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(71) Applicant: **TAKEDA PHARMACEUTICAL COMPANY LIMITED** [JP/JP]; 1-1, Doshomachi 4-chome, Chuoku, Osaka-shi, Osaka 541-0045 (JP).

(72) Inventors; and

(71) Applicants (for US only): **KOMANDLA, Mallareddy** [US/US]; c/o Takeda California, Inc., 9625 Town Centre Drive, San Diego, California 92121 (US). **MIURA, Joanne** [US/US]; c/o Takeda California, Inc., 9625 Town Centre Drive, San Diego, California 92121 (US). **WANG, Haixia** [US/US]; c/o Takeda California, Inc., 9625 Town Centre Drive, San Diego, California 92121 (US). **WANG, Xiaolun**

[US/US]; c/o Takeda California, Inc., 9625 Town Centre Drive, San Diego, California 92121 (US).

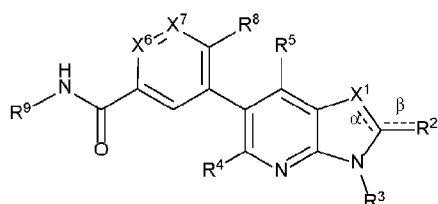
(72) Inventors: **LAWSON, John David**; c/o Takeda California, Inc., 9625 Town Centre Drive, San Diego, California 92121 (US). **TYHONAS, John**; c/o Takeda California, Inc., 9625 Town Centre Drive, San Diego, California 92121 (US).

(74) Agent: **RUSO, Matthew J.** et al.; c/o Takeda California, Inc., 9625 Town Centre Drive, San Diego, California 92121 (US).

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(54) Title: 2-OXO-2,3-DIHYDRO-1H-IMIDAZO[4,5-B]PYRIDIN-6-YL)-4-METHYLBENZAMIDE DERIVATIVES AND SIMILAR COMPOUNDS AS RIPK2 INHIBITORS FOR TREATING E.G. AUTOIMMUNE DISEASES



(I)

(57) Abstract: Disclosed are compounds of Formula 1, and pharmaceutically acceptable salts thereof, wherein α , β , R^2 , R^3 , R^4 , R^5 , R^8 , R^9 , X^1 , X^6 , and X^7 are defined in the specification. The compounds of formula 1 are receptor-interacting protein kinase 2 (RIPK2) inhibitors for treating e.g. type I hypersensitivity reactions, autoimmune diseases, inflammatory disorders, cancer and non-malignant proliferative disorders, such as e.g. allergic rhinitis, asthma, atopic dermatitis, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, lupus nephritis, psoriasis, immune thrombocytopenic purpura, inflammatory bowel disease, chronic obstructive pulmonary disease, Sjogren's syndrome, ankylosing spondylitis, Behcet's disease, graft versus host disease, pemphigus vulgaris, idiopathic plasmacytic lymphadenopathy, atherosclerosis, myocardial infarction and thrombosis. The present description discloses the preparation of exemplary compounds as well as pharmacological data thereof (e.g. pages 107 to 208; examples 1 to 109; table 1). An exemplary compound is e.g. N-cyclopropyl-2-fluoro-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-6-yl)-4-methylbenzamide (example 1).



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2-OXO-2,3-DIHYDRO-1H-IMIDAZO[4,5-B]PYRIDIN-6-YL)-4-METHYLBENZAMIDE DERIVATIVES AND SIMILAR COMPOUNDS AS RIPK2 INHIBITORS FOR TREATING E.G. AUTOIMMUNE DISEASES

FIELD OF THE INVENTION

[0001] This invention relates to pyridine-fused imidazole and pyrrole derivatives which are selective inhibitors of receptor-interacting protein kinase 2 (RIPK2), to pharmaceutical compositions which contain them, and to their use to treat diseases, disorders, and conditions associated with RIPK2, including inflammatory bowel disease (IBD).

BACKGROUND OF THE INVENTION

[0002] Receptor-interacting protein kinase 2 (RIPK2) is a serine/threonine protein kinase which mediates a pro-inflammatory signaling cascade involving nucleotide-binding oligomerization domain-containing protein 1 and 2 (NOD1 and NOD2). The cytosolic pattern recognition receptors (PPRs) NOD1 and NOD2 function in the innate immune system, detecting invasive bacteria via binding to diaminopimelic acid or muramyl dipeptide (MDP) residues present in bacterial peptidoglycan. Following activation, NOD1 and NOD2 associate with RIPK2, which subsequently undergoes autophosphorylation and polyubiquitination via interaction with XIAP and other E3 ligases. The RIPK2-ubiquitin complex activates TAK1 and IKK kinases, which promote upregulation of the mitogen-activated protein kinase and NF- κ B signaling pathways. *See, e.g.,* P. Canning, Q. Ruan, T. Schwerd, *et al.*, “Inflammatory signaling by NOD-RIPK2 is inhibited by clinically relevant Type II Kinase Inhibitors,” *Chemistry & Biology* 22:1174-84 (2015) and M. Hrdinka, L. Schlicher, B. Dai, *et al.*, “Small molecule inhibitors reveal an indispensable scaffolding role of RIPK2 in NOD2 signaling,” *The EMBO Journal* 37: e99372 (2018) and references cited therein.

[0003] Dysregulation of the RIPK2-NOD signaling pathway has been implicated in several inflammatory and autoimmune diseases, including IBD. *See* R. Caruso, N. Warner, N. Inohara, and G. Nunez, “NOD1 and NOD2: signaling, host defense, and inflammatory disease,” *Immunity* 41: 898–908 (2014); L. Jostins, S. Ripke, R. Weersma, *et al.*, “Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease,” *Nature* 491: 119–24 (2012); and D. Philpott, M. Sorbara, M. Robertson, *et al.*, “NOD proteins: regulators of inflammation in health and disease,” *Nat. Rev. Immunol.* 14: 9–23 (2014). Genetic variants in NOD2 are known risk factors in Crohn’s disease. *See* J. Hugot, M. Chamaillard, H. Zouali, *et al.*, “Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn’s disease,” *Nature* 411: 599–603 (2001) and Y. Ogura, D. Bonen, N.

Inohara, *et al.*, “A frameshift mutation in NOD2 associated with susceptibility to Crohn’s disease,” *Nature* 411: 603–06 (2001). Certain mutations in NOD2 reduce its binding to MDP and may promote excessive inflammatory signaling from other PPRs, including NOD1. *See* A. Couturier-Maillard, T. Secher, A. Rehman, *et al.*, “NOD2-mediated dysbiosis predisposes mice to transmissible colitis and colorectal cancer,” *J. Clin. Invest.* 123: 700–11 (2013); N. Inohara, Y. Ogura, A. Fontalba, *et al.*, “Host recognition of bacterial muramyl dipeptide mediated through NOD2. Implications for Crohn’s disease,” *J. Biol. Chem.* 278: 5509–12 (2003). Another mutation disrupts NOD2 inhibition, increasing RIPK2 activation. *See* M. Sorbara, L. Ellison, M. Ramjeet, *et al.*, “The protein ATG16L1 suppresses inflammatory cytokines induced by the intracellular sensors Nod1 and Nod2 in an autophagy-independent manner,” *Immunity* 39: 858–73 (2013). Excessive RIPK2 activation has also been identified in pediatric patients with Crohn’s disease. *See* A. Negroni, L. Stronati, M. Pierdomenico, *et al.*, “Activation of NOD2-mediated intestinal pathway in a pediatric population with Crohn’s disease,” *Inflamm. Bowel Dis.* 15: 1145–54 (2009).

[0004] In addition to Crohn’s disease, mutations in the RIPK2-NOD signaling pathways have been linked to other disorders, including Blau Syndrome and early-onset sarcoidosis, which are pediatric granulomatous diseases characterized by arthritis, dermatitis, uveitis and cranial neuropathies. Other mutations in the RIPK2-NOD signaling pathways have been linked to allergic airway inflammation, arthritis and multiple sclerosis. *See, e.g.*, F. Caso F, Galozzi P, Costa L, *et al.*, “Autoinflammatory granulomatous diseases: from Blau Syndrome and Early-Onset Sarcoidosis to NOD2-mediated disease and Crohn’s disease,” *RMD Open* 1: e000097 (2015); J. Jun, F. Cominelli, and D. Abbott, “RIP2 activity in inflammatory disease and implications for novel therapeutics,” *J. Leukoc. Biol.* 94: 927–32 (2013); F. Goh, K. Cook, N. Upton, *et al.*, “Receptor-interacting protein 2 gene silencing attenuates allergic airway inflammation,” *J. Immunol.* 191: 2691–99 (2013); and P. Shaw, M. Barr, R. Lukens, *et al.*, “Signaling via the RIP2 adaptor protein in central nervous system-infiltrating dendritic cells promotes inflammation and autoimmunity,” *Immunity* 34: 75–84 (2011).

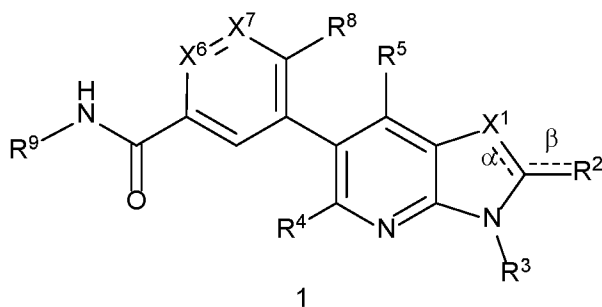
[0005] Inhibitors of RIPK2 are expected to be useful for treating inflammatory and autoimmune diseases, including IBD.

SUMMARY OF THE INVENTION

[0006] This invention provides pyridine-fused imidazole and pyrrole derivatives and pharmaceutically acceptable salts thereof. This invention also provides pharmaceutical compositions that contain the pyridine-fused imidazole and pyrrole derivatives and provides

for their use to treat diseases, disorders and conditions associated with RIPK2, including IBD and other gastrointestinal diseases, disorders and conditions.

