

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property

Organization

International Bureau

(43) International Publication Date

16 December 2021 (16.12.2021)



(10) International Publication Number

WO 2021/252488 A1

(51) International Patent Classification:

C07D 487/04 (2006.01) A61P 37/00 (2006.01)

C07D 471/04 (2006.01) A61K 31/519 (2006.01)

(21) International Application Number:

PCT/US2021/036398

(22) International Filing Date:

08 June 2021 (08.06.2021)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

63/036,244 08 June 2020 (08.06.2020) US

63/170,776 05 April 2021 (05.04.2021) US

63/185,257 06 May 2021 (06.05.2021) US

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(81) Designated States (unless otherwise indicated, for every

kind of national protection available): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ,

CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO,

DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN,

HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN,

KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD,

ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO,

NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW,

SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN,

TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

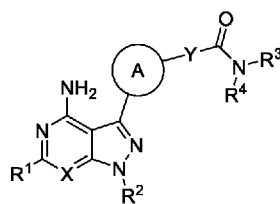
(84) Designated States (unless otherwise indicated, for every

kind of regional protection available): ARIPO (BW, GH,

GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ,

UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,

(54) Title: INHIBITORS OF NEK7 KINASE



(I)

(57) Abstract: Compounds having activity as inhibitors of NEK7 are provided. The compounds have structure (I): or a pharmaceutically acceptable salt, stereoisomer or prodrug thereof, wherein A, X, Y, R¹, R², R³ and R⁴ are as defined herein. Methods associated with preparation and use of such compounds, pharmaceutical compositions comprising such compounds and methods to modulate the activity of the NLRP3 inflammasome are also provided.



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INHIBITORS OF NEK7 KINASE

BACKGROUND

Technical Field

Embodiments of the present disclosure are generally directed to compounds and
5 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:
10 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-1 β 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.

15 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
20 cells, which has an intimate connection to tumors, such as retinoblastoma, gallbladder
cancer and carcinoma of the head and neck.

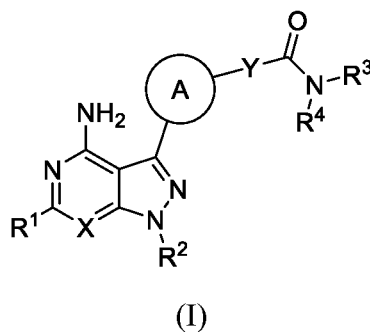
A great number of inhibitors have been widely used to disturb effector signaling
pathways, involving IL-1 β or IL-18 without abolishing the inflammation response.
Inhibitors of NLRP3 inflammasome activation that block the NLRP3-NEK7 interaction
25 can have therapeutic or prophylactic activity in several 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 of the NLRP3 inflammasome.

In one aspect, the invention provides compounds of Structure (I):



pharmaceutically acceptable salts, stereoisomers or prodrug thereof, wherein each of A, X, Y, R¹, R², R³ and R⁴ are as defined below.

In another aspect, 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".

5 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 $\pm 20\%$, $\pm 10\%$, $\pm 5\%$ or $\pm 1\%$ of the indicated range, value, or
10 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"
15 means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment of the present invention. 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
20 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.

25 "Amino" refers to the $-\text{NH}_2$ radical.

"Carboxy" or "carboxyl" refers to the $-\text{CO}_2\text{H}$ radical.

"Cyano" refers to the $-\text{CN}$ radical.

"Hydroxy" or "hydroxyl" refers to the $-\text{OH}$ radical.

"Nitro" refers to the $-\text{NO}_2$ radical.

30 "Oxo" refers to the $=\text{O}$ 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 from one to twelve carbon atoms (C₁-C₁₂ alkyl), one to eight carbon atoms (C₁-C₈ alkyl) or one to six carbon atoms (C₁-C₆ alkyl), or any value within these ranges, such as C₄-C₆ 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 (C₂-C₁₂ alkenyl), two to eight carbon atoms (C₂-C₈ alkenyl) or two to six carbon atoms (C₂-C₆ 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 (C₂-C₁₂ alkynyl), two to nine carbon atoms (C₂-C₉ alkynyl), or two to six carbon atoms (C₂-C₆ 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
5 is optionally substituted.

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

"Aminylalkylcycloalkyl" refers to a radical of the formula $-R_aR_bNR_cR_d$ where R_a
10 is cycloalkyl as defined herein, R_b is C_1 - C_6 alkyl, R_c is H or C_1 - C_6 alkyl and R_d is C_1 - C_6 alkyl as defined above. The cycloalkyl and each C_1 - C_6 alkyl portion of an aminylalkylcycloalkyl group are 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
15 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,
20 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 invention, the aryl radical is a
25 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
30 specifically in the specification, an aryl group is optionally substituted.

"Cyanoalkyl" refers to an alkyl group comprising at least one cyano substituent. The –CN substituent may be on a primary, secondary or tertiary carbon. Unless stated otherwise specifically in the specification, a cyanoalkyl group is optionally substituted. "Carbocyclic" or "carbocycle" refers to a ring system, wherein each of the
5 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 (C₃-C₁₅ cycloalkyl), from three to ten ring carbon atoms (C₃-C₁₀ cycloalkyl), or from three to eight ring carbon
10 atoms (C₃-C₈ cycloalkyl), or any value within these ranges such as three to four carbon atoms (C₃-C₄ 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,
15 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Unless otherwise stated specifically in the specification, a cycloalkyl group is optionally substituted.

"Alkylcycloalkyl" refers to a radical group of the formula –R_aR_b where R_a is a cycloalkyl group and R_b is an alkyl group as defined above. Unless otherwise stated specifically in the specification, an alkylcycloalkyl group is optionally substituted.

20 "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,
25 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,
30 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.

"Haloalkylcycloalkyl" refers to a radical group of the formula $-R_aR_b$ where R_a is a cycloalkyl group and R_b is a haloalkyl group as defined above. Unless otherwise stated specifically in the specification, a haloalkylcycloalkyl group is optionally substituted.

"Halocycloalkylalkyl" refers to a radical group of the formula $-R_aR_b$ where R_a is an alkyl group and R_b is a halocycloalkyl group as defined above. Unless otherwise stated specifically in the specification, a halocycloalkylalkyl group is optionally substituted.

"Heterocyclylcycloalkyl" refers to a radical group of the formula $-R_aR_b$ where R_a is a cycloalkyl group and R_b is a heterocyclyl group as defined herein. Unless otherwise stated specifically in the specification, a heterocyclylcycloalkyl group is optionally substituted.

"Hydroxylalkyl" 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 hydroxylalkyl 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, imidazoliny, imidazolidiny, isothiazolidiny, isoxazolidiny, morpholiny, octahydroindolyl, octahydroisoindolyl, hexahydro-1H-pyrrolizine, 2-oxopiperaziny, 2-oxopiperidiny, 2-oxopyrrolidiny, oxazolidiny, oxiranyl, piperidiny, piperaziny, 4-piperidonyl, azetidiny, pyrrolidiny, pyrazolidiny, quinuclidiny, thiazolidiny, 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.

"Haloheterocyclyl" refers to a heterocyclyl group comprising at least one halo substituent. The halo substituent may be on a primary, secondary or tertiary carbon. Unless stated otherwise specifically in the specification, a haloheterocyclyl group is optionally substituted

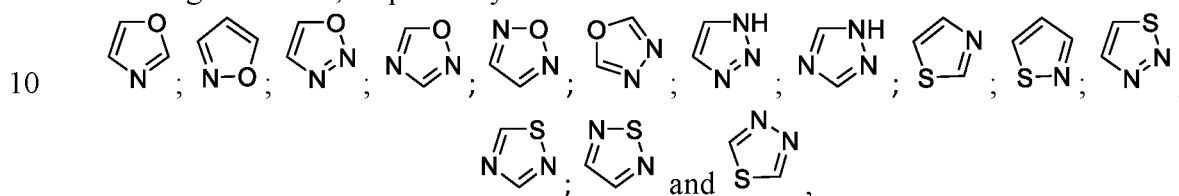
"Haloheterocyclalkyl" refers to a radical group of the formula $-R_aR_b$ where R_a is an alkyl group and R_b is a haloheterocyclyl group as defined herein. Unless otherwise stated specifically in the specification, a haloheterocyclalkyl group is optionally substituted.

"Heterocyclalkyl" refers to a radical group of the formula $-R_aR_b$ where R_a is an alkyl group and R_b is a heterocyclyl group as defined herein. Unless otherwise stated specifically in the specification, a heterocyclalkyl 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, benzothieryl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-*a*]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indoliziny, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1*H*-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
 5 the specification, a heteroaryl group is optionally substituted.

Oxazolyl, isoxazolyl, 1, 2, 3-oxadiazolyl, 1, 2, 4-oxadiazolyl, 1, 2, 5-oxadiazolyl, 1, 3, 4-oxadiazolyl, 1, 2, 3-triazolyl, 1, 2, 4-triazolyl, thiazolyl, isothiazolyl, 1, 2, 3-thiadiazolyl, 1, 2, 4-thiadiazolyl, 1, 2, 5-thiadiazolyl and 1, 3, 4-thiadiazolyl refer to the following structures, respectively:



wherein the oxazolyl, isoxazolyl, 1, 2, 3-oxadiazolyl, 1, 2, 4-oxadiazolyl, 1, 2, 5-oxadiazolyl, 1, 3, 4-oxadiazolyl, 1, 2, 3-triazolyl, 1, 2, 4-triazolyl, thiazolyl, isothiazolyl, 1, 2, 3-thiadiazolyl, 1, 2, 4-thiadiazolyl, 1, 2, 5-thiadiazolyl, and 1, 3, 4-thiadiazolyl are
 15 attached to the remainder of the molecule by a covalent bond to one of the carbon atoms in the ring of the oxazolyl, isoxazolyl, 1, 2, 3-oxadiazolyl, 1, 2, 4-oxadiazolyl, 1, 2, 5-oxadiazolyl, 1, 3, 4-oxadiazolyl, 1, 2, 3-triazolyl, 1, 2, 4-triazolyl, thiazolyl, isothiazolyl, 1, 2, 3-thiadiazolyl, 1, 2, 4-thiadiazolyl, 1, 2, 5-thiadiazolyl, and 1, 3, 4-thiadiazolyl.

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.
 25

In some specific embodiments, the optional substitutions are independently selected from the group consisting of halo, hydroxyl, cyano, aminyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, C₃-C₈ halocycloalkyl, C₆-C₁₀ aryl, 5- or 6-membered heteroaryl, C₁-C₆ alkoxy and 3-8 membered heterocyclyl.

5 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
10 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
15 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
20 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
25 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
30 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
5 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
10 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
15 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,
20 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,
25 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,
30 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.

10 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
15 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.

20 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
25 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),
30 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).

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,
5 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.

10 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
15 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.

20 "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
25 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.

5 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.

10 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
15 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
20 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.

25 Embodiments of the present disclosure include all manner of rotamers and conformationally restricted states of a compound of the invention. 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.

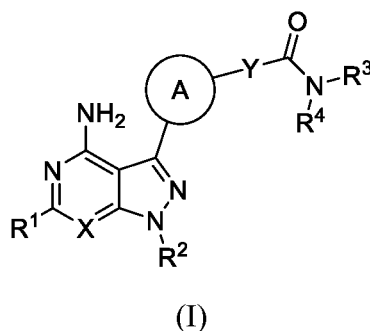
A "tautomer" refers to a proton shift from one atom of a molecule to another atom of the same molecule. Embodiments thus include tautomers of the disclosed compounds.

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 Profesional 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):



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

A is C₆-C₁₀ aryl, C₃-C₁₀ cycloalkyl, 3-10 membered heterocyclyl or 5-6 membered monocyclic heteroaryl, each of which is optionally substituted with one or more R⁵;

X is N or CH;

5 Y is CHOH or NH;

R¹ is H or C₁-C₆ alkyl;

R² is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, 3-8 membered heterocyclyl or 5- or 6-membered heteroaryl, each of which is optionally substituted with one more substituents selected from halo, hydroxyl, cyano, aminyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy and 3-8 membered heterocyclyl;

R³ is a heteroaryl selected from oxazolyl, isoxazolyl, 1, 2, 3-oxadiazolyl, 1, 2, 4-oxadiazolyl, 1, 2, 5-oxadiazolyl, 1, 3, 4-oxadiazolyl, 1, 2, 3-triazolyl, 1, 2, 4-triazolyl, thiazolyl, isothiazolyl, 1, 2, 3-thiadiazolyl, 1, 2, 4-thiadiazolyl, 1, 2, 5-thiadiazolyl and 1, 3, 4-thiadiazolyl, each of which is optionally substituted with one more substituents selected from amino, halo, cyano, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, C₃-C₈ alkylcycloalkyl, C₃-C₈ haloalkylcycloalkyl, C₃-C₈ aminylalkylcycloalkyl, C₁-C₆ cyanoalkyl, C₁-C₆ aminyl, C₁-C₆ hydroxylalkyl, 3-8 membered heterocyclyl, 3-8 membered heterocyclalkyl, 3-8 membered heterocyclcycloalkyl, 3-8 membered haloheterocyclyl, 3-8 membered haloheterocyclalkyl, C₃-C₈ halocycloalkyl and C₃-C₈ halocycloalkylalkyl, and combinations thereof;

R⁴ is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, 3-8 membered heterocyclyl, C₆-C₁₀ aryl or 5- or 6-membered heteroaryl, each of which is optionally substituted with one more substituents selected from halo, hydroxyl, cyano, aminyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl and C₁-C₆ alkoxy; and

R⁵ is, at each occurrence, independently halo, cyano, C₁-C₆ alkyl, C₁-C₆ hydroxylalkyl or C₁-C₆ haloalkyl.

In some embodiments of structure (I), A is C₆-C₁₀ aryl, C₃-C₁₀ cycloalkyl, 3-10 membered heterocyclyl or 5-6 membered monocyclic heteroaryl, each of which is optionally substituted with one or more R⁵;

X is N or CH;

Y is CHOH or NH;

R¹ is H or C₁-C₆ alkyl;

R² is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, 3-8 membered
5 heterocyclyl or 5- or 6-membered heteroaryl, each of which is optionally substituted with
one more substituents selected from halo, hydroxyl, cyano, aminyl, C₁-C₆ alkyl, C₂-C₆
alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy and 3-8 membered heterocyclyl;

R³ is a heteroaryl selected from oxazolyl, isoxazolyl, 1, 2, 3-oxadiazolyl, 1, 2, 4-
oxadiazolyl, 1, 2, 5-oxadiazolyl, 1, 3, 4-oxadiazolyl, 1, 2, 3-triazolyl, 1, 2, 4-triazolyl,
10 thiazolyl, isothiazolyl, 1, 2, 3-thiadiazolyl, 1, 2, 4-thiadiazolyl, 1, 2, 5-thiadiazolyl and 1,
3, 4-thiadiazolyl, each of which is optionally substituted with one more substituents
selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₃-C₈
cycloalkyl and C₃-C₈ halocycloalkyl;

R⁴ is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, 3-8
15 membered heterocyclyl, C₆-C₁₀ aryl or 5- or 6-membered heteroaryl, each of which is
optionally substituted with one more substituents selected from halo, hydroxyl, cyano,
aminyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl and C₁-C₆ alkoxy; and

R⁵ is, at each occurrence, independently halo, C₁-C₆ alkyl, C₁-C₆ alkyl or C₁-C₆
haloalkyl.

20 One embodiment provides a compound of structure (I) or a pharmaceutically
acceptable salt, stereoisomer or prodrug thereof, wherein:

A is C₆-C₁₀ aryl, C₃-C₁₀ cycloalkyl, 3-10 membered heterocyclyl or 5-6
membered monocyclic heteroaryl, each of which is optionally substituted with one or
more R⁵;

25 X is N or CH;

Y is CHOH or NH;

R¹ is H or C₁-C₆ alkyl;

R² is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, 3-8
membered heterocyclyl or 5- or 6-membered heteroaryl, each of which is optionally

substituted with one more substituents selected from halo, hydroxyl, cyano, aminyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy and 3-8 membered heterocyclyl;

R³ is a heteroaryl selected from oxazolyl, isoxazolyl, 1, 2, 3-oxadiazolyl, 1, 2, 4-oxadiazolyl, 1, 2, 5-oxadiazolyl, 1, 3, 4-oxadiazolyl, 1, 2, 3-triazolyl, 1, 2, 4-triazolyl, 5 thiazolyl, isothiazolyl, 1, 2, 3-thiadiazolyl, 1, 2, 4-thiadiazolyl, 1, 2, 5-thiadiazolyl and 1, 3, 4-thiadiazolyl, each of which is optionally substituted with one more substituents selected from amino, halo, cyano, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, C₃-C₈ alkylcycloalkyl, C₃-C₈ haloalkylcycloalkyl, C₃-C₈ aminylalkylcycloalkyl, C₁-C₆ cyanoalkyl, C₁-C₆ aminyl, C₁-C₆ hydroxylalkyl, 3-8 10 membered heterocyclyl, 3-8 membered heterocyclylalkyl, 3-8 membered heterocyclylcycloalkyl, 3-8 membered haloheterocyclyl, 3-8 membered haloheterocyclylalkyl, C₃-C₈ halocycloalkyl and C₃-C₈ halocycloalkylalkyl, and combinations thereof;

R⁴ is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, 3-8 15 membered heterocyclyl, C₆-C₁₀ aryl or 5- or 6-membered heteroaryl, each of which is optionally substituted with one more substituents selected from halo, hydroxyl, cyano, aminyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl and C₁-C₆ alkoxy; and

R⁵ is, at each occurrence, independently halo, cyano, C₁-C₆ alkyl, C₁-C₆ hydroxylalkyl, C₁-C₆ alkoxy, or C₁-C₆ haloalkyl.

20 In certain embodiment, R¹ is H. In other embodiments, R¹ is C₁-C₆ alkyl, such as methyl.

In one embodiment, compounds of Structure (I) are provided, where R² is branched C₄-C₆ alkyl, C₃-C₄ cycloalkyl, C₃-C₈ heterocyclyl or 5- or 6-membered heteroaryl, each of which is optionally substituted with one more substituent selected 25 from halo, hydroxyl, cyano, aminyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy and 3- to 8-membered heterocyclyl.

In another embodiment, compounds of Structure (I) are provided, where R² is branched C₄-C₆ alkyl, C₃-C₄ cycloalkyl, or C₃-C₈ heterocyclyl, each of which is optionally substituted with one more substituent selected from halo, hydroxyl, cyano,

aminyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy and 3- to 8-membered heterocyclyl.

In specific embodiments, R² is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, each of which is optionally substituted with one more substituent selected from halo, hydroxyl, cyano, aminyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy and 3- to 8-membered heterocyclyl.

In different embodiments, R² is methyl, isopropyl, 2-methylpropyl or allyl, each of which is optionally substituted with one more substituent selected from halo, hydroxyl, cyano, aminyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy and 3- to 8-membered heterocyclyl.

In different embodiments, R² is methyl, ethyl, isopropyl, 2-methylpropyl or allyl, each of which is optionally substituted with one more substituent selected from halo, hydroxyl, cyano, aminyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy and 3- to 8-membered heterocyclyl.

In other embodiments, R² is oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl or dioxidotetrahydrothiophenyl, each of which is optionally substituted with one more substituent selected from halo, hydroxyl, cyano, aminyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy and 3- to 8-membered heterocyclyl.

In other embodiments, R² is oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, azetidiny or dioxidotetrahydrothiophenyl, each of which is optionally substituted with one more substituent selected from halo, hydroxyl, cyano, aminyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, and 3- to 8-membered heterocyclyl.

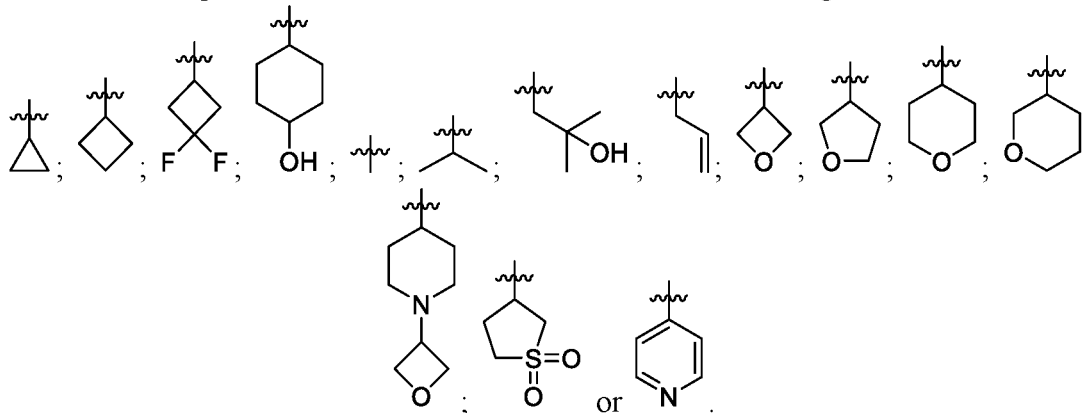
In other embodiments, R² is oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, azetidiny pyrrolidinyl, or dioxidotetrahydrothiophenyl, each of which is optionally substituted with one more substituent selected from halo, hydroxyl, cyano, aminyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, and 3- to 8-membered heterocyclyl.

In still more embodiments, R² is pyridinyl optionally substituted with one more substituent selected from halo, hydroxyl, cyano, aminyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy and 3- to 8-membered heterocyclyl.

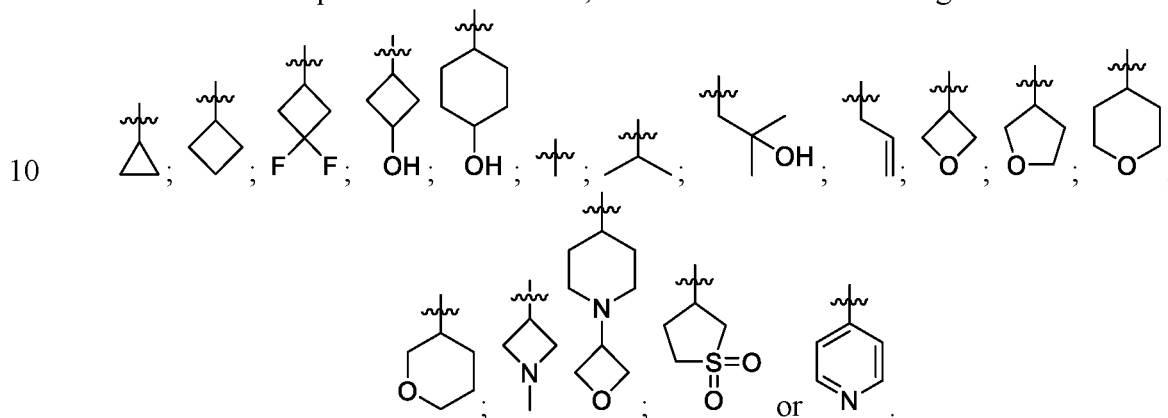
In any of the foregoing embodiments, R² is unsubstituted. In other of the foregoing embodiments, R² is substituted with one or more of hydroxyl and fluoro.

In any of the foregoing embodiments, R² is unsubstituted. In other of the foregoing embodiments, R² is substituted with one or more of hydroxyl, methyl, methoxy, and fluoro.

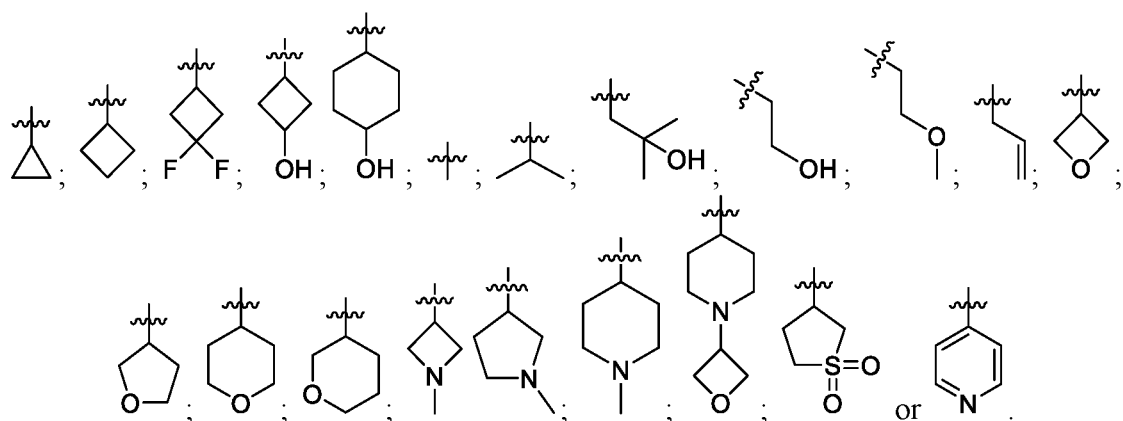
In more specific embodiments, R^2 has one of the following structures:



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

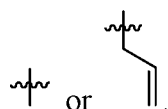


In further specific embodiments, $\mathbf{R}^2$ has one of the following structures:



In some embodiments, optionally R² is substituted with one or more substituents selected from the group consisting of halo, hydroxyl, cyano, aminyl, C₁-C₆ alkyl, and 3-8 membered heterocyclyl.

In some embodiments, R^2 does not have the following structures:



In any of the foregoing embodiments, R³ is oxazolyl, isoxazolyl, 1, 2, 3-oxadiazolyl or 1, 3, 4-oxadiazolyl, each of which is optionally substituted with one more substituents selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl and C₃-C₈ halocycloalkyl. For example, in certain embodiments, R³ is isoxazolyl optionally substituted with one more substituents selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl and C₃-C₈ halocycloalkyl. In further specific embodiments, R³ is substituted with C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl or C₃-C₈ halocycloalkyl.

In further embodiments, R³ is oxazolyl, isoxazolyl, 1, 2, 3-oxadiazolyl, 1, 3, 4-oxadiazolyl, thiazolyl, isothiazolyl, 1, 2, 4-thiadiazolyl, 1, 3, 4-thiadiazolyl or 1, 2, 4-triazolyl, each of which is optionally substituted with one more substituents selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, cyano, C₁-C₆ aminyl, C₁-C₆ hydroxylalkyl, 3-8 membered heterocyclyl and C₃-C₈ halocycloalkyl, or combinations thereof.

In certain embodiments, R³ is isoxazolyl optionally substituted with one more substituents selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆

haloalkyl, C₃-C₈ cycloalkyl, cyano, C₁-C₆ aminyl, C₁-C₆ hydroxylalkyl, 3-8 membered heterocyclyl and C₃-C₈ halocycloalkyl, or combinations thereof.

In certain embodiments, R³ is thiazolyl optionally substituted with one more substituents selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, cyano, C₁-C₆ aminyl, C₁-C₆ hydroxylalkyl, 3-8 membered heterocyclyl and C₃-C₈ halocycloalkyl, or combinations thereof.

In certain embodiments, R³ is isothiazolyl optionally substituted with one more substituents selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, cyano, C₁-C₆ aminyl, C₁-C₆ hydroxylalkyl, 3-8 membered heterocyclyl and C₃-C₈ halocycloalkyl, or combinations thereof.

In certain embodiments, R³ is 1,2,4-thiadiazolyl optionally substituted with one more substituents selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, cyano, C₁-C₆ aminyl, C₁-C₆ hydroxylalkyl, 3-8 membered heterocyclyl and C₃-C₈ halocycloalkyl, or combinations thereof.

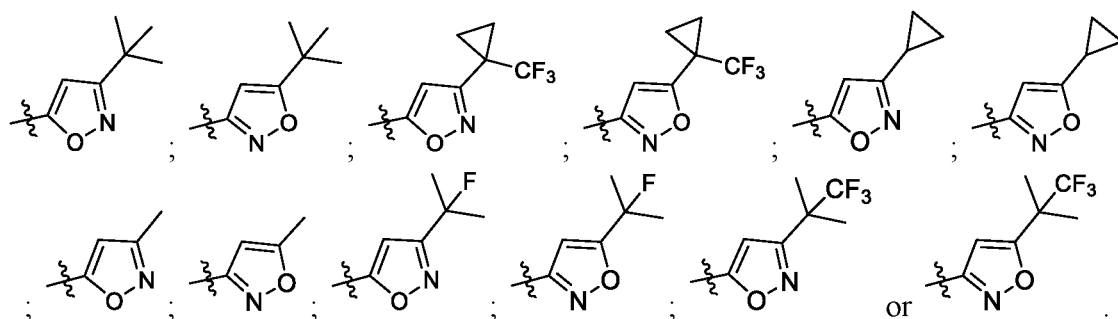
In certain embodiments, R³ is 1,3,4-thiadiazolyl optionally substituted with one more substituents selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, cyano, C₁-C₆ aminyl, C₁-C₆ hydroxylalkyl, 3-8 membered heterocyclyl and C₃-C₈ halocycloalkyl, or combinations thereof.

In certain embodiments, R³ is 1,3,4-oxadiazolyl optionally substituted with one more substituents selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, cyano, C₁-C₆ aminyl, C₁-C₆ hydroxylalkyl, 3-8 membered heterocyclyl and C₃-C₈ halocycloalkyl, or combinations thereof.

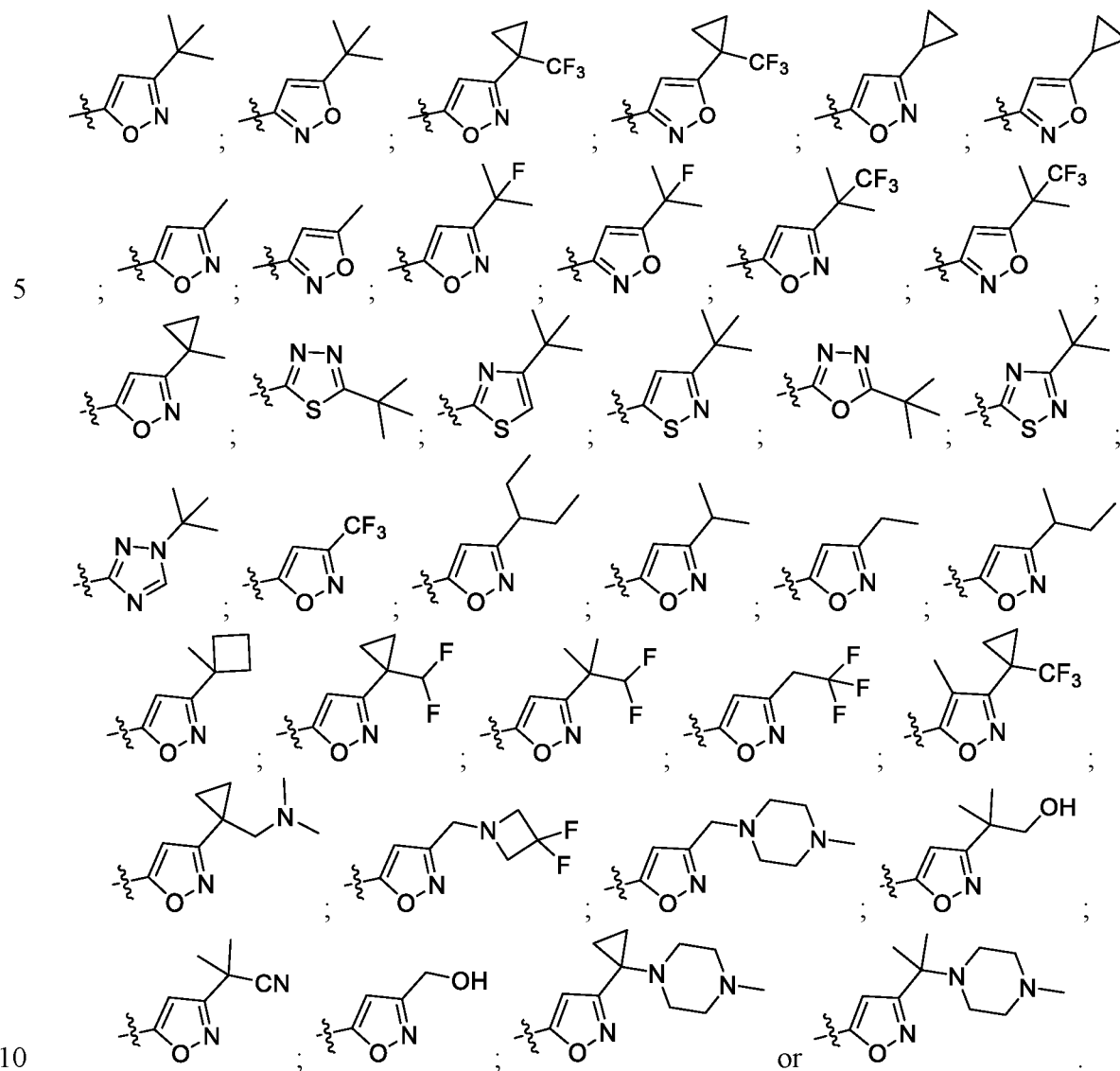
In certain embodiments, R³ is 1,2,4-triazolyl optionally substituted with one more substituents selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, cyano, C₁-C₆ aminyl, C₁-C₆ hydroxylalkyl, 3-8 membered heterocyclyl and C₃-C₈ halocycloalkyl, or combinations thereof.

In further embodiments, R³ is substituted with C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, cyano, C₁-C₆ aminyl, C₁-C₆ hydroxylalkyl, 3-8 membered heterocyclyl or C₃-C₈ halocycloalkyl, or combinations thereof.

In various embodiments, R³ has one of the following structures:



In further embodiments, R^3 has one of the following structures:



In further embodiments, R^3 has one of the following structures:



10 methyl.

In certain embodiments, Y is CHOH. In other embodiments, Y is NH.

In other embodiments, X is N. In more embodiments, X is CH.

15 understood that A is a divalent radical.

In certain embodiments, A is a divalent optionally substituted C₆₋₁₀ aryl. In certain embodiments, A is a divalent optionally substituted 3-8 membered saturated or partially unsaturated carbocyclic ring. In certain embodiments, A is a divalent optionally substituted 3-10 membered heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In certain embodiments, A is a divalent optionally substituted 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

In certain embodiments, A is a divalent group selected from phenyl, pyridinyl, cyclohexyl, and cyclohexenyl; each of which is optionally substituted.

10 In other embodiments, A is phenyl. In different embodiments, A is saturated or unsaturated cyclohexyl. In more embodiments, A is pyridinyl.

In further embodiments, A is pyrimidinyl, which is optionally substituted.

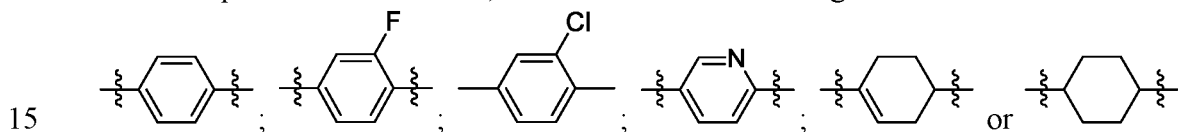
In any of the foregoing embodiments, A is unsubstituted. In different of the foregoing embodiments, A is substituted with one or more R⁵. For example, in some
15 embodiments R⁵ is halo. In other embodiments, R⁵ is fluoro. In other different embodiments, R⁵ is chloro.

In some embodiments, R⁵ is cyano. In some embodiments, R⁵ is C₁-C₆ alkyl. In certain embodiments, R⁵ is methyl. In some embodiments, R⁵ is C₁-C₆ haloalkyl. In certain embodiments R⁵ is difluoromethyl. In further embodiments, R⁵ is C₁-C₆
20 hydroxylalkyl. In certain embodiments R⁵ is -CH₂OH.

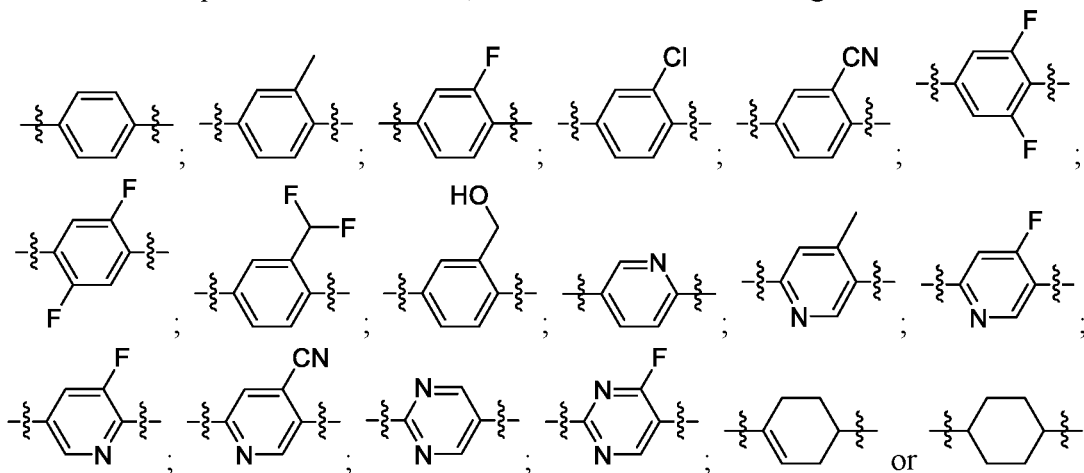
In certain embodiments, A is a divalent group selected from phenyl, naphthyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctanyl, [4.3.0]bicyclononanyl, [4.4.0]bicyclodecanyl, [2.2.2]bicyclooctanyl, fluorenyl, indanyl, tetrahydronaphthyl, acridinyl, azocinyl,
25 benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazoliny, carbazolyl, NH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, dithiazinyl, tetrahydrofuranyl, furanyl, furazanyl, imidazolidinyl, imidazoliny, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indoliziny, indolyl,
30 3-indolyl, isoindolinyl, isoindolenyl, isobenzofuranyl, isochromanyl,

isindazolyl, isindolyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, morpholyl, naphthyridinyl, octahydroisoquinolyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl;- 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, 5 phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2-pyrrolyl, pyrrolyl, quinazolyl, quinolyl, 4H-quinolizyl, quinoxalyl, quinuclidinyl, tetrahydro furanyl, tetrahydroisoquinolyl, tetrahydroquinolyl, 10 thiadiazinyl, 1,2,3- thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, oxetanyl, azetidyl, and xanthenyl; each of which is optionally substituted.

In specific embodiments, A has one of the following structures:



In other specific embodiments, A has one of the following structures:

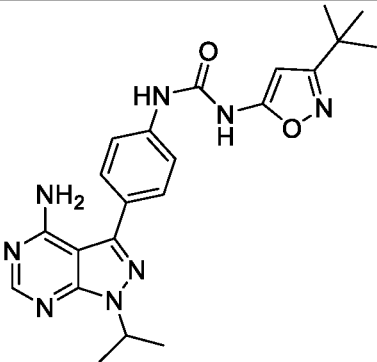
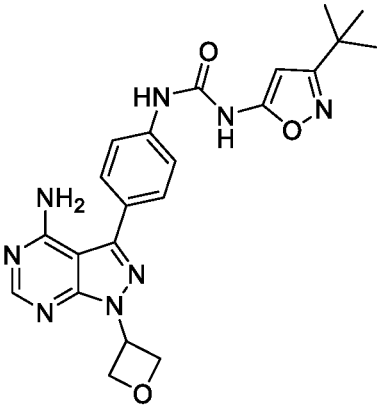
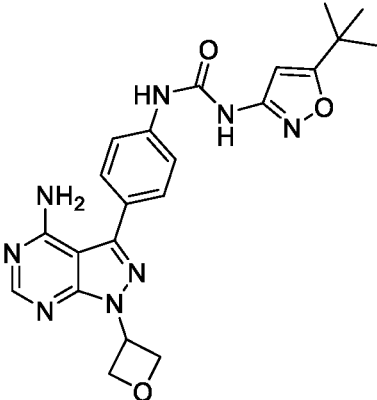


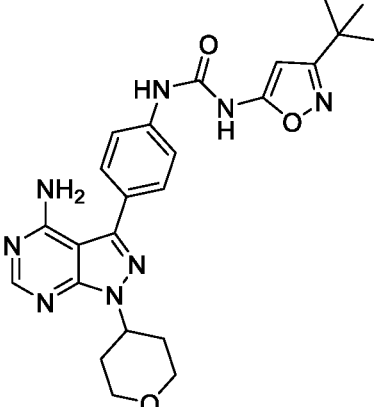
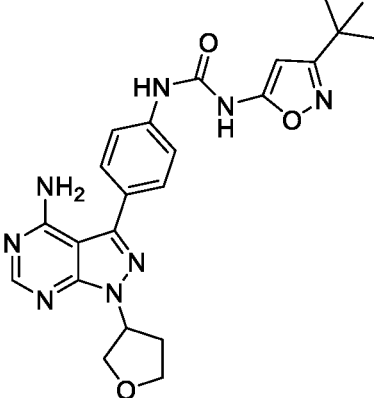
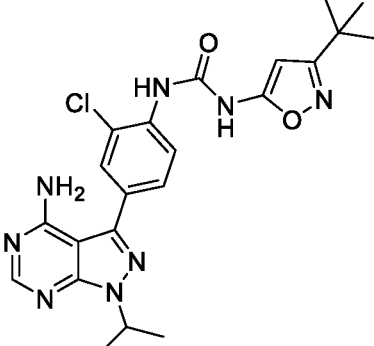
20 In a certain embodiment, the compound of Structure (I) is a modulator of the
NLRP3 inflammasome.

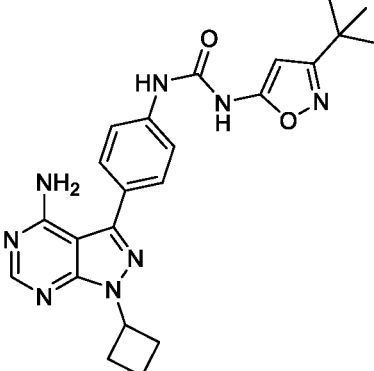
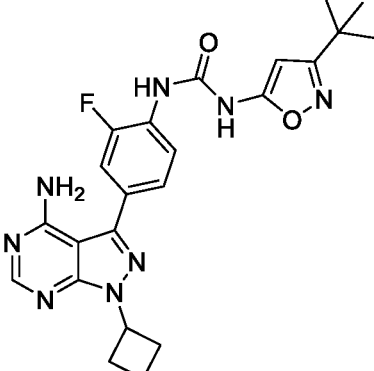
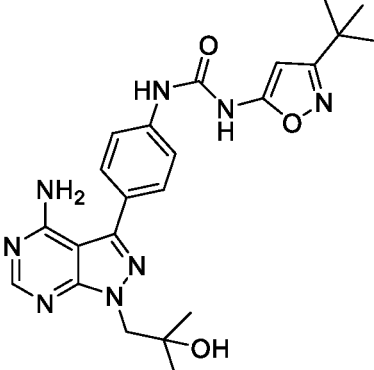
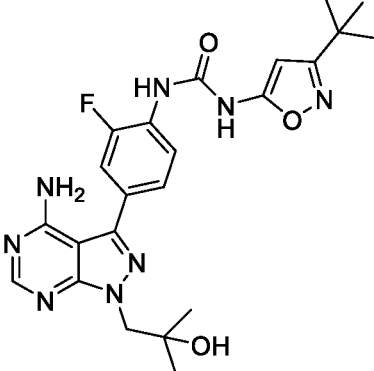
In a specific embodiment, the compound of Structure (I) is an inhibitor of NEK7 in a patient or in a biological sample.

