-pyrazolo[4,3-*c*]pyridin-4-amine (A11, 0.370 g, 0.748 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.177 g, 0.748 mmol), and was obtained as a brown solid (0.15 g, 48% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.82 (d, *J* = 6.0 Hz, 1H), 7.07-7.19 (m, 3H), 6.83-6.89 (m, 2H), 6.51 (d, *J* = 2.0 Hz, 1H), 6.40-6.43 (m, 1H), 5.62 (t, *J* = 5.6 Hz, 1H), 5.49 (bs, 2H), 4.49 (d, *J* = 5.6 Hz, 2H), 3.65-3.72 (m, 7*H*), 1.08-1.09 (m, 4H). LCMS: 434.2 [M+H].

INTERMEDIATE B12

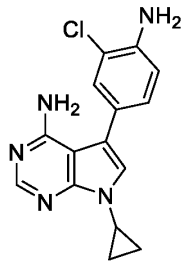
3-(6-AMINOPYRIDIN-3-YL)-1-CYCLOPROPYL-*N*-(2,4-DIMETHOXYBENZYL)-1H-PYRAZOLO[4,3-*C*]PYRIDIN-4-AMINE



The title compound was prepared via a similar procedure described for intermediate B5, starting from 1-cyclopropyl-*N*-(2,4-dimethoxybenzyl)-3-iodo-1H-pyrazolo[4,3-*c*]pyridin-4-amine (A11, 0.300 g, 0.666 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (0.147 g, 0.666 mmol), and was obtained as a brown gum (0.11 g, 30% yield). LCMS: 416.9 [M+H].

INTERMEDIATE B13

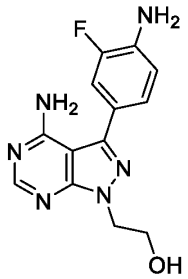
5-(4-AMINO-3-CHLOROPHENYL)-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-4-AMINE



The title compound was prepared via a similar procedure described for intermediate B5, starting from 7-cyclopropyl-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (A1, 0.250 g, 0.833 mmol) and 2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.211 g, 0.833 mmol), and was obtained as a yellow solid (0.03 g, 12% yield). LCMS: 300.1 [M+H].

INTERMEDIATE B14

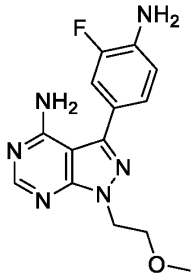
2-(4-AMINO-3-(4-AMINO-3-FLUOROPHENYL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-1-YL)ETHAN-1-OL



The title compound was prepared via a similar procedure described for intermediate B5, starting from 2-(4-amino-3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethan-1-ol (A12, 0.420 g, 1.377 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.327 g, 1.379 mmol), and was obtained as a brown solid (0.39 g, 92% yield). LCMS: 289.1 [M+H].

INTERMEDIATE B15

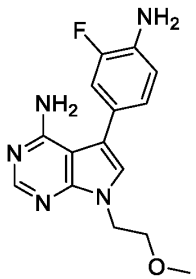
3-(4-AMINO-3-FLUOROPHENYL)-1-(2-METHOXYETHYL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-4-AMINE



The title compound was prepared via a similar procedure described for intermediate B5, starting from 3-iodo-1-(2-methoxyethyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (A13, 0.620 g, 1.943 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.461 g, 1.943 mmol), and was obtained as a brown solid (0.42 g) which was used without further purification. LCMS: 302.9 [M+H].

INTERMEDIATE B16

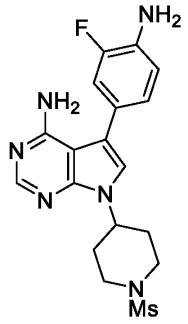
5-(4-AMINO-3-FLUOROPHENYL)-7-(2-METHOXYETHYL)-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-4-AMINE



The title compound was prepared via a similar procedure described for intermediate B5, starting from 5-iodo-7-(2-methoxyethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (A14, 0.500 g, 1.572 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.372 g, 1.569 mmol), and was obtained as a brown solid (0.236 g, 50% yield) which was used without further purification. LCMS: 302.2 [M+H].

INTERMEDIATE B17

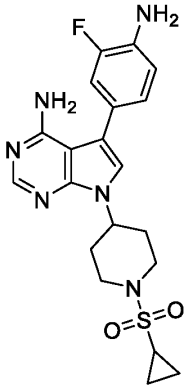
5-(4-AMINO-3-FLUOROPHENYL)-7-(1-(METHYLSULFONYL)PIPERIDIN-4-YL)-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-4-AMINE



The title compound was prepared via a similar procedure described for intermediate B5, starting from 5-iodo-7-(1-(methylsulfonyl)piperidin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (A15, 0.500 g, 0.843 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.220 g, 0.927 mmol), and was obtained as a brown solid (0.020 g, 5.9% yield). LCMS: 405.2 [M+H].

INTERMEDIATE B18

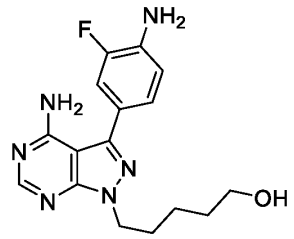
5-(4-AMINO-3-FLUOROPHENYL)-7-(1-(CYCLOPROPYLSULFONYL)PIPERIDIN-4-YL)-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-4-AMINE



The title compound was prepared via a similar procedure described for intermediate B5, starting from 7-(1-(cyclopropylsulfonyl)piperidin-4-yl)-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (A16, 0.103 g, 0.231 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.060 g, 0.254 mmol), and was obtained as a brown solid (0.052 g, 52% yield). LCMS: 431.1 [M+H].

INTERMEDIATE B19

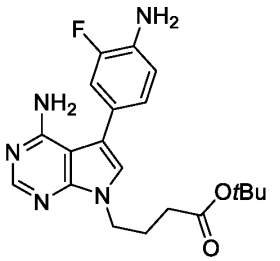
5-(4-AMINO-3-(4-AMINO-3-FLUOROPHENYL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-1-YL)PENTAN-1-OL



The title compound was prepared via a similar procedure described for intermediate B5, starting from 5-(4-amino-3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)pentan-1-ol (A17, 0.194 g, 0.559 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.070 g, 0.559 mmol), and was obtained as a brown gum (0.052 g, 38% yield). LCMS: 331.1 [M+H].

INTERMEDIATE B20

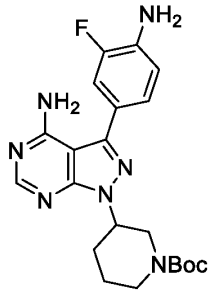
TERT-BUTYL 4-(4-AMINO-5-(4-AMINO-3-FLUOROPHENYL)-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-7-YL)BUTANOATE



The title compound was prepared via a similar procedure described for intermediate B5, starting from *tert*-butyl 4-(4-amino-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)butanoate (A21, 1.280 g, 3.18 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.754 g, 3.18 mmol), and was obtained as a brown solid (0.40 g, 33% yield). LCMS: 386.2 [M+H].

INTERMEDIATE B21

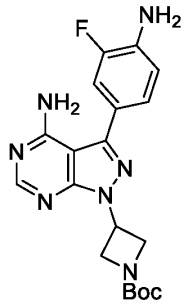
TERT-BUTYL 3-(4-AMINO-3-(4-AMINO-3-FLUOROPHENYL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-1-YL)PIPERIDINE-1-CARBOXYLATE



The title compound was prepared via a similar procedure described for intermediate B5, starting from *tert*-butyl 3-(4-amino-3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidine-1-carboxylate (A23, 1.800 g, 4.05 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.961 g, 4.05 mmol), and was obtained as a yellow solid (1.0 g, 58% yield). LCMS: 428.2 [M+H].

INTERMEDIATE B22

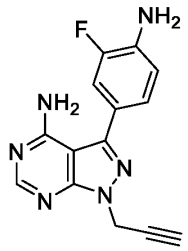
TERT-BUTYL 3-(4-AMINO-3-(4-AMINO-3-FLUOROPHENYL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-1-YL)AZETIDINE-1-CARBOXYLATE



The title compound was prepared via a similar procedure described for intermediate B5, starting from *tert*-butyl 3-(4-amino-3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)azetidine-1-carboxylate (A25, 0.650 g, 1.562 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.370 g, 1.562 mmol), and was obtained as a yellow solid (0.35 g, 56% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.23 (s, 1H), 7.22-7.32 (m, 2H), 6.89-6.94 (m, 1H), 5.60-5.66 (m, 1H), 5.52 (s, 2H), 4.30-4.36 (m, 4H), 1.42 (s, 9H). LCMS: 400.2 [M+H].

INTERMEDIATE B23

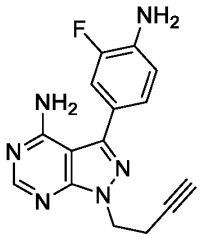
3-(4-AMINO-3-FLUOROPHENYL)-1-(PROP-2-YN-1-YL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-4-AMINE



The title compound was prepared via a similar procedure described for intermediate B5, starting from 3-iodo-1-(prop-2-yn-1-yl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (A27, 0.846 g, 2.83 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.671 g, 2.83 mmol), and was obtained as a brown solid (0.136 g, 17% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.25 (s, 1H), 7.19-7.28 (m, 2H), 6.87-6.93 (m, 1H), 5.50 (s, 2H), 5.15 (s, 2H), 3.37 (s, 1H). LCMS: 283.0 [M+H].

INTERMEDIATE B24

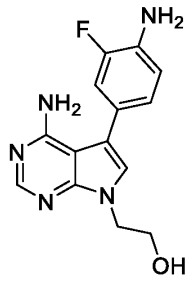
3-(4-AMINO-3-FLUOROPHENYL)-1-(BUT-3-YN-1-YL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-4-AMINE



The title compound was prepared via a similar procedure described for intermediate B5, starting from 1-(but-3-yn-1-yl)-3-iodo-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (A28, 1.000 g, 3.19 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.757 g, 3.18 mmol), and was obtained as a brown solid (0.276 g, 29% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.23 (s, 1H), 7.19-7.27 (m, 2H), 6.90 (t, *J* = 8.4 Hz, 1H), 5.49 (s, 2H), 4.42 (t, *J* = 6.8 Hz, 2H), 2.75-2.82 (m, 3H). LCMS: 297.2 [M+H].

INTERMEDIATE B25

2-(4-AMINO-5-(4-AMINO-3-FLUOROPHENYL)-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-7-YL)ETHAN-1-OL



The title compound was prepared via a similar procedure described for intermediate B5, starting from 2-(4-amino-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)ethan-1-ol (A29, 0.50 g, 1.644 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.39 g, 1.644 mmol), and was obtained as a brown solid (0.30 g, 63% yield). LCMS: 288.1 [M+H].

CARBAMATE INTERMEDIATES C

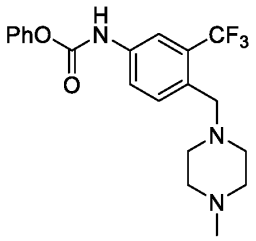
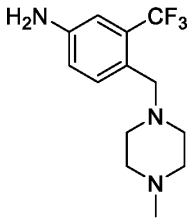
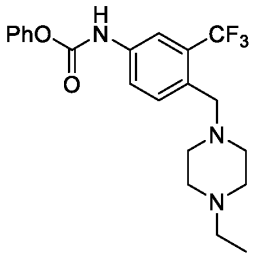
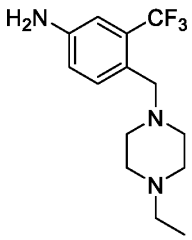
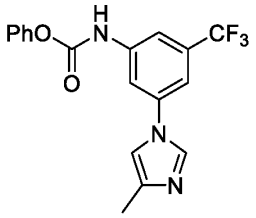
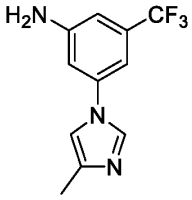
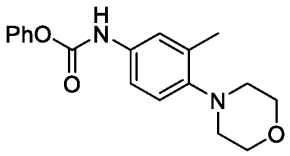
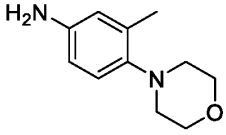
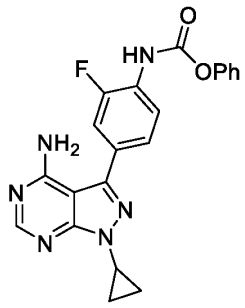
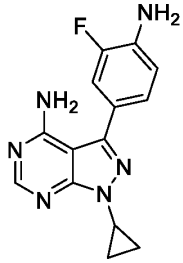
General procedure for the synthesis of carbamate Intermediates C

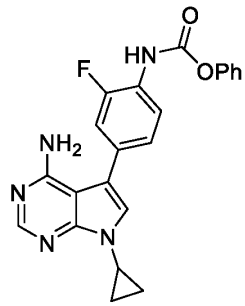
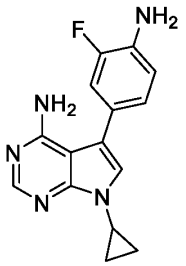
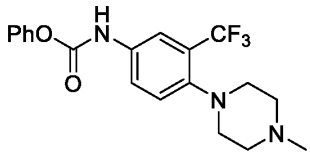
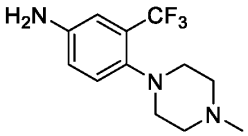
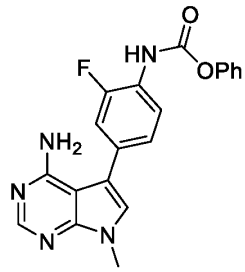
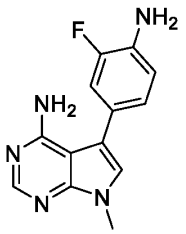
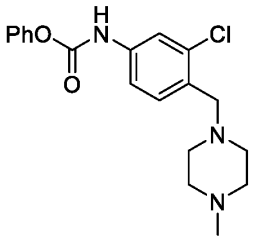
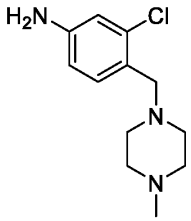
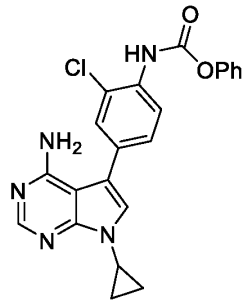
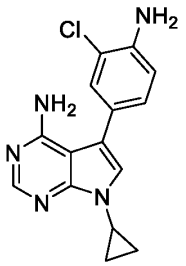
Pyridine (1.2 eq.) and phenyl chloroformate (1.5 eq.) were added to a solution of amine (1.0 eq.) in THF (10 vol) at 0 °C. The reaction mixture was allowed to warm to 25 °C and was stirred for 16 h. Following completion of the reaction (as indicated by TLC):

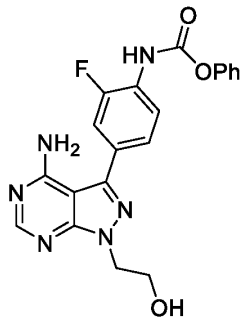
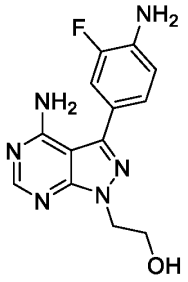
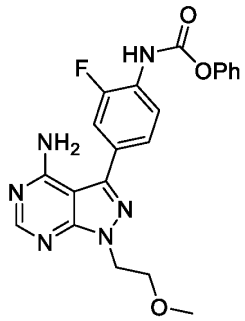
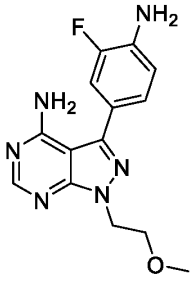
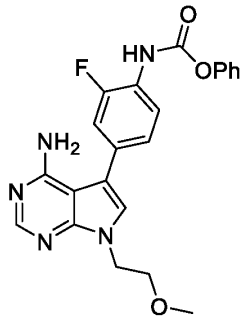
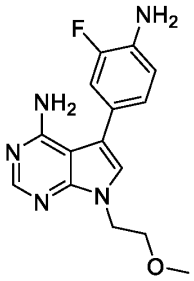
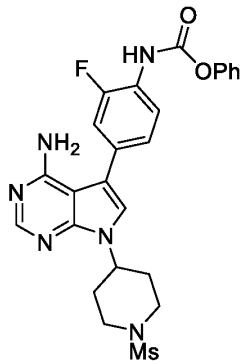
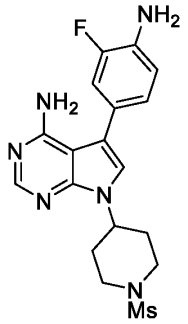
(i) the precipitated solid was filtered, washed with THF, and dried to afford the desired carbamate *OR*

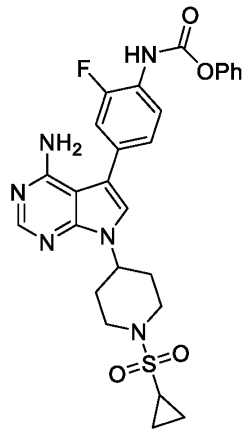
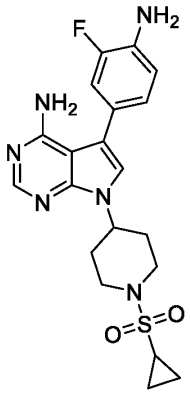
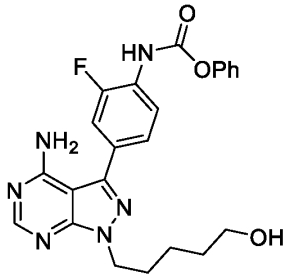
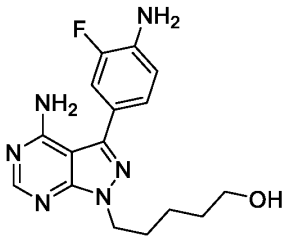
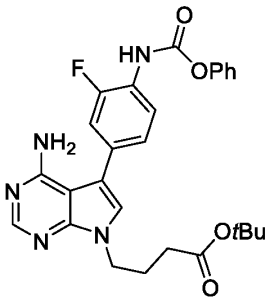
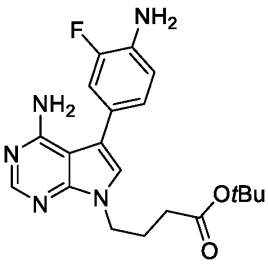
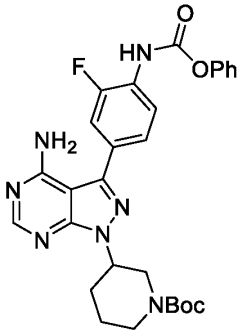
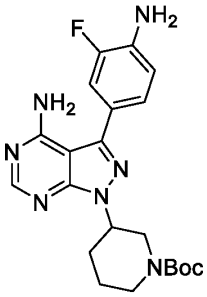
(ii) the reaction mixture was diluted with EtOAc (10 mL) and washed with brine (5 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield crude material which was purified by flash chromatography (silica gel 230-400 mesh, eluting with 10 to 20% EtOAc in petroleum ether), giving the desired carbamate.

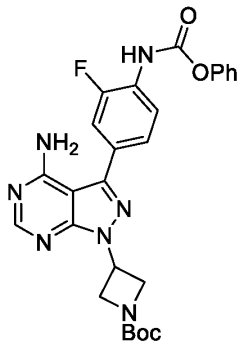
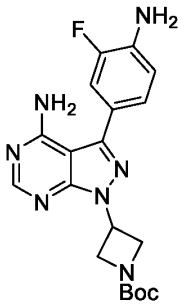
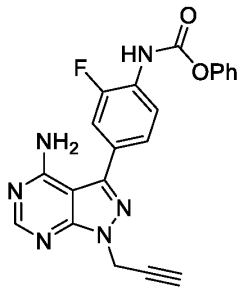
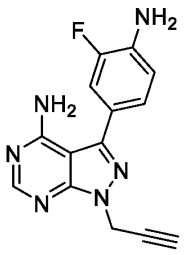
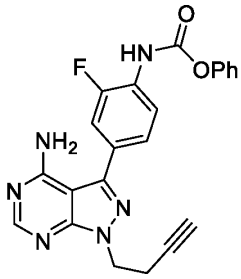
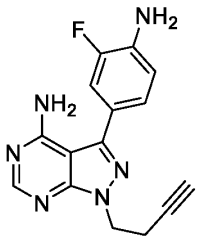
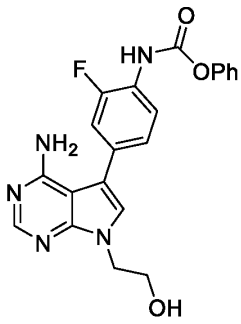
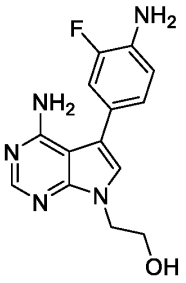
The following carbamates were prepared using the above general procedure:

Intermediate	Carbamate structure (product)	Amine structure (starting material)	LCMS
C1			394.2 [M+H]
C2			408.2 [M+H]
C3			362.0 [M+H]
C4			313.2 [M+H]
C5			405.1 [M+H]

Intermediate	Carbamate structure (product)	Amine structure (starting material)	LCMS
C6			404.2 [M+H]
C7			380.2 [M+H]
C8			378.2 [M+H]
C9			360.1 [M+H]
C10			420.1 [M+H]

Intermediate	Carbamate structure (product)	Amine structure (starting material)	LCMS
C11			409.1 [M+H]
C12			423.2 [M+H]
C13			422.2 [M+H]
C14			525.2 [M+H]

Intermediate	Carbamate structure (product)	Amine structure (starting material)	LCMS
C15			551.2 [M+H]
C16			451.3 [M+H]
C17			506.2 [M+H]
C18			548.2 [M+H]

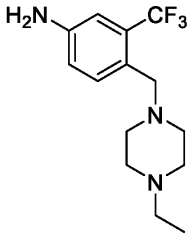
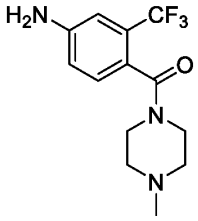
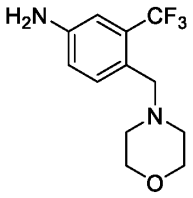
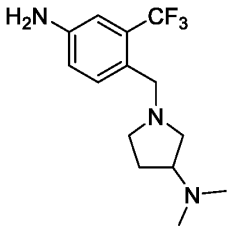
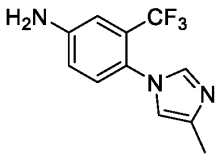
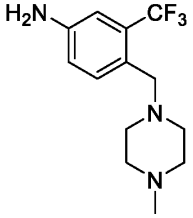
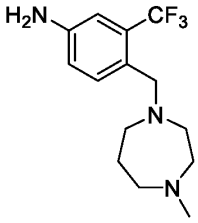
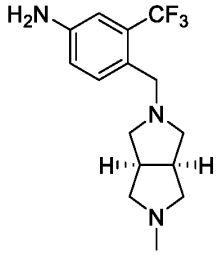
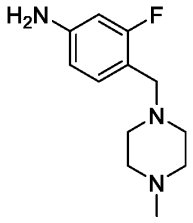
Intermediate	Carbamate structure (product)	Amine structure (starting material)	LCMS
C19			520.3 [M+H]
C20			403.1 [M+H]
C21			417.1 [M+H]
C22			XX [M+H]

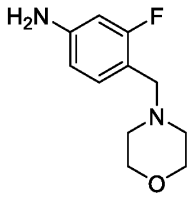
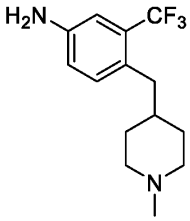
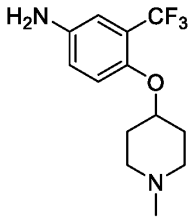
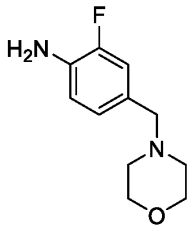
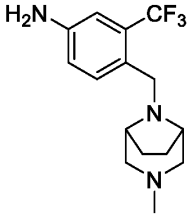
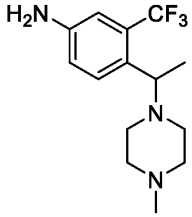
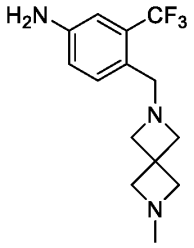
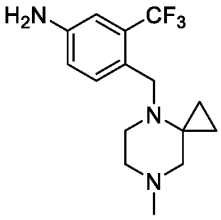
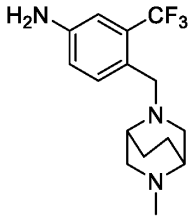
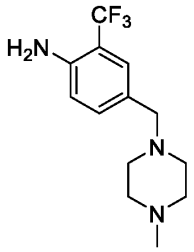
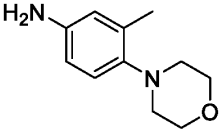
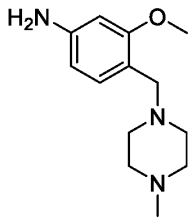
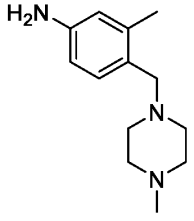
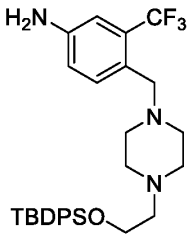
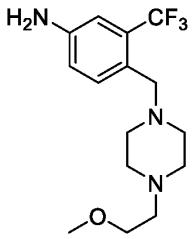
All amines used for the synthesis of carbamate Intermediates C are commercially available except for the following:

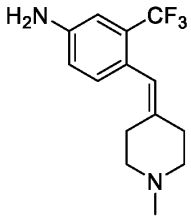
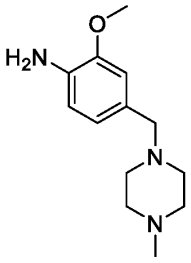
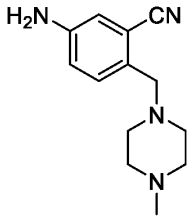
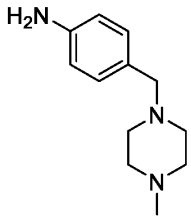
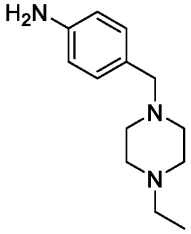
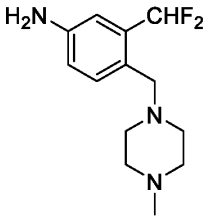
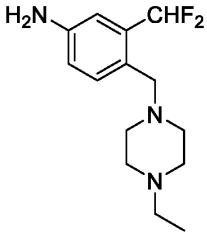
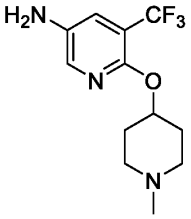
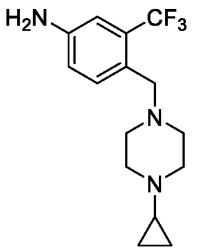
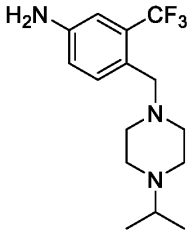
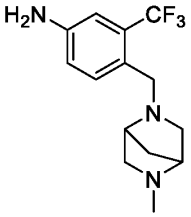
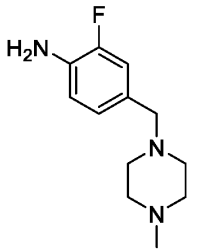
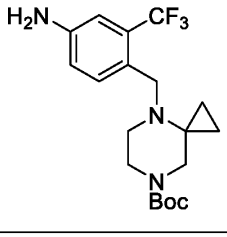
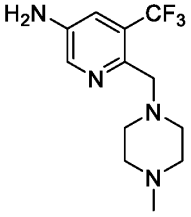
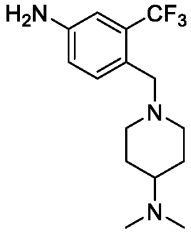
3-Methyl-4-morpholinoaniline (precursor to C4) was synthesized from 4-(2-methyl-4-nitrophenyl)morpholine as reported in *J. Med. Chem.* 2017, 60(12), 5099–5119.

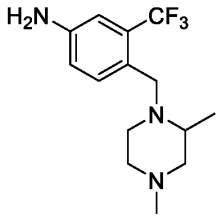
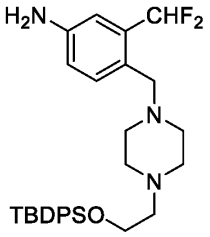
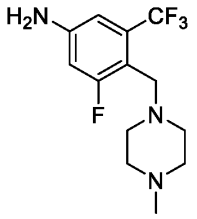
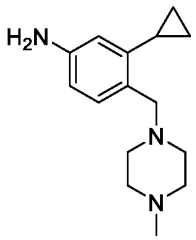
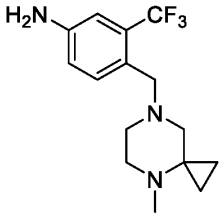
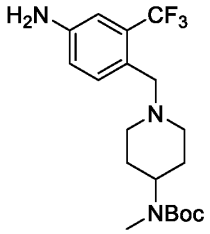
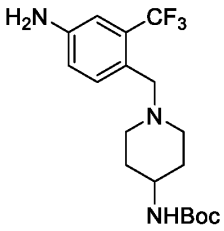
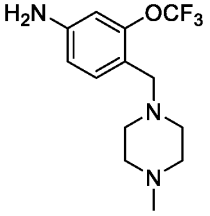
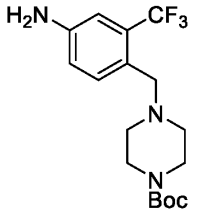
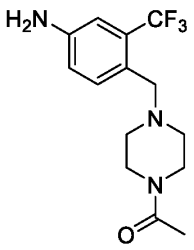
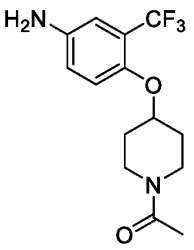
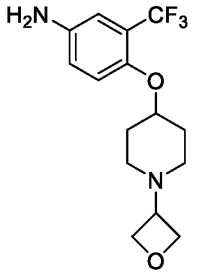
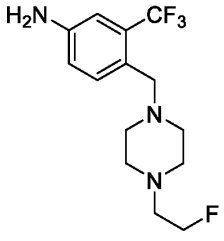
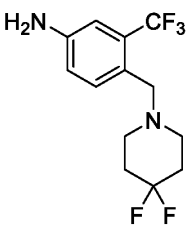
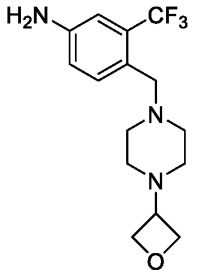
3-Chloro-4-((4-methylpiperazin-1-yl)methyl)aniline (precursor to C9) was synthesized from (4-amino-2-chlorophenyl)(4-methylpiperazin-1-yl)methanone as reported in PCT publication No. WO 2020/135507 A1.

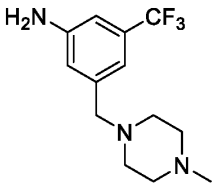
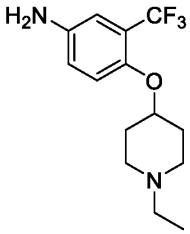
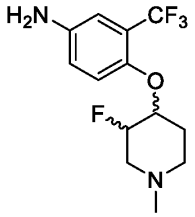
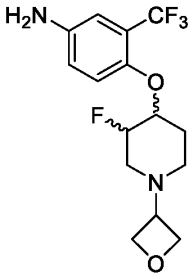
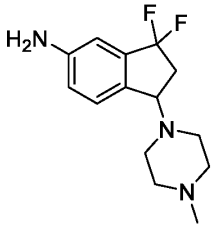
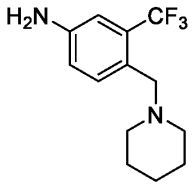
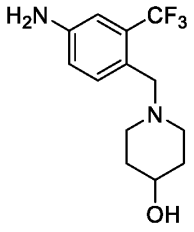
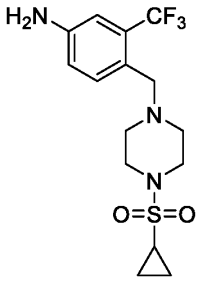
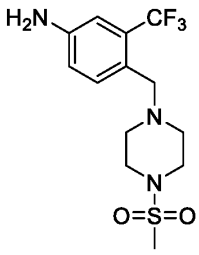
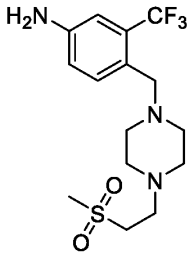
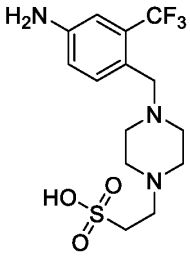
AMINE INTERMEDIATES D

Intermediate	D1	D2	D3
Structure			
Intermediate	D4	D5	D6
Structure			
Intermediate	D7	D8	D9
Structure			
Intermediate	D10	D11	D12

Structure			
Intermediate	D13	D14	D15
Structure			
Intermediate	D16	D17	D18
Structure			
Intermediate	D19	D20	D21
Structure			
Intermediate	D22	D23	D24
Structure			
Intermediate	D25	D26	D27

Structure			
Intermediate	D28	D29	D30
Structure			
Intermediate	D31	D32	D33
Structure			
Intermediate	D34	D35	D36
Structure			
Intermediate	D37	D38	D39
Structure			
Intermediate	D40	D41	D42

Structure			
Intermediate	D43	D44	D45
Structure			
Intermediate	D46	D47	D48
Structure			
Intermediate	D49	D50	D51
Structure			
Intermediate	D52	D53	D54
Structure			
Intermediate	D55	D56	D57a & D57b

Structure			
Intermediate	D58a & D58b	D59	D60
Structure			
Intermediate	D61	D62	D63
Structure			
Intermediate	D64	D65	
Structure			

All amine Intermediates D are commercially available except for the following:

Intermediate D3 was prepared as reported in PCT Publication No. WO 2018/215668 A1.

Intermediate D4 was prepared as reported in PCT Publication No. WO 2020/206583 A1.

Intermediate D5 was prepared as reported in PCT Publication No. WO 2016/029776 A1.

Intermediate D7 was prepared as reported in PCT Publication No. WO 2017/222285 A1.

Intermediate D8 was prepared as reported in *J. Med. Chem.* 2012, 55(22), 10033–10046.

Intermediate D9 was prepared as reported in PCT Publication No. WO 2020/135507 A1.