[0007] One aspect of the invention provides compounds of Formula 1:



or a pharmaceutically acceptable salt thereof in which:

α is a single bond, β is a double bond, X^1 is NR^{1N} , and R^2 is oxo; or

α is a double bond, β is a single bond, X^1 is selected from N and CR^{1C} , and R^2 is selected from hydrogen, C_{1-4} alkyl, and C_{1-4} alkoxy;

R^{1C} is selected from hydrogen, halo, and C_{1-6} alkyl which is substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, C_{1-4} alkoxy, and amino which is optionally substituted with one or two C_{1-4} alkyl;

R^{1N} is selected from C_{1-4} alkyl, C_{3-8} cycloalkyl- $(CH_2)_n$, C_{2-8} heterocyclyl- $(CH_2)_n$, and C_{1-9} heteroaryl- $(CH_2)_n$, wherein each of the C_{1-4} alkyl, C_{3-8} cycloalkyl, C_{2-8} heterocyclyl, and C_{1-9} heteroaryl moieties is substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, and amino which is optionally substituted with one or two C_{1-4} alkyl, and wherein the C_{1-4} alkyl and C_{1-4} alkoxy optional substituents are each independently substituted with from 0 to 3 optional substituents independently selected from halo;

n is selected from 0, 1, 2, and 3;

R^3 is C_{1-6} alkyl which is substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, C_{1-4} alkoxy which is optionally substituted with C_{1-4} alkoxy, and from amino which is optionally substituted with one or two C_{1-4} alkyl, wherein one or more of the hydrogen atoms on R^3 may optionally be deuterium;

R^4 and R^5 are each independently selected from hydrogen, halo, and C_{1-4} alkyl;

X^6 is selected from N and $C(R^6)$;

X^7 is selected from N and $C(R^7)$;

R⁶ and R⁷ are each independently from hydrogen, halo, C₁₋₄ alkyl, and C₁₋₄ alkoxy;
R⁸ is selected from hydrogen, halo, C₁₋₄ alkyl, and C₁₋₄ alkoxy, wherein the C₁₋₄ alkyl and C₁₋₄ alkoxy substituents are substituted with from 0 to 3 optional substituents independently selected from halo; and
R⁹ is selected from C₁₋₆ alkyl, C₃₋₈ cycloalkyl, C₂₋₈ heterocyclyl, and C₁₋₉ heteroaryl, each substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, oxo, C₁₋₄ alkyl, C₁₋₄ alkoxy, and amino which is optionally substituted with one or two C₁₋₄ alkyl, wherein the C₁₋₄ alkyl and C₁₋₄ alkoxy optional substituents are each independently substituted with from 0 to 3 optional substituents independently selected from halo; and
wherein each of the heterocyclyl and heteroaryl moieties independently has 1 to 4 ring members which are heteroatoms, each of the heteroatoms independently selected from N, O, and S.

[0008] Another aspect of the invention provides a compound which is selected from the group of compounds described in the examples and their pharmaceutically acceptable salts.

[0009] A further aspect of the invention provides a pharmaceutical composition which includes a compound of Formula 1 or a pharmaceutically acceptable salt thereof, or any one of the compounds or pharmaceutically acceptable salts defined in the preceding paragraph; and a pharmaceutically acceptable excipient.

[0010] An additional aspect of the invention provides a compound of Formula 1 or a pharmaceutically acceptable salt thereof, or any one of the compounds described in the examples or a pharmaceutically acceptable salt thereof, for use as a medicament.

[0011] Another aspect of the invention provides a compound of Formula 1 or a pharmaceutically acceptable salt thereof, or any one of the compounds described in the examples or a pharmaceutically acceptable salt thereof, for treating a disease, disorder or condition associated with RIPK2.

[0012] A further aspect of the invention provides a compound of Formula 1 or a pharmaceutically acceptable salt thereof, or any one of the compounds described in the examples or a pharmaceutically acceptable salt thereof, for use in treating a disease, disorder or condition selected from allergic rhinitis, asthma, atopic dermatitis, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, lupus nephritis, psoriasis, immune thrombocytopenic purpura, inflammatory bowel disease, chronic obstructive pulmonary disease, Sjögren's syndrome, ankylosing spondylitis, Behcet's disease, graft versus host

disease, pemphigus vulgaris, idiopathic plasmacytic lymphadenopathy, atherosclerosis, myocardial infarction, and thrombosis.

[0013] An additional aspect of the invention provides a compound of Formula 1 or a pharmaceutically acceptable salt thereof, or any one of the compounds described in the examples or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a disease, disorder or condition associated with RIPK2.

[0014] Another aspect of the invention provides a method for inhibiting RIPK2 in a subject, the method comprising administering to the subject a compound of Formula 1 or a pharmaceutically acceptable salt thereof, or any one of the compounds described in the examples or a pharmaceutically acceptable salt thereof.

[0015] A further aspect of the invention provides a method for treating a disease, disorder or condition associated with RIPK2, the method comprising administering to the subject an effective amount of a compound of Formula 1 or a pharmaceutically acceptable salt thereof, or any one of the compounds described in the examples or a pharmaceutically acceptable salt thereof.

[0016] An additional aspect of the invention provides a method for treating a disease, disorder or condition in a subject, the method comprising administering to the subject an effective amount of a compound of Formula 1 or a pharmaceutically acceptable salt thereof, or any one of the compounds described in the examples or a pharmaceutically acceptable salt thereof, wherein the disease, disorder or condition is selected from Type I hypersensitivity reactions, autoimmune diseases, and inflammatory disorders, cancer, and non-malignant proliferative disorders

[0017] Another aspect of the invention provides a method for treating a disease, disorder or condition in a subject, the method comprising administering to the subject an effective amount of a compound of Formula 1 or a pharmaceutically acceptable salt thereof, or any one of the compounds described in the examples or a pharmaceutically acceptable salt thereof, wherein the disease, disorder or condition is selected from allergic rhinitis, asthma, atopic dermatitis, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, lupus nephritis, psoriasis, immune thrombocytopenic purpura, inflammatory bowel disease, chronic obstructive pulmonary disease, Sjögren's syndrome, ankylosing spondylitis, Behcet's disease, graft versus host disease, pemphigus vulgaris, idiopathic plasmacytic lymphadenopathy, atherosclerosis, myocardial infarction, and thrombosis.

[0018] A further aspect of the invention provides a compound of Formula 1 or a pharmaceutically acceptable salt thereof, or any one of the compounds described in the examples or a pharmaceutically acceptable salt thereof; and at least one additional pharmacologically active agent.

DETAILED DESCRIPTION OF THE INVENTION

[0019] Unless otherwise indicated, this disclosure uses definitions provided below.

[0020] “Substituted,” when used about a chemical substituent or moiety (e.g., a C₁₋₆ alkyl group), means that one or more hydrogen atoms of the substituent or moiety have been replaced with one or more non-hydrogen atoms or groups, provided valence requirements are met and a chemically stable compound results from the substitution.

[0021] “About” or “approximately,” when used about a measurable numerical variable, refers to the indicated value of the variable and to all values of the variable that are within the experimental error of the indicated value or within ± 10 percent of the indicated value, whichever is greater.

[0022] “Alkyl” refers to straight chain and branched saturated hydrocarbon groups, generally having a specified number of carbon atoms (e.g., C₁₋₄ alkyl refers to an alkyl group having 1 to 4 (i.e., 1, 2, 3 or 4) carbon atoms, C₁₋₆ alkyl refers to an alkyl group having 1 to 6 carbon atoms, and so on). Examples of alkyl groups include methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *s*-butyl, *i*-butyl, *t*-butyl, pent-1-yl, pent-2-yl, pent-3-yl, 3-methylbut-1-yl, 3-methylbut-2-yl, 2-methylbut-2-yl, 2,2,2-trimethyleth-1-yl, *n*-hexyl, and the like.

[0023] “Alkanediyl” refers to divalent alkyl groups, where alkyl is defined above, and generally having a specified number of carbon atoms (e.g., C₁₋₄ alkanediyl refers to an alkanediyl group having 1 to 4 (i.e., 1, 2, 3 or 4) carbon atoms, C₁₋₆ alkanediyl refers to an alkanediyl group having 1 to 6 carbon atoms, and so on). Examples of alkanediyl groups include methylene, ethane-1,1-diyl, ethane-1,2-diyl, propane-1,3-diyl, propane-1,2-diyl, propane-1,1-diyl, propane-2,2-diyl, butane-1,4-diyl, butane-1,3-diyl, butane-1,2-diyl, butane-1,1-diyl, isobutane-1,3-diyl, isobutane-1,1-diyl, isobutane-1,2-diyl, and the like.

[0024] “Alkenyl” refers to straight chain and branched hydrocarbon groups having one or more carbon-carbon double bonds, and generally having a specified number of carbon atoms. Examples of alkenyl groups include ethenyl, 1-propen-1-yl, 1-propen-2-yl, 2-propen-1-yl, 1-buten-1-yl, 1-buten-2-yl, 3-buten-1-yl, 3-buten-2-yl, 2-buten-1-yl, 2-buten-2-yl, 2-methyl-1-propen-1-yl, 2-methyl-2-propen-1-yl, 1,3-butadien-1-yl, 1,3-butadien-2-yl, and the like.

[0025] “Alkynyl” refers to straight chain or branched hydrocarbon groups having one or more triple carbon-carbon bonds, and generally having a specified number of carbon atoms. Examples of alkynyl groups include ethynyl, 1-propyn-1-yl, 2-propyn-1-yl, 1-butyne-1-yl, 3-butyne-1-yl, 3-butyne-2-yl, 2-butyne-1-yl, and the like.

[0026] “Alkoxy” refers to straight chain and branched saturated hydrocarbon groups attached through an oxygen atom, generally having a specified number of carbon atoms (e.g., C₁₋₄ alkoxy refers to an alkoxy group having 1 to 4 (i.e., 1, 2, 3 or 4) carbon atoms, C₁₋₆ alkoxy refers to an alkoxy group having 1 to 6 carbon atoms, and so on). Examples of alkoxy groups include methoxy, ethoxy, *n*-propoxy, *i*-propoxy, *n*-butoxy, *s*-butoxy, *i*-butoxy, *t*-butoxy, pent-1-yloxy, pent-2-yloxy, pent-3-yloxy, 3-methylbut-1-yloxy, 3-methylbut-2-yloxy, 2-methylbut-2-yloxy, 2,2,2-trimethyleth-1-yloxy, *n*-hexoxy, and the like.

[0027] “Halo,” “halogen” and “halogeno” may be used interchangeably and refer to fluoro, chloro, bromo, and iodo.

[0028] “Haloalkyl,” “haloalkenyl,” and “haloalkynyl,” refer, respectively, to alkyl, alkenyl, and alkynyl groups substituted with one or more halogen atoms, where alkyl, alkenyl, and alkynyl are defined above, and generally having a specified number of carbon atoms. Examples of haloalkyl groups include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 1-fluoroethyl, 1,1-difluoroethyl, 1-chloroethyl, 1,1-dichloroethyl, 1-fluoro-1-methylethyl, 1-chloro-1-methylethyl, and the like.

[0029] “Cycloalkyl” refers to saturated monocyclic and bicyclic hydrocarbon groups, generally having a specified number of carbon atoms that comprise the ring or rings (e.g., C₃₋₈ cycloalkyl refers to a cycloalkyl group having 3 to 8 carbon atoms as ring members). Bicyclic hydrocarbon groups may include isolated rings (two rings sharing no carbon atoms), spiro rings (two rings sharing one carbon atom), fused rings (two rings sharing two carbon atoms and the bond between the two common carbon atoms), and bridged rings (two rings sharing two carbon atoms, but not a common bond). The cycloalkyl group may be attached through any ring atom unless such attachment would violate valence requirements, and where indicated, may optionally include one or more non-hydrogen substituents unless such substitution would violate valence requirements.