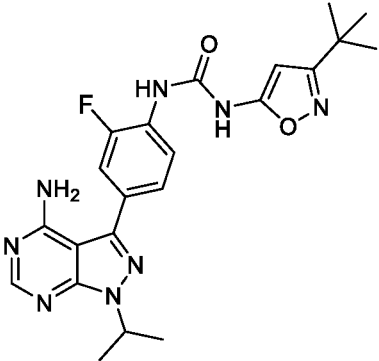
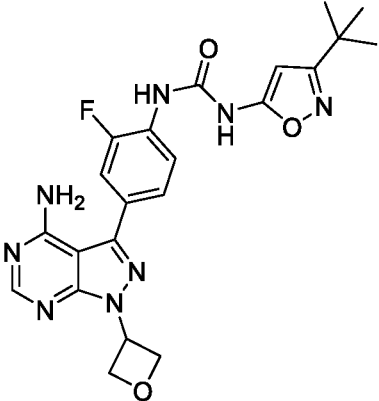
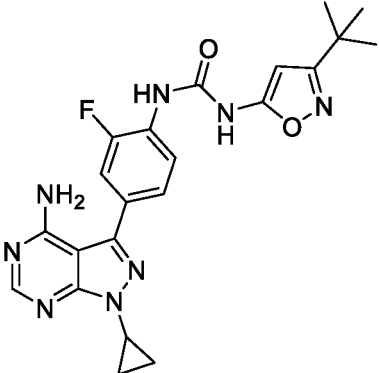
In various different embodiments, the compound has one of the structures set forth in Table 1 below, or a pharmaceutically acceptable salt, stereoisomer or prodrug thereof. Compounds in Table 1 were prepared as described in the Examples or methods known in the art and analyzed by mass spectrometry and/or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

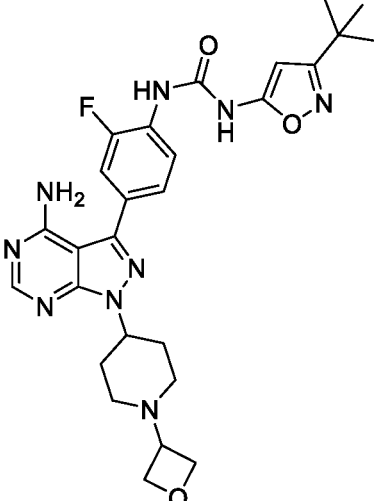
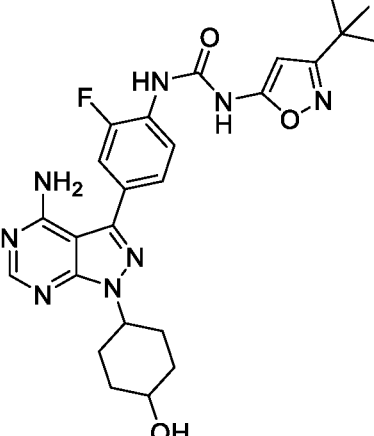
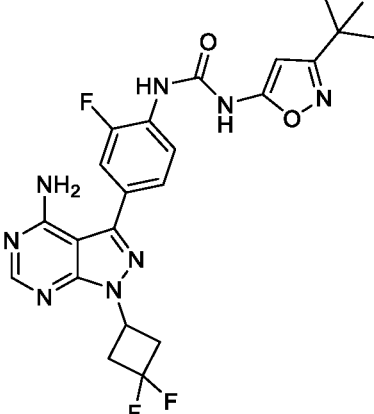
5 *Table 1. Representative Compounds of Structure (I)*

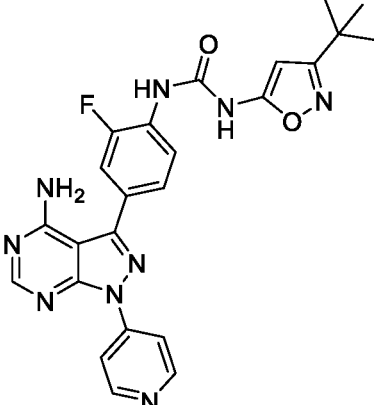
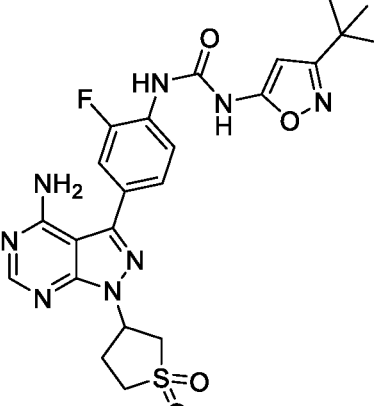
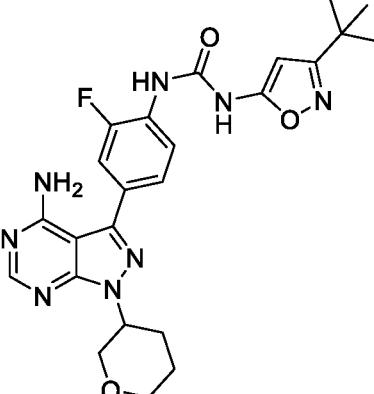
No.	Structure	Name
1		1-(4-(4-amino-1-isopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)phenyl)-3-(3-(<i>tert</i> -butyl)isoxazol-5-yl)urea
2		1-(4-(4-amino-1-(oxetan-3-yl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)phenyl)-3-(3-(<i>tert</i> -butyl)isoxazol-5-yl)urea
3		1-(4-(4-amino-1-(oxetan-3-yl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)phenyl)-3-(5-(<i>tert</i> -butyl)isoxazol-3-yl)urea

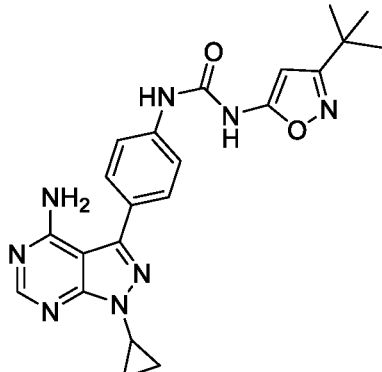
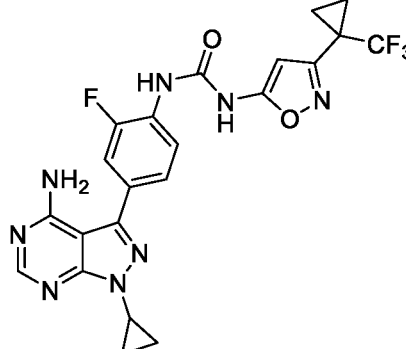
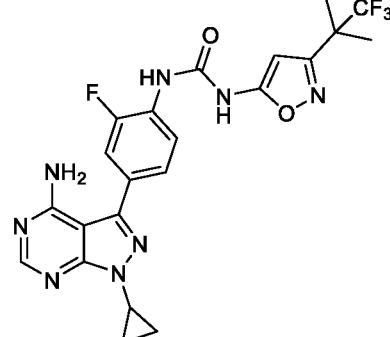
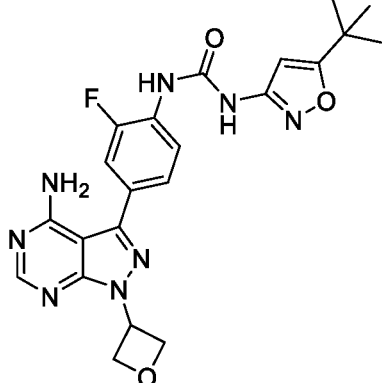
No.	Structure	Name
4		1-(4-(4-amino-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)-3-(3-(tert-butyl)isoxazol-5-yl)urea
5		1-(4-(4-amino-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)-3-(3-(tert-butyl)isoxazol-5-yl)urea
6		1-(4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-chlorophenyl)-3-(3-(tert-butyl)isoxazol-5-yl)urea

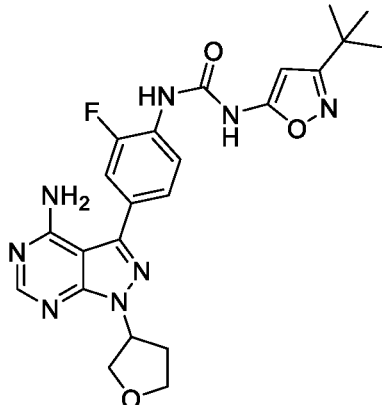
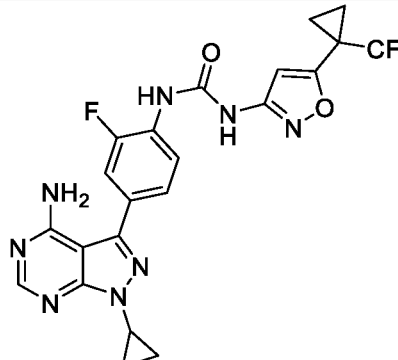
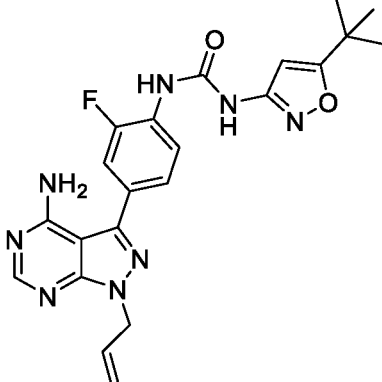
No.	Structure	Name
7		1-(4-(4-amino-1-cyclobutyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)phenyl)-3-(3-(<i>tert</i> -butyl)isoxazol-5-yl)urea
8		1-(4-(4-amino-1-cyclobutyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(<i>tert</i> -butyl)isoxazol-5-yl)urea
9		1-(4-(4-amino-1-(2-hydroxy-2-methylpropyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)phenyl)-3-(3-(<i>tert</i> -butyl)isoxazol-5-yl)urea
10		1-(4-(4-amino-1-(2-hydroxy-2-methylpropyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(<i>tert</i> -butyl)isoxazol-5-yl)urea

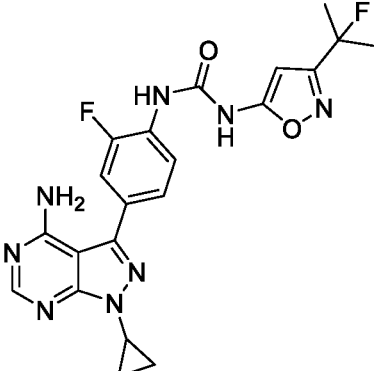
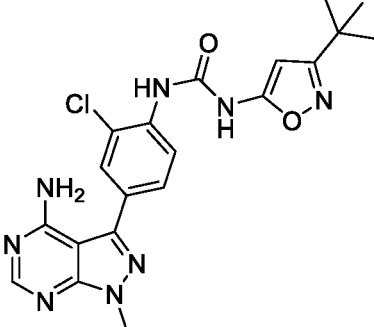
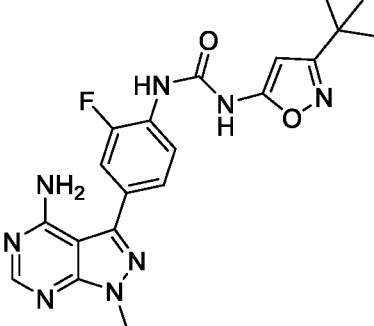
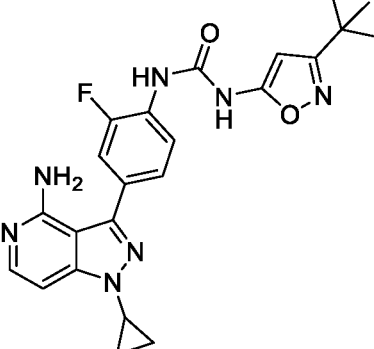
No.	Structure	Name
11		1-(4-(4-amino-1-isopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(<i>tert</i> -butyl)isoxazol-5-yl)urea
12		1-(4-(4-amino-1-(oxetan-3-yl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(<i>tert</i> -butyl)isoxazol-5-yl)urea
13		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(<i>tert</i> -butyl)isoxazol-5-yl)urea

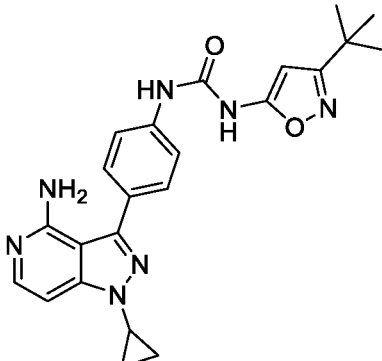
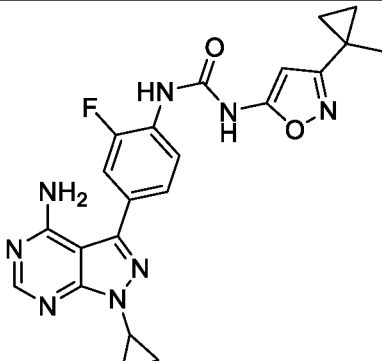
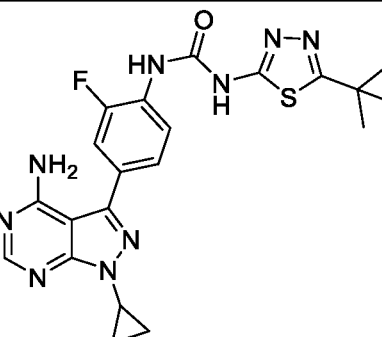
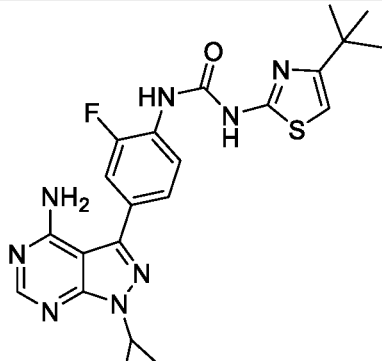
No.	Structure	Name
14		1-(4-(4-amino-1-(1-(oxetan-3-yl)piperidin-4-yl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(<i>tert</i> -butyl)isoxazol-5-yl)urea
15		1-(4-(4-amino-1-(4-hydroxycyclohexyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(<i>tert</i> -butyl)isoxazol-5-yl)urea
16		1-(4-(4-amino-1-(3,3-difluorocyclobutyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(<i>tert</i> -butyl)isoxazol-5-yl)urea

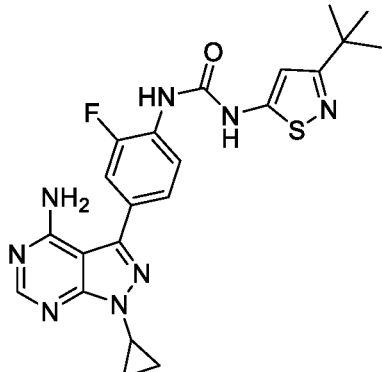
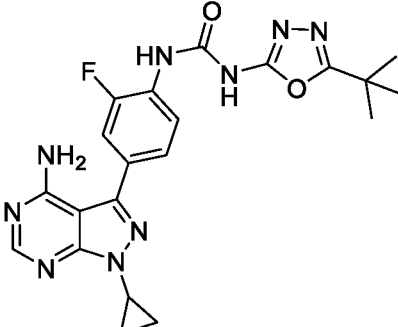
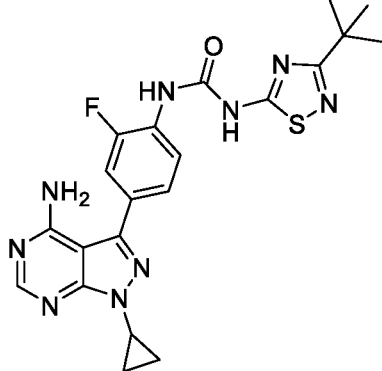
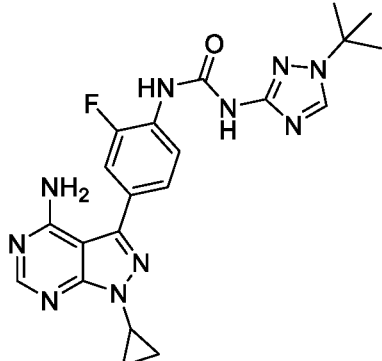
No.	Structure	Name
17		1-(4-(4-amino-1-(pyridin-4-yl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(<i>tert</i> -butyl)isoxazol-5-yl)urea
18		1-(4-(4-amino-1-(1,1-dioxido-2,3-dihydrothiophen-3-yl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(<i>tert</i> -butyl)isoxazol-5-yl)urea
19		1-(4-(4-amino-1-(tetrahydro-2 <i>H</i> -pyran-3-yl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(<i>tert</i> -butyl)isoxazol-5-yl)urea

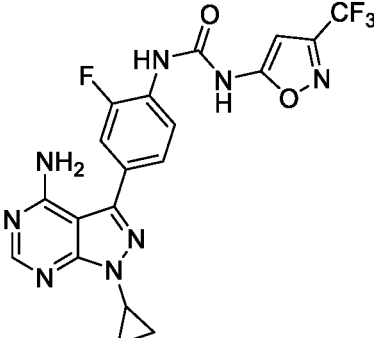
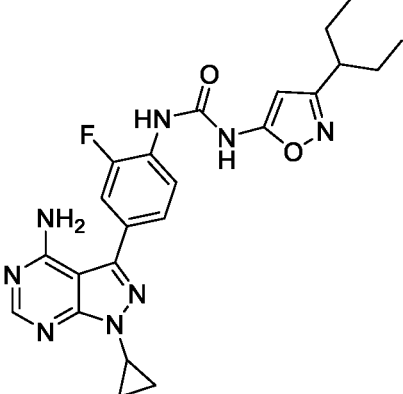
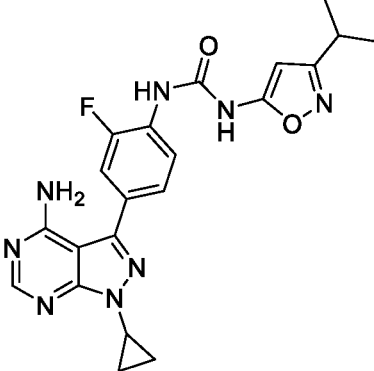
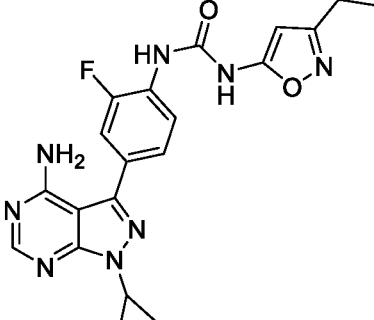
No.	Structure	Name
20		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)phenyl)-3-(3-(<i>tert</i> -butyl)isoxazol-5-yl)urea
21		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea
22		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-5-yl)urea
23		1-(4-(4-amino-1-(oxetan-3-yl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(5-(<i>tert</i> -butyl)isoxazol-3-yl)urea

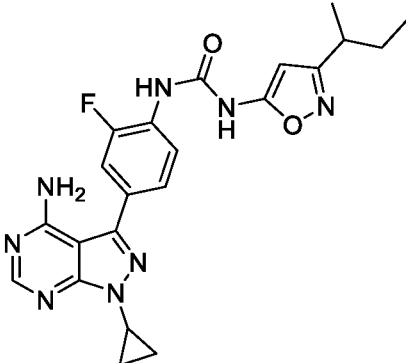
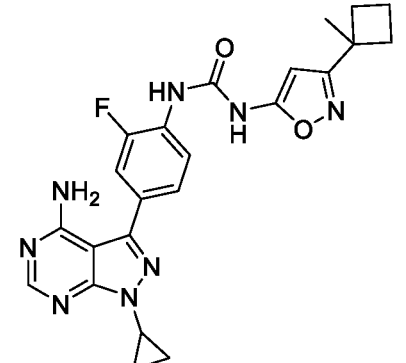
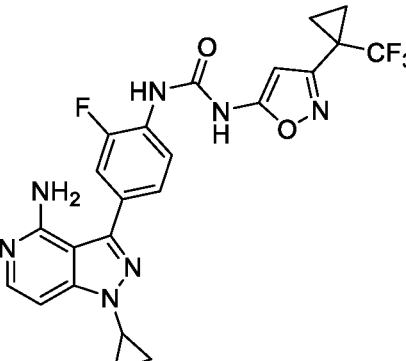
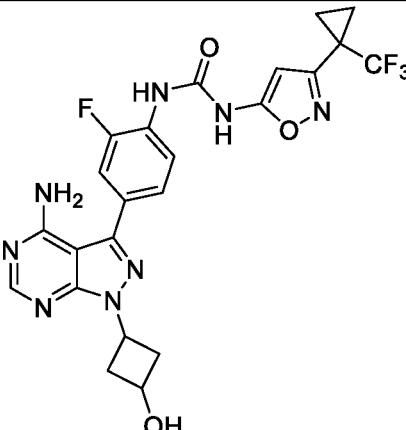
No.	Structure	Name
24		1-(4-(4-amino-1-(tetrahydrofuran-3-yl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(<i>tert</i> -butyl)isoxazol-5-yl)urea
25		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)urea
26		1-(4-(1-allyl-4-amino-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(5-(<i>tert</i> -butyl)isoxazol-3-yl)urea

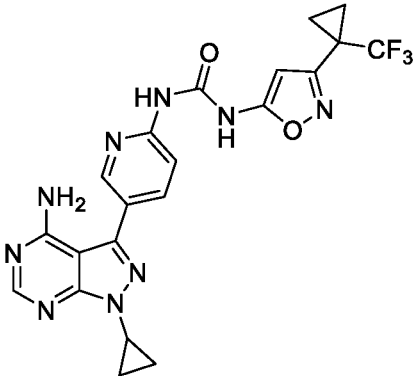
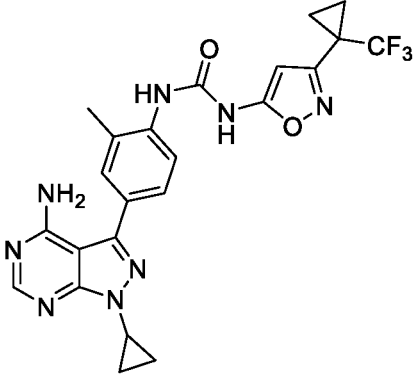
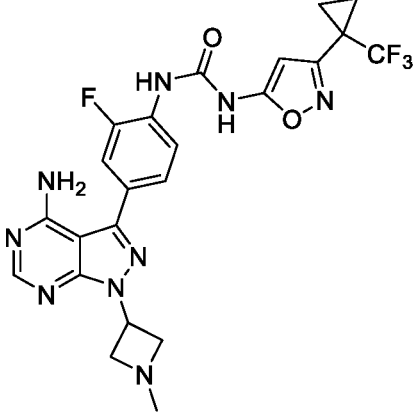
No.	Structure	Name
27		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)urea
28		1-(4-(4-amino-1-methyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-chlorophenyl)-3-(3-(<i>tert</i> -butyl)isoxazol-5-yl)urea
29		1-(4-(4-amino-1-methyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(<i>tert</i> -butyl)isoxazol-5-yl)urea
30		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-3-yl)-2-fluorophenyl)-3-(3-(<i>tert</i> -butyl)isoxazol-5-yl)urea

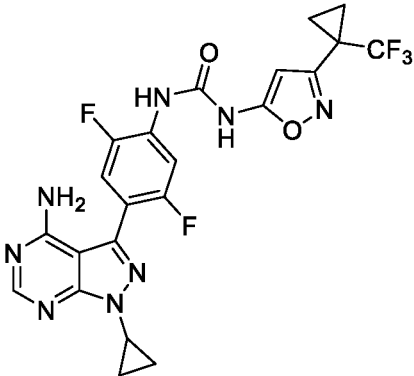
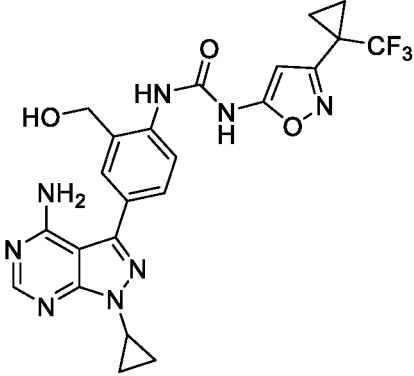
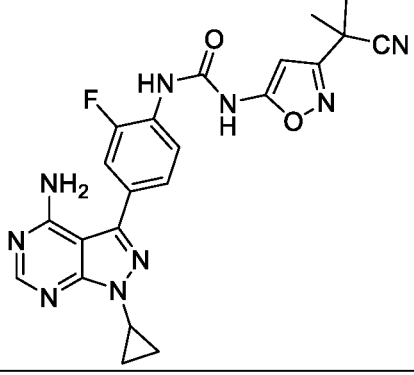
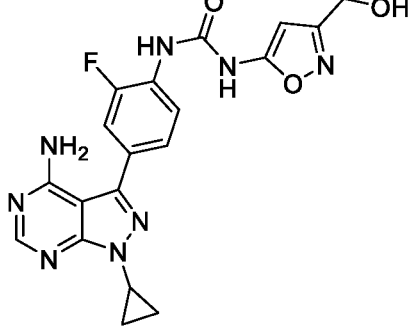
No.	Structure	Name
31		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-3-yl)phenyl)-3-(3-(<i>tert</i> -butyl)isoxazol-5-yl)urea
32		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(1-methylcyclopropyl)isoxazol-5-yl)urea
33		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(5-(<i>tert</i> -butyl)-1,3,4-thiadiazol-2-yl)urea
34		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(4-(<i>tert</i> -butyl)thiazol-2-yl)urea

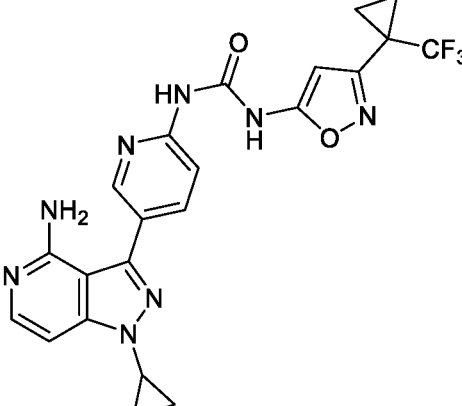
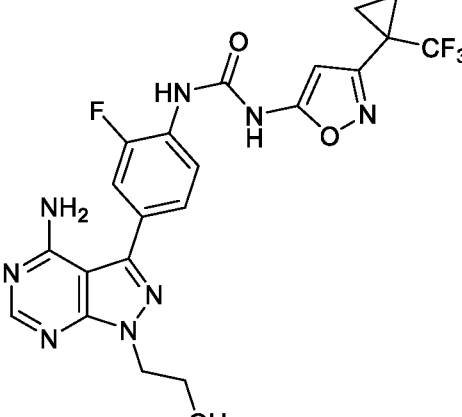
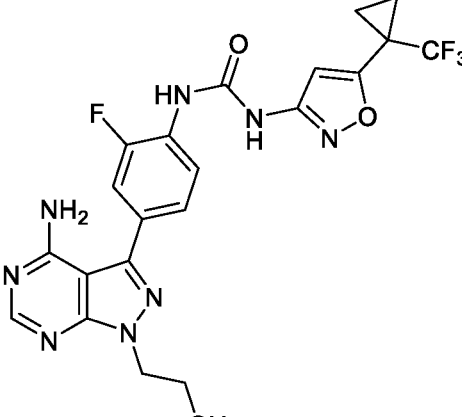
No.	Structure	Name
35		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(<i>tert</i> -butyl)isothiazol-5-yl)urea
36		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(5-(<i>tert</i> -butyl)-1,3,4-oxadiazol-2-yl)urea
37		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(<i>tert</i> -butyl)-1,2,4-thiadiazol-5-yl)urea
38		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(1-(<i>tert</i> -butyl)-1 <i>H</i> -1,2,4-triazol-3-yl)urea

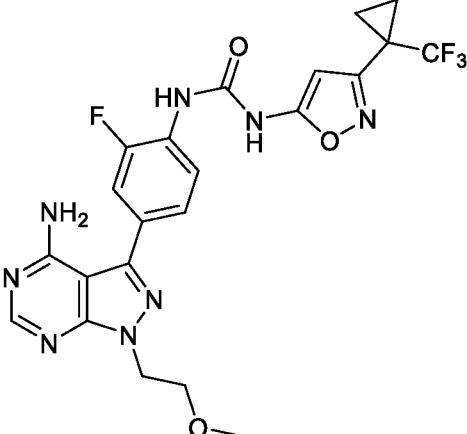
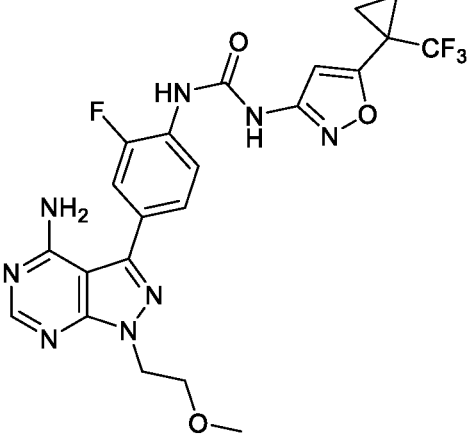
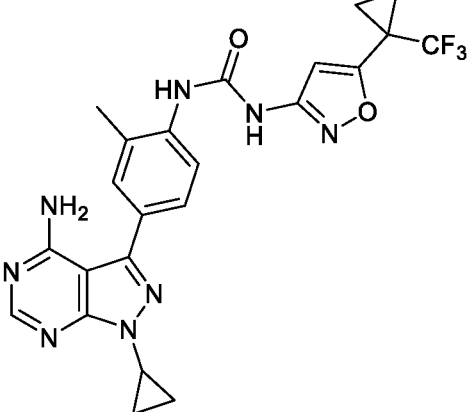
No.	Structure	Name
39		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(trifluoromethyl)isoxazol-5-yl)urea
40		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(pentan-3-yl)isoxazol-5-yl)urea
41		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-isopropylisoxazol-5-yl)urea
42		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-ethylisoxazol-5-yl)urea

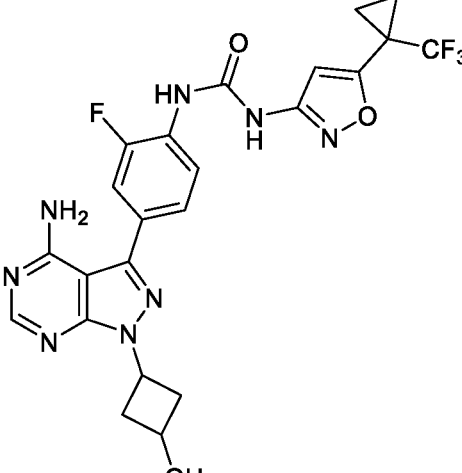
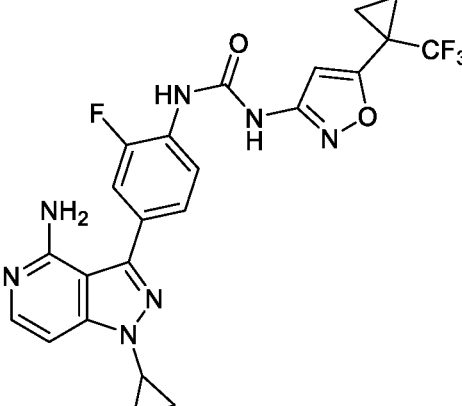
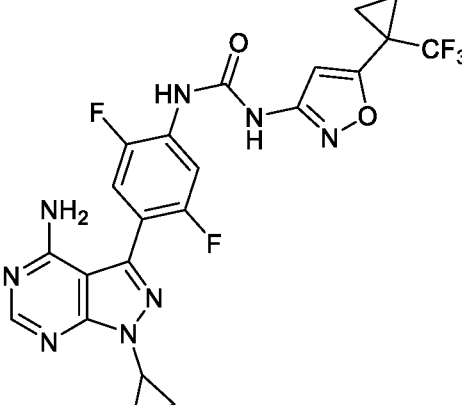
No.	Structure	Name
43		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(<i>sec</i> -butyl)isoxazol-5-yl)urea
44		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(1-methylcyclobutyl)isoxazol-5-yl)urea
45		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-3-yl)-2-fluorophenyl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea
46		1-(4-(4-amino-1-(3-hydroxycyclobutyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea

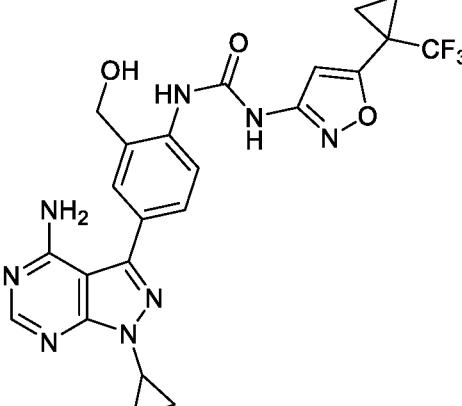
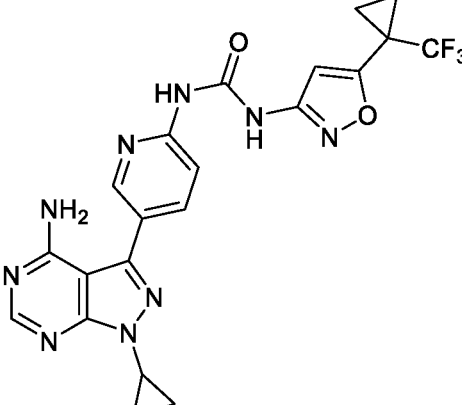
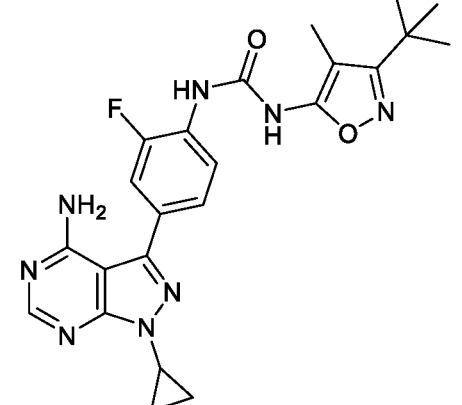
No.	Structure	Name
47		1-(5-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)pyridin-2-yl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea
48		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-methylphenyl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea
49		1-(4-(4-amino-1-(1-methylazetidin-3-yl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea

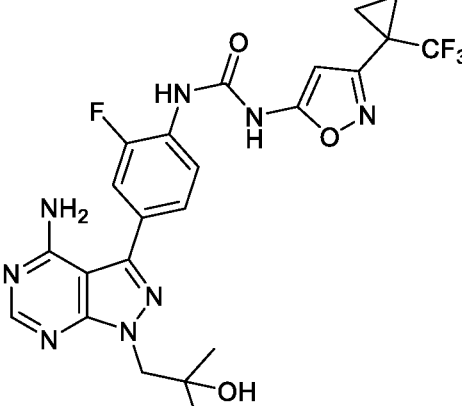
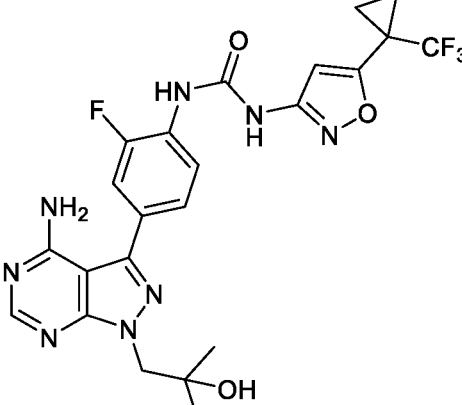
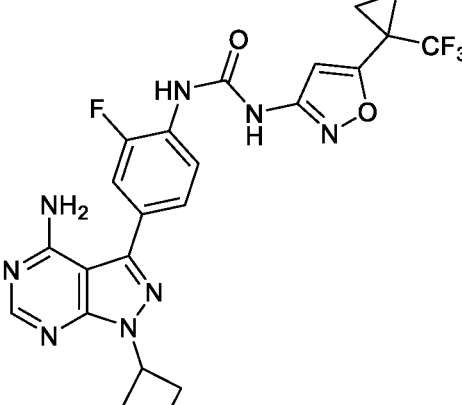
No.	Structure	Name
50		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2,5-difluorophenyl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea
51		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-(hydroxymethyl)phenyl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea
52		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(2-cyanopropan-2-yl)isoxazol-5-yl)urea
53		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(hydroxymethyl)isoxazol-5-yl)urea

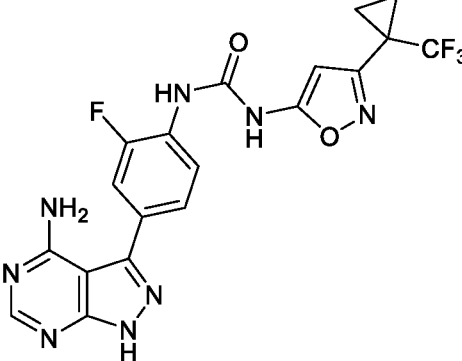
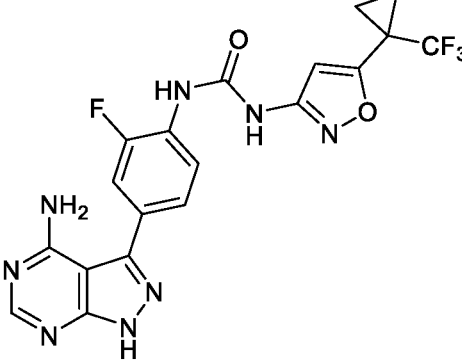
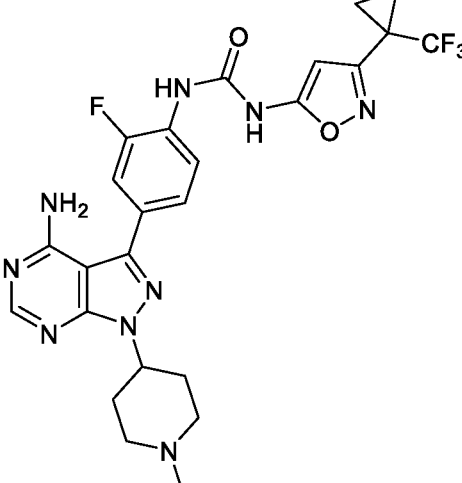
No.	Structure	Name
54		1-(5-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-3-yl)pyridin-2-yl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea
55		1-(4-(4-amino-1-(2-hydroxyethyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea
56		1-(4-(4-amino-1-(2-hydroxyethyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)urea

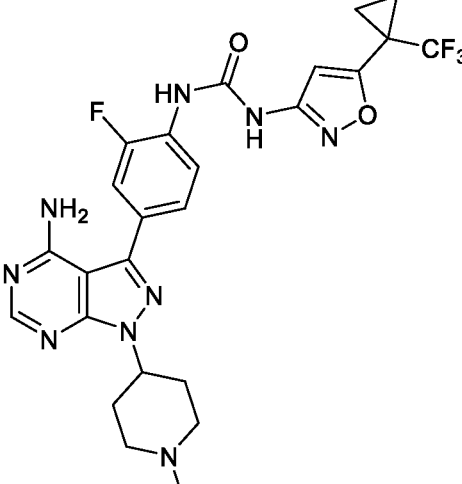
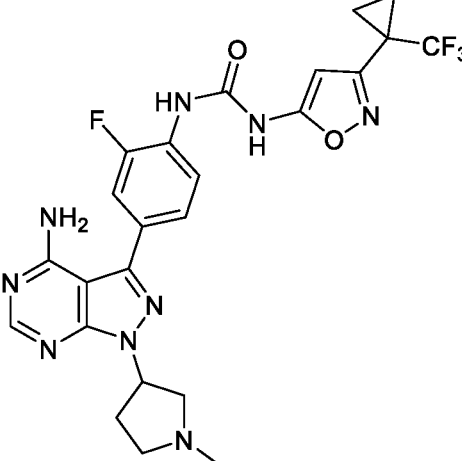
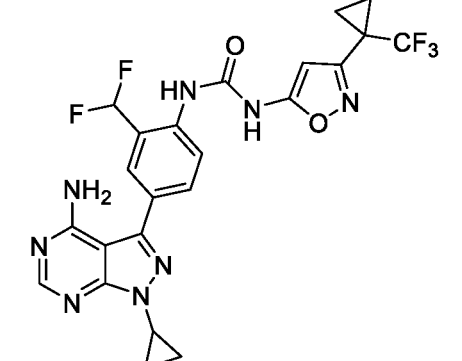
No.	Structure	Name
57		1-(4-(4-amino-1-(2-methoxyethyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea
58		1-(4-(4-amino-1-(2-methoxyethyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)urea
59		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-methylphenyl)-3-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)urea

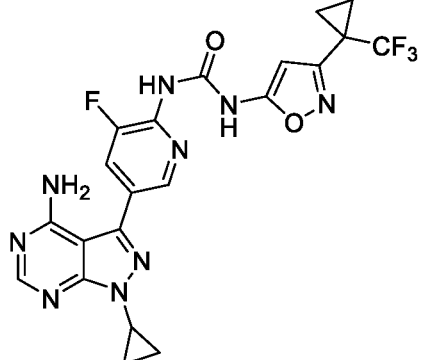
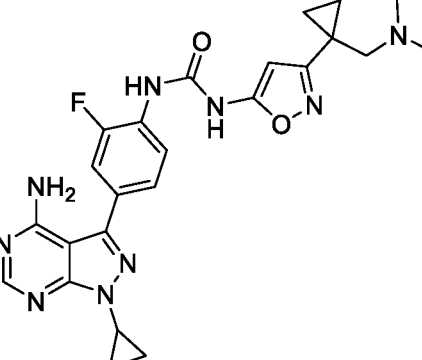
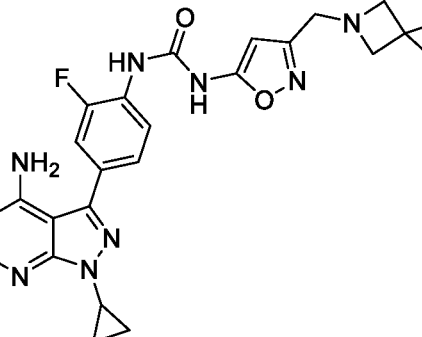
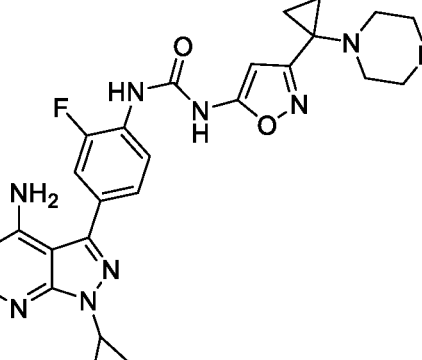
No.	Structure	Name
60		1-(4-(4-amino-1-(3-hydroxycyclobutyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)urea
61		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-3-yl)-2-fluorophenyl)-3-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)urea
62		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2,5-difluorophenyl)-3-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)urea

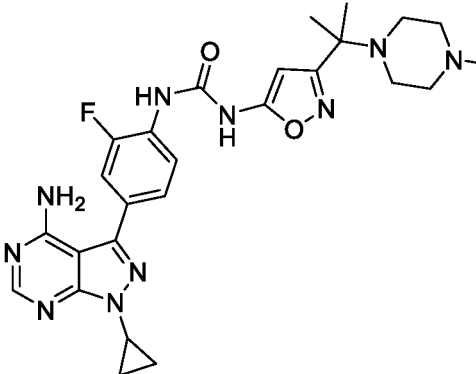
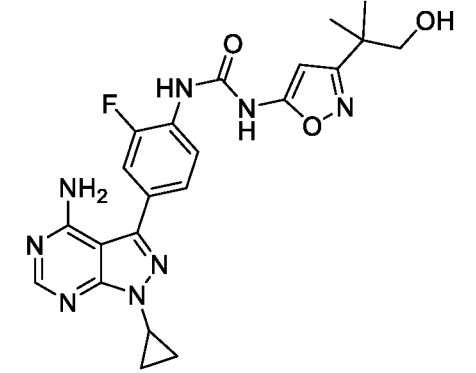
No.	Structure	Name
63		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-(hydroxymethyl)phenyl)-3-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)urea
64		1-(5-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)pyridin-2-yl)-3-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)urea
65		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(tert-butyl)-4-methylisoxazol-5-yl)urea

No.	Structure	Name
66		1-(4-(4-amino-1-(2-hydroxy-2-methylpropyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea
67		1-(4-(4-amino-1-(2-hydroxy-2-methylpropyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)urea
68		1-(4-(4-amino-1-(1-methylazetidin-3-yl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)urea

No.	Structure	Name
69		1-(4-(4-amino-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea
70		1-(4-(4-amino-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)urea
71		1-(4-(4-amino-1-(1-methylpiperidin-4-yl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea

No.	Structure	Name
72		1-(4-(4-amino-1-(1-methylpiperidin-4-yl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)urea
73		1-(4-(4-amino-1-(1-methylpyrrolidin-3-yl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea
74		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-(difluoromethyl)phenyl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea

No.	Structure	Name
75		1-(5-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-3-fluoropyridin-2-yl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea
76		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(1-((dimethylamino)methyl)cyclopropyl)isoxazol-5-yl)urea
77		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-((3,3-difluoroazetidin-1-yl)methyl)isoxazol-5-yl)urea
78		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(1-(4-methylpiperazin-1-yl)cyclopropyl)isoxazol-5-yl)urea

No.	Structure	Name
79		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(2-(4-methylpiperazin-1-yl)propan-2-yl)isoxazol-5-yl)urea
80		1-(4-(4-amino-1-cyclopropyl-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(1-hydroxy-2-methylpropan-2-yl)isoxazol-5-yl)urea

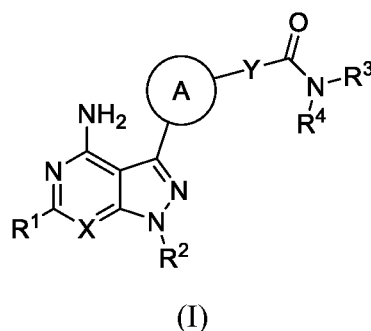
It is understood that in the present description, combinations of substituents and/or variables of the depicted formulae are permissible only if such contributions result in stable compounds.

5 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.

10 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.

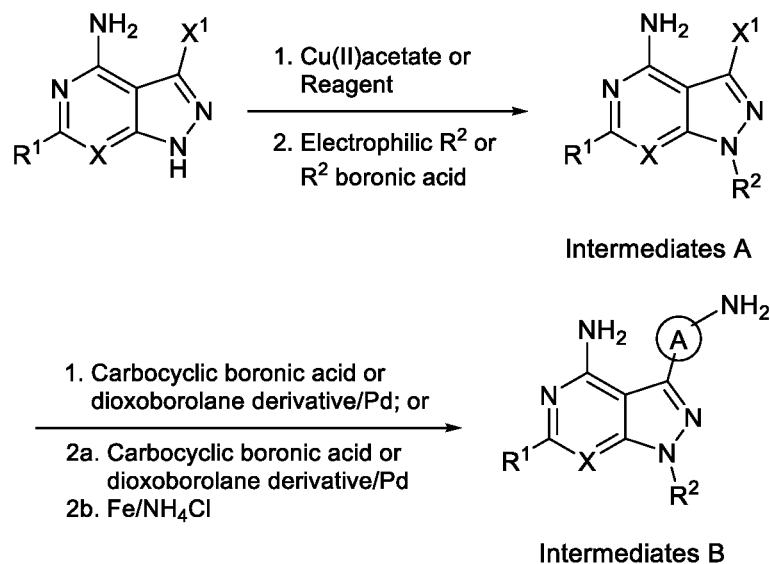
The following General Reaction Schemes illustrate exemplary methods for preparation of compounds of Structure (I):



or pharmaceutically acceptable salts, stereoisomers or prodrug thereof, wherein each of A, X, Y, R¹, R², R³ and R⁴ are as defined herein.