Intermediate D10 was prepared as reported in PCT Publication No. WO 2014/012360 A1.

Intermediate D11 was prepared as reported in PCT Publication No. WO 2008/046802 A1.

Intermediate D12 was prepared as reported in PCT Publication No. WO 2019/200120 A1.

Intermediate D13 was prepared as reported in PCT Publication No. WO 2021/067569 A1.

Intermediates D14, D15, and D46 were prepared as reported in PCT Publication No. WO 2018/102751 A1.

Intermediates D18, D24, D35, D47, and D52 were prepared as reported in PCT Publication No. WO 2022/008383 A1.

Intermediate D20 was prepared as reported in *J. Med. Chem.* 2017, 60(12), 5099–5119.

Intermediate D21 was prepared as reported in PCT Publication No. WO 2006/066174 A1.

Intermediate D25 was prepared as reported in PCT Publication No. WO 2008/046802 A1.

Intermediate D26 was prepared as reported in CN 113717156 A1.

Intermediates D30 and D31 were prepared as reported in PCT Publication No. WO 2021/226547 A2.

Intermediates D32, D38, and D41 were prepared as reported in PCT Publication No. WO 2019/200120 A1.

Intermediates D33 and D60 were prepared as reported in PCT Publication No. WO 2014/072220 A1.

Intermediates D34, D49, and D56 were prepared as reported in PCT Publication No. WO 2018/215668 A1.

Intermediate D39 was prepared as reported in *J. Med. Chem.* 2012, 55(22), 10033–10046.

Intermediate D43 was prepared as reported in PCT Publication No. WO 2013/170774 A1.

Intermediate D48 was prepared as reported in PCT Publication No. WO 2019/196812 A1.

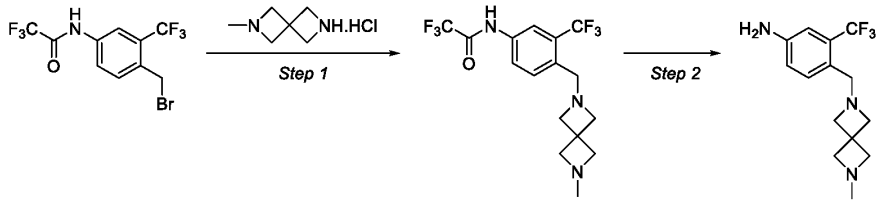
Intermediates D51 and D58 were prepared as reported in PCT Publication No. WO 2013/152198 A1.

Intermediate D53 was prepared as reported in PCT Publication No. WO 2017/222285 A1.

Intermediate D54 was prepared as reported in PCT Publication No. WO 2021/164742 A1.

Intermediate D59 was prepared as reported in PCT Publication No: WO 2014/019338 A1.

Intermediate D16 was prepared according to the following synthetic scheme:



INTERMEDIATE D16

4-((6-METHYL-2,6-DIAZASPIRO[3.3]HEPTAN-2-YL)METHYL)-3-(TRIFLUOROMETHYL)ANILINE

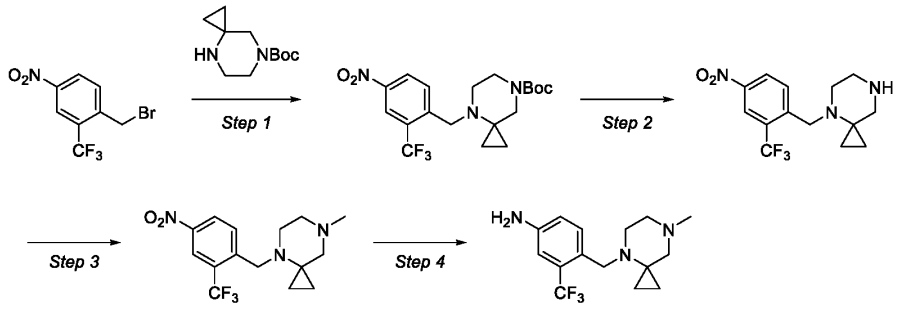
Step 1: Synthesis of 2,2,2-trifluoro-*N*-(4-((6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide

Cs_2CO_3 (0.548 g, 1.682 mmol) and 2-methyl-2,6-diazaspiro[3.3]heptane hydrochloride (0.250 g, 1.682 mmol) were added to a solution of *N*-(4-(bromomethyl)-3-(trifluoromethyl)phenyl)-2,2,2-trifluoroacetamide (synthesized as reported in *Org Process Res Dev* 2008, 12(6), 1146-1155, 0.589 g, 1.682 mmol) in ACN (5 mL) and the resulting mixture was stirred at 25 °C for 12 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was filtered through a pad of Celite® (*i.e.*, diatomaceous earth) and the resulting filtrate was concentrated under reduced pressure to give the title compound (0.7 g, crude) which was used without further purification. LCMS: 382.1 [M+H].

Step 2: Synthesis of 4-((6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)-3-(trifluoromethyl)aniline

K_2CO_3 (0.178 g, 1.285 mmol) was added to a solution of 2,2,2-trifluoro-*N*-(4-((6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide (0.700 g, 1.836 mmol) in MeOH (2 mL) and water (2 mL) and the resulting solution was stirred at 25 °C for 12 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was concentrated under reduced pressure to give crude material which was purified by preparative HPLC (eluting with 0.1% TFA in water and ACN), affording the title compound as a colorless gum (0.075 g, 14% yield). LCMS: 286.2 [M+H].

Intermediate D17 was prepared according to the following synthetic scheme:



INTERMEDIATE D17

4-((7-METHYL-4,7-DIAZASPIRO[2.5]OCTAN-4-YL)METHYL)-3-(TRIFLUOROMETHYL)ANILINE

Step 1: Synthesis of *tert*-butyl 4-(4-nitro-2-(trifluoromethyl)benzyl)-4,7-diazaspiro[2.5]octane-7-carboxylate

The title compound was prepared via a similar procedure described for step 1 of intermediate D16, starting from 1-(bromomethyl)-4-nitro-2-(trifluoromethyl)benzene (synthesized as reported in PCT Publication No. WO 2014/206343 A1, 0.228 g, 0.804 mmol) and *tert*-butyl 4,7-diazaspiro[2.5]octane-7-carboxylate hydrochloride (0.200 g, 0.804 mmol), and was obtained as a white solid (0.091 g, 26% yield) following purification by flash chromatography (silica gel 230-400 mesh, eluting with 5% EtOAc in petroleum ether). LCMS: 416.2 [M+H].

Step 2: Synthesis of 4-(4-nitro-2-(trifluoromethyl)benzyl)-4,7-diazaspiro[2.5]octane

HCl in 1,4-dioxane (4M, 1.5 mL, 0.335 mmol) was added to a solution of *tert*-butyl 4-(4-nitro-2-(trifluoromethyl)benzyl)-4,7-diazaspiro[2.5]octane-7-carboxylate (0.139 g, 0.335 mmol) in DCM (6 mL) at 0 °C and the resulting mixture was stirred at 25 °C for 16 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was concentrated under reduced pressure to afford the title compound as a pale brown solid (0.10 g, 38 % yield). LCMS: 316.1 [M+H].

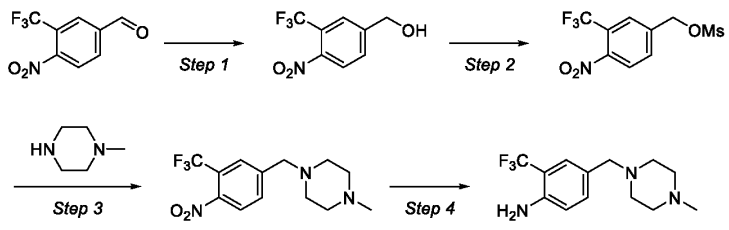
Step 3 Synthesis of 7-methyl-4-(4-nitro-2-(trifluoromethyl)benzyl)-4,7-diazaspiro[2.5]octane

Formaldehyde (37 % in water, 0.070 g, 0.856 mmol), acetic acid (0.031 g, 0.514 mmol), and STAB (0.145 g, 0.685 mmol) were added to a solution of 4-(4-nitro-2-(trifluoromethyl)benzyl)-4,7-diazaspiro[2.5]octane (0.108 g, 0.343 mmol) in THF (8 mL) at 0 °C and the resulting mixture was stirred at 25 °C for 16 h. Following completion of the reaction (as indicated by UPLC), the reaction mixture was quenched with aqueous $NaHCO_3$ (10%, 5 mL) and extracted with EtOAc (2 ×10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the title compound as a brown gum (0.076 g, crude) which was used without further purification. LCMS: 330.1[M+H].

Step 4: Synthesis of 4-((7-methyl-4,7-diazaspiro[2.5]octan-4-yl)methyl)-3-(trifluoromethyl)aniline

Iron powder (0.129 g, 2.308 mmol) and NH_4Cl (0.123 g, 2.308 mmol) were added to a suspension of 7-methyl-4-(4-nitro-2-(trifluoromethyl)benzyl)-4,7-diazaspiro[2.5]octane (0.076 g, 0.231 mmol) in ethanol (5 mL) and water (1.25 mL) and the resulting mixture was stirred at 80 °C for 2 h. Following completion of the reaction (as indicated by UPLC), the reaction mixture was filtered through a pad of Celite® (*i.e.*, diatomaceous earth) which was then rinsed with DCM (5 mL). The combined filtrates were concentrated under reduced pressure, giving crude material which was taken in DCM (10 mL), washed with brine (2 mL), dried over Na_2SO4, filtered, and concentrated under reduced pressure to afford the title compound (0.055 g, crude) as a pale brown gum which was used without further purification. LCMS: 300.1 [M+H].

Intermediate D19 was prepared according to the following synthetic scheme:



INTERMEDIATE D19

4-((4-METHYLPIPERAZIN-1-YL)METHYL)-2-(TRIFLUOROMETHYL)ANILINE

Step 1: Synthesis of (4-nitro-3-(trifluoromethyl)phenyl)methanol

$NaBH_4$ (0.0518 g, 1.369 mmol) was added portionwise to a solution of 4-nitro-3-(trifluoromethyl)benzaldehyde (0.250 g, 1.141 mmol) in THF (8 mL) at 0 °C and the resulting mixture was stirred at 25 °C for 1 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was quenched with a saturated NH_4Cl solution (6 mL) and extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the title compound (0.259 g, crude) which was used without further purification or characterization.

Step 2: Synthesis of 4-nitro-3-(trifluoromethyl)benzyl methanesulfonate

TEA (0.173 g, 1.709 mmol) and MsCl (0.144 g, 1.254 mmol) were added to a solution of (4-nitro-3-(trifluoromethyl)phenyl)methanol (0.252 g, 1.140 mmol) in DCM (7 mL) at 0 °C and the resulting mixture was stirred at 25 °C for 1 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was diluted with DCM (10 mL) and washed with brine (2 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the title compound (0.276 g, crude) which was used without further purification or characterization.

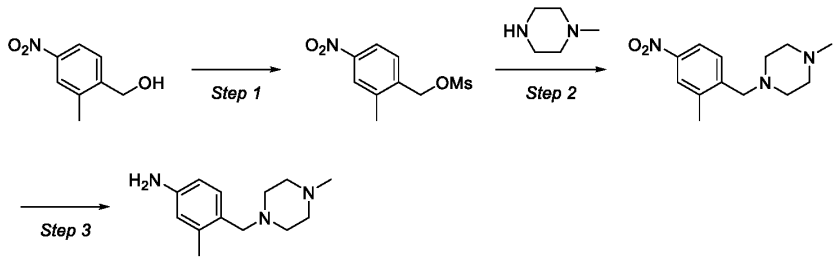
Step 3 Synthesis of 1-methyl-4-(4-nitro-3-(trifluoromethyl)benzyl)piperazine

K_2CO_3 (0.255 g, 1.845 mmol) and 1-methylpiperazine (0.092 g, 0.922 mmol) were added to a solution of 4-nitro-3-(trifluoromethyl)benzyl methanesulfonate (0.276 g, 0.922 mmol) in ACN (6 mL) and the resulting mixture was stirred at 60 °C for 16 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was filtered through a pad of Celite® (*i.e.*, diatomaceous earth) which was then rinsed with ACN (2 × 2 mL). The combined filtrates were concentrated under reduced pressure to afford the title compound (0.251 g, 74% yield) which was used without further purification. LCMS: 304.4 [M+H].

Step 4: Synthesis of 4-((4-methylpiperazin-1-yl)methyl)-2-(trifluoromethyl)aniline

Pd/C (10%, 0.025 g) was added to a solution of 1-methyl-4-(4-nitro-3-(trifluoromethyl)benzyl)piperazine (0.251 g, 0.828 mmol) in MeOH (8 mL) and the resulting suspension was stirred at 25 °C under H_2 atmosphere (bladder pressure) for 16 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was filtered through a pad Celite® (*i.e.*, diatomaceous earth) which was then rinsed with MeOH (5 mL). The combined filtrates were concentrated under reduced pressure to give the title compound (0.209 g, 67% yield) which was used without further purification. LCMS: 274.1 [M+H].

Intermediate D22 was prepared according to the following synthetic scheme:



INTERMEDIATE D22

3-METHYL-4-((4-METHYLPIPERAZIN-1-YL)METHYL)ANILINE

Step 1: Synthesis of 2-methyl-4-nitrobenzyl methanesulfonate

The title compound was prepared via a similar procedure described for step 2 of intermediate D19, starting from (2-methyl-4-nitrophenyl)methanol (synthesized as reported in PCT Publication No. WO 2015/117147 A1, 0.240 g, 1.436 mmol), and was used without further purification or characterization (0.250 g, 71% yield).

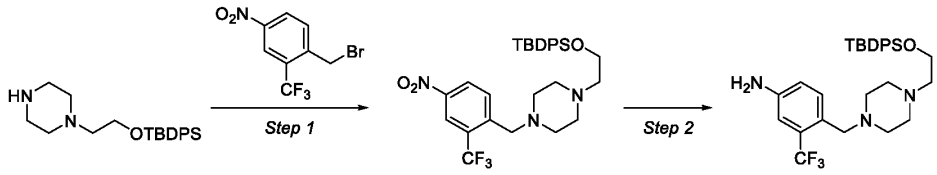
Step 2: Synthesis of 1-methyl-4-(2-methyl-4-nitrobenzyl)piperazine

The title compound was prepared via a similar procedure described for step 3 of intermediate D19, starting from 2-methyl-4-nitrobenzyl methanesulfonate (0.250 g, 1.019 mmol) and 1-methylpiperazine (0.102 g, 1.019 mmol), and was used without further purification (0.254 g, 74% yield). LCMS: 250.3 [M+H].

Step 3 Synthesis of 3-methyl-4-((4-methylpiperazin-1-yl)methyl)aniline

The title compound was prepared via a similar procedure described for step 4 of intermediate D19, starting from 1-methyl-4-(2-methyl-4-nitrobenzyl)piperazine (0.240 g, 0.963 mmol), and was used without further purification (0.169 g, 80% yield). LCMS: 220.2 [M+H].

Intermediate D23 was prepared according to the following synthetic scheme:



INTERMEDIATE D23

4-((4-(2-((*TERT*-BUTYLDIPHENYLSILYL)OXY)ETHYL)PIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)ANILINE

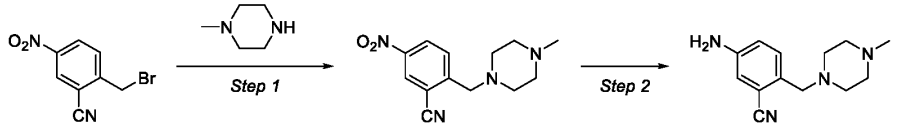
Step 1: Synthesis of 1-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-4-(4-nitro-2-(trifluoromethyl)benzyl)piperazine

Cs_2CO_3 (0.688 g, 2.112 mmol) and 1-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl) piperazine (synthesized as reported in PCT Publication No. WO 2012/017251 A1, 0.519 g, 1.408 mmol) were added to a solution of 1-(bromomethyl)-4-nitro-2-(trifluoromethyl)benzene (synthesized as reported in PCT Publication No. WO 2014/206343 A1, 0.400 g, 1.408 mmol) in THF (6 mL) and the resulting mixture was stirred 25 °C for 12 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was filtered through a pad of Celite® (*i.e.*, diatomaceous earth) and the filtrate was concentrated under reduced pressure to give crude material which was purified by flash chromatography (silica gel 230-400 mesh, eluting with 10% EtOAc in petroleum ether), giving the title compound as a white solid (0.560 g, 69% yield). LCMS: 572.2 [M+H].

Step 2: Synthesis of 4-((4-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)piperazin-1-yl)methyl)-3-(trifluoromethyl)aniline

The title compound was prepared via a similar procedure described for step 4 of intermediate D17, starting from 1-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-4-(4-nitro-2-(trifluoromethyl)benzyl)piperazine (0.560 g, 0.980 mmol), and obtained as a yellow gum (0.530 g, quantitative yield) which was used without further purification. LCMS: 542.3 [M+H].

Intermediate D27 was prepared according to the following synthetic scheme:



INTERMEDIATE D27

5-AMINO-2-((4-METHYLPIPERAZIN-1-YL)METHYL)BENZONITRILE

Step 1: Synthesis of 2-((4-methylpiperazin-1-yl)methyl)-5-nitrobenzonitrile

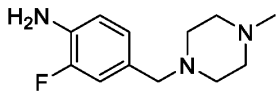
The title compound was prepared via a similar procedure described for step 1 of intermediate D23, starting from 2-(bromomethyl)-5-nitrobenzonitrile (0.100 g, 0.415 mmol) and 1-methylpiperazine (0.042 g, 0.415 mmol), and was obtained as a yellow gum (0.077 g, 71% yield) which was used without further purification. LCMS: 261.1 [M+H].

Step 2: Synthesis of 5-amino-2-((4-methylpiperazin-1-yl)methyl)benzonitrile

The title compound was prepared via a similar procedure described for step 4 of intermediate D17, starting from 2-((4-methylpiperazin-1-yl)methyl)-5-nitrobenzonitrile (0.077 g, 0.296 mmol), and was obtained as a yellow gum (0.068 g, 85% yield) which was used without further purification. LCMS: 231.2 [M+H].

INTERMEDIATE D36

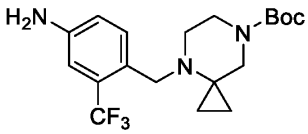
2-FLUORO-4-((4-METHYLPIPERAZIN-1-YL)METHYL)ANILINE



The title compound was prepared via a similar procedure described for step 4 of intermediate D17, starting from 1-(3-fluoro-4-nitrobenzyl)-4-methylpiperazine (synthesized as reported in PCT Publication No. WO 2009/002916 A2, 0.125 g, 0.494 mmol), and was obtained as a brown gum (0.065 g, 59% yield) which was used without further purification. LCMS: 224.3 [M+H].

INTERMEDIATE D37

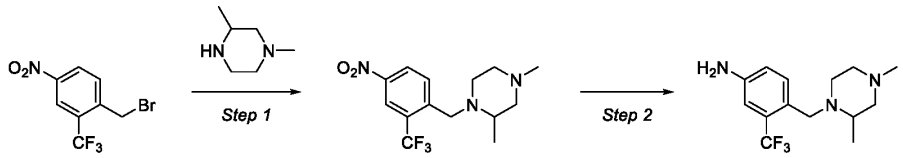
2-FLUORO-4-((4-METHYLPIPERAZIN-1-YL)METHYL)ANILINE



The title compound was prepared via a similar procedure described for step 4 of intermediate D17, starting from *tert*-butyl 4-(4-nitro-2-(trifluoromethyl)benzyl)-4,7-

diazaspiro[2.5]octane-7-carboxylate (step 1 of intermediate D17, 0.120 g, 0.289 mmol), and was obtained as a pale brown solid (0.080 g, 72% yield) which was used without further purification. LCMS: 386.2 [M+H].

Intermediate D40 was prepared according to the following synthetic scheme:



INTERMEDIATE D40

4-((2,4-DIMETHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)ANILINE

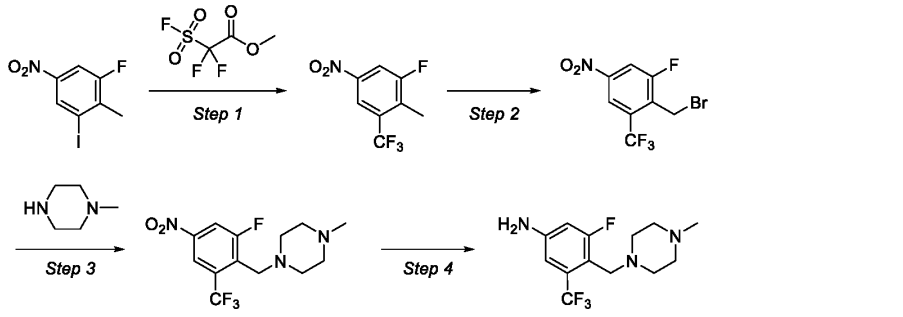
Step 1: Synthesis of 2,4-dimethyl-1-(4-nitro-2-(trifluoromethyl)benzyl)piperazine

The title compound was prepared via a similar procedure described for step 1 of intermediate D23, starting from 1-(bromomethyl)-4-nitro-2-(trifluoromethyl)benzene (0.250 g, 0.880 mmol) and 1,3-dimethylpiperazine (0.101 g, 0.880 mmol), and was obtained as a yellow gum (0.270 g, quantitative yield) which was used without further purification. LCMS: 318.1 [M+H].

Step 2: Synthesis of 4-((2,4-dimethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline

The title compound was prepared via a similar procedure described for step 4 of intermediate D17, starting from 2,4-dimethyl-1-(4-nitro-2-(trifluoromethyl)benzyl) piperazine (0.287 g, 0.904 mmol), and was obtained as a yellow gum (0.074 g, 26% yield) which was used without further purification. LCMS: 288.2 [M+H].

Intermediate D42 was prepared according to the following synthetic scheme:



INTERMEDIATE D42

3-FLUORO-4-((4-METHYLPIPERAZIN-1-YL)METHYL)-5-(TRIFLUOROMETHYL)ANILINE

Step 1: Synthesis of 1-fluoro-2-methyl-5-nitro-3-(trifluoromethyl)benzene

A mixture of methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (2.57 mL, 20.07 mmol), copper(I) iodide (0.38 g, 2.007 mmol), and 1-fluoro-3-iodo-2-methyl-5-nitrobenzene (synthesized as reported in PCT Publication No. WO 2019/044946 A1, 0.940 g, 3.34 mmol) in DMF (8 mL)was purged with N_2 for 15 minutes then stirred at 110 °C for 16 h. Following completion of the reaction (as indicated by GCMS), the reaction mixture was filtered through a pad of Celite® (*i.e.*, diatomaceous earth) which was then washed with DCM (20 mL). The combined filtrates were concentrated under reduced pressure to give crude material which was purified by flash chromatography (silica gel 230-400 mesh, eluting with petroleum ether), affording the title compound as a colorless liquid (0.461 g, 62% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.46-8.48 (m, 1H), 8.28 (s, 1H), 2.41 (s, 3H); GCMS: 223 [M].

Step 2: Synthesis of 2-(bromomethyl)-1-fluoro-5-nitro-3-(trifluoromethyl)benzene

AIBN (0.068 g, 0.413 mmol) and NBS (0.368 g, 2.066 mmol) were added to a solution of 1-fluoro-2-methyl-5-nitro-3-(trifluoromethyl)benzene (0.461 g, 2.066 mmol) in DCE (25 mL) and the resulting mixture was stirred at 90 °C for 16 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was concentrated under reduced pressure to give crude material which was purified by flash chromatography (silica gel 230-400 mesh, eluting with petroleum ether), affording the title compound as a yellow liquid (0.20 g, 32% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.60-8.63 (m, 1H), 8.34 (s, 1H), 4.77 (s, 2H).

Step 3: Synthesis of 1-(2-fluoro-4-nitro-6-(trifluoromethyl)benzyl)-4-methylpiperazine

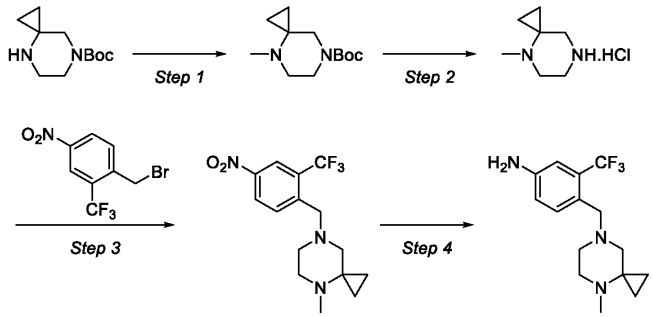
The title compound was prepared via a similar procedure described for step 1 of intermediate D23, starting from 2-(bromomethyl)-1-fluoro-5-nitro-3-(trifluoromethyl)benzene (0.200 g, 0.662 mmol) and 1-methylpiperazine (0.066 g, 0.662 mmol), and was obtained as a yellow gum (0.145 g, 68% yield). ^{1}H NMR (400

MHz, DMSO-d_6) δ = 8.47-8.51 (m, 1H), 8.31 (s, 1H), 3.70 (s, 2H), 2.42 (s, 4H), 2.19-2.34 (m, 4H), 2.13 (s, 3H). LCMS: 322.1 [M+H].

Step 4: Synthesis of 3-fluoro-4-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)aniline

The title compound was prepared via a similar procedure described for step 4 of intermediate D19, starting from 1-(2-fluoro-4-nitro-6-(trifluoromethyl)benzyl)-4-methylpiperazine (0.143 g, 0.445 mmol), and was obtained as a pale brown gum (0.074 g, 26% yield) which was used without further purification. LCMS: 292.3 [M+H].

Intermediate D44 was prepared according to the following synthetic scheme:



INTERMEDIATE D44

4-((4-METHYL-4,7-DIAZASPIRO[2.5]OCTAN-7-YL)METHYL)-3-(TRIFLUOROMETHYL)ANILINE

Step 1: Synthesis of *tert*-butyl 4-methyl-4,7-diazaspiro[2.5]octane-7-carboxylate

The title compound was prepared via a similar procedure described for step 3 of intermediate D17, starting from *tert*-butyl 4,7-diazaspiro[2.5]octane-7-carboxylate (0.200 g, 0.942 mmol), and was obtained as a colorless gum (0.139 g, crude) which was used without further purification. LCMS: 227.1 [M+H].

Step 2: Synthesis of 4-methyl-4,7-diazaspiro[2.5]octane hydrochloride

The title compound was prepared via a similar procedure described for step 2 of intermediate A15, starting from *tert*-butyl 4-methyl-4,7-diazaspiro[2.5]octane-7-carboxylate (0.139 g, 0.614 mmol) with 1,4-dioxane as a solvent (3 mL), and was

obtained as an off-white solid (0.080 g, crude) which was used without further purification. LCMS: 127.3 [M+H].

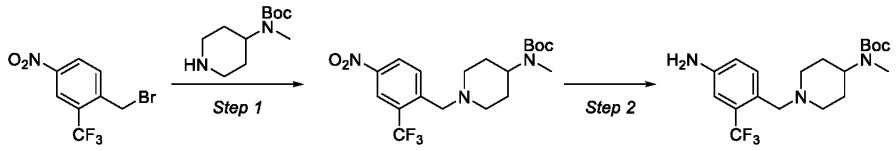
Step 3: Synthesis of 4-methyl-7-(4-nitro-2-(trifluoromethyl)benzyl)-4,7-diazaspiro[2.5] octane

The title compound was prepared via a similar procedure described for step 1 of intermediate D23, starting from 1-(bromomethyl)-4-nitro-2-(trifluoromethyl)benzene (0.150 g, 0.528 mmol) and 4-methyl-4,7-diazaspiro[2.5]octane (0.066 g, 0.528 mmol), and was obtained as a yellow gum (0.045 g, 26% yield). LCMS: 330.2 [M+H].

Step 4: Synthesis of 4-((4-methyl-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3-(trifluoromethyl) aniline

The title compound was prepared via a similar procedure described for step 2 of intermediate B2, starting from 4-methyl-7-(4-nitro-2-(trifluoromethyl)benzyl)-4,7-diazaspiro[2.5]octane (0.045 g, 0.137 mmol), and was obtained as a pale yellow solid (0.033 g, 81% yield) which was used without further purification. LCMS: 300.2 [M+H].

Intermediate D45 was prepared according to the following synthetic scheme:



INTERMEDIATE D45

TERT-BUTYL (1-(4-AMINO-2-(TRIFLUOROMETHYL)BENZYL)PIPERIDIN-4-YL)(METHYL)CARBAMATE

Step 1: Synthesis of *tert*-butyl methyl(1-(4-nitro-2-(trifluoromethyl)benzyl)piperidin-4-yl)carbamate

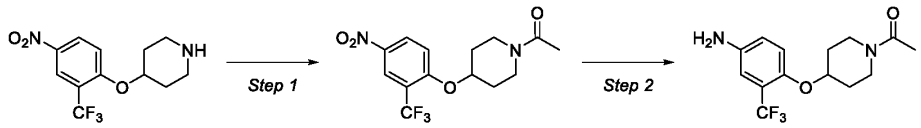
The title compound was prepared via a similar procedure described for step 1 of intermediate D23, starting from 1-(bromomethyl)-4-nitro-2-(trifluoromethyl)benzene

(0.199 g, 0.700 mmol) and *tert*-butyl methyl(piperidin-4-yl)carbamate (0.150 g, 0.700 mmol), and was obtained as a yellow gum (0.284 g, 97% yield). LCMS: 418.2 [M+H].

Step 2: Synthesis of *tert*-butyl (1-(4-amino-2-(trifluoromethyl)benzyl)piperidin-4-yl)(methyl)carbamate

The title compound was prepared via a similar procedure described for step 2 of intermediate B2, starting from *tert*-butyl methyl(1-(4-nitro-2-(trifluoromethyl)benzyl) piperidin-4-yl)carbamate (0.285 g, 0.683 mmol), and was obtained as a pale yellow solid (0.260 g, quantitative) which was used without further purification. LCMS: 388.2 [M+H].

Intermediate D50 was prepared according to the following synthetic scheme:



INTERMEDIATE D50

1-(4-(4-AMINO-2-(TRIFLUOROMETHYL)PHENOXY)PIPERIDIN-1-YL)ETHAN-1-ONE

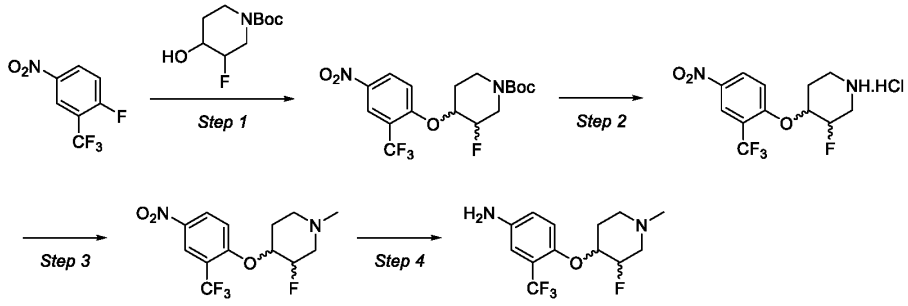
Step 1: Synthesis of 1-(4-(4-nitro-2-(trifluoromethyl)phenoxy)piperidin-1-yl)ethan-1-one

TEA (0.425 ml, 3.050 mmol) and acetic anhydride (0.125 ml, 1.321 mmol) were added to a solution of 4-(4-nitro-2-(trifluoromethyl)phenoxy)piperidine (synthesized as reported in PCT Publication No. WO 2018/222917 A1, 0.295 g, 1.016 mmol) in DCM (4 mL) at 0 °C and the resulting mixture was stirred at 25 °C for 16 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was quenched with ice water (10 mL) and extracted with DCM (2 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude material which was purified by flash column chromatography (silica gel 230-400, eluting with 80% EtOAc in petroleum ether), affording the title compound as a yellow gum (0.232 g, 70% yield). LCMS: 333.2 [M+H].

Step 2: Synthesis of 1-(4-(4-amino-2-(trifluoromethyl)phenoxy)piperidin-1-yl)ethan-1-one

The title compound was prepared via a similar procedure described for step 2 of intermediate B2, starting from 1-(4-(4-nitro-2-(trifluoromethyl)phenoxy)piperidin-1-yl)ethan-1-one (0.230 g, 0.692 mmol), and was obtained as a pale brown gum (0.131 g, 63% yield) following purification by flash column chromatography (silica gel 230-400, eluting with 5% MeOH in DCM). LCMS: 303.1 [M+H].

Intermediates D57a and D57b was prepared according to the following synthetic scheme:



INTERMEDIATES D57A AND D57B

4-((3-FLUORO-1-METHYLPIPERIDIN-4-YL)OXY)-3-(TRIFLUOROMETHYL)ANILINE

Step 1: Synthesis of *tert*-butyl 3-fluoro-4-(4-nitro-2-(trifluoromethyl)phenoxy)piperidine-1-carboxylate

Cs_2CO_3 (0.896 g, 2.750 mmol) was added to a solution of 1-fluoro-4-nitro-2-(trifluoromethyl)benzene (0.250 g, 1.196 mmol) and *tert*-butyl 3-fluoro-4-hydroxypiperidine-1-carboxylate (0.288 g, 1.315 mmol) in DMF (6 mL) and the resulting mixture was stirred at 100 °C for 16 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was poured into ice water (60 mL) and extracted with EtOAc (2 × 25 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude material which was purified by flash column chromatography (silica gel 230-400 mesh, eluting with 20% EtOAc in petroleum ether), giving two diastereomers

of the title compound as colorless gums (first eluting peak: 0.123 g, 30% yield; second eluting peak: 0.159 g, 39% yield). LCMS: 309.1 [M+H-Boc] for both diastereomers.

Step 2: Synthesis of 3-fluoro-4-(4-nitro-2-(trifluoromethyl)phenoxy)piperidine

Two diastereomers of the title compound were prepared via a similar procedure described for step 2 of intermediate A15, starting from *tert*-butyl 3-fluoro-4-(4-nitro-2-(trifluoromethyl)phenoxy)piperidine-1-carboxylate (first diastereomer: 0.123 g, 0.301 mmol; second diastereomer: 0.159 g, 0.389 mmol) with 1,4-dioxane as a solvent (3 or 5 mL), and were obtained as off-white solids (first diastereomer: 0.119 g; second diastereomer: 0.125 g; crude hydrochloride salts) which were used without further purification. LCMS: 309.1 [M+H] for both diastereomers.