[0030] Examples of monocyclic cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. Examples of fused bicyclic cycloalkyl groups include bicyclo[2.1.0]pentanyl (i.e., bicyclo[2.1.0]pentan-1-yl, bicyclo[2.1.0]pentan-2-yl, and bicyclo[2.1.0]pentan-5-yl), bicyclo[3.1.0]hexanyl, bicyclo[3.2.0]heptanyl,

bicyclo[4.1.0]heptanyl, bicyclo[3.3.0]octanyl, bicyclo[4.2.0]octanyl, bicyclo[4.3.0]nonanyl, bicyclo[4.4.0]decanyl, and the like. Examples of bridged cycloalkyl groups include bicyclo[2.1.1]hexanyl, bicyclo[2.2.1]heptanyl, bicyclo[3.1.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[3.2.1]octanyl, bicyclo[4.1.1]octanyl, bicyclo[3.3.1]nonanyl, bicyclo[4.2.1]nonanyl, bicyclo[3.3.2]decanyl, bicyclo[4.2.2]decanyl, bicyclo[4.3.1]decanyl, bicyclo[3.3.3]undecanyl, bicyclo[4.3.2]undecanyl, bicyclo[4.3.3]dodecanyl, and the like. Examples of spiro cycloalkyl groups include spiro[3.3]heptanyl, spiro[2.4]heptanyl, spiro[3.4]octanyl, spiro[2.5]octanyl, spiro[3.5]nonanyl, and the like. Examples of isolated bicyclic cycloalkyl groups include those derived from bi(cyclobutane), cyclobutanecyclopentane, bi(cyclopentane), cyclobutanecyclohexane, cyclopentanecyclohexane, bi(cyclohexane), etc.

[0031] “Cycloalkanediyl” refers to divalent cycloalkyl groups, where cycloalkyl is defined above, and generally having a specified number of carbon atoms (e.g., C₃₋₄ cycloalkanediyl refers to a cycloalkanediyl group having 3 to 4 (i.e., 3 or 4) carbon atoms, C₃₋₆ cycloalkanediyl refers to a cycloalkanediyl group having 3 to 6 carbon atoms, and so on). Examples of cycloalkanediyl groups include cyclopropan-1,1-diyl, cyclopropan-1,2-diyl, cyclobutan-1,1-diyl, cyclobutan-1,2-diyl, and the like.

[0032] “Cycloalkylidene” refers to divalent monocyclic cycloalkyl groups, where cycloalkyl is defined above, which are attached through a single carbon atom of the group, and generally having a specified number of carbon atoms that comprise the ring (e.g., C₃₋₆ cycloalkylidene refers to a cycloalkylidene group having 3 to 6 carbon atoms as ring members). Examples include cyclopropylidene, cyclobutylidene, cyclopentylidene, and cyclohexylidene.

[0033] “Cycloalkenyl” refers to partially unsaturated monocyclic and bicyclic hydrocarbon groups, generally having a specified number of carbon atoms that comprise the ring or rings. As with cycloalkyl groups, the bicyclic cycloalkenyl groups may include isolated, spiro, fused, or bridged rings. Similarly, the cycloalkenyl group may be attached through any ring atom, and where indicated, may optionally include one or more non-hydrogen substituents unless such attachment or substitution would violate valence requirements. Examples of cycloalkenyl groups include the partially unsaturated analogs of the cycloalkyl groups described above, such as cyclobutenyl (i.e., cyclobuten-1-yl and cyclobuten-3-yl), cyclopentenyl, cyclohexenyl, bicyclo[2.2.1]hept-2-enyl, and the like.

[0034] “Aryl” refers to fully unsaturated monocyclic aromatic hydrocarbons and to polycyclic hydrocarbons having at least one aromatic ring, both monocyclic and polycyclic aryl groups generally having a specified number of carbon atoms that comprise their ring members (e.g., C₆₋₁₄ aryl refers to an aryl group having 6 to 14 carbon atoms as ring members). The group may be attached through any ring atom, and where indicated, may optionally include one or more non-hydrogen substituents unless such attachment or substitution would violate valence requirements. Examples of aryl groups include phenyl, biphenyl, cyclobutabenzenyl, indenyl, naphthalenyl, benzocycloheptanyl, biphenylenyl, fluorenyl, groups derived from cycloheptatriene cation, and the like.

[0035] “Arylene” refers to divalent aryl groups, where aryl is defined above. Examples of arylene groups include phenylene (i.e., benzene-1,2-diyl).

[0036] “Heterocycle” and “heterocyclyl” may be used interchangeably and refer to saturated or partially unsaturated monocyclic or bicyclic groups having ring atoms composed of carbon atoms and 1 to 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. Both the monocyclic and bicyclic groups generally have a specified number of carbon atoms in their ring or rings (e.g., C₂₋₈ heterocyclyl refers to a heterocyclyl group having 2 to 8 carbon atoms and 1 to 4 heteroatoms as ring members). As with bicyclic cycloalkyl groups, bicyclic heterocyclyl groups may include isolated rings, spiro rings, fused rings, and bridged rings in which at least one of the rings includes one or more heteroatoms. The heterocyclyl group may be attached through any ring atom, and where indicated, may optionally include one or more non-hydrogen substituents unless such attachment or substitution would violate valence requirements or result in a chemically unstable compound. Examples of heterocyclyl groups include oxiranyl, thiiranyl, aziridinyl (e.g., aziridin-1-yl and aziridin-2-yl), oxetanyl, thietanyl, azetidiny, tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, 1,4-dioxanyl, 1,4-oxathianyl, morpholinyl, 1,4-dithianyl, piperazinyl, 1,4-azathianyl, oxepanyl, thiepanyl, azepanyl, 1,4-dioxepanyl, 1,4-oxathiepanyl, 1,4-oxaazepanyl, 1,4-dithiepanyl, 1,4-thiazepanyl, 1,4-diazepanyl, 3,4-dihydro-2*H*-pyranyl, 3,6-dihydro-2*H*-pyranyl, 2*H*-pyranyl, 1,2-dihydropyridinyl, 1,2,3,4-tetrahydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,6-dihydropyrimidinyl, 1,2,3,4-tetrahydropyrimidinyl, and 1,2-dihydropyrazolo[1,5-*d*][1,2,4]triazinyl.

[0037] “Heterocycle-diyl” refers to heterocyclyl groups which are attached through two ring atoms of the group, where heterocyclyl is defined above. They generally have a specified number of carbon atoms in their ring or rings (e.g., C₂₋₈ heterocycle-diyl refers to a

heterocycle-diyl group having 2 to 8 carbon atoms and 1 to 4 heteroatoms as ring members). Examples of heterocycle-diyl groups include the multivalent analogs of the heterocycle groups described above, such as morpholine-3,4-diyl, pyrrolidine-1,2-diyl, 1-pyrrolidinyl-2-ylidene, 1-pyridinyl-2-ylidene, 1-(4*H*)-pyrazolyl-5-ylidene, 1-(3*H*)-imidazolyl-2-ylidene, 3-oxazolyl-2-ylidene, 1-piperidinyl-2-ylidene, 1-piperazinyl-6-ylidene, and the like.

[0038] “Heteroaromatic” and “heteroaryl” may be used interchangeably and refer to unsaturated monocyclic aromatic groups and to polycyclic groups having at least one aromatic ring, each of the groups having ring atoms composed of carbon atoms and 1 to 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. Both the monocyclic and polycyclic groups generally have a specified number of carbon atoms as ring members (e.g., C₁₋₉ heteroaryl refers to a heteroaryl group having 1 to 9 carbon atoms and 1 to 4 heteroatoms as ring members) and may include any bicyclic group in which any of the above-listed monocyclic heterocycles are fused to a benzene ring. The heteroaryl group may be attached through any ring atom (or ring atoms for fused rings), and where indicated, may optionally include one or more non-hydrogen substituents unless such attachment or substitution would violate valence requirements or result in a chemically unstable compound. Examples of heteroaryl groups include monocyclic groups such as pyrrolyl (e.g., pyrrol-1-yl, pyrrol-2-yl, and pyrrol-3-yl), furanyl, thienyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, 1,2,3-triazolyl, 1,3,4-triazolyl, 1-oxa-2,3-diazolyl, 1-oxa-2,4-diazolyl, 1-oxa-2,5-diazolyl, 1-oxa-3,4-diazolyl, 1-thia-2,3-diazolyl, 1-thia-2,4-diazolyl, 1-thia-2,5-diazolyl, 1-thia-3,4-diazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, and pyrazinyl.

[0039] Examples of heteroaryl groups also include bicyclic groups such as benzofuranyl, isobenzofuranyl, benzothienyl, benzo[*c*]thienyl, 1*H*-indolyl, 3*H*-indolyl, isoindolyl, 1*H*-isoindolyl, indolinyl, isoindolinyl, benzimidazolyl, 1*H*-indazolyl, 2*H*-indazolyl, benzotriazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, 1*H*-pyrrolo[2,3-*c*]pyridinyl, 1*H*-pyrrolo[3,2-*c*]pyridinyl, 1*H*-pyrrolo[3,2-*b*]pyridinyl, 3*H*-imidazo[4,5-*b*]pyridinyl, 3*H*-imidazo[4,5-*c*]pyridinyl, 1*H*-pyrazolo[4,3-*b*]pyridinyl, 1*H*-pyrazolo[4,3-*c*]pyridinyl, 1*H*-pyrazolo[3,4-*c*]pyridinyl, 1*H*-pyrazolo[3,4-*b*]pyridinyl, 7*H*-purinyl, indolizinyl, imidazo[1,2-*a*]pyridinyl, imidazo[1,5-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, pyrrolo[1,2-*b*]pyridazinyl, imidazo[1,2-*c*]pyrimidinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, 1,6-naphthyridinyl, 1,7-naphthyridinyl, 1,8-naphthyridinyl, 1,5-naphthyridinyl, 2,6-naphthyridinyl, 2,7-naphthyridinyl, pyrido[3,2-*d*]pyrimidinyl, pyrido[4,3-*d*]pyrimidinyl, pyrido[3,4-*d*]pyrimidinyl, pyrido[2,3-*d*]pyrimidinyl, pyrido[2,3-*b*]pyrazinyl, pyrido[3,4-

b]pyrazinyl, pyrimido[5,4-*d*]pyrimidinyl, pyrazino[2,3-*b*]pyrazinyl, pyrimido[4,5-*d*]pyrimidinyl, 1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazinyl, 2,3-dihydrobenzo[*b*][1,4]dioxinyl, 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazinyl, 2,3-dihydro-1*H*-benzo[*d*]imidazolyl, benzo[*d*]thiazolyl, 2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, [1,2,4]triazolo[1,5-*a*]pyridinyl, 2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridinyl, tetrazolo[1,5-*a*]pyridinyl, 7*H*-pyrrolo[2,3-*d*]pyrimidinyl, pyrazolo[1,5-*a*]pyrimidinyl, imidazo[1,2-*a*]pyrimidinyl, 4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidinyl, 2,3,6,7-tetrahydro-1*H*-purinyl, 5*H*-pyrrolo[2,3-*b*]pyrazinyl, imidazo[1,2-*a*]pyrazinyl, imidazo[1,2-*b*]pyridazinyl, and 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazinyl.