10 General Reaction Scheme 1

The following General Reaction Scheme, wherein X¹ is halogen, and X, R¹, R², and A have the meanings described herein, illustrates examples of methods of making the amine intermediates B:

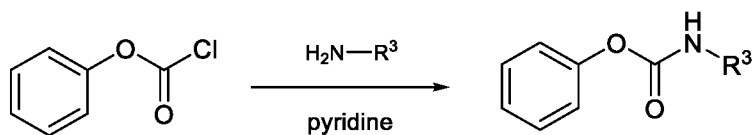


15 As shown in General Reaction Scheme 1, functionalization of the pyrazolopyrimidine with an alkyl or aryl boronic acid or an appropriate electrophile in presence of a base affords intermediate A which can then be subject to palladium

catalyzed arylation (followed as needed by a reduction step) to form amine intermediate B.

General Reaction Scheme 2

- 5 The following General Reaction Scheme illustrates examples of methods of making the carbamate intermediates C:

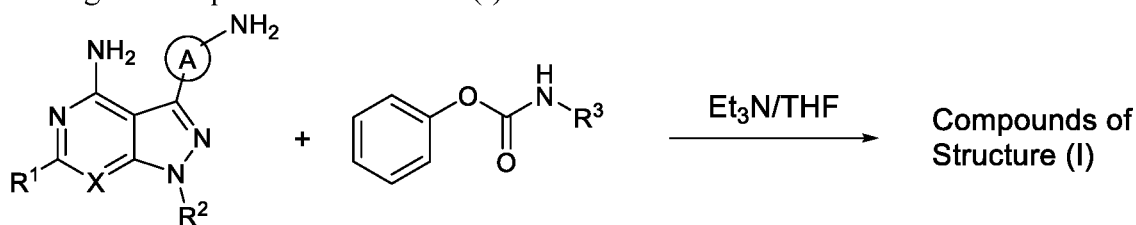


Intermediates C

- As shown in General Reaction Scheme 2, intermediates C can be prepared in the presence of a base by reaction of phenyl chloroformates and the indicated heteroaryl amine (an amine-substituted analogue of R³). General Reaction Scheme 2 depicts preparation of compounds wherein R⁴ is H; however, compounds wherein R⁴ is other than H can be prepared by similar methods by installing R⁴ after preparation of intermediate I or by using an appropriately substituted heteroaryl amine.

15 General Reaction Scheme 3

The following General Reaction Scheme illustrates examples of methods of making the compounds of Structure (I):



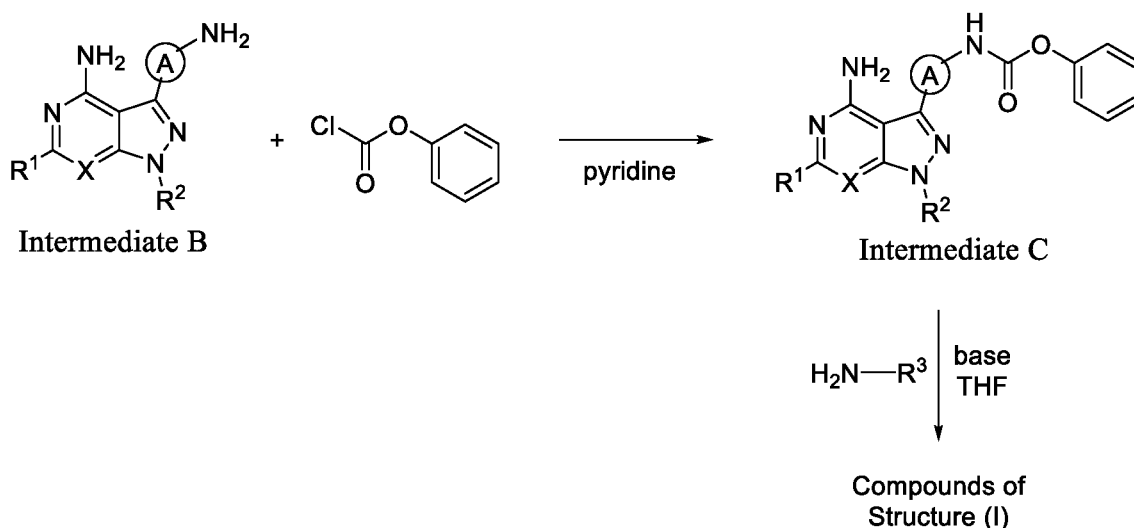
Intermediates B

Intermediates C

- Intermediates B and intermediates C are treated with a base, such as trimethylamine, in THF to afford the compounds of Structure (I).

General Reaction Scheme 4

The following General Reaction Scheme illustrates examples of methods of making the compounds of Structure (I):



- 5 Intermediate B is reacted with phenyl chloroformate under appropriate conditions to yield Intermediate C. Intermediate C is then coupled with the amine using a suitable base (e.g., trimethylamine, DIPEA, DMAP, and the like) in THF to afford the compounds of Structure (I).

Any of the above reaction schemes can be modified at any step to add and/or
 10 modify a substituent or change the order of the steps as appropriate during any stage of the overall synthesis of desired compounds. For example, one of ordinary skill in the art will readily understand that a carbamate analogue of Intermediate B could alternatively be prepared and reacted with an amine analogue of R³ to prepare compounds of Structure (I).

15 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
 20 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
5 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.

10 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
15 included within the scope of embodiments of the invention.

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
20 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.

25 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
5 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 an organ-specific antibody. In such embodiments, the
10 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.

15 In treatment methods according to embodiments of the invention, 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
20 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
25 100 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 intersubject 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.,
5 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 & Wilkins 1999).

10 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
15 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).

20 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
25 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
30 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
5 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,
10 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 transmucosal administration. In specific embodiments, transmucosal 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
15 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
20 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
25 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
30 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

5 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

10 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.

15 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,

20 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 unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated

25 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.

5 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
10 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,
15 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
20 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
25 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-reclosable containers. Alternatively, multiple-dose reclosable 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%, 1.25%, 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%,
 5 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
 10 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%,
 15 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
 25 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.

5 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
10 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.

15 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
20 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
25 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
30 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.

10 *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-1 β and IL-18.

15 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-1 β , IL-18, and caspase-1.

Embodiments of the invention 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 invention 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 invention 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, and Muckle-Wells syndrome.

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, and cancer.

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
5 onset Still's disease, gout, pseudogout, SAPHO syndrome, Castleman's disease, sepsis, stroke, atherosclerosis, celiac disease, DIRA (Deficiency of IL-1 Receptor Antagonist), Alzheimer's disease, Parkinson's disease, and Cancer.

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
10 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
15 sodium and misoprostol, sulindac, oxaprozin, diflunisal, piroxicam, indomethacin, etodolac, fenoprofen calcium, ketoprofen, sodium nabumetone, sulfasalazine, tolmetin sodium, and hydroxychloroquine.

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

20 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,
25 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
30 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, isoliquiritigenin, 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, mechlorethamine, carboquone; apaziquone,
 5 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;

10 DNA altering agents: such as amrubicin, bisantrene, decitabine, mitoxantrone, procarbazine, trabectedin, clofarabine; amsacrine, brostallicin, pixantrone, laromustine 1,3 ;

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

15 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,
 20 thioguanine, carmofur; doxifluridine, elacytarabine, raltitrexed, sapacitabine, tegafur2,3 , trimetrexate;

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

25 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;
 30 acolbifene, danazol, deslorelin, epitiostanol, orteronel, enzalutamide 1,3 ;

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 acetone 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 invention 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 the invention 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 IC₅₀ 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 IC₅₀ 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.

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 singlet).

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.

5 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 μ g/ μ L) were mixed in assay buffer (20 mM Hepes pH 7.5, 10 mM MgCl₂, 1 mM EGTA, 0.02% Brij35, 0.02 mg/ml BSA, 0.1 mM Na₃VO₄, 2 mM DTT, 1% DMSO). Compounds of interest (serial 3-fold dilution in DMSO from 10 μ M 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 [³³P]-ATP (specific activity 10 μ Ci/ μ l) 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. IC₅₀ values and curve fits were obtained using Prism (GraphPad Software).

IL-1 β 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 μ M 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 μ M 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-1 β was determined using a JESS instrument
5 (Protein Simple) and standard protocols. Cleaved IL-1 β 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.

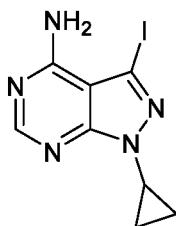
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Abbreviations:

$^{\circ}$ C (degree Celsius); ^{1} H NMR (proton Nuclear Magnetic Resonance); ACN (acetonitrile); Boc (*tert*-butoxycarbonyl); DCM (dichloromethane); DIPEA (*N,N*-diisopropylethylamine); DMAP (4-dimethylaminopyridine); DMF (*N,N*-
15 dimethylformamide); DMSO-*d*₆ (deuterated dimethylsulfoxide); eq (equivalent); EtOAc (ethyl acetate); g (gram); (g) gas; h (hour); HPLC (High Performance Liquid Chromatography); LCMS (Liquid Chromatography Mass Spectrometry); MeOH (methanol); mg (milligram); min (minute); mL (milliliter); mmol (millimole); N (normal); *n*-BuOH (1-butanol); Pd(PPh₃)₄ (palladium-tetrakis(triphenylphosphine));
20 PdCl₂(dppf) ([1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride); *sec*- (secondary); TBAF (tetra-*n*-butylammonium fluoride); *tert*- (tertiary); TFA (trifluoroacetic acid); THF (tetrahydrofuran); TLC (Thin Layer Chromatography); UPLC (Ultra Performance Liquid Chromatography).

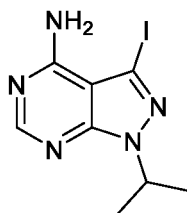
Preparation of Synthetic Intermediates

INTERMEDIATE A1

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

- 5 Copper (II) acetate (0.348 g, 1.916 mmol), 2,2'-bipyridine (0.299 g, 1.916 mmol), and sodium bicarbonate (0.322 g, 3.830 mmol) were added to a stirred solution of 3-iodo-1*H*-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
- 10 by TLC), the reaction mixture was filtered through a pad of diatomaceous earth which was then rinsed with DCM (20 mL × 2). The combined filtrates were washed with water (20 mL) and brine (25 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give 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
- 15 an off-white solid (0.24 g, 36% yield). ¹H 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-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-4-AMINE

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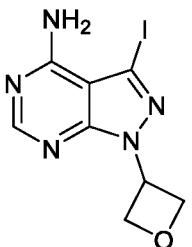
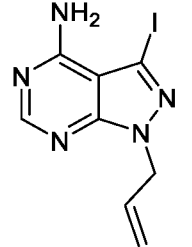
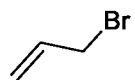
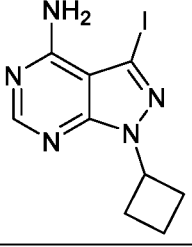
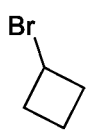
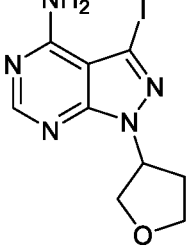
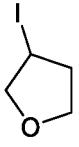
Cs₂CO₃ (12.38 g, 38.31 mmol) and 2-iodopropane (3.60 g, 21.16 mmol) were added to a stirred solution of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (5.00 g, 19.15 mmol) in DMF (25 mL) in a sealed 25 mL tube. The reaction mixture was stirred at 90 °C for 16 h

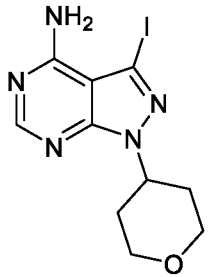
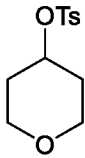
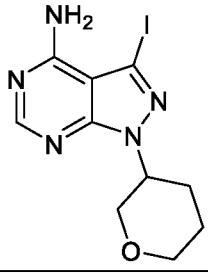
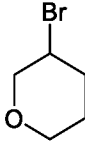
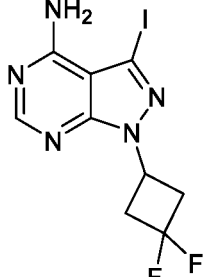
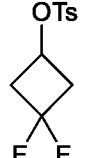
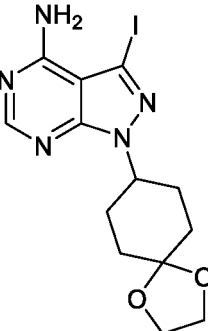
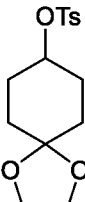
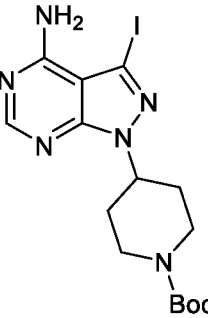
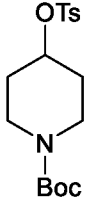
and, following completion of the reaction (as indicated by TLC), poured into crushed ice (50 g) and stirred for 15 min. The resulting solid was filtered, washed with water (2×5 mL), and dried to afford the title compound as an off-white solid (3.25 g, 56% yield). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 8.18 (s, 1H), 4.93-4.99 (m, 1H), 1.42 (d, J = 6.8 Hz, 5 6H). LCMS: 303.8 [M+H].

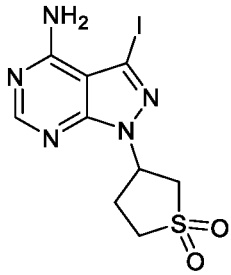
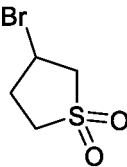
INTERMEDIATES A3 TO A12

The following intermediates were prepared via a similar procedure described for intermediate A2, replacing 2-iodopropane with the appropriate reagent (alkyl halide or tosylate) as shown below:

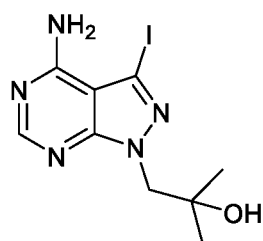
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Intermediate	Structure	Reagent	^1H NMR (400 MHz, $\text{DMSO}-d_6$)	LCMS
A3			δ = 8.21 (s, 1H), 5.89-5.93 (m, 1H), 4.93-5.00 (m, 4H).	318.0 [M+H]
A4			δ = 8.21 (s, 1H), 5.93-6.03 (m, 1H), 5.16-5.20 (m, 1H), 5.03-5.09 (m, 1H), 4.89-4.91 (m, 2H).	301.8 [M+H]
A5			δ = 8.19 (s, 1H), 5.20-5.26 (m, 1H), 2.28-2.73 (m, 4H), 1.84-1.86 (m, 2H).	315.8 [M+H]
A6			δ = 8.21 (s, 1H), 5.38-5.44 (m, 1H), 4.00-4.07 (m, 2H), 3.83-3.88 (m, 2H), 2.32-2.43 (m, 2H).	332.0 [M+H]

Intermediate	Structure	Reagent	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆)	LCMS
A7			δ = 8.20 (s, 1H), 4.82-4.89 (m, 1H), 3.96-4.00 (m, 2H), 3.48-3.54 (m, 2H), 2.05-2.16 (m, 2H), 1.82-1.86 (m, 2H).	345.9 [M+H]
A8			δ = 8.21 (s, 1H), 4.65-4.71 (m, 1H), 3.85-3.92 (m, 2H), 3.40-3.44 (m, 2H), 2.08-2.20 (m, 2H), 1.74-1.79 (m, 2H).	346.0 [M+H]
A9			δ = 8.27 (s, 1H), 5.19-5.21 (m, 1H), 3.35 (bs, 4H).	352.0 [M+H]
A10			No recorded (the crude material was taken as such into the next step).	402.0 [M+H]
A11			No recorded (the crude material was taken as such into the next step).	444.8 [M+H]

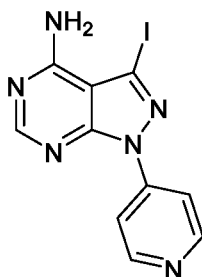
Intermediate	Structure	Reagent	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆)	LCMS
A12			δ = 8.24 (s, 1H), 5.59-5.67 (m, 1H), 3.70-3.75 (m, 2H), 3.44-3.52 (m, 2H), 2.56-2.64 (m, 2H).	379.7 [M+H]

INTERMEDIATE A13

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

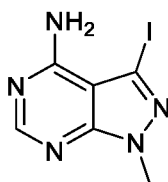
- 5 NaH_2PO_4 (0.044 g, 0.372 mmol) was added to a mixture of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.100 g, 0.380 mmol), 2,2-dimethyloxirane (0.055 g, 0.760 mmol), and K_2CO_3 (0.050 g, 0.372 mmol) in acetonitrile (3 mL) and water (1 mL) and the resulting solution subjected to microwave irradiation at 150 °C for 1 h. Following completion of the reaction (as indicated by TLC), the solvents were removed under
- 10 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). ¹H 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 A14

3-iodo-1-(pyridin-4-yl)-1*H*-pyrazolo[3,4-*D*]pyrimidin-4-amine

The title compound was prepared via a similar procedure described for intermediate A1, starting from 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (1.00 g, 3.83 mmol) and pyridin-4-ylboronic acid (0.94 g, 7.66 mmol), and was obtained as a pale brown solid (0.27 g, 21% yield). LCMS: 338.8 [M+H].

INTERMEDIATE A15

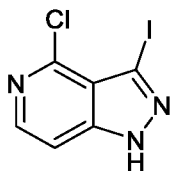
3-iodo-1-methyl-1*H*-pyrazolo[3,4-*D*]pyrimidin-4-amine

Cs_2CO_3 (0.780 g, 2.394 mmol) and methyl iodide (0.138 mL, 2.203 mmol) were added to a solution of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.500 g, 1.916 mmol) in DMF (3 mL) at 0 °C in a sealed 25 mL tube. The reaction mixture was stirred at 25 °C for 1 h and, following completion of the reaction (as indicated by TLC), was poured into crushed ice (50 g) and stirred for 30 min. The resulting solid was filtered, washed with water (2×5 mL), and dried to afford the title compound as a yellow solid (0.380 g, 67% yield). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 8.22 (s, 1H), 6.79 (s, 2H), 3.89 (s, 3H). LCMS: 276.0 [M+H].

INTERMEDIATE A16

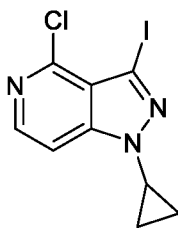
1-cyclopropyl-3-iodo-1*H*-pyrazolo[4,3-*C*]pyridin-4-amine

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



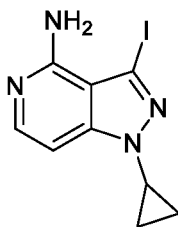
KOH (1.320 g, 23.0 mmol) and iodine (1.620 g, 12.8 mmol) were added to a solution of 4-chloro-1*H*-pyrazolo[4,3-*c*]pyridine (1.000 g, 6.4 mmol) in dioxane (10 mL) and the resulting mixture was stirred at 75 °C for 4 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was filtered over a pad of diatomaceous earth and the 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). ¹H 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].

10 *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-1*H*-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). ¹H 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].

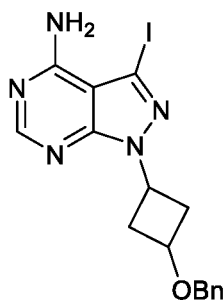
*Step 3: Synthesis of 1-cyclopropyl-3-iodo-1H-pyrazolo[4,3-*c*]pyridin-4-amine*



A mixture of 4-chloro-1-cyclopropyl-3-iodo-1*H*-pyrazolo[4,3-*c*]pyridine (0.20 g) and aqueous ammonium hydroxide (25% in water, 8 mL) was subjected to microwave irradiation at 150 °C for 2 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was concentrated under reduced pressure to yield the title compound as an off-white solid (0.19 g, quantitative yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.11 (s, 1H), 7.38 (s, 1H), 6.68 (bs, 2H), 3.48-3.54 (m, 1H), 0.97-0.99 (m, 4H). LCMS: 301.0 [M+H].

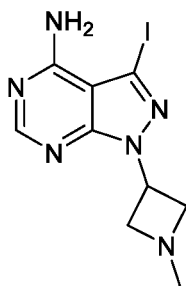
INTERMEDIATE A17

10 1-(3-(BENZYLOXY)CYCLOBUTYL)-3-iodo-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-4-AMINE



3-(Benzyloxy)cyclobutyl methanesulfonate (prepared as described in PCT Pub. No. WO 2019/092170, 0.491 g, 1.916 mmol) and Cs₂CO₃ (0.624 g, 1.916 mmol) were added to a solution of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.250 g, 0.958 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 TLC), the reaction mixture was poured into ice water (50 mL) and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were dried over Na₂SO₄, filtered, and evaporated under reduced pressure to yield the title compound as a pale brown gum (0.400 g, 75% LCMS purity) which was taken used without further purification. LCMS: 422.0 [M+H]

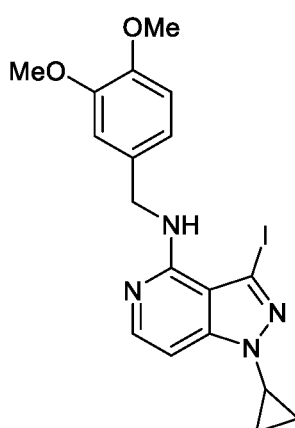
INTERMEDIATE A18

3-iodo-1-(1-methylazetidin-3-yl)-1*H*-pyrazolo[3,4-*D*]pyrimidin-4-amine

The title compound was prepared as described in PCT Pub. No. WO 2002/076986.

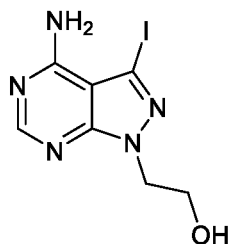
5

INTERMEDIATE A19

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

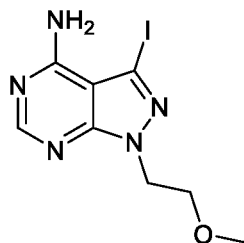
- 10 A mixture of 4-chloro-1-cyclopropyl-3-iodo-1*H*-pyrazolo[4,3-*c*]pyridine (A16, 0.880 g, 2.75 mmol) and (2,5-dimethoxyphenyl)methanamine (1.245 mL, 8.26 mmol) in *n*-BuOH (10 mL) was stirred at 110 °C for 12 h. Following completion of the reaction (as indicated by LCMS), the reaction mixture was concentrated under reduced pressure to give crude material which was purified by Isolera (silica gel 230-400 mesh, eluting with 40% EtOAc
- 15 in petroleum ether), affording the title product as a yellow gum (1.0 g, 80% yield). ¹H 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 A20

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

- 5 The title compound was prepared as described in PCT Pub. No. WO 2011/119663.

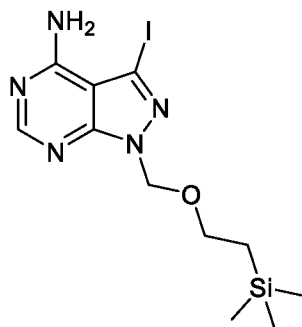
INTERMEDIATE A21

3-iodo-1-(2-methoxyethyl)-1*H*-pyrazolo[3,4-*D*]pyrimidin-4-amine

- 10 K₂CO₃ (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-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.500 g, 1.916 mmol) in DMF (6 mL) and the resulting mixture 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
- 15 organic extracts were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford the title product (0.500 g, crude) which was used without further purification. ¹H 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 A22

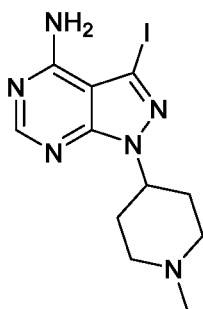
3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[3,4-*D*]pyrimidin-4-amine



- 5 The title compound was prepared as described in USPTO Pub. No. WO 2015/165279.

INTERMEDIATE A23

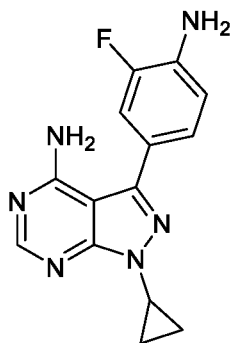
3-iodo-1-(1-methylpiperidin-4-yl)-1*H*-pyrazolo[3,4-*D*]pyrimidin-4-amine



- 10 The title compound was prepared as described in USPTO Pub. No. WO 2018/121228.

INTERMEDIATE B1

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

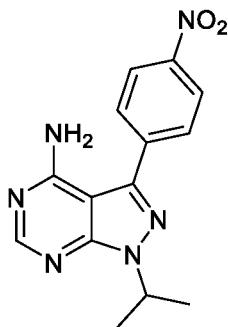


- 5 A mixture of 1-cyclopropyl-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (A1, 0.500 g, 1.66 mmol), 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.433 g, 1.82 mmol), and K₂CO₃ (0.688 g, 4.98 mmol) in 1,4-dioxane (25 mL) and water (2.5 mL) was purged with N₂ for 10 min. Pd(PPh₃)₄ (0.092 g, 0.08 mmol) was then added and the reaction mixture was stirred at 100 °C for 16 h. Following completion of the reaction (as
- 10 indicated by TLC), the mixture was filtered through a pad 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). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.23 (s, 1H),
- 15 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

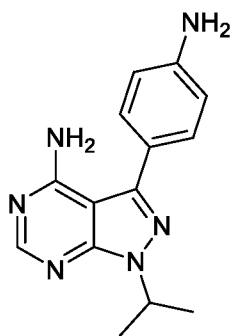


5

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 (1.56 g, 9.34 mmol), and was obtained as a yellow solid (1.242 g, 67% yield). ¹H 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].

10

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



15

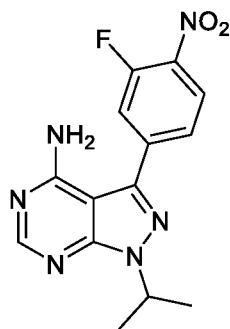
Iron powder (2.320 g, 41.60 mmol) and ammonium chloride (2.220 g, 41.60 mmol) were added to a stirred solution of 1-isopropyl-3-(4-nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (1.242 g, 4.16 mmol) in ethanol (50 mL) and water (20 mL) and the resulting mixture was heated to 80 °C for 3 h. Following completion of the reaction (as

indicated by TLC), the reaction mixture was filtered through a pad of 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
5 title compound as a pale yellow solid (1.042 g, quantitative yield) which was taken forward without further purification.

INTERMEDIATE B3

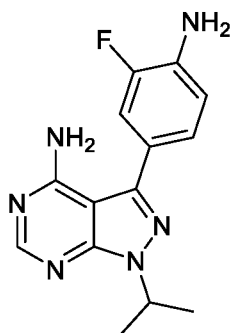
3-(4-AMINO-3-FLUOROPHENYL)-1-ISOPROPYL-1H-PYRAZOLO[3,4-D]PYRIMIDIN-4-AMINE

10 *Step 1: Synthesis of 3-(3-fluoro-4-nitrophenyl)-1-isopropyl-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, 0.10 g, 0.32 mmol) and (3-fluoro-4-nitrophenyl)boronic acid (0.71 g, 0.39 mmol), and was
15 obtained as a yellow solid (0.07 g, 67% yield). LCMS: 315.1 [M-H].

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

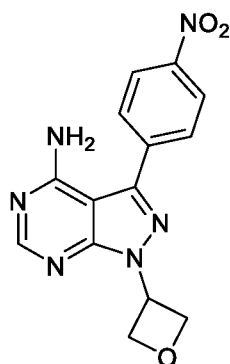


The title compound was prepared via a similar procedure described for step 2 of intermediate B2, starting from 3-(3-fluoro-4-nitrophenyl)-1-isopropyl-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.07 g, 0.22 mmol) and Fe/NH₄Cl, and was obtained as a pale-yellow solid (0.09 g, quantitative yield) which was taken forward without further purification. LCMS: 287.1 [M+H].

INTERMEDIATE B4

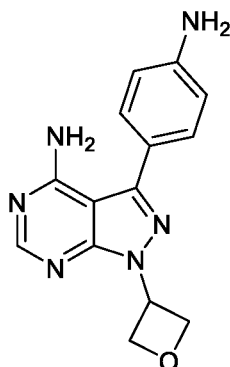
3-(4-AMINOPHENYL)-1-(OXETAN-3-YL)-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-4-AMINE

10 *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). ¹H 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

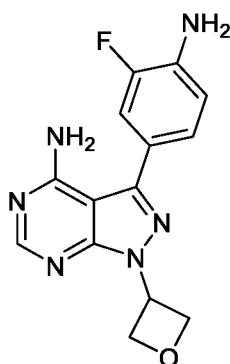


The title compound was prepared via a similar procedure described for step 2 of intermediate B2, starting from 3-(4-nitrophenyl)-1-(oxetan-3-yl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.596 g, 1.91 mmol) and Fe/NH₄Cl, and was obtained as a pale yellow solid (0.42 g, quantitative yield) which was taken forward without further purification. LCMS: 283.0 [M+H].

10

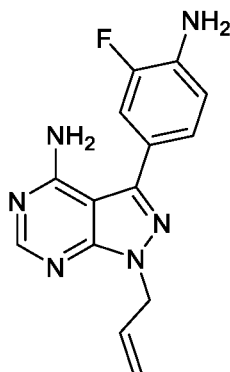
INTERMEDIATE B5

3-(4-AMINO-3-FLUOROPHENYL)-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, 0.110 g, 0.346 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.099 g, 0.420 mmol), and was obtained as a pale yellow gum (0.077 g, 74% yield). LCMS: 317.1 [M+H].

INTERMEDIATE B6

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

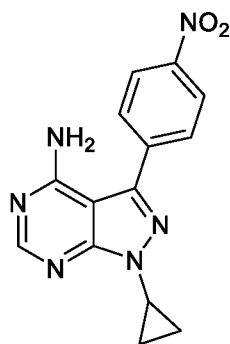
- 5 The title compound was prepared via a similar procedure described for intermediate B1, starting from 1-allyl-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (A4, 0.15 g, 0.49 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.13 g, 0.54 mmol), and was obtained as a yellow gum (0.13 g, 92% yield). LCMS: 285.0 [M+H].

10

INTERMEDIATE B7

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

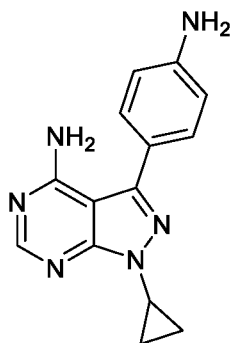
Step 1: Synthesis of 1-cyclopropyl-3-(4-nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine



- 15 The title compound was prepared via a similar procedure described for intermediate B1, starting from 1-cyclopropyl-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (A1, 0.110 g, 0.36 mmol) and (4-nitrophenyl)boronic acid (0.067 g, 0.40 mmol), and was obtained as a pale yellow solid (0.060 g, 56% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.37 (d, *J*

= 8.8 Hz, 2H), 8.30 (s, 1H), 7.91 (d, J = 8.8 Hz, 2H), 3.91-3.94 (m, 1H), 1.23-1.24 (m, 2H), 1.11-1.14 (m, 2H). LCMS: 297.0 [M+H].

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



5

The title compound was prepared via a similar procedure described for step 2 of intermediate B2, starting from 1-cyclopropyl-3-(4-nitrophenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.060 g, 0.2 mmol) and Fe/NH₄Cl, and was obtained as a pale yellow solid (0.047 g, 89% yield) which was taken forward without further purification.

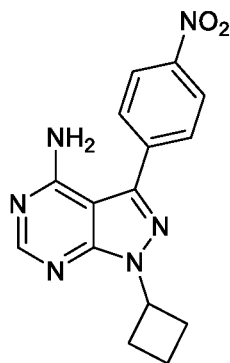
10 LCMS: 266.9 [M+H].

INTERMEDIATE B8

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

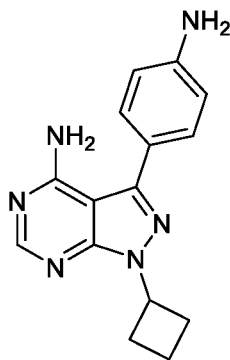
*Step 1: Synthesis of 1-cyclobutyl-3-(4-nitrophenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine*

15



The title compound was prepared via a similar procedure described for intermediate B1, starting from 1-cyclobutyl-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (A5, 0.150 g, 0.47 mmol) and (4-nitrophenyl)boronic acid (0.087 g, 0.52 mmol), and was obtained as a pale yellow solid (0.160 g, quantitative yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.34-8.41 (m, 2H), 8.28 (s, 1H), 7.94-7.97 (m, 2H), 5.32-5.43 (m, 1H), 2.65-2.75 (m, 2H), 1.86-1.94 (m, 4H). LCMS: 311.2 [M+H].

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

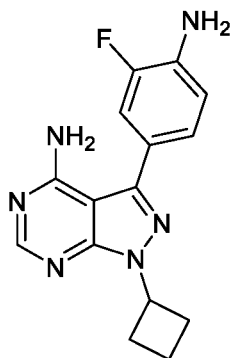


The title compound was prepared via a similar procedure described for step 2 of intermediate B2, starting from 1-cyclobutyl-3-(4-nitrophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.16 g, 0.51 mmol) and Fe/NH₄Cl, and was obtained as a pale yellow solid (0.140 g, quantitative yield) which was taken forward without further purification. LCMS: 281.0 [M+H].

15

INTERMEDIATE B9

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



- 5 The title compound was prepared via a similar procedure described for intermediate B1, starting from 1-cyclobutyl-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (A5, 0.250 g, 0.793 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.225 g, 0.952 mmol), and was obtained as a pale yellow solid (0.100 g, 32% yield). LCMS: 299.1 [M+H].

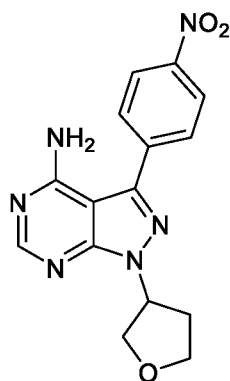
10

INTERMEDIATE B10

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

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

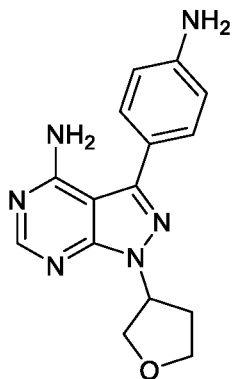
15



The title compound was prepared via a similar procedure described for intermediate B1, starting from 3-iodo-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

(A6, 0.165 g, 0.49 mmol) and (4-nitrophenyl)boronic acid (0.091 g, 0.54 mmol), and was obtained as pale yellow solid (0.086 g, 53% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.38-8.40 (m, 2H), 8.30 (s, 1H), 7.93-7.95 (m, 2H), 5.52-5.58 (m, 1H), 4.06-4.15 (m, 2H), 3.88-3.99 (m, 2H), 2.50-2.51 (m, 2H). LCMS: 327.2 [M+H].

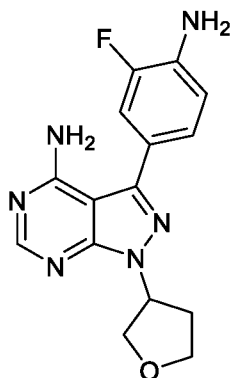
5 *Step 2: Synthesis of 3-(4-aminophenyl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine*



The title compound was prepared via a similar procedure described for step 2 of intermediate B2, starting from 3-(4-nitrophenyl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.115 g, 0.35 mmol) and Fe/NH₄Cl, and was obtained as a pale yellow solid (0.083 g, 80% yield) which was taken forward without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.22 (s, 1H), 7.33 (dd, *J* = 2.0, 6.6 Hz, 2H), 6.71 (dd, *J* = 2.0, 6.4 Hz, 2H), 5.48 (bs, 2H), 5.44-5.47 (m, 1H), 4.04-4.12 (m, 2H), 3.86-3.94 (m, 2H), 2.34-2.41 (m, 2H). LCMS: 296.9 [M+H].

INTERMEDIATE B11

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



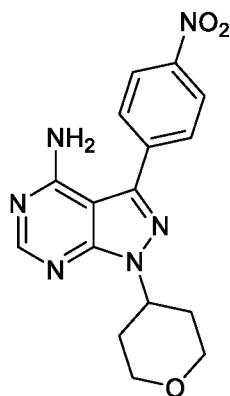
- 5 The title compound was prepared via a similar procedure described for intermediate B1, starting from 3-iodo-1-(tetrahydrofuran-3-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (A6, 0.351 g, 1.00 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.301 g, 1.27 mmol), and was obtained as a pale yellow solid (0.200 g, 60% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.23 (s, 1H), 7.24-7.28 (m, 1H), 7.18-7.21 (m, 1H), 6.88-6.92 (m, 1H), 5.46-5.50 (m, 3H), 4.04-4.12 (m, 2H), 3.87-3.94 (m, 2H), 2.33-2.41 (m, 2H). LCMS: 315.1 [M+H].
- 10

INTERMEDIATE B12

3-(4-AMINOPHENYL)-1-(TETRAHYDRO-2*H*-PYRAN-4-YL)-1*H*-PYRAZOLO[3,4-
D]PYRIMIDIN-4-AMINE

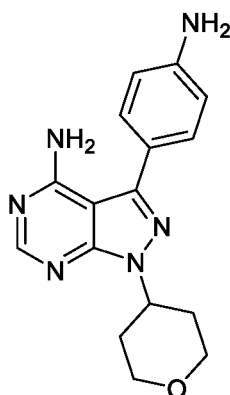
15

*Step 1: Synthesis of 3-(4-nitrophenyl)-1-(tetrahydro-2H-pyran-4-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-(tetrahydrofuran-3-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (A7, 0.094 g, 0.273 mmol) and (4-nitrophenyl)boronic acid (0.055 g, 0.328 mmol), and
 5 was obtained as a pale yellow solid (0.078 g, 84% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.37-8.40 (m, 2H), 8.29 (s, 1H), 7.93-7.96 (m, 2H), 4.96-5.02 (m, 1H), 4.00-4.04 (m, 2H), 3.54-3.59 (m, 2H), 2.16-2.24 (m, 2H), 1.89-1.94 (m, 2H). LCMS: 340.9 [M+H].

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

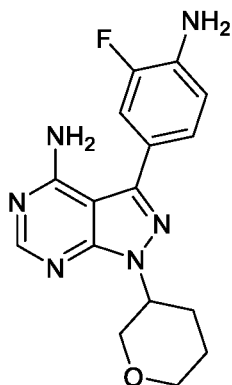


10

The title compound was prepared via a similar procedure described for step 2 of intermediate B2, starting from 3-(4-nitrophenyl)-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.078 g, 0.23 mmol) and Fe/NH₄Cl, and was obtained as a pale yellow solid (0.052 g, 73% yield) which was taken forward without
 15 further purification. LCMS: 311.1 [M+H].

INTERMEDIATE B13

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

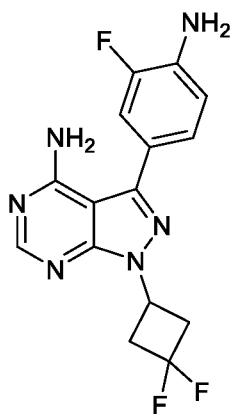


- 5 The title compound was prepared via a similar procedure described for intermediate B1, starting from 3-iodo-1-(tetrahydro-2*H*-pyran-3-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (A8, 0.050 g, 0.14 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.040 g, 0.17 mmol), and was obtained as a yellow gum (0.015 g, 32% yield). LCMS: 329.2 [M+H].

10

INTERMEDIATE B14

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



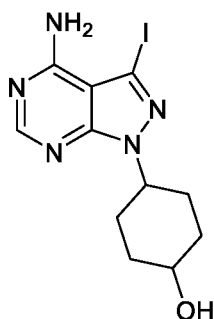
- 15 The title compound was prepared via a similar procedure described for intermediate B1, starting from 1-(3,3-difluorocyclobutyl)-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (A9, 0.100 g, 0.285 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

yl)aniline (0.810 g, 0.341 mmol), and was obtained as a pale yellow solid (0.088 g, 93% yield). LCMS: 334.9 [M+H].

INTERMEDIATE B15

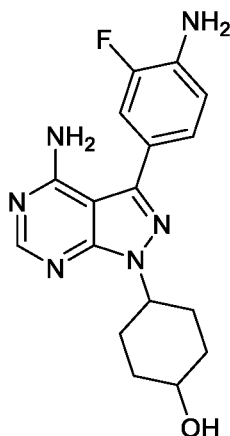
5 4-(4-AMINO-3-(4-AMINO-3-FLUOROPHENYL)-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-1-
YL)CYCLOHEXAN-1-OL

*Step 1: Synthesis of 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)cyclohexan-1-ol*



10 Aqueous HCl (1.5 N, 5 mL) was added to a solution of 3-iodo-1-(1,4-dioxaspiro[4.5]decan-8-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (A10, 0.313 g, 0.780 mmol) and the resulting mixture was stirred at room temperature for 12 h. Following completion of the reaction (as indicated by UPLC), the solvent was removed under reduced pressure to yield as residue (0.232 g, LCMS: 358.0 [M+H]) which was dissolved
15 in THF (5 mL). The resulting solution was cooled to 0 °C, NaBH₄ (0.050 g, 1.322 mmol) was added, and the mixture was stirred at room temperature for 1 h. Following completion of the reaction (as indicated by UPLC), aqueous HCl (1.5 N, 5 mL) was added and the mixture was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to yield the title product
20 as a pale brown gum (0.196 g) which was taken forward without further purification. LCMS: 359.8 [M+H].

Step 2: Synthesis of 4-(4-amino-3-(4-amino-3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexan-1-ol



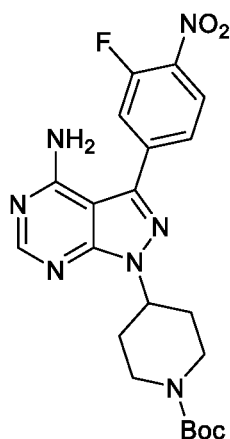
The title compound was prepared via a similar procedure described for intermediate B1, starting from 4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexan-1-ol (0.196 g, 0.550 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.160 g, 0.655 mmol), and was obtained as a yellow gum (0.120 g, 64% yield). LCMS: 343.0 [M+H].

10

INTERMEDIATE B16

3-(4-AMINO-3-FLUOROPHENYL)-1-(1-(OXETAN-3-YL)PIPERIDIN-4-YL)-1H-PYRAZOLO[3,4-D]PYRIMIDIN-4-AMINE

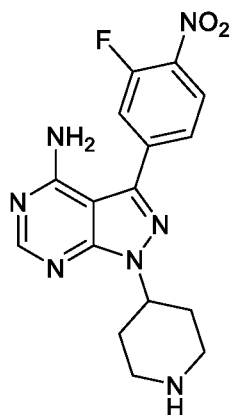
Step 1: Synthesis of tert-butyl 4-(4-amino-3-(3-fluoro-4-nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxylate



15

The title compound was prepared via a similar procedure described for intermediate B1, starting from *tert*-butyl 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidine-1-carboxylate (A11, 0.10 g, 0.23 mmol) and (3-fluoro-4-nitrophenyl)boronic acid (0.05 g, 0.27 mmol), and was obtained as a yellow solid (0.04 g, 40% yield). LCMS: 458.1 [M-H].

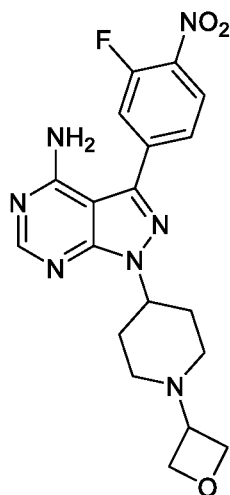
*Step 2: Synthesis of 3-(3-fluoro-4-nitrophenyl)-1-(piperidin-4-yl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine*



TFA (0.5 mL) was added to a solution of *tert*-butyl 4-(4-amino-3-(3-fluoro-4-nitrophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidine-1-carboxylate (100 mg, 0.218 mmol) in dry DCM (5 mL) and the resulting mixture was stirred at room temperature for 2 h. Following completion of the reaction (as indicated by UPLC), the solvent was evaporated under reduced pressure to yield the title product as a pale brown

gum (110 mg) which was taken forward without further purification. LCMS: 358.1 [M-H].

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



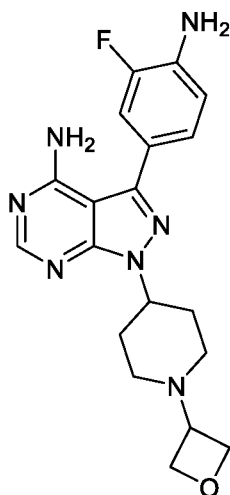
5

Oxetan-3-one (0.020 g, 0.277 mmol) and glacial acetic acid (catalytic amount) were added to a solution of 3-(3-fluoro-4-nitrophenyl)-1-(piperidin-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.100 g, 0.280 mmol) in DCM (5 mL) and the resulting mixture was stirred at room temperature for 4 h. Sodium triacetoxyborohydride (0.178 g, 0.840 mmol) was then added and the resulting mixture was stirred at room temperature for 12 h. Following completion of the reaction (as indicated by UPLC), the solution was diluted with DCM (5 mL) and washed with aqueous 10% NaHCO₃ (5 mL) and brine (5 mL). The organic layer was dried over Na₂SO₄, filtered, and the solvents were evaporated under reduced pressure to yield the title product (110 mg) which was taken forward without further purification. LCMS: 414.2 [M-H].

10

15

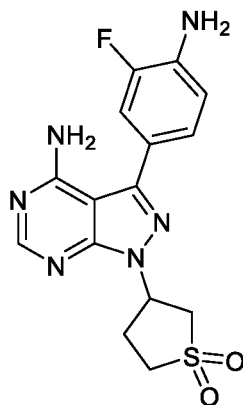
Step 4: Synthesis of 3-(4-amino-3-fluorophenyl)-1-(1-(oxetan-3-yl)piperidin-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine



Iron powder (0.135 g, 2.417 mmol) and ammonium chloride (0.142 g, 2.655 mmol) were added to a solution of 3-(3-fluoro-4-nitrophenyl)-1-(1-(oxetan-3-yl)piperidin-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.110 g, 0.266 mmol) in ethanol (5 mL) and water (2 mL) and the resulting mixture was stirred at 80 °C for 2 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was filtered through a pad of diatomaceous earth which was then rinsed with EtOAc (5 mL × 2). The combined filtrates were concentrated under reduced pressure to give a residue which was dissolved in EtOAc (10 mL) then washed with brine (5 mL). The organic layer separated, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to yield the title compound as an off-white solid (0.05 g, 50% yield) which was taken forward without further purification. LCMS: 383.9 [M+H].