Step 3: Synthesis of 3-fluoro-1-methyl-4-(4-nitro-2-(trifluoromethyl)phenoxy)piperidine

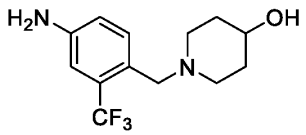
Two diastereomers of the title compound were prepared via a similar procedure described for step 3 of intermediate D17, starting from 3-fluoro-4-(4-nitro-2-(trifluoromethyl)phenoxy)piperidine (first diastereomer: 0.196 g, 0.636 mmol; second diastereomer: 0.093 g, 0.302 mmol), and were obtained as colorless gums (first diastereomer: 0.189 g; second diastereomer: 0.055 g; crude) which were used without further purification. LCMS: first diastereomer 323.2 [M+H]; second diastereomer 323.1 [M+H].

Step 2: Synthesis of 4-((3-fluoro-1-methylpiperidin-4-yl)oxy)-3-(trifluoromethyl)aniline

Two diastereomers of the title compound were prepared via a similar procedure described for step 4 of intermediate D19, starting from 3-fluoro-1-methyl-4-(4-nitro-2-(trifluoromethyl)phenoxy) piperidine (first diastereomer: 0.220 g, 0.683 mmol; second diastereomer: 0.055 g, 0.683 mmol), and were obtained as pale brown gums (first diastereomer: 0.085 g, 42% yield; second diastereomer: 0.045 g, 90% yield) which were used without further purification. LCMS: first diastereomer 293.1 [M+H]; second diastereomer 293.2 [M+H].

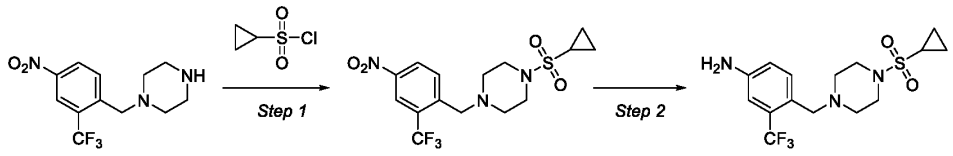
INTERMEDIATE D61

1-(4-AMINO-2-(TRIFLUOROMETHYL)BENZYL)PIPERIDIN-4-OL



The title compound was prepared via a similar procedure described for step 4 of intermediate D19, starting from 1-(4-nitro-2-(trifluoromethyl)benzyl)piperidin-4-ol (0.254 g, 0.835 mmol), and was obtained as a pale brown gum (0.173 g, 75% yield) which was used without further purification. LCMS: 275.2 [M+H].

Intermediate D62 was prepared according to the following synthetic scheme:



INTERMEDIATE D62

4-((4-(CYCLOPROPYLSULFONYL)PIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)ANILINE

Step 1: Synthesis of 1-(cyclopropylsulfonyl)-4-(4-nitro-2-(trifluoromethyl)benzyl) piperazine

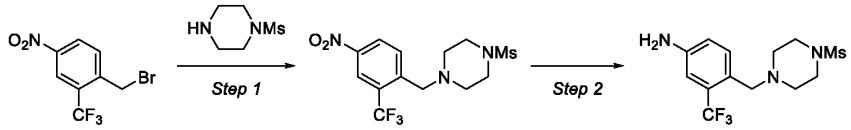
The title compound was prepared via a similar procedure described for step 3 of intermediate A15, starting from 1-(4-nitro-2-(trifluoromethyl)benzyl)piperazine (synthesized as reported in PCT Publication No. WO 2014/072220 A1, 0.408 g, 1.411 mmol) and cyclopropanesulfonyl chloride (0.198 g, 1.411 mmol), and was obtained as an off-white solid (0.275 g, 49% yield). LCMS: 394.0 [M+H].

Step 2: Synthesis of 4-((4-(cyclopropylsulfonyl)piperazin-1-yl)methyl)-3-(trifluoromethyl) aniline

The title compound was prepared via a similar procedure described for step 4 of intermediate D19, starting from 1-(cyclopropylsulfonyl)-4-(4-nitro-2-(trifluoromethyl)benzyl)piperazine (0.272 g, 0.691 mmol), and was obtained as a pale

brown gum (0.225 g, 90% yield) which was used without further purification. LCMS: 364.2 [M+H].

Intermediate D63 was prepared according to the following synthetic scheme:



INTERMEDIATE D63

4-((4-(METHYLSULFONYL)PIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)ANILINE

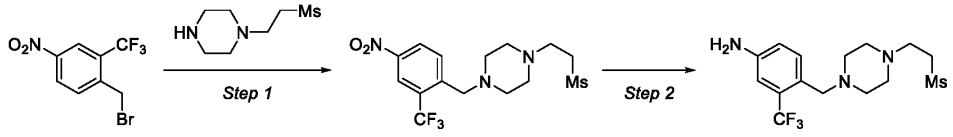
Step 1: Synthesis of 1-(methylsulfonyl)-4-(4-nitro-2-(trifluoromethyl)benzyl)piperazine

The title compound was prepared via a similar procedure described for step 1 of intermediate D23, starting from 1-(bromomethyl)-4-nitro-2-(trifluoromethyl)benzene (0.250 g, 0.880 mmol) and 1-(methylsulfonyl)piperazine (0.145 g, 0.880 mmol), and was obtained as a pale yellow solid (0.060 g, 19% yield). LCMS: 368.1 [M+H].

Step 2: Synthesis of 4-((4-(methylsulfonyl)piperazin-1-yl)methyl)-3-(trifluoromethyl)aniline

The title compound was prepared via a similar procedure described for step 4 of intermediate D19, starting from 1-(methylsulfonyl)-4-(4-nitro-2-(trifluoromethyl)benzyl)piperazine (0.050 g, 0.136 mmol), and was obtained as a pale brown gum (0.037 g, 81% yield) which was used without further purification. LCMS: 338.2 [M+H].

Intermediate D64 was prepared according to the following synthetic scheme:



INTERMEDIATE D64

4-((4-(2-(METHYLSULFONYL)ETHYL)PIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)ANILINE

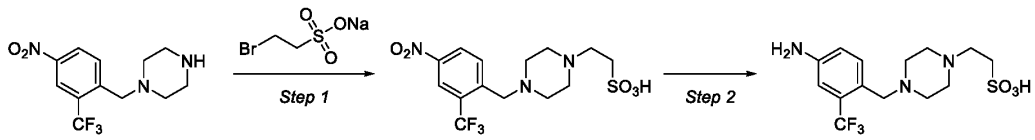
Step 1: Synthesis of 1-(2-(methylsulfonyl)ethyl)-4-(4-nitro-2-(trifluoromethyl)benzyl) piperazine

The title compound was prepared via a similar procedure described for step 1 of intermediate D23, starting from 1-(bromomethyl)-4-nitro-2-(trifluoromethyl)benzene (0.250 g, 0.880 mmol) and 1-(2-(methylsulfonyl)ethyl)piperazine dihydrochloride (0.233 g, 0.880 mmol), and was obtained as a pale yellow gum (0.175 g, 50% yield). LCMS: 396.1 [M+H].

Step 2: Synthesis of 4-((4-(2-(methylsulfonyl)ethyl)piperazin-1-yl)methyl)-3-(trifluoromethyl)aniline

The title compound was prepared via a similar procedure described for step 4 of intermediate D19, starting from 1-(2-(methylsulfonyl)ethyl)-4-(4-nitro-2-(trifluoromethyl)benzyl)piperazine (0.173 g, 0.438 mmol), and was obtained as a pale brown gum (0.135 g, 84% yield) which was used without further purification. LCMS: 366.2 [M+H].

Intermediate D65 was prepared according to the following synthetic scheme:



INTERMEDIATE D65

2-(4-(4-AMINO-2-(TRIFLUOROMETHYL)BENZYL)PIPERAZIN-1-YL)ETHANE-1-SULFONIC ACID

Step 1: Synthesis of 2-(4-(4-nitro-2-(trifluoromethyl)benzyl)piperazin-1-yl)ethane-1-sulfonic acid

Sodium 2-bromoethane-1-sulfonate (0.292 g, 1.383 mmol) and Cs_2CO_3 (0.676 g, 2.074 mmol) were added to a solution of 1-(4-nitro-2-(trifluoromethyl)benzyl)piperazine (synthesized as reported in PCT Publication No. WO 2014/072220 A1, 0.200 g, 0.691 mmol) in water (5 mL) at 0 °C and the resulting mixture was stirred at 25 °C for 16 h. Following completion of the reaction (as

indicated by LCMS), the reaction mixture was directly purified by preparative HPLC (eluting with 0.1% HCOOH in water and ACN), giving the title compound as an off-white solid (0.045 g, 16% yield). LCMS: 398.2 [M+H].

Step 2: Synthesis of 2-(4-(4-amino-2-(trifluoromethyl)benzyl)piperazin-1-yl)ethane-1-sulfonic acid

Zinc powder (0.074 g, 1.132 mmol) and NH_4Cl (0.061 g, 1.132 mmol) were added to a solution of 2-(4-(4-nitro-2-(trifluoromethyl)benzyl)piperazin-1-yl)ethane-1-sulfonic acid (0.045 g, 0.113 mmol) in MeOH (6 mL) and the resulting mixture was stirred at 25 °C for 12 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was filtered through a pad of Celite® (*i.e.*, diatomaceous earth) and the resulting filtrate was concentrated under reduced pressure to afford crude material which was purified by preparative HPLC (eluting with 10mM NH_4OAc in water and ACN), giving the title compound as a pale brown gum (0.03 g, 71 % yield). LCMS: 368.1 [M+H].

PREPARATION OF EXAMPLES

General urea formation procedure for the synthesis of Examples 1-115:

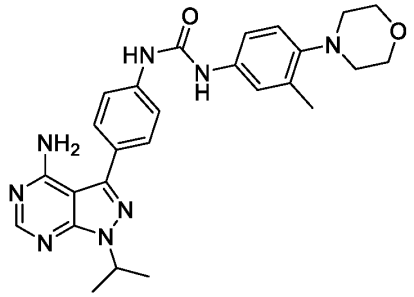
Method A – DMAP (0.05 eq.) and DIPEA (1.5 eq.) were added to a solution of carbamate Intermediate C (1.0 eq.) and amine Intermediate D (1.0 eq.) in THF (10 vol.) and the resulting mixture was stirred at 60 °C for 12 h in a sealed tube. Following completion of the reaction (as indicated by LCMS), the reaction mixture was concentrated under reduced pressure to yield crude material which was purified by reverse phase preparative HPLC, affording the title product.

Method B – TEA (2.0 eq.) was added to a mixture of carbamate Intermediate C (1.0 eq.) and amine Intermediate D (1.0 eq.) in THF (5 mL) and the resulting mixture was stirred at 60 °C for 12 h in a sealed tube. Following completion of the reaction (as indicated by LCMS), the reaction mixture was concentrated under reduced pressure to

yield crude material which was purified by reverse phase preparative HPLC, affording the title product.

EXAMPLE 1

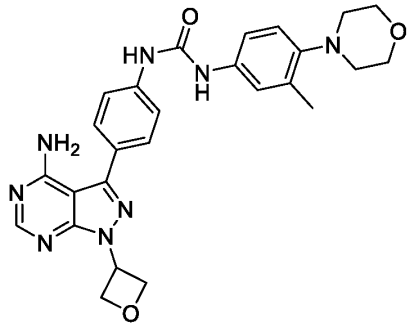
1-(4-(4-AMINO-1-ISOPROPYL-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)PHENYL)-3-(3-METHYL-4-MORPHOLINOPHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method B), starting from 3-(4-aminophenyl)-1-isopropyl-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (B2, 0.100 g, 0.372 mmol) and phenyl (3-methyl-4-morpholinophenyl)carbamate (C4, 0.116 g, 0.372 mmol), and was obtained as an off-white solid (0.023 g, 13% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.84 (bs, 1H), 8.54 (bs, 1H), 8.24 (bs, 1H), 7.56-7.64 (m, 4H), 7.26-7.29 (m, 2H), 6.99 (d, J = 8.4 Hz, 1H), 5.04-5.08 (m, 1H), 3.73-3.74 (m, 4H), 2.79-2.80 (m, 4H), 2.26 (s, 3H), 1.49 (d, J = 6.6 Hz, 6H). LCMS: 487.2 [M+H].

EXAMPLE 2

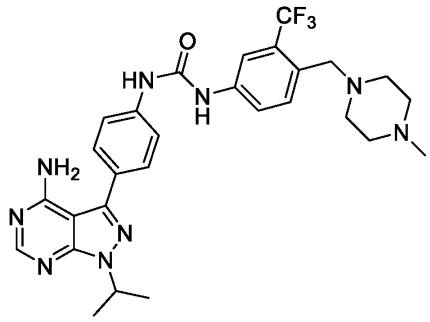
1-(4-(4-AMINO-1-(OXETAN-3-YL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)PHENYL)-3-(3-METHYL-4-MORPHOLINOPHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method B), starting from 3-(4-aminophenyl)-1-(oxetan-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (B3, 0.090 g, 0.318 mmol) and phenyl (3-methyl-4-morpholinophenyl)carbamate (C4, 0.099 g, 0.318 mmol), and was obtained as an off-white solid (0.015 g, 10% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 9.04 (bs, 1H), 8.72 (bs, 1H), 8.25 (bs, 1H), 7.62-7.68 (m, 4H), 7.26-7.30 (m, 2H), 6.99 (d, *J* = 8.5 Hz, 1H), 5.98-6.05 (m, 1H), 5.10 (t, *J* = 6.4 Hz, 2H), 4.99 (t, *J* = 6.8 Hz, 2H), 3.72-3.74 (m, 4H), 2.78-2.80 (m, 4H), 2.26 (s, 3H). LCMS: 501.2 [M+H].

EXAMPLE 3

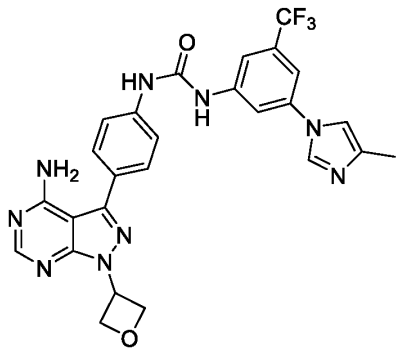
1-(4-(4-AMINO-1-ISOPROPYL-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)PHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method B), starting from 3-(4-aminophenyl)-1-isopropyl-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (B2, 0.080 g, 0.298 mmol) and phenyl (4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)carbamate (C1, 0.117 g, 0.298 mmol), and was obtained as an off-white solid (0.038 g, 22% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 9.33 (bs, 1H), 9.26 (bs, 1H), 8.24 (s, 1H), 8.01 (s, 1H), 7.58-7.68 (m, 6H), 5.03-5.08 (m, 1H), 3.54 (s, 2H), 2.34-2.39 (m, 8H), 2.17 (s, 3H), 1.50 (d, *J* = 6.8 Hz, 6H). LCMS: 568.2[M+H].

EXAMPLE 4

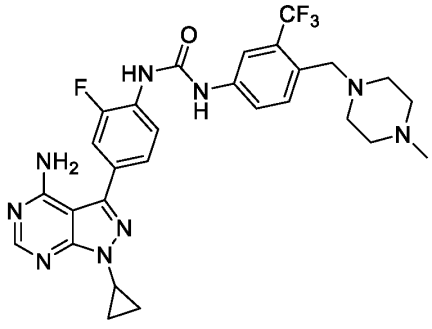
1-(4-(4-AMINO-1-(OXETAN-3-YL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)PHENYL)-3-(3-(4-METHYL-1H-IMIDAZOL-1-YL)-5-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method B), starting from 3-(4-aminophenyl)-1-(oxetan-3-yl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (B3, 0.080 g, 0.22 mmol) and phenyl (3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)carbamate (C3, 0.062 g, 0.22 mmol), and was obtained as an off-white solid (0.020 g, 16% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.54 (bs, 1H), 9.50 (bs, 1H), 8.26 (s, 1H), 8.22 (bs, 1H), 7.90 (d, *J* = 6.0 Hz, 2H), 7.66-7.73 (m, 4H), 7.59 (s, 1H), 7.50 (s, 1H), 6.00-6.04 (m, 1H), 5.11 (t, *J* = 6.4 Hz, 2H), 5.00 (t, *J* = 6.8 Hz, 2H), 2.19 (s, 3H). LCMS: 549.9[M+H].

EXAMPLE 5

1-(4-(4-AMINO-1-CYCLOPROPYL-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA

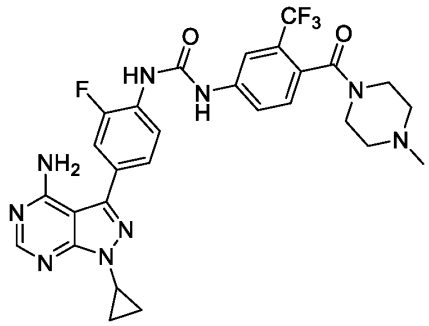


The title compound was obtained following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-cyclopropyl-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (B1, 0.100 g, 0.352 mmol) and phenyl (4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)carbamate (C1, 0.208 g, 0.528

mmol), and was obtained as an off-white solid (0.019 g, 8% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.41 (s, 1H), 8.34-8.38 (m, 1H), 7.96-7.96 (m, 1H), 7.68-7.91 (m, 2H), 7.48-7.55 (m, 2H), 3.98-4.01 (m, 1H), 3.76 (s, 2H), 3.50-3.52 (m, 2H), 3.11-3.15 (m, 4H), 2.93 (s, 3H), 2.48 (bs, 2H), 1.36-1.40 (m, 2H), 1.20-1.25 (m, 2H). LCMS: 584.2 [M+H].

EXAMPLE 6

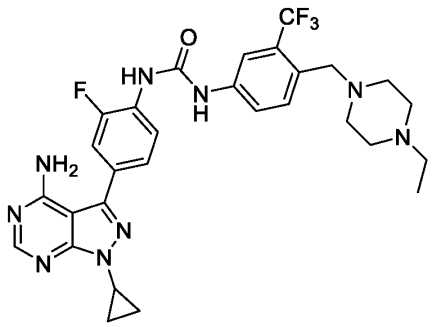
1-(4-(4-AMINO-1-CYCLOPROPYL-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(4-(4-METHYLPIPERAZINE-1-CARBONYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-1-cyclopropyl-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-fluorophenyl)carbamate (C5, 0.090 g, 0.223 mmol) and (4-amino-2-(trifluoromethyl)phenyl)(4-methylpiperazin-1-yl)methanone (D2, 0.064 g, 0.223 mmol), and was obtained as an off-white solid (0.008 g, 6% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.33-8.37 (m, 1H), 8.30 (s, 1H), 8.08 (d, *J* = 2.0 Hz, 1H), 7.75-7.78 (m, 1H), 7.48-7.53 (m, 2H), 7.39-7.41 (m, 1H), 3.81-3.85 (m, 3H), 3.24-3.28 (m, 2H), 2.53-2.61 (m, 2H), 2.42 (s, 2H), 2.37 (s, 3H), 1.29-1.33 (m, 2H), 1.16-1.21 (m, 2H). LCMS: 598.4 [M+H].

EXAMPLE 7

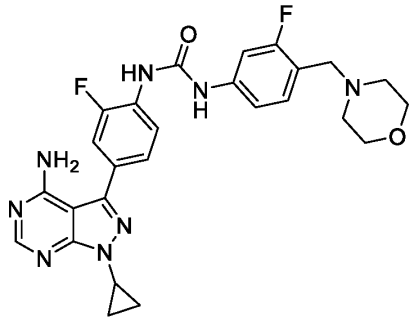
1-(4-(4-AMINO-1-CYCLOPROPYL-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(4-((4-ETHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-1-cyclopropyl-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-fluorophenyl)carbamate (C5, 0.098 g, 0.213 mmol) and 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (D1, 0.067 g, 0.235 mmol), and was obtained as an off-white solid (0.037 g, 28% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.39 (s, 1H), 8.33-8.37 (m, 1H), 7.95-7.95 (m, 1H), 7.68-7.74 (m, 2H), 7.48-7.55 (m, 2H), 3.95-3.99 (m, 1H), 3.77 (bs, 2H), 3.35 (bs, 2H), 3.28-3.29 (m, 2H), 3.14-3.16 (m, 4H), 2.52 (bs, 2H), 1.35-1.39 (m, 5H), 1.20-1.24 (m, 2H). LCMS: 598.2 [M+H].

EXAMPLE 8

1-(4-(4-AMINO-1-CYCLOPROPYL-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-FLUORO-4-(MORPHOLINOMETHYL)PHENYL)UREA

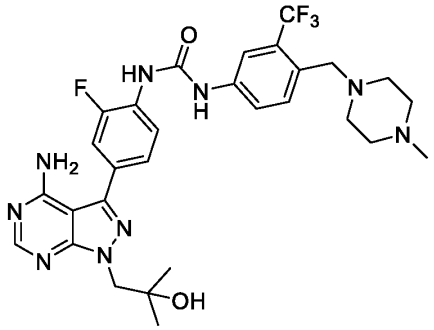


The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-1-cyclopropyl-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-fluorophenyl)carbamate (C5, 0.140 g, 0.305 mmol) and 3-fluoro-4-(morpholinomethyl)aniline (D10, 0.064 g, 0.305 mmol), and was

obtained as an off-white solid (0.018 g, 11% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.32-8.36 (m, 1H), 8.29 (s, 1H), 7.46-7.55 (m, 3H), 7.34-7.38 (m, 1H), 7.13-7.16 (m, 1H), 3.79-3.84 (m, 1H), 3.72-3.75 (m, 4H), 3.68 (s, 2H), 2.61-2.63 (m, 4H), 1.29-1.33 (m, 2H), 1.17-1.21 (m, 2H). LCMS: 521.2 [M+H].

EXAMPLE 9

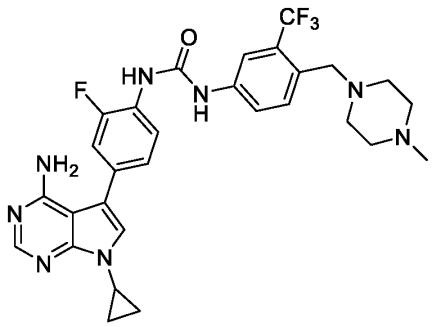
1-(4-(4-AMINO-1-(2-HYDROXY-2-METHYLPROPYL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from 1-(4-amino-3-(4-amino-3-fluorophenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)-2-methylpropan-2-ol (B4, 0.100 g, 0.316 mmol) and phenyl (4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)carbamate (C1, 0.187 g, 0.474 mmol), and was obtained as an off-white solid (0.010 g, 5% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.37-8.40 (m, 2H), 7.96 (d, *J* = 2.0 Hz, 1H), 7.70-7.72 (m, 2H), 7.56-7.59 (m, 2H), 4.48 (s, 2H), 3.76 (s, 2H), 3.52 (bs, 2H), 2.99-3.24 (m, 4H), 2.93 (s, 3H), 2.50 (bs, 2H), 1.32 (s, 6H). LCMS: 615.8 [M+H].

EXAMPLE 10

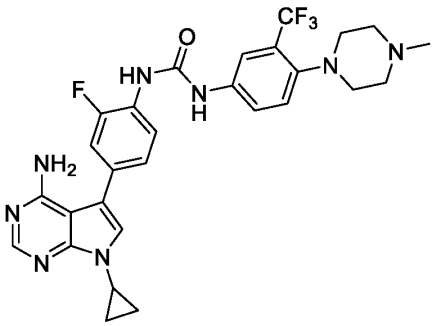
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from 5-(4-amino-3-fluorophenyl)-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (B5, 0.100 g, 0.353 mmol) and phenyl (4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)carbamate (C1, 0.139 g, 0.353 mmol), and was obtained as an off-white solid (0.039 g, 20% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.36 (s, 1H), 8.21 (t, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 2.0 Hz, 1H), 7.67-7.73 (m, 2H), 7.47 (s, 1H), 7.29-7.37 (m, 2H), 3.72 (s, 2H), 3.67-3.71 (m, 1H), 3.49-3.51 (m, 2H), 3.04-3.18 (m, 4H), 2.93 (s, 3H), 2.48 (s, 2H), 1.15-1.25 (m, 4H). LCMS: 583.3 [M+H].

EXAMPLE 11

1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-(4-METHYLPIPERAZIN-1-YL)-3-(TRIFLUOROMETHYL)PHENYL)UREA

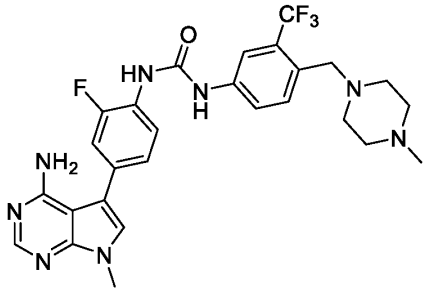


The title compound was obtained following the general procedure for urea formation (Method A), starting from 5-(4-amino-3-fluorophenyl)-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (B5, 0.100 g, 0.353 mmol) and phenyl (4-(4-methylpiperazin-1-yl)-3-(trifluoromethyl)phenyl)carbamate (C7, 0.201 g, 0.529 mmol),

and was obtained as an off-white solid (0.027 g, 13% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.34 (s, 1H), 8.20 (t, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 2.4 Hz, 1H), 7.72-7.75 (m, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.44 (s, 1H), 7.29-7.36 (m, 2H), 3.62-3.77 (m, 3H), 3.19-3.24 (m, 6H), 3.01 (s, 3H), 1.17-1.21 (m, 4H). LCMS: 569.3 [M+H].

EXAMPLE 12

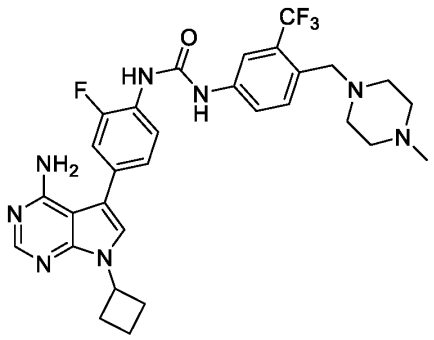
1-(4-(4-AMINO-7-METHYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C8, 0.060 g, 0.159 mmol) and 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (D6, 0.048 g, 0.175 mmol), and was obtained as white solid (0.009 g, 8% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.41 (bs, 1H), 8.70 (d, *J* = 2.4 Hz, 1H), 8.11-8.23 (m, 2H), 8.01 (d, *J* = 2.0 Hz, 1H), 7.64-7.66 (m, 1H), 7.54-7.57 (m, 1H), 7.34 (s, 1H), 7.23-7.33 (m, 2H), 6.16 (bs, 2H), 3.74 (s, 3H), 3.55 (s, 2H), 2.41 (bs, 8H), 2.20 (s, 3H). LCMS: 556.8 [M+H].

EXAMPLE 13

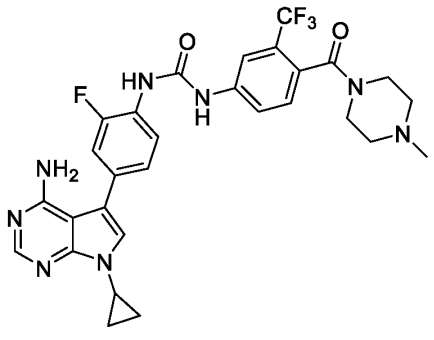
1-(4-(4-AMINO-7-CYCLOBUTYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from 5-(4-amino-3-fluorophenyl)-7-cyclobutyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (B7, 0.135 g, 0.454 mmol) and phenyl (4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)carbamate (C1, 0.179 g, 0.454 mmol), and was obtained as a white solid (0.043 g, 15%). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.53 (bs, 1H), 8.83 (bs, 1H), 8.40 (s, 1H), 8.25 (t, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 1.6 Hz, 1H), 7.94 (s, 1H), 7.60-7.66 (m, 2H), 7.39-7.42 (m, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 5.24-5.26 (m, 1H), 3.88 (s, 2H), 3.40-3.43 (m, 2H), 2.90-3.03 (m, 4H), 2.82 (s, 3H), 2.56-2.68 (m, 2H), 2.40-2.46 (m, 4H), 1.85-1.90 (m, 2H). LCMS: 597.2 [M+H].

EXAMPLE 14

1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-(4-METHYLPIPERAZINE-1-CARBONYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA

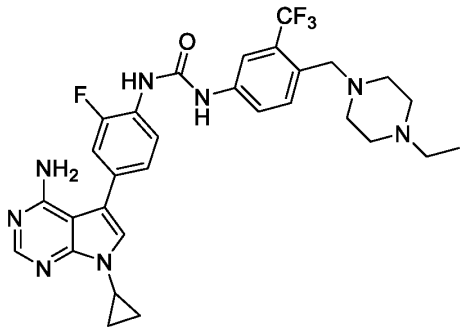


The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.100 g, 0.248 mmol) and

(4-amino-2-(trifluoromethyl)phenyl)(4-methylpiperazin-1-yl)methanone (D2, 0.078 g, 0.273 mmol), and was obtained as a white solid (0.009 g, 6% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.36 (s, 1H), 8.17-8.21 (m, 1H), 8.11 (d, *J* = 1.6 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.48-7.50 (m, 2H), 7.30-7.37 (m, 2H), 3.68-3.72 (m, 1H), 3.46 (s, 8H), 2.98 (s, 3H), 1.18-1.22 (m, 4H). LCMS: 597.3 [M+H].

EXAMPLE 15

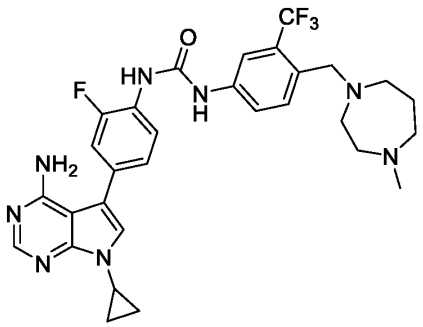
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-ETHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.168 g, 0.418 mmol) and 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (D1, 0.120 g, 0.418 mmol), and was obtained as an off-white solid (0.009 g, 4% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.36 (s, 1H), 8.21 (t, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 2.0 Hz, 1H), 7.66-7.73 (m, 2H), 7.48 (s, 1H), 7.29-7.37 (m, 2H), 3.73 (s, 2H), 3.69-3.72 (m, 1H), 3.50-3.57 (m, 2H), 3.21-3.27 (m, 2H), 3.09-3.16 (m, 4H), 2.49 (bs, 2H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.18-1.22 (m, 4H). LCMS: 597.3 [M+H].

EXAMPLE 16

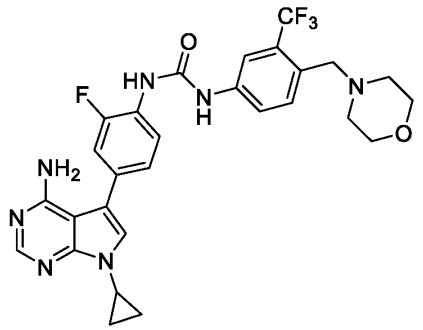
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYL-1,4-DIAZEPAN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.160 g, 0.397 mmol) and 4-((4-methyl-1,4-diazepan-1-yl)methyl)-3-(trifluoromethyl)aniline (D7, 0.080 g, 0.278 mmol), and was obtained as an off-white solid (0.010 g, 4% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.15-8.21 (m, 2H), 7.90 (d, *J* = 2.0 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.69-7.72 (m, 1H), 7.27-7.33 (m, 2H), 7.21 (s, 1H), 3.84 (s, 2H), 3.51-3.54 (m, 1H), 3.35-3.38 (m, 2H), 3.24-3.28 (m, 2H), 2.79-2.91 (m, 7*H*), 2.04-2.07 (m, 2H), 1.13-1.17 (m, 2H), 1.07-1.10 (m, 2H). LCMS: 596.9 [M+H].

EXAMPLE 17

1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-(MORPHOLINOMETHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA

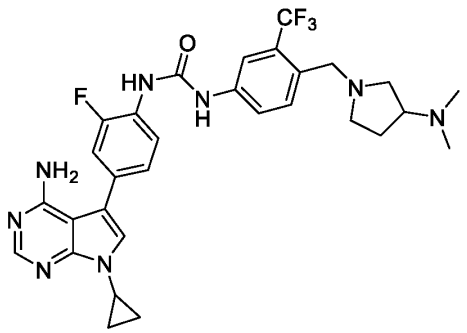


The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.077 g, 0.191 mmol) and 4-(morpholinomethyl)-3-(trifluoromethyl)aniline (D3, 0.071 g, 0.273 mmol), and was

obtained as an off-white solid (0.012 g, 7% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.65 (bs, 1H), 8.88 (bs, 1H), 8.41 (s, 1H), 8.20-8.24 (m, 1H), 8.09 (bs, 1H), 7.70-7.78 (m, 2H), 7.70 (s, 1H), 7.35-7.39 (m, 1H), 7.24-7.28 (m, 1H), 4.35 (s, 2H), 3.67-3.72 (m, 5H), 3.20 (bs, 4H), 1.09-1.11 (m, 4H). LCMS: 570.3 [M+H].

EXAMPLE 18

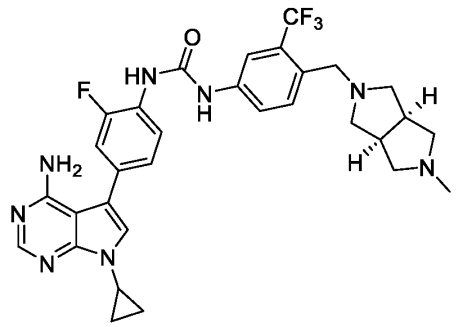
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((3-(DIMETHYLAMINO)PYRROLIDIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.100 g, 0.193 mmol) and 1-(4-amino-2-(trifluoromethyl)benzyl)-*N*,*N*-dimethylpyrrolidin-3-amine (D4, 0.061 g, 0.213 mmol), and was obtained as an off-white solid (0.040 g, 34% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.37 (s, 1H), 8.21 (t, *J* = 8.0 Hz, 1H), 8.04 (s, 1H), 7.73-7.73 (m, 2H), 7.49 (s, 1H), 7.30-7.37 (m, 2H), 4.15-4.16 (m, 2H), 4.02-4.04 (m, 1H), 3.71-3.73 (m, 1H), 3.40-3.41 (m, 1H), 3.24-3.28 (m, 2H), 2.92-2.95 (m, 7*H*), 2.45-2.48 (m, 1H), 2.18-2.24 (m, 1H), 1.18-1.22 (m, 4H). LCMS: 597.3 [M+H].