[0040] “Heteroarylene” refers to heteroaryl groups which are attached through two ring atoms of the group, where heteroaryl is defined above. They generally have a specified number of carbon atoms in their ring or rings (e.g., C₃₋₅ heteroarylene refers to a heteroarylene group having 3 to 5 carbon atoms and 1 to 4 heteroatoms as ring members). Examples of heteroarylene groups include the multivalent analogs of the heteroaryl groups described above, such as pyridine-2,3-diyl, pyridine-3,4-diyl, pyrazole-4,5-diyl, pyrazole-3,4-diyl, and the like.

[0041] “Oxo” refers to a double bonded oxygen (=O).

[0042] “Leaving group” refers to any group that leaves a molecule during a fragmentation process, including substitution reactions, elimination reactions, and addition-elimination reactions. Leaving groups may be nucleofugal, in which the group leaves with a pair of electrons that formerly served as the bond between the leaving group and the molecule, or may be electrofugal, in which the group leaves without the pair of electrons. The ability of a nucleofugal leaving group to leave depends on its base strength, with the strongest bases being the poorest leaving groups. Common nucleofugal leaving groups include nitrogen (e.g., from diazonium salts); sulfonates, including alkylsulfonates (e.g., mesylate), fluoroalkylsulfonates (e.g., triflate, hexaflate, nonaflate, and tresylate), and arylsulfonates (e.g., tosylate, brosylate, closylate, and nosylate). Others include carbonates, halide ions, carboxylate anions, phenolate ions, and alkoxides. Some stronger bases, such as NH₂[−] and OH[−] can be made better leaving groups by treatment with an acid. Common electrofugal leaving groups include the proton, CO₂, and metals.

[0043] “Opposite enantiomer” refers to a molecule that is a non-superimposable mirror image of a reference molecule, which may be obtained by inverting all the stereogenic centers of the reference molecule. For example, if the reference molecule has *S* absolute

stereochemical configuration, then the opposite enantiomer has *R* absolute stereochemical configuration. Likewise, if the reference molecule has *S,S* absolute stereochemical configuration, then the opposite enantiomer has *R,R* stereochemical configuration, and so on.

[0044] “Stereoisomer” and “stereoisomers” of a compound with given stereochemical configuration refer to the opposite enantiomer of the compound and to any diastereoisomers, including geometrical isomers (*Z/E*) of the compound. For example, if a compound has *S,R,Z* stereochemical configuration, its stereoisomers would include its opposite enantiomer having *R,S,Z* configuration, and its diastereomers having *S,S,Z* configuration, *R,R,Z* configuration, *S,R,E* configuration, *R,S,E* configuration, *S,S,E* configuration, and *R,R,E* configuration. If the stereochemical configuration of a compound is not specified, then “stereoisomer” refers to any one of the possible stereochemical configurations of the compound.

[0045] “Substantially pure stereoisomer” and variants thereof refer to a sample containing a compound having a specific stereochemical configuration and which comprises at least about 95% of the sample.

[0046] “Pure stereoisomer” and variants thereof refer to a sample containing a compound having a specific stereochemical configuration and which comprises at least about 99.5% of the sample.

[0047] “Subject” refers to a mammal, including a human.

[0048] “Pharmaceutically acceptable” substances refer to those substances which are suitable for administration to subjects.

[0049] “Treating” refers to reversing, alleviating, inhibiting the progress of, or preventing a disease, disorder or condition to which such term applies, or to reversing, alleviating, inhibiting the progress of, or preventing one or more symptoms of such disease, disorder or condition.

[0050] “Treatment” refers to the act of “treating,” as defined immediately above.

[0051] “Drug,” “drug substance,” “active pharmaceutical ingredient,” and the like, refer to a compound (e.g., compounds of Formula 1, including subgeneric compounds and compounds specifically named in the specification) that may be used for treating a subject in need of treatment.

[0052] “Effective amount” of a drug, “therapeutically effective amount” of a drug, and the like, refer to the quantity of the drug that may be used for treating a subject and may depend on the weight and age of the subject and the route of administration, among other things.

[0053] “Excipient” refers to any diluent or vehicle for a drug.

[0054] “Pharmaceutical composition” refers to the combination of one or more drug substances and one or more excipients.

[0055] “Drug product,” “pharmaceutical dosage form,” “dosage form,” “final dosage form” and the like, refer to a pharmaceutical composition suitable for treating a subject in need of treatment and generally may be in the form of tablets, capsules, sachets containing powder or granules, liquid solutions or suspensions, patches, films, and the like.

[0056] “Condition associated with RIPK2” and similar phrases relate to a disease, disorder or condition in a subject for which inhibition of RIPK2 may provide a therapeutic or prophylactic benefit.

[0057] The following abbreviations may be used in the specification: Ac (acetyl); ACN (acetonitrile); AIBN (azo-bis-isobutyronitrile); API (active pharmaceutical ingredient); aq (aqueous); B₂pin₂ (4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane)); BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl); Boc (*tert*-butoxycarbonyl); Cbz (carbobenzyloxy); CDI (1,1'-carbonyldiimidazole); dba (dibenzylideneacetone); DAST (*N,N*-diethylaminosulfur trifluoride); DCC (1,3-dicyclohexylcarbodiimide); DCE (1,1-dichloroethane); DCM (dichloromethane); DIAD (diisopropyl azodicarboxylate); DIPEA (*N,N*-diisopropylethylamine, Hünig's Base); DMA (*N,N*-dimethylacetamide); DMAP (4-dimethylaminopyridine); DME (1,2-dimethoxyethane); DMF (*N,N*-dimethylformamide); DMSO (dimethylsulfoxide); dppf (1,1'-bis(diphenylphosphino)ferrocene); DTT (dithiothreitol); EC₅₀ (effective concentration at half maximal response); EDA (ethoxylated dodecyl alcohol, Brj®35); EDC (*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide); EDTA (ethylenediaminetetraacetic acid); ee (enantiomeric excess); eq (equivalents); Et (ethyl); Et₃N (triethylamine); EtOAc (ethyl acetate); EtOH (ethanol); HATU (2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate(V)); HEPES (4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid); HOAc (acetic acid); HOBt (1*H*-benzo[*d*][1,2,3]triazol-1-ol); IC₅₀ (concentration at 50% inhibition); IPA (isopropanol); IPAc (isopropyl acetate); IPE (isopropylether); KO^{*t*}-Bu (potassium tertiary butoxide); LDA (lithium diisopropylamide); LiHMDS (lithium bis(trimethylsilyl)amide); mCPBA (*m*-chloroperoxybenzoic acid); Me (methyl); MeOH (methanol); MTBE (methyl *tert*-butyl ether); mp (melting point); n-BuLi (*n*-butyl lithium); NaO^{*t*}-Bu (sodium tertiary butoxide); NBS (*N*-bromosuccinimide); NCS (*N*-chlorosuccinimide); NIS (*N*-iodosuccinimide); NMM (*N*-methylmorpholine); NMP (*N*-methyl-pyrrolidone); OTf (triflate); PdCl₂(dtbpf) (dichloro[1,1'-bis(di-*tert*-butylphosphino)ferrocene]palladium(II)); PE (petroleum ether); Ph (phenyl); pEC₅₀

($-\log_{10}(\text{EC}_{50})$, where EC_{50} is given in molar (M) units); pIC_{50} ($-\log_{10}(\text{IC}_{50})$, where IC_{50} is given in molar (M) units); Pr (propyl); *c*-Pr (cyclopropyl), *i*-Pr (isopropyl); PTFE (polytetrafluoroethylene); Rac (racemic); RT (room temperature, approximately 20°C to 25°C); SEM (2-(trimethylsilyl)ethoxymethyl); SEM-Cl ((2-chloromethoxyethyl)trimethylsilane); SFC (supercritical fluid chromatography); T3P (2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide); TBAF (tetrabutylammonium fluoride); TBS (*tert*-butyldimethylsilyl); TBSCl (*tert*-butylchlorodimethylsilane); TCEP (*tris*(2-carboxyethyl)phosphine); TFA (trifluoroacetic acid); TFAA (2,2,2-trifluoroacetic anhydride); THF (tetrahydrofuran); TLC (thin layer chromatography); TMEDA (tetramethylethylenediamine); TMS (trimethylsilyl); and Tris buffer (2-amino-2-hydroxymethyl-propane-1,3-diol buffer).

[0058] As described, below, this disclosure concerns compounds of Formula 1 and their pharmaceutically acceptable salts. This disclosure also concerns materials and methods for preparing compounds of Formula 1, pharmaceutical compositions which contain them, and the use of compounds of Formula 1 and their pharmaceutically acceptable salts (optionally in combination with other pharmacologically active agents) for treating diseases, disorders or conditions associated with RIPK2.

[0059] The compounds of Formula 1 include those in which (1):

α is a single bond, β is a double bond, X^1 is $\text{NR}^{1\text{N}}$, and R^2 is oxo; or

α is a double bond, β is a single bond, X^1 is selected from N and $\text{CR}^{1\text{C}}$, and R^2 is selected from hydrogen, C_{1-4} alkyl, and C_{1-4} alkoxy;

$\text{R}^{1\text{C}}$ is selected from hydrogen, halo, and C_{1-6} alkyl which is substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, C_{1-4} alkoxy, and amino which is optionally substituted with one or two C_{1-4} alkyl;

$\text{R}^{1\text{N}}$ is selected from C_{1-4} alkyl, C_{3-8} cycloalkyl-(CH_2)_n, C_{2-8} heterocyclyl-(CH_2)_n, and C_{1-9} heteroaryl-(CH_2)_n, wherein each of the C_{1-4} alkyl, C_{3-8} cycloalkyl, C_{2-8} heterocyclyl, and C_{1-9} heteroaryl moieties is substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, and amino which is optionally substituted with one or two C_{1-4} alkyl, and wherein the C_{1-4} alkyl and C_{1-4} alkoxy optional substituents are each independently substituted with from 0 to 3 optional substituents independently selected from halo;

n is selected from 0, 1, 2, and 3;

R³ is C₁₋₆ alkyl which is substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkoxy which is optionally substituted with C₁₋₄ alkoxy, and from amino which is optionally substituted with one or two C₁₋₄ alkyl, wherein one or more of the hydrogen atoms on R³ may optionally be deuterium;

R⁴ and R⁵ are each independently selected from hydrogen, halo, and C₁₋₄ alkyl;

X⁶ is selected from N and C(R⁶);

X⁷ is selected from N and C(R⁷);

R⁶ and R⁷ are each independently from hydrogen, halo, C₁₋₄ alkyl, and C₁₋₄ alkoxy;

R⁸ is selected from hydrogen, halo, C₁₋₄ alkyl, and C₁₋₄ alkoxy, wherein the C₁₋₄ alkyl and C₁₋₄ alkoxy substituents are substituted with from 0 to 3 optional substituents independently selected from halo; and

R⁹ is selected from C₁₋₆ alkyl, C₃₋₈ cycloalkyl, C₂₋₈ heterocyclyl, and C₁₋₉ heteroaryl, each substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, oxo, C₁₋₄ alkyl, C₁₋₄ alkoxy, and amino which is optionally substituted with one or two C₁₋₄ alkyl, wherein the C₁₋₄ alkyl and C₁₋₄ alkoxy optional substituents are each independently substituted with from 0 to 3 optional substituents independently selected from halo; and

wherein each of the heterocyclyl and heteroaryl moieties independently has 1 to 4 ring members which are heteroatoms, each of the heteroatoms independently selected from N, O, and S.