INTERMEDIATE B17

3-(4-AMINO-3-(4-AMINO-3-FLUOROPHENYL)-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-1-
YL)TETRAHYDROTHIOPHENE 1,1-DIOXIDE



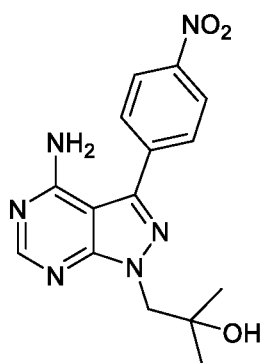
- 5 The title compound was prepared via a similar procedure described for intermediate B1, starting from 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydrothiophene 1,1-dioxide (A12, 0.08 g, 0.21 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.06 g, 0.25 mmol), and was obtained as a yellow gum (0.03 g, 40% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.26 (s, 1H), 7.27-7.31 (m, 1H), 7.20-7.23 (m, 1H), 6.88-6.93 (m, 1H), 5.69 (bs, 2H), 5.53 (bs, 2H), 3.72-3.78 (m, 2H), 3.51-3.56 (m, 2H), 2.61-2.70 (m, 2H). LCMS: 362.8 [M+H].

INTERMEDIATE B18

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

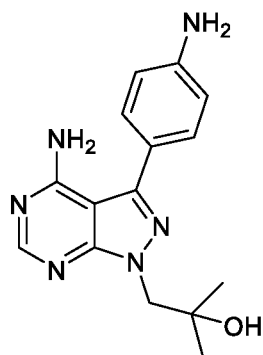
15

Step 1: Synthesis of 1-(4-amino-3-(4-nitrophenyl)-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-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-2-methylpropan-2-ol (A13, 0.067 g, 0.201 mmol) and (4-nitrophenyl)boronic acid (0.054 g, 0.302 mmol), and was obtained as a yellow solid (0.059 g, 90% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.40 (d, *J* = 7.6 Hz, 2H), 8.30 (s, 1H), 7.94 (d, *J* = 6.8 Hz, 2H), 4.32 (bs, 2H), 1.16 (bs, 6H). LCMS: 328.9 [M-H].

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

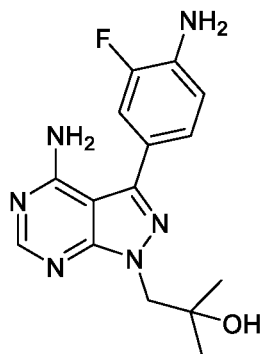


The title compound was prepared via a similar procedure described for step 2 of intermediate B2, starting from 1-(4-amino-3-(4-nitrophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-2-methylpropan-2-ol (0.072 g, 0.219 mmol) and Fe/NH₄Cl, and was obtained as a pale yellow solid (0.07 g, quantitative yield) which was taken forward without further purification. LCMS: 299.0 [M+H].

15

INTERMEDIATE B19

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

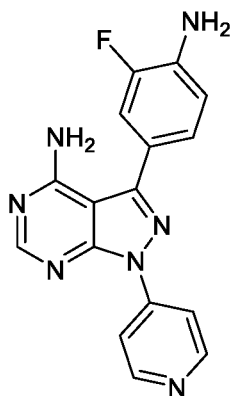


- 5 The title compound was prepared via a similar procedure described for intermediate B1, starting from 1-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-2-methylpropan-2-ol (A13, 0.110 g, 0.330 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.094 g, 0.396 mmol), and was obtained as a pale yellow solid (0.077 g, 66% yield). LCMS: 317.1 [M+H].

10

INTERMEDIATE B20

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



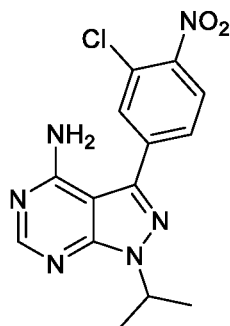
- 15 The title compound was prepared via a similar procedure described for intermediate B1, starting from 3-iodo-1-(pyridin-4-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (A14, 0.250 g, 0.73 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

(0.193 g, 0.81 mmol), and was obtained as a yellow gum (0.140 g, 59% yield). LCMS: 321.9 [M+H].

INTERMEDIATE B21

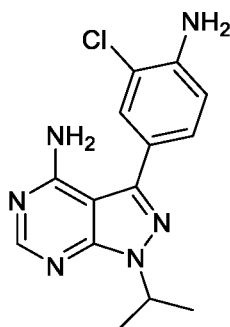
5 3-(4-AMINO-3-CHLOROPHENYL)-1-ISOPROPYL-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-4-AMINE

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



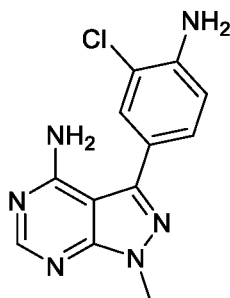
The title compound was prepared via a similar procedure described for intermediate B1, starting from 3-iodo-1-isopropyl-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (A2, 0.115 g, 0.379 mmol) and 2-(3-chloro-4-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.129 g, 0.455 mmol), and was obtained as an off-white solid (0.083 g, 66% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.28 (s, 1H), 8.21-8.23 (m, 1H), 7.95-7.95 (m, 1H), 7.82-7.85 (m, 1H), 5.07-5.13 (m, 1H), 1.51 (d, *J* = 6.4 Hz, 6H). LCMS: 332.9 [M+H].

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



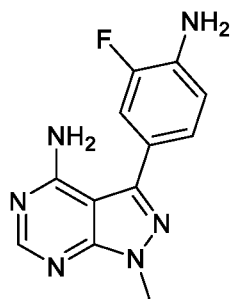
The title compound was prepared via a similar procedure described for step 2 of intermediate B2, starting from 3-(3-chloro-4-nitrophenyl)-1-isopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.083 g, 0.25 mmol) and Fe/NH₄Cl, and was obtained as a pale yellow solid (0.900 g, quantitative yield) which was taken forward without further purification. LCMS: 302.9 [M+H].

INTERMEDIATE B22

3-(4-AMINO-3-CHLOROPHENYL)-1-METHYL-1*H*-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-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (A15, 0.100 g, 0.364 mmol) and 2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.092 g, 0.364 mmol), and was obtained as a yellow solid (0.094 g, 94% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.23 (s, 1H), 7.45-7.46 (m, 1H), 7.31-7.33 (m, 1H), 6.91-6.93 (m, 1H), 5.68 (bs, 2H), 3.91 (s, 3H). LCMS: 275.0[M+H].

INTERMEDIATE B23

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

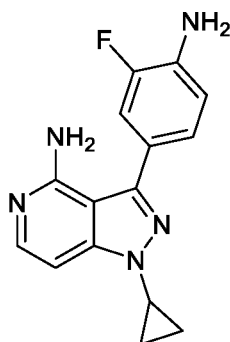
The title compound was prepared via a similar procedure described for intermediate B1, starting from 3-iodo-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B15, 0.110 g,

0.400 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.104 g, 0.440 mmol), and was obtained as a brown gum (0.130 g, 97% yield). LCMS: 259.1[M+H].

5

INTERMEDIATE B24

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



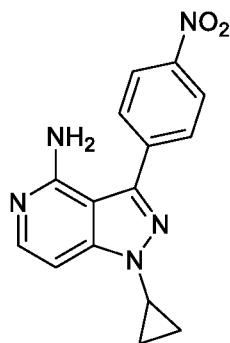
The title compound was prepared via a similar procedure described for intermediate B1, starting from 1-cyclopropyl-3-iodo-1*H*-pyrazolo[4,3-*c*]pyridin-4-amine (A16, 0.190 g, 0.63 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.180 g, 0.75 mmol), and was obtained as a yellow gum (0.070 g, 39% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.75-7.76 (m, 1H), 7.21-7.24 (m, 1H), 7.14-7.16 (m, 2H), 6.85-6.87 (m, 1H), 5.78 (bs, 2H), 5.46 (bs, 2H), 3.67-3.69 (m, 1H), 1.09-1.10 (m, 4H). LCMS: 317.1 [M+H].

15

INTERMEDIATE B25

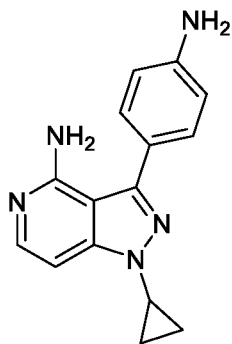
3-(4-AMINOPHENYL)-1-CYCLOPROPYL-1*H*-PYRAZOLO[4,3-*C*]PYRIDIN-4-AMINE

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



The title compound was prepared via a similar procedure described for intermediate B1, starting from 1-cyclopropyl-3-iodo-1*H*-pyrazolo[4,3-*c*]pyridin-4-amine (A16, 0.190 g, 0.63 mmol) and (4-nitrophenyl)boronic acid (0.126 g, 0.75 mmol), and was obtained as a pale yellow solid (0.090 g, 50% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.36-8.39 (m, 2H), 7.93-7.96 (m, 2H), 7.84 (d, *J* = 6.0 Hz, 1H), 6.95 (d, *J* = 6.0 Hz, 1H), 5.98 (bs, 2H), 3.78-3.81 (m, 1H), 1.13-1.16 (m, 4H). LCMS: 296.1 [M+H].

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

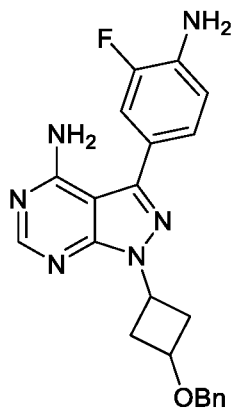


The title compound was prepared via a similar procedure described for step 2 of intermediate B2, starting from 1-cyclopropyl-3-(4-nitrophenyl)-1*H*-pyrazolo[4,3-*c*]pyridin-4-amine (0.093 g, 0.31 mmol) and Fe/NH₄Cl, and was obtained as a pale yellow solid (0.052 g, 63% yield) which was taken forward without further purification. LCMS: 266.0 [M+H].

15

INTERMEDIATE B26

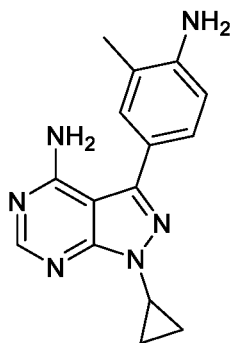
3-(4-AMINO-3-FLUOROPHENYL)-1-(3-(BENZYLOXY)CYCLOBUTYL)-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-4-AMINE



- 5 A mixture of 1-(3-(benzyloxy)cyclobutyl)-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (A17, 0.400 g, 0.712 mmol), 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.186 g, 0.783 mmol), and K₂CO₃ (0.197 g, 1.424 mmol) in dioxane (7 mL), ethanol (3 mL), and water (3 mL) was purged with N₂ for 10 minutes. PdCl₂(dppf) (0.026 g, 0.036 mmol) was then added and the resulting mixture was again purged with N₂ for
- 10 10 minutes then stirred at 80 °C for 16 h in a sealed tube. Following completion of the reaction (as indicated by TLC and LCMS), the reaction mixture was filtered through a pad of diatomaceous earth which was then rinsed with EtOAc (3 × 10 mL × 3). 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 4% MeOH
- 15 in DCM), affording the title compound as a pale brown solid (0.179 g, 62% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.21 (s, 1H), 7.20-7.40 (m, 7H), 6.89-6.93 (m, 1H), 5.42-5.48 (m, 3H), 4.47-4.48 (m, 3H), 2.74-2.83 (m, 2H), 2.60 (s, 2H). LCMS: 405.1 [M+H].

INTERMEDIATE B27

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

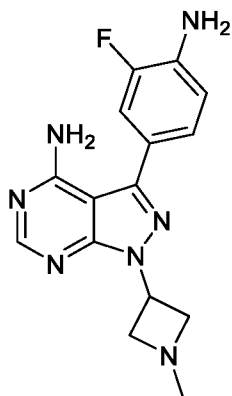


- 5 The title compound was prepared via a similar procedure described for intermediate B26, starting from 1-cyclopropyl-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (A1, 0.250 g, 0.830 mmol) and 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.213 g, 0.913 mmol), and was obtained as a brown gum (0.22 g) which was taken forward without further purification. LCMS: 281.3 [M+H]

10

INTERMEDIATE B28

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

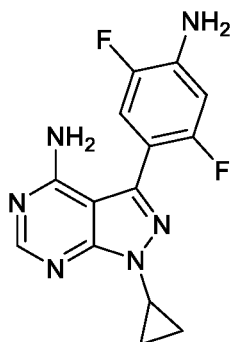


- 15 The title compound was obtained by following a similar procedure described for intermediate B26, starting from 3-iodo-1-(1-methylazetidin-3-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (A18, 0.380 g, 1.151 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-

1,3,2-dioxaborolan-2-yl)aniline (0.300 g, 1.266 mmol), and was obtained as a brown solid (0.26 g, 48% yield). LCMS: 314.4 [M+H].

INTERMEDIATE B29

- 5 3-(4-AMINO-2,5-DIFLUOROPHENYL)-1-CYCLOPROPYL-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-4-AMINE

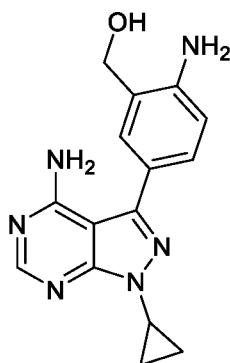


- The title compound was obtained by following a similar procedure described for intermediate B26, starting from 1-cyclopropyl-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (A1, 0.165 g, 0.548 mmol) and 2,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (prepared as described in PCT Pub. No. WO 2020/172093, 0.300 g, 1.266 mmol), and was obtained as a pale yellow solid (0.051 g, 27% yield). LCMS: 303.2 [M+H].
- 10

15

INTERMEDIATE B30

- (2-AMINO-5-(4-AMINO-1-CYCLOPROPYL-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)PHENYL)METHANOL



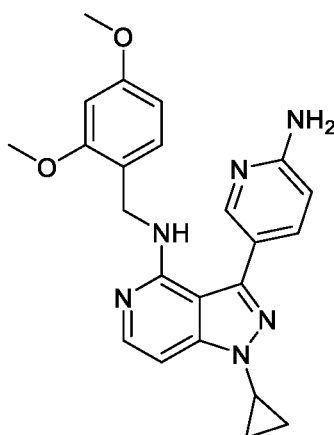
The title compound was obtained by following a similar procedure described for intermediate B26, starting from 1-cyclopropyl-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (A1, 0.250 g, 0.830 mmol) and (2-amino-5-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)phenyl)methanol (prepared as described in PCT Pub. No. WO 2011/8130628, 0.207 g, 0.830 mmol), and was obtained as a pale pink solid (0.122 g, 47% yield). LCMS: 297.1 [M+H].

INTERMEDIATE B31

3-(6-AMINOPYRIDIN-3-YL)-1-CYCLOPROPYL-*N*-(2,4-DIMETHOXYBENZYL)-1*H*-

10

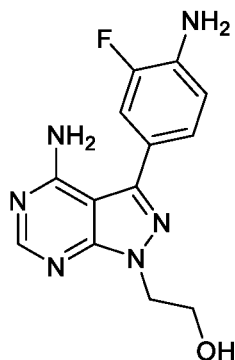
PYRAZOLO[4,3-*C*]PYRIDIN-4-AMINE



The title compound was obtained by following a similar procedure described for intermediate B26, starting from 1-cyclopropyl-*N*-(2,4-dimethoxybenzyl)-3-iodo-1*H*-pyrazolo[4,3-*c*]pyridin-4-amine (A19, 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 B32

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

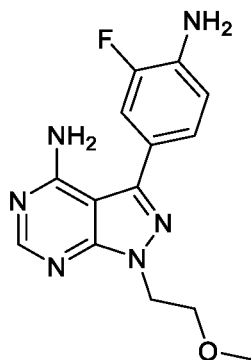


- 5 The title compound was obtained by following a similar procedure described for intermediate B26, starting from 2-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethan-1-ol (A20, 0.420 g, 1.377 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.327 g, 1.379 mmol), and was obtained as a brown solid (0.390 g, 92% yield). LCMS: 289.1 [M+H].

10

INTERMEDIATE B33

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

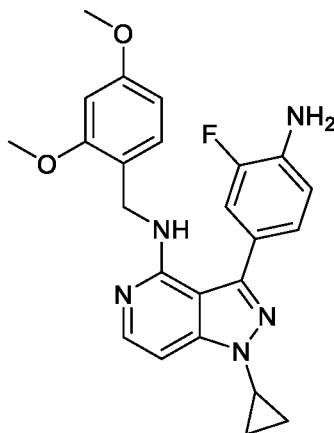


- 15 The title compound was obtained by following a similar procedure described for intermediate B26, starting from 3-iodo-1-(2-methoxyethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (A21, 0.620 g, 1.943 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-

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].

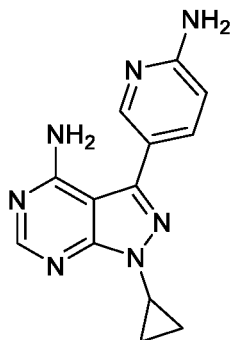
INTERMEDIATE B34

5 3-(4-AMINO-3-FLUOROPHENYL)-1-CYCLOPROPYL-*N*-(2,4-DIMETHOXYBENZYL)-1*H*-
PYRAZOLO[4,3-*C*]PYRIDIN-4-AMINE



The title compound was obtained by following a similar procedure described for intermediate B26, starting from 1-cyclopropyl-*N*-(2,4-dimethoxybenzyl)-3-iodo-1*H*-
10 pyrazolo[4,3-*c*]pyridin-4-amine (A19, 0.600 g, 1.333 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.316 g, 1.333 mmol), and was obtained as a brown solid (0.43 g, 72% yield). ¹H 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, 7H),
15 1.08-1.09 (m, 4H). LCMS: 434.2 [M+H].

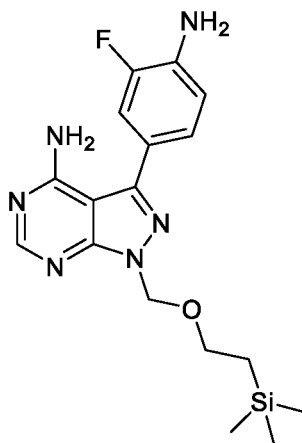
INTERMEDIATE B35

3-(6-AMINOPYRIDIN-3-YL)-1-CYCLOPROPYL-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-4-AMINE

The title compound was obtained by following a similar procedure described for
 5 intermediate B26, starting from 1-cyclopropyl-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (A1, 0.250 g, 0.830 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (0.183 g, 0.830 mmol), and was obtained as a brown solid (0.085 g, 38% yield). LCMS: 268.6 [M+H].

10

INTERMEDIATE B36

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

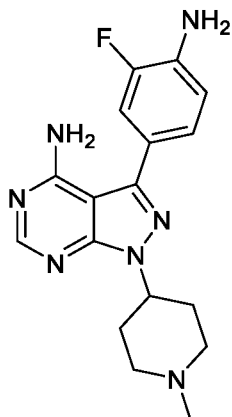
The title compound was obtained by following a similar procedure described for
 15 intermediate B26, starting from 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (A22, 0.500 g, 1.278 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.454 g, 1.917 mmol), and was obtained as

a brown solid (0.16 g, 30% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.26 (s, 1H), 7.20-7.27 (m, 2H), 6.88-6.93 (m, 1H), 5.62 (s, 2H), 5.52 (bs, 2H), 3.62 (t, *J* = 8.0 Hz, 2H), 0.84 (t, *J* = 8.0 Hz, 2H), -0.12 (s, 9H). LCMS: 375.4 [M+H].

5

INTERMEDIATE B37

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



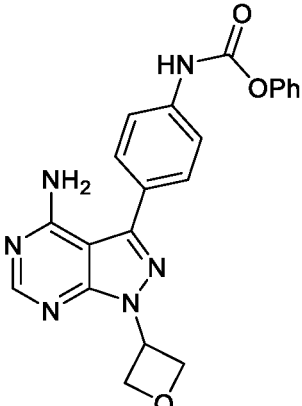
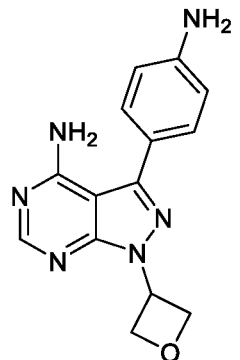
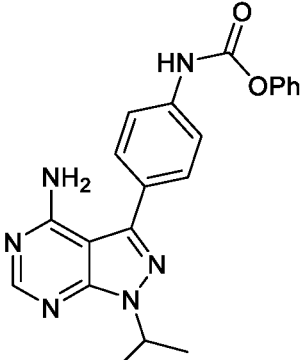
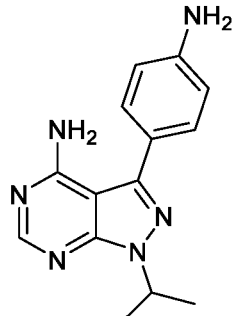
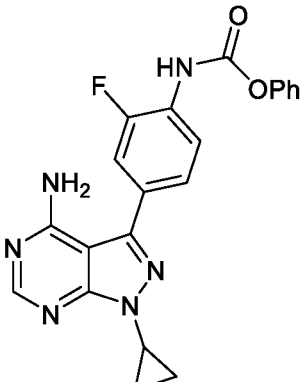
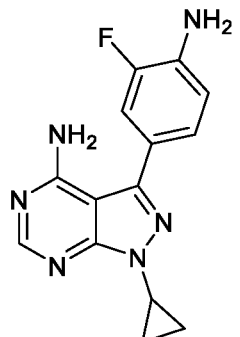
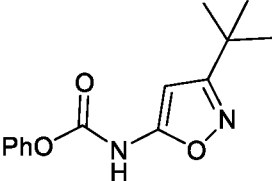
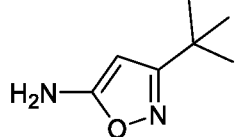
The title compound was obtained by following a similar procedure described for
 10 intermediate B26, starting from 3-iodo-1-(1-methylpiperidin-4-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (A23, 0.180 g, 0.503 mmol) and 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.131 g, 0.553 mmol), and was obtained as a brown solid (0.22 g, 72% yield). LCMS: 342.2 [M+H].

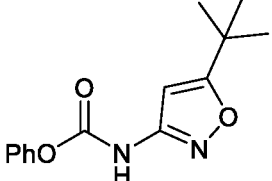
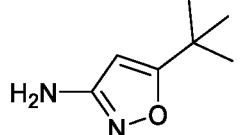
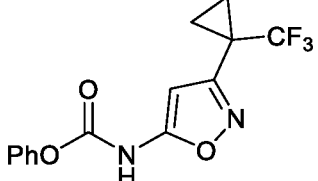
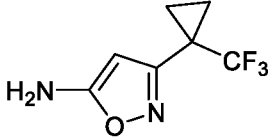
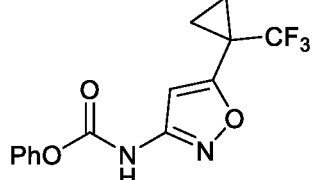
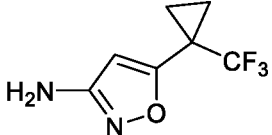
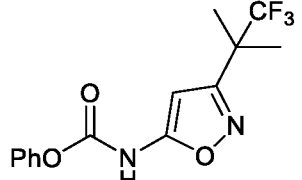
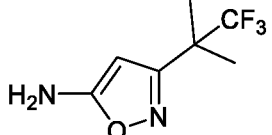
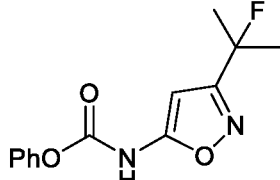
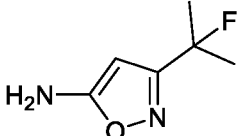
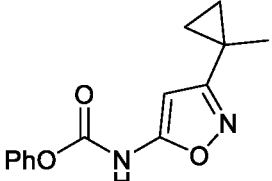
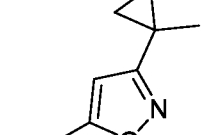
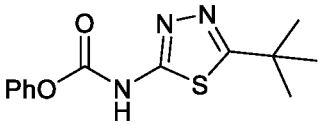
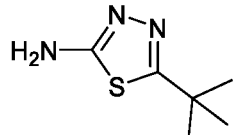
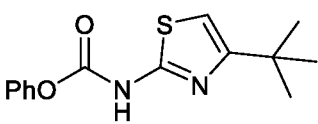
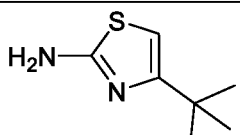
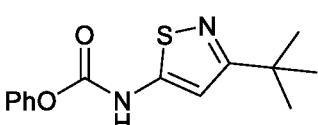
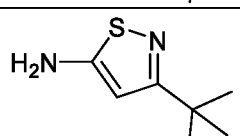
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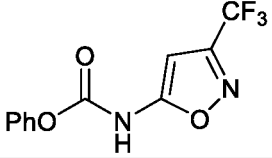
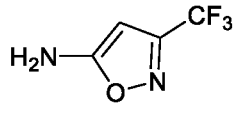
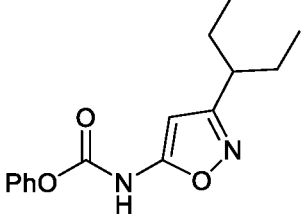
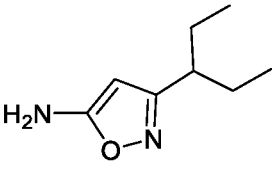
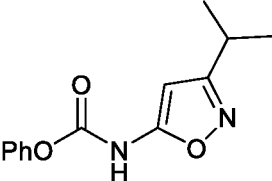
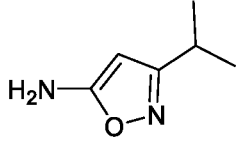
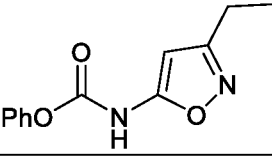
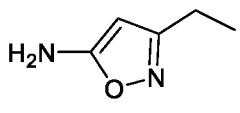
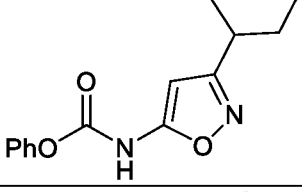
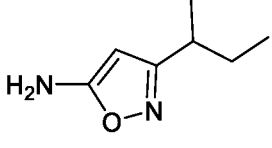
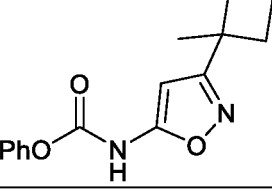
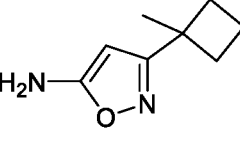
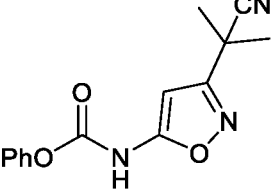
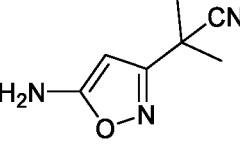
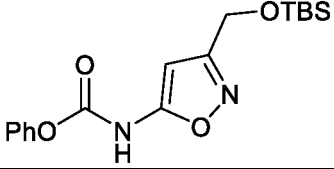
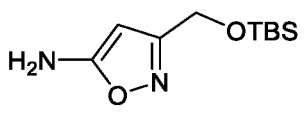
General procedure for the synthesis of carbamates Intermediates C

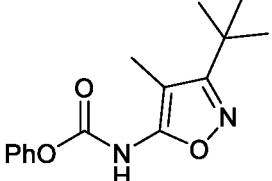
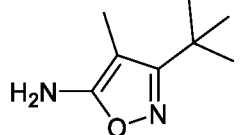
Pyridine (1.2 eq) and phenyl chloroformate (1.5 eq) were added to a solution of amine (1.0 eq) in THF (10 vol) at 0 °C. The reaction mixture was allowed to warm to 25 °C and was stirred for 12 h. Following completion of the reaction (as indicated by TLC),
 20 the mixture was diluted with EtOAc (10 mL) and washed with brine (5 mL). The organic layer was dried over Na₂SO₄, 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), affording the desired carbamate.

The following carbamates were prepared using the above general procedure.

Carbamate	Structure	Starting material	¹ H NMR/LCMS
C1			403.1 [M+H]
C2			389.1 [M+H]
C3			405.2 [M+H]
C4			261.0 [M+H]

Carbamate	Structure	Starting material	¹ H NMR/LCMS
C5			261.0 [M+H]
C6			312.9 [M+H]
C7			312.9 [M+H]
C8			315.1 [M+H]
C9			265.1 [M+H]
C10			259.1 [M+H]
C11			278.0 [M+H]
C12			277.1 [M+H]
C13			277.1 [M+H]

Carbamate	Structure	Starting material	¹ H NMR/LCMS
C14			270.9 [M-H]
C15			273.0 [M-H]
C16			247.1 [M+H]
C17			233.0 [M+H]
C18			261.0 [M+H]
C19			272.5 [M+H]
C20			272.5 [M+H]
C21			349.6 [M+H]

Carbamate	Structure	Starting material	¹ H NMR/LCMS
C22			274.9 [M+H]

Note: Amines used for the synthesis of carbamates are either commercially available or were synthesized using literature procedures as follows:

3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-amine (precursor to C6) and 5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-amine (precursor to C7) were synthesized from 1-(trifluoromethyl)cyclopropane-1-carboxylic acid methyl ester as reported in Synthesis 2013, 45, 171–173.

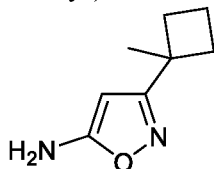
3-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-5-amine (precursor to C8) and 3-(2-fluoropropan-2-yl)isoxazol-5-amine (precursor to C9) were synthesized from methyl 3,3,3-trifluoro-2,2-dimethylpropanoate and methyl 2-fluoro-2-methylpropanoate, respectively, followed by the procedure reported in Synthesis 2013, 45, 171–173.

2-(5-Aminoisoxazol-3-yl)-2-methylpropanenitrile (precursor to C20) was synthesized from 2,2-dimethyl-3-oxopentanedinitrile as reported in J. Med. Chem. 2012, 55, 1082–1105.

3-(((*Tert*-butyldimethylsilyl)oxy)methyl)isoxazol-5-amine (precursor to C21) was synthesized from 4-(((*tert*-butyldiphenylsilyl)oxy)-3-oxobutanenitrile as reported in PCT Pub. No. WO 2013/104561.

3-(*Tert*-butyl)-4-methylisoxazol-5-amine (precursor to C22) was synthesized from 2,4,4-trimethyl-3-oxopentanenitrile as reported in PCT Pub. No. WO 2012/019015.

Synthesis of 3-(1-methylcyclobutyl)isoxazol-5-amine (precursor to C19):



NH₂OH·H₂SO₄ (0.699 g, 4.25 mmol) was added to a stirred solution of 3-(1-methylcyclobutyl)-3-oxopropanenitrile (prepared as reported in PCT Pub. No. WO 2017/060874, 0.500 g, 3.86 mmol) and sodium hydroxide (0.170 g, 4.25 mmol) in EtOH (10 mL) and water (10 mL). The pH of the resulting mixture was adjusted to 7.5 using aqueous NaOH (1 M) and the reaction mixture was stirred at 80 °C for 15 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was concentrated under reduced pressure, giving a residue which was taken in DCM (25 mL), washed with water (10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude material was purified by flash chromatography (silica gel 230-400 mesh, eluting with 40% EtOAc in petroleum ether) to afford the title product as an off-white solid (0.110 g, 19% yield). ¹H NMR (400 MHz, CDCl₃) δ = 5.04 (s, 1H), 2.43-2.49 (m, 2H), 1.96-2.02 (m, 4H), 1.50 (s, 3H). LCMS: 153.2 [M+H].

PREPARATION OF EXAMPLES

General urea formation procedure for the synthesis of Examples 1-72

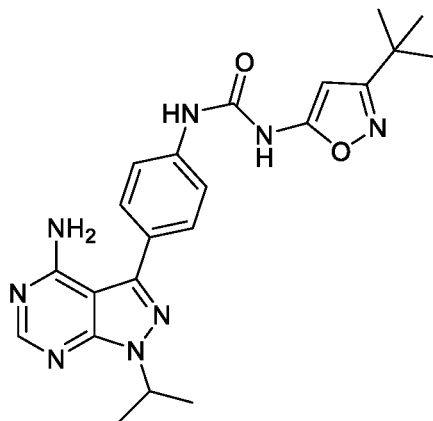
Method A – Triethylamine (2.0 eq.) was added to a mixture of amine Intermediate D (1.0 eq.) and carbamate Intermediate E (1.0 eq.) in THF (10 Vol.) and the resulting mixture was stirred at 60 °C for 12 h in a sealed tube. Following completion of the reaction (as indicated by LCMS), the reaction mixture was concentrated under reduced pressure to give crude material which was purified by reverse phase preparative HPLC to afford the desired product.

Method B – DMAP (0.05 eq.) and DIPEA (1.5 eq.) were added to a solution of amine Intermediate D (1.0 eq.) and carbamate Intermediate E (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 the crude material which was purified by reverse phase preparative HPLC to afford the desired product.

The following compounds were prepared using the above general procedures.

EXAMPLE 1

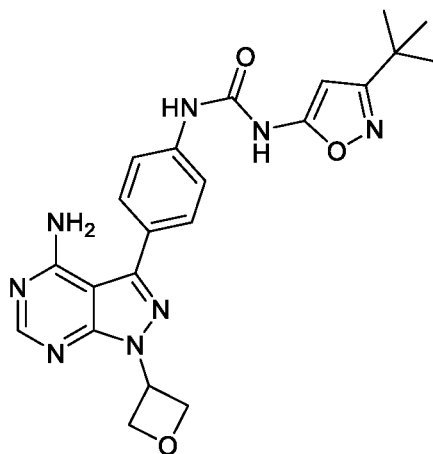
1-(4-(4-AMINO-1-ISOPROPYL-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)PHENYL)-3-(3-(*TERT*-BUTYL)ISOXAZOL-5-YL)UREA



- 5 The title compound was prepared following the general procedure for urea formation (Method A), starting from 3-(4-aminophenyl)-1-isopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B2, 0.250 g, 0.93 mmol) and phenyl (3-(tert-butyl)isoxazol-5-yl)carbamate (C4, 0.242 g, 0.93 mmol), and was obtained as an off-white solid (0.150 g, 37% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.15 (bs, 1H), 9.09 (bs, 1H), 8.24 (bs, 1H), 7.55-7.66 (m, 4H), 6.10 (s, 1H), 5.03-5.10 (m, 1H), 1.49 (d, *J* = 6.4 Hz, 6H), 1.27 (s, 9H). LCMS: 435.3 [M+H].
- 10

EXAMPLE 2

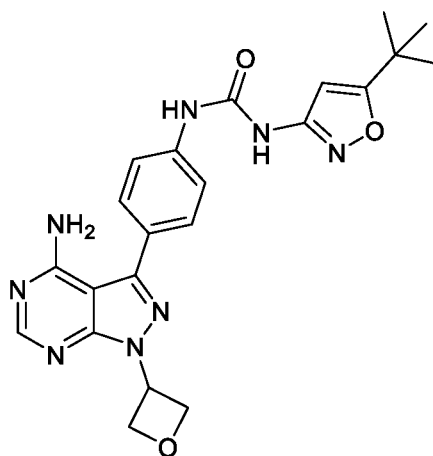
1-(4-(4-AMINO-1-(OXETAN-3-YL)-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)PHENYL)-3-(3-(*TERT*-BUTYL)ISOXAZOL-5-YL)UREA



The title compound was prepared following the general procedure for urea formation (Method A), starting from 3-(4-aminophenyl)-1-(oxetan-3-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B4, 0.210 g, 0.744 mmol) and phenyl (3-(*tert*-butyl)isoxazol-5-yl)carbamate (C4, 0.193 g, 0.744 mmol), and was obtained as an off-white solid (0.053 g, 16% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.23 (bs, 1H), 9.15 (bs, 1H), 8.31 (s, 1H), 7.74 (s, 4H), 6.16 (s, 1H), 6.06-6.10 (m, 1H), 5.16 (t, *J* = 6.4 Hz, 2H), 5.05 (t, *J* = 6.8 Hz, 2H), 1.33 (s, 9H). LCMS: 449.2[M+H].

EXAMPLE 3

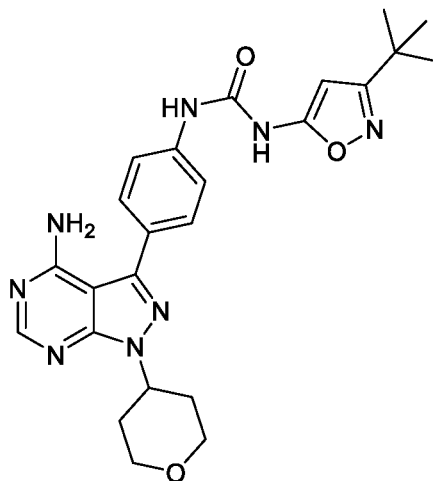
1-(4-(4-AMINO-1-(OXETAN-3-YL)-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)PHENYL)-3-(5-(*TERT*-BUTYL)ISOXAZOL-3-YL)UREA



The title compound was prepared following the general procedure for urea formation (Method A), starting from 3-(4-aminophenyl)-1-(oxetan-3-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B4, 0.070 g, 0.248 mmol) and phenyl (5-(*tert*-butyl)isoxazol-3-yl)carbamate (C5, 0.065 g, 0.248 mmol), and was obtained as an off-white solid (0.035 g, 32% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.59 (bs, 1H), 9.07 (bs, 1H), 8.26 (s, 1H), 7.66 (bs, 4H), 6.53 (s, 1H), 5.98-6.04 (m, 1H), 5.09 (t, *J* = 6.4 Hz, 2H), 5.00 (t, *J* = 6.8 Hz, 2H), 1.31 (s, 9H). LCMS: 449.2[M+H].

EXAMPLE 4

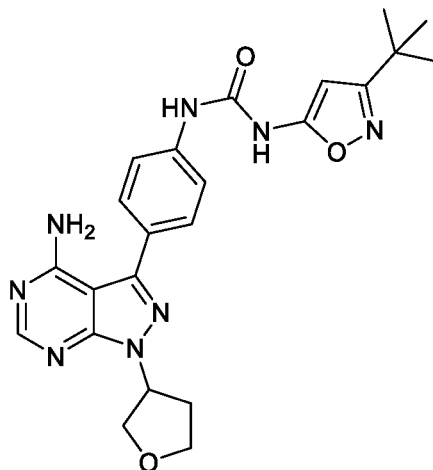
1-(4-(4-AMINO-1-(TETRAHYDRO-2*H*-PYRAN-4-YL)-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)PHENYL)-3-(3-(*tert*-BUTYL)ISOXAZOL-5-YL)UREA



- 5 The title compound was prepared following the general procedure for urea formation (Method A), starting from 3-(4-aminophenyl)-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B12, 0.05 g, 0.16 mmol) and phenyl (3-(*tert*-butyl)isoxazol-5-yl)carbamate (C4, 0.042 g, 0.16 mmol), and was obtained as an off-white solid (0.013 g, 20% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.13 (bs, 1H), 9.08 (bs, 1H), 8.25 (s, 1H), 7.61-7.67 (m, 4H), 6.10 (s, 1H), 4.90-4.98 (m, 1H), 4.00-4.03 (m, 2H), 3.53-3.58 (m, 2H), 2.19-2.26 (m, 2H), 1.87-1.91 (m, 2H), 1.27 (s, 9H). LCMS: 477.1[M+H].
- 10

EXAMPLE 5

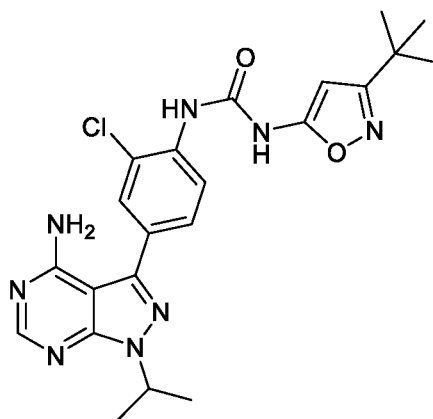
1-(4-(4-AMINO-1-(TETRAHYDROFURAN-3-YL)-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)PHENYL)-3-(3-(*tert*-BUTYL)ISOXAZOL-5-YL)UREA



- 5 The title compound was prepared following the general procedure for urea formation (Method A), starting from 3-(4-aminophenyl)-1-(tetrahydrofuran-3-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B10, 0.083 g, 0.28 mmol) and phenyl 3-(*tert*-butyl)isoxazol-5-yl)carbamate (C4, 0.072 g, 0.28 mmol), and was obtained as a white solid (0.048 g, 36% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.17 (bs, 1H), 9.08 (bs, 1H), 8.26 (s, 1H),
 10 7.60-7.67 (m, 4H), 6.10 (s, 1H), 5.49-5.52 (m, 1H), 4.07-4.14 (m, 2H), 3.89-3.97 (m, 2H), 2.38-2.43 (m, 2H), 1.27 (s, 9H). LCMS: 463.0[M+H].

EXAMPLE 6

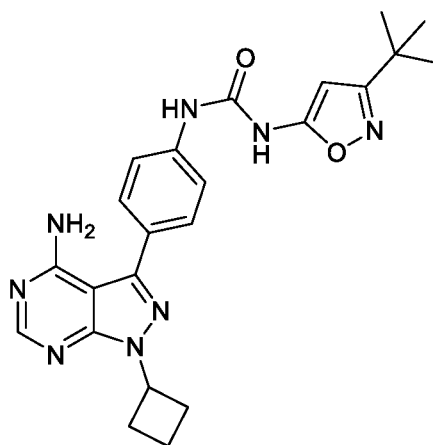
1-(4-(4-AMINO-1-ISOPROPYL-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-CHLOROPHENYL)-3-(3-(*tert*-BUTYL)ISOXAZOL-5-YL)UREA



The title compound was prepared following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-chlorophenyl)-1-isopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B21, 0.080 g, 0.264 mmol) and phenyl (3-(*tert*-butyl)isoxazol-5-yl)carbamate (C4, 0.067 g, 0.264 mmol), and was obtained as an off-white solid (0.003 g, 3% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.85 (bs, 1H), 8.66 (bs, 1H), 8.35 (d, *J* = 8.4 Hz, 1H), 8.25 (s, 1H), 7.72 (d, *J* = 2.0 Hz, 1H), 7.61-7.64 (m, 1H), 6.12 (s, 1H), 5.04-5.10 (m, 1H), 1.50 (d, *J* = 6.8 Hz, 6H), 1.28 (s, 9H). LCMS: 469.1[M+H].

EXAMPLE 7

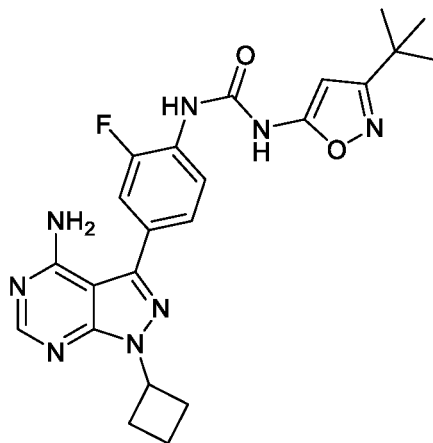
1-(4-(4-AMINO-1-CYCLOBUTYL-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)PHENYL)-3-(3-(*tert*-BUTYL)ISOXAZOL-5-YL)UREA



The title compound was prepared following the general procedure for urea formation (Method A), starting from 3-(4-aminophenyl)-1-cyclobutyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B8, 0.140 g, 0.49 mmol) and phenyl (3-(*tert*-butyl)isoxazol-5-yl)carbamate (C4, 0.130 g, 0.49 mmol), and was obtained as an off-white solid (0.067 g, 29% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.15 (bs, 1H), 9.09 (bs, 1H), 8.24 (s, 1H), 7.62-7.68 (m, 4H), 6.10 (s, 1H), 5.32-5.36 (m, 1H), 2.69-2.74 (m, 2H), 2.39-2.42 (m, 2H), 1.87-1.89 (m, 2H), 1.27 (s, 9H). LCMS: 447.2[M+H].