EXAMPLE 19

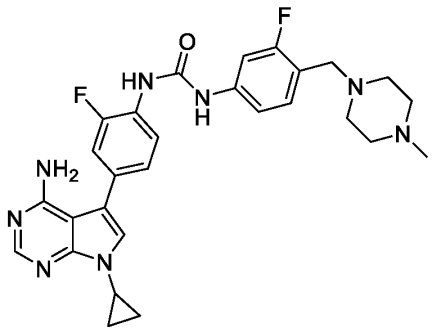
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-(((3A*R*,6A*S*)-5-METHYLHEXAHYDROPYRROLO[3,4-*C*]PYRROL-2(1H)-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and 4-(((3a*R*,6a*S*)-5-methylhexahydropyrrolo[3,4-*c*]pyrrol-2(1H)-yl)methyl)-3-(trifluoromethyl)aniline (D8, 0.056 g, 0.186 mmol), and was obtained as an off-white solid (0.016 g, 13% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.17-8.20 (m, 2H), 7.91 (bs, 1H), 7.71-7.73 (m, 2H), 7.28-7.33 (m, 2H), 7.21 (bs, 1H), 3.79 (bs, 2H), 3.52-3.53 (m, 3H), 3.03 (bs, 4H), 2.88 (s, 3H), 2.78-2.81 (m, 2H), 2.41 (bs, 2H), 1.09-1.17 (m, 4H). LCMS: 609.3 [M+H].

EXAMPLE 20

1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(3-FLUORO-4-((4-METHYLPIPERAZIN-1-YL)METHYL)PHENYL)UREA

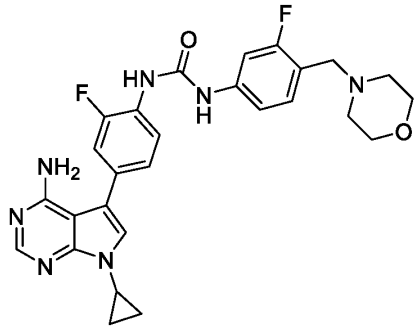


The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and 3-fluoro-4-((4-methylpiperazin-1-yl)methyl)aniline (D9, 0.042 g, 0.186 mmol), and was

obtained as an off-white solid (0.005 g, 5% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.20 (s, 1H), 8.14-8.18 (m, 1H), 7.49-7.53 (m, 1H), 7.27-7.36 (m, 3H), 7.21 (s, 1H), 7.13-7.16 (m, 1H), 3.70 (s, 2H), 3.50-3.55 (m, 1H), 3.15-3.19 (m, 4H), 2.80-2.87 (m, 7*H*), 1.06-1.18 (m, 4H). LCMS: 533.3 [M+H].

EXAMPLE 21

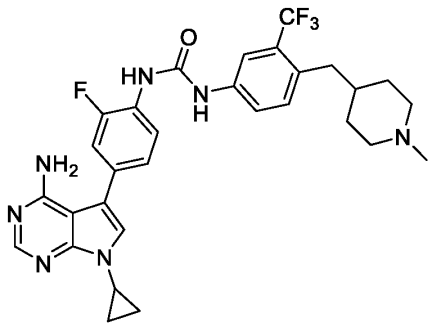
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(3-FLUORO-4-(MORPHOLINOMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.140 g, 0.347 mmol) and 3-fluoro-4-(morpholinomethyl)aniline (D10, 0.073 g, 0.347 mmol), and was obtained as an off-white solid (0.035 g, 17% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.21 (s, 1H), 8.17-8.19 (m, 1H), 7.58-7.62 (m, 1H), 7.39-7.44 (m, 1H), 7.27-7.33 (m, 2H), 7.23 (s, 1H), 7.18-7.20 (m, 1H), 3.95 (s, 2H), 3.74-3.82 (m, 4H), 3.55-3.58 (m, 1H), 2.90 (bs, 4H), 1.07-1.19 (m, 4H). LCMS: 520.2 [M+H].

EXAMPLE 22

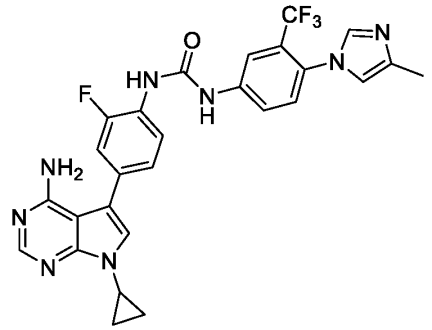
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((1-METHYLPIPERIDIN-4-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and 4-((1-methylpiperidin-4-yl)methyl)-3-(trifluoromethyl)aniline (D11, 0.051 g, 0.186 mmol), and was obtained as a white solid (0.040 g, 33% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.30-8.34 (m, 2H), 7.94 (d, *J* = 2.4 Hz, 1H), 7.64-7.67 (m, 1H), 7.50-7.58 (m, 2H), 7.40-7.42 (m, 1H), 6.90 (s, 1H), 3.60-3.62 (m, 1H), 3.51-3.54 (m, 2H), 2.94-3.00 (m, 2H), 2.86 (s, 3H), 2.78-2.79 (m, 2H), 1.92-1.95 (m, 3H), 1.55-1.58 (m, 2H), 1.12-1.14 (m, 2H), 0.80-0.83 (m, 2H). LCMS: 582.3 [M+H].

EXAMPLE 23

1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-(4-METHYL-1H-IMIDAZOL-1-YL)-3-(TRIFLUOROMETHYL)PHENYL)UREA

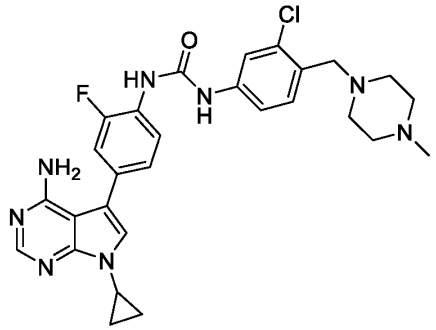


The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.160 g, 0.397 mmol) and

4-(4-methyl-1H-imidazol-1-yl)-3-(trifluoromethyl)aniline (D5, 0.096 g, 0.397 mmol), and was obtained as a white solid (0.010 g, 5% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.20-8.22 (m, 2H), 8.15-8.15 (m, 1H), 7.79-7.82 (m, 1H), 7.66 (s, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.29-7.34 (m, 2H), 7.22 (s, 1H), 7.00 (s, 1H), 3.50-3.54 (m, 1H), 2.27 (s, 3H), 1.07-1.17 (m, 4H). LCMS: 551.1 [M+H].

EXAMPLE 24

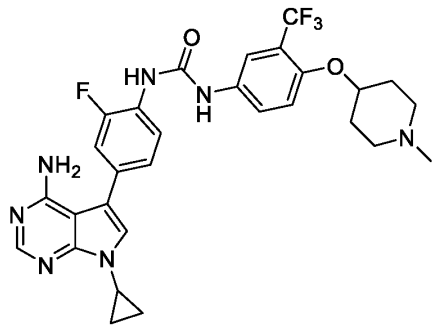
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(3-CHLORO-4-((4-METHYLPIPERAZIN-1-YL)METHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from 5-(4-amino-3-fluorophenyl)-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (B5, 0.060 g, 0.212 mmol) and phenyl (3-chloro-4-((4-methylpiperazin-1-yl)methyl)phenyl)carbamate (C9, 0.084 g, 0.233 mmol), and was obtained as an off-white gum (0.010 g, 8% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.37 (s, 1H), 8.22 (t, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 2.4 Hz, 1H), 7.49 (s, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.33-7.44 (m, 2H), 7.29-7.31 (m, 1H), 3.70-3.75 (m, 3H), 2.90 (s, 3H), 2.40-2.89 (m, 8H), 1.18-1.23 (m, 4H). LCMS: 549.3 [M+H].

EXAMPLE 25

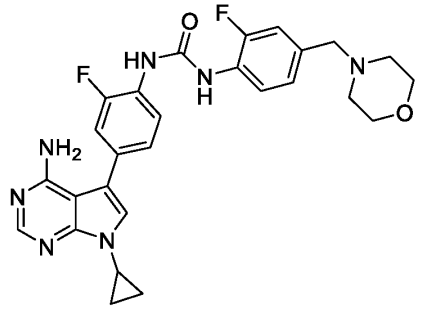
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((1-METHYLPIPERIDIN-4-YL)OXY)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.150 g, 0.372 mmol) and 4-((1-methylpiperidin-4-yl)oxy)-3-(trifluoromethyl)aniline (D12, 0.102 g, 0.372 mmol), and was obtained as pale brown solid (0.100 g, 44% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.36 (s, 1H), 8.19 (t, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 2.4 Hz, 1H), 7.63-7.66 (m, 1H), 7.48 (s, 1H), 7.24-7.36 (m, 3H), 4.96 (bs, 1H), 3.69-3.72 (m, 2H), 3.49-3.51 (m, 1H), 3.23-3.30 (m, 2H), 2.93 (bs, 3H), 1.90-2.48 (m, 4H), 1.18-1.23 (m, 4H). LCMS: 584.3 [M+H].

EXAMPLE 26

1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(2-FLUORO-4-(MORPHOLINOMETHYL)PHENYL)UREA

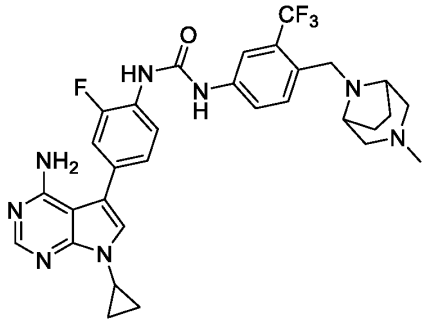


The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and 2-fluoro-4-(morpholinomethyl)aniline (D10, 0.039 g, 0.186 mmol), and was obtained as

an off-white solid (0.009 g, 9.7% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.20-8.24 (m, 2H), 8.07-8.11 (m, 1H), 7.26-7.32 (m, 2H), 7.15-7.22 (m, 3H), 3.71-3.73 (m, 4H), 3.50-3.52 (m, 3H), 2.48-2.50 (m, 4H), 1.14-1.16 (m, 2H), 1.08-1.09 (m, 2H). LCMS: 520.2 [M+H].

EXAMPLE 27

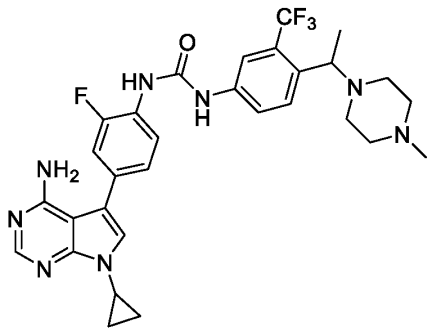
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((3-METHYL-3,8-DIAZABICYCLO[3.2.1]OCTAN-8-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.054 g, 0.134 mmol) and 4-((3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)methyl)-3-(trifluoromethyl)aniline (D14, 0.040 g, 0.134 mmol), and was obtained as an off-white solid (0.008 g, 10% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.35 (s, 1H), 8.22 (t, *J* = 8.0 Hz, 1H), 7.95 (s, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.46 (s, 1H), 7.30-7.37 (m, 2H), 3.66-3.81 (m, 3H), 3.49-3.51 (m, 2H), 3.15 (s, 2H), 2.86 (s, 3H), 2.32-2.34 (m, 2H), 1.94-1.96 (m, 2H), 1.17-1.35 (m, 6H). LCMS: 609.5 [M+H].

EXAMPLE 28

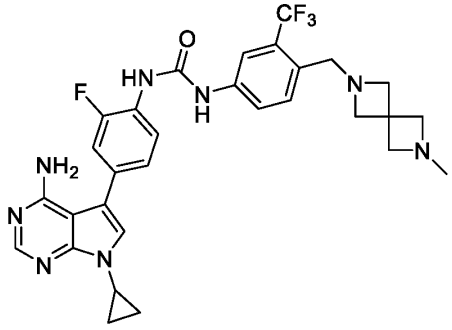
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-(1-(4-METHYLPIPERAZIN-1-YL)ETHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.085 g, 0.211 mmol) and 4-(1-(4-methylpiperazin-1-yl)ethyl)-3-(trifluoromethyl)aniline (D15, 0.061 g, 0.211 mmol), and was obtained as an off-white solid (0.020 g, 16% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.25 (t, *J* = 8.4 Hz, 1H), 8.16 (s, 1H), 7.91 (bs, 1H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.47-7.52 (m, 2H), 6.64 (s, 1H), 3.69-3.70 (m, 1H), 3.47-3.51 (m, 1H), 2.80-2.88 (m, 4H), 2.49-2.60 (m, 7*H*), 1.34-1.35 (m, 3H), 1.05-1.10 (m, 2H), 0.66-0.70 (m, 2H). LCMS: 597.3 [M+H].

EXAMPLE 29

1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((6-METHYL-2,6-DIAZASPIRO[3.3]HEPTAN-2-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA

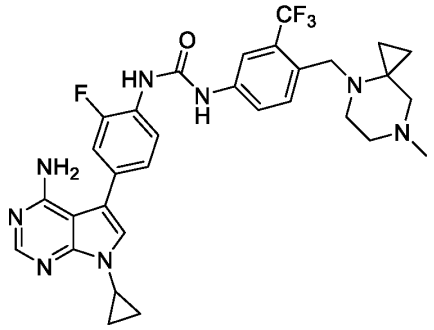


The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.106 g, 0.263 mmol) and

4-((6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)-3-(trifluoromethyl)aniline (D16, 0.075 g, 0.263 mmol), and was obtained as an off-white solid (0.002 g, 1.3% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.31-8.35 (m, 2H), 8.12 (d, *J* = 2.0 Hz, 1H), 7.80-7.83 (m, 1H), 7.53-7.64 (m, 3H), 6.91 (s, 1H), 4.50 (bs, 2H), 4.43 (bs, 4H), 3.61-3.64 (m, 3H), 2.93 (s, 3H), 2.45-2.50 (m, 2H), 1.05-1.10 (m, 2H), 0.66-0.70 (m, 2H). LCMS: 595.4 [M+H].

EXAMPLE 30

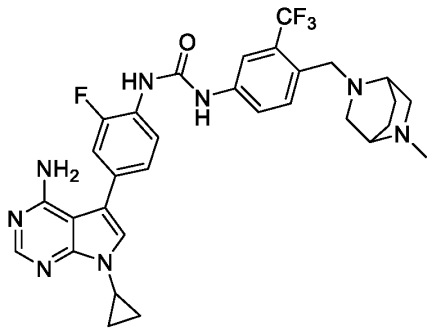
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((7-METHYL-4,7-DIAZASPIRO[2.5]OCTAN-4-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and 4-((7-methyl-4,7-diazaspiro[2.5]octan-4-yl)methyl)-3-(trifluoromethyl)aniline (D17, 0.056 g, 0.186 mmol), and was obtained as an off-white solid (0.006 g, 5% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.34 (s, 1H), 8.21 (t, *J* = 8.4 Hz, 1H), 7.95 (bs, 1H), 7.60-7.66 (m, 2H), 7.44 (s, 1H), 7.29-7.38 (m, 2H), 4.19-4.23 (m, 1H), 3.93-3.96 (m, 1H), 3.65-3.69 (m, 3H), 3.15-3.22 (m, 2H), 2.80-2.95 (m, 5H), 1.16-1.21 (m, 4H), 0.77-0.93 (m, 4H). LCMS: 609.6 [M+H].

EXAMPLE 31

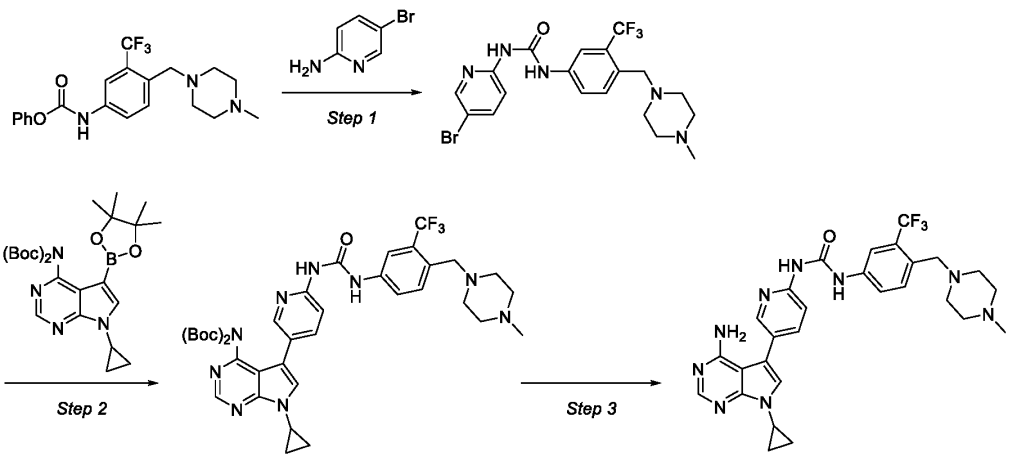
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((5-METHYL-2,5-DIAZABICYCLO[2.2.2]OCTAN-2-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.080 g, 0.198 mmol) and 4-((5-methyl-2,5-diazabicyclo[2.2.2]octan-2-yl)methyl)-3-(trifluoromethyl)aniline (D18, 0.059 g, 0.198 mmol), and was obtained as an off-white solid (0.007 g, 5.8% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.15-8.21 (m, 2H), 7.91 (bs, 1H), 7.73-7.76 (m, 1H), 7.66-7.69 (m, 1H), 7.27-7.33 (m, 2H), 7.21 (s, 1H), 3.89 (s, 2H), 3.50-3.54 (m, 1H), 3.27-3.30 (m, 2H), 3.12-3.15 (m, 2H), 2.77-2.81 (m, 5H), 1.93-2.12 (m, 3H), 1.69-1.70 (m, 1H), 1.08-1.17 (m, 4H). LCMS: 609.3 [M+H].

EXAMPLE 32

1-(5-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)PYRIDIN-2-YL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



Step 1: Synthesis of 1-(5-bromopyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

The title compound was obtained following the general procedure for urea formation (Method A), starting from 5-bromopyridin-2-amine (0.044 g, 0.254 mmol) and phenyl (4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)carbamate (C1, 0.100 g, 0.254 mmol), and was obtained as an off-white solid (0.035 g, 28 % yield) following purification by preparative HPLC (eluting with 0.1% TFA in water and ACN). LCMS: 472.1 [M+H].

Step 2: Synthesis of *tert*-butyl (*tert*-butoxycarbonyl)(7-cyclopropyl-5-(6-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)pyridin-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)carbamate

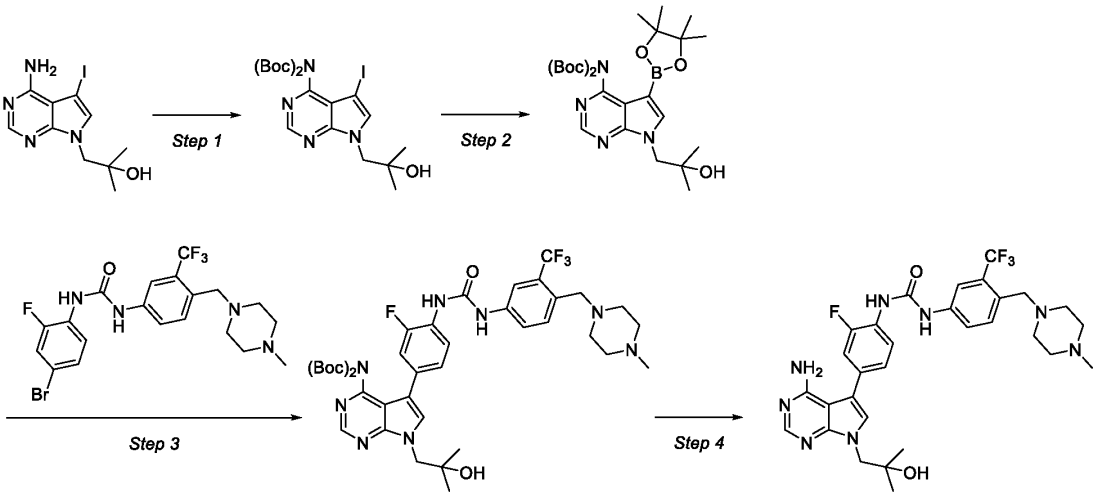
The title compound was prepared via a similar procedure described for intermediate B5, starting from 1-(5-bromopyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (0.033 g, 0.070 mmol) and *tert*-butyl (*tert*-butoxycarbonyl)(7-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)carbamate (prepared as reported in IN 2016/11024887 A, 0.035 g, 0.070 mmol), and was obtained as a brown gum (0.025 g, 46% yield) following purification by preparative HPLC (eluting with 10 mM NH_4OAc in H_2O and ACN). LCMS: 766.8 [M+H].

Step 3: Synthesis of 1-(5-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

TFA (0.125 mL) was added to a solution of *tert*-butyl (*tert*-butoxycarbonyl)(7-cyclopropyl-5-(6-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido) pyridin-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)carbamate (0.025 g, 0.033 mmol) in DCM (2 mL) at 0 °C and the resulting mixture was stirred at 25 °C for 12 h. Following completion of the reaction (as indicated by LCMS), the reaction mixture was concentrated under reduced pressure to afford crude material which was purified by preparative HPLC (eluting with 10 mM NH_4OAc in H_2O and ACN), giving the title product as an off-white solid (0.003 g, 16% yield). ^1H NMR (400 MHz, CD_3OD) δ = 8.47 (bs, 1H), 8.22 (bs, 1H), 8.03 (bs, 1H), 7.87-7.89 (m, 1H), 7.74 (bs, 2H), 7.35-7.37 (m, 1H), 7.27 (s, 1H), 3.70 (bs, 4H), 3.59 (bs, 3H), 2.78 (bs, 2H), 2.62 (bs, 2H), 2.50 (s, 3H), 1.10-1.17 (m, 4H). LCMS: 566.3 [M+H].

EXAMPLE 33

1-(4-(4-AMINO-7-(2-HYDROXY-2-METHYLPROPYL)-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



Step 1: Synthesis of *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-hydroxy-2-methylpropyl)-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)carbamate

The title compound was prepared via a similar procedure described for step 1 of intermediate B10, starting from 1-(4-amino-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-2-methylpropan-2-ol (A8, 0.400 g, 1.204 mmol), and was obtained as a pale brown solid (0.400 g, 61% yield). LCMS: 533.1 [M+H].

Step 2: Synthesis of *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-hydroxy-2-methylpropyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)carbamate

TEA (0.348 mL, 2.479 mmol) and XPhos (0.030 g, 0.062 mmol) were added to a solution of *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-hydroxy-2-methylpropyl)-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)carbamate (0.330 g, 0.620 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.357 mL, 2.479 mmol) in 1,4-dioxane (10 mL) and the resulting mixture was purged with N_2 for 10 minutes. $Pd_2(dba)_3$ (0.057 g, 0.062 mmol) was then added and the resulting mixture was stirred at 100 °C for 6 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was filtered through a pad of Celite® (*i.e.*, diatomaceous earth) which was washed with DCM (2 ×20 mL). The combined filtrates were concentrated under reduced pressure to give crude material which was purified by flash chromatography (silica gel 230-400 mesh, eluting with 75% EtOAc in petroleum ether), affording the title compound as a pale-yellow gum (0.100 g, 30% yield). LCMS: 533.2 [M+H].

Step 3: Synthesis of *tert*-butyl (*tert*-butoxycarbonyl)(5-(3-fluoro-4-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)phenyl)-7-(2-hydroxy-2-methylpropyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)carbamate

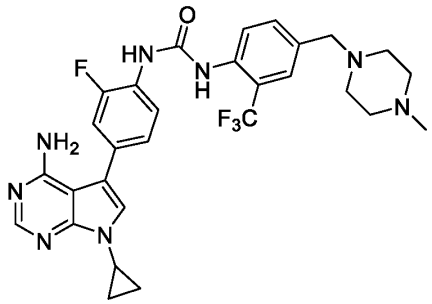
The title compound was prepared via a similar procedure described for intermediate B5, starting from 1-(5-bromopyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (0.092 g, 0.188 mmol) and *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-hydroxy-2-methylpropyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)carbamate (0.100 g, 0.188 mmol), and was obtained as a brown gum (0.030 g, 20% yield) following purification by preparative HPLC (eluting with 0.1% TFA in H_2O and ACN). LCMS: 815.3 [M+H].

Step 4: Synthesis of 1-(4-(4-amino-7-(2-hydroxy-2-methylpropyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

The title compound was prepared via a similar procedure described for step 3 of example 32, starting from *tert*-butyl (*tert*-butoxycarbonyl)(5-(3-fluoro-4-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)phenyl)-7-(2-hydroxy-2-methylpropyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)carbamate (0.030 g, 0.037 mmol), and was obtained as an off-white solid (0.007 g, 31% yield) following purification by preparative HPLC (eluting with 0.1% TFA in H_2O and ACN). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.50 (bs, 1H), 8.79 (bs, 1H), 8.37 (s, 1H), 8.25 (t, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 2.0 Hz, 1H), 7.59-7.66 (m, 2H), 7.50 (s, 1H), 7.28-7.38 (m, 1H), 7.25-7.26 (m, 1H), 4.85 (bs, 1H), 4.17 (s, 2H), 3.65 (s, 2H), 3.35 (bs, 2H), 3.02-3.04 (m, 2H), 2.77 (bs, 2H), 2.69 (s, 3H), 2.33-2.35 (m, 2H), 1.11 (s, 6H). LCMS: 615.3 [M+H].

EXAMPLE 34

1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-2-(TRIFLUOROMETHYL)PHENYL)UREA

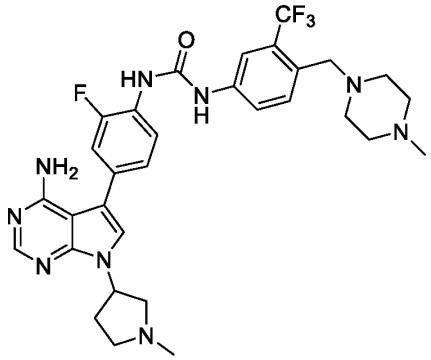


The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and 4-((4-methylpiperazin-1-yl)methyl)-2-(trifluoromethyl)aniline (D19, 0.051 g, 0.186 mmol), and was obtained as an off-white solid (0.004 g, 3.7% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.49-7.55 (m, 2H), 7.12 (d, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 1.6 Hz,

1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.69-6.78 (m, 2H), 6.07 (s, 1H), 2.91 (s, 2H), 2.79-2.82 (m, 1H), 2.48-2.51 (m, 4H), 2.24 (bs, 2H), 2.10 (s, 3H), 1.72 (bs, 2H), 0.31-0.33 (m, 2H), 0.01-0.03 (m, 2H). LCMS: 583.3 [M+H].

EXAMPLE 35

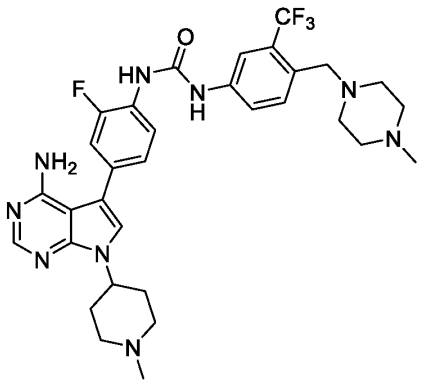
1-(4-(4-AMINO-7-(1-METHYLPYRROLIDIN-3-YL)-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from 5-(4-amino-3-fluorophenyl)-7-(1-methylpyrrolidin-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (B8, 0.048 g, 0.147 mmol) and phenyl (4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)carbamate (C1, 0.057 g, 0.145 mmol), and was obtained as an off-white solid (0.003 g, 3.6% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.38 (s, 1H), 8.21-8.27 (m, 1H), 7.97 (s, 1H), 7.66-7.73 (m, 2H), 7.31-7.38 (m, 2H), 5.59-5.62 (m, 1H), 4.08 (bs, 2H), 3.50-3.77 (m, 7*H*), 3.06-3.13 (m, 7*H*), 2.92-2.93 (m, 5H), 2.54 (bs, 2H). LCMS: 626.3 [M+H].

EXAMPLE 36

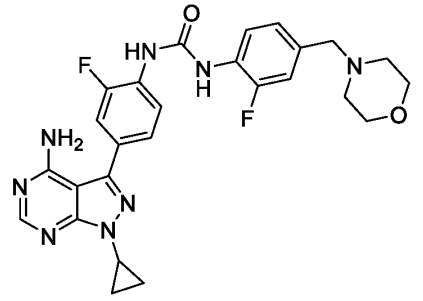
1-(4-(4-AMINO-7-(1-METHYLPIPERIDIN-4-YL)-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from 5-(4-amino-3-fluorophenyl)-7-(1-methylpiperidin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (B9, 0.080 g, 0.235 mmol) and phenyl (4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)carbamate (C1, 0.092 g, 0.235 mmol), and was obtained as a white solid (0.015 g, 10% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.38 (s, 1H), 8.23 (t, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 2.0 Hz, 1H), 7.66-7.73 (m, 2H), 7.63 (s, 1H), 7.32-7.40 (m, 2H), 5.08-5.14 (m, 1H), 3.74-3.77 (m, 4H), 3.37-3.38 (m, 10H), 2.99 (s, 3H), 2.93 (s, 3H), 2.53-2.62 (m, 2H), 2.38-2.41 (m, 2H). LCMS: 640.4 [M+H].

EXAMPLE 37

1-(4-(4-AMINO-1-CYCLOPROPYL-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(2-FLUORO-4-(MORPHOLINOMETHYL)PHENYL)UREA

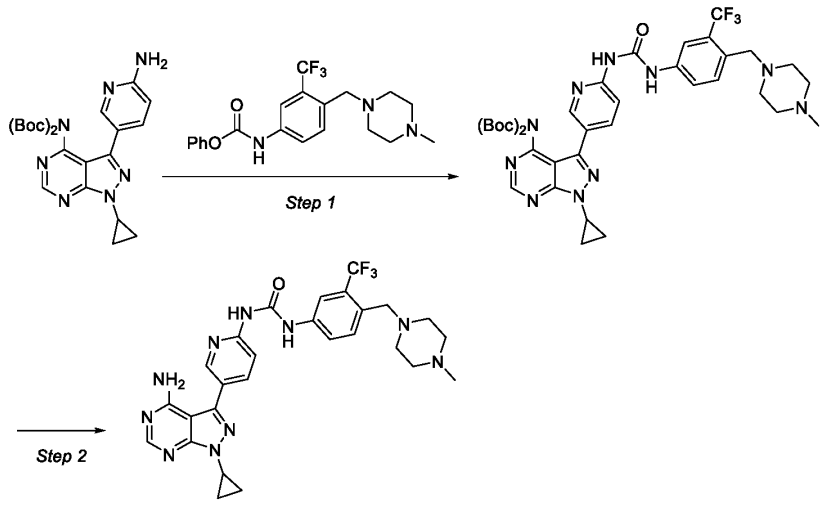


The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-1-cyclopropyl-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-fluorophenyl)carbamate (C5, 0.090 g, 0.223 mmol) and 2-fluoro-4-(morpholinomethyl)aniline (D10, 0.047 g, 0.223 mmol), and was

obtained as a white solid (0.009 g, 7.9% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.36-8.42 (m, 3H), 7.47-7.55 (m, 2H), 7.33-7.42 (m, 2H), 4.36 (s, 2H), 3.95-4.06 (m, 2H), 3.73-3.78 (m, 3H), 3.34-3.37 (m, 2H), 3.22-3.33 (m, 2H), 1.35-1.41 (m, 2H), 1.21-1.25 (m, 2H). LCMS: 521.2 [M+H].

EXAMPLE 38

1-(5-(4-AMINO-1-CYCLOPROPYL-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)PYRIDIN-2-YL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



Step 1: Synthesis of *tert*-butyl (*tert*-butoxycarbonyl)(1-cyclopropyl-3-(6-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)pyridin-3-yl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-yl)carbamate

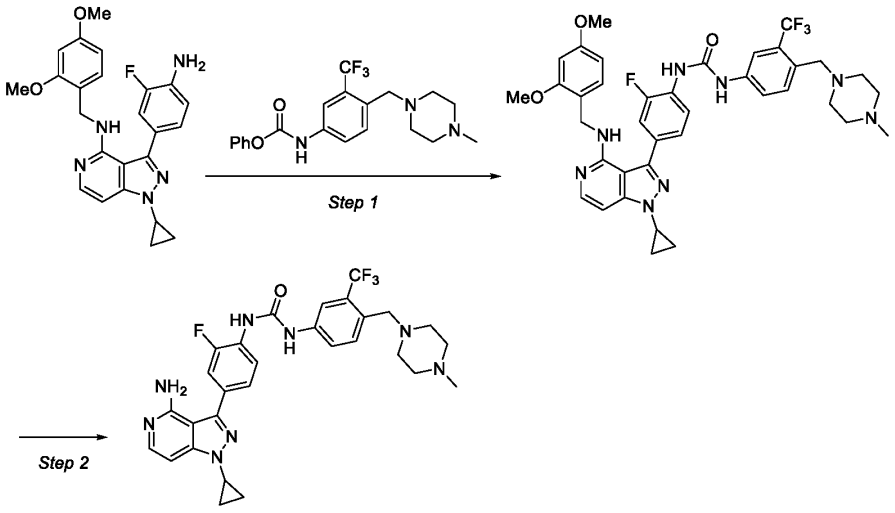
The title compound was obtained following the general procedure for urea formation (Method A), starting from di-*tert*-butyl (3-(6-aminopyridin-3-yl)-1-cyclopropyl-1H-pyrazolo[3,4-*d*]pyrimidin-4-yl)iminodicarbonate (B10, 0.200 g, 0.428 mmol) and phenyl (4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)carbamate (C1, 0.185 g, 0.471 mmol), and was obtained as an off-white solid (0.028 g, 8.5% yield). LCMS: 767.3 [M+H].

Step 2: Synthesis of 1-(5-(4-amino-1-cyclopropyl-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl)pyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

The title compound was prepared via a similar procedure described for step 3 of example 32, starting from *tert*-butyl (*tert*-butoxycarbonyl)(1-cyclopropyl-3-(6-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)pyridin-3-yl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-yl)carbamate (0.028 g, 0.037 mmol), and was obtained as an off-white solid (0.019 g, 92% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.63 (d, *J* = 2.0 Hz, 1H), 8.40 (s, 1H), 8.04-8.08 (m, 2H), 7.79-7.81 (m, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 3.96-3.99 (m, 1H), 3.78 (s, 2H), 3.50-3.51 (m, 2H), 3.15-3.32 (m, 4H), 2.93 (s, 3H), 2.51 (bs, 2H), 1.35-1.38 (m, 2H), 1.21-1.25 (m, 2H). LCMS: 566.9 [M+H].