[0060] In addition to embodiment (1) in the preceding paragraph, the compounds of Formula 1 include those in which (2) α is a single bond, β is a double bond, X¹ is NR^{1N}, and R² is oxo.

[0061] In addition to embodiment (2) in the preceding paragraph, the compounds of Formula 1 include those in which R^{1N} is selected from:

(3) C₁₋₄ alkyl, C₃₋₈ cycloalkyl-(CH₂)_n, C₂₋₈ heterocyclyl-(CH₂)_n, and C₁₋₅ heteroaryl-(CH₂)_n, wherein each of the C₁₋₄ alkyl, C₃₋₈ cycloalkyl, C₂₋₈ heterocyclyl, and C₁₋₉ heteroaryl moieties is substituted with from 0 to 3 optional substituents as defined in embodiment (1);

- (4) C₁₋₄ alkyl, C₃₋₈ cycloalkyl-(CH₂)_n, C₃₋₅ heterocyclyl-(CH₂)_n, and C₁₋₅ heteroaryl-(CH₂)_n, wherein each of the C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₃₋₅ heterocyclyl, and C₁₋₅ heteroaryl moieties is substituted with from 0 to 3 optional substituents as defined in embodiment (1); or
- (5) C₁₋₄ alkyl, C₃₋₆ cycloalkyl-(CH₂)_n, C₃₋₅ heterocyclyl-(CH₂)_n, and C₁₋₅ heteroaryl-(CH₂)_n, wherein each of the C₁₋₄ alkyl, C₃₋₆ cycloalkyl, C₃₋₅ heterocyclyl, and C₁₋₅ heteroaryl moieties is substituted with from 0 to 3 optional substituents as defined in embodiment (1).

[0062] In addition to any one of embodiments (1) to (5) in the preceding paragraphs, the compounds of Formula 1 include those in which each of the 0 to 3 optional substituents of R^{1N} is independently selected from:

- (6) halo, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, and amino which is optionally substituted with one or two C₁₋₄ alkyl, wherein the C₁₋₄ alkyl and C₁₋₄ alkoxy optional substituents are each independently substituted with from 0 to 3 optional substituents independently selected from halo;
- (7) halo, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, and amino which is optionally substituted with one or two C₁₋₄ alkyl;
- (8) fluoro, chloro, hydroxy, methyl, methoxy, and amino which is optionally substituted with one or two methyl; or
- (9) fluoro, hydroxy, methyl, methoxy, and amino which is optionally substituted with one or two methyl.

[0063] In addition to any one of embodiments (1) and (2), the compounds of Formula 1 include those in which (10) R^{1N} is C₁₋₄ alkyl which is substituted with from 0 to 3 optional substituents as defined in embodiment (1).

[0064] In addition to embodiment (10) in the preceding paragraph, the compounds of Formula 1 include those in which the C₁₋₄ alkyl substituent of R^{1N} is selected from:

- (11) methyl, ethyl and propyl, each substituted with from 0 to 3 optional substituents as defined in embodiment (1);
- (12) methyl and ethyl, each substituted with from 0 to 3 optional substituents as defined in embodiment (1); or
- (13) ethyl which is substituted with from 0 to 3 optional substituents as defined in embodiment (1).

[0065] In addition to any one of embodiments (10) to (13) in the preceding paragraphs, the compounds of Formula 1 include those in which the C₁₋₄ alkyl substituent of R^{1N} is:

- (14) substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, and amino which is optionally substituted with one or two C₁₋₄ alkyl, wherein the C₁₋₄ alkyl and C₁₋₄ alkoxy optional substituents are each independently substituted with from 0 to 3 optional substituents independently selected from halo;
- (15) substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, and amino which is optionally substituted with one or two C₁₋₄ alkyl;
- (16) substituted with from 0 to 3 optional substituents independently selected from fluoro, chloro, hydroxy, methyl, methoxy, and amino which is optionally substituted with one or two methyl;
- (17) substituted with from 0 to 3 optional substituents independently selected from fluoro and hydroxy;
- (18) substituted with from 0 to 1 optional substituents selected from fluoro and hydroxy; or
- (19) unsubstituted.

[0066] In addition to any one of embodiments (1) and (2), the compounds of Formula 1 include those in which (20) R^{1N} is C₃₋₆ cycloalkyl-(CH₂)_n in which the C₃₋₆ cycloalkyl moiety is substituted with from 0 to 3 optional substituents as defined in embodiment (1).

[0067] In addition to embodiment (20) in the preceding paragraph, the compounds of Formula 1 include those in which the C₃₋₆ cycloalkyl moiety of R^{1N} is selected from:

- (21) cyclopropyl, cyclobutyl and cyclopentyl; or
- (22) cyclopropyl and cyclobutyl.

[0068] In addition to any one of embodiments (20) to (22) in the preceding paragraphs, the compounds of Formula 1 include those in which the C₃₋₆ cycloalkyl moiety of R^{1N} is substituted with from 0 to 3 optional substituents independently selected from:

- (23) halo, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, and amino which is optionally substituted with one or two C₁₋₄ alkyl, wherein the C₁₋₄ alkyl and C₁₋₄ alkoxy optional substituents are each independently substituted with from 0 to 3 optional substituents independently selected from halo;

- (24) halo, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, and amino which is optionally substituted with one or two C₁₋₄ alkyl;
- (25) fluoro, chloro, hydroxy, methyl, methoxy, and amino which is optionally substituted with one or two methyl;
- (26) fluoro and methyl;
- (27) fluoro; or
- (28) methyl.

[0069] In addition to any one of embodiments (20) to (22) in the preceding paragraphs, the compounds of Formula 1 include those in which (29) the C₃₋₆ cycloalkyl moiety of R^{1N} is unsubstituted.

[0070] In addition to any one of embodiments (1) and (2), the compounds of Formula 1 include those in which (30) R^{1N} is C₃₋₅ heterocyclyl-(CH₂)_n in which the C₃₋₅ heterocyclyl moiety is substituted with from 0 to 3 optional substituents as defined in embodiment (1).

[0071] In addition to embodiment (30) in the preceding paragraph, the compounds of Formula 1 include those in which the C₃₋₅ heterocyclyl moiety of the R^{1N} substituent has:

- (31) one or two heteroatoms as ring members, each of the heteroatoms independently selected from N, O and S; or
- (32) one or two heteroatoms as ring members, each of the heteroatoms selected from O.

[0072] In addition to any one of embodiments (30) to (32) in the preceding paragraphs, the compounds of Formula 1 include those in which (33) the C₃₋₅ heterocyclyl moiety of the R^{1N} substituent is monocyclic.

[0073] In addition to embodiment (30) in the preceding paragraph, the compounds of Formula 1 include those in which the C₃₋₅ heterocyclyl moiety of the R^{1N} substituent is selected from:

- (34) oxetanyl, tetrahydrofuranyl, tetrahydro-2*H*-pyranyl, and 1,4-dioxanyl; or
- (35) oxetanyl and tetrahydrofuranyl.

[0074] In addition to any one of embodiments (30) to (35) in the preceding paragraphs, the compounds of Formula 1 include those in which the C₃₋₅ heterocyclyl moiety of R^{1N} is:

- (36) substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, and amino which is optionally substituted with one or two C₁₋₄ alkyl, wherein the C₁₋₄ alkyl and C₁₋₄ alkoxy

optional substituents are each independently substituted with from 0 to 3 optional substituents independently selected from halo;

(37) substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, and amino which is optionally substituted with one or two C₁₋₄ alkyl;

(38) substituted with from 0 to 3 optional substituents independently selected from fluoro, chloro, hydroxy, methyl, methoxy, and amino which is optionally substituted with one or two methyl;

(39) substituted with from 0 to 3 optional substituents independently selected from fluoro and methyl;

(40) substituted with from 0 to 3 optional substituents independently selected from fluoro;

(41) substituted with from 0 to 3 optional substituents independently selected from methyl; or

(42) unsubstituted.

[0075] In addition to any one of embodiments (1) and (2), the compounds of Formula 1 include those in which (43) R^{1N} is C₁₋₅ heteroaryl-(CH₂)_n in which the C₁₋₅ heteroaryl moiety is substituted with from 0 to 3 optional substituents as defined in embodiment (1).

[0076] In addition to embodiment (43) in the preceding paragraph, the compounds of Formula 1 include those in which (44) the C₁₋₅ heteroaryl moiety of the R^{1N} substituent has one or two heteroatoms as ring members, each of the heteroatoms independently selected from N, O and S.

[0077] In addition to any one of embodiment (43) to (44) in the preceding paragraphs, the compounds of Formula 1 include those in which (45) the C₁₋₅ heteroaryl moiety of the R^{1N} substituent is monocyclic.

[0078] In addition to embodiment (43) in the preceding paragraph, the compounds of Formula 1 include those in which the C₁₋₅ heteroaryl moiety of the R^{1N} substituent is selected from:

(46) pyrrolyl, furanyl, thienyl, imidazolyl, pyrazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl;

(47) imidazolyl, pyrazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, and pyridinyl; or

(48) pyrazolyl, isoxazolyl, oxazolyl, isothiazolyl, and pyridinyl.

[0079] In addition to any one of embodiments (43) to (48) in the preceding paragraphs, the compounds of Formula 1 include those in which the C₁₋₅ heteroaryl moiety of R^{1N} is:

- (49) substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, and amino which is optionally substituted with one or two C₁₋₄ alkyl, wherein the C₁₋₄ alkyl and C₁₋₄ alkoxy optional substituents are each independently substituted with from 0 to 3 optional substituents independently selected from halo;
- (50) substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, and amino which is optionally substituted with one or two C₁₋₄ alkyl;
- (51) substituted with from 0 to 3 optional substituents independently selected from fluoro, chloro, hydroxy, methyl, methoxy, and amino which is optionally substituted with one or two methyl;
- (52) substituted with from 0 to 3 optional substituents independently selected from methyl; or
- (53) unsubstituted.