EXAMPLE 8

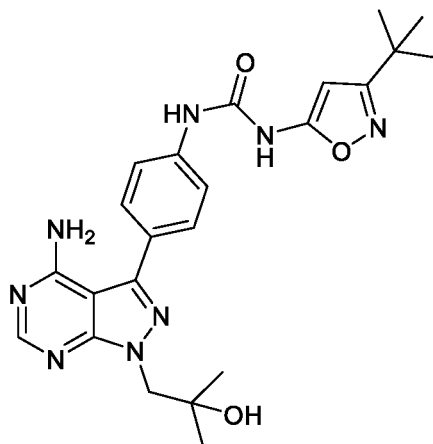
1-(4-(4-AMINO-1-CYCLOBUTYL-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(*TERT*-BUTYL)ISOXAZOL-5-YL)UREA



- 5 The title compound was prepared following the general procedure for urea formation (Method A), starting from 3-(4-aminophenyl)-1-cyclobutyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B9, 0.100 g, 0.33 mmol] and phenyl (3-(*tert*-butyl)isoxazol-5-yl)carbamate (C4, 0.087 g, 0.33 mmol), and was obtained as a pale yellow solid (0.005 g, 4% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.10 (bs, 1H), 8.23-8.28 (m, 2H), 7.47-7.53 (m, 2H), 6.90 (bs, 1H), 6.09 (s, 1H), 5.29-5.37 (m, 1H), 2.67-2.73 (m, 2H), 2.38-2.41 (m, 2H), 1.85-1.89 (m, 2H), 1.26 (s, 9H). LCMS: 465.1[M+H].
- 10

EXAMPLE 9

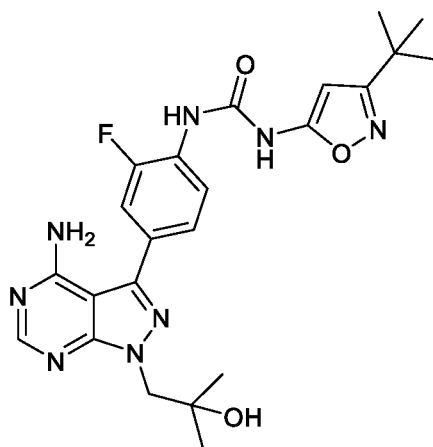
1-(4-(4-AMINO-1-(2-HYDROXY-2-METHYLPROPYL)-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)PHENYL)-3-(3-(*TERT*-BUTYL)ISOXAZOL-5-YL)UREA



The title compound was prepared following the general procedure for urea formation (Method A), starting from 1-(4-amino-3-(4-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-2-methylpropan-2-ol (B18, 0.119 g, 0.4 mmol) and phenyl (3-(*tert*-butyl)isoxazol-5-yl)carbamate (C4, 0.103 g, 0.4 mmol), and was obtained as an off-white solid (0.017 g, 9% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.44 (bs, 1H), 8.24 (s, 1H), 7.59-7.68 (m, 4H), 6.07 (s, 1H), 4.81 (bs, 1H), 4.27 (bs, 2H), 1.26 (s, 9H), 1.15 (s, 6H). LCMS: 465.1[M+H].

EXAMPLE 10

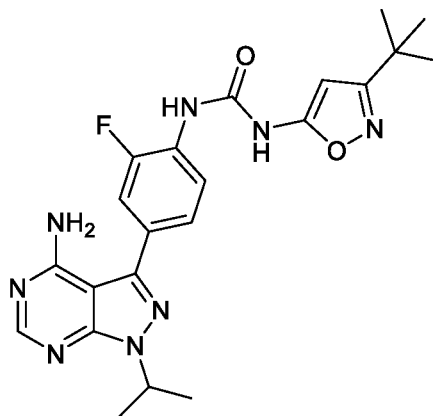
1-(4-(4-AMINO-1-(2-HYDROXY-2-METHYLPROPYL)-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-
YL)-2-FLUOROPHENYL)-3-(3-(*TERT*-BUTYL)ISOXAZOL-5-YL)UREA



The title compound was prepared following the general procedure for urea formation (Method A), starting from 1-(4-amino-3-(4-amino-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-2-methylpropan-2-ol (B19, 0.077 g, 0.243 mmol) and phenyl (3-(*tert*-butyl)isoxazol-5-yl)carbamate (C4, 0.063 g, 0.243 mmol), and was obtained as an off-white solid (0.013 g, 11% yield). ¹H NMR (400 MHz, CD₃OD) δ = 8.33-8.37 (m, 1H), 8.29 (s, 1H), 7.53-7.59 (m, 2H), 6.19 (s, 1H), 4.42 (s, 2H), 1.35 (s, 9H), 1.29 (s, 6H). LCMS: 483.3[M+H].

EXAMPLE 11

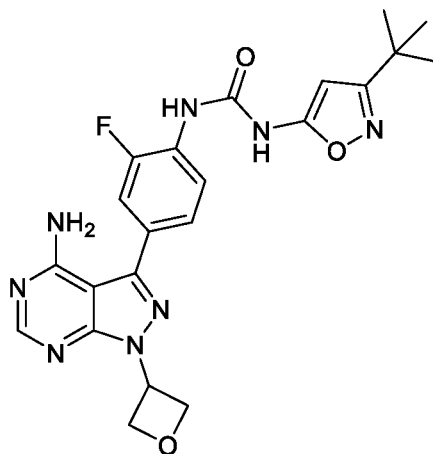
1-(4-(4-AMINO-1-ISOPROPYL-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-
3-(3-(*TERT*-BUTYL)ISOXAZOL-5-YL)UREA



- 5 The title compound was prepared following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-isopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B3, 0.200 g, 0.69 mmol) and phenyl 3-(*tert*-butyl)isoxazol-5-yl)carbamate (C4, 0.182 g, 0.69 mmol), and was obtained as an off-white solid (0.011 g, 3% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.40 (bs, 1H), 8.93 (bs, 1H), 8.24-8.30 (m, 2H), 7.47-7.52 (m, 2H), 6.95 (bs, 2H), 6.11 (s, 1H), 5.03-5.10 (m, 1H), 1.49 (d, *J* = 6.4 Hz, 6H), 1.27 (s, 9H). LCMS: 453.2[M+H].
- 10

EXAMPLE 12

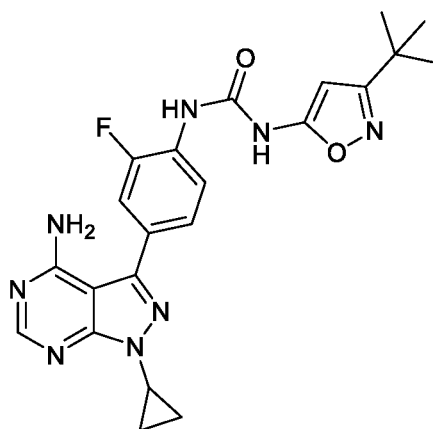
1-(4-(4-AMINO-1-(OXETAN-3-YL)-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-
FLUOROPHENYL)-3-(3-(*TERT*-BUTYL)ISOXAZOL-5-YL)UREA



The title compound was prepared following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-(oxetan-3-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B5, 0.200 g, 0.66 mmol) and phenyl (3-(*tert*-butyl)isoxazol-5-yl)carbamate (C4, 0.173 g, 0.66 mmol), and was obtained as an off-white solid (0.027 g, 10% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.97 (bs, 1H), 8.29-8.33 (m, 1H), 8.25 (s, 1H), 7.52-7.59 (m, 2H), 6.11 (s, 1H), 5.98-6.05 (m, 1H), 5.01-5.11 (m, 2H), 4.98-4.99 (m, 2H), 1.27 (s, 9H). LCMS: 467.1[M+H].

EXAMPLE 13

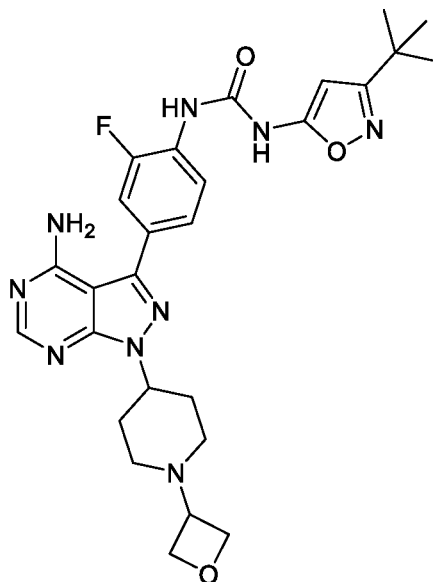
10 1-(4-(4-AMINO-1-CYCLOPROPYL-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(*tert*-BUTYL)ISOXAZOL-5-YL)UREA



The title compound was prepared following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-cyclopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B1, 0.150 g, 0.52 mmol) and phenyl (3-(*tert*-butyl)isoxazol-5-yl)carbamate (C4, 0.137 g, 0.52 mmol), and was obtained as a white solid (0.035 g, 15% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.42 (bs, 1H), 8.98 (bs, 1H), 8.25-8.29 (m, 2H), 7.44-7.50 (m, 2H), 6.95 (bs, 2H), 6.10 (s, 1H), 3.85-3.87 (m, 1H), 1.27 (s, 9H), 1.20-1.23 (m, 2H), 1.08-1.10 (m, 2H). LCMS: 451.2[M+H].

EXAMPLE 14

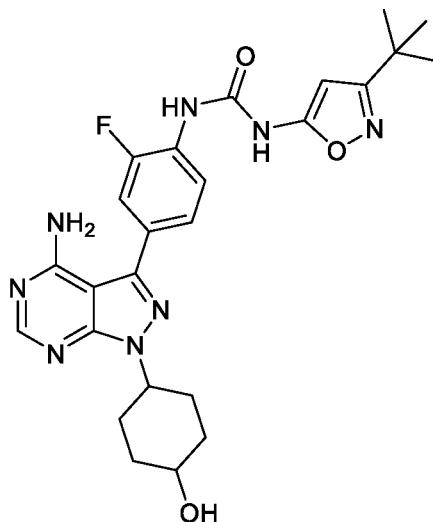
1-(4-(4-AMINO-1-(1-(OXETAN-3-YL)PIPERIDIN-4-YL)-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(*TERT*-BUTYL)ISOXAZOL-5-YL)UREA



- 5 The title compound was prepared following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-(1-(oxetan-3-yl)piperidin-4-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B16, 0.050 g, 0.13 mmol) and phenyl (3-(*tert*-butyl)isoxazol-5-yl)carbamate (C4, 0.034 g, 0.13 mmol), and was obtained as an off-white solid (0.006 g, 8% yield). ¹H NMR (400 MHz, CD₃OD) δ = 8.32-8.36 (m, 1H), 8.27 (s, 1H), 7.51-7.57 (m, 2H), 6.19 (s, 1H), 4.65-4.82 (m, 5H), 3.61-3.64 (m, 1H), 2.98-3.01 (m, 2H), 2.37-2.44 (m, 2H), 2.13-2.19 (m, 2H), 2.04-2.07 (m, 2H), 1.35 (s, 9H). LCMS: 550.0[M+H].
- 10

EXAMPLE 15

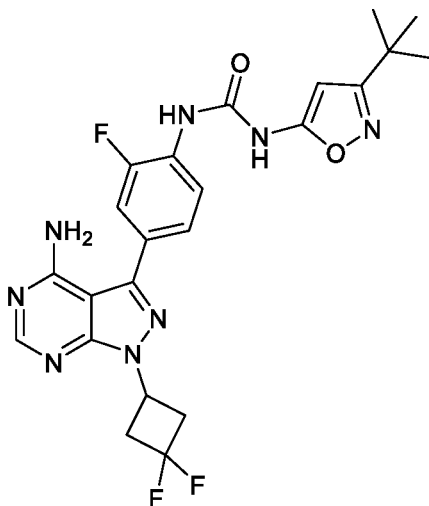
1-(4-(4-AMINO-1-(4-HYDROXYCYCLOHEXYL)-1H-PYRAZOLO[3,4-D]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(*tert*-BUTYL)ISOXAZOL-5-YL)UREA



- 5 The title compound was prepared following the general procedure for urea formation (Method A), starting from 4-(4-amino-3-(4-amino-3-fluorophenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)cyclohexan-1-ol (B15, 0.075 g, 0.22 mmol) and phenyl 3-(*tert*-butyl)isoxazol-5-yl)carbamate (C4, 0.057 g, 0.22 mmol), and was obtained as an off-white solid (0.007 g, 6% yield). ¹H NMR (400 MHz, CD₃OD) δ = 8.32-8.36 (m, 1H), 8.27 (s, 1H), 7.50-7.55 (m, 2H), 6.19 (s, 1H), 4.74-4.80 (m, 1H), 3.72-3.73 (m, 1H), 2.14-2.21 (m, 4H), 2.03-2.06 (m, 2H), 1.55-1.59 (m, 2H), 1.35 (s, 9H). LCMS: 509.2[M+H].
- 10

EXAMPLE 16

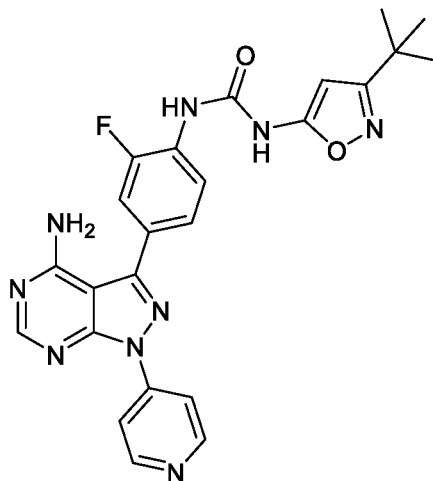
1-(4-(4-AMINO-1-(3,3-DIFLUOROCYCLOBUTYL)-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-
2-FLUOROPHENYL)-3-(3-(*tert*-BUTYL)ISOXAZOL-5-YL)UREA



- 5 The title compound was prepared following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-(3,3-difluorocyclobutyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B14, 0.110 g, 0.33 mmol) and phenyl (3-(*tert*-butyl)isoxazol-5-yl)carbamate (C4, 0.086 g, 0.33 mmol), and was obtained as an off-white solid (0.020 g, 13% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.28 (bs, 1H), 8.26-8.30 (m, 2H), 7.48-7.55 (m, 2H), 7.08 (bs, 1H), 6.07 (s, 1H), 5.28-5.33 (m, 1H), 3.25-3.34 (m, 4H), 1.27 (s, 9H). LCMS: 501.1[M+H].
- 10

EXAMPLE 17

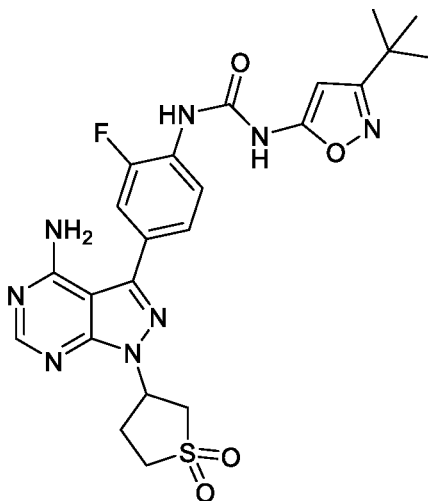
1-(4-(4-AMINO-1-(PYRIDIN-4-YL)-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(*TERT*-BUTYL)ISOXAZOL-5-YL)UREA



- 5 The title compound was prepared following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-(pyridin-4-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B20, 0.140 g, 0.43 mmol) and phenyl (3-(*tert*-butyl)isoxazol-5-yl)carbamate (C4, 0.113 g, 0.43 mmol), and was obtained as an off-white solid (0.006 g, 3% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.44 (bs, 1H), 9.00 (bs, 1H), 8.73-8.74 (m, 2H), 8.34-8.47 (m, 4H), 7.59-7.68 (m, 2H), 6.13 (s, 1H), 1.28 (s, 9H). LCMS: 488.2[M+H].
- 10

EXAMPLE 18

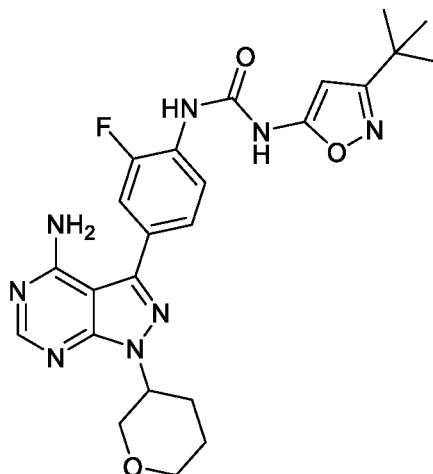
1-(4-(4-AMINO-1-(1,1-DIOXIDOTETRAHYDROTHIOPHEN-3-YL)-1*H*-PYRAZOLO[3,4-
D]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(*tert*-BUTYL)ISOXAZOL-5-YL)UREA



- 5 The title compound was prepared following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-(4-amino-3-fluorophenyl)-1*H*-pyrazolo[3,4-
d]pyrimidin-1-yl)tetrahydrothiophene 1,1-dioxide (B17, 0.030 g, 0.082 mmol) and
 phenyl (3-(*tert*-butyl)isoxazol-5-yl)carbamate (C4, 0.021 g, 0.082 mmol), and was
 obtained as a white solid (0.003 g, 7% yield). ¹H NMR (400 MHz, CD₃OD) δ = 8.31-
 10 8.36 (m, 2H), 7.54-7.60 (m, 2H), 6.19 (s, 1H), 5.78-5.80 (m, 1H), 3.58-3.63 (m, 3H),
 2.78-2.89 (m, 2H), 1.32 (s, 9H). LCMS: 529.2[M+H].

EXAMPLE 19

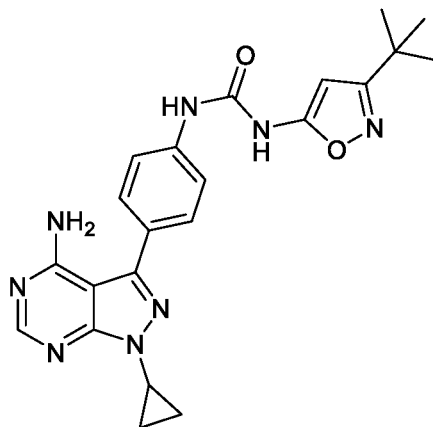
1-(4-(4-AMINO-1-(TETRAHYDRO-2*H*-PYRAN-3-YL)-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(*TERT*-BUTYL)ISOXAZOL-5-YL)UREA



- 5 The title compound was prepared following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-(tetrahydro-2*H*-pyran-3-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B13, 0.015 g, 0.045 mmol) and phenyl 3-(*tert*-butyl)isoxazol-5-yl)carbamate (C4, 0.011 g, 0.045 mmol), and was obtained as an off-white solid (0.002 g, 9% yield). ¹H NMR (400 MHz, CD₃OD) δ = 8.54 (s, 1H), 8.35 (d, *J* = 7.2 Hz, 1H), 8.28 (s, 1H), 7.50-7.56 (m, 2H), 6.19 (s, 1H), 4.60 (s, 1H), 3.87-4.05 (m, 3H), 3.50-3.58 (m, 1H), 2.38-2.42 (m, 1H), 2.21-2.23 (m, 1H), 1.92-2.03 (m, 2H), 1.35 (s, 9H). LCMS: 495.1[M+H].
- 10

EXAMPLE 20

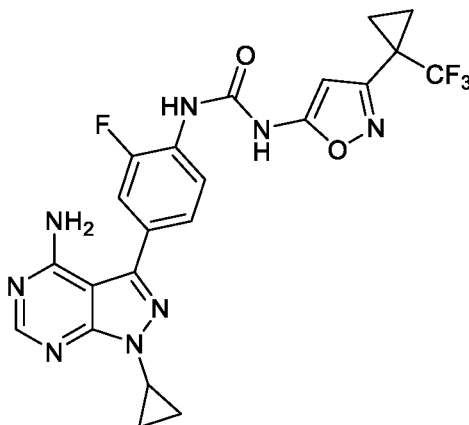
1-(4-(4-AMINO-1-CYCLOPROPYL-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)PHENYL)-3-(3-(*TERT*-BUTYL)ISOXAZOL-5-YL)UREA



- 5 The title compound was prepared following the general procedure for urea formation (Method A), starting from 3-(4-aminophenyl)-1-cyclopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B7, 0.100 g, 0.38 mmol) and phenyl (3-(*tert*-butyl)isoxazol-5-yl)carbamate (C4, 0.100 g, 0.38 mmol), and was obtained as a white solid (0.045 g, 27% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.11 (bs, 1H), 9.10 (bs, 1H), 8.26 (s, 1H), 7.58-7.65 (m, 4H), 6.09 (s, 1H), 3.83-3.89 (m, 1H), 1.24 (s, 9H), 1.19-1.23 (m, 2H), 1.06-1.11 (m, 2H). LCMS: 433.2[M+H].
- 10

EXAMPLE 21

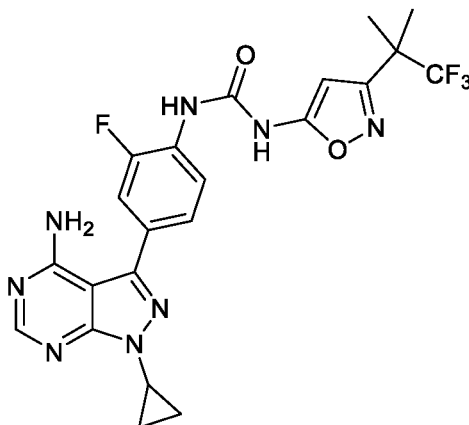
1-(4-(4-AMINO-1-CYCLOPROPYL-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(1-(TRIFLUOROMETHYL)CYCLOPROPYL)ISOXAZOL-5-YL)UREA



The title compound was prepared following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-cyclopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B1, 0.100 g, 0.31 mmol) and phenyl (3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)carbamate (C6, 0.091 g, 0.31 mmol), and was obtained as an off-white solid (0.020 g, 12% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.63 (bs, 1H), 8.92 (bs, 1H), 8.25-8.29 (m, 2H), 7.44-7.51 (m, 2H), 6.87 (bs, 2H), 6.20 (s, 1H), 3.84-3.89 (m, 1H), 1.45-1.76 (m, 2H), 1.36-1.41 (m, 2H), 1.19-1.23 (m, 2H), 1.06-1.11 (m, 2H). LCMS: 503.1[M+H].

EXAMPLE 22

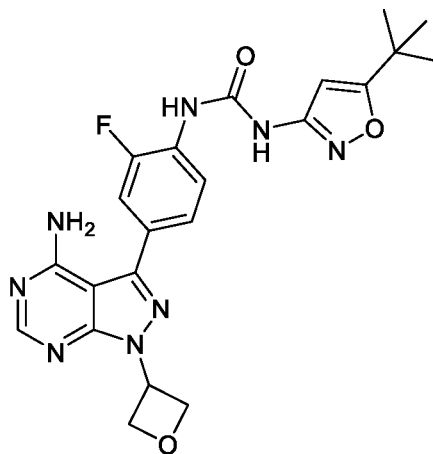
10 1-(4-(4-AMINO-1-CYCLOPROPYL-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(1,1,1-TRIFLUORO-2-METHYLPROPAN-2-YL)ISOXAZOL-5-YL)UREA



The title compound was prepared following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-cyclopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B1, 0.050 g, 0.17 mmol) and phenyl (3-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-5-yl)carbamate (C8, 0.045 g, 0.17 mmol), and was obtained as an off-white solid (0.004 g, 4% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.62 (bs, 1H), 8.96 (bs, 1H), 8.25-8.28 (m, 2H), 7.45-7.52 (m, 2H), 6.99 (bs, 2H), 6.25 (s, 1H), 3.84-3.90 (m, 1H), 1.53 (s, 6H), 1.19-1.23 (m, 2H), 1.10-1.12 (m, 2H). LCMS: 505.1[M+H].

EXAMPLE 23

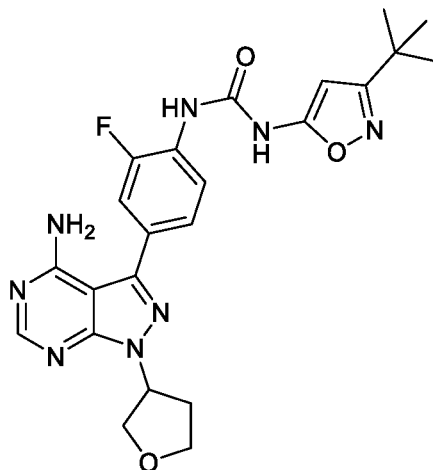
1-(4-(4-AMINO-1-(OXETAN-3-YL)-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(5-(*tert*-BUTYL)ISOXAZOL-3-YL)UREA



- 5 The title compound was prepared following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-(oxetan-3-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B5, 0.150 g, 0.5 mmol) and phenyl (5-(*tert*-butyl)isoxazol-3-yl)carbamate (C5, 0.130 g, 0.5 mmol), and was obtained as an off-white solid (0.015 g, 6% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.00 (bs, 1H), 9.09 (bs, 1H), 8.32-8.37 (m, 1H), 8.26 (s, 1H), 7.51-7.59 (m, 2H), 6.80 (bs, 2H), 6.53 (s, 1H), 5.99-6.04 (m, 1H), 5.10 (t, *J* = 6.4 Hz, 2H), 5.00 (t, *J* = 6.4 Hz, 2H), 1.31 (s, 9H). LCMS: 467.2[M+H].
- 10

EXAMPLE 24

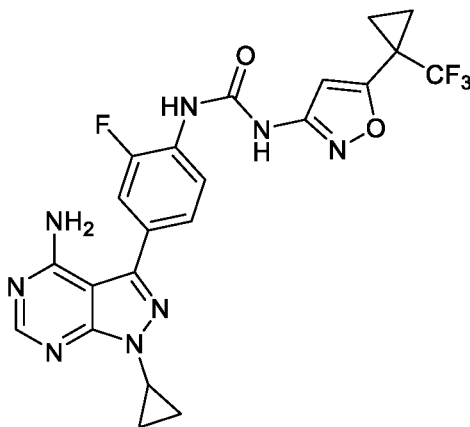
1-(4-(4-AMINO-1-(TETRAHYDROFURAN-3-YL)-1H-PYRAZOLO[3,4-D]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(*tert*-BUTYL)ISOXAZOL-5-YL)UREA



- 5 The title compound was prepared following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-(tetrahydrofuran-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (B11, 0.200 g, 0.59 mmol) and phenyl (3-(*tert*-butyl)isoxazol-5-yl)carbamate (C4, 0.154 g, 0.59 mmol), and was obtained as a white solid (0.030 g, 10% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.40 (bs, 1H), 8.92 (bs, 1H), 8.26-8.31 (m, 2H), 7.47-7.54 (m, 2H), 6.80 (bs, 2H), 6.11 (s, 1H), 5.47-5.53 (m, 1H), 4.05-4.13 (m, 2H), 3.87-3.96 (m, 2H), 2.40-2.41 (m, 2H), 1.27 (s, 9H). LCMS: 481.2[M+H].
- 10

EXAMPLE 25

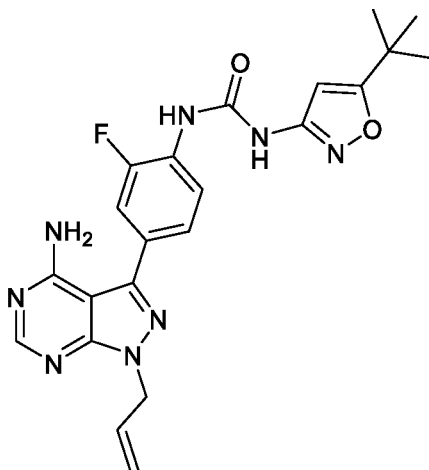
1-(4-(4-AMINO-1-CYCLOPROPYL-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(5-(1-(TRIFLUOROMETHYL)CYCLOPROPYL)ISOXAZOL-3-YL)UREA



- 5 The title compound was prepared following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-cyclopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B1, 0.070 g, 0.24 mmol) and phenyl (5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)carbamate (C7, 0.077 g, 0.24 mmol), and was obtained as an off-white solid; (0.013 mg, 11% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ
- 10 = 11.78 (bs, 1H), 8.76 (s, 1H), 7.43-7.45 (m, 2H), 6.84-6.88 (m, 2H), 5.46 (s, 2H), 3.91-3.97 (m, 1H), 1.49-1.54 (m, 4H), 1.19-1.22 (m, 2H), 1.10-1.15 (m, 2H). LCMS: 503.1[M+H].

EXAMPLE 26

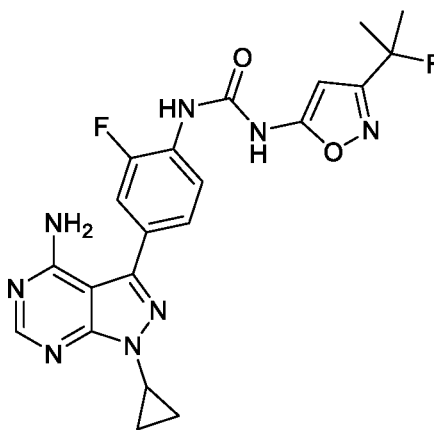
1-(4-(1-ALLYL-4-AMINO-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(5-(*TERT*-BUTYL)ISOXAZOL-3-YL)UREA



- 5 The title compound was prepared following the general procedure for urea formation (Method A), starting from 1-allyl-3-(4-amino-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B6, 0.130 g, 0.45 mmol) and phenyl (5-(*tert*-butyl)isoxazol-3-yl)carbamate (C5, 0.119 g, 0.45 mmol), and was obtained as an off-white solid; (0.012 g, 6% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.46 (bs, 1H), 9.52 (bs, 1H), 8.24-8.28 (m, 2H), 7.45-7.50 (m, 2H), 6.95 (bs, 2H), 6.52 (s, 1H), 6.00-6.10 (m, 1H), 5.18-5.21 (m, 2H), 5.13 (d, *J* = 1.6 Hz, 2H), 1.31 (s, 9H). LCMS: 451.2[M+H].
- 10

EXAMPLE 27

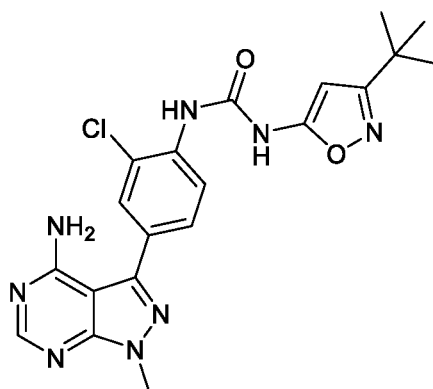
1-(4-(4-AMINO-1-CYCLOPROPYL-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(2-FLUOROPROPAN-2-YL)ISOXAZOL-5-YL)UREA



The title compound was prepared following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-cyclopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B1, 0.050 g, 0.176 mmol) and phenyl (3-(2-fluoropropan-2-yl)isoxazol-5-yl)carbamate (C9, 0.047 g, 0.176 mmol), and was obtained as an off-white solid (0.007 mg, 9% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.32-8.35 (m, 1H), 8.25 (s, 1H), 7.32-7.37 (m, 2H), 5.92 (s, 1H), 3.83-3.89 (m, 1H), 1.66 (s, 3H), 1.61 (s, 3H), 1.20-1.24 (m, 2H), 1.07-1.09 (m, 2H). LCMS: 455.1[M+H].

EXAMPLE 28

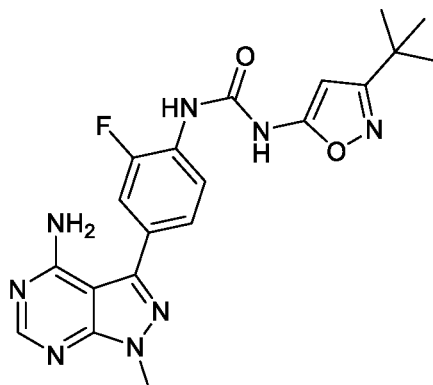
1-(4-(4-AMINO-1-METHYL-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-CHLOROPHENYL)-3-(3-(*TERT*-BUTYL)ISOXAZOL-5-YL)UREA



The title compound was prepared following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-chlorophenyl)-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B22, 0.068 g, 0.248 mmol) and phenyl (3-(*tert*-butyl)isoxazol-5-yl)carbamate (C4, 0.064 g, 0.248 mmol), and was obtained as an off-white solid; (0.005 g, 4% yield). ¹H NMR (400 MHz, CD₃OD) δ = 8.70-8.68 (m, 1H), 7.47-7.67 (m, 2H), 7.00-7.02 (m, 1H), 6.20 (s, 1H), 4.10 (s, 3H), 1.34 (s, 9H). LCMS: 441.1[M+H].

EXAMPLE 29

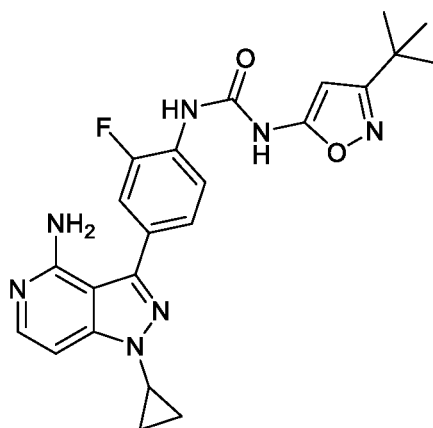
1-(4-(4-AMINO-1-METHYL-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(*TERT*-BUTYL)ISOXAZOL-5-YL)UREA



- 5 The title compound was prepared following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B23, 0.052 g, 0.201 mmol) and phenyl 3-(*tert*-butyl)isoxazol-5-yl)carbamate (C4, 0.052 g, 0.201 mmol), and was obtained as an off-white solid; (0.005 g, 6% yield). ¹H NMR (400 MHz, CD₃OD) δ = 10.60 (bs, 1H), 9.05 (bs, 1H), 8.25-8.30 (m, 2H), 7.45-7.51 (m, 2H), 6.90 (s, 2H), 6.09 (s, 1H), 3.95 (s, 3H), 1.27 (s, 9H). LCMS: 423.1[M-H].
- 10

EXAMPLE 30

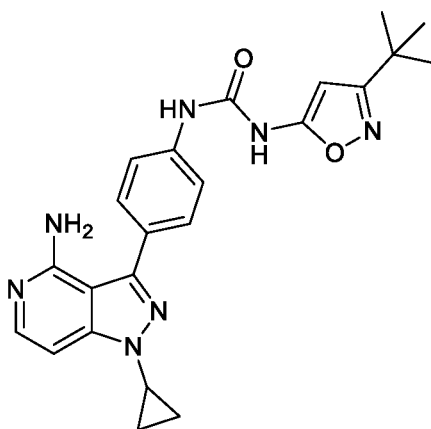
1-(4-(4-AMINO-1-CYCLOPROPYL-1*H*-PYRAZOLO[4,3-*C*]PYRIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(*TERT*-BUTYL)ISOXAZOL-5-YL)UREA



The title compound was prepared following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-cyclopropyl-1*H*-pyrazolo[4,3-*c*]pyridin-4-amine (B24, 0.070 g, 0.24 mmol) and phenyl (3-(*tert*-butyl)isoxazol-5-yl)carbamate (C4, 0.064 g, 0.24 mmol), and was obtained as an off-white solid (0.004 g, 4% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.52 (bs, 1H), 9.09 (bs, 1H), 8.23-8.27 (m, 1H), 7.80 (s, 1H), 7.44-7.53 (m, 2H), 6.90 (d, *J* = 6.0 Hz, 1H), 6.10 (s, 1H), 5.86 (bs, 2H), 3.72-3.74 (m, 1H), 1.27 (s, 9H), 1.12-1.13 (m, 4H). LCMS: 450.2[M+H].

EXAMPLE 31

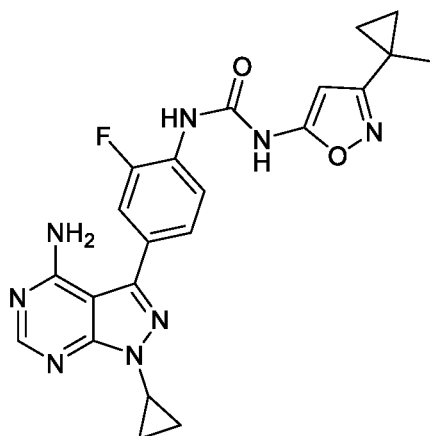
10 1-(4-(4-AMINO-1-CYCLOPROPYL-1*H*-PYRAZOLO[4,3-*C*]PYRIDIN-3-YL)PHENYL)-3-(3-(*tert*-BUTYL)ISOXAZOL-5-YL)UREA



The title compound was prepared following the general procedure for urea formation (Method A), starting from 3-(4-aminophenyl)-1-cyclopropyl-1*H*-pyrazolo[4,3-*c*]pyridin-4-amine (B25, 0.052 g, 0.2 mmol) and phenyl (3-(*tert*-butyl)isoxazol-5-yl)carbamate (C4, 0.05 g, 0.2 mmol), and was obtained as a white solid (0.007 g, 8% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.85 (bs, 1H), 9.68 (bs, 1H), 7.78 (bs, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 6.0 Hz, 1H), 6.08 (s, 1H), 5.75 (bs, 2H), 3.68-3.73 (m, 1H), 1.26 (s, 9H), 1.11-1.12 (m, 4H). LCMS: 432.3[M+H].

EXAMPLE 32

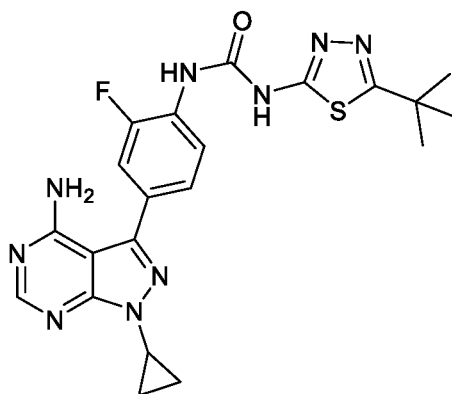
1-(4-(4-AMINO-1-CYCLOPROPYL-1H-PYRAZOLO[3,4-D]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(1-METHYLCYCLOPROPYL)ISOXAZOL-5-YL)



- 5 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, 0.050 g, 0.176 mmol) and phenyl (3-(1-methylcyclopropyl)isoxazol-5-yl)carbamate (C10, 0.045 g, 0.176 mmol), and was obtained as an off-white solid (0.009 g, 11% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ =
- 10 10.29 (bs, 1H), 8.90 (bs, 1H), 8.24-8.28 (m, 2H), 7.44-7.51 (m, 2H), 6.94 (bs, 2H), 5.86 (s, 1H), 3.84-3.89 (m, 1H), 1.38 (s, 3H), 1.19-1.22 (m, 2H), 1.08-1.11 (m, 2H), 0.94-0.97 (m, 2H), 0.82-0.85 (m, 2H). LCMS: 449.1 [M+H].

EXAMPLE 33

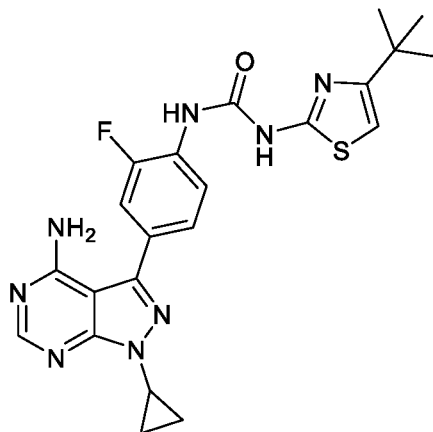
15 1-(4-(4-AMINO-1-CYCLOPROPYL-1H-PYRAZOLO[3,4-D]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(5-(*TERT*-BUTYL)-1,3,4-THIADIAZOL-2-YL)



The title compound was obtained following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-cyclopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B1, 0.050 g, 0.176 mmol) and phenyl (5-(*tert*-butyl)-1,3,4-thiadiazol-2-yl)carbamate (C11, 0.049 g, 0.176 mmol), and was obtained as an off-white solid (0.012 mg, 14% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.67 (bs, 1H), 8.33-8.41 (m, 1H), 8.25 (s, 1H), 7.34-7.39 (m, 2H), 6.87 (bs, 2H), 3.83-3.87 (m, 1H), 1.34 (s, 9H), 1.20-1.23 (m, 2H), 1.06-1.11 (m, 2H). LCMS: 468.2 [M+H].

EXAMPLE 34

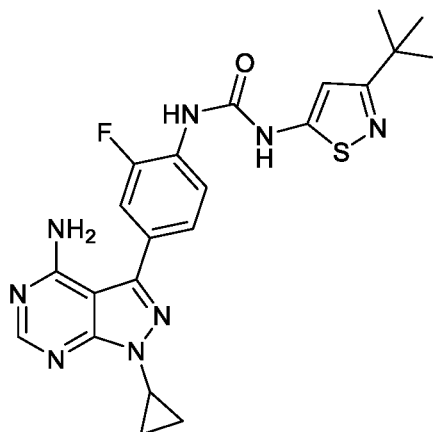
1-(4-(4-AMINO-1-CYCLOPROPYL-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(4-(*tert*-BUTYL)THIAZOL-2-YL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-cyclopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B1, 0.050 g, 0.176 mmol) and phenyl (4-(*tert*-butyl)thiazol-2-yl)carbamate (C12, 0.049 g, 0.176 mmol), and was obtained as an off-white solid (0.004 g, 5% yield). ¹H NMR (400 MHz, CD₃OD) δ = 8.45-8.49 (m, 1H), 8.40 (s, 1H), 7.50-7.58 (m, 2H), 6.65 (s, 1H), 3.96-4.02 (m, 1H), 1.31-1.40 (m, 11H), 1.21-1.25 (m, 2H). LCMS: 467.2 [M+H].

EXAMPLE 35

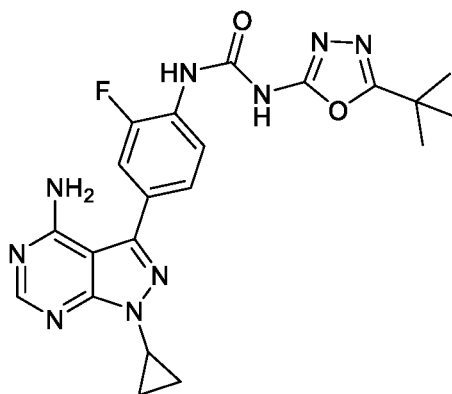
1-(4-(4-AMINO-1-CYCLOPROPYL-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(*TERT*-BUTYL)ISOTHIAZOL-5-YL)UREA



- 5 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, 0.050 g, 0.176 mmol) and phenyl 3-(*tert*-butyl)isothiazol-5-yl)carbamate (C13, 0.049 g, 0.176 mmol), and was obtained as an off-white solid (0.016 g, 19% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 11.42 (bs, 1H), 8.51 (bs, 1H), 8.26 (s, 1H), 8.07-8.11 (m, 1H), 7.39-7.43 (m, 2H), 6.70 (s, 1H), 3.84-3.87 (m, 1H), 1.21-1.26 (m, 11H), 1.08-1.10 (m, 2H). LCMS: 465.1 [M-H].
- 10

EXAMPLE 36

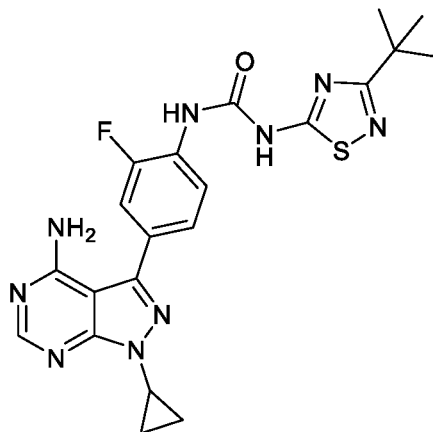
1-(4-(4-AMINO-1-CYCLOPROPYL-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(5-(*TERT*-BUTYL)-1,3,4-OXADIAZOL-2-YL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-1-cyclopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-fluorophenyl)carbamate (C3, 0.050 g, 0.124 mmol) and 5-(*tert*-butyl)-1,3,4-oxadiazol-2-amine (0.017 g, 0.124 mmol), and was obtained as an off-white solid (0.002 g, 4% yield). ¹H NMR (400 MHz, CD₃OD) δ = 8.37-8.43 (m, 2H), 7.46-7.62 (m, 2H), 3.93-3.95 (m, 1H), 1.45 (s, 9H), 1.31-1.38 (m, 2H), 1.20-1.23 (m, 2H). LCMS: 451.9 [M+H].

EXAMPLE 37

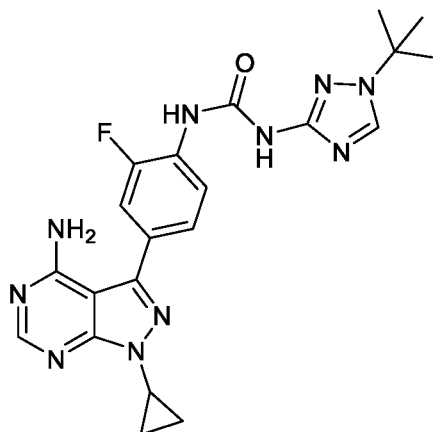
1-(4-(4-AMINO-1-CYCLOPROPYL-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(*tert*-BUTYL)-1,2,4-THIADIAZOL-5-YL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from phenyl (4-(4-amino-1-cyclopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-fluorophenyl)carbamate (C3, 0.050 g, 0.124 mmol) and 3-(*tert*-butyl)-1,2,4-thiadiazol-5-amine (0.019 g, 0.124 mmol), and was obtained as an off-white solid (0.001 g, 1% yield). ¹H NMR (400 MHz, CD₃OD) δ = 8.27-8.39 (m, 2H), 7.51-7.56 (m, 2H), 3.80-3.86 (m, 1H), 1.40 (s, 9H), 1.31-1.33 (m, 2H), 1.17-1.21 (m, 2H). LCMS: 468.0 [M+H].