EXAMPLE 39

1-(4-(4-AMINO-1-CYCLOPROPYL-1H-PYRAZOLO[4,3-*C*]PYRIDIN-3-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



Step 1: Synthesis of 1-(4-(1-cyclopropyl-4-((2,4-dimethoxybenzyl)amino)-1H-pyrazolo[4,3-*c*]pyridin-3-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

The title compound was obtained following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-cyclopropyl-*N*-(2,4-dimethoxybenzyl)-1H-pyrazolo[4,3-*c*]pyridin-4-amine (B11, 0.150 g, 0.346 mmol) and

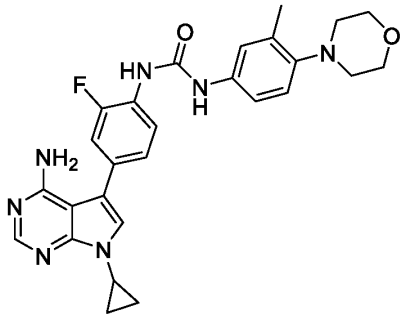
phenyl (4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)carbamate (C1, 0.136 g, 0.346 mmol), and was obtained as an off-white solid (0.030 g, 12% yield). LCMS: 733.3 [M+H].

Step 2: Synthesis of 1-(4-(4-amino-1-cyclopropyl-1H-pyrazolo[4,3-*c*]pyridin-3-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

Triethylsilane (0.012 g, 0.102 mmol) and TFA (0.004 g, 0.034 mmol) were added to a solution of 1-(4-(1-cyclopropyl-4-((2,4-dimethoxybenzyl)amino)-1H-pyrazolo[4,3-*c*]pyridin-3-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (0.025 g, 0.034 mmol) in DCM (2 mL) at 0 °C and the resulting mixture was stirred at 25 °C for 12 h. Following completion of the reaction (as indicated by LCMS), the reaction mixture was concentrated under reduced pressure to afford crude material which was purified by preparative HPLC (eluting with 0.1% TFA in H_2O and ACN), affording the title product as an off-white solid (0.010 g, 50 % yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 9.64 (bs, 1H), 8.99 (bs, 1H), 8.36 (t, *J* = 8.4 Hz, 1H), 7.95-8.03 (m, 3H), 7.84 (d, *J* = 7.2 Hz, 1H), 7.61-7.67 (m, 2H), 7.52-7.55 (m, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 7.2 Hz, 1H), 3.93-3.99 (m, 1H), 3.65 (bs, 2H), 3.38-3.40 (m, 2H), 2.90-3.03 (m, 4H), 2.81 (s, 3H), 2.34-2.39 (m, 2H), 1.19-1.20 (m, 4H). LCMS: 583.3 [M+H].

EXAMPLE 40

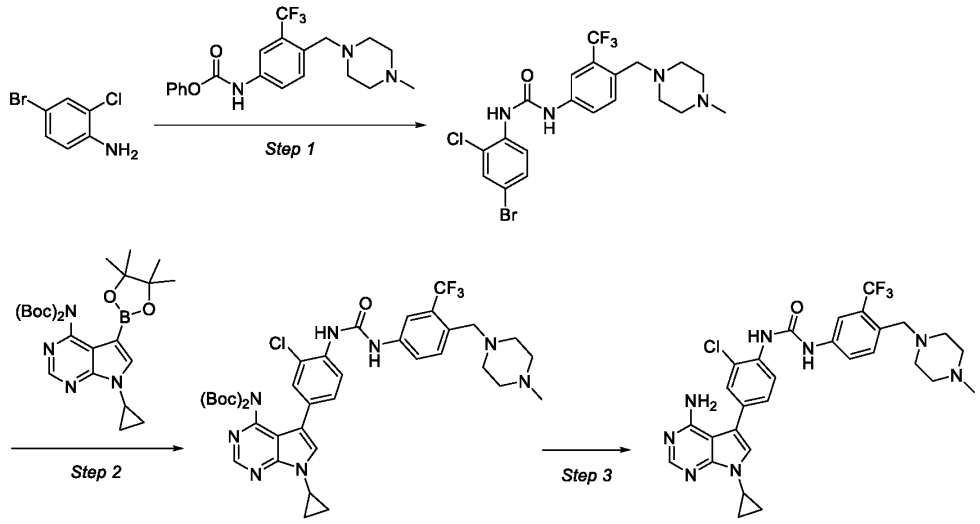
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(3-METHYL-4-MORPHOLINOPHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.150 g, 0.293 mmol) and 4-((7-methyl-4,7-diazaspiro[2.5]octan-4-yl)methyl)-3-(trifluoromethyl)aniline (D20, 0.056 g, 0.293 mmol), and was obtained as an off-white solid (0.090 g, 61% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.99 (bs, 1H), 8.72 (bs, 1H), 8.42 (s, 1H), 8.35 (t, *J* = 8.4 Hz, 1H), 7.26-7.29 (m, 1H), 7.14-7.18 (m, 2H), 7.01 (d, *J* = 8.8 Hz, 1H), 6.96 (s, 1H), 6.76 (t, *J* = 8.0 Hz, 1H), 3.68-3.75 (m, 5H), 2.79-2.81 (m, 4H), 2.27 (s, 3H), 1.03-1.06 (m, 2H), 0.67-0.71 (m, 2H). LCMS: 502.3 [M+H].

EXAMPLE 41

1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-CHLOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



Step 1: Synthesis of 1-(4-bromo-2-chlorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

The title compound was obtained following the general procedure for urea formation (Method A), starting from 4-bromo-2-chloroaniline (0.100 g, 0.484 mmol) and phenyl (4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)carbamate (C1, 0.191 g, 0.484 mmol), and was obtained as an off-white solid (0.030 g, 12% yield)

after purification by preparative HPLC (eluting with 10 mM NH_4OAc in water and ACN). LCMS: 505.1 [M+H].

Step 2: Synthesis of di-tert-butyl (5-(3-chloro-4-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)phenyl)-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)iminodicarbonate

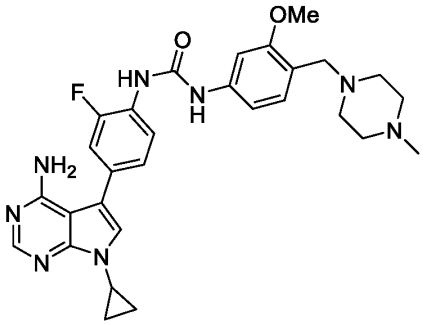
The title compound was prepared via a similar procedure described for intermediate B5, starting from 1-(4-bromo-2-chlorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (0.030 g, 0.060 mmol) and *tert*-butyl (*tert*-butoxycarbonyl)(7-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)carbamate (prepared as reported in IN 2016/11024887 A, 0.030 g, 0.060 mmol), and was obtained as a brown gum (0.020 g, 42% yield) following purification by preparative HPLC (eluting with 0.1% TFA in H_2O and ACN). LCMS: 799.3 [M+H].

Step 3: Synthesis of 1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-d]pyrimidin-5-yl)-2-chlorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

The title compound was prepared via a similar procedure described for step 3 of example 32, starting from *tert*-butyl (*tert*-butoxycarbonyl)(5-(3-chloro-4-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)phenyl)-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)carbamate (0.020 g, 0.025 mmol), and was obtained as an off-white solid (0.42 mg, 2.8% yield). LCMS: 599.2 [M+H].

EXAMPLE 42

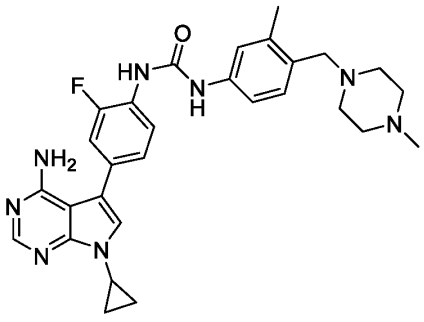
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(3-METHOXY-4-((4-METHYLPIPERAZIN-1-YL)METHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.106 g, 0.262 mmol) and 3-methoxy-4-((4-methylpiperazin-1-yl)methyl)aniline (D21, 0.062 g, 0.262 mmol), and was obtained as pale brown solid (0.037 g, 26% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.27 (t, *J* = 8.0 Hz, 1H), 8.16 (s, 1H), 7.47-7.53 (m, 2H), 7.41 (d, *J* = 2.0 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 6.92-6.94 (m, 1H), 6.64 (s, 1H), 3.89 (s, 3H), 3.71 (s, 2H), 3.49-3.51 (m, 1H), 2.74 (bs, 8H), 2.45 (s, 3H), 1.07-1.09 (m, 2H), 0.69-0.70 (m, 2H). LCMS: 545.3 [M+H].

EXAMPLE 43

1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(3-METHYL-4-((4-METHYLPIPERAZIN-1-YL)METHYL)PHENYL)UREA

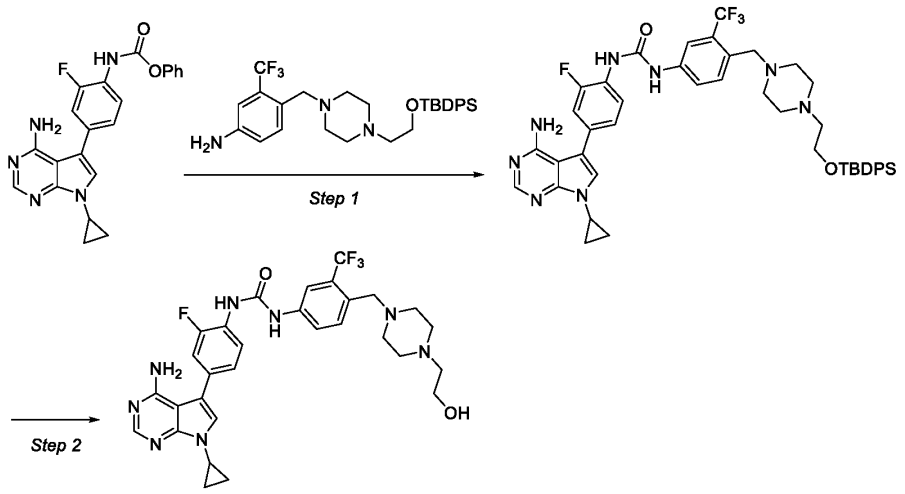


The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.100 g, 0.248 mmol) and 3-methyl-4-((4-methylpiperazin-1-yl)methyl)aniline (D22, 0.054 g, 0.248 mmol), and

was obtained as pale yellow solid (0.020 g, 15% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 9.16 (bs, 1H), 8.80 (bs, 1H), 8.41 (s, 1H), 8.34 (t, *J* = 8.4 Hz, 1H), 7.63-7.67 (m, 1H), 7.46-7.48 (m, 1H), 7.29-7.31 (m, 2H), 7.10-7.23 (m, 1H), 6.95 (s, 1H), 3.56-3.72 (m, 3H), 2.94-2.98 (m, 8H), 2.78 (s, 3H), 2.34 (s, 3H), 1.02-1.04 (m, 2H), 0.66-0.67 (m, 2H). LCMS: 529.5 [M+H].

EXAMPLE 44

1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-(2-HYDROXYETHYL)PIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



Step 1: Synthesis of 1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)piperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

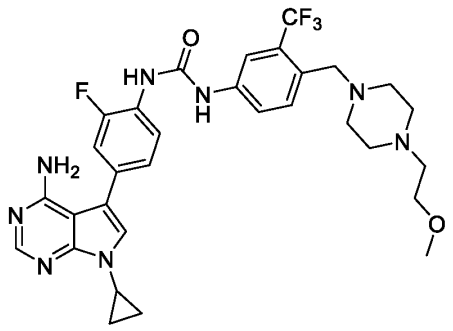
The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (D23, 0.101 g, 0.186 mmol), and was obtained as an off-white solid (0.050 g, 31% yield). LCMS: 852.3 [M+H].

Step 2: Synthesis of 1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-(2-hydroxyethyl)piperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

TBAF (1M in THF, 0.053 mL, 0.037 mmol) was added to a solution of 1-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)piperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (0.045 g, 0.053 mmol) in THF (5 mL) at 0 °C and the resulting solution was stirred at 25 °C for 1 h. Following completion of the reaction (as indicated by LCMS), the reaction mixture was concentrated under reduced pressure to give crude material which was purified by preparative HPLC (eluting with 0.1% TFA in water and ACN), affording the title compound as a white solid (0.010 g, 32% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.37 (s, 1H), 8.22 (t, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 2.0 Hz, 1H), 7.69-7.74 (m, 2H), 7.50 (s, 1H), 7.29-7.37 (m, 2H), 3.89-3.91 (m, 2H), 3.70-3.73 (m, 3H), 3.58 (bs, 2H), 3.10-3.29 (m, 4H), 3.03 (bs, 2H), 2.57-2.60 (m, 2H), 1.18-1.32 (m, 4H). LCMS: 613.2 [M+H].

EXAMPLE 45

1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-(2-METHOXYETHYL)PIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA

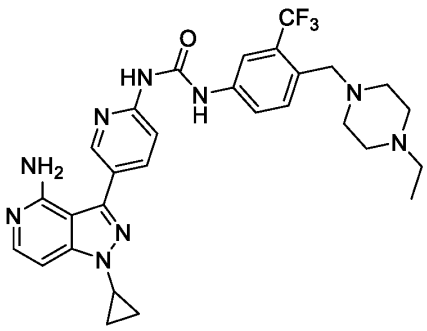


The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and 4-((4-methylpiperazin-1-yl)methyl)-2-(trifluoromethyl)aniline (D24, 0.059 g, 0.186

mmol), and was obtained as an off-white solid (0.043 g, 37% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.37 (s, 1H), 8.22 (t, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 2.0 Hz, 1H), 7.67-7.73 (m, 2H), 7.50 (s, 1H), 7.29-7.38 (m, 2H), 3.70-3.77 (m, 5H), 3.43 (s, 3H), 3.37-3.38 (m, 2H), 2.61-3.03 (m, 8H), 1.18-1.23 (m, 4H). LCMS: 627.3 [M+H].

EXAMPLE 46

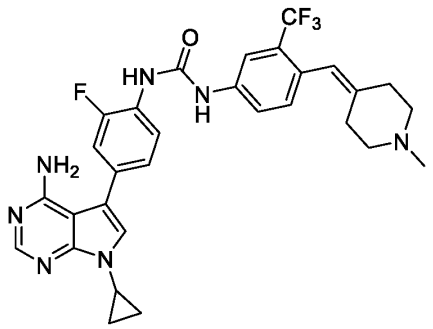
1-(4-(4-AMINO-1-CYCLOPROPYL-1H-PYRAZOLO[4,3-*C*]PYRIDIN-3-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was prepared via a similar procedure described for example 39, starting from 3-(6-aminopyridin-3-yl)-1-cyclopropyl-*N*-(2,4-dimethoxybenzyl)-1H-pyrazolo[4,3-*c*]pyridin-4-amine (B12, 0.110 g, 0.264 mmol) and phenyl (4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)carbamate (C2, 0.108 g, 0.264 mmol) in step 1, and was obtained as an off-white solid (0.002 g, 1.3% yield over 2 steps). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.64 (d, *J* = 1.6 Hz, 1H), 8.06-8.08 (m, 2H), 7.80 (d, *J* = 6.4 Hz, 1H), 7.74-7.75 (m, 2H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 6.4 Hz, 1H), 3.68-3.71 (m, 3H), 2.51-2.57 (m, 8H), 2.02-2.08 (m, 2H), 1.22-1.31 (m, 4H), 1.13-1.17 (m, 3H). LCMS: 580.2 [M+H].

EXAMPLE 47

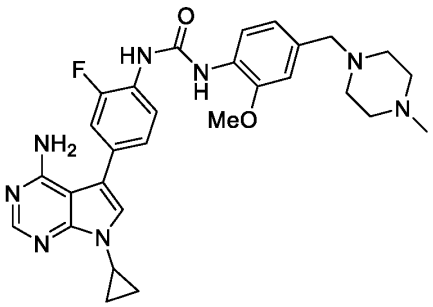
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((1-METHYLPIPERIDIN-4-YLIDENE)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.040 g, 0.099 mmol) and 4-((1-methylpiperidin-4-ylidene)methyl)-3-(trifluoromethyl)aniline (D25, 0.027 g, 0.099 mmol), and was obtained as a white solid (0.006 g, 11% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.28 (t, *J* = 8.0 Hz, 1H), 8.16 (s, 1H), 7.95 (d, *J* = 2.4 Hz, 1H), 7.65-7.67 (m, 1H), 7.48-7.55 (m, 2H), 7.27 (d, *J* = 8.4 Hz, 1H), 6.64 (s, 1H), 6.53 (s, 1H), 3.48-3.52 (m, 1H), 2.86-2.88 (m, 2H), 2.72-2.75 (m, 2H), 2.55-2.58 (m, 5H), 2.41-2.44 (m, 2H), 1.06-1.11 (m, 2H), 0.67-0.71 (m, 2H). LCMS: 580.3 [M+H].

EXAMPLE 48

1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(2-METHOXY-4-((4-METHYLPIPERAZIN-1-YL)METHYL)PHENYL)UREA

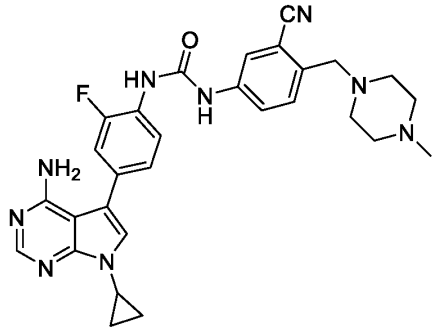


The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and 2-methoxy-4-((4-methylpiperazin-1-yl)methyl)aniline (D26, 0.044 g, 0.186 mmol), and was obtained as a pale brown solid (0.024 g, 23% yield). ^{1}H NMR (400 MHz, CD_3OD)

δ = 8.36 (t, *J* = 8.4 Hz, 1H), 8.31 (s, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.49-7.57 (m, 2H), 7.08 (d, *J* = 1.6 Hz, 1H), 6.97-6.99 (m, 1H), 6.90 (s, 1H), 3.97 (s, 3H), 3.83 (s, 2H), 3.60-3.64 (m, 1H), 2.92-2.95 (m, 8H), 2.87 (s, 3H), 1.11-1.14 (m, 2H), 0.82-0.84 (m, 2H). LCMS: 545.3 [M+H].

EXAMPLE 49

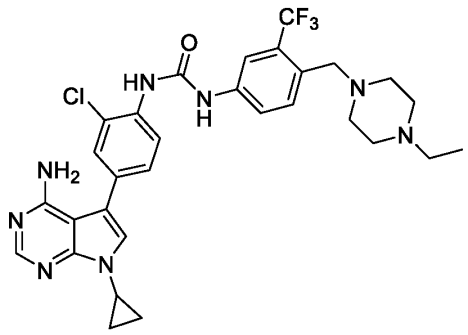
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(3-CYANO-4-((4-METHYLPIPERAZIN-1-YL)METHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and 5-amino-2-((4-methylpiperazin-1-yl)methyl)benzonitrile (D27, 0.043 g, 0.186 mmol), and was obtained as a pale brown solid (0.004 g, 4% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.31-8.37 (m, 2H), 8.05 (d, *J* = 2.4 Hz, 1H), 7.65-7.68 (m, 1H), 7.51-7.59 (m, 3H), 6.90 (s, 1H), 3.78 (s, 2H), 3.61-3.64 (m, 1H), 3.49-3.51 (m, 2H), 3.13 (s, 4H), 2.92 (s, 3H), 2.54 (bs, 2H), 1.11-1.16 (m, 2H), 0.79-0.84 (m, 2H). LCMS: 540.3 [M+H].

EXAMPLE 50

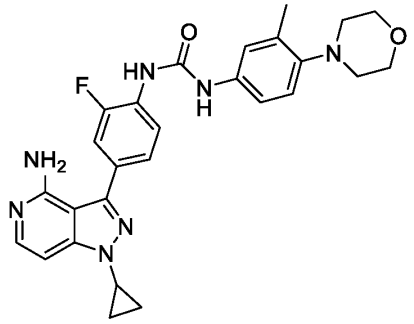
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-CHLOROPHENYL)-3-(4-((4-ETHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-chlorophenyl)carbamate (C10, 0.100 g, 0.238 mmol) and 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (D1, 0.068 g, 0.238 mmol), and was obtained as an off-white solid (0.026 g, 18% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 11.14 (bs, 1H), 9.76 (bs, 1H), 8.17 (s, 1H), 8.00-8.07 (m, 2H), 7.66-7.69 (m, 2H), 7.52 (d, *J* = 2.0 Hz, 1H), 7.36-7.38 (m, 1H), 7.32 (s, 1H), 6.13 (bs, 2H), 3.56-3.61 (m, 1H), 3.53 (s, 2H), 2.29-2.35 (m, 2H), 1.73 (bs, 8H), 0.97-1.08 (m, 7*H*). LCMS: 613.3 [M+H].

EXAMPLE 51

1-(4-(4-AMINO-1-CYCLOPROPYL-1H-PYRAZOLO[4,3-*C*]PYRIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-METHYL-4-MORPHOLINOPHENYL)UREA

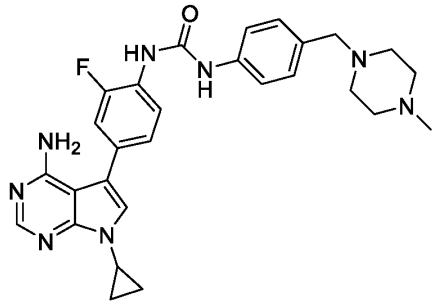


The title compound was prepared via a similar procedure described for example 39, starting from 3-(4-amino-3-fluorophenyl)-1-cyclopropyl-*N*-(2,4-dimethoxybenzyl)-1H-pyrazolo[4,3-*c*]pyridin-4-amine (B11, 0.100 g, 0.231 mmol) and phenyl (3-methyl-4-morpholinophenyl)carbamate (C4, 0.072 g, 0.231 mmol) in step 1, and was obtained

as an off-white solid (0.005 g, 4.3% yield over 2 steps). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.33-8.38 (m, 1H), 7.72 (d, *J* = 7.2 Hz, 1H), 7.44-7.52 (m, 2H), 7.34 (d, *J* = 7.2 Hz, 1H), 7.28-7.31 (m, 2H), 7.06-7.09 (m, 1H), 3.85-3.87 (m, 5H), 2.91-2.93 (m, 4H), 2.35 (s, 3H), 1.27-1.32 (m, 4H). LCMS: 502.2 [M+H].

EXAMPLE 52

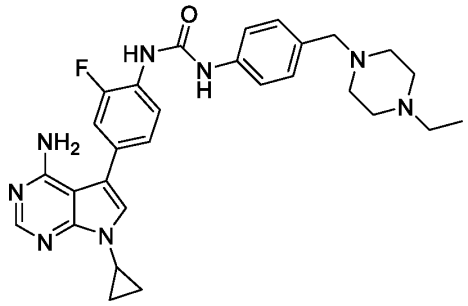
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and 4-((4-methylpiperazin-1-yl)methyl)aniline (D28, 0.038 g, 0.186 mmol), and was obtained as an off-white solid (0.010 g, 10% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.31-8.36 (m, 2H), 7.50-7.58 (m, 4H), 7.37 (d, *J* = 8.4 Hz, 2H), 6.90 (s, 1H), 3.82 (s, 2H), 3.61-3.64 (m, 1H), 3.32-3.33 (m, 4H), 2.87-2.93 (m, 7*H*), 1.11-1.16 (m, 2H), 0.80-0.84 (m, 2H). LCMS: 515.3 [M+H].

EXAMPLE 53

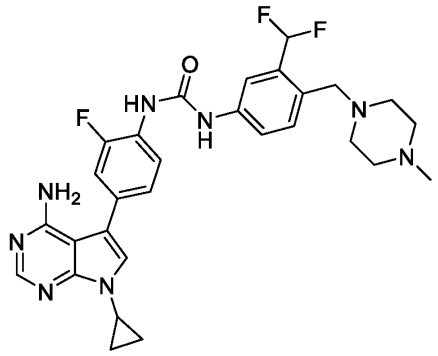
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-ETHYLPIPERAZIN-1-YL)METHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and 4-((4-ethylpiperazin-1-yl)methyl)aniline (D29, 0.041 g, 0.186 mmol), and was obtained as an off-white solid (0.020 g, 20% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.31-8.37 (m, 2H), 7.50-7.58 (m, 4H), 7.37 (d, *J* = 8.4 Hz, 2H), 6.90 (s, 1H), 3.81 (s, 2H), 3.61-3.64 (m, 1H), 3.15-3.33 (m, 6H), 2.97 (bs, 4H), 1.31-1.37 (m, 3H), 1.11-1.16 (m, 2H), 0.80-0.84 (m, 2H). LCMS: 529.3 [M+H].

EXAMPLE 54

1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(3-(DIFLUOROMETHYL)-4-((4-METHYLPIPERAZIN-1-YL)METHYL)PHENYL)UREA

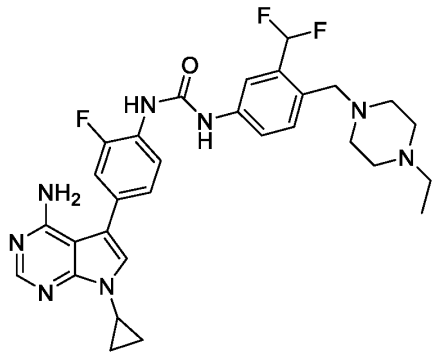


The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.077 g, 0.192 mmol) and 3-(difluoromethyl)-4-((4-methylpiperazin-1-yl)methyl)aniline (D30, 0.070 g, 0.274

mmol), and was obtained as an off-white solid (0.031 g, 20% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.26 (t, *J* = 8.4 Hz, 1H), 8.16 (s, 1H), 7.79 (s, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.47-7.53 (m, 2H), 7.13-7.37 (m, 2H), 6.64 (s, 1H), 3.67 (s, 2H), 3.49-3.50 (m, 1H), 2.88 (bs, 4H), 2.59 (bs, 7*H*), 1.08-1.11 (m, 2H), 0.80-0.84 (m, 2H). LCMS: 565.5 [M+H].

EXAMPLE 55

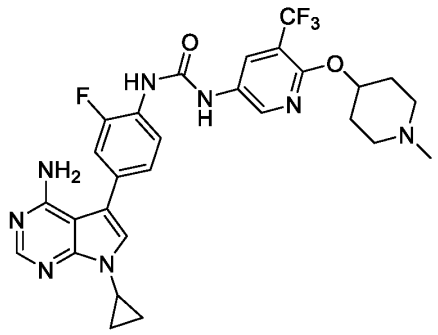
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(3-(DIFLUOROMETHYL)-4-((4-ETHYLPIPERAZIN-1-YL)METHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and 3-(difluoromethyl)-4-((4-ethylpiperazin-1-yl)methyl)aniline (D31, 0.050 g, 0.186 mmol), and was obtained as an off-white solid (0.005 g, 4.8% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.31-8.36 (m, 2H), 7.83 (d, *J* = 2.0 Hz, 1H), 7.50-7.62 (m, 3H), 7.12-7.40 (m, 2H), 6.90 (s, 1H), 3.75 (s, 2H), 3.49-3.64 (m, 3H), 3.19-3.24 (m, 2H), 3.02 (bs, 4H), 2.49 (bs, 2H), 1.34-1.40 (m, 3H), 1.11-1.16 (m, 2H), 0.79-0.84 (m, 2H). LCMS: 579.2 [M+H].

EXAMPLE 56

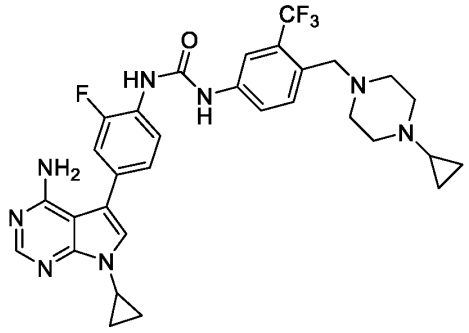
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(6-((1-METHYLPIPERIDIN-4-YL)OXY)-5-(TRIFLUOROMETHYL)PYRIDIN-3-YL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.050 g, 0.124 mmol) and 6-((1-methylpiperidin-4-yl)oxy)-5-(trifluoromethyl)pyridin-3-amine (D32, 0.034 g, 0.124 mmol), and was obtained as an off-white solid (0.008 g, 11% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.44-8.45 (m, 1H), 8.29-8.35 (m, 3H), 7.51-7.59 (m, 2H), 6.87 (s, 1H), 5.40-5.60 (m, 1H), 3.50-3.62 (m, 5H), 2.96 (s, 3H), 2.35-2.50 (m, 2H), 2.18 (bs, 1H), 1.98 (bs, 1H), 1.10-1.13 (m, 2H), 0.78-0.82 (m, 2H). LCMS: 585.2 [M+H].

EXAMPLE 57

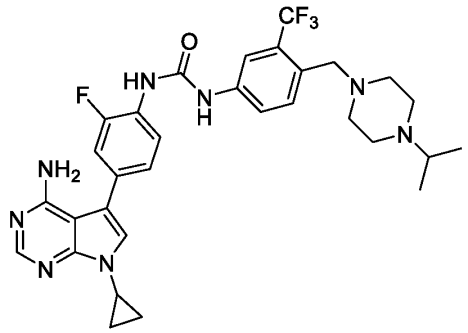
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-CYCLOPROPYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and 4-((4-cyclopropylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (D33, 0.056 g, 0.186 mmol), and was obtained as an off-white solid (0.017 g, 15% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.14-8.19 (m, 2H), 7.91 (d, *J* = 2.0 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.62-7.65 (m, 1H), 7.25-7.30 (m, 2H), 7.19 (s, 1H), 3.64 (s, 2H), 3.48-3.53 (m, 1H), 2.75 (bs, 4H), 2.52 (bs, 4H), 1.75-1.99 (m, 1H), 1.05-1.18 (m, 4H), 0.47-0.56 (m, 4H). LCMS: 609.2 [M+H].

EXAMPLE 58

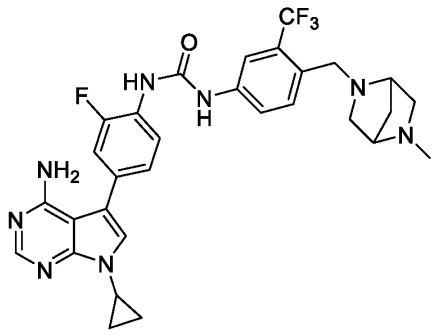
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-ISOPROPYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and 4-((4-isopropylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (D34, 0.056 g, 0.186 mmol), and was obtained as an off-white solid (0.006 g, 5.3% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.37 (s, 1H), 8.21 (t, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 2.0 Hz, 1H), 7.67-7.74 (m, 2H), 7.50 (s, 1H), 7.29-7.37 (m, 2H), 3.70-3.77 (m, 3H), 3.48-3.55 (m, 3H), 3.11-3.18 (m, 4H), 2.53 (bs, 2H), 1.40 (d, *J* = 6.4 Hz, 6H), 1.18-1.23 (m, 4H). LCMS: 611.3 [M+H].

EXAMPLE 59

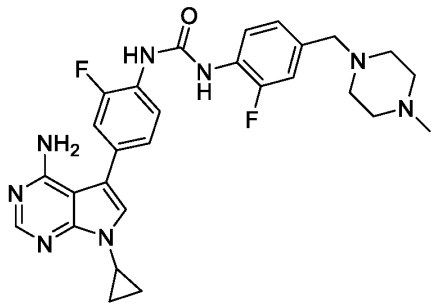
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((5-METHYL-2,5-DIAZABICYCLO[2.2.1]HEPTAN-2-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and 4-((5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)methyl)-3-(trifluoromethyl)aniline (D35, 0.053 g, 0.186 mmol), and was obtained as an off-white solid (0.002 g, 1.8% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.37 (s, 1H), 8.21 (t, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 2.0 Hz, 1H), 7.66-7.75 (m, 2H), 7.49 (s, 1H), 7.29-7.37 (m, 2H), 4.19 (s, 1H), 3.89-4.02 (m, 2H), 3.68-3.74 (m, 4H), 3.37 (s, 2H), 2.94 (bs, 5H), 1.19-1.19 (m, 4H). LCMS: 595.2 [M+H].

EXAMPLE 60

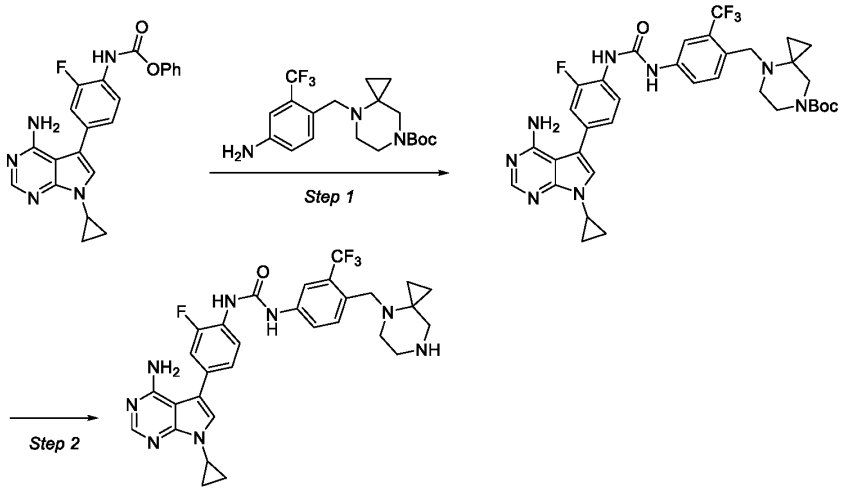
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(2-FLUORO-4-((4-METHYLPIPERAZIN-1-YL)METHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and 2-fluoro-4-((4-methylpiperazin-1-yl)methyl)aniline (D36, 0.041 g, 0.186 mmol), and was obtained as an off-white solid (0.009 g, 9.5% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.36 (s, 1H), 8.27 (t, *J* = 8.0 Hz, 1H), 8.13 (t, *J* = 8.4 Hz, 1H), 7.48 (s, 1H), 7.29-7.37 (m, 2H), 7.15-7.24 (m, 2H), 3.66-3.73 (m, 3H), 3.12 (bs, 4H), 2.90 (s, 3H), 2.51 (bs, 4H), 1.18-1.22 (m, 4H). LCMS: 533.3 [M+H].