[0080] In addition to any one of embodiments (1) to (53) in the preceding paragraphs, the compounds of Formula 1 include those in which:

- (54) n is selected from 0, 1, and 2;
- (55) n is selected from 0 and 1;
- (56) n is 1; or
- (57) n is 0.

[0081] In addition to embodiment (1), compounds of Formula 1 include those in which (58) α is a double bond, β is a single bond, X¹ is N, and R² is selected from hydrogen, C₁₋₄ alkyl, and C₁₋₄ alkoxy.

[0082] In addition to embodiment (1), compounds of Formula 1 include those in which (59) α is a double bond, β is a single bond, X¹ is CR^{1C}, and R² is selected from hydrogen, C₁₋₄ alkyl, and C₁₋₄ alkoxy.

[0083] In addition to embodiment (59) in the preceding paragraph, the compounds of Formula 1 include those in which R^{1C} is selected from:

- (60) hydrogen, halo, and C₁₋₄ alkyl which is substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkoxy, and amino which is optionally substituted with one or two C₁₋₄ alkyl;

- (61) hydrogen, halo, and C₁₋₄ alkyl which is substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, and C₁₋₄ alkoxy;
- (62) hydrogen, halo, and C₁₋₄ alkyl which is substituted with from 0 to 1 optional substituents selected from halo, hydroxy, cyano, and C₁₋₄ alkoxy;
- (63) hydrogen, halo, and C₁₋₄ alkyl which is substituted with from 0 to 1 optional substituents selected from hydroxy;
- (64) hydrogen, halo, and C₁₋₄ alkyl which is substituted with hydroxy; or
- (65) hydrogen, halo, and C₁₋₄ alkyl which is unsubstituted.

[0084] In addition to any one of embodiments (59) to (65) in the preceding paragraphs, the compounds of Formula 1 include those in which R^{1C} is selected from:

- (66) hydrogen, halo, and C₁₋₄ alkyl which is selected methyl, ethyl, propyl and isopropyl, each substituted or unsubstituted;
- (67) hydrogen, halo, and C₁₋₄ alkyl which is selected methyl and ethyl, each substituted or unsubstituted; or
- (68) hydrogen, halo, and C₁₋₄ alkyl which is selected methyl and ethyl, each unsubstituted.

[0085] In addition to embodiment (59), compounds of Formula 1 include those in which R^{1C} is selected from:

- (69) hydrogen, fluoro, chloro, methyl, ethyl, propyl, isopropyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, and hydroxyisopropyl;
- (70) hydrogen, chloro, methyl, ethyl, isopropyl, and hydroxyethyl;
- (71) hydrogen, methyl, and ethyl; or
- (72) hydrogen.

[0086] In addition to any one of embodiments (58) to (72) in the preceding paragraphs, the compounds of Formula 1 include those in which R² is selected from:

- (73) hydrogen, methyl, ethyl, propyl, methoxy, ethoxy, and propoxy;
- (74) hydrogen, methyl, ethyl, propyl, methoxy, and ethoxy;
- (75) hydrogen, methyl, ethyl, methoxy, and ethoxy;
- (76) hydrogen, methoxy and ethoxy; or
- (77) methoxy and ethoxy.

[0087] In addition to any one of embodiments (1) to (77) in the preceding paragraphs, the compounds of Formula 1 include those in which R³ is C₁₋₄ alkyl which is:

(78) substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkoxy which is optionally substituted with C₁₋₄ alkoxy, and from amino which is optionally substituted with one or two C₁₋₄ alkyl;

(79) substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, and C₁₋₄ alkoxy which is optionally substituted with C₁₋₄ alkoxy;

(80) substituted with from 0 to 1 optional substituents independently selected from halo, hydroxy, cyano, and C₁₋₄ alkoxy which is optionally substituted with C₁₋₄ alkoxy;

(81) substituted with hydroxy or C₁₋₄ alkoxy which is optionally substituted with C₁₋₄ alkoxy; or

(82) substituted with hydroxy.

[0088] In addition to any one of embodiments (1) to (77) in the preceding paragraphs, the compounds of Formula 1 include those in which R³ is selected from:

(83) ethyl, isopropyl, and *tert*-butyl, each of which is substituted with hydroxy;

(84) hydroxy-*tert*-butyl; or

(85) C₁₋₄ alkyl which is unsubstituted.

[0089] In addition to any one of embodiments (1) to (85) in the preceding paragraphs, the compounds of Formula 1 include those in which R⁴ and R⁵ are each independently selected from:

(86) hydrogen and C₁₋₄ alkyl;

(87) hydrogen and methyl; or

(88) hydrogen.

[0090] In addition to any one of embodiments (1) to (88) in the preceding paragraphs, the compounds of Formula 1 include those in which:

(89) at most one of X⁶ and X⁷ is N; or

(90) X⁶ is C(R⁶) and X⁷ is C(R⁷).

[0091] In addition to any one of embodiments (1) to (90) in the preceding paragraphs, the compounds of Formula 1 include those in which R⁶ and R⁷ are each independently selected from:

(91) hydrogen, halo, methyl and methoxy;

(92) hydrogen, fluoro, chloro, methyl and methoxy;

(93) hydrogen and fluoro; or

(94) hydrogen.

[0092] In addition to any one of embodiments (1) to (94) in the preceding paragraphs, the compounds of Formula 1 include those in which R⁸ is selected from:

(95) halo and C₁₋₄ alkyl which is substituted with from 0 to 3 optional substituents independently selected from halo;

(96) halo, and methyl which is substituted with from 0 to 3 optional substituents independently selected from halo;

(97) fluoro, chloro and methyl which is substituted with from 0 to 3 optional substituents independently selected from halo;

(98) fluoro, chloro and methyl, fluoromethyl, difluoromethyl, and trifluoromethyl; or

(99) methyl.

[0093] In addition to any one of embodiments (1) to (99) in the preceding paragraphs, the compounds of Formula 1 include those in which R⁹ is selected from:

(100) C₁₋₆ alkyl, C₃₋₈ cycloalkyl, and C₁₋₉ heteroaryl, each substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, oxo, C₁₋₄ alkyl, C₁₋₄ alkoxy, and amino which is optionally substituted with one or two C₁₋₄ alkyl, wherein the C₁₋₄ alkyl and C₁₋₄ alkoxy optional substituents are each independently substituted with from 0 to 3 optional substituents independently selected from halo;

(101) C₁₋₄ alkyl, C₃₋₆ cycloalkyl, C₃₋₅ heterocyclyl, and C₁₋₅ heteroaryl, each substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, oxo, C₁₋₄ alkyl, C₁₋₄ alkoxy, and amino which is optionally substituted with one or two C₁₋₄ alkyl; wherein the C₁₋₄ alkyl and C₁₋₄ alkoxy optional substituents are each independently substituted with from 0 to 3 optional substituents independently selected from halo; or

(102) C₁₋₄ alkyl, C₃₋₆ cycloalkyl, and C₁₋₅ heteroaryl, each substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, oxo, C₁₋₄ alkyl, C₁₋₄ alkoxy, and amino which is optionally substituted with one or two C₁₋₄ alkyl; wherein the C₁₋₄ alkyl and C₁₋₄ alkoxy optional substituents are each independently substituted with from 0 to 3 optional substituents independently selected from halo.

[0094] In addition to any one of embodiments (100) to (102) in the preceding paragraph, the compounds of Formula 1 include those in which each of the 0 to 3 optional substituents of R⁹ is independently selected from:

(103) halo, hydroxy, cyano, oxo, C₁₋₄ alkyl, C₁₋₄ alkoxy, and amino which is optionally substituted with one or two C₁₋₄ alkyl;

(104) halo, hydroxy, cyano, oxo, methyl, methoxy, and amino which is optionally substituted with one or two methyl; or

(105) halo, hydroxy, oxo, methyl, and methoxy.

[0095] In addition to any one of embodiments (100) to (102), the compounds of Formula 1 include those in which each of the R⁹ substituents is substituted with from 0 to 1 optional substituents independently selected from:

(106) halo, hydroxy, oxo, methyl, and methoxy; or

(107) oxo and methyl.

[0096] In addition to any one of embodiments (100) to (102), the compounds of Formula 1 include those in which (108) each of the R⁹ substituents is unsubstituted.

[0097] In addition to any one of embodiments (101) to (102), the compounds of Formula 1 include those in which (109) R⁹ is C₁₋₄ alkyl which is substituted with from 0 to 3 optional substituents as defined in embodiment (1).

[0098] In addition to embodiment (109) in the preceding paragraph, the compounds of Formula 1 include those in which R⁹ is C₁₋₄ alkyl which is selected from:

(110) methyl, ethyl and propyl, each substituted with from 0 to 3 optional substituents as defined in embodiment (1); or

(111) methyl and ethyl, each substituted with from 0 to 3 optional substituents as defined in embodiment (1).

[0099] In addition to any one of embodiments (109) to (111) in the preceding paragraphs, the compounds of Formula 1 include those in which the C₁₋₄ alkyl substituent of R⁹ is:

(112) substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, oxo, C₁₋₄ alkoxy, and amino which is optionally substituted with one or two C₁₋₄ alkyl;

(113) substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, oxo, methoxy, and amino which is optionally substituted with one or two methyl;

(114) substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, oxo, and methoxy;

(115) substituted with from 0 to 1 optional substituents selected from halo, hydroxy, oxo, and methoxy;

(116) is unsubstituted or substituted with oxo; or

(117) is unsubstituted.

[0100] In addition to embodiment (100), the compounds of Formula 1 include those in which (118) R^9 is C_{3-8} cycloalkyl which is substituted with from 0 to 3 optional substituents as defined in embodiment (1).

[0101] In addition to any one of embodiments (101) to (102), the compounds of Formula 1 include those in which (119) R^9 is C_{3-6} cycloalkyl which is substituted with from 0 to 3 optional substituents as defined in embodiment (1).

[0102] In addition to embodiment (119) in the preceding paragraph, the compounds of Formula 1 include those in which R^9 is C_{3-6} cycloalkyl which is:

(120) selected from cyclopropyl, cyclobutyl and cyclopentyl, each substituted with from 0 to 3 optional substituents as defined in embodiment (1);

(121) selected from cyclopropyl and cyclobutyl, each substituted with from 0 to 3 optional substituents as defined in embodiment (1); or

(122) cyclopropyl substituted with from 0 to 3 optional substituents as defined in embodiment (1).