EXAMPLE 38

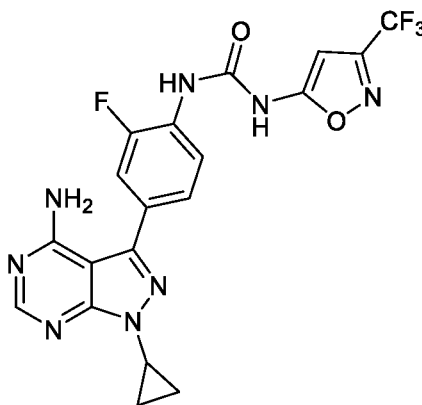
1-(4-(4-AMINO-1-CYCLOPROPYL-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(1-(*tert*-BUTYL)-1H-1,2,4-TRIAZOL-3-YL)UREA



- 5 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 (C3, 0.050 g, 0.124 mmol) and 1-(*tert*-butyl)-1H-1,2,4-triazol-3-amine (0.017 g, 0.124 mmol), and was obtained as an off-white solid (0.009 g, 15% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.80 (bs, 1H), 10.21 (bs, 1H), 8.55 (s, 1H), 8.42-8.46 (m, 1H), 8.26 (s, 1H), 7.44-7.52 (m, 2H), 6.94 (bs, 2H), 3.83-3.88 (m, 1H), 1.57 (s, 9H), 1.19-1.23 (m, 2H), 1.06-1.11 (m, 2H). LCMS: 451.0 [M+H].
- 10

EXAMPLE 39

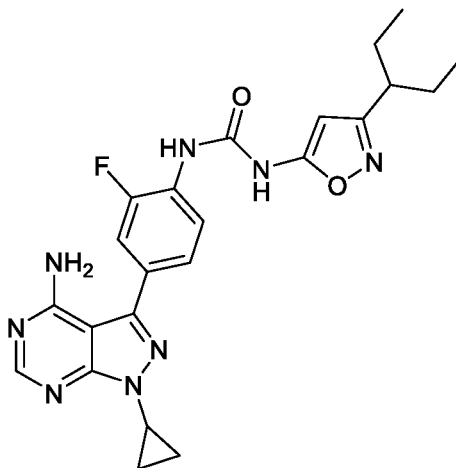
1-(4-(4-AMINO-1-CYCLOPROPYL-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(TRIFLUOROMETHYL)ISOXAZOL-5-YL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-cyclopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B1, 0.050 g, 0.176 mmol) and phenyl (3-(trifluoromethyl)isoxazol-5-yl)carbamate (C14, 0.048 g, 0.176 mmol), and was obtained as white solid (0.004 g, 5% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 11.11 (bs, 1H), 8.97 (bs, 1H), 8.23-8.27 (m, 2H), 7.46-7.52 (m, 2H), 6.95 (bs, 2H), 6.53 (s, 1H), 3.84-3.88 (m, 1H), 1.19-1.24 (m, 2H), 1.07-1.12 (m, 2H). LCMS: 462.9 [M+H].

EXAMPLE 40

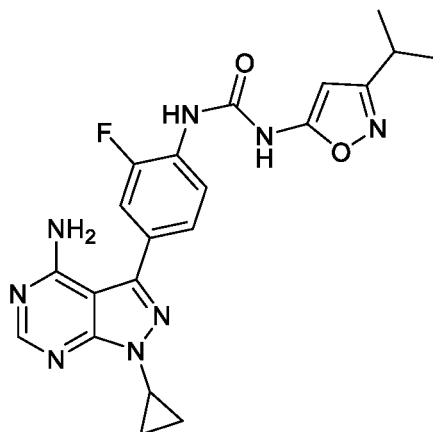
10 1-(4-(4-AMINO-1-CYCLOPROPYL-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(PENTAN-3-YL)ISOXAZOL-5-YL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-cyclopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B1, 0.05 g, 0.176 mmol) and phenyl (3-(pentan-3-yl)isoxazol-5-yl)carbamate (C15, 0.048 g, 0.176 mmol), and was obtained as a pale brown solid (0.006 g, 7% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.44 (bs, 1H), 8.97 (bs, 1H), 8.26-8.29 (m, 2H), 7.44-7.50 (m, 2H), 6.81 (bs, 2H), 6.00 (s, 1H), 3.84-3.86 (m, 1H), 1.51-1.66 (m, 4H), 1.08-1.21 (m, 4H), 0.79-0.82 (m, 6H). LCMS: 465.0 [M+H].

EXAMPLE 41

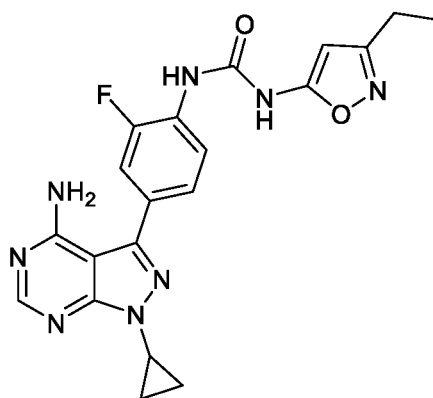
1-(4-(4-AMINO-1-CYCLOPROPYL-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-ISOPROPYLLISOXAZOL-5-YL)UREA



- 5 The title compound was obtained following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-cyclopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B1, 0.050 g, 0.176 mmol) and phenyl (3-isopropylisoxazol-5-yl)carbamate (C16, 0.043 g, 0.176 mmol), and was obtained as an off-white solid (0.007 g, 9% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.49 (bs, 1H), 9.01 (bs, 1H), 8.27-8.32 (m, 2H), 7.44-7.52 (m, 2H), 6.07 (s, 1H), 3.87-3.92 (m, 1H), 2.90-2.97 (m, 1H), 1.18-1.24 (m, 8H), 1.10-1.12 (m, 2H). LCMS: 437.0 [M+H].
- 10

EXAMPLE 42

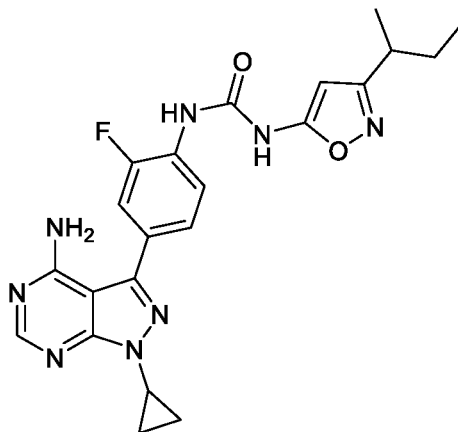
1-(4-(4-AMINO-1-CYCLOPROPYL-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-ETHYLLISOXAZOL-5-YL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-cyclopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B1, 0.050 g, 0.176 mmol) and phenyl (3-ethylisoxazol-5-yl)carbamate (C17, 0.041 g, 0.176 mmol), and was obtained as an off-white solid (0.006 g, 8% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.44 (bs, 1H), 8.94 (bs, 1H), 8.26-8.30 (m, 2H), 7.44-7.51 (m, 2H), 6.99 (bs, 2H), 6.05 (s, 1H), 3.84-3.89 (m, 1H), 2.53-2.59 (m, 2H), 1.18-1.21 (m, 5H), 1.08-1.10 (m, 2H). LCMS: 423.0 [M+H].

EXAMPLE 43

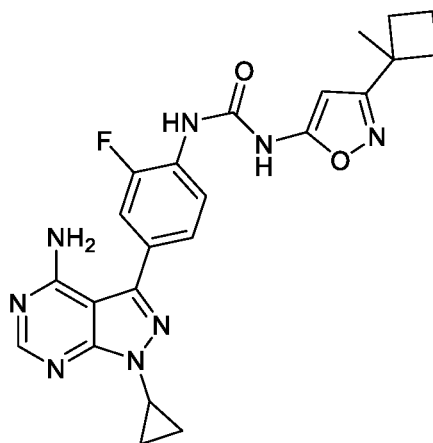
1-(4-(4-AMINO-1-CYCLOPROPYL-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(*SEC*-BUTYL)ISOXAZOL-5-YL)UREA



The title compound was obtained following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-cyclopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B1, 0.080 g, 0.281 mmol) and phenyl (3-(*sec*-butyl)isoxazol-5-yl)carbamate (C18, 0.073 g, 0.281 mmol), and was obtained as a white solid (0.004 g, 4% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.42 (bs, 1H), 8.96 (bs, 1H), 8.26-8.33 (m, 2H), 7.44-7.52 (m, 2H), 6.04 (s, 1H), 3.87-3.92 (m, 1H), 2.68-2.73 (m, 1H), 1.54-1.60 (m, 2H), 1.08-1.24 (m, 7H), 0.82-0.84 (m, 3H). LCMS: 451.1 [M+H].

EXAMPLE 44

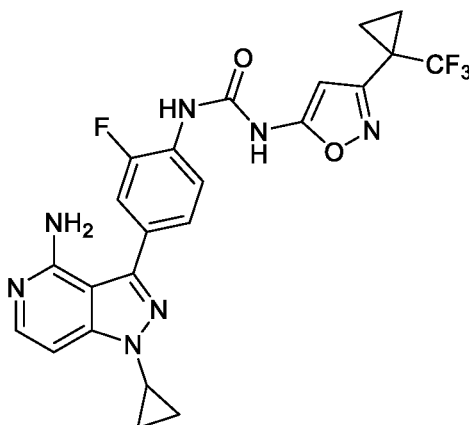
1-(4-(4-AMINO-1-CYCLOPROPYL-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(1-METHYLCYCLOBUTYL)ISOXAZOL-5-YL)UREA



- 5 The title compound was obtained following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-cyclopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B1, 0.100 g, 0.352 mmol and phenyl 3-(1-methylcyclobutyl)isoxazol-5-yl)carbamate (C19, 0.096 g, 0.352 mmol), and was obtained as a white solid (0.002 g, 1% yield). ¹H NMR (400 MHz, CD₃OD) δ = 8.35-8.41 (m, 2H), 7.49-7.56 (m, 2H), 6.16 (s, 1H), 3.98-4.02 (m, 1H), 2.46-2.51 (m, 2H), 1.96-2.13 (m, 4H), 1.54 (s, 3H), 1.23-1.38 (m, 4H). LCMS: 463.1 [M+H].
- 10

EXAMPLE 45

1-(4-(4-AMINO-1-CYCLOPROPYL-1*H*-PYRAZOLO[4,3-*C*]PYRIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(1-(TRIFLUOROMETHYL)CYCLOPROPYL)ISOXAZOL-5-YL)UREA

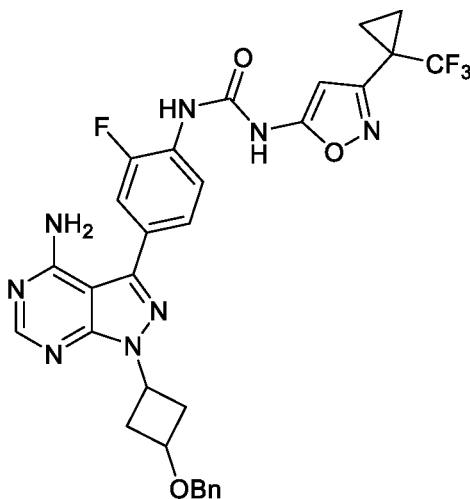


The title compound was obtained following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-cyclopropyl-1*H*-pyrazolo[4,3-*c*]pyridin-4-amine (B24, 0.160 g, 0.565 mmol) and phenyl (3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)carbamate (C6, 0.176 g, 0.565 mmol), and
 5 was obtained as an off-white solid (0.012 g, 4% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.69 (bs, 1H), 8.97 (bs, 1H), 8.23-8.27 (m, 1H), 7.80 (d, *J* = 6.0 Hz, 1H), 7.46-7.54 (m, 2H), 6.91 (d, *J* = 6.0 Hz, 1H), 6.22 (s, 1H), 5.85 (bs, 2H), 3.72-3.74 (m, 1H), 1.39-1.49 (m, 4H), 1.12-1.13 (m, 4H). LCMS: 502.2 [M+H].

EXAMPLE 46

10 1-(4-(4-AMINO-1-(3-HYDROXYCYCLOBUTYL)-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(1-(TRIFLUOROMETHYL)CYCLOPROPYL)ISOXAZOL-5-YL)UREA

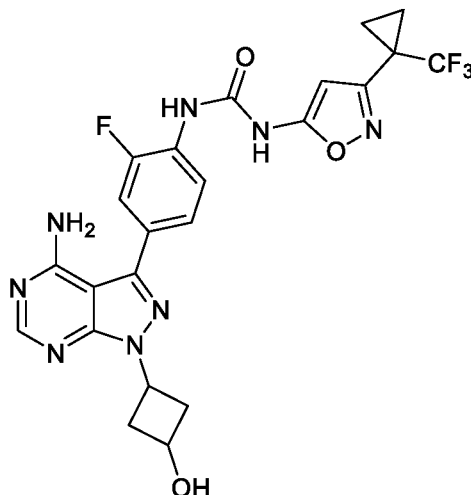
*Step 1: Synthesis of 1-(4-(4-amino-1-(3-(benzyloxy)cyclobutyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea*



15

The title compound was obtained following the general procedure for urea formation (Method B), starting from 3-(4-amino-3-fluorophenyl)-1-(3-(benzyloxy)cyclobutyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B26, 0.090 g, 0.223 mmol) and phenyl (3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)carbamate (C6, 0.076 g, 0.245 mmol), and
 20 was obtained as a brown gum (70 mg) which was used without further purification. LCMS: 623.4 [M+H].

Step 2: Synthesis of 1-(4-(4-amino-1-(3-hydroxycyclobutyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea

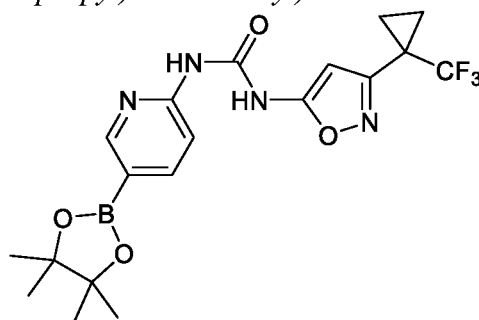


- 5 Boron trichloride (1 M in DCM, 0.899 mL, 0.899 mmol) was added dropwise to a solution of 1-(4-(4-amino-1-(3-(benzyloxy)cyclobutyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea (0.070 g, 0.112 mmol) in dry DCM (5 mL) at -60 °C and the resulting mixture was stirred at 0 °C for 3 h. Following completion of the reaction (as indicated by TLC and LCMS), the
- 10 reaction mixture was cooled to -70 °C, neutralized with aqueous ammonia (25% in water), and extracted with DCM (10 mL × 2). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give crude material which was purified by preparative HPLC (eluting with 1% TFA in a water and ACN mixture) to afford the title product as a white solid (0.009 g, 15% yield). ¹H NMR (400
- 15 MHz, CD₃OD) δ = 8.34-8.38 (m, 2H), 7.53-7.61 (m, 2H), 6.34 (s, 1H), 5.61-5.64 (m, 1H), 4.73-4.79 (m, 1H), 2.94-3.01 (m, 2H), 2.57-2.63 (m, 2H), 1.39-1.48 (m, 4H). LCMS: 533.7 [M+H].

EXAMPLE 47

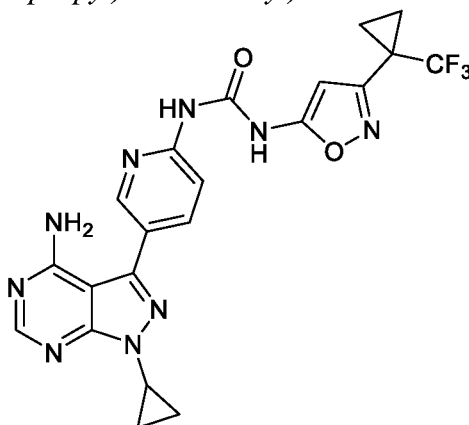
1-(5-(4-AMINO-1-CYCLOPROPYL-1H-PYRAZOLO[3,4-D]PYRIMIDIN-3-YL)PYRIDIN-2-YL)-3-(3-(1-(TRIFLUOROMETHYL)CYCLOPROPYL)ISOXAZOL-5-YL)

Step 1: Synthesis of 1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea



The title compound was obtained following the general procedure for urea formation (Method A), starting from 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (0.100 g, 0.454 mmol) and phenyl 3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)carbamate (C6, 0.142 g, 0.454 mmol), and was obtained as a brown gum (150 mg) which was used without further purification. LCMS: 439.5 [M+H].

Step 2: Synthesis of 1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea



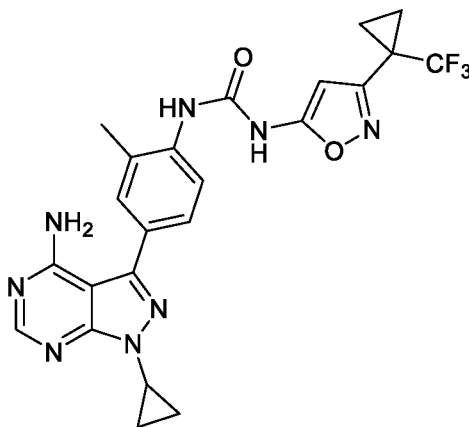
The title compound was obtained by following a similar procedure described for intermediate B26, starting from 1-cyclopropyl-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (A1, 0.100 g, 0.332 mmol) and 1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea (0.146 g, 0.332

mmol), and was obtained as an off-white solid (0.013 g, 8% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 11.68 (bs, 1H), 9.93 (bs, 1H), 8.53 (d, *J* = 2.0 Hz, 1H), 8.28 (s, 1H), 8.02-8.05 (m, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 6.27 (s, 1H), 3.86-3.90 (m, 1H), 1.10-1.49 (m, 8H). LCMS: 486.2 [M+H].

5

EXAMPLE 48

1-(4-(4-AMINO-1-CYCLOPROPYL-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-METHYLPHENYL)-3-(3-(1-(TRIFLUOROMETHYL)CYCLOPROPYL)ISOXAZOL-5-YL)UREA

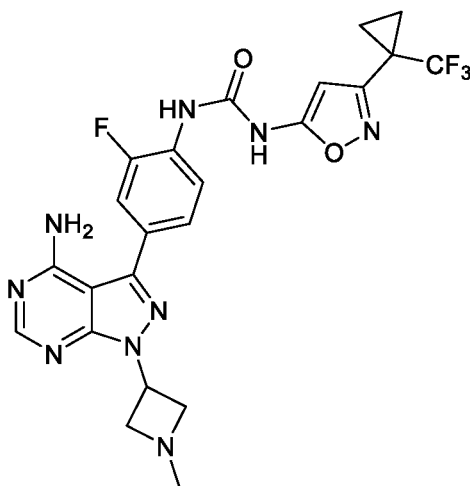


The title compound was obtained following the general procedure for urea formation (Method B), starting from 3-(4-amino-3-methylphenyl)-1-cyclopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B27, 0.110 g, 0.392 mmol) and phenyl 3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-ylcarbamate (C6, 0.135 g, 0.432 mmol), and was obtained as a pale brown solid (0.051 g, 26% yield). ¹H NMR (400 MHz, CD₃OD) δ = 8.41 (s, 1H), 7.95-7.97 (m, 1H), 7.52-7.57 (m, 2H), 6.31 (s, 1H), 3.98-4.01 (m, 1H), 2.41 (s, 3H), 1.21-1.48 (m, 8H). LCMS: 499.1 [M+H].

15

EXAMPLE 49

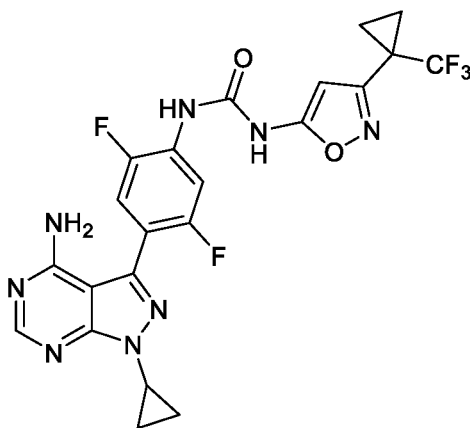
1-(4-(4-AMINO-1-(1-METHYLAZETIDIN-3-YL)-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(1-(TRIFLUOROMETHYL)CYCLOPROPYL)ISOXAZOL-5-YL)UREA



The title compound was obtained following the general procedure for urea formation (Method B), starting from 3-(4-amino-3-fluorophenyl)-1-(1-methylazetidin-3-yl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (B28, 0.130 g, 0.278 mmol) and phenyl (3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)carbamate (C6, 0.095 g, 0.306 mmol), and was obtained as a white solid (0.010 g, 7% yield). ¹H NMR (400 MHz, CD₃OD) δ = 8.35-8.39 (m, 1H), 8.30 (s, 1H), 7.58-7.65 (m, 2H), 6.35 (s, 1H), 5.74-5.78 (m, 1H), 4.38-4.48 (m, 4H), 2.92 (s, 3H), 1.40-1.49 (m, 4H). LCMS: 532.2 [M+H].

EXAMPLE 50

10 1-(4-(4-AMINO-1-CYCLOPROPYL-1H-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2,5-DIFLUOROPHENYL)-3-(3-(1-(TRIFLUOROMETHYL)CYCLOPROPYL)ISOXAZOL-5-YL)UREA

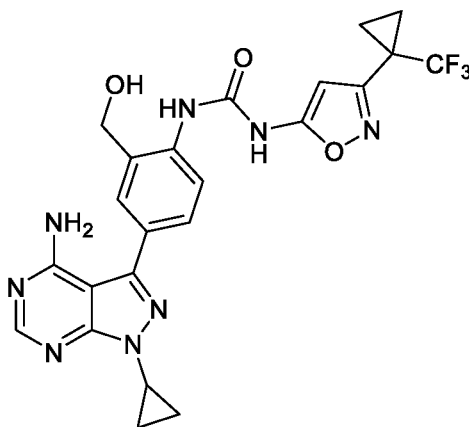


The title compound was obtained following the general procedure for urea formation (Method B), starting from 3-(4-amino-2,5-difluorophenyl)-1-cyclopropyl-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (B29, 0.050 g, 0.165 mmol) and phenyl (3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)carbamate (C6, 0.095 g, 0.306 mmol), and was obtained as a white solid (0.010 g, 7% yield). ¹H NMR (400 MHz, CD₃OD) δ = 8.35-8.39 (m, 1H), 8.30 (s, 1H), 7.58-7.65 (m, 2H), 6.35 (s, 1H), 5.74-5.78 (m, 1H), 4.38-4.48 (m, 4H), 2.92 (s, 3H), 1.40-1.49 (m, 4H). LCMS: 532.2 [M+H].

(trifluoromethyl)cyclopropyl)isoxazol-5-yl)carbamate (C6, 0.0516 g, 0.165 mmol), and was obtained as an off-white solid (0.002 g, 3% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.60 (bs, 1H), 9.08 (bs, 1H), 8.17 (s, 1H), 8.03-8.08 (m, 1H), 7.37-7.42 (m, 1H), 6.16 (s, 1H), 3.78-3.82 (m, 1H), 1.32-1.42 (m, 4H), 1.02-1.20 (m, 4H). LCMS: 521.3 [M+H].

EXAMPLE 51

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



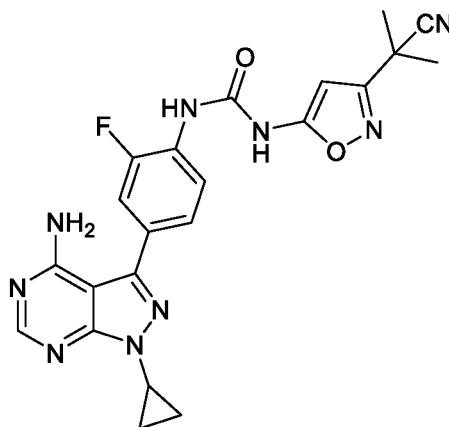
10

The title compound was obtained following the general procedure for urea formation (Method B), starting from (2-amino-5-(4-amino-1-cyclopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)methanol (B30, 0.120 g, 0.405 mmol)) and phenyl (3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)carbamate (C6, 0.126 g, 0.405 mmol), and was obtained as an off-white solid (0.025 g, 12% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 11.14 (bs, 1H), 8.65 (bs, 1H), 8.38 (s, 1H), 8.06-8.08 (m, 1H), 7.54-7.62 (m, 2H), 6.19 (s, 1H), 4.60 (s, 2H), 3.90-3.94 (m, 1H), 1.24-1.48 (m, 8H). LCMS: 515.2 [M+H].

15

EXAMPLE 52

1-(4-(4-AMINO-1-CYCLOPROPYL-1H-PYRAZOLO[3,4-D]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(2-CYANOPROPAN-2-YL)ISOXAZOL-5-YL)UREA

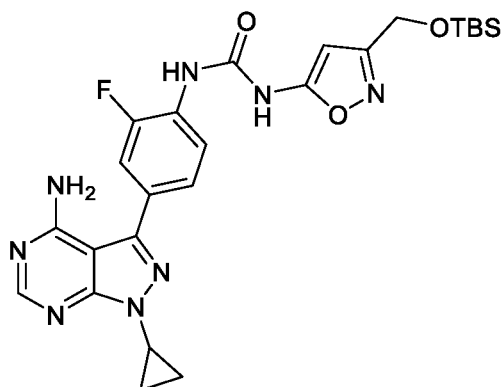


- 5 The title compound was obtained following the general procedure for urea formation (Method B), starting from 3-(4-amino-3-fluorophenyl)-1-cyclopropyl-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (B1, 0.120 g, 0.422 mmol) and phenyl 3-(2-cyanopropan-2-yl)isoxazol-5-yl)carbamate (C20, 0.126 g, 0.464 mmol), and was obtained as an off-white solid (0.029 mg, 14% yield). ¹H NMR (400 MHz, CD₃OD) δ = 8.30-8.37 (m, 2H), 7.50-7.55 (m, 2H), 6.35 (s, 1H), 3.80-3.86 (m, 1H), 1.78 (s, 6H), 1.17-1.37 (m, 4H). LCMS: 462.2 [M+H].

EXAMPLE 53

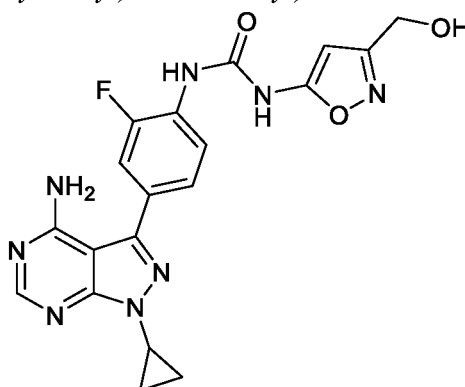
1-(4-(4-AMINO-1-CYCLOPROPYL-1H-PYRAZOLO[3,4-D]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(HYDROXYMETHYL)ISOXAZOL-5-YL)UREA

- 15 *Step 1: Synthesis of 1-(4-(4-amino-1-cyclopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(((tert-butyl)dimethylsilyl)oxy)methyl)isoxazol-5-yl)urea*



The title compound was obtained following the general procedure for urea formation (Method B), 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 (3-(((*tert*-
5 butyldimethylsilyl)oxy)methyl)isoxazol-5-yl)carbamate (C21, 0.135 g, 0.387 mmol), and was obtained as a white solid (0.020 g, 8% yield). ¹H NMR (400 MHz, CD₃OD) δ = 8.30-8.36 (m, 2H), 7.49-7.54 (m, 2H), 6.24 (s, 1H), 4.73 (s, 2H), 3.80-3.85 (m, 1H), 1.29-1.33 (m, 2H), 1.16-1.21 (m, 2H), 0.99 (s, 9H), 0.12 (s, 6H). LCMS: 539.3 [M+H].

*Step 2: Synthesis of 1-(4-(4-amino-1-cyclopropyl-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(hydroxymethyl)isoxazol-5-yl)urea*
10



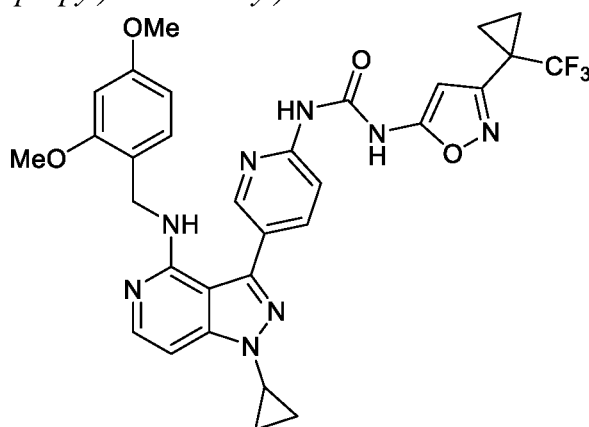
TBAF (1 M in THF, 0.037 ml, 0.037 mmol) was added to a solution of 1-(4-(4-amino-1-cyclopropyl-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(((*tert*-
butyldimethylsilyl)oxy)methyl)isoxazol-5-yl)urea (0.020 g, 0.037 mmol) in THF (3 ml)
15 at 0 °C and the resulting mixture was stirred at 25 °C for 1 h. Following completion of the reaction (as indicated by TLC), the reaction mixture was concentrated under reduced pressure to give crude material which was purified by preparative HPLC (ELSD method, eluting with 1% TFA in a mixture of water and CAN), affording the title compound as a

white solid (0.005 g, 31% yield, TFA salt). ¹H NMR (400 MHz, DMSO-*d*₆) δ = δ 10.46 (bs, 1H), 8.98 (bs, 1H), 8.27-8.35 (m, 2H), 7.45-7.53 (m, 2H), 6.14 (s, 1H), 4.44 (s, 2H), 3.87-3.92 (m, 1H), 1.10-1.23 (m, 4H). LCMS: 425.2 [M+H].

EXAMPLE 54

5 1-(5-(4-AMINO-1-CYCLOPROPYL-1H-PYRAZOLO[4,3-*C*]PYRIDIN-3-YL)PYRIDIN-2-YL)-3-(3-(1-(TRIFLUOROMETHYL)CYCLOPROPYL)ISOXAZOL-5-YL)UREA

*Step 1: Synthesis of 1-(5-(1-cyclopropyl-4-((2,4-dimethoxybenzyl)amino)-1H-pyrazolo[4,3-*c*]pyridin-3-yl)pyridin-2-yl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea*

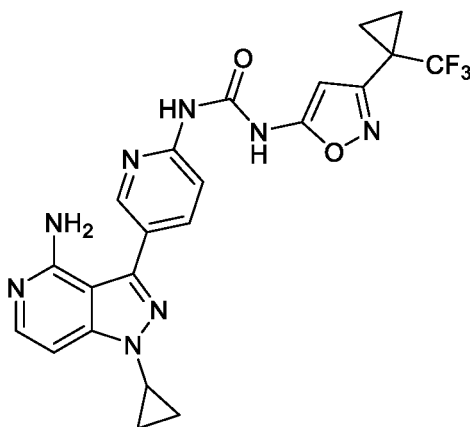


10

The title compound was obtained following the general procedure for urea formation (Method B), starting from 3-(6-aminopyridin-3-yl)-1-cyclopropyl-*N*-(2,4-dimethoxybenzyl)-1H-pyrazolo[4,3-*c*]pyridin-4-amine (B31, 0.050 g, 0.120 mmol) and phenyl (3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)carbamate (C6, 0.037 g, 0.120 mmol), and was obtained as an off-white gum (0.012 g, 15% yield). LCMS: 635.2 [M+H].

15

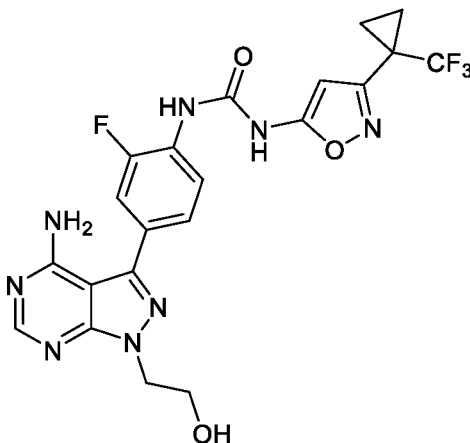
*Step 2: Synthesis of 1-(5-(4-amino-1-cyclopropyl-1H-pyrazolo[4,3-*c*]pyridin-3-yl)pyridin-2-yl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea*



Triethylsilane (0.1 mL, 0.626 mmol) and TFA (0.1 mL, 1.298 mmol) were added to a solution of 1-(5-(1-cyclopropyl-4-((2,4-dimethoxybenzyl)amino)-1H-pyrazolo[4,3-c]pyridin-3-yl)pyridin-2-yl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea (0.012 g, 0.019 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 give crude material which was purified by preparative HPLC (eluting with 10 mM NH₄OAc in ACN), affording the title product as an off-white solid (0.001 g, 10% yield). ¹H NMR (400 MHz, CD₃OD) δ = 8.64 (d, *J* = 1.6 Hz, 1H), 8.09-8.11 (m, 1H), 7.80 (d, *J* = 6.0 Hz, 1H), 7.47-7.49 (m, 1H), 7.04 (d, *J* = 6.4 Hz, 1H), 6.39 (s, 1H), 3.80-3.86 (m, 1H), 0.90-1.50 (m, 8H). LCMS: 485.4 [M+H].

EXAMPLE 55

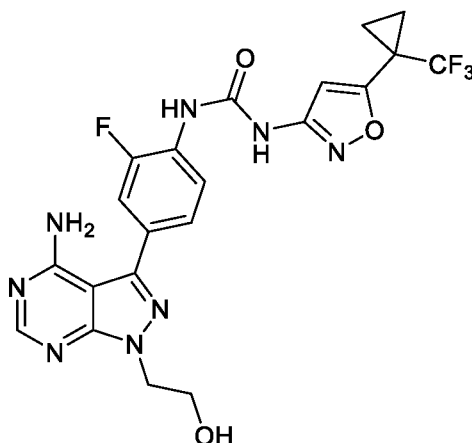
1-(4-(4-AMINO-1-(2-HYDROXYETHYL)-1H-PYRAZOLO[3,4-D]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(1-(TRIFLUOROMETHYL)CYCLOPROPYL)ISOXAZOL-5-YL)UREA



The title compound was obtained following the general procedure for urea formation (Method B), starting from 2-(4-amino-3-(4-amino-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethan-1-ol (B32, 0.11 g, 0.382 mmol) and phenyl (3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)carbamate (C6, 0.10 g, 0.320 mmol), and was
 5 obtained as an off-white solid (0.002 g, 1% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.66 (bs, 1H), 8.99 (bs, 1H), 8.26-8.30 (m, 2H), 7.48-7.54 (m, 2H), 6.94 (bs, 2H), 6.22 (s, 1H), 4.90 (bs, 1H), 4.39 (t, *J* = 6.0 Hz, 2H), 3.85 (t, *J* = 6.0 Hz, 2H), 1.39-1.49 (m, 4H). LCMS: 507.2 [M+H].

EXAMPLE 56

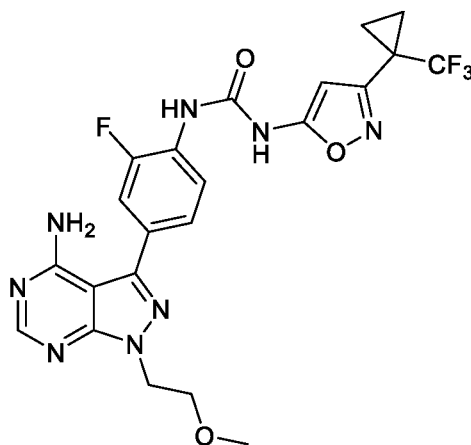
10 1-(4-(4-AMINO-1-(2-HYDROXYETHYL)-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(5-(1-(TRIFLUOROMETHYL)CYCLOPROPYL)ISOXAZOL-3-YL)UREA



The title compound was obtained following the general procedure for urea formation (Method B), starting from 2-(4-amino-3-(4-amino-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethan-1-ol (B32, 0.100 g, 0.347 mmol) and phenyl (5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)carbamate (C7, 0.108 g, 0.347 mmol), and
 15 was obtained as an off-white solid (0.004 g, 3% yield). ¹H NMR (400 MHz, CD₃OD) δ = 8.36-8.41 (m, 2H), 7.52-7.59 (m, 2H), 6.83 (s, 1H), 4.58 (t, *J* = 5.6 Hz, 2H), 4.07 (t, *J* = 5.2 Hz, 2H), 1.49-1.59 (m, 4H). LCMS: 507.2 [M+H].

EXAMPLE 57

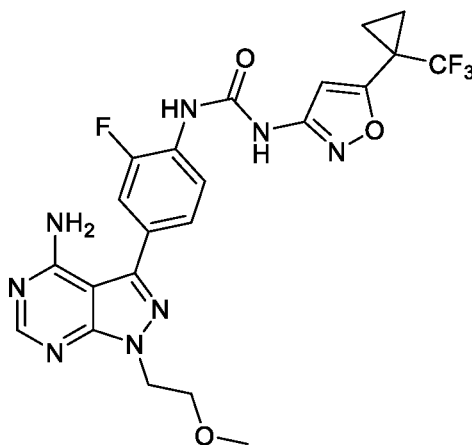
1-(4-(4-AMINO-1-(2-METHOXYETHYL)-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(1-(TRIFLUOROMETHYL)CYCLOPROPYL)ISOXAZOL-5-YL)UREA



- 5 The title compound was obtained following the general procedure for urea formation (Method B), starting from 3-(4-amino-3-fluorophenyl)-1-(2-methoxyethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B33, 0.125 g, 0.413 mmol) and phenyl (3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)carbamate (C6, 0.129 g, 0.413 mmol), and was obtained as an off-white solid (0.020 g, 9% yield). ¹H NMR (400 MHz, DMSO-*d*₆)
- 10 δ = 10.61 (bs, 1H), 8.98 (bs, 1H), 8.25-8.29 (m, 2H), 7.48-7.54 (m, 2H), 6.96 (bs, 2H), 6.22 (s, 1H), 4.50 (t, *J* = 5.2 Hz, 2H), 3.82 (t, *J* = 5.2 Hz, 2H), 3.23 (s, 3H), 1.38-1.47 (m, 4H). LCMS: 521.2 [M+H].

EXAMPLE 58

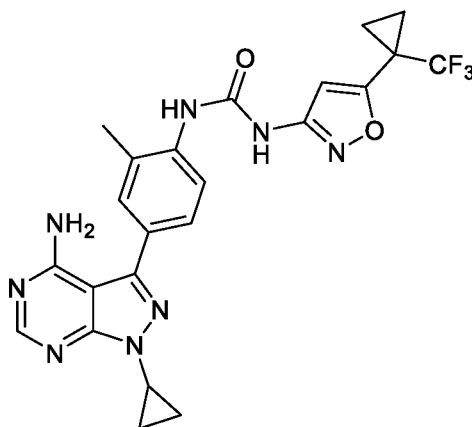
1-(4-(4-AMINO-1-(2-METHOXYETHYL)-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(5-(1-(TRIFLUOROMETHYL)CYCLOPROPYL)ISOXAZOL-3-YL)UREA



- 5 The title compound was obtained following the general procedure for urea formation (Method B), starting from 3-(4-amino-3-fluorophenyl)-1-(2-methoxyethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B33, 0.125 g, 0.413 mmol) and phenyl (5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)carbamate (C7, 0.129 g, 0.413 mmol), and was obtained as an off-white solid (0.015 g, 7% yield). ¹H NMR (400 MHz, DMSO-*d*₆)
- 10 δ = 10.07 (bs, 1H), 9.00 (bs, 1H), 8.31-8.35 (m, 2H), 7.47-7.55 (m, 2H), 6.92 (s, 1H), 4.53 (bs, 2H), 3.83 (t, *J* = 5.2 Hz, 2H), 3.23 (s, 3H), 1.51-1.52 (m, 4H). LCMS: 521.2 [M+H].

EXAMPLE 59

1-(4-(4-AMINO-1-CYCLOPROPYL-1H-PYRAZOLO[3,4-D]PYRIMIDIN-3-YL)-2-METHYLPHENYL)-3-(5-(1-(TRIFLUOROMETHYL)CYCLOPROPYL)ISOXAZOL-3-YL)UREA

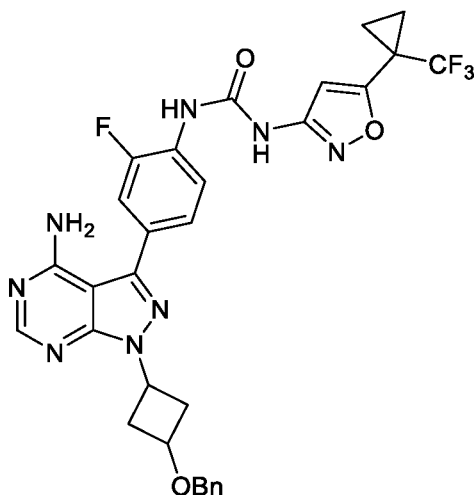


- 5 The title compound was obtained following the general procedure for urea formation (Method B), starting from 3-(4-amino-3-methylphenyl)-1-cyclopropyl-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (B27, 0.100 g, 0.357 mmol) and phenyl (5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)carbamate (C7, 0.123 g, 0.392 mmol), and was obtained as a white solid (0.026 g, 15% yield). ¹H NMR (400 MHz, CD₃OD) δ =
- 10 8.40 (s, 1H), 8.01-8.03 (m, 1H), 7.51-7.57 (m, 2H), 6.74 (s, 1H), 3.97-4.01 (m, 1H), 2.42 (s, 3H), 1.49-1.59 (m, 4H), 1.21-1.38 (m, 4H). LCMS: 499.5 [M+H].

EXAMPLE 60

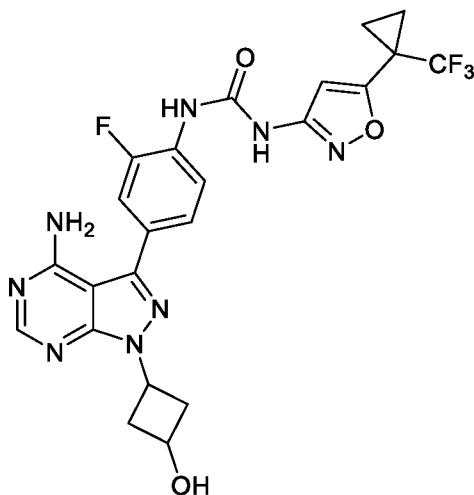
1-(4-(4-AMINO-1-(3-HYDROXYCYCLOBUTYL)-1H-PYRAZOLO[3,4-D]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(5-(1-(TRIFLUOROMETHYL)CYCLOPROPYL)ISOXAZOL-3-YL)UREA

- 15 *Step 1: Synthesis of 1-(4-(4-amino-1-(3-(benzyloxy)cyclobutyl)-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-fluorophenyl)-3-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)urea*



The title compound was obtained following the general procedure for urea formation (Method B), starting from 3-(4-amino-3-fluorophenyl)-1-(3-(benzyloxy)cyclobutyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (B26, 0.090 g, 0.223 mmol) and phenyl (5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)carbamate (C7, 0.076 g, 0.245 mmol), and was obtained as a brown gum (70 mg) which was used without further purification. LCMS: 623.4 [M+H].

*Step 2: Synthesis of 1-(4-(4-amino-1-(3-hydroxycyclobutyl)-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-fluorophenyl)-3-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)urea*



Boron trichloride (1 M in DCM, 0.899 mL, 0.899 mmol) was added dropwise to a solution of 1-(4-(4-amino-1-(3-(benzyloxy)cyclobutyl)-1H-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-fluorophenyl)-3-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)urea (0.070 g,

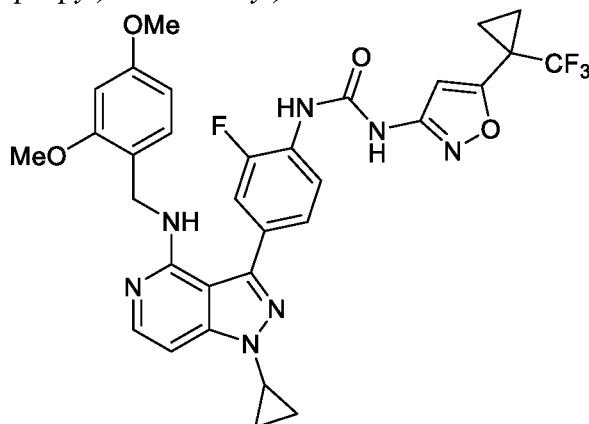
0.112 mmol) in dry DCM (5 mL) at -60 °C and the resulting mixture was at 0 °C for 3 h. Following completion of the reaction (as indicated by TLC and LCMS), the reaction mixture was cooled to -70 °C, neutralized with aqueous ammonia (25% in water), and extracted with DCM (2 × 10 mL). The combined organic layers were dried over Na₂SO₄,
 5 filtered, and concentrated under reduced pressure to yield crude material which was purified by preparative HPLC (eluting with 1% TFA in a water and ACN mixture), affording the title product as a white solid (0.009 g, 15% yield). ¹H NMR (400 MHz, CD₃OD) δ = 8.36-8.40 (m, 2H), 7.53-7.61 (m, 2H), 6.82 (s, 1H), 5.62-5.69 (m, 1H), 4.74-4.80 (m, 1H), 2.94-2.99 (m, 2H), 2.58-2.63 (m, 2H), 1.49-1.58 (m, 4H). LCMS: 533.7
 10 [M+H].

EXAMPLE 61

1-(4-(4-AMINO-1-CYCLOPROPYL-1H-PYRAZOLO[4,3-C]PYRIDIN-3-YL)-2-FLUOROPHENYL)-3-(5-(1-(TRIFLUOROMETHYL)CYCLOPROPYL)ISOXAZOL-3-YL)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-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)urea

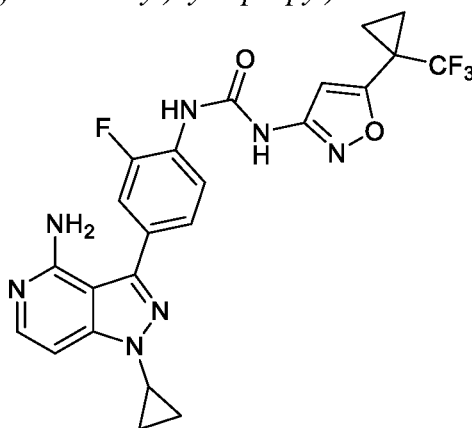
15



The title compound was obtained following the general procedure for urea formation (Method B), starting from 3-(4-amino-3-fluorophenyl)-1-cyclopropyl-N-(2,4-dimethoxybenzyl)-1H-pyrazolo[4,3-c]pyridin-4-amine (B34, 0.220 g, 0.508 mmol) and
 20 phenyl (5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)carbamate (C7, 0.158 g, 0.508

mmol), and was obtained as a brown gum (0.093 g, 28% yield) which was used without further purification. LCMS: 652.3 [M+H].