EXAMPLE 61

1-(4-((4,7-DIAZASPIRO[2.5]OCTAN-4-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)-3-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)UREA



Step 1: Synthesis of *tert*-butyl 4-(4-(3-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)ureido)-2-(trifluoromethyl)benzyl)-4,7-diazaspiro[2.5]octane-7-carboxylate

The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and *tert*-butyl 4-(4-amino-2-(trifluoromethyl)benzyl)-4,7-diazaspiro[2.5]octane-7-

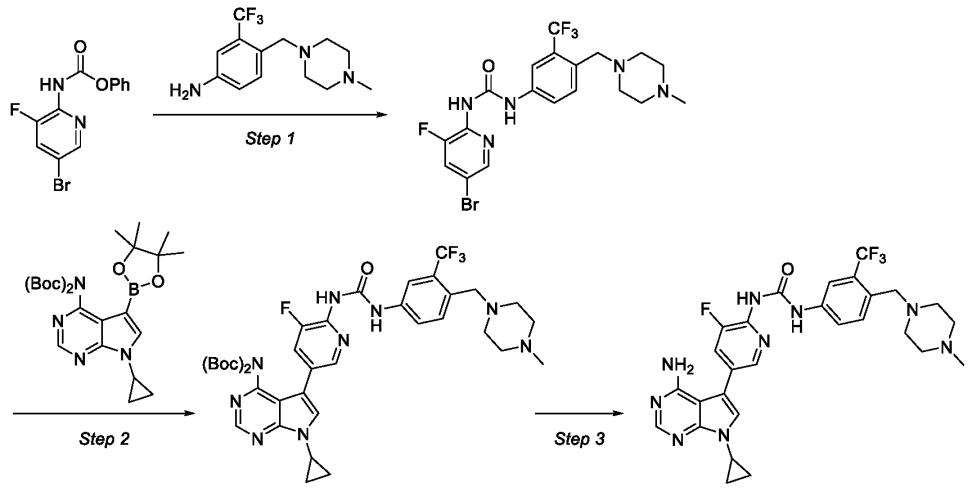
carboxylate (D37, 0.072 g, 0.186 mmol), and was obtained as an off-white solid (0.020 g, 15% yield). LCMS: 695.2 [M+H].

Step 2: Synthesis of 1-(4-((4,7-diazaspiro[2.5]octan-4-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)urea

The title compound was prepared via a similar procedure described for step 2 of intermediate A15, starting from *tert*-butyl 4-(4-(3-(4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)ureido)-2-(trifluoromethyl)benzyl)-4,7-diazaspiro[2.5]octane-7-carboxylate (0.022 g, 0.032 mmol), and was obtained as an off-white solid (0.09 g, 48% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.38 (s, 1H), 8.22 (t, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 2.0 Hz, 1H), 7.62-7.63 (m, 2H), 7.51 (s, 1H), 7.29-7.37 (m, 2H), 4.09 (s, 2H), 3.70-3.72 (m, 1H), 3.15-3.24 (m, 4H), 3.04-3.07 (m, 2H), 1.18-1.23 (m, 4H), 0.80-0.92 (m, 2H), 0.77-0.79 (m, 2H). LCMS: 595.3 [M+H].

EXAMPLE 62

1-(4-((4,7-DIAZASPIRO[2.5]OCTAN-4-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)-3-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)UREA



Step 1: Synthesis of 1-(5-bromo-3-fluoropyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (5-bromo-3-fluoropyridin-2-yl)carbamate (synthesized as reported in PCT Publication No. WO 2017/117393 A1, 0.163 g, 0.524 mmol) and 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (0.143 g, 0.524 mmol), and was obtained as an off-white solid (0.260 g, quantitative yield) following purification by preparative HPLC (eluting with 0.1% TFA in water and ACN). LCMS: 490.1 [M+H].

Step 2: Synthesis of *tert*-butyl (*tert*-butoxycarbonyl)(7-cyclopropyl-5-(5-fluoro-6-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)pyridin-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)carbamate

The title compound was prepared via a similar procedure described for intermediate B5, starting from 1-(5-bromo-3-fluoropyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (0.280 g, 0.560 mmol) and *tert*-butyl (*tert*-butoxycarbonyl)(7-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)carbamate (prepared as reported in IN 2016/11024887 A, 0.274 g, 0.560 mmol), and was obtained as a brown solid (0.100 g, 23% yield) following purification by preparative HPLC (eluting with 10 mM NH_4OAc in water and ACN). LCMS: 784.3 [M+H].

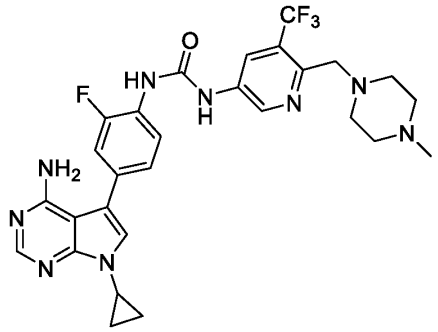
Step 3: Synthesis of 1-(5-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-3-fluoropyridin-2-yl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

The title compound was prepared via a similar procedure described for step 2 of intermediate A15, starting from *tert*-butyl (*tert*-butoxycarbonyl)(7-cyclopropyl-5-(5-fluoro-6-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)pyridin-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)carbamate (0.100 g, 0.128 mmol), and was obtained as a white solid (0.063 g, 84% yield) following purification by preparative HPLC (eluting with 0.1% TFA in water and ACN). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.75 (s, 1H), 9.50 (s, 1H), 8.45 (s, 1H), 8.30 (s, 1H), 8.05 (d, J = 2.0 Hz, 1H), 7.79-7.86 (m, 2H), 7.66-7.68 (m, 2H), 3.66-3.75 (m,

3H), 3.39-3.42 (m, 2H), 3.03 (s, 4H), 2.90-2.93 (m, 2H), 2.81 (s, 3H), 2.33-2.36 (m, 2H), 1.11-1.12 (m, 4H). LCMS: 584.2 [M+H].

EXAMPLE 63

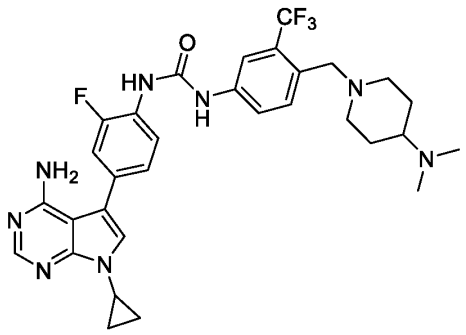
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(6-((4-METHYLPIPERAZIN-1-YL)METHYL)-5-(TRIFLUOROMETHYL)PYRIDIN-3-YL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.100 g, 0.248 mmol) and 6-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)pyridin-3-amine (D38, 0.068 g, 0.248 mmol), and was obtained as an off-white solid (0.005 g, 3.4% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.85 (d, *J* = 2.4 Hz, 1H), 8.48 (d, *J* = 2.4 Hz, 1H), 8.37 (s, 1H), 8.21 (t, *J* = 8.0 Hz, 1H), 7.49 (s, 1H), 7.31-7.39 (m, 2H), 3.93 (s, 2H), 3.70-3.73 (m, 1H), 3.28-3.32 (m, 4H), 2.90 (bs, 7*H*), 1.18-1.31 (m, 4H). LCMS: 584.4 [M+H].

EXAMPLE 64

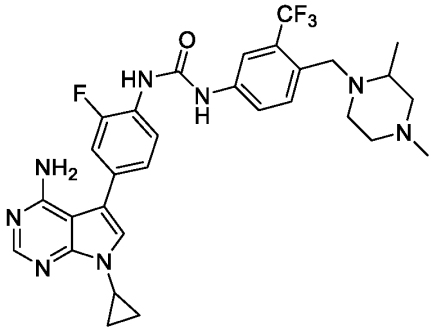
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-(DIMETHYLAMINO)PIPERIDIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and 1-(4-amino-2-(trifluoromethyl)benzyl)-*N*,*N*-dimethylpiperidin-4-amine (D39, 0.056 g, 0.186 mmol), and was obtained as an off-white solid (0.004 g, 3.5% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.15-8.21 (m, 2H), 7.89 (d, *J* = 2.0 Hz, 1H), 7.66-7.73 (m, 2H), 7.28-7.33 (m, 2H), 7.21 (s, 1H), 3.66 (s, 2H), 3.50-3.54 (m, 1H), 3.03-3.15 (m, 3H), 2.82 (s, 6H), 2.14-2.19 (m, 2H), 2.04-2.07 (m, 2H), 1.73-1.77 (m, 2H), 1.07-1.17 (m, 4H). LCMS: 611.3 [M+H].

EXAMPLE 65

1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((2,4-DIMETHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA

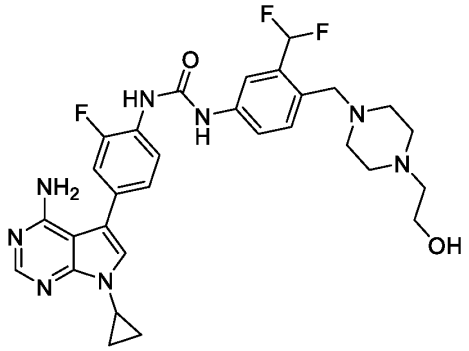


The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and

4-((2,4-dimethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (D40, 0.053 g, 0.186 mmol), and was obtained as an off-white solid (0.014 g, 13% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.35 (s, 1H), 8.22 (t, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 2.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.66-7.69 (m, 1H), 7.47 (s, 1H), 7.29-7.37 (m, 2H), 3.70 (s, 2H), 3.48-3.51 (m, 1H), 3.15-3.16 (m, 1H), 2.89-2.92 (m, 5H), 2.74-0.00 (m, 2H), 2.49 (bs, 2H), 1.26 (d, *J* = 6.0 Hz, 3H), 1.17-1.22 (m, 4H). LCMS: 597.3 [M+H].

EXAMPLE 66

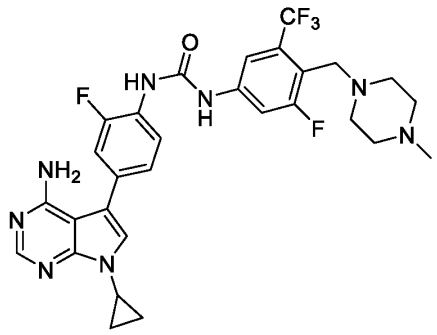
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-(2-HYDROXYETHYL)PIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was prepared via a similar procedure described for example 44, starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.060 g, 0.149 mmol) and 4-((4-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)piperazin-1-yl)methyl)-3-(difluoromethyl)aniline (D41, 0.078 g, 0.149 mmol) in step 1, and was obtained as a white solid (0.004 g, 4.4% yield over 2 steps) following purification by preparative HPLC (eluting with 0.1% TFA in water and ACN). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.37 (s, 1H), 8.23 (t, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 2.0 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.49 (s, 1H), 7.13-7.40 (m, 4H), 3.87-3.90 (m, 2H), 3.50-3.75 (m, 4H), 3.27-3.29 (m, 2H), 3.00 (bs, 4H), 2.52 (bs, 4H), 1.15-1.25 (m, 4H). LCMS: 595.3 [M+H].

EXAMPLE 67

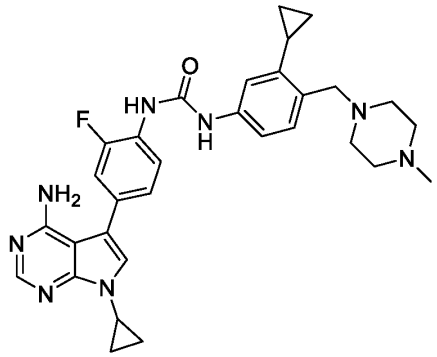
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(3-FLUORO-4-((4-METHYLPIPERAZIN-1-YL)METHYL)-5-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.100 g, 0.248 mmol) and 3-fluoro-4-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)aniline (D42, 0.072 g, 0.248 mmol), and was obtained as an off-white solid (0.002 g, 1.3% yield). LCMS: 601.3 [M+H].

EXAMPLE 68

1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(3-CYCLOPROPYL-4-((4-METHYLPIPERAZIN-1-YL)METHYL)PHENYL)UREA

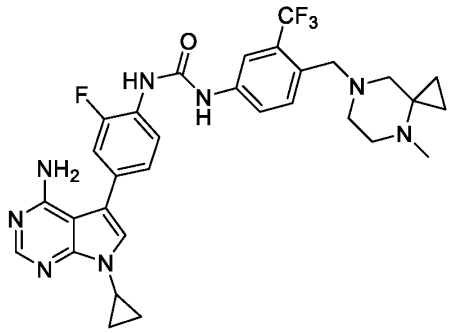


The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-

d]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and 3-cyclopropyl-4-((4-methylpiperazin-1-yl)methyl)aniline (D43, 0.046 g, 0.186 mmol), and was obtained as an off-white gum (0.010 g, 9.7% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.13 (bs, 1H), 8.66 (bs, 1H), 8.35 (s, 1H), 8.24 (t, *J* = 8.4 Hz, 1H), 7.47 (s, 1H), 7.32-7.35 (m, 1H), 7.18-7.24 (m, 3H), 7.08 (s, 1H), 3.55-3.62 (m, 3H), 2.95-2.97 (m, 4H), 2.78 (bs, 4H), 2.20 (bs, 1H), 2.08 (s, 3H), 1.07-1.09 (m, 4H), 0.94-0.96 (m, 2H), 0.60-0.61 (m, 2H). LCMS: 555.3 [M+H].

EXAMPLE 69

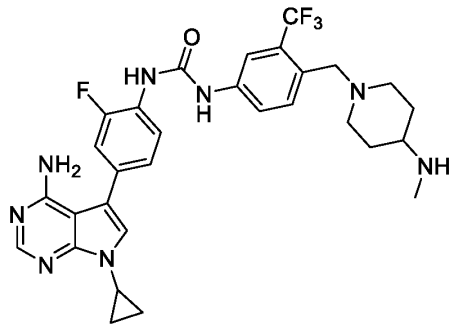
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYL-4,7-DIAZASPIRO[2.5]OCTAN-7-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and 4-((4-methyl-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3-(trifluoromethyl)aniline (D44, 0.056 g, 0.186 mmol), and was obtained as an off-white gum (0.004 g, 3.3% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.36 (s, 1H), 8.22 (t, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 1.6 Hz, 1H), 7.69-7.73 (m, 2H), 7.48 (s, 1H), 7.29-7.37 (m, 2H), 3.85 (s, 2H), 3.69-3.73 (m, 1H), 3.48-3.51 (m, 2H), 2.92-2.95 (m, 7*H*), 1.18-1.31 (m, 6H), 0.80-0.93 (m, 2H). LCMS: 609.3 [M+H].

EXAMPLE 70

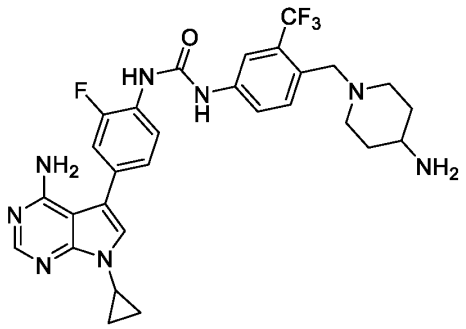
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-(METHYLAMINO)PIPERIDIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was prepared via a similar procedure described for example 61, starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and *tert*-butyl (1-(4-amino-2-(trifluoromethyl)benzyl)piperidin-4-yl)(methyl)carbamate (D45, 0.072 g, 0.186 mmol) in step 1, and was obtained as a an off-white solid (HCl salt, 0.013 g, 7.2% yield over 2 steps). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.38 (s, 1H), 8.23 (t, J = 8.4 Hz, 1H), 8.15 (bs, 1H), 7.93-7.95 (m, 1H), 7.82-7.84 (m, 1H), 7.51 (s, 1H), 7.31-7.39 (m, 2H), 4.48 (bs, 2H), 3.50-3.74 (m, 4H), 3.02 (bs, 2H), 2.77 (s, 3H), 2.36 (bs, 2H), 2.08 (bs, 2H), 1.18-1.23 (m, 4H). LCMS: 597.3 [M+H].

EXAMPLE 71

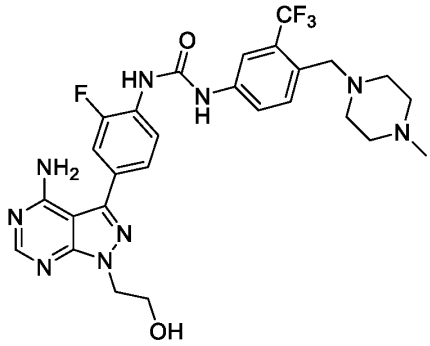
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-AMINOPIPERIDIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was prepared via a similar procedure described for example 61, starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and tert-butyl (1-(4-amino-2-(trifluoromethyl)benzyl)piperidin-4-yl)carbamate (D46, 0.069 g, 0.186 mmol) in step 1, and was obtained as a an off-white solid (HCl salt, 0.015 g, 14% yield over 2 steps). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.38 (s, 1H), 8.23 (t, *J* = 8.4 Hz, 1H), 8.17 (bs, 1H), 7.95 (bs, 1H), 7.82-7.84 (m, 1H), 7.51 (s, 1H), 7.31-7.39 (m, 2H), 4.47 (bs, 2H), 3.50-3.74 (m, 4H), 2.26-2.29 (m, 2H), 2.09-2.12 (m, 2H), 1.18-1.23 (m, 4H). LCMS: 583.3 [M+H].

EXAMPLE 72

1-(4-(4-AMINO-1-(2-HYDROXYETHYL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA

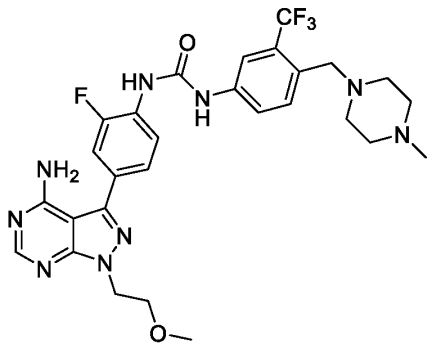


The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-1-(2-hydroxyethyl)-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-fluorophenyl)carbamate (C11, 0.280 g, 0.686 mmol)

and 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (D6, 0.187 g, 0.686 mmol), and was obtained as an off-white solid (0.104 g, 26% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 9.59 (bs, 1H), 8.93 (bs, 1H), 8.39 (s, 1H), 8.35 (t, *J* = 8.4 Hz, 1H), 8.03 (s, 1H), 7.64-7.67 (m, 2H), 7.47-7.54 (m, 2H), 4.42 (t, *J* = 6.0 Hz, 2H), 3.86 (t, *J* = 5.6 Hz, 2H), 3.66 (s, 2H), 3.40-3.43 (m, 2H), 2.91-3.03 (m, 4H), 2.82 (s, 3H), 2.34-2.37 (m, 2H). LCMS: 588.3 [M+H].

EXAMPLE 73

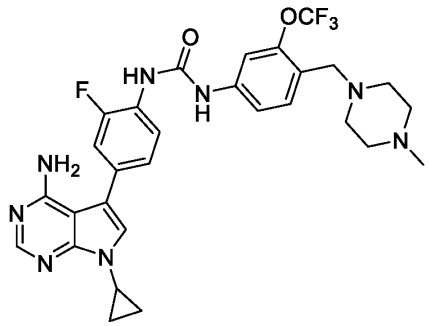
1-(4-(4-AMINO-1-(2-METHOXYETHYL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-1-(2-methoxyethyl)-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-fluorophenyl)carbamate (C12, 0.200 g, 0.473 mmol) and 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (D6, 0.129 g, 0.473 mmol), and was obtained as pale brown solid (0.040 g, 14% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 9.47 (bs, 1H), 8.84 (bs, 1H), 8.34 (t, *J* = 8.0 Hz, 1H), 8.25 (s, 1H), 8.02 (d, *J* = 2.0 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.55-7.57 (m, 1H), 7.45-7.51 (m, 2H), 4.49 (t, *J* = 6.0 Hz, 2H), 3.82 (t, *J* = 5.6 Hz, 2H), 3.54 (s, 2H), 3.23 (s, 3H), 2.38 (bs, 8H), 2.17 (s, 3H). LCMS: 602.4 [M+H].

EXAMPLE 74

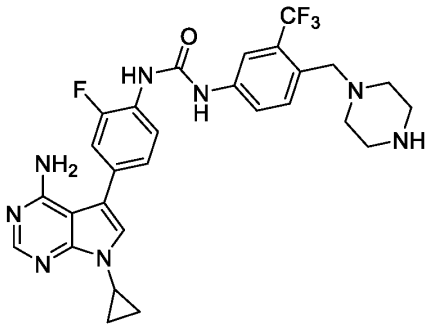
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHOXY)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.035 g, 0.087 mmol) and 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethoxy)aniline (D47, 0.025 g, 0.087 mmol), and was obtained as an off-white gum (0.005 g, 9.6% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.36 (s, 1H), 8.20 (t, J = 8.4 Hz, 1H), 7.78 (s, 1H), 7.48-7.50 (m, 2H), 7.29-7.37 (m, 3H), 3.69-3.72 (m, 3H), 3.45 (bs, 2H), 3.06 (bs, 4H), 2.90 (s, 3H), 2.52 (bs, 2H), 1.17-1.22 (m, 4H). LCMS: 599.7 [M+H].

EXAMPLE 75

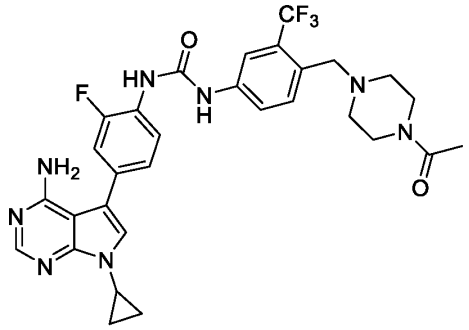
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-(PIPERAZIN-1-YLMETHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was prepared via a similar procedure described for example 61, starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and *tert*-butyl 4-(4-amino-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (D48, 0.067 g, 0.186 mmol) in step 1, and was obtained as a an off-white solid (HCl salt, 0.009 g, 8.4% yield over 2 steps). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 10.03 (bs, 1H), 9.00 (bs, 1H), 8.92 (bs, 1H), 8.50 (s, 1H), 8.19 (t, *J* = 8.4 Hz, 1H), 8.05 (s, 1H), 7.68 (d, *J* = 8.8 Hz, 1H), 7.59 (bs, 2H), 7.24-7.39 (m, 2H), 3.70-3.73 (m, 3H), 3.13 (bs, 4H), 2.68 (bs, 4H), 1.10-1.13 (m, 4H). LCMS: 569.2 [M+H].

EXAMPLE 76

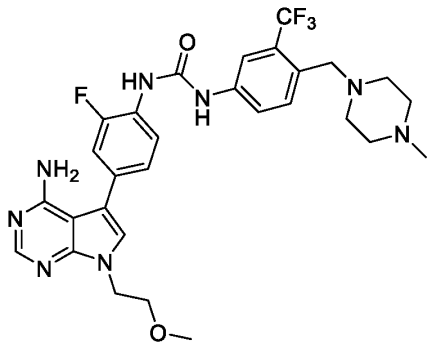
1-(4-((4-ACETYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)-3-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and 1-(4-(4-amino-2-(trifluoromethyl)benzyl)piperazin-1-yl)ethan-1-one (D49, 0.056 g, 0.186 mmol), and was obtained as an off-white solid (0.013 g, 11 % yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 9.40 (bs, 1H), 8.68 (bs, 1H), 8.18-8.23 (m, 2H), 8.02 (d, *J* = 2.0 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.23-7.35 (m, 3H), 6.20 (bs, 2H), 3.58 (bs, 3H), 3.44 (bs, 4H), 2.33-2.34 (m, 4H), 1.99 (s, 3H), 1.02-1.06 (m, 4H). LCMS: 611.4 [M+H].

EXAMPLE 77

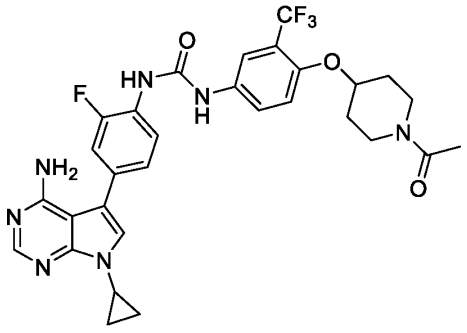
1-(4-(4-AMINO-7-(2-METHOXYETHYL)-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-(2-methoxyethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C13, 0.290 g, 0.688 mmol) and 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (D6, 0.188 g, 0.688 mmol), and was obtained as a white solid (0.08 g, 19% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.35 (s, 1H), 8.21-8.23 (m, 1H), 7.96 (d, J = 2.0 Hz, 1H), 7.67-7.73 (m, 2H), 7.56 (s, 1H), 7.31-7.39 (m, 2H), 4.54 (t, J = 5.2 Hz, 2H), 3.82 (t, J = 4.8 Hz, 2H), 3.76 (s, 2H), 3.49-3.51 (m, 2H), 3.37 (s, 3H), 3.14-3.19 (m, 2H), 3.04-3.06 (m, 2H), 2.93 (s, 3H), 2.47 (bs, 2H). LCMS: 601.5 [M+H].

EXAMPLE 78

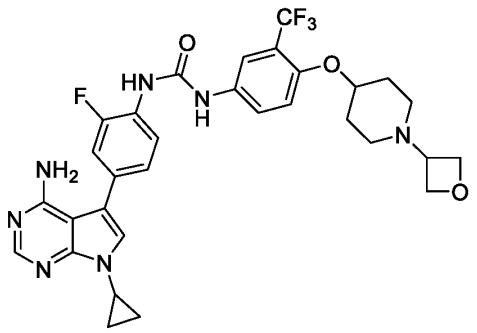
1-(4-((1-ACETYLPIPERIDIN-4-YL)OXY)-3-(TRIFLUOROMETHYL)PHENYL)-3-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.08 g, 0.198 mmol) and 1-(4-(4-amino-2-(trifluoromethyl)benzyl)piperazin-1-yl)ethan-1-one (D50, 0.06 g, 0.198 mmol), and was obtained as an off-white solid (0.04 g, 33% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.36 (s, 1H), 8.20 (t, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 2.4 Hz, 1H), 7.59-7.62 (m, 1H), 7.48 (s, 1H), 7.22-7.36 (m, 3H), 4.82-4.84 (m, 1H), 3.58-3.80 (m, 5H), 2.15 (s, 3H), 1.89 (bs, 4H), 1.18-1.22 (m, 4H). LCMS: 612.2 [M+H].

EXAMPLE 79

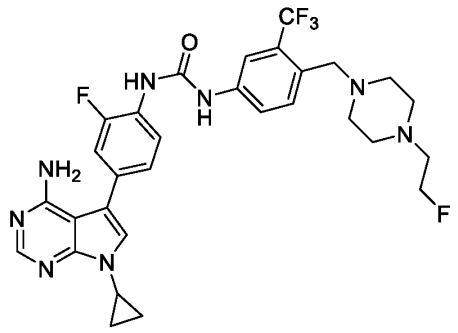
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((1-(OXETAN-3-YL)PIPERIDIN-4-YL)OXY)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.060 g, 0.149 mmol) and 4-((1-(oxetan-3-yl)piperidin-4-yl)oxy)-3-(trifluoromethyl)aniline (D51, 0.047 g, 0.149 mmol), and was obtained as a white solid (0.058 g, 62% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.29 (bs, 1H), 8.73 (bs, 1H), 8.40 (s, 1H), 8.23 (t, *J* = 8.4 Hz, 1H), 7.92 (s, 1H), 7.56-7.59 (m, 1H), 7.54 (s, 1H), 7.35-7.38 (m, 2H), 7.26 (d, *J* = 8.4 Hz, 1H), 4.70-4.78 (m, 5H), 4.38-4.41 (m, 1H), 3.66-3.72 (m, 1H), 2.83-2.98 (m, 4H), 2.12 (bs, 3H), 1.83 (bs, 1H), 1.06-1.11 (m, 4H). LCMS: 626.2 [M+H].

EXAMPLE 80

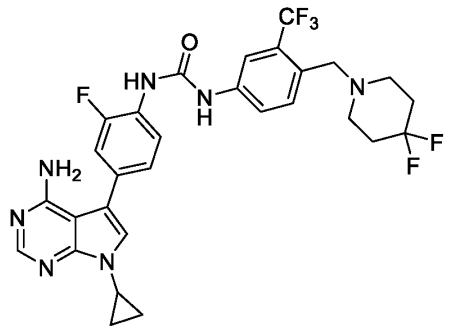
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-(2-FLUOROETHYL)PIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and 4-((4-(2-fluoroethyl)piperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (D52, 0.057 g, 0.186 mmol), and was obtained as an off-white solid (0.026 g, 23% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 9.38 (bs, 1H), 8.67 (bs, 1H), 8.14-8.22 (m, 2H), 8.01 (d, J = 2.4 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.54-7.57 (m, 1H), 7.29-7.34 (m, 2H), 7.23-7.26 (m, 1H), 6.15 (bs, 2H), 4.59 (t, J = 4.8 Hz, 1H), 4.47 (t, J = 5.2 Hz, 1H), 3.55-3.60 (m, 3H), 2.66-2.67 (m, 2H), 2.40 (bs, 2H), 2.08 (bs, 6H), 1.02-1.06 (m, 4H). LCMS: 615.3 [M+H].

EXAMPLE 81

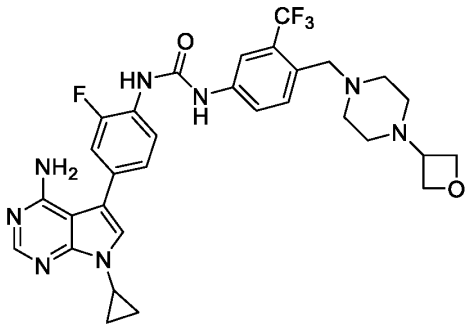
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4,4-DIFLUOROPIPERIDIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.050 g, 0.124 mmol) and 4-((4,4-difluoropiperidin-1-yl)methyl)-3-(trifluoromethyl)aniline (D53, 0.036 g, 0.124 mmol), and was obtained as an off-white solid (0.006 g, 8.3% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.16-8.20 (m, 2H), 7.92 (d, *J* = 2.0 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.63-7.66 (m, 1H), 7.26-7.32 (m, 2H), 7.21 (s, 1H), 3.68 (s, 2H), 3.50-3.53 (m, 1H), 2.57-2.59 (m, 4H), 1.96-2.05 (m, 4H), 1.07-1.16 (m, 4H). LCMS: 604.3 [M+H].

EXAMPLE 82

1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-(OXETAN-3-YL)PIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA

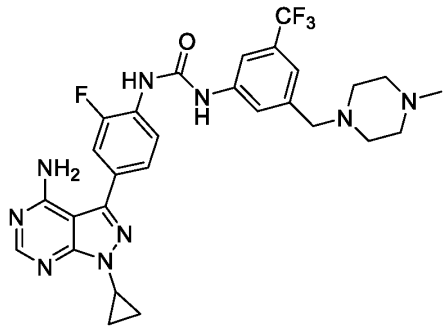


The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and 4-((4-(oxetan-3-yl)piperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (D54, 0.059 g, 0.186 mmol), and was obtained as an off-white solid (0.023 g, 20% yield). ^{1}H NMR (400 MHz,

DMSO-d_6) δ = 10.88 (bs, 1H), 10.05 (bs, 1H), 8.16 (d, *J* = 3.6 Hz, 1H), 7.99-8.06 (m, 2H), 7.58-7.66 (m, 2H), 7.20-7.30 (m, 3H), 6.13 (bs, 2H), 4.52 (t, *J* = 6.4 Hz, 2H), 4.42 (t, *J* = 6.0 Hz, 2H), 3.54-3.60 (m, 3H), 2.42 (bs, 4H), 2.28-2.34 (m, 4H), 1.02-1.07 (m, 4H). LCMS: 625.3 [M+H].

EXAMPLE 83

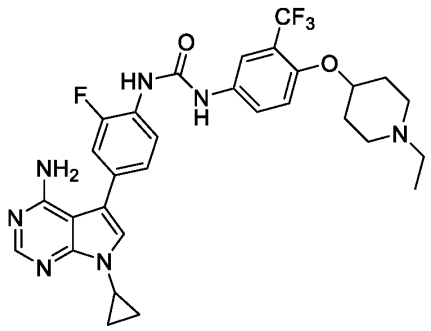
1-(4-(4-AMINO-1-CYCLOPROPYL-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-((4-METHYLPIPERAZIN-1-YL)METHYL)-5-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-1-cyclopropyl-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-fluorophenyl)carbamate (C5, 0.100 g, 0.247 mmol) and 3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)aniline (D55, 0.068 g, 0.247 mmol), and was obtained as an off-white solid (0.005 g, 3.5% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.29-8.36 (m, 2H), 7.84 (s, 1H), 7.69 (s, 1H), 7.47-7.52 (m, 2H), 7.34 (s, 1H), 3.80-3.84 (m, 1H), 3.64 (s, 2H), 2.77 (bs, 4H), 2.64 (bs, 4H), 2.49 (s, 3H), 1.29-1.33 (m, 2H), 1.18-1.21 (m, 2H). LCMS: 584.3 [M+H].

EXAMPLE 84

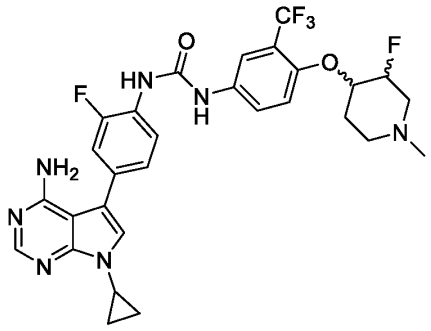
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((1-ETHYLPIPERIDIN-4-YL)OXY)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and 4-((1-ethylpiperidin-4-yl)oxy)-3-(trifluoromethyl)aniline (D56, 0.054 g, 0.186 mmol), and was obtained as an off-white solid (0.026 g, 23% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 9.30 (bs, 1H), 8.73 (bs, 1H), 8.39 (s, 1H), 8.22 (t, *J* = 8.4 Hz, 1H), 7.89-7.93 (m, 1H), 7.50-7.59 (m, 2H), 7.24-7.37 (m, 3H), 4.66-4.93 (m, 1H), 3.45-3.71 (m, 3H), 3.13-3.17 (m, 2H), 2.91-3.06 (m, 2H), 2.27-2.33 (m, 1H), 2.04-2.13 (m, 2H), 1.76-1.79 (m, 1H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.09-1.10 (m, 4H). LCMS: 598.4 [M+H].