[0103] In addition to any one of embodiments (119) to (122) in the preceding paragraphs, the compounds of Formula 1 include those in which the C_{3-6} cycloalkyl substituent of R^9 is:

(123) substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, and amino which is optionally substituted with one or two C_{1-4} alkyl;

(124) substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, methyl, methoxy, and amino which is optionally substituted with one or two C_{1-4} alkyl;

(125) substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, methyl, and methoxy;

(126) substituted with from 0 to 1 optional substituents independently selected from halo, hydroxy, methyl, and methoxy;

(127) unsubstituted or substituted with methyl; or

(128) unsubstituted.

[0104] In addition to any one of embodiments (1) to (99), the compounds of Formula 1 include those in which (129) R⁹ is C₂₋₈ heterocyclyl which is substituted with from 0 to 3 optional substituents as defined in embodiment (1).

[0105] In addition to embodiment (101), the compounds of Formula 1 include those in which (130) R⁹ is C₃₋₅ heterocyclyl which is substituted with from 0 to 3 optional substituents as defined in embodiment (1).

[0106] In addition to any one of embodiments (129) to (130) in the preceding paragraphs, the compounds of Formula 1 include those in which the heterocyclyl substituent of R⁹ has:

(131) one or two heteroatoms as ring members, each of the heteroatoms independently selected from N, O and S; or

(132) one or two heteroatoms as ring members.

[0107] In addition to any one of embodiments (129) to (132) in the preceding paragraphs, the compounds of Formula 1 include those in which (133) the heterocyclyl substituent of R⁹ is monocyclic.

[0108] In addition to any one of embodiments (129) to (133) in the preceding paragraphs, the compounds of Formula 1 include those in which the heterocyclyl substituent of R⁹ is:

(134) substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl, C₁₋₄ alkoxy, and amino which is optionally substituted with one or two C₁₋₄ alkyl;

(135) substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, methyl, methoxy, and amino which is optionally substituted with one or two C₁₋₄ alkyl;

(136) substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, methyl, and methoxy;

(137) substituted with from 0 to 1 optional substituents independently selected from halo, hydroxy, methyl, and methoxy;

(138) unsubstituted or substituted with methyl; or

(139) unsubstituted.

[0109] In addition to embodiment (100), the compounds of Formula 1 include those in which (140) R⁹ is C₁₋₉ heteroaryl which is substituted with from 0 to 3 optional substituents as defined in embodiment (1).

[0110] In addition to embodiments (101) to (102), the compounds of Formula 1 include those in which (141) R^9 is C_{1-5} heteroaryl which is substituted with from 0 to 3 optional substituents as defined in embodiment (1).

[0111] In addition to embodiments (140) to (141), the compounds of Formula 1 include those in which (142) the heteroaryl substituent of R^9 has one or two heteroatoms as ring members, each of the heteroatoms independently selected from N, O and S.

[0112] In addition to embodiments (140) to (142), the compounds of Formula 1 include those in which (143) the heteroaryl substituent of R^9 is monocyclic.

[0113] In addition to embodiments (140) to (141), the compounds of Formula 1 include those in which the heteroaryl substituent of R^9 is:

(144) selected from pyrrolyl, furanyl, thienyl, imidazolyl, pyrazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl;
or

(145) selected from imidazolyl, pyrazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, and pyridinyl.

[0114] In addition to embodiments (140) to (145), the compounds of Formula 1 include those in which the heteroaryl substituent of R^9 is:

(146) substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, and amino which is optionally substituted with one or two C_{1-4} alkyl;

(147) substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, methyl, methoxy, and amino which is optionally substituted with one or two C_{1-4} alkyl;

(148) substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, methyl, and methoxy;

(149) substituted with from 0 to 1 optional substituents independently selected from halo, hydroxy, methyl, and methoxy;

(150) unsubstituted or substituted with methyl; or

(151) unsubstituted.

[0115] Compounds of Formula 1 include embodiments (1) through (151) described in the preceding paragraphs and all compounds specifically named in the examples, and may exist as salts, complexes, solvates, hydrates, and liquid crystals. Likewise, compounds of Formula 1 that are salts may exist as complexes, solvates, hydrates, and liquid crystals.

[0116] Compounds of Formula 1 may form pharmaceutically acceptable complexes, salts, solvates and hydrates. These salts include acid addition salts (including di-acids) and base salts. Pharmaceutically acceptable acid addition salts include salts derived from inorganic acids such as hydrochloric acid, nitric acid, phosphoric acid, sulfuric acid, hydrobromic acid, hydroiodic acid, hydrofluoric acid, and phosphorous acids, as well nontoxic salts derived from organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanolic acids, hydroxy alkanolic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts include acetate, adipate, aspartate, benzoate, besylate, bicarbonate, carbonate, bisulfate, sulfate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulfate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate, hydrogen phosphate, dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinofoate salts.

[0117] Pharmaceutically acceptable base salts include salts derived from bases, including metal cations, such as an alkali or alkaline earth metal cation, as well as amines. Examples of suitable metal cations include sodium, potassium, magnesium, calcium, zinc, and aluminum. Examples of suitable amines include arginine, *N,N'*-dibenzylethylenediamine, chloroprocaine, choline, diethylamine, diethanolamine, dicyclohexylamine, ethylenediamine, glycine, lysine, *N*-methylglucamine, olamine, 2-amino-2-hydroxymethyl-propane-1,3-diol, and procaine. For a discussion of useful acid addition and base salts, see S. M. Berge et al., *J. Pharm. Sci.* (1977) 66:1-19; see also Stahl and Wermuth, *Handbook of Pharmaceutical Salts: Properties, Selection, and Use* (2002).

[0118] Pharmaceutically acceptable salts may be prepared using various methods. For example, a compound of Formula 1 may be reacted with an appropriate acid or base to give the desired salt. Alternatively, a precursor of the compound of Formula 1 may be reacted with an acid or base to remove an acid- or base-labile protecting group or to open a lactone or lactam group of the precursor. Additionally, a salt of the compound of Formula 1 may be converted to another salt (or free form) through treatment with an appropriate acid or base or through contact with an ion exchange resin. Following reaction, the salt may be isolated by filtration if it precipitates from solution, or by evaporation to recover the salt. The degree of ionization of the salt may vary from completely ionized to almost non-ionized.

[0119] Compounds of Formula 1 may exist in a continuum of solid states ranging from fully amorphous to fully crystalline. The term “amorphous” refers to a state in which the material lacks long range order at the molecular level and, depending upon temperature, may exhibit the physical properties of a solid or a liquid. Typically, such materials do not give distinctive X-ray diffraction patterns and, while exhibiting the properties of a solid, are more formally described as a liquid. Upon heating, a change from solid to liquid properties occurs which is characterized by a change of state, typically second order (“glass transition”). The term “crystalline” refers to a solid phase in which the material has a regular ordered internal structure at the molecular level and gives a distinctive X-ray diffraction pattern with defined peaks. Such materials when heated sufficiently will also exhibit the properties of a liquid, but the change from solid to liquid is characterized by a phase change, typically first order (“melting point”).

[0120] Compounds of Formula 1 may also exist in unsolvated and solvated forms. The term “solvate” describes a molecular complex comprising the compound and one or more pharmaceutically acceptable solvent molecules (e.g., ethanol). The term “hydrate” is a solvate in which the solvent is water. Pharmaceutically acceptable solvates include those in which the solvent may be isotopically substituted (e.g., D₂O, acetone-*d*₆, DMSO-*d*₆).

[0121] A currently accepted classification system for solvates and hydrates of organic compounds is one that distinguishes between isolated site, channel, and metal-ion coordinated solvates and hydrates. See, e.g., K. R. Morris (H. G. Brittain ed.) *Polymorphism in Pharmaceutical Solids* (1995). Isolated site solvates and hydrates are ones in which the solvent (e.g., water) molecules are isolated from direct contact with each other by intervening molecules of the organic compound. In channel solvates, the solvent molecules lie in lattice channels where they are next to other solvent molecules. In metal-ion coordinated solvates, the solvent molecules are bonded to the metal ion.

[0122] When the solvent or water is tightly bound, the complex will have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly bound, as in channel solvates and in hygroscopic compounds, the water or solvent content will depend on humidity and drying conditions. In such cases, non-stoichiometry will typically be observed.

[0123] Compounds of Formula 1 may also exist as multi-component complexes (other than salts and solvates) in which the compound (drug) and at least one other component are present in stoichiometric or non-stoichiometric amounts. Complexes of this type include

clathrates (drug-host inclusion complexes) and co-crystals. The latter are typically defined as crystalline complexes of neutral molecular constituents which are bound together through non-covalent interactions but could also be a complex of a neutral molecule with a salt. Co-crystals may be prepared by melt crystallization, by recrystallization from solvents, or by physically grinding the components together. See, e.g., O. Almarsson and M. J. Zaworotko, *Chem. Commun.* (2004) 17:1889-1896. For a general review of multi-component complexes, see J. K. Halebian, *J. Pharm. Sci.* (1975) 64(8):1269-88.

[0124] When subjected to suitable conditions, compounds of Formula 1 may exist in a mesomorphic state (mesophase or liquid crystal). The mesomorphic state lies between the true crystalline state and the true liquid state (either melt or solution). Mesomorphism arising as the result of a change in temperature is described as “thermotropic” and mesomorphism resulting from the addition of a second component, such as water or another solvent, is described as “lyotropic.” Compounds that have the potential to form lyotropic mesophases are described as “amphiphilic” and include molecules which possess a polar ionic moiety (e.g., $-\text{COO}^-\text{Na}^+$, $-\text{COO}^-\text{K}^+$, $-\text{SO}_3^-\text{Na}^+$) or polar non-ionic moiety (such as $-\text{N}^+\text{N}^+(\text{CH}_3)_3$). See, e.g., N. H. Hartshorne and A. Stuart, *Crystals and the Polarizing Microscope* (4th ed, 1970).

[0125] Each compound of Formula 1 may exist as polymorphs, stereoisomers, tautomers, or some combination thereof, may be isotopically-labeled, may result from the administration of a prodrug, or form a metabolite following administration.

[0126] “Prodrugs” refer to compounds having little or no pharmacological activity that can, when metabolized *in vivo*, undergo conversion to compounds having desired pharmacological activity. Prodrugs may be prepared by replacing appropriate functionalities present in pharmacologically active compounds with “pro-moieties” as described, for example, in H. Bundgaard, *Design of Prodrugs* (1985). Examples of prodrugs include ester, ether or amide derivatives of compounds of Formula 1 having carboxylic acid, hydroxy, or amino functional groups, respectively. For further discussions of prodrugs, see e.g., T. Higuchi and V. Stella “Pro-drugs as Novel Delivery Systems,” *ACS Symposium Series* 14 (1975) and E. B. Roche ed., *Bioreversible Carriers in Drug Design* (1987).

[0127] “Metabolites” refer to compounds formed *in vivo* upon administration of pharmacologically active compounds. Examples include hydroxymethyl, hydroxy, secondary amino, primary amino, phenol, and carboxylic acid derivatives of compounds of Formula 1 having methyl, alkoxy, tertiary amino, secondary amino, phenyl, and amide groups, respectively.