Step 2: Synthesis of 1-(4-(4-amino-1-cyclopropyl-1H-pyrazolo[4,3-c]pyridin-3-yl)-2-fluorophenyl)-3-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)urea



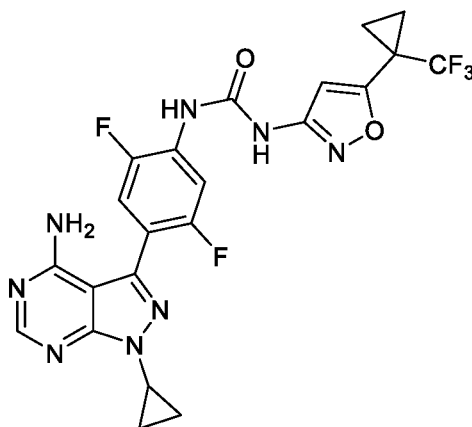
5

Triethylsilane (0.1 mL) and TFA (0.1 mL) 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-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)urea (0.093 g, 0.143 mmol) in DCM (2 mL) at 0 °C and the resulting mixture was stirred at 25 °C for 12 h.

10 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 a water and ACN mixture), affording the title product as a white solid (0.050 g, 68% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.10 (bs, 1H), 9.06 (bs, 1H), 8.33-8.37 (m, 1H), 7.89 (bs, 2H), 7.83 (d, *J* = 7.2 Hz, 1H),
 15 7.54-7.57 (m, 1H), 7.44-7.47 (m, 1H), 7.32 (d, *J* = 7.2 Hz, 1H), 6.91 (s, 1H), 3.94-3.96 (m, 1H), 1.51-1.56 (m, 4H), 1.19-1.20 (m, 4H). LCMS: 502.5 [M+H].

EXAMPLE 62

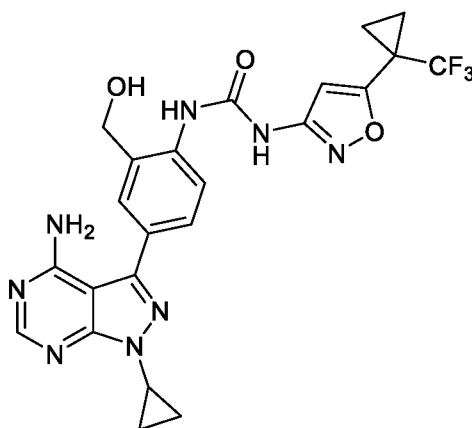
1-(4-(4-AMINO-1-CYCLOPROPYL-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2,5-DIFLUOROPHENYL)-3-(5-(1-(TRIFLUOROMETHYL)CYCLOPROPYL)ISOXAZOL-3-YL)UREA



- 5 The title compound was obtained following the general procedure for urea formation (Method B), starting from 3-(4-amino-2,5-difluorophenyl)-1-cyclopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B29, 0.100 g, 0.331 mmol) and phenyl (5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)carbamate (C7, 0.103 g, 0.331 mmol), and was obtained as an off-white solid (0.002 g, 1% yield). ¹H NMR (400 MHz, CD₃OD) δ
- 10 = 8.24-8.29 (m, 2H), 7.38-7.43 (m, 1H), 6.85 (s, 1H), 3.80-3.85 (m, 1H), 1.47-1.59 (m, 4H), 1.20-1.33 (m, 4H). LCMS: 521.2 [M+H].

EXAMPLE 63

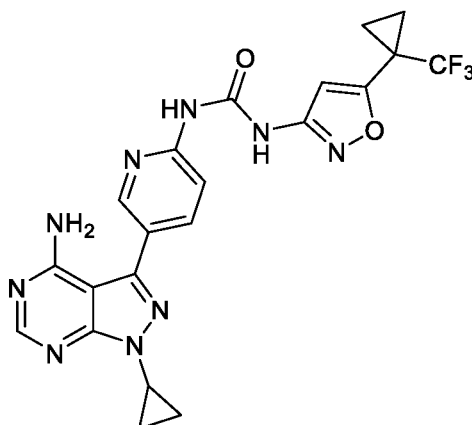
1-(4-(4-AMINO-1-CYCLOPROPYL-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-(HYDROXYMETHYL)PHENYL)-3-(5-(1-(TRIFLUOROMETHYL)CYCLOPROPYL)ISOXAZOL-3-YL)UREA



The title compound was obtained following the general procedure for urea formation (Method B), starting from (2-amino-5-(4-amino-1-cyclopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)methanol (B30, 0.086 g, 0.290 mmol) and phenyl (5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)carbamate (C7, 0.091 g, 0.290 mmol), and
 5 was obtained as an off-white solid (0.004 g, 3% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.39 (bs, 1H), 8.58 (bs, 1H), 8.27 (s, 1H), 8.06-8.08 (m, 1H), 7.52-7.62 (m, 2H), 6.89 (s, 1H), 5.45 (t, *J* = 5.6 Hz, 1H), 4.59 (d, *J* = 5.6 Hz, 2H), 3.84-3.89 (m, 1H), 1.50-1.57 (m, 4H), 1.20-1.23 (m, 4H). LCMS: 515.2 [M+H].

EXAMPLE 64

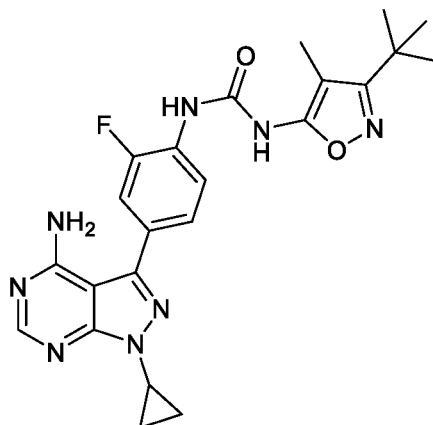
10 1-(5-(4-AMINO-1-CYCLOPROPYL-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)PYRIDIN-2-YL)-3-(5-(1-(TRIFLUOROMETHYL)CYCLOPROPYL)ISOXAZOL-3-YL)UREA



The title compound was obtained following the general procedure for urea formation (Method B), starting from 3-(6-aminopyridin-3-yl)-1-cyclopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B35, 0.085 g, 0.318 mmol) and 1 phenyl (5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)carbamate (C7, 0.099 g, 0.318 mmol), and
 15 was obtained as an off-white solid (0.003 g, 2% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 11.03 (bs, 1H), 9.83 (bs, 1H), 8.51 (bs, 1H), 8.27 (s, 1H), 8.01-8.04 (m, 1H), 7.72-7.74 (m, 1H), 6.97 (s, 1H), 3.86-3.88 (m, 1H), 1.49-1.58 (m, 4H), 1.12-1.24 (m, 4H).
 20 LCMS: 486.1 [M+H].

EXAMPLE 65

1-(4-(4-AMINO-1-CYCLOPROPYL-1H-PYRAZOLO[3,4-D]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(*TERT*-BUTYL)-4-METHYLISOXAZOL-5-YL)UREA



5

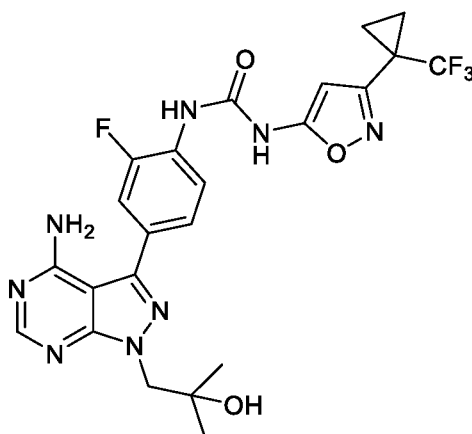
The title compound was obtained following the general procedure for urea formation (Method B), starting from 3-(4-amino-3-fluorophenyl)-1-cyclopropyl-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (B1, 0.100 g, 0.352 mmol) and phenyl 3-(*tert*-butyl)-4-methylisoxazol-5-yl)carbamate (C22, 0.096 g, 0.350 mmol), and was obtained as a white solid (0.013 g, 8% yield). ¹H NMR (400 MHz, CD₃OD) δ = 8.39 (s, 1H), 8.22-8.26 (m, 1H), 7.46-7.55 (m, 2H), 3.94-3.97 (m, 1H), 2.09 (s, 3H), 1.35-1.39 (m, 11H), 1.21-1.23 (m, 2H). LCMS: 465.2 [M+H].

10

EXAMPLE 66

1-(4-(4-AMINO-1-(2-HYDROXY-2-METHYLPROPYL)-1H-PYRAZOLO[3,4-D]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(1-(TRIFLUOROMETHYL)CYCLOPROPYL)ISOXAZOL-5-YL)UREA

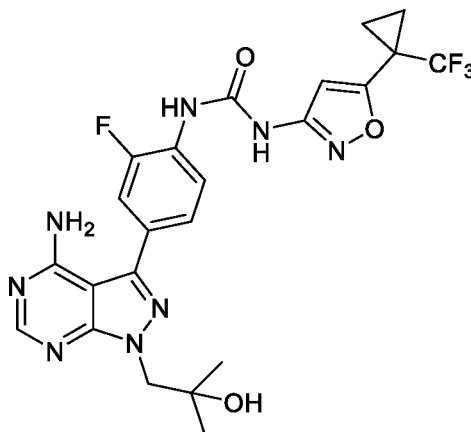
15



The title compound was obtained following the general procedure for urea formation (Method B), starting from 1-(4-amino-3-(4-amino-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-2-methylpropan-2-ol (B19, 0.100 g, 0.316 mmol) and phenyl (3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)carbamate (C6, 0.099 g, 0.316 mmol), and
 5 was obtained as a white solid (0.033 g, 19% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.63 (bs, 1H), 8.97 (bs, 1H), 8.26-8.30 (m, 2H), 7.48-7.54 (m, 2H), 6.96 (bs, 2H), 6.22 (s, 1H), 4.77 (bs, 1H), 4.28 (s, 2H), 1.39-1.49 (m, 4H), 1.15 (s, 6H). LCMS: 535.3 [M+H].

EXAMPLE 67

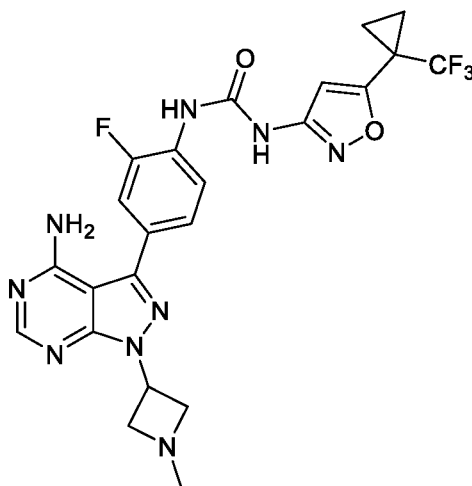
1-(4-(4-AMINO-1-(2-HYDROXY-2-METHYLPROPYL)-1*H*-PYRAZOLO[3,4-*D*]PYRIMIDIN-3-YL)-2-
 10 FLUOROPHENYL)-3-(5-(1-(TRIFLUOROMETHYL)CYCLOPROPYL)ISOXAZOL-3-YL)UREA



The title compound was obtained following the general procedure for urea formation (Method B), starting from 1-(4-amino-3-(4-amino-3-fluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-2-methylpropan-2-ol (B19, 0.100 g, 0.316 mmol) and phenyl (5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)carbamate (C7, 0.099 g, 0.316 mmol), and
 15 was obtained as a white solid (0.022 g, 13% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.08 (bs, 1H), 9.04 (bs, 1H), 8.42 (s, 1H), 8.31-8.35 (m, 1H), 7.47-7.55 (m, 2H), 6.91 (s, 1H), 4.31 (s, 2H), 1.48-1.58 (m, 4H), 1.17 (s, 6H). LCMS: 535.3 [M+H].

EXAMPLE 68

1-(4-(4-AMINO-1-(1-METHYLAZETIDIN-3-YL)-1H-PYRAZOLO[3,4-D]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(5-(1-(TRIFLUOROMETHYL)CYCLOPROPYL)ISOXAZOL-3-YL)UREA

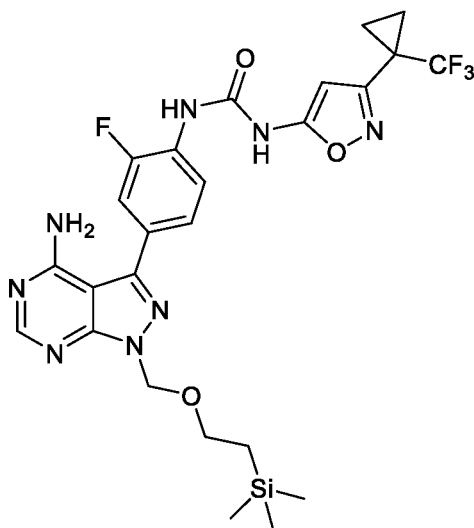


- 5 The title compound was obtained following the general procedure for urea formation (Method B), starting from 3-(4-amino-3-fluorophenyl)-1-(1-methylazetidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (B28, 0.130 g, 0.278 mmol) and phenyl (5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)carbamate (C7, 0.095 g, 0.306 mmol), and was obtained as a white solid (0.006 mg, 4% yield). ¹H NMR (400 MHz, CD₃OD δ =
- 10 8.26-8.41 (m, 2H), 7.56-7.64 (m, 2H), 6.84 (s, 1H), 5.71-5.74 (m, 1H), 4.29-4.90 (m, 4H), 2.85 (s, 3H), 1.52-1.59 (m, 4H). LCMS: 532.3 [M+H].

EXAMPLE 69

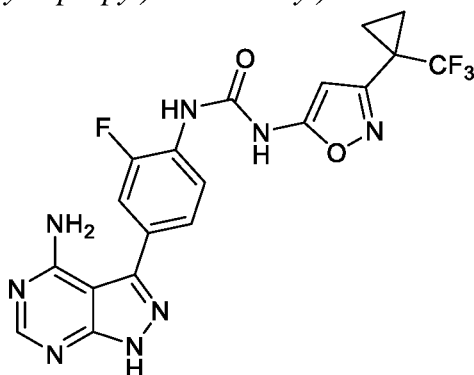
1-(4-(4-AMINO-1H-PYRAZOLO[3,4-D]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(1-(TRIFLUOROMETHYL)CYCLOPROPYL)ISOXAZOL-5-YL)UREA

- 15 *Step 1: Synthesis of 1-(4-(4-amino-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea*



The title compound was obtained following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (B36, 0.06 g, 0.160 mmol) and phenyl 3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)carbamate (C6, 0.05 g, 0.160 mmol), and was obtained as a pale brown solid (80 mg) which was used without further purification. LCMS: 593.3 [M+H].

Step 2: Synthesis of 1-(4-(4-amino-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea



10

HCl (g) in dioxane (4 M, 1 mL, 0.135 mmol) was added to a solution of 1-(4-(4-amino-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)urea (0.08 g, 0.135 mmol) in DCM (5 mL) at 0 °C and the resulting mixture was stirred at 25 °C for 12 h.

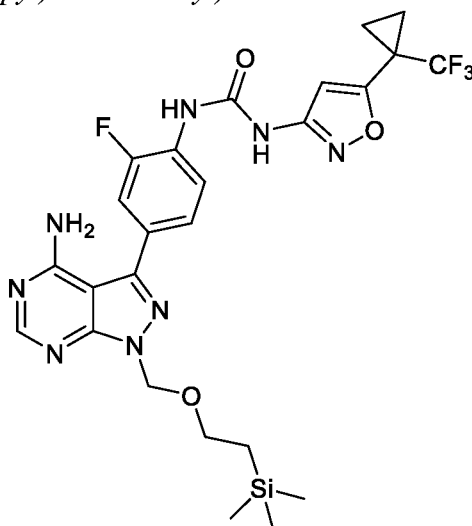
15 Following completion of the reaction (as indicated by UPLC), the reaction mixture was

concentrated under reduced pressure to give crude material which was purified by preparative HPLC (eluting with 10 mM NH₄OAc in ACN), affording the title product as an off-white solid (0.003 g, 5% yield). ¹H NMR (400 MHz, CD₃OD) δ = 8.30-8.34 (m, 1H), 8.24 (s, 1H), 7.49-7.54 (m, 2H), 6.31 (s, 1H), 1.37-1.46 (m, 4H). LCMS: 463.3 [M+H].

EXAMPLE 70

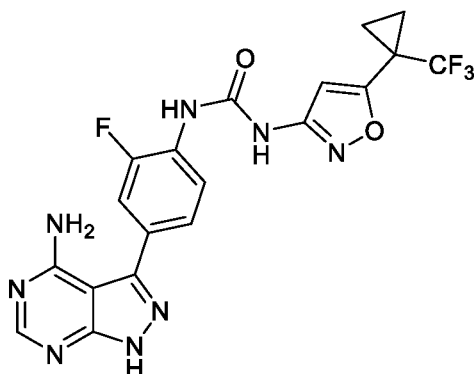
1-(4-(4-AMINO-1H-PYRAZOLO[3,4-D]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(5-(1-(TRIFLUOROMETHYL)CYCLOPROPYL)ISOXAZOL-3-YL)UREA

Step 1: Synthesis of 1-(4-(4-amino-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)urea



The title compound was obtained following the general procedure for urea formation (Method A), starting from 3-(4-amino-3-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (B36, 0.06 g, 0.160 mmol) and phenyl (5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)carbamate (C7, 0.05 g, 0.160 mmol), and was obtained as a pale brown solid (80 mg) which was used without further purification. LCMS: 593.3 [M+H].

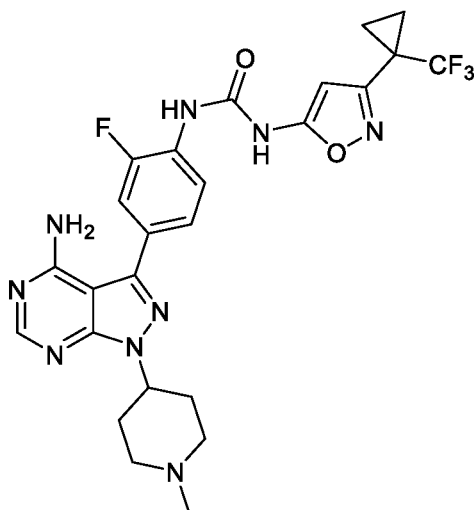
Step 2: Synthesis of 1-(4-(4-amino-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)urea



HCl (g) in dioxane (4 M, 1 mL, 0.135 mmol) was added to a solution of 1-(4-(4-amino-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenyl)-3-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)urea (0.08 g, 0.135 mmol) in DCM (5 mL) at 0 °C 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 give crude material which was purified by preparative HPLC (eluting with 10 mM NH₄OAc in CAN), affording the title product as an off-white solid (0.007 g, 11% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 13.61 (bs, 1H), 10.04 (bs, 1H), 8.96 (bs, 1H), 8.27-8.30 (m, 1H), 8.22 (s, 1H), 7.46-7.53 (m, 2H), 6.92 (s, 1H), 1.51-1.58 (m, 4H). LCMS: 463.3 [M+H].

EXAMPLE 71

1-(4-(4-AMINO-1-(1-METHYLPYPERIDIN-4-YL)-1H-PYRAZOLO[3,4-D]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(3-(1-(TRIFLUOROMETHYL)CYCLOPROPYL)ISOXAZOL-5-YL)UREA

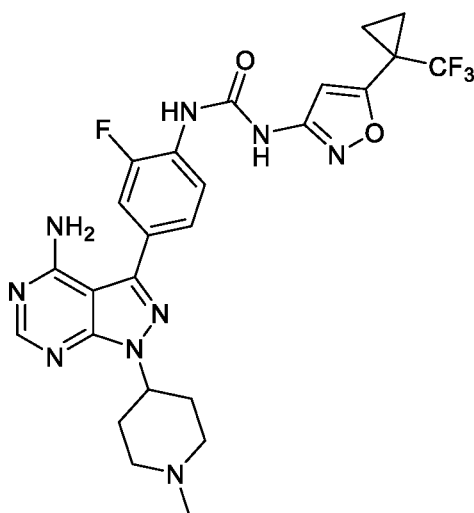


The title compound was obtained following the general procedure for urea formation (Method B), starting from 3-(4-amino-3-fluorophenyl)-1-(1-methylpiperidin-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (B37, 0.100 g, 0.179 mmol) and phenyl (3-(1-(trifluoromethyl)cyclopropyl)isoxazol-5-yl)carbamate (C6, 0.061 g, 0.197 mmol), and was obtained as a white solid (0.008 g, 8% yield). ¹H NMR (400 MHz, CD₃OD) δ = 8.34-8.38 (m, 2H), 7.52-7.57 (m, 2H), 6.35 (s, 1H), 5.12-5.17 (m, 1H), 3.73-3.76 (m, 2H), 3.33-3.39 (m, 2H), 3.00 (s, 3H), 2.59-2.62 (m, 2H), 2.35-2.39 (m, 2H), 1.45-1.49 (m, 4H). LCMS: 560.2 [M+H].

10

EXAMPLE 72

1-(4-(4-AMINO-1-(1-METHYLPIPERIDIN-4-YL)-1H-PYRAZOLO[3,4-D]PYRIMIDIN-3-YL)-2-FLUOROPHENYL)-3-(5-(1-(TRIFLUOROMETHYL)CYCLOPROPYL)ISOXAZOL-3-YL)UREA



The title compound was obtained following the general procedure for urea formation (Method B), starting from 3-(4-amino-3-fluorophenyl)-1-(1-methylpiperidin-4-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (B37, 0.100 g, 0.179 mmol) and phenyl (5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)carbamate (C7, 0.061 g, 0.197 mmol), and
 5 was obtained as a brown solid (0.004 g, 4% yield). ¹H NMR (400 MHz, CD₃OD) δ = 8.36-8.40 (m, 2H), 7.51-7.56 (m, 2H), 6.82 (s, 1H), 5.10-5.18 (m, 1H), 3.73-3.76 (m, 2H), 3.37-3.39 (m, 2H), 3.00 (s, 3H), 2.59-2.62 (m, 2H), 2.35-2.38 (m, 2H), 1.39-1.59 (m, 4H). LCMS: 560.3 [M+H].

10

BIOLOGICAL EXAMPLE 1

BIOCHEMICAL ASSAY OF THE COMPOUNDS

Representative compounds were tested for inhibitory activity against NEK7 and IL-1 β release according to the procedures described above. Results are given in the following table.

15

Table 2. Activity of Representative Compounds

No.	NEK7 IC ₅₀ (nM)	Il-1 β release IC ₅₀ (nM)
1	**	-
2	***	-
3	***	-
4	**	-
5	***	-
6	*	-
7	***	-
8	****	-
9	**	-
10	****	-
11	****	-
12	****	+++
13	****	++++
14	****	++++
15	****	-
16	*	-
17	**	-
18	***	-

No.	NEK7 IC ₅₀ (nM)	Il-1 β release IC ₅₀ (nM)
19	**	-
20	****	-
21	****	++++
22	***	-
23	****	-
24	****	-
25	****	+++
26	***	-
27	*	-
28	*	-
29	****	-
30	****	++++
31	*	-
32	****	+++
33	*	++
34	*	-
35	*	-
36	*	-
37	*	-
38	*	-
39	***	-
40	**	-
41	****	-
42	***	-
43	***	-
44	***	-
45	***	+++
46	****	-
48	**	-
49	*	-
50	**	-
52	****	-
53	*	-
54	***	-
55	****	-
57	***	-
58	***	-
59	*	-
60	****	-
61	*	-
62	**	-
63	*	-
64	***	-
66	***	-
67	**	-

No.	NEK7 IC ₅₀ (nM)	Il-1 β release IC ₅₀ (nM)
68	*	-

For NEK7 IC₅₀ activity in Table 2:

- * IC₅₀ greater than 501 nM
- ** IC₅₀ range from 301 – 500 nM
- *** IC₅₀ range from 151 – 300 nM
- 5 **** IC₅₀ less than 150 nM

For IL-1 β IC₅₀ activity in Table 2:

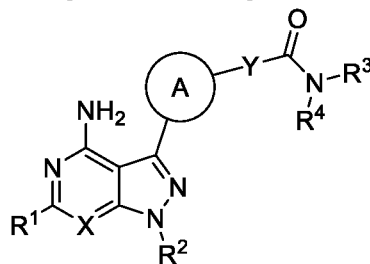
- + IC₅₀ greater than 501 nM
- ++ IC₅₀ range from 201 – 500 nM
- +++ IC₅₀ from 51 – 200 nM
- 10 +++++ IC₅₀ less than 50 nM
- denotes a value was not determined

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 U.S. Provisional Application Serial No. 63/036,244 filed June 8, 2020, U.S. Provisional Application Serial No. 63/170,776 filed April 5, 2021, and U.S. Provisional Application Serial No. 63/185,257 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 C₆-C₁₀ aryl, C₃-C₁₀ cycloalkyl, 3-10 membered heterocyclyl or 5-6 membered monocyclic heteroaryl, each of which is optionally substituted with one or more R⁵;

X is N or CH;

Y is CHOH or NH;

R¹ is H or C₁-C₆ alkyl;

R² is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, 3-8 membered heterocyclyl or 5- or 6-membered heteroaryl, each of which is optionally substituted with one more substituents selected from halo, hydroxyl, cyano, aminyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy and 3-8 membered heterocyclyl;

R³ is a heteroaryl selected from oxazolyl, isoxazolyl, 1, 2, 3-oxadiazolyl, 1, 2, 4-oxadiazolyl, 1, 2, 5-oxadiazolyl, 1, 3, 4-oxadiazolyl, 1, 2, 3-triazolyl, 1, 2, 4-triazolyl, thiazolyl, isothiazolyl, 1, 2, 3-thiadiazolyl, 1, 2, 4-thiadiazolyl, 1, 2, 5-thiadiazolyl and 1, 3, 4-thiadiazolyl, each of which is optionally substituted with one more substituents selected from amino, halo, cyano, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, C₃-C₈ alkylcycloalkyl, C₃-C₈ haloalkylcycloalkyl, C₃-C₈ aminylalkylcycloalkyl, C₁-C₆ cyanoalkyl, C₁-C₆ aminyl, C₁-C₆ hydroxylalkyl, 3-8 membered heterocyclyl, 3-8 membered heterocyclylalkyl, 3-8 membered heterocyclylcycloalkyl, 3-8 membered haloheterocyclyl, 3-8 membered haloheterocyclylalkyl, C₃-C₈ halocycloalkyl and C₃-C₈ halocycloalkylalkyl, and combinations thereof;

R⁴ is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, 3-8 membered heterocyclyl, C₆-C₁₀ aryl or 5- or 6-membered heteroaryl, each of which is optionally substituted with one more substituents selected from halo, hydroxyl, cyano, aminyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl and C₁-C₆ alkoxy; and

R⁵ is, at each occurrence, independently halo, cyano, C₁-C₆ alkyl, C₁-C₆ hydroxylalkyl, C₁-C₆ alkoxy, or C₁-C₆ haloalkyl.

2. The compound of claim 1, wherein R¹ is H.

3. The compound of claim 1 or 2, wherein R² is branched C₃-C₆ alkyl, C₂-C₆ alkenyl, C₃-C₆ cycloalkyl, C₃-C₈ heterocyclyl or 5- or 6-membered heteroaryl, each of which is optionally substituted with one more substituent selected from halo, hydroxyl, cyano, aminyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy and 3- to 8-membered heterocyclyl.

4. The compound of any one of claims 1-3, wherein R² is branched C₄-C₆ alkyl, C₃-C₄ cycloalkyl, or C₃-C₈ heterocyclyl, each of which is optionally substituted with one more substituent selected from halo, hydroxyl, cyano, aminyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy and 3- to 8-membered heterocyclyl.

5. The compound of any one of claims 1-4, wherein R² is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, each of which is optionally substituted with one more substituent selected from halo, hydroxyl, cyano, aminyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy and 3- to 8-membered heterocyclyl.

6. The compound of any one of claims 1-4, wherein R² is methyl, ethyl, isopropyl, 2-methylpropyl or allyl, each of which is optionally substituted with one more substituent selected from halo, hydroxyl, cyano, aminyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy and 3- to 8-membered heterocyclyl.

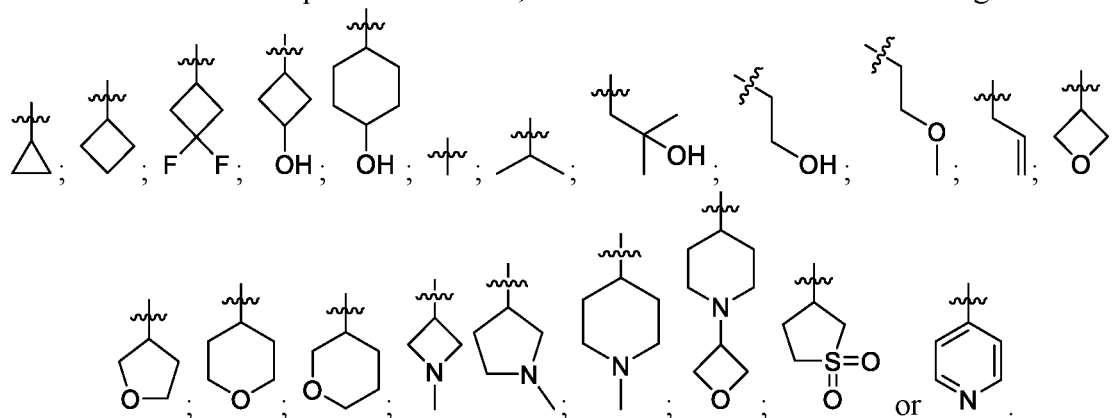
7. The compound of any one of claims 1-4, wherein R² is oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, azetidiny, pyrrolidinyl, or dioxidotetrahydrothiophenyl, each of which is optionally substituted with one more substituent selected from halo, hydroxyl, cyano, aminyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy and 3- to 8-membered heterocyclyl.

8. The compound of any one of claims 1-4, wherein R² is pyridinyl optionally substituted with one more substituent selected from halo, hydroxyl, cyano, aminyl, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy and 3- to 8-membered heterocyclyl.

9. The compound of any one of claims 1-8, wherein R² is unsubstituted.

10. The compound of any one of claims 1-8, wherein R² is substituted with one or more of hydroxyl, methyl, methoxy, and fluoro.

11. The compound of claim 1, wherein R² has one of the following structures:



12. The compound of any one of claims 1-11, wherein R³ is oxazolyl, isoxazolyl, 1, 2, 3-oxadiazolyl, 1, 3, 4-oxadiazolyl, thiazolyl, isothiazolyl, 1, 2, 4-thiadiazolyl, 1, 3, 4-thiadiazolyl or 1, 2, 4-triazolyl, each of which is optionally substituted with one more substituents selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, cyano, C₁-C₆ aminyl, C₁-C₆

hydroxylalkyl, 3-8 membered heterocyclyl and C₃-C₈ halocycloalkyl, or combinations thereof.

13. The compound of claim 12, wherein R³ is isoxazolyl optionally substituted with one more substituents selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, cyano, C₁-C₆ aminyl, C₁-C₆ hydroxylalkyl, 3-8 membered heterocyclyl and C₃-C₈ halocycloalkyl, or combinations thereof.

14. The compound of claim 12, wherein R³ is thiazolyl optionally substituted with one more substituents selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, cyano, C₁-C₆ aminyl, C₁-C₆ hydroxylalkyl, 3-8 membered heterocyclyl and C₃-C₈ halocycloalkyl, or combinations thereof.

15. The compound of claim 12, wherein R³ is isothiazolyl optionally substituted with one more substituents selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, cyano, C₁-C₆ aminyl, C₁-C₆ hydroxylalkyl, 3-8 membered heterocyclyl and C₃-C₈ halocycloalkyl, or combinations thereof.

16. The compound of claim 12, wherein R³ is 1,2,4-thiadiazolyl optionally substituted with one more substituents selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, cyano, C₁-C₆ aminyl, C₁-C₆ hydroxylalkyl, 3-8 membered heterocyclyl and C₃-C₈ halocycloalkyl, or combinations thereof.

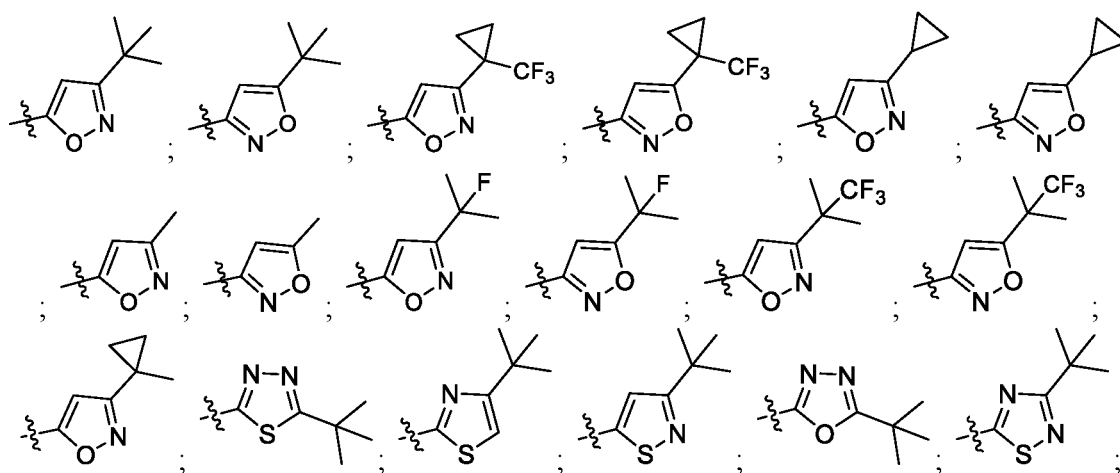
17. The compound of claim 12, wherein R³ is 1,3,4-thiadiazolyl optionally substituted with one more substituents selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, cyano, C₁-C₆ aminyl, C₁-C₆ hydroxylalkyl, 3-8 membered heterocyclyl and C₃-C₈ halocycloalkyl, or combinations thereof.

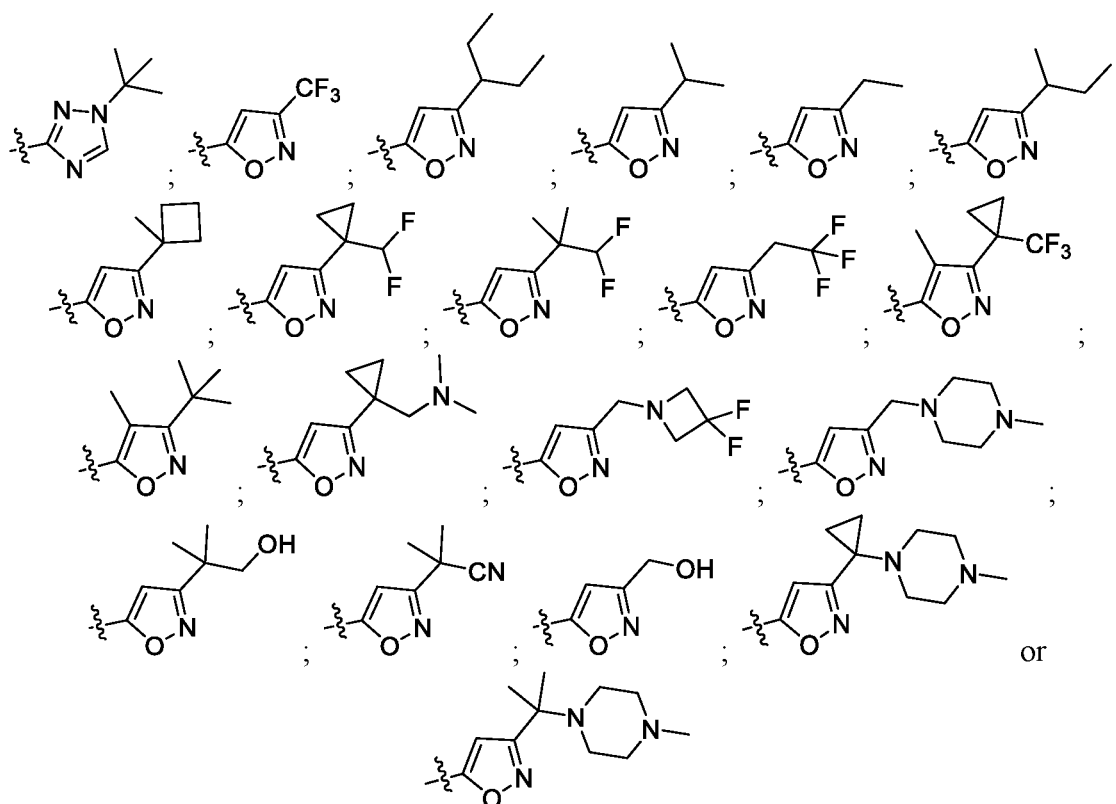
18. The compound of claim 12, wherein R^3 is 1,3,4-oxadiazolyl optionally substituted with one more substituents selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, cyano, C₁-C₆ aminyl, C₁-C₆ hydroxylalkyl, 3-8 membered heterocyclyl and C₃-C₈ halocycloalkyl, or combinations thereof.

19. The compound of claim 12, wherein R^3 is 1,2,4-triazolyl optionally substituted with one more substituents selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, cyano, C₁-C₆ aminyl, C₁-C₆ hydroxylalkyl, 3-8 membered heterocyclyl and C₃-C₈ halocycloalkyl, or combinations thereof.

20. The compound of any one of claims 1-19, wherein R^3 is substituted with C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, cyano, C₁-C₆ aminyl, C₁-C₆ hydroxylalkyl, 3-8 membered heterocyclyl or C₃-C₈ halocycloalkyl, or combinations thereof.

21. The compound of any one of claims 1-20, wherein R^3 has one of the following structures:

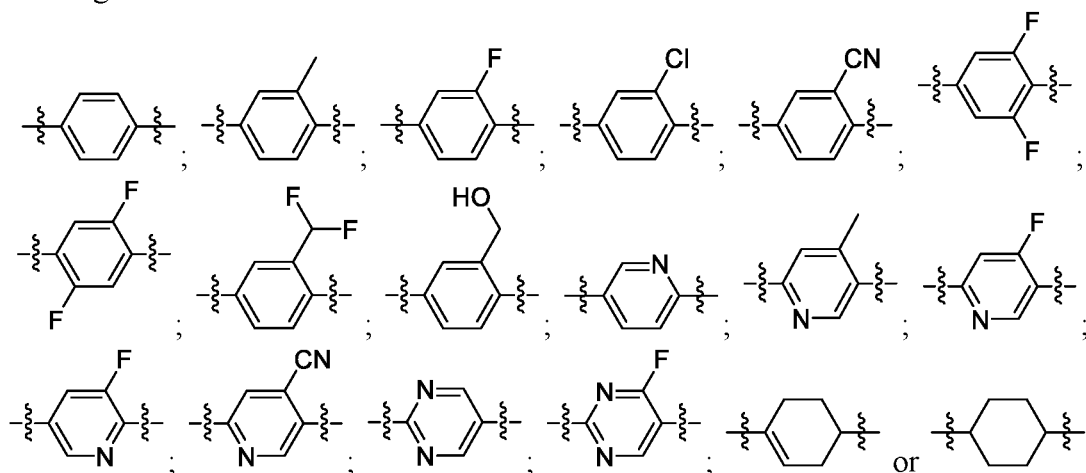




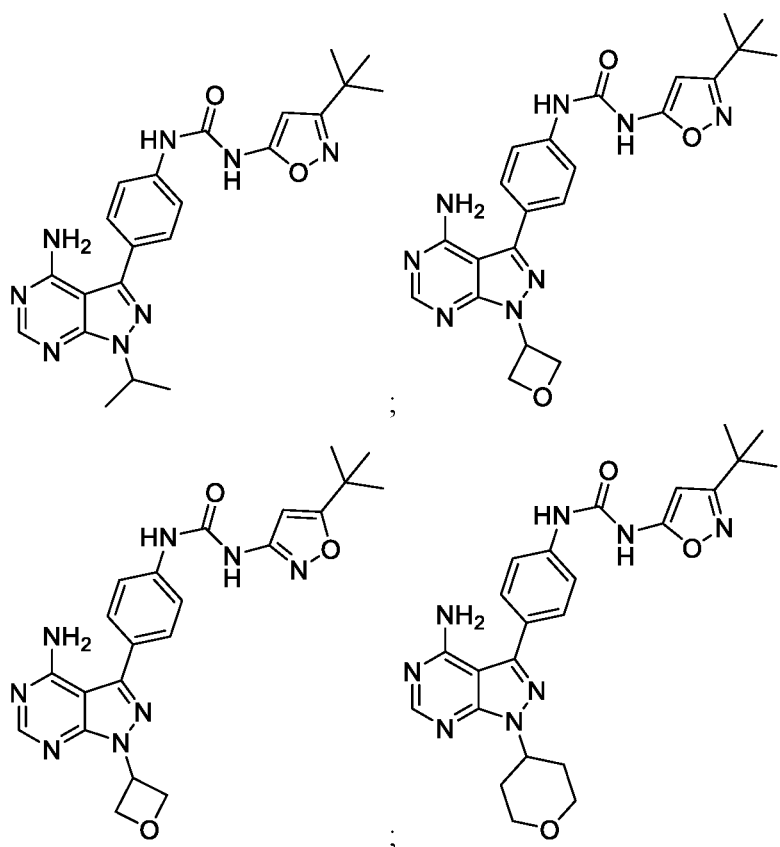
22. The compound of any one of claims 1-21, wherein R⁴ is H.
23. The compound of any one of claims 1-22, wherein Y is NH.
24. The compound of any one of claims 1-22, wherein Y is CHOH.
25. The compound of any one of claims 1-24, wherein X is N.
26. The compound of any one of claims 1-24, wherein X is CH.
27. The compound of any one of claims 1-26, wherein A is C₆-C₁₀ aryl, C₃-C₁₀ cycloalkyl or 5-6 membered monocyclic heteroaryl, each of which is optionally substituted with one or more R⁶.
28. The compound of claim 27, wherein A is phenyl.

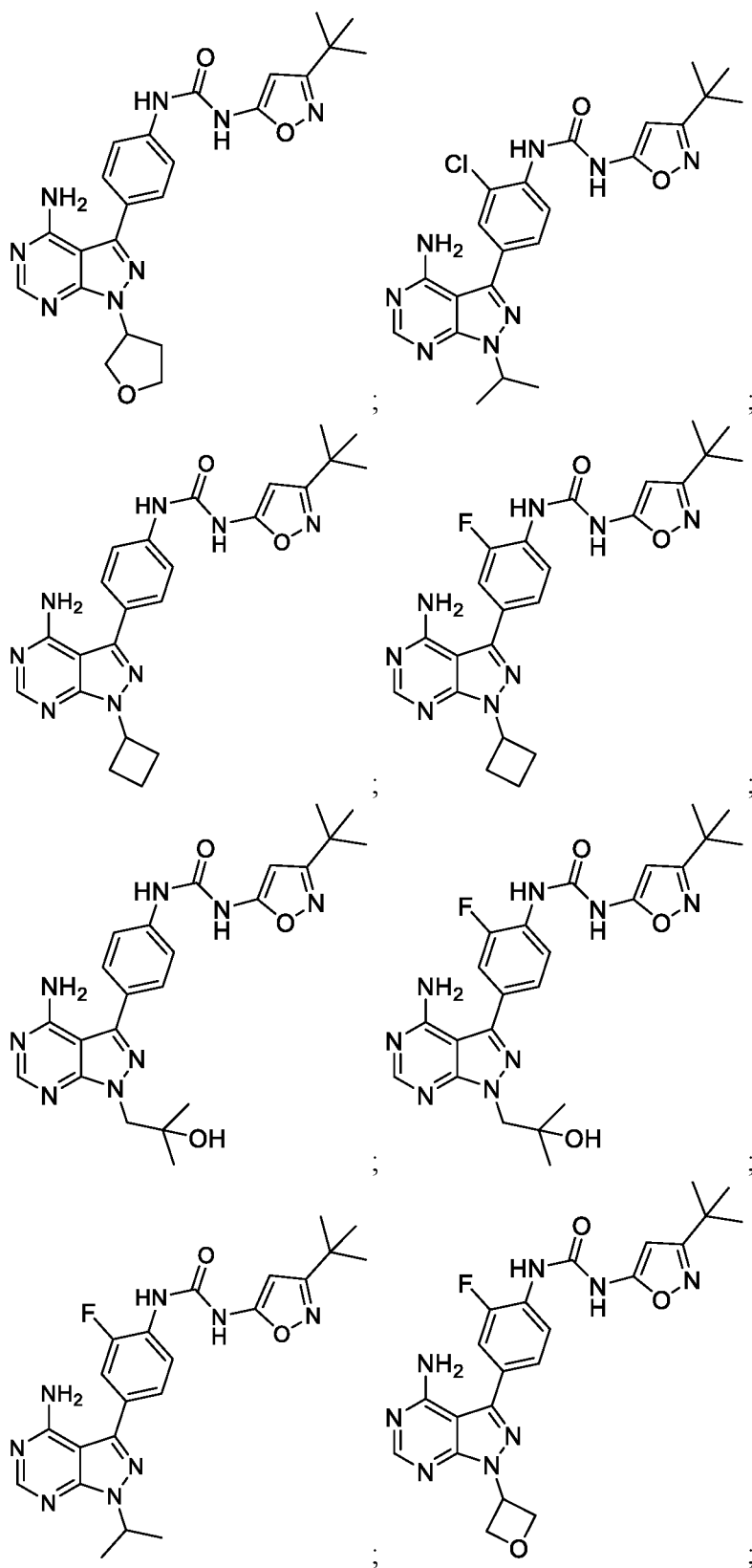
29. The compound of claim 27, wherein A is saturated or unsaturated cyclohexyl.
30. The compound of claim 27, wherein A is pyridinyl.
31. The compound of claim 27, wherein A is pyrimidinyl.
32. The compound of any one of claims 1-31, wherein A is unsubstituted.
33. The compound of any one of claims 1-31, wherein A is substituted with one or more R⁵.
34. The compound of claim 33 wherein R⁵ is halo.
35. The compound of claim 34, wherein halo is fluoro or chloro.
36. The compound of claim 33, wherein R⁵ is cyano.
37. The compound of claim 33, wherein R⁵ is C₁-C₆ alkyl.
38. The compound of claim 37, wherein the C₁-C₆ alkyl is methyl.
39. The compound of claim 33, wherein R⁵ is C₁-C₆ haloalkyl.
40. The compound of claim 39, wherein the C₁-C₆ haloalkyl is difluoromethyl.
41. The compound of claim 33, wherein R⁵ is C₁-C₆ hydroxylalkyl.
42. The compound of claim 41, wherein the C₁-C₆ hydroxylalkyl is -CH₂OH.