EXAMPLES 85 AND 86

1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((3-FLUORO-1-METHYLPIPERIDIN-4-YL)OXY)-3-(TRIFLUOROMETHYL)PHENYL)UREA



Two diastereomers of the title compound were obtained following the general procedure for urea formation (Method A).

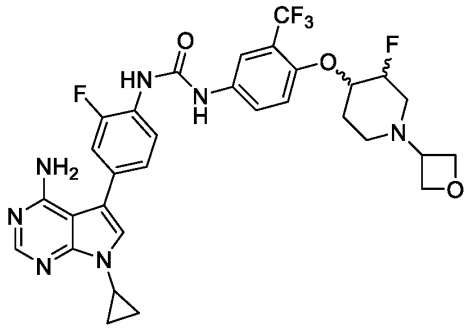
Example 85 was prepared using phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.070 g, 0.174 mmol) and

one diastereomer of 4-((3-fluoro-1-methylpiperidin-4-yl)oxy)-3-(trifluoromethyl)aniline (D57a, 0.051 g, 0.174 mmol), and was obtained as an off-white solid (0.010 g, 9.5% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.14-8.20 (m, 2H), 7.79 (d, *J* = 2.8 Hz, 1H), 7.60-7.63 (m, 1H), 7.20-7.31 (m, 4H), 4.60-4.84 (m, 2H), 3.49-3.54 (m, 1H), 2.97 (bs, 1H), 2.70-2.72 (m, 2H), 2.50 (bs, 1H), 2.40 (s, 3H), 2.13-2.15 (m, 1H), 1.94-1.99 (m, 1H), 1.06-1.18 (m, 4H). LCMS: 602.3 [M+H].

Example 86 was prepared using phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and another diastereomer of 4-((3-fluoro-1-methylpiperidin-4-yl)oxy)-3-(trifluoromethyl)aniline (D57b, 0.054 g, 0.186 mmol), and was obtained as an off-white solid (0.007 g, 6% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.25 (bs, 1H), 8.66 (bs, 1H), 8.14-8.19 (m, 2H), 7.87 (d, *J* = 2.4 Hz, 1H), 7.52-7.55 (m, 1H), 7.22-7.37 (m, 4H), 6.13 (bs, 2H), 4.56-4.71 (m, 2H), 2.94-3.00 (m, 1H), 2.59-2.68 (m, 1H), 2.04-2.33 (m, 7*H*), 1.58-1.61 (m, 1H), 1.02-1.04 (m, 4H). LCMS: 602.3 [M+H].

EXAMPLES 87 AND 88

1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((3-FLUORO-1-(OXETAN-3-YL)PIPERIDIN-4-YL)OXY)-3-(TRIFLUOROMETHYL)PHENYL)UREA



Two diastereomers of the title compound were obtained following the general procedure for urea formation (Method A).

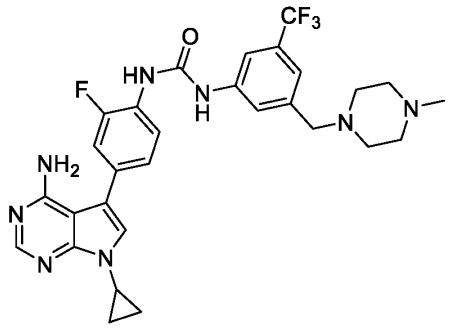
Example 87 was prepared using phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.050 g, 0.124 mmol) and one diastereomer of 4-((3-fluoro-1-(oxetan-3-yl)piperidin-4-yl)oxy)-3-

(trifluoromethyl)aniline (D58a, 0.041 g, 0.124 mmol), and was obtained as an off-white solid (0.005 g, 6.3% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.14-8.20 (m, 2H), 7.79 (d, *J* = 2.8 Hz, 1H), 7.59-7.62 (m, 1H), 7.21-7.31 (m, 4H), 4.60-4.88 (m, 6H), 3.64-3.67 (m, 1H), 3.50-3.54 (m, 1H), 2.42-2.76 (m, 4H), 1.92-2.18 (m, 2H), 1.06-1.18 (m, 4H). LCMS: 644.3 [M+H].

Example 88 was prepared using phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and another diastereomer of 4-((3-fluoro-1-(oxetan-3-yl)piperidin-4-yl)oxy)-3-(trifluoromethyl)aniline (D58b, 0.062 g, 0.186 mmol), and was obtained as an off-white solid (0.006 g, 5.4% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.21 (bs, 1H), 8.63 (bs, 1H), 8.17-8.21 (m, 2H), 7.88 (d, *J* = 2.4 Hz, 1H), 7.52-7.55 (m, 1H), 7.22-7.38 (m, 4H), 6.15 (bs, 2H), 4.41-4.56 (m, 7*H*), 3.51-3.59 (m, 2H), 2.92-2.97 (m, 1H), 2.33-2.34 (m, 1H), 2.08-2.13 (m, 2H), 1.60-1.62 (m, 1H), 1.02-1.07 (m, 4H). LCMS: 644.3 [M+H].

EXAMPLE 89

1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-D]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(3-((4-METHYLPIPERAZIN-1-YL)METHYL)-5-(TRIFLUOROMETHYL)PHENYL)UREA

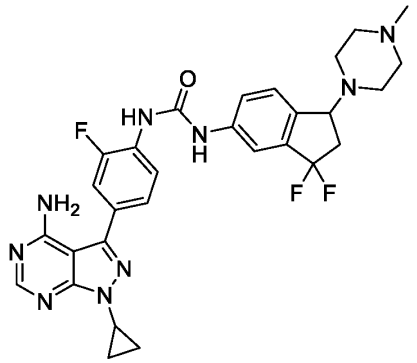


The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.100 g, 0.248 mmol) and 3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)aniline (D55, 0.068 g, 0.248 mmol), and was obtained as an off-white solid (0.025 g, 17% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.15-8.20 (m, 2H), 7.82 (s, 1H), 7.65 (s, 1H), 7.20-7.33 (m, 4H), 3.64 (s,

2H), 3.50-3.53 (m, 1H), 2.81 (bs, 4H), 2.64-2.68 (m, 4H), 2.51 (s, 3H), 1.08-1.16 (m, 4H). LCMS: 583.3 [M+H].

EXAMPLE 90

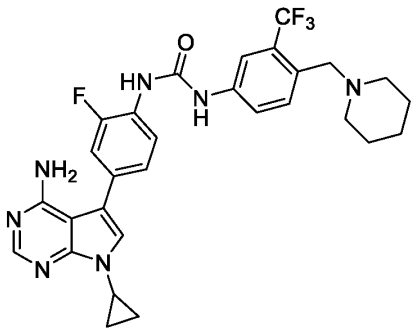
1-(4-(4-AMINO-1-CYCLOPROPYL-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3,3-DIFLUORO-1-(4-METHYLPIPERAZIN-1-YL)-2,3-DIHYDRO-1H-INDEN-5-YL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-1-cyclopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)carbamate (C5, 0.065 g, 0.161 mmol) and 3,3-difluoro-1-(4-methylpiperazin-1-yl)-2,3-dihydro-1H-inden-5-amine (D59, 0.043 g, 0.161 mmol), and was obtained as an off-white solid (0.010 g, 11% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.29-8.35 (m, 2H), 7.81 (s, 1H), 7.58-7.60 (m, 1H), 7.46-7.52 (m, 3H), 3.78-3.84 (m, 1H), 2.63-2.83 (m, 9H), 2.52-2.58 (m, 5H), 1.18-1.33 (m, 4H). LCMS: 578.3 [M+H].

EXAMPLE 91

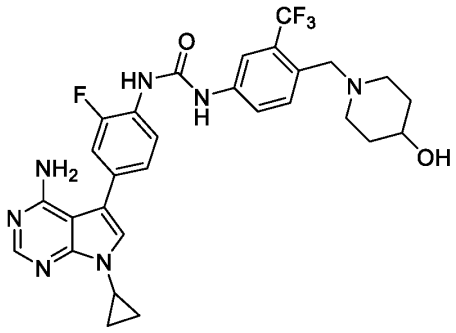
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-(PIPERIDIN-1-YLMETHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.083 g, 0.205 mmol) and 4-(piperidin-1-ylmethyl)-3-(trifluoromethyl)aniline (D60, 0.061 g, 0.205 mmol), and was obtained as an off-white solid (0.018 g, 15% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.16-8.20 (m, 2H), 7.94 (d, *J* = 2.0 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.64-7.66 (m, 1H), 7.27-7.32 (m, 2H), 7.21 (s, 1H), 3.68 (bs, 2H), 3.49-3.55 (m, 1H), 2.54 (bs, 4H), 1.53-1.69 (m, 6H), 1.09-1.18 (m, 4H). LCMS: 568.2 [M+H].

EXAMPLE 92

1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-HYDROXYPIPERIDIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA

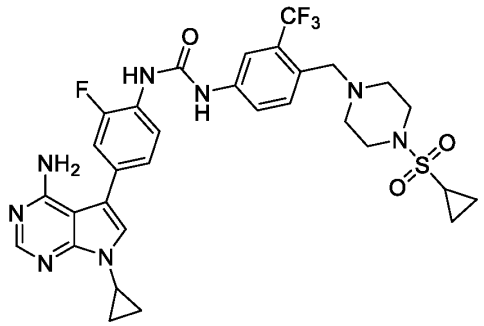


The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.085 g, 0.211 mmol) and 1-(4-amino-2-(trifluoromethyl)benzyl)piperidin-4-ol (D61, 0.058 g, 0.211 mmol), and was obtained as an off-white solid (0.015 g, 12% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.16-8.20

(m, 2H), 7.94 (d, J = 2.0 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.64-7.67 (m, 1H), 7.27-7.32 (m, 2H), 7.21 (s, 1H), 3.69-3.71 (m, 3H), 3.50-3.54 (m, 1H), 2.86-2.88 (m, 2H), 2.29-2.34 (m, 2H), 1.87-1.96 (m, 2H), 1.60-1.64 (m, 2H), 1.07-1.18 (m, 4H). LCMS: 584.2 [M+H].

EXAMPLE 93

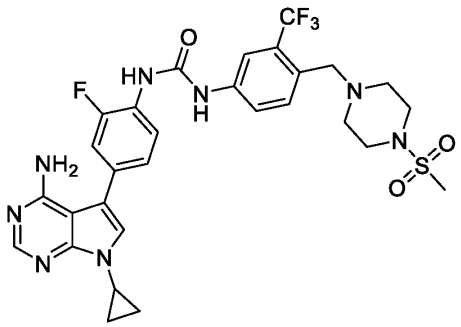
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-(CYCLOPROPYLSULFONYL)PIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.10 g, 0.248 mmol) and 4-((4-(cyclopropylsulfonyl)piperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (D62, 0.09 g, 0.248 mmol), and was obtained as an off-white solid (0.016 g, 9.3% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.92-8.20 (m, 2H), 7.92 (d, J = 2.0 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 2.0 Hz, 1H), 7.27-7.32 (m, 2H), 7.21 (s, 1H), 3.69 (s, 2H), 3.51-3.53 (m, 1H), 2.49-2.59 (m, 9H), 1.03-1.16 (m, 8H). LCMS: 673.3 [M+H].

EXAMPLE 94

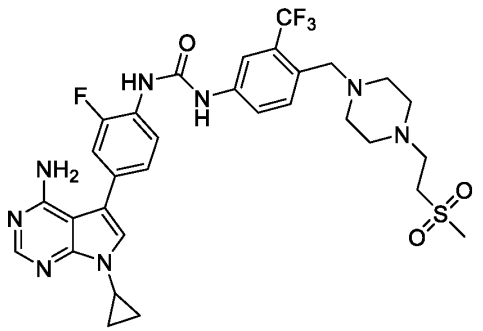
1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-(METHYLSULFONYL)PIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.065 g, 0.161 mmol) and 4-((4-(methylsulfonyl)piperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (D63, 0.054 g, 0.161 mmol), and was obtained as an off-white solid (0.002 g, 1.9% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.37 (s, 1H), 8.22 (t, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 2.0 Hz, 1H), 7.76-7.79 (m, 2H), 7.50 (s, 1H), 7.30-7.38 (m, 2H), 4.35 (s, 2H), 3.69-3.75 (m, 1H), 3.50-3.51 (m, 4H), 3.28-3.35 (m, 4H), 2.95 (s, 3H), 1.18-1.23 (m, 4H). LCMS: 647.1 [M+H].

EXAMPLE 95

1-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-(2-(METHYLSULFONYL)ETHYL)PIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA

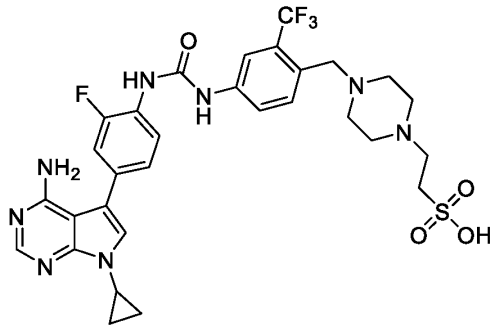


The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.075 g, 0.186 mmol) and 4-((4-(2-(methylsulfonyl)ethyl)piperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (D64, 0.068 mg, 0.186 mmol), and was obtained as an off-white solid (0.005 g, 4% yield). ^{1}H NMR

(400 MHz, CD_3OD) δ = 8.36 (s, 1H), 8.21 (t, *J* = 8.4 Hz, 1H), 8.07 (bs, 1H), 7.72-7.80 (m, 2H), 7.48 (s, 1H), 7.30-7.38 (m, 2H), 4.23 (bs, 2H), 3.68-3.73 (m, 1H), 3.49-3.51 (m, 2H), 3.12-3.29 (m, 10H), 3.09 (s, 3H), 1.17-1.23 (m, 4H). LCMS: 675.5 [M+H].

EXAMPLE 96

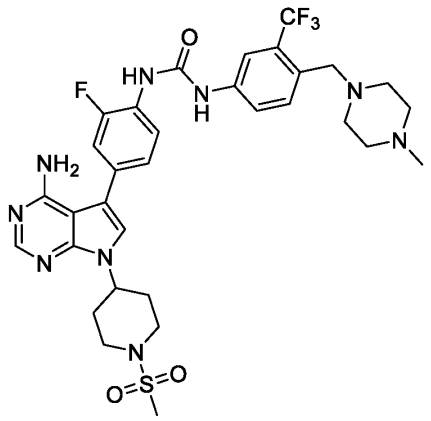
2-(4-(4-(3-(4-(4-AMINO-7-CYCLOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)UREIDO)-2-(TRIFLUOROMETHYL)BENZYL)PIPERAZIN-1-YL)ETHANE-1-SULFONIC ACID



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-cyclopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C6, 0.050 g, 0.124 mmol) and 2-(4-(4-amino-2-(trifluoromethyl)benzyl)piperazin-1-yl)ethane-1-sulfonic acid (D65, 0.046 g, 0.124 mmol), and was obtained as an off-white solid (0.003 g, 3.6% yield). ^1H NMR (400 MHz, CD_3OD) δ = 8.37 (s, 1H), 8.22 (t, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 2.0 Hz, 1H), 7.66-7.74 (m, 2H), 7.50 (s, 1H), 7.29-7.38 (m, 2H), 3.70-3.91 (m, 3H), 3.51-3.69 (m, 4H), 3.21-3.25 (m, 2H), 3.08 (bs, 4H), 2.60 (bs, 2H), 1.18-1.23 (m, 4H). LCMS: 677.1 [M+H].

EXAMPLE 97

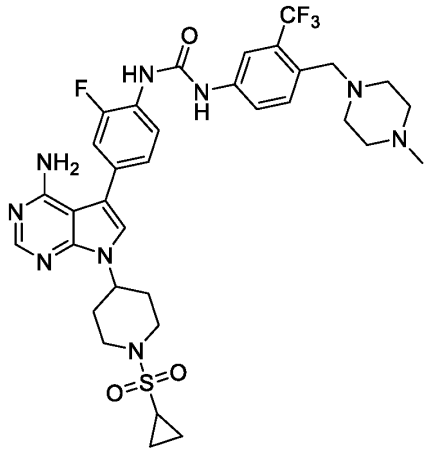
1-(4-(4-AMINO-7-(1-(METHYLSULFONYL)PIPERIDIN-4-YL)-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-(1-(methylsulfonyl)piperidin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C14, 0.02 g, 0.038 mmol) and 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (D6, 0.01 g, 0.038 mmol), and was obtained as an off-white solid (0.003 g, 33% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.17-8.21 (m, 2H), 7.92 (d, *J* = 2.0 Hz, 1H), 7.65-7.73 (m, 2H), 7.41 (s, 1H), 7.29-7.35 (m, 2H), 4.79-4.82 (m, 1H), 3.94-3.97 (m, 2H), 3.68 (s, 2H), 3.01-3.08 (m, 2H), 2.94 (s, 3H), 2.77 (bs, 4H), 2.61 (bs, 4H), 2.50 (s, 3H), 2.18-2.24 (m, 4H). LCMS: 704.3 [M+H].

EXAMPLE 98

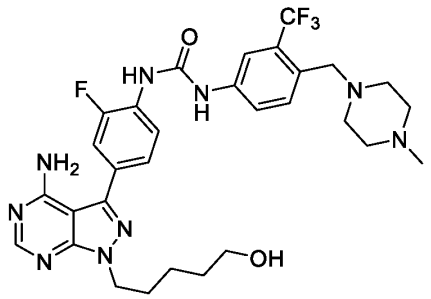
1-(4-(4-AMINO-7-(1-(CYCLOPROPYLSULFONYL)PIPERIDIN-4-YL)-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-(1-(methylsulfonyl)piperidin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C15, 0.06 g, 0.109 mmol) and 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (D6, 0.03 g, 0.109 mmol), and was obtained as an off-white solid (0.011 g, 14% yield. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.36 (s, 1H), 8.23 (t, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 4.0 Hz, 1H), 7.69-7.73 (m, 3H), 7.32-7.40 (m, 2H), 4.92-4.96 (m, 1H), 3.97-4.00 (m, 2H), 3.76 (s, 2H), 3.49-3.51 (m, 1H), 3.14-3.18 (m, 6H), 2.93 (s, 3H), 2.56-2.60 (m, 4H), 2.17-2.32 (m, 4H), 1.08-1.12 (m, 4H). LCMS: 730.3 [M+H].

EXAMPLE 99

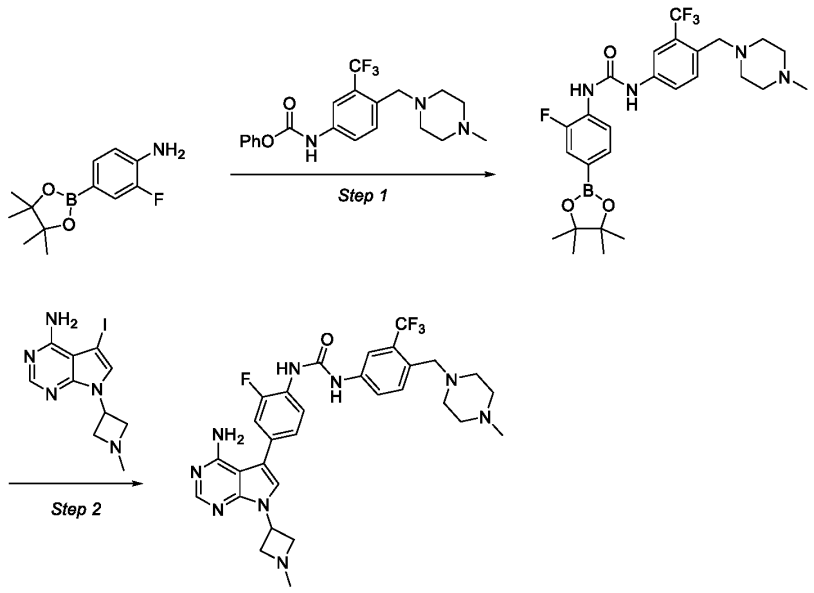
1-(4-(4-AMINO-1-(5-HYDROXYPENTYL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-7-(1-(methylsulfonyl)piperidin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)carbamate (C16, 0.042 g, 0.093 mmol) and 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (D6, 0.025 g, 0.093 mmol), and was obtained as an off-white solid (0.003 g, 5.2% yield). LCMS: 630.5 [M+H].

EXAMPLE 100

1-(4-(4-AMINO-7-(1-METHYLAZETIDIN-3-YL)-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



Step 1: Synthesis of 1-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

The title compound was obtained following the general procedure for urea formation (Method A), starting from 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.300 g, 1.265 mmol) and phenyl (4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)carbamate (C1, 0.498 g, 1.265 mmol), and was obtained as an off-white solid (0.120 g, 18% yield). LCMS: 537.3 [M+H].

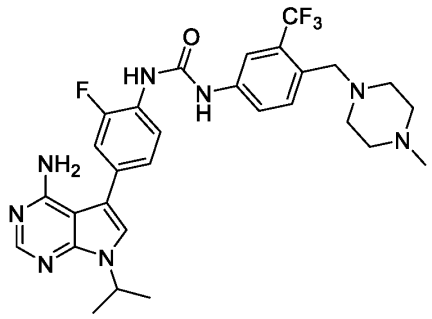
Step 2: Synthesis of 1-(4-(4-amino-7-(1-methylazetidin-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea

The title compound was prepared via a similar procedure described for intermediate B5, starting from 5-iodo-7-(1-methylazetidin-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (A18, 0.035 g, 0.106 mmol) and 1-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (0.057 g, 0.106 mmol), and was obtained as an off-white solid (0.014 g, 22% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 9.99 (bs, 1H), 9.52 (bs, 1H), 8.81 (s, 1H), 8.24-8.32 (m, 2H), 8.03 (d, *J* = 2.0 Hz, 1H), 7.59-7.66 (m, 2H), 7.10-7.37 (m, 2H), 6.97 (bs, 2H), 5.60-5.72 (m, 1H), 4.49-4.82 (m, 4H), 3.65 (bs, 2H), 3.40-

3.43 (m, 2H), 3.03-3.07 (m, 4H), 2.89-2.92 (m, 2H), 2.82 (s, 3H), 2.51 (s, 3H). LCMS: 612.3 [M+H].

EXAMPLE 101

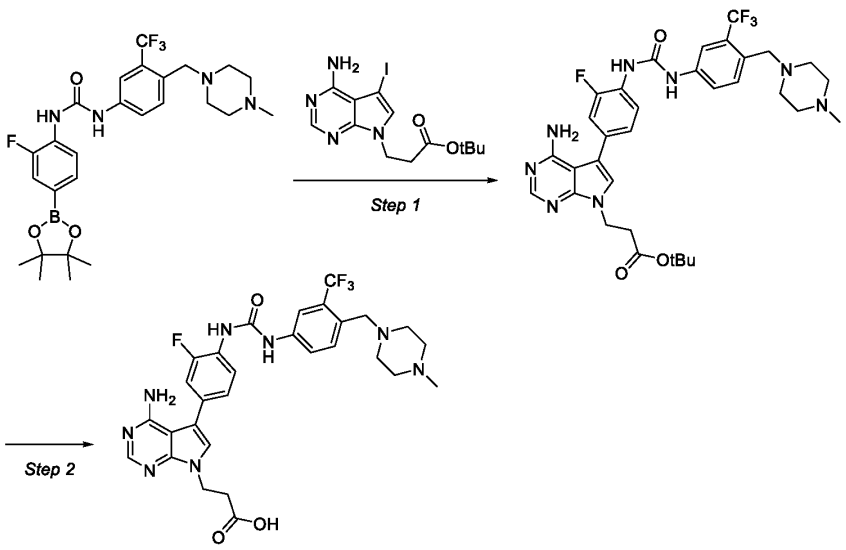
1-(4-(4-AMINO-7-ISOPROPYL-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was prepared via a similar procedure described for example 100, starting from 5-iodo-7-isopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (A19, 0.035 g, 0.116 mmol) and 1-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (step 1 of example 100, 0.062 g, 0.116 mmol), and was obtained as an off-white solid (0.005 g, 7.4% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.17-8.21 (m, 2H), 7.92 (d, *J* = 2.0 Hz, 1H), 7.63-7.73 (m, 2H), 7.38 (s, 1H), 7.29-7.34 (m, 2H), 5.01-5.06 (m, 1H), 3.66 (s, 2H), 2.58 (bs, 8H), 2.37 (s, 3H), 1.56 (d, *J* = 6.8 Hz, 6H). LCMS: 585.3 [M+H].

EXAMPLE 102

3-(4-AMINO-5-(3-FLUORO-4-(3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREIDO)PHENYL)-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-7-YL)PROPANOIC ACID



Step 1: Synthesis of *tert*-butyl 3-(4-amino-5-(3-fluoro-4-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)phenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)propanoate

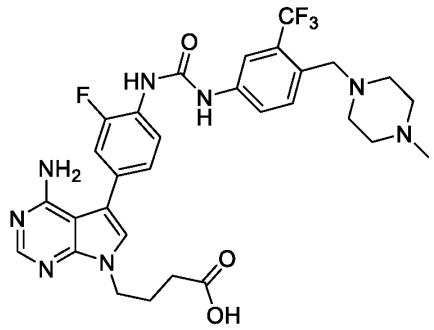
The title compound was prepared via a similar procedure described for intermediate B5, starting from *tert*-butyl 3-(4-amino-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)propanoate (A20, 0.045 g, 0.116 mmol) and 1-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (step 1 of example 100, 0.062 g, 0.116 mmol), and was obtained as a white solid (0.020 g, 26% yield). LCMS: 671.3 [M+H].

Step 2: Synthesis of 3-(4-amino-5-(3-fluoro-4-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)phenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)propanoic acid

The title compound was prepared via a similar procedure described for step 3 of example 32, starting from *tert*-butyl 3-(4-amino-5-(3-fluoro-4-(3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)ureido)phenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)propanoate (0.020 g, 0.030 mmol), and was obtained as an off-white solid (0.002 g, 11% yield). LCMS: 615.4 [M+H].

EXAMPLE 103

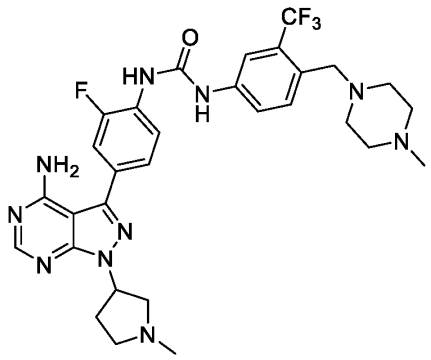
4-(4-AMINO-5-(3-FLUORO-4-(3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREIDO)PHENYL)-7*H*-PYRROLO[2,3-*D*]PYRIMIDIN-7-YL)BUTANOIC ACID



The title compound was prepared via a similar procedure described for example 102, starting from *tert*-butyl 4-(4-amino-5-(3-fluoro-4-((phenoxycarbonyl)amino)phenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)butanoate (C17, 0.050 g, 0.099 mmol) and 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (D6, 0.027 g, 0.099 mmol) in step 1, and was obtained as an off-white solid (0.009 g, 14% yield over 2 steps). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 10.00 (bs, 1H), 8.90 (bs, 1H), 8.35 (s, 1H), 8.24 (t, *J* = 8.8 Hz, 1H), 8.01 (s, 1H), 7.59-7.66 (m, 3H), 7.34-7.37 (m, 1H), 7.15-7.27 (m, 1H), 4.25 (t, *J* = 7.2 Hz, 2H), 3.64 (s, 2H), 3.37-3.49 (m, 2H), 3.00-3.03 (m, 2H), 2.88-2.91 (m, 2H), 2.79 (s, 3H), 2.22-2.38 (m, 4H), 2.02-2.04 (m, 2H). LCMS: 629.3 [M+H].

EXAMPLE 104

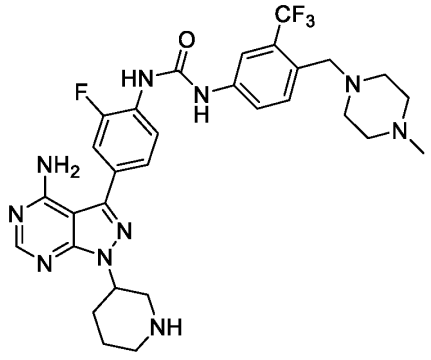
1-(4-(4-AMINO-1-(1-METHYLPYRROLIDIN-3-YL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was prepared via a similar procedure described for example 100, starting from 3-iodo-1-(1-methylpyrrolidin-3-yl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (A22, 0.030 g, 0.087 mmol) and 1-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (step 1 of example 100, 0.051 g, 0.096 mmol), and was obtained as an off-white solid (0.002 g, 3.6% yield). LCMS: 627.2 [M+H].

EXAMPLE 105

1-(4-(4-AMINO-1-(PIPERIDIN-3-YL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA

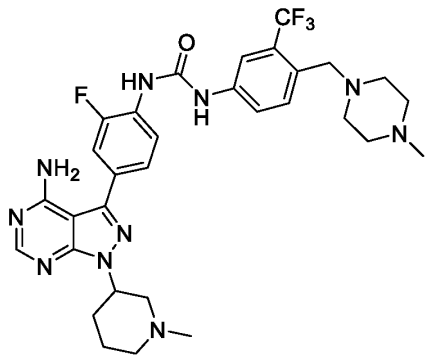


The title compound was prepared via a similar procedure described for example 61, starting from *tert*-butyl 3-(4-amino-3-(3-fluoro-4-((phenoxycarbonyl)amino)phenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidine-1-carboxylate (C18, 0.434 g, 0.793 mmol) and 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (D6, 0.217 g, 0.793 mmol) in step 1, and was obtained as an

off-white solid (0.012 g, 30% yield over 2 steps) following purification by preparative HPLC (eluting with 10 mM $NaHCO_3$ in water and ACN). ^1H NMR (400 MHz, DMSO-d_6) δ = 9.54 (bs, 1H), 8.90 (bs, 1H), 8.25-8.35 (m, 2H), 8.03 (d, *J* = 2.0 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.56-7.58 (m, 1H), 7.44-7.51 (m, 2H), 6.95 (bs, 2H), 4.68-4.75 (m, 1H), 3.55 (s, 2H), 2.94-3.14 (m, 4H), 2.52-2.55 (m, 2H), 2.34-2.42 (m, 4H), 2.17 (s, 3H), 2.04-2.13 (m, 4H), 1.77-1.79 (m, 1H), 1.58-1.61 (m, 1H). LCMS: 627.2 [M+H].

EXAMPLE 106

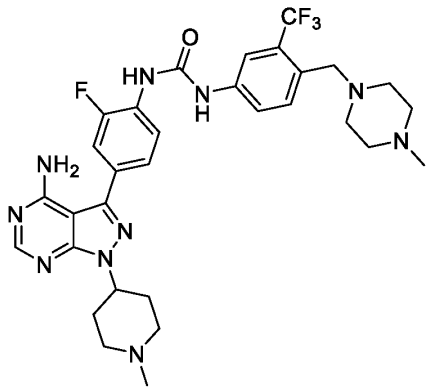
1-(4-(4-AMINO-1-(1-METHYLPIPERIDIN-3-YL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was prepared via a similar procedure described for step 3 of intermediate D17, starting from 1-(4-(4-amino-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (Example 105, 0.10 g, 0.160 mmol), and was obtained as an off-white solid (0.037 g, 36% yield) following purification by preparative HPLC (eluting with 10 mM $NaHCO_3$ in water and ACN). ^1H NMR (400 MHz, DMSO-d_6) δ = 9.62 (bs, 1H), 8.97 (bs, 1H), 8.32 (t, *J* = 8.4 Hz, 1H), 8.25 (s, 1H), 8.03 (d, *J* = 2.0 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.56-7.58 (m, 1H), 7.43-7.49 (m, 2H), 6.94 (bs, 2H), 4.75-4.81 (m, 1H), 3.54 (s, 2H), 2.92-2.96 (m, 1H), 2.79-2.81 (m, 1H), 2.33-2.46 (m, 8H), 2.23 (s, 3H), 2.16 (s, 3H), 1.90-1.97 (m, 4H), 1.80-1.83 (m, 1H), 1.65-1.73 (m, 1H). LCMS: 641.3 [M+H].

EXAMPLE 107

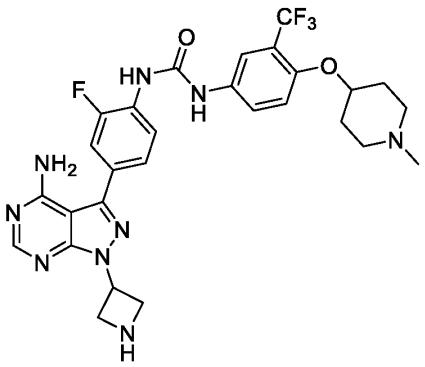
1-(4-(4-AMINO-1-(1-METHYLPIPERIDIN-4-YL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was prepared via a similar procedure described for example 100, starting from 3-iodo-1-(1-methylpiperidin-4-yl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (A24, 0.12 g, 0.335 mmol) and 1-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (step 1 of example 100, 0.18 g, 0.335 mmol), and was obtained as an off-white solid (0.04 g, 19% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 9.47 (bs, 1H), 8.84 (bs, 1H), 8.34 (t, *J* = 8.4 Hz, 1H), 8.26 (s, 1H), 8.02 (s, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.55-7.57 (m, 1H), 7.45-7.50 (m, 2H), 7.00 (bs, 2H), 4.61-4.67 (m, 1H), 3.55 (s, 2H), 2.90-2.93 (m, 2H), 2.34-2.39 (m, 8H), 2.21-2.24 (m, 5H), 2.16 (s, 3H), 2.06-2.12 (m, 2H), 1.87-1.89 (m, 2H). LCMS: 641.2 [M+H].

EXAMPLE 108

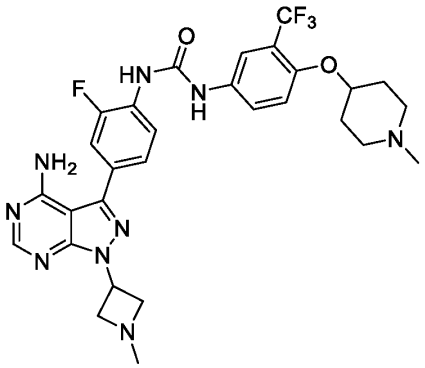
1-(4-(4-AMINO-1-(AZETIDIN-3-YL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(4-((1-METHYLPIPERIDIN-4-YL)OXY)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was prepared via a similar procedure described for example 61, starting from *tert*-butyl 3-(4-amino-3-(3-fluoro-4-((phenoxycarbonyl)amino)phenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)azetidine-1-carboxylate (C19, 0.400 g, 0.770 mmol) and 4-((1-methylpiperidin-4-yl)oxy)-3-(trifluoromethyl)aniline (D12, 0.211 g, 0.770 mmol) in step 1, and was obtained as an off-white solid (0.013 g, 20% yield over 2 steps) following purification by preparative HPLC (eluting with 10 mM $NaHCO_3$ in water and ACN). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.51 (bs, 1H), 8.88 (bs, 1H), 8.38 (t, *J* = 8.4 Hz, 1H), 8.29 (s, 1H), 7.90 (d, *J* = 2.4 Hz, 1H), 7.47-7.58 (m, 3H), 7.28-7.30 (m, 1H), 5.80-5.84 (m, 1H), 4.82 (bs, 1H), 4.44-4.57 (m, 4H), 3.02 (bs, 4H), 2.56 (s, 3H), 2.09 (bs, 2H), 1.88-1.90 (m, 2H). LCMS: 600.2 [M+H].

EXAMPLE 109

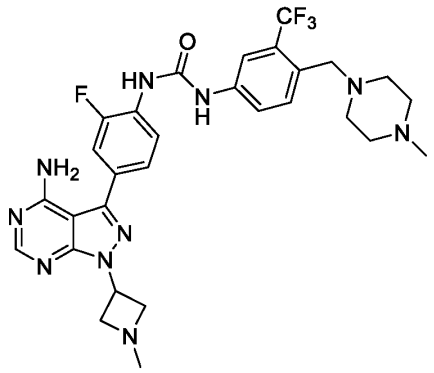
1-(4-(4-AMINO-1-(1-METHYLAZETIDIN-3-YL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(4-((1-METHYLPIPERIDIN-4-YL)OXY)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was prepared via a similar procedure described for step 3 of intermediate D17, starting from 1-(4-(4-amino-1-(azetidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(4-((1-methylpiperidin-4-yl)oxy)-3-(trifluoromethyl)phenyl)urea (Example 108, 0.075 g, 0.125 mmol), and was obtained as an off-white solid (0.003 g, 3.9% yield) following purification by preparative HPLC (eluting with 10 mM $NaHCO_3$ in water and ACN). ^1H NMR (400 MHz, CD_3OD) δ = 8.33 (t, *J* = 8.0 Hz, 1H), 8.27 (s, 1H), 7.80 (d, *J* = 2.8 Hz, 1H), 7.52-7.63 (m, 3H), 7.21 (d, *J* = 8.8 Hz, 1H), 5.56-5.64 (m, 1H), 4.82 (bs, 1H), 4.03-4.07 (m, 2H), 3.95-3.99 (m, 2H), 2.82 (bs, 2H), 2.62-2.68 (m, 5H), 2.44 (s, 3H), 1.94-2.10 (m, 4H). LCMS: 614.3 [M+H].

EXAMPLE 110

1-(4-(4-AMINO-1-(1-METHYLAZETIDIN-3-YL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA

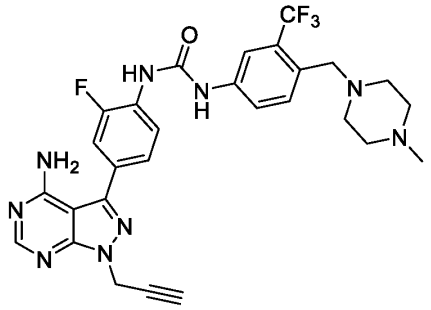


The title compound was prepared via a similar procedure described for example 100, starting from 3-iodo-1-(1-methylazetidin-3-yl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (A26, 0.130 g, 0.394 mmol) and 1-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)urea (step 1 of example 100, 0.211 g, 0.394 mmol), and was obtained as an off-white solid (0.02 g, 8.3% yield). ^1H NMR (400 MHz, DMSO-d_6) δ = 9.44 (bs, 1H), 8.82 (bs, 1H), 8.36 (bs, 1H), 8.25 (s, 1H), 8.02 (s, 1H), 7.65-7.68 (m,

1H), 7.47-7.57 (m, 3H), 7.10 (bs, 2H), 5.38 (bs, 1H), 3.80 (bs, 2H), 3.55-3.58 (m, 4H), 2.38 (bs, 8H), 2.17 (bs, 6H). LCMS: 613.3 [M+H].

EXAMPLE 111

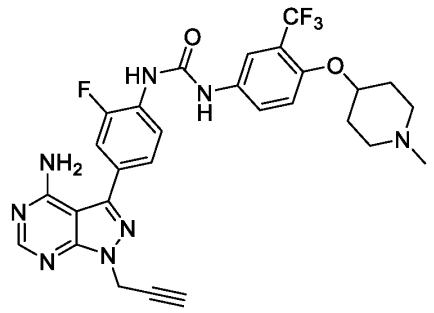
1-(4-(4-AMINO-1-(PROP-2-YN-1-YL)-1H-PYRAZOLO[3,4-D]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-1-(prop-2-yn-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)carbamate (C20, 0.061 g, 0.152 mmol) and 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (D6, 0.041 g, 0.152 mmol), and was obtained as an off-white solid (0.023 g, 34% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.36 (t, J = 8.4 Hz, 1H), 8.31 (s, 1H), 7.93 (d, J = 2.0 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.65-7.67 (m, 1H), 7.51-7.57 (m, 2H), 5.24 (s, 2H), 3.67 (s, 2H), 2.85 (s, 1H), 2.70 (bs, 4H), 2.59 (bs, 4H), 2.44 (s, 3H). LCMS: 582.1 [M+H].

EXAMPLE 112

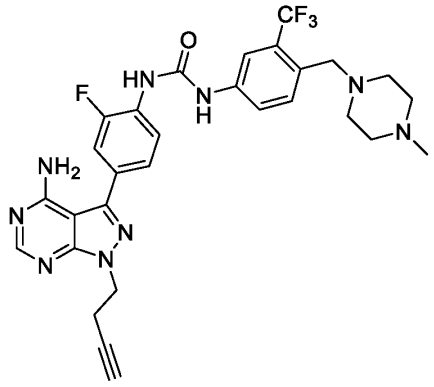
1-(4-(4-AMINO-1-(PROP-2-YN-1-YL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(4-((1-METHYLPIPERIDIN-4-YL)OXY)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-1-(prop-2-yn-1-yl)-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-fluorophenyl)carbamate (C20, 0.061 g, 0.152 mmol) and 4-((1-methylpiperidin-4-yl)oxy)-3-(trifluoromethyl)aniline (D12, 0.042 g, 0.152 mmol), and was obtained as an off-white solid (0.024 g, 27% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.31-8.36 (m, 2H), 7.79 (d, *J* = 2.4 Hz, 1H), 7.50-7.62 (m, 3H), 7.19 (d, *J* = 8.8 Hz, 1H), 5.24 (s, 2H), 4.62 (s, 1H), 2.85 (s, 1H), 2.71 (bs, 2H), 2.50 (bs, 2H), 2.34 (s, 3H), 1.93-2.06 (m, 4H). LCMS: 583.2 [M+H].

EXAMPLE 113

1-(4-(4-AMINO-1-(BUT-3-YN-1-YL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA

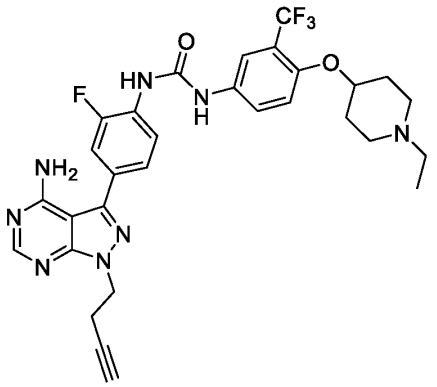


The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-1-(but-3-yn-1-yl)-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-fluorophenyl)carbamate (C21, 0.07 g, 0.180 mmol) and 4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (D6, 0.049 g, 0.180

mmol), and was obtained as an off-white solid (0.025 g, 23% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.45 (s, 1H), 8.82 (s, 1H), 8.35 (t, J = 8.4 Hz, 1H), 8.26 (s, 1H), 8.02 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.46-7.57 (m, 3H), 7.02 (bs, 2H), 4.45-4.48 (m, 2H), 3.55 (s, 2H), 2.78-2.82 (m, 3H), 2.33-2.38 (m, 8H), 2.18 (s, 3H). LCMS: 596.2 [M+H].

EXAMPLE 114

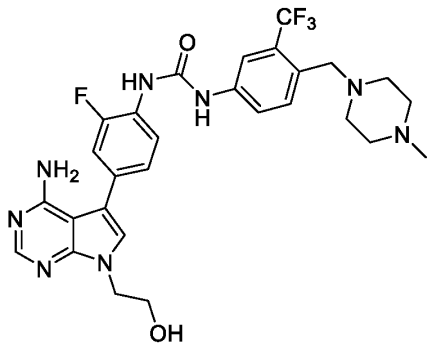
1-(4-(4-AMINO-1-(BUT-3-YN-1-YL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(4-((1-ETHYLPIPERIDIN-4-YL)OXY)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-1-(but-3-yn-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)carbamate (C21, 0.076 g, 0.183 mmol) and 4-((1-ethylpiperidin-4-yl)oxy)-3-(trifluoromethyl)aniline (D56, 0.053 g, 0.183 mmol), and was obtained as an off-white solid (0.023 g, 21% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.21 (s, 1H), 8.74 (s, 1H), 8.34 (t, J = 8.4 Hz, 1H), 8.26 (s, 1H), 7.87 (d, J = 2.4 Hz, 1H), 7.45-7.54 (m, 3H), 7.27-7.29 (m, 1H), 7.02 (bs, 2H), 4.45-4.56 (m, 3H), 2.78-2.82 (m, 3H), 2.60-2.67 (m, 2H), 2.27-2.36 (m, 4H), 1.90-1.93 (m, 2H), 1.66-1.68 (m, 2H), 1.00 (t, J = 6.80 Hz, 3H). LCMS: 611.2 [M+H].

EXAMPLE 115

1-(4-(4-AMINO-7-(2-HYDROXYETHYL)-7*H*-PYRROLO[2,3-D]PYRIMIDIN-5-YL)-2-FLUOROPHENYL)-3-(4-((4-METHYLPIPERAZIN-1-YL)METHYL)-3-(TRIFLUOROMETHYL)PHENYL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from 2-(4-amino-5-(4-amino-3-fluorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)ethan-1-ol (B25, 0.109 g, 0.379 mmol) and phenyl (4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)carbamate (C1, 0.149 g, 0.379 mmol), and was obtained as an off-white solid (0.007 mg, 3.4% yield). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.14-8.18 (m, 2H), 7.92 (d, *J* = 2.0 Hz, 1H), 7.64-7.71 (m, 2H), 7.28-7.33 (m, 3H), 4.31-4.34 (m, 2H), 3.93 (t, *J* = 5.2 Hz, 2H), 3.69 (s, 2H), 2.88 (bs, 4H), 2.64 (bs, 4H), 2.58 (s, 3H); LCMS: 587.3 [M+H].

BIOLOGICAL EXAMPLE 1

NEK7 ENZYMATIC ASSAY

Casein substrate (from bovine milk, hydrolyzed and partially dephosphorylated mixture of α, β and κ caseins, obtained from Sigma Aldrich, catalogue # C4765, diluted in distilled water to a final concentration of 1 mg/mL, assay concentration 20 μM) and full-length recombinant human Nek7 (expressed by baculovirus in Sf9 insect cells using a N-terminal GST tag, obtained from SignalChem, catalogue # N09-10G, 0.1 μg/μL, assay concentration 70 nM) were mixed in assay buffer (20 mM Hepes pH 7.5, 10 mM $MgCl_2$, 1 mM EGTA, 0.02% Brij35, 0.02 mg/ml BSA, 0.1 mM $NB3VO_4$, 2 mM DTT, 1% DMSO). Compounds of interest (in DMSO, serial 3-fold dilution from 10 μM to 0.5 nM) or control (1% DMSO) were dispensed into the kinase reaction mixture by Acoustic technology (Echo550; nanoliter range). After incubation at room temperature for 20 minutes, the kinase reaction was initiated by addition of [^{32}P]-ATP (Specific activity 10 μCi/μl) and the mixture was incubated at room temperature for 2 hours. The reaction was then stopped by spotting the reaction mixture on strips of phosphocellulose

P81 paper. Following washing, the radioactivity of the P81 paper was measured and kinase activity data were expressed as the percent remaining kinase activity in test samples compared to vehicle (dimethyl sulfoxide) reactions. IC_{50} values and curve fits were obtained using Prism (GraphPad Software).

BIOLOGICAL EXAMPLE 2

IL-1B RELEASE ASSAY

Approximately 1.5 million THP-1 cells were plated in each well of a 6-well TC plate and incubated with 40 nM PMA in RPMI (10% FBS, 1% Penstrep) for 24 hours. The media was then removed and cells were rested in RPMI (10% FBS, 1% Penstrep) for 24 hours after which time the media was removed and cells were pre-treated for 2 hours with various concentrations of compounds of interest (typically serial 3-fold dilution in RPMI + 5% FBS, concentrations ranging from 1 μM to 0.5 nM) in RPMI (5% FBS). The media was again removed and cells were incubated with 250 ng/mL LPS and compounds of interest (concentrations as above) in RMPI (5% FBS) for 2 hours. The media was removed for a last time and cells were incubated with 20 μM nigericin and compounds of interest (concentrations as above) in Opti-MEM for 30 minutes. Cell media was then collected and the amount of cleaved IL-1β was determined using a JESS instrument (Protein Simple) and standard protocols. Cleaved Il-1β antibody was obtained from Cell Signaling (catalogue #83186S) and was used at 1:20 dilution in antibody diluent 2. Protein Simple 1× anti-Rabbit HRP secondary antibody was used along with Protein Simple luminol and peroxide for chemiluminescent detection. Primary antibody incubation time was increased from 30 minutes to 60 minutes.

BIOLOGICAL EXAMPLE 3

BIOCHEMICAL ASSAYS OF REPRESENTATIVE COMPOUNDS

Representative compounds were tested for inhibitory activity against NEK7 and IL-1β release according to the procedures described above. Results are given in the table below.

Table 2: Activity of Representative compounds of Structure (I)

Compound	Nek7 IC_{50} (nM)	IL-1β release IC_{50} (nM)	Compound	Nek7 IC_{50} (nM)	IL-1β release IC_{50} (nM)
I-1	*	-	I-2	*	-
I-3	**	**	I-4	***	-
I-5	***	-	I-6	*	*
I-7	*	-	I-8	***	-
I-9	***	-	I-10	***	***
I-11	*	-	I-12	****	-
I-13	-	-	I-14	****	-
I-15	****	****	I-16	*	*
I-17	-	-	I-18	****	****
I-19	***	-	I-20	****	****
I-21	****	*	I-22	***	-
I-23	*	-	I-24	****	****
I-25	***	-	I-26	*	-
I-27	-	-	I-28	****	****
I-29	****	****	I-30	***	-
I-31	****	****	I-32	**	**
I-33	*	-	I-34	****	****
I-35	***	-	I-36	***	-
I-37	***	-	I-38	*	-
I-39	*	-	I-40	***	**
I-41	****	-	I-42	****	****
I-43	****	***	I-44	****	-
I-45	****	****	I-46	**	-
I-47	****	****	I-48	*	-
I-49	***	***	I-50	****	****
I-51	***	***	I-52	**	-
I-53	*	-	I-54	*	-
I-55	****	-	I-56	*	-
I-57	*	-	I-58	*	-
I-59	*	-	I-60	*	-
I-61	*	*	I-62	***	-
I-63	****	****	I-64	****	-
I-65	**	-	I-66	****	**
I-67	***	-	I-68	***	***
I-69	****	-	I-70	***	-
I-71	****	-	I-72	****	***
I-73	**	-	I-74	***	-
I-75	***	*	I-76	****	***
I-77	****	****	I-78	***	***
I-79	****	***	I-80	***	*
I-81	****	****	I-82	***	**

Compound	Nek7 IC_{50} (nM)	IL-1β release IC_{50} (nM)	Compound	Nek7 IC_{50} (nM)	IL-1β release IC_{50} (nM)
I-83	***	***	I-84	****	****
I-85	*	-	I-86	***	-
I-87	****	*	I-88	****	-
I-89	***	-	I-90	****	****
I-91	***	-	I-92	***	-
I-93	****	-	I-94	****	***
I-95	**	-	I-96	***	-
I-97	**	-	I-98	**	*
I-99	****	***	I-100	****	*
I-101	****	***	I-102	****	***
I-103	****	-	I-104	****	-
I-105	****	-	I-106	****	-
I-107	-	-	I-108	-	-
I-109	-	-	I-110	-	-
I-111	-	-	I-112	-	-
I-113	-	-	I-114	-	-
I-115	-	-	I-116	-	-
I-117	-	-	I-118	-	-

For Nek 7 IC_{50} activity in Table 2:
* represents a value above 2,000 nM
** represents a value between 500 up to 2,000 nM
*** represents a value between 100 up to 500 nM
**** represents a value below 100 nM
- denotes a value was not determined

For IL-1β release IC_{50} activity in Table 2:
* represents a value above 1,000 nM
** represents a value between 250 and 1,000 nM
*** represents a value between 50 nM and 250 nM
**** represents a value below 50 nM
- denotes a value was not determined

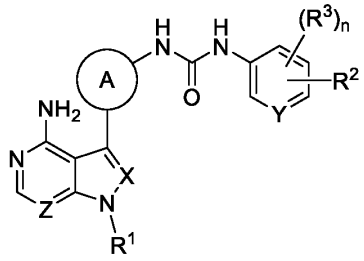
The various embodiments described above can be combined to provide further embodiments. All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet, including but not limited to Provisional Application Serial No. 63/170,708 filed April 5, 2021, and Provisional Application Serial No. 63/185,282 filed May 6, 2021, are incorporated

herein by reference, in their entirety. Aspects of the embodiments can be modified, if necessary to employ concepts of the various patents, applications and publications to provide yet further embodiments.

These and other changes can be made to the embodiments in light of the above-detailed description. In general, in the following claims, the terms used should not be construed to limit the claims to the specific embodiments disclosed in the specification and the claims, but should be construed to include all possible embodiments along with the full scope of equivalents to which such claims are entitled. Accordingly, the claims are not limited by the disclosure.

CLAIMS

1. A compound having the following Structure (I):



(I)

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

A is C_6-C_{10} arylene, C_3-C_{10} cycloalkylene, 3-10 membered heterocyclylene, or 5-6 membered heteroarylene;

X is N or CR^4;

Y is N or CH;

Z is N or CH;

R^1 is C_1-C_6 alkyl, C_1-C_6 alkynyl, C_1-C_6 hydroxylalkyl, C_1-C_6 carboxyalkyl, C_1-C_6 alkoxyalkyl, C_3-C_{10} cycloalkyl, or 3-10 membered heterocyclyl;

R^2 is a 3-10 membered heterocyclyl, 3-10 membered heterocyclylalkyl, 3-10 membered heterocyclylalkenyl, 3-10 membered heterocyclylcarbonyl, 3-10 membered heterocyclyloxy, or 5-6 membered heteroaryl, or

R^2 joins with an occurrence of R^3 attached to a carbon adjacent to a carbon to which R^2 is attached to form a C_3-C_8 cycloalkyl;

R^3 is, at each occurrence, independently halo, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, or C_3-C_8 cycloalkyl;

R^4 is H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_3-C_8 cycloalkyl; and

n is 0, 1, 2, 3, or 4.

2. The compound of claim 1, wherein A is C_6-C_{10} arylene.

3. The compound of claim 1 or 2, wherein A is phenylene.

4. The compound of claim 1, wherein A is 5-6 membered heteroarylene.

5. The compound of claim 1 or 4, wherein A is pyridinylene.

6. The compound of claim 1, wherein A is C_3-C_{10} cycloalkylene or 3-10 membered heterocyclylene.

7. The compound of any one of claims 1-6, wherein A is substituted with one or more substituents selected from halo, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, or C_3-C_8 cycloalkyl.

8. The compound of any one or claims 1-7, wherein A is substituted with one or more halo substituents.

9. The compound of any one of claims 1-6, wherein A is unsubstituted.

10. The compound of any one of claims 1-9, wherein X is CR^4.

11. The compound of any one of claims 1-10, wherein R^4 is H or C_1-C_6 alkyl.

12. The compound of any one of claims 1-11, wherein R^4 is H.

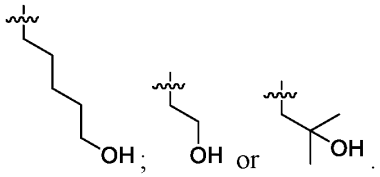
13. The compound of any one of claims 1-9, wherein X is N.

14. The compound of any one of claims 1-13, wherein R^1 is C_1-C_6 alkyl.

15. The compound of any one of claims 1-14, wherein R^1 is methyl or iso-propyl.

16. The compound of any one of claims 1-13, wherein R^1 is C_1-C_6 hydroxylalkyl.

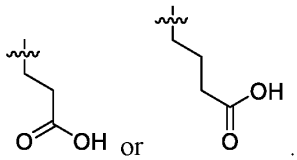
17. The compound of claim 16, wherein R^1 has one of the following structures:



; or .

18. The compound of any one of claims 1-13, wherein R^1 is C_1-C_6 carboxyalkyl.

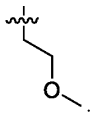
19. The compound of claim 18, wherein R^1 has one of the following structures:



or .

20. The compound of any one of claims 1-13, wherein R^1 is C_1-C_6 alkoxyalkyl.

21. The compound of claim 20, wherein R^1 has the following structure:



.

22. The compound of any one of claims 1-13, wherein R^1 is C_3-C_{10} cycloalkyl.

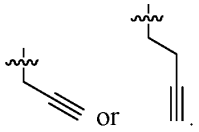
23. The compound of claim 22, wherein R^1 is cyclopropyl or cyclobutyl.

24. The compound of any one of claims 1-13, wherein R^1 is 3-10 membered heterocyclyl.

25. The compound of claim 24, wherein R^1 is oxetanyl, pyrrolidinyl, azetidinyl, or piperidinyl.

26. The compound of any one of claims 1-13, wherein R^1 is C_1-C_6 alkynyl.

27. The compound of claim 26, wherein R^1 has one of the following structures:

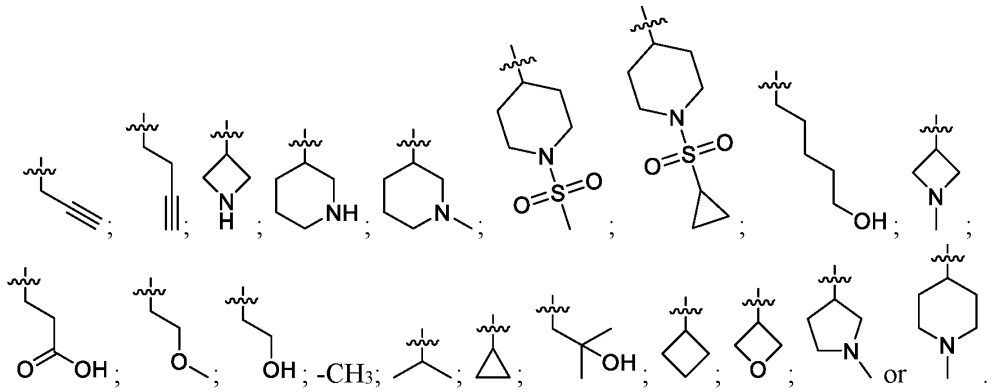


28. The compound of any one of claims 1-27, wherein R^1 is substituted with one or more substituents selected from halo, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, -$S(O)_2CH_3$, -$S(O)_2$cyclopropyl, or C_3-C_8 cycloalkyl.

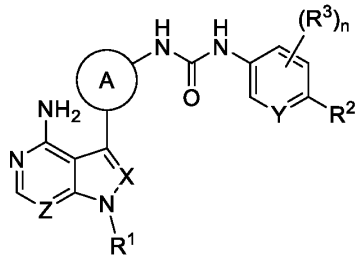
29. The compound of any one of claims 1-28, wherein R^1 is substituted with one or more C_1-C_6 alkyl substituents.

30. The compound of any one of claims 1-27, wherein R^1 is unsubstituted.

31. The compound of any one of claims 1-30, wherein R^1 has one of the following structures:



32. The compound of any one of claims 1-31, wherein the compound has the following Structure (Ia):



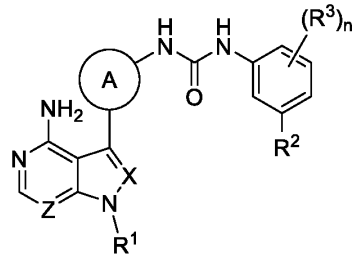
(Ia)

or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof.

33. The compound of any one of claims 1-32, wherein Y is N.

34. The compound of any one of claims 1-32, wherein Y is CH.

35. The compound of any one of claims 1-31, wherein the compound has the following Structure (Ib):



(Ib)

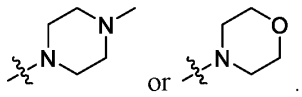
or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof.

36. The compound of any one of claims 1-35, wherein R^2 is a 3-10 membered heterocyclyl.

37. The compound of claim 36, wherein R^2 is morpholino.

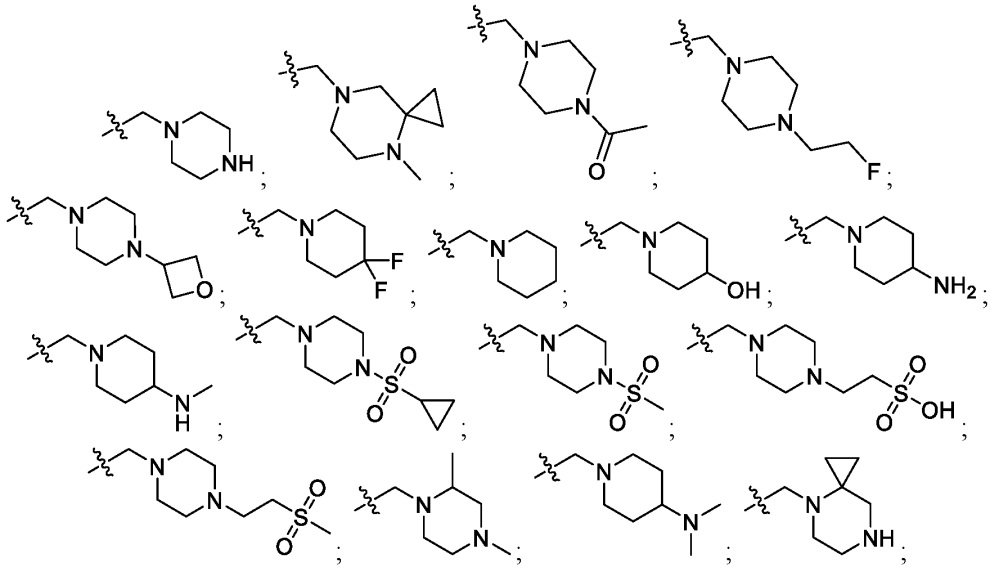
38. The compound of claim 36, wherein R^2 is piperazinyl.

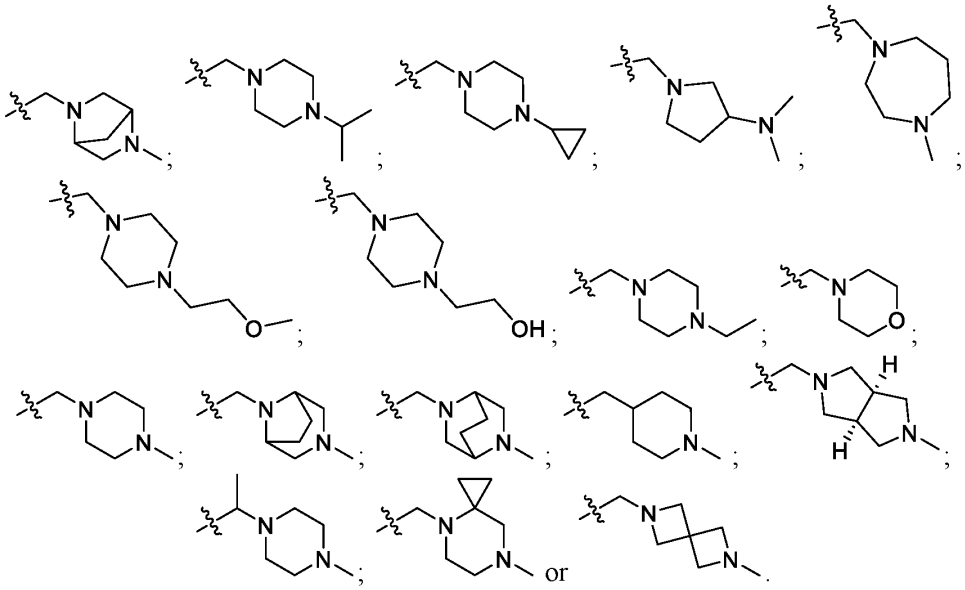
39. The compound of any one of claims 36-38, wherein R^2 has one of the following structures:



40. The compound of any one of claims 1-35, wherein R^2 is a 3-10 membered heterocyclylalkyl.

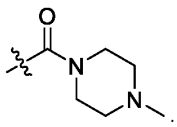
41. The compound of claim 40, wherein R^2 has one of the following structures:





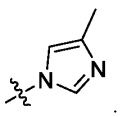
42. The compound of any one of claims 1-35, wherein R^2 is 3-10 membered heterocyclylcarbonyl.

43. The compound of claim 42, wherein R^2 has the following structure:



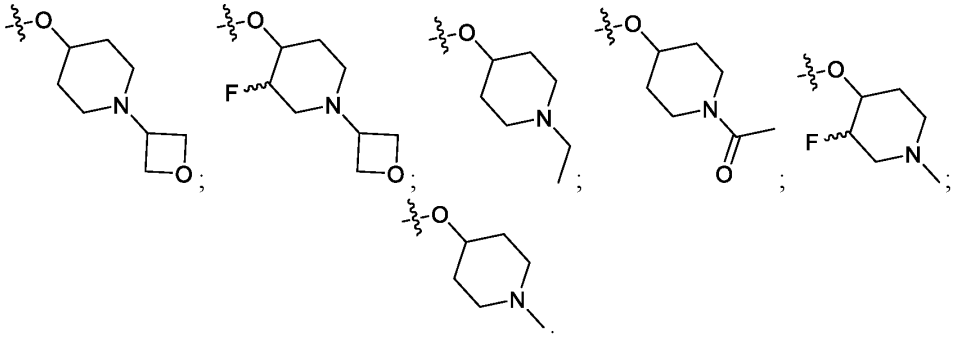
44. The compound of any one of claims 1-35, wherein R^2 is a 5-6 membered heteroaryl.

45. The compound of claim 44, wherein R^2 has the following structure:

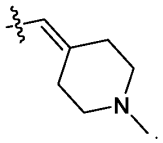


46. The compound of any one of claims 1-35, wherein R^2 is 3-10 membered heterocyclyloxy.

47. The compound of claim 46, wherein R^2 has the following structure:



48. The compound of any one of claims 1-35, wherein R^2 has the following structure:



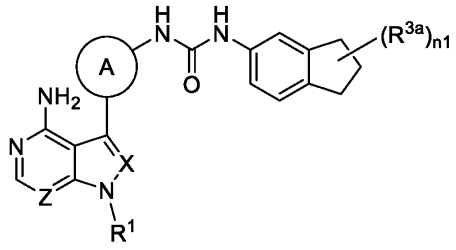
49. The compound of any one of claims 1-48, wherein n is 1 or 2.

50. The compound of claim 49, wherein n is 1.

51. The compound of any one of claims 1-50, wherein R^3 is halo, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, or C_3-C_8 cycloalkyl.

52. The compound of claim 51, wherein R^3 is methyl, chloro, fluoro, cyano, difluoromethyl, trifluoromethyl, methoxy, trifluoromethoxy, or cyclopropyl.

53. The compound of any one of claims 1-31, wherein the compound has the following Structure (Ic):



(Ic)

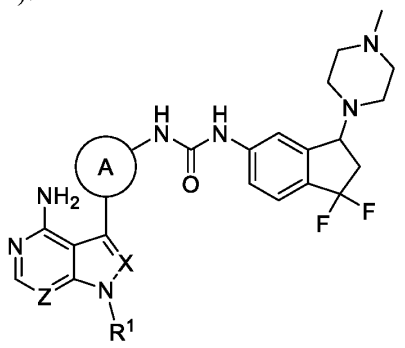
or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof, wherein:

R^{3a} is halo or 3-10 membered heterocyclyl; and

n1 is 1, 2, or 3.

54. The compound of claim 53, wherein R^{3a} is fluoro or piperazinyl.

55. The compound of any one of claims 53-54, wherein the compound has the following Structure (Ic1):



(Ic1)

or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof.

56. The compound of any one of claims 1-55, wherein Z is N.

57. The compound of any one of claims 1-55, wherein Z is CH.

58. A compound having a structure in Table 1 or a pharmaceutically acceptable salt, stereoisomer, or prodrug thereof.

59. The compound of any one of claims 1-58, wherein the compound is a modulator of the NLRP3 inflammasome.

60. The compound of any one of claims 1-59, wherein the compound is an inhibitor of NEK7.

61. A pharmaceutical composition comprising the compound of any one of claims 1-60, and a pharmaceutically acceptable carrier, diluent, or excipient.

62. A method of treating a NLRP3-mediated disorder, comprising administering a therapeutically effective amount of a compound of any one of claims 1-60, or the pharmaceutical composition of claim 61, to a subject in need thereof.

63. The method of claim 62, wherein the disorder is selected from auto-immune, inflammatory disorders, cardiovascular diseases, neurodegenerative disorders, bacterial and viral infections, allergy, asthma, pancreatitis, multi-organ failure, kidney diseases, platelet aggregation, cancer, transplantation, sperm motility, erythrocyte deficiency, graft rejection, lung injuries, respiratory diseases, ischemic conditions, and combinations thereof.

64. The method of claim 62 or 63, wherein the disorder is selected from type II diabetes, atherosclerosis, Alzheimer's disease, aging, fatty liver, metabolic syndrome, asthma, psoriasis, obesity, acute and chronic tissue damage caused by infection, gout, arthritis, macular degeneration, enteritis, hepatitis, peritonitis, silicosis, UV-induced skin sunburn, contact hypersensitivity, sepsis, cancer, neurodegenerative disease, multiple sclerosis, Muckle-Wells syndrome, and combinations thereof.