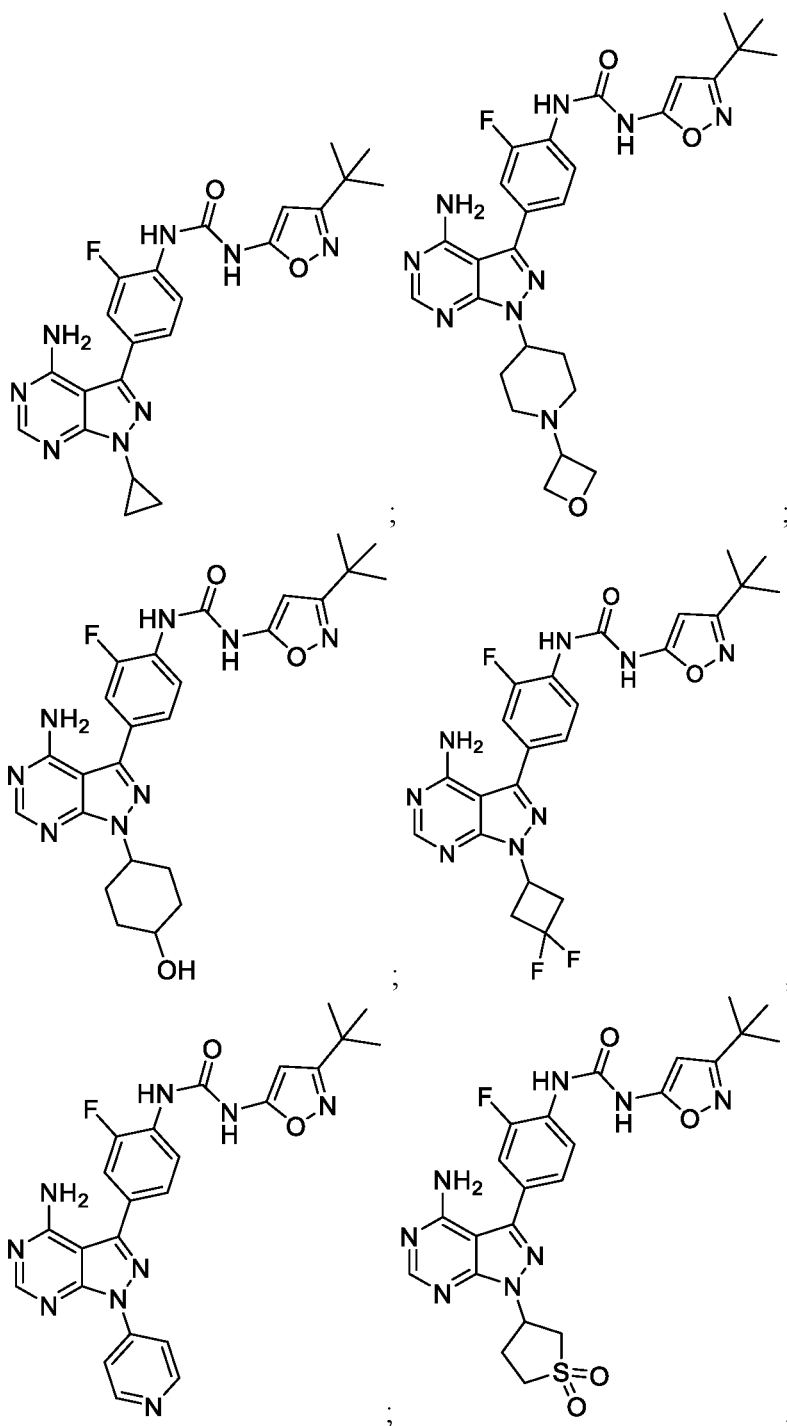
43. The compound of any one of claims 1-42, wherein A has one of the following structures:

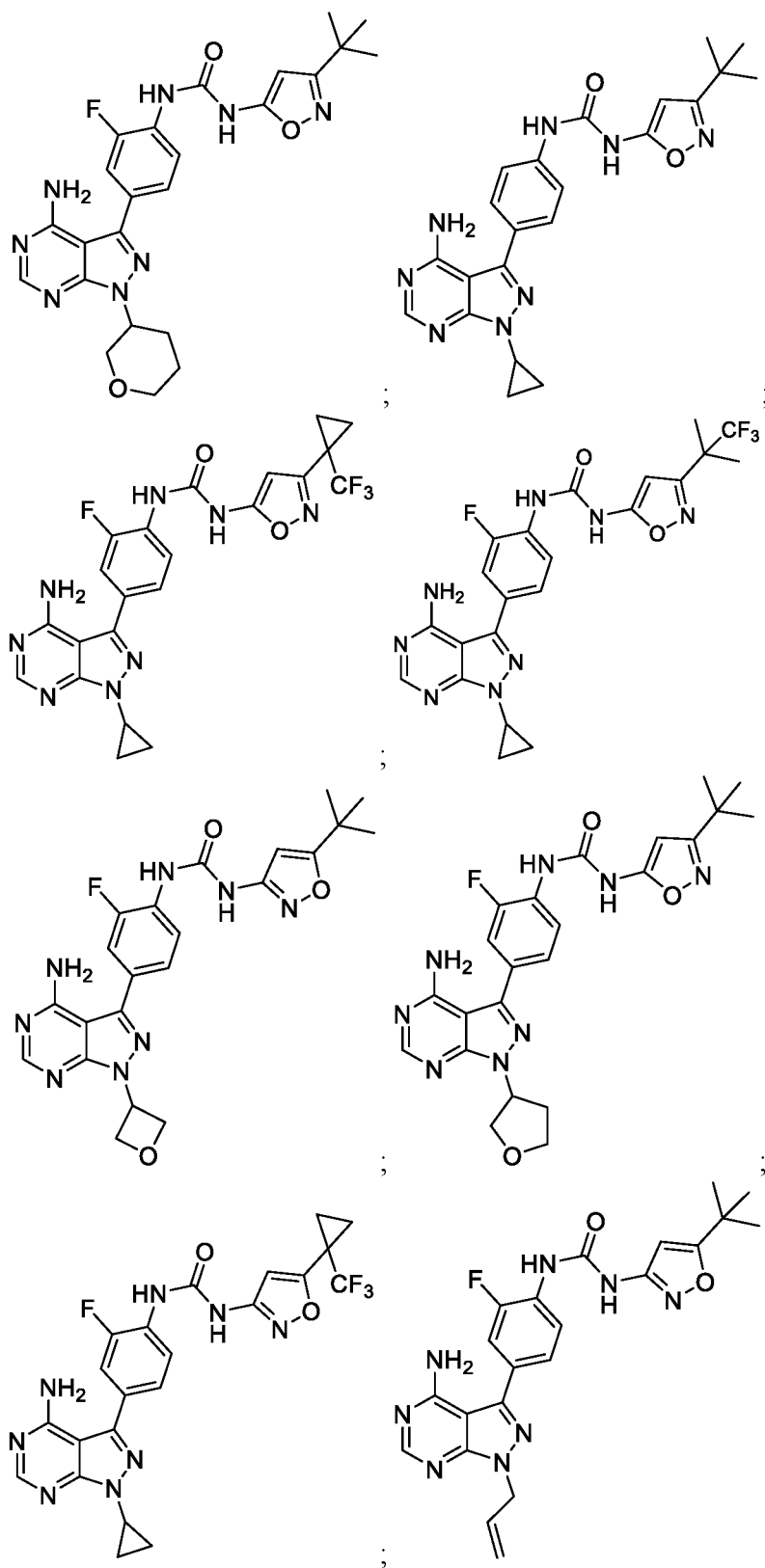


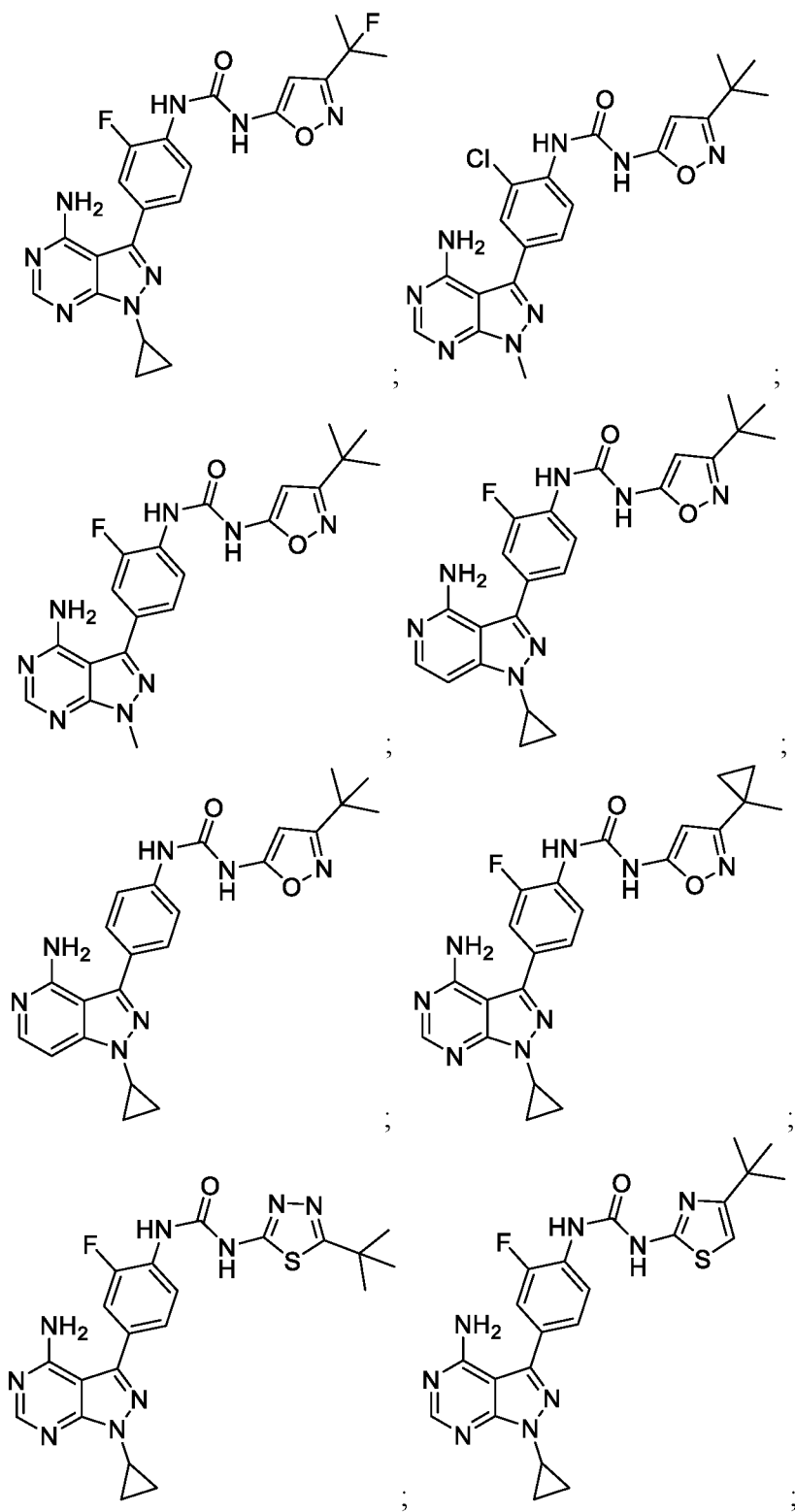
44. The compound of claim 1, wherein the compound has one of the following structures:

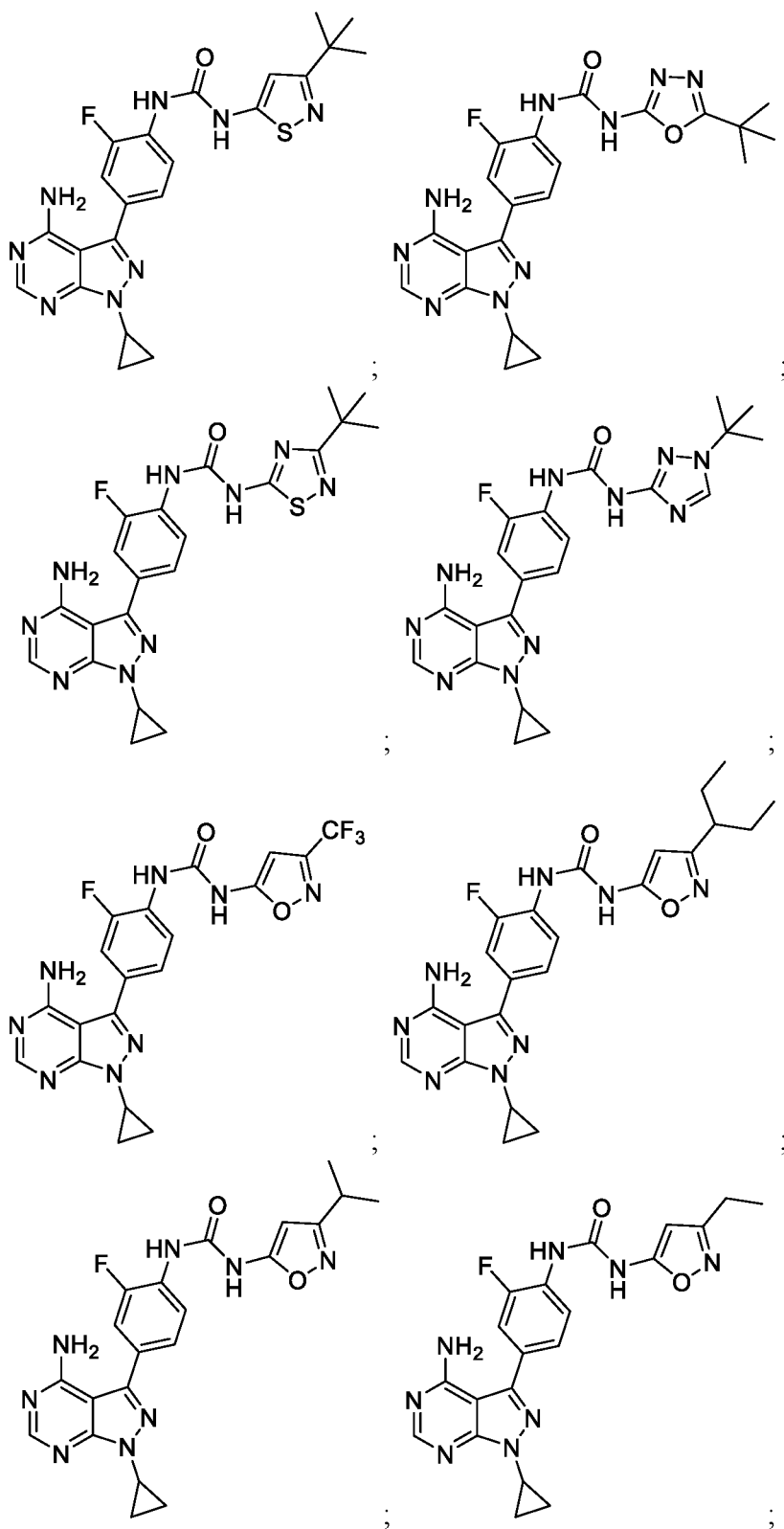


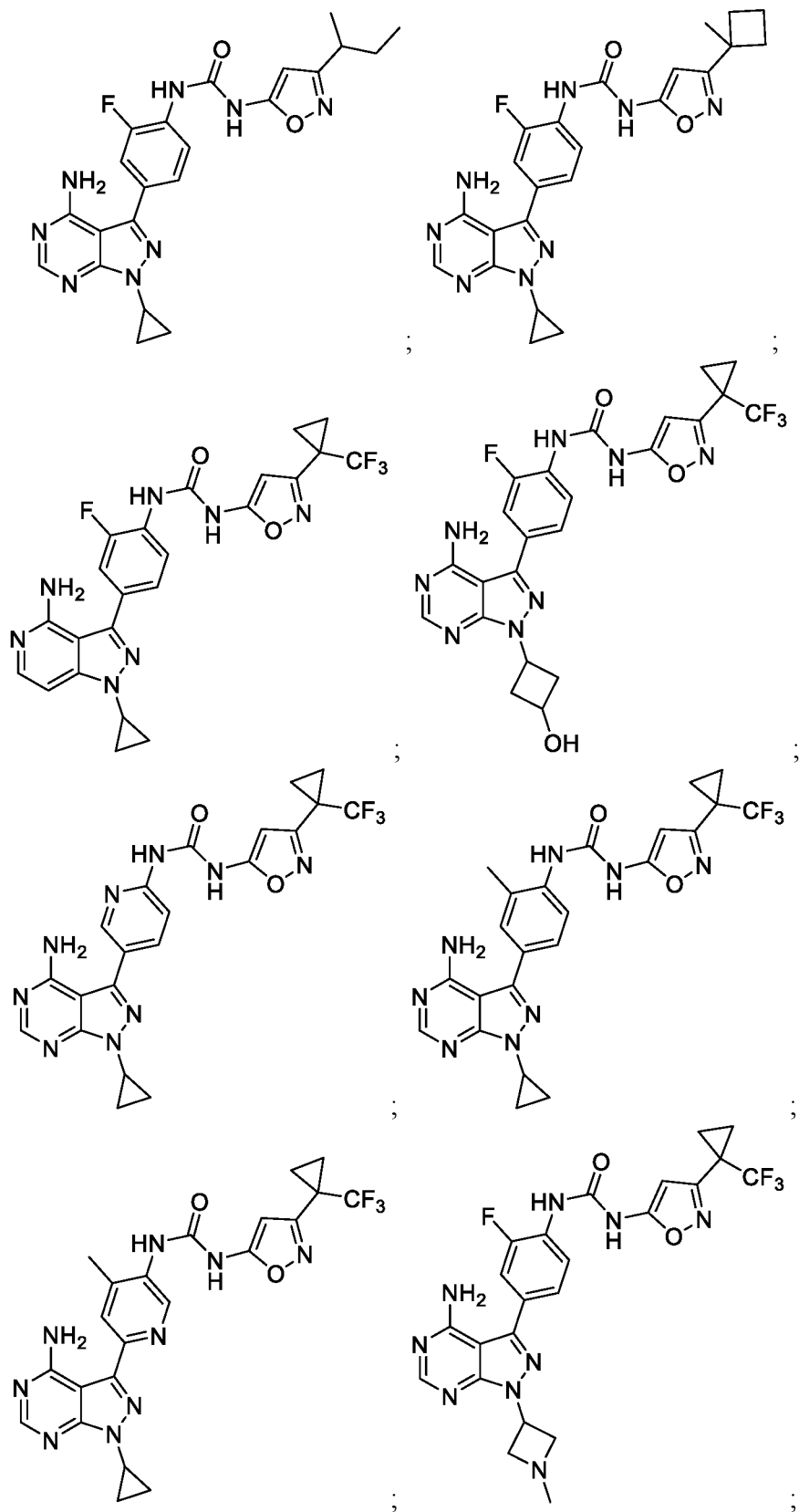


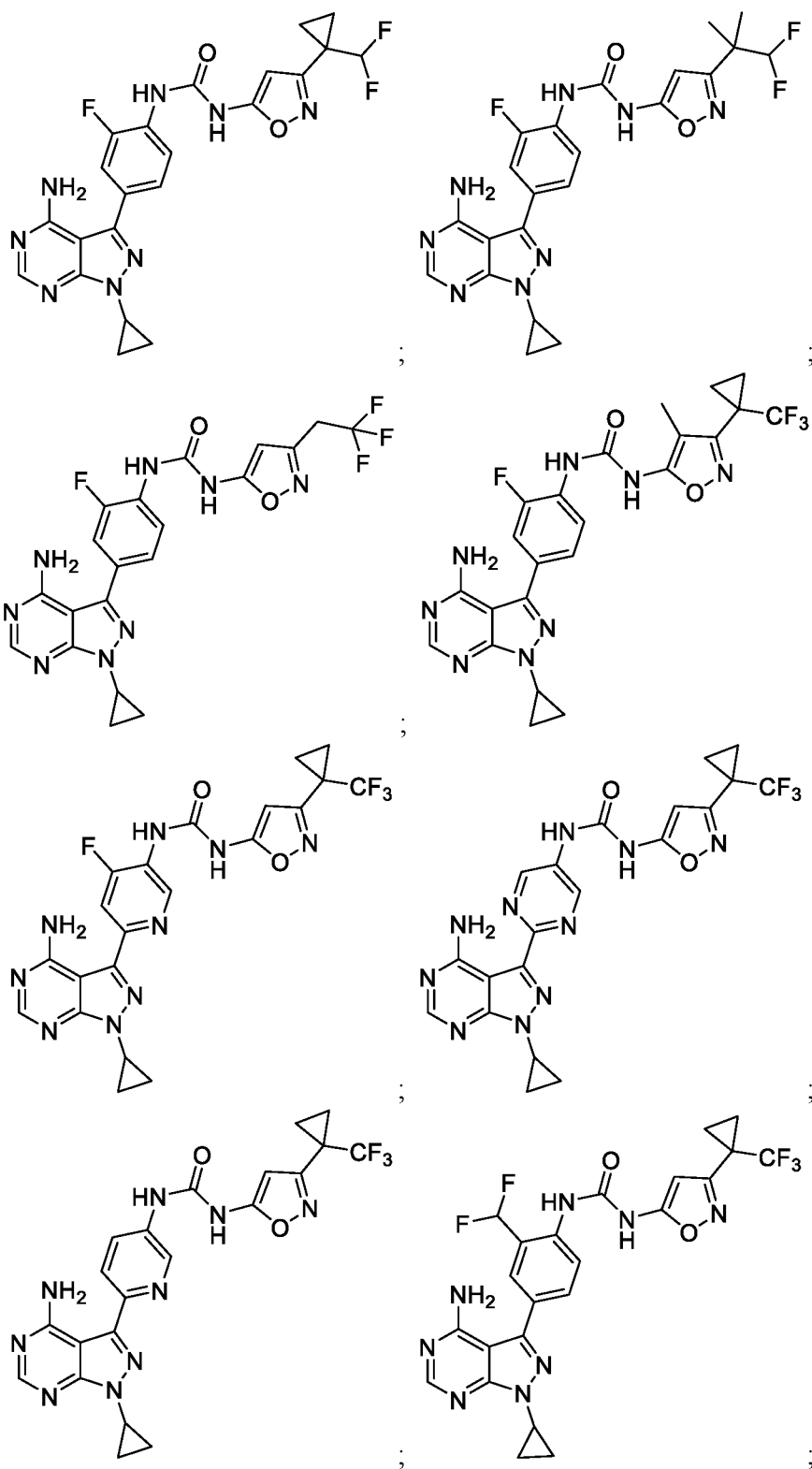


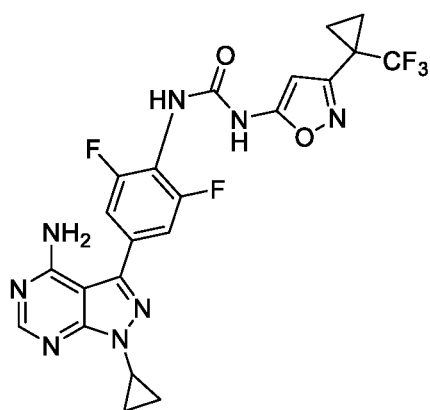




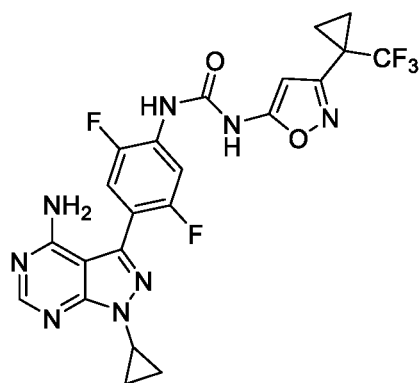




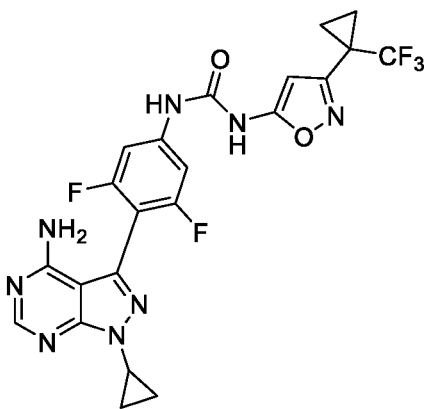




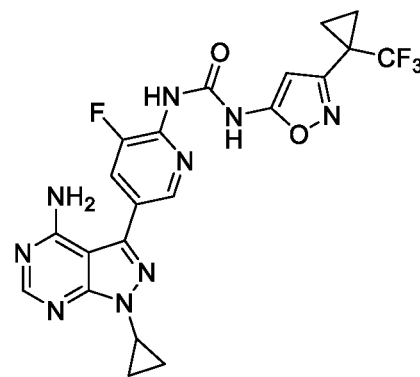
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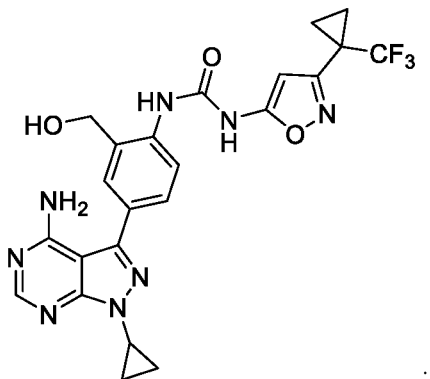
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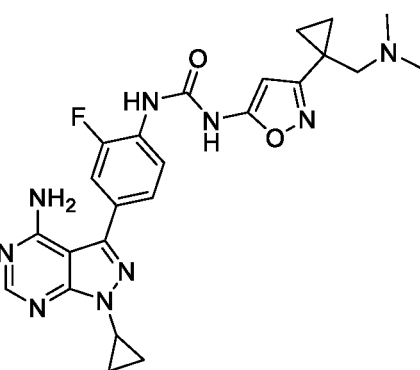
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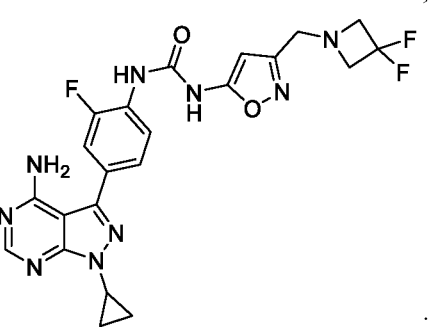
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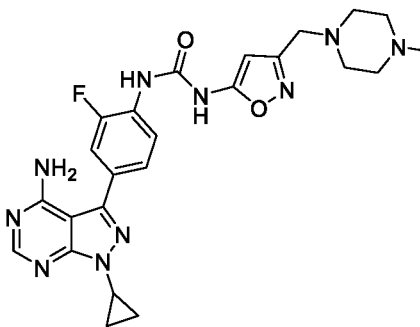
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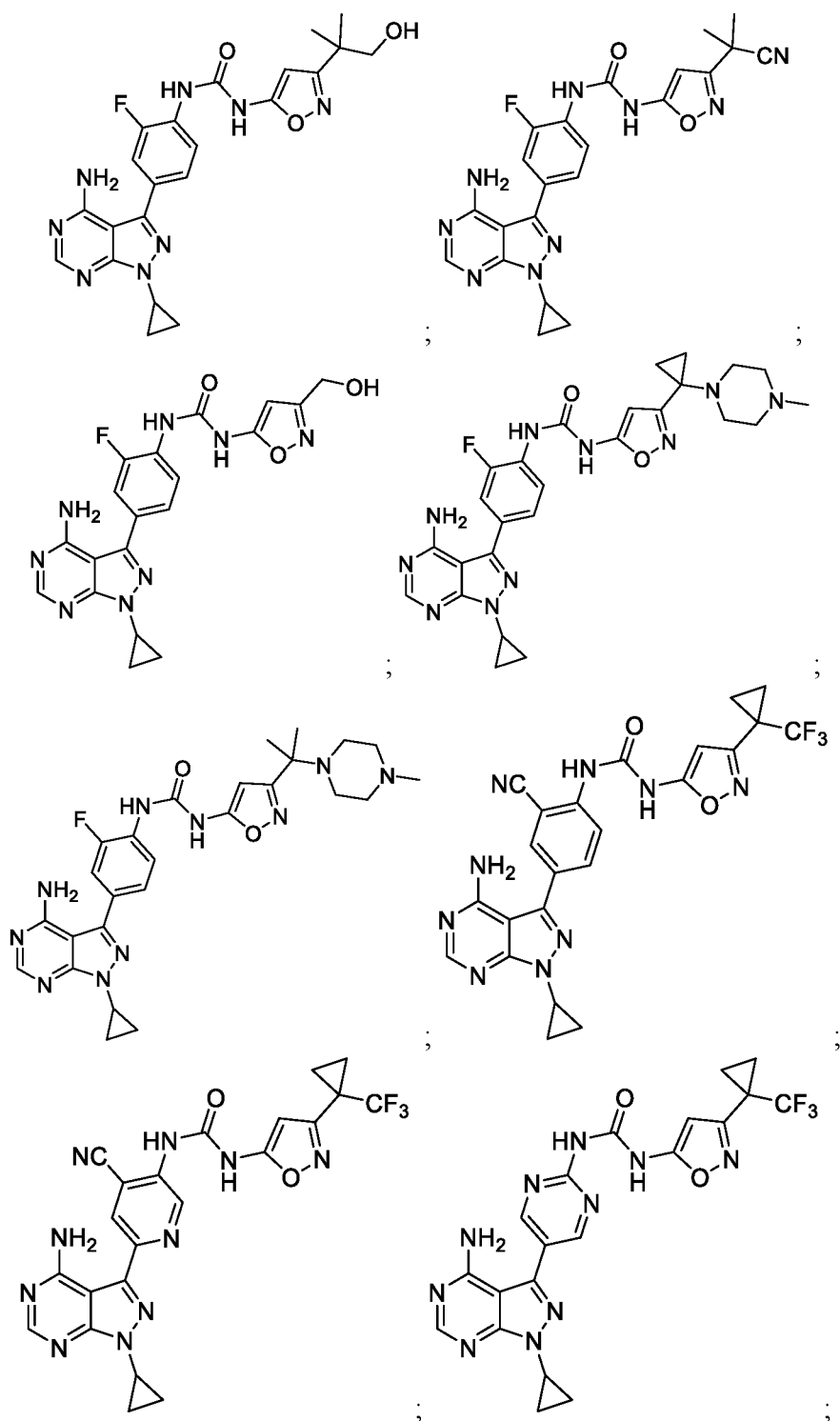
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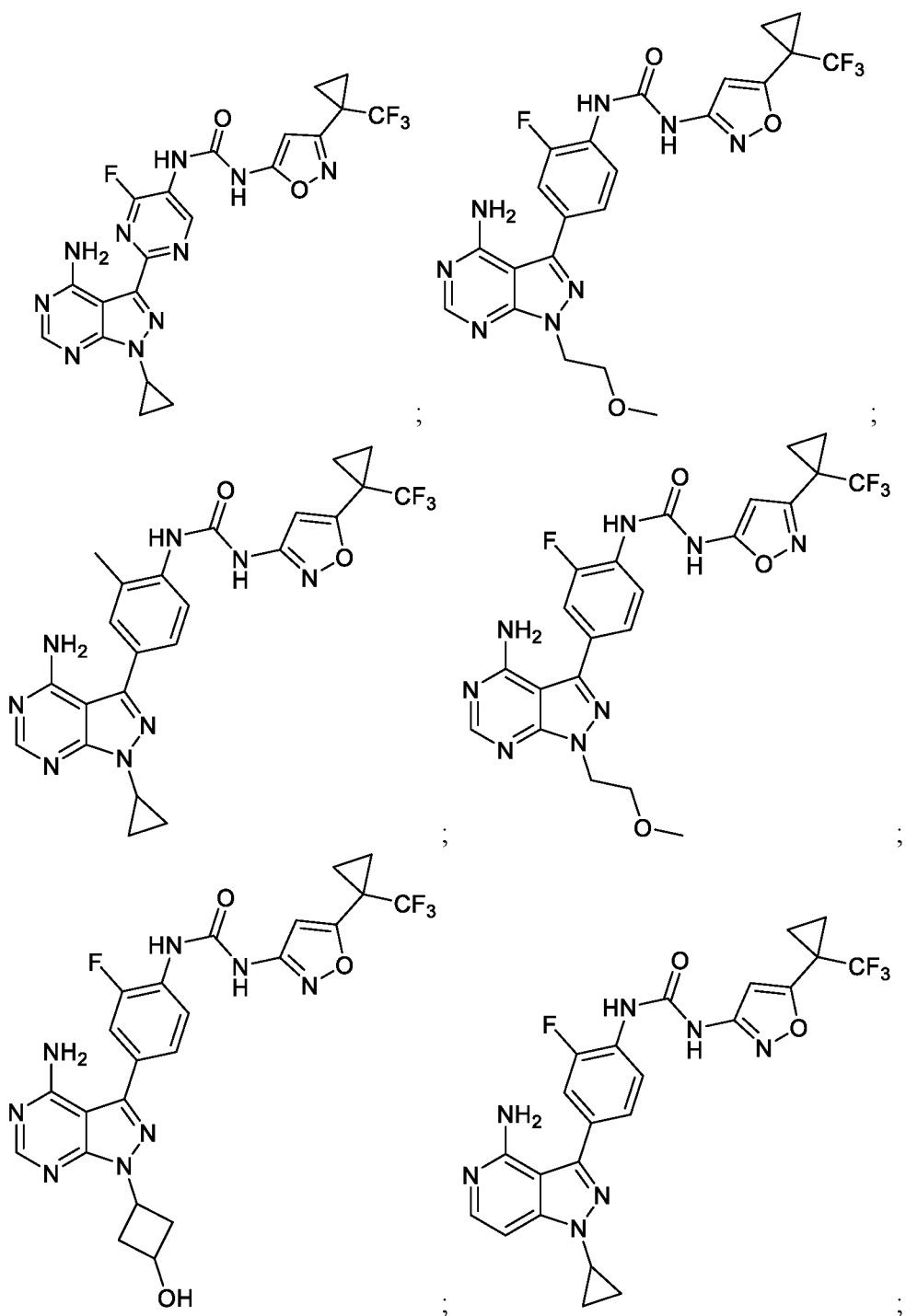


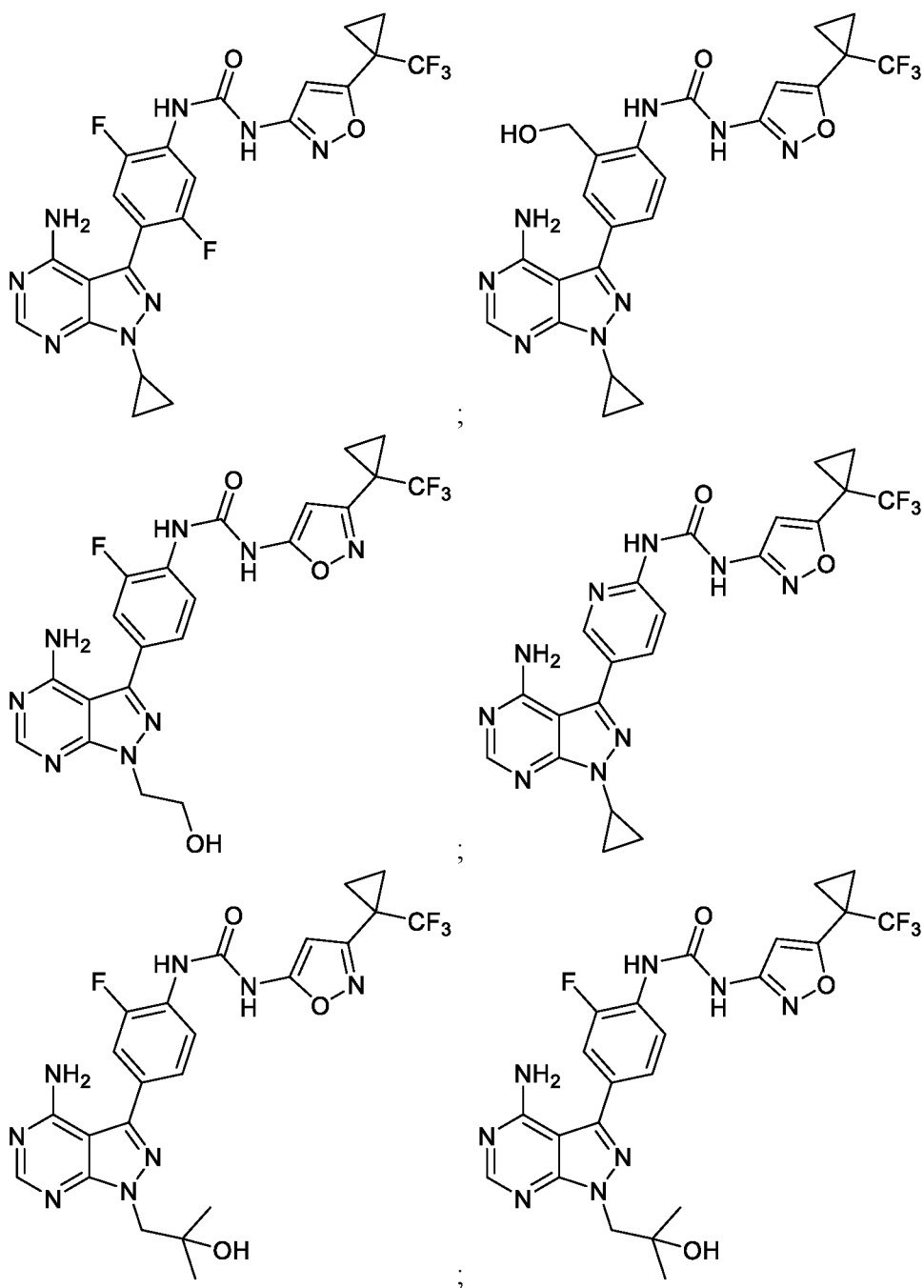
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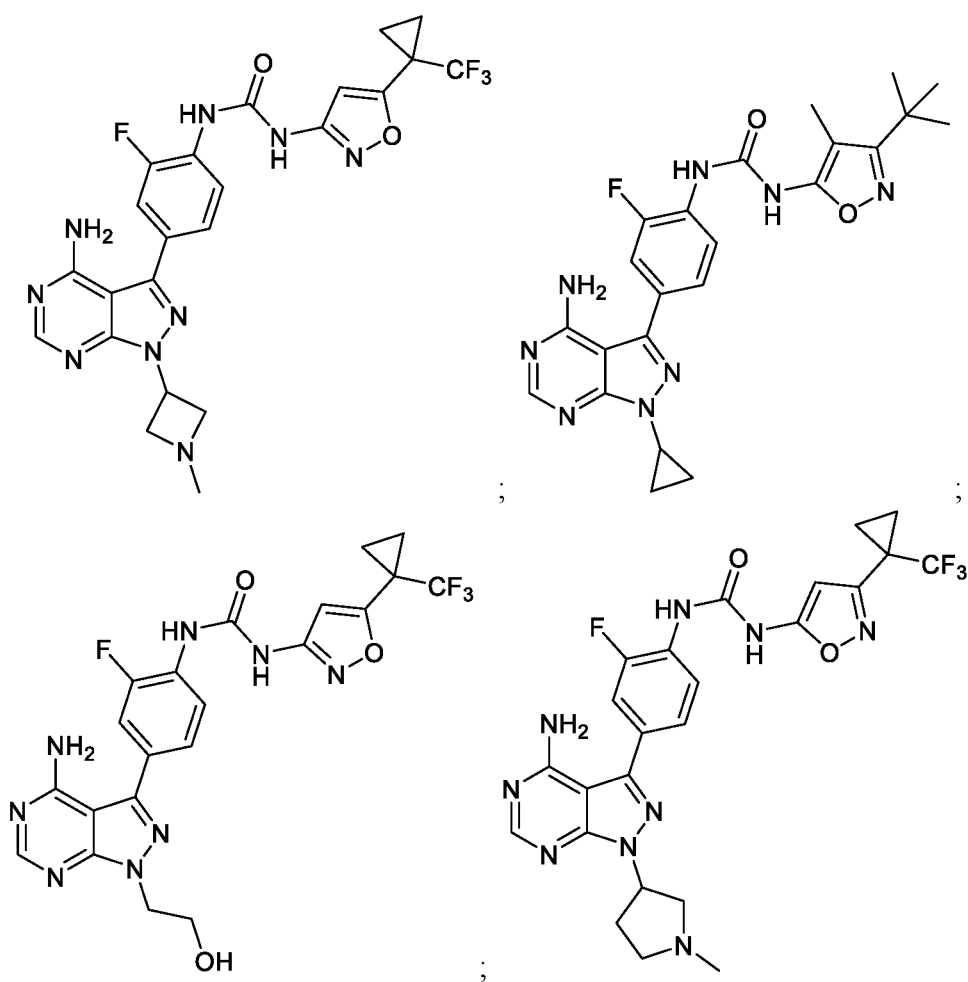


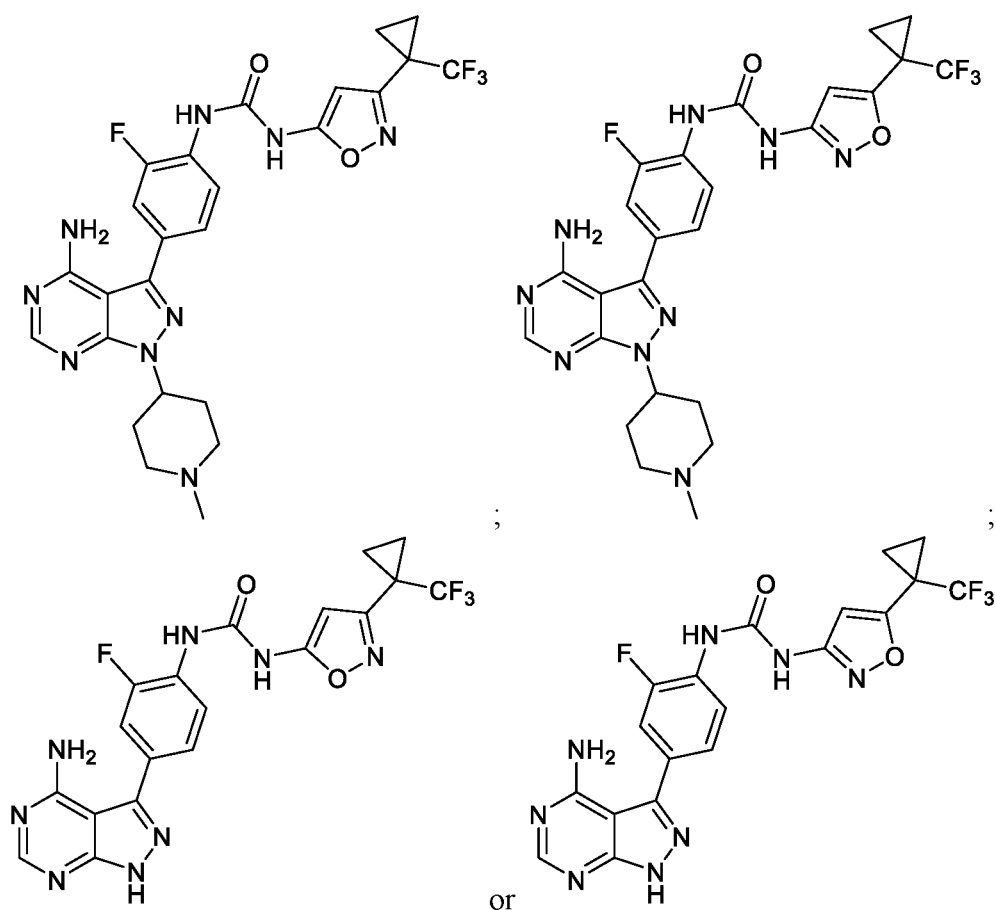
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or a pharmaceutically acceptable salt, stereoisomer or prodrug thereof.

45. The compound of any one of claims 1-44, wherein the compound is a modulator of the NLRP3 inflammasome.

46. The compound of any one of claims 1-45, wherein the compound is an inhibitor of NEK7.

47. A pharmaceutical composition comprising the compound of any one of claims 1-46, and a pharmaceutically acceptable carrier, diluent or excipient.

48. A method of treating a NLRP3-mediated disorder, comprising administering a therapeutically effective amount of a compound of any one of claims 1-46, or the pharmaceutical composition of claim 47, to a subject in need thereof.

49. The method of claim 48, 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 and ischemic conditions.

50. The method of claim 48 or 49, 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, and Muckle-Wells syndrome.