[0128] Compounds of Formula 1 may exist as stereoisomers that result from the presence of one or more stereogenic centers, one or more double bonds, or both. The stereoisomers may be pure, substantially pure, or mixtures. Such stereoisomers may also result from acid addition or base salts in which the counter-ion is optically active, for example, when the counter-ion is D-lactate or L-lysine.

[0129] Compounds of Formula 1 may exist as tautomers, which are isomers resulting from tautomerization. Tautomeric isomerism includes, for example, imine-enamine, keto-enol, oxime-nitroso, and amide-imidic acid tautomerism.

[0130] Compounds of Formula 1 may exhibit more than one type of isomerism.

[0131] Geometrical (*cis/trans*) isomers may be separated by conventional techniques such as chromatography and fractional crystallization.

[0132] Conventional techniques for preparing or isolating a compound having a specific stereochemical configuration include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high-pressure liquid chromatography (HPLC). Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of Formula 1 contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting diastereomeric mixture may be separated by chromatography, fractional crystallization, etc., and the appropriate diastereoisomer converted to the compound having the requisite stereochemical configuration. For a further discussion of techniques for separating stereoisomers, see E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds* (1994).

[0133] Compounds of Formula 1 may possess isotopic variations, in which at least one atom is replaced by an atom having the same atomic number, but an atomic mass different from the atomic mass usually found in nature. Isotopes suitable for inclusion in compounds of Formula 1 include, for example, isotopes of hydrogen, such as ^2H and ^3H ; isotopes of carbon, such as ^{11}C , ^{13}C and ^{14}C ; isotopes of nitrogen, such as ^{13}N and ^{15}N ; isotopes of oxygen, such as ^{15}O , ^{17}O and ^{18}O ; isotopes of sulfur, such as ^{35}S ; isotopes of fluorine, such as ^{18}F ; isotopes of chlorine, such as ^{36}Cl , and isotopes of iodine, such as ^{123}I and ^{125}I . Use of isotopic variations (e.g., deuterium, ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements. Additionally, certain isotopic variations of the disclosed compounds may incorporate a radioactive isotope (e.g., tritium, ^3H , or ^{14}C), which may be useful in drug

and/or substrate tissue distribution studies. Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , may be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds may be prepared by processes analogous to those described elsewhere in the disclosure using an appropriate isotopically-labeled reagent in place of a non-labeled reagent.

[0134] The compounds of Formula 1 may be prepared using the techniques described below. Some of the schemes and examples may omit details of common reactions, including oxidations, reductions, and so on, separation techniques (extraction, evaporation, precipitation, chromatography, filtration, trituration, crystallization, and the like), and analytical procedures, which are known to persons of ordinary skill in the art of organic chemistry. The details of such reactions and techniques can be found in several treatises, including Richard Larock, *Comprehensive Organic Transformations* (1999), and the multi-volume series edited by Michael B. Smith and others, *Compendium of Organic Synthetic Methods* (1974 *et seq.*). Starting materials and reagents may be obtained from commercial sources or may be prepared using literature methods. Some of the reaction schemes may omit minor products resulting from chemical transformations (e.g., an alcohol from the hydrolysis of an ester, CO_2 from the decarboxylation of a di-acid, etc.). In addition, in some instances, reaction intermediates may be used in subsequent steps without isolation or purification (i.e., *in situ*).

[0135] In some of the reaction schemes and examples below, certain compounds can be prepared using protecting groups, which prevent undesirable chemical reaction at otherwise reactive sites. Protecting groups may also be used to enhance solubility or otherwise modify physical properties of a compound. For a discussion of protecting group strategies, a description of materials and methods for installing and removing protecting groups, and a compilation of useful protecting groups for common functional groups, including amines, carboxylic acids, alcohols, ketones, aldehydes, and so on, see T. W. Greene and P. G. Wuts, *Protecting Groups in Organic Chemistry* (1999) and P. Kocienski, *Protective Groups* (2000).

[0136] Generally, the chemical transformations described throughout the specification may be carried out using substantially stoichiometric amounts of reactants, though certain reactions may benefit from using an excess of one or more of the reactants. Additionally, many of the reactions disclosed throughout the specification may be carried out at about room temperature (RT) and ambient pressure, but depending on reaction kinetics, yields, and so on, some reactions may be run at elevated pressures or employ higher temperatures (e.g., reflux

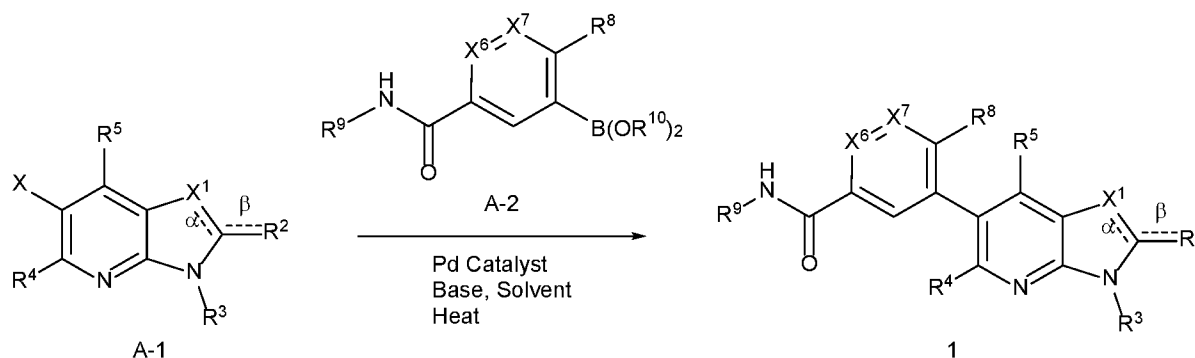
conditions) or lower temperatures (e.g., -78°C to 0°C). Any reference in the disclosure and claims to a stoichiometric range, a temperature range, a pH range, etc., whether expressly using the word “range,” also includes the indicated endpoints.

[0137] Many of the chemical transformations may also employ one or more compatible solvents, which may influence the reaction rate and yield. Depending on the nature of the reactants, the one or more solvents may be polar protic solvents (including water), polar aprotic solvents, non-polar solvents, or some combination. Representative solvents include saturated aliphatic hydrocarbons (e.g., *n*-pentane, *n*-hexane, *n*-heptane, *n*-octane, cyclohexane, methylcyclohexane); aromatic hydrocarbons (e.g., benzene, toluene, xylenes); halogenated hydrocarbons (e.g., methylene chloride, chloroform, carbon tetrachloride); aliphatic alcohols (e.g., methanol, ethanol, propan-1-ol, propan-2-ol, butan-1-ol, 2-methylpropan-1-ol, butan-2-ol, 2-methylpropan-2-ol, pentan-1-ol, 3-methylbutan-1-ol, hexan-1-ol, 2-methoxy-ethanol, 2-ethoxy-ethanol, 2-butoxy-ethanol, 2-(2-methoxy-ethoxy)-ethanol, 2-(2-ethoxy-ethoxy)-ethanol, 2-(2-butoxy-ethoxy)-ethanol); ethers (e.g., diethyl ether, di-isopropyl ether, dibutyl ether, 1,2-dimethoxy-ethane, 1,2-diethoxy-ethane, 1-methoxy-2-(2-methoxy-ethoxy)-ethane, 1-ethoxy-2-(2-ethoxy-ethoxy)-ethane, tetrahydrofuran, 1,4-dioxane); ketones (e.g., acetone, methyl ethyl ketone); esters (methyl acetate, ethyl acetate); nitrogen-containing solvents (e.g., formamide, *N,N*-dimethylformamide, acetonitrile, *N*-methylpyrrolidone, pyridine, quinoline, nitrobenzene); sulfur-containing solvents (e.g., carbon disulfide, dimethyl sulfoxide, tetrahydro-thiophene-1,1,-dioxide); and phosphorus-containing solvents (e.g., hexamethylphosphoric triamide).

[0138] In the schemes, below, substituent identifiers (α , β , n , R^{1C} , R^{1N} , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , X^1 , X^6 , X^7) are as defined above for Formula 1. As mentioned earlier, however, some of the starting materials and intermediates may include protecting groups, which are removed prior to the final product. In such cases, the substituent identifier refers to moieties defined in Formula 1 and to those moieties with appropriate protecting groups (unless explicitly shown). For example, a starting material or intermediate in the schemes may include X^1 substituent having a potentially reactive hydroxy group. In such cases, X^1 would include the moiety with or without, say, a TBS or Ac group attached to the oxygen atom.

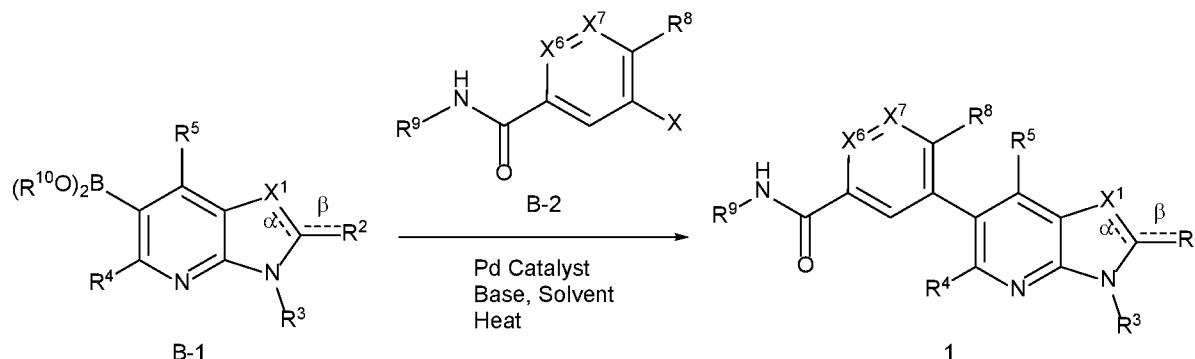
[0139] Schemes A and B show general methods for preparing compounds of Formula 1. As indicated in Scheme A, a heteroaromatic halide (A-1 in which, e.g., X is Cl, Br or I) is reacted with an aromatic (or heteroaromatic) boronic acid or ester (A-2 in which, e.g., each R^{10} is H or C₁₋₄ alkyl) in the presence of a palladium catalyst (e.g., XPhos Pd G3,

Pd(dppf)Cl₂, PdCl₂(dtbpf), etc.), a base (e.g., K₂CO₃, Na₂CO₃, KF, etc.) and one or more polar solvents (e.g., dioxane, DMF, water, etc.). The palladium catalyzed cross-coupling reaction is carried out at elevated temperature (e.g., 80-130°C) and gives the compound of Formula 1 directly or indirectly, e.g., after removal of protecting groups, further elaboration of functional groups, etc.



Scheme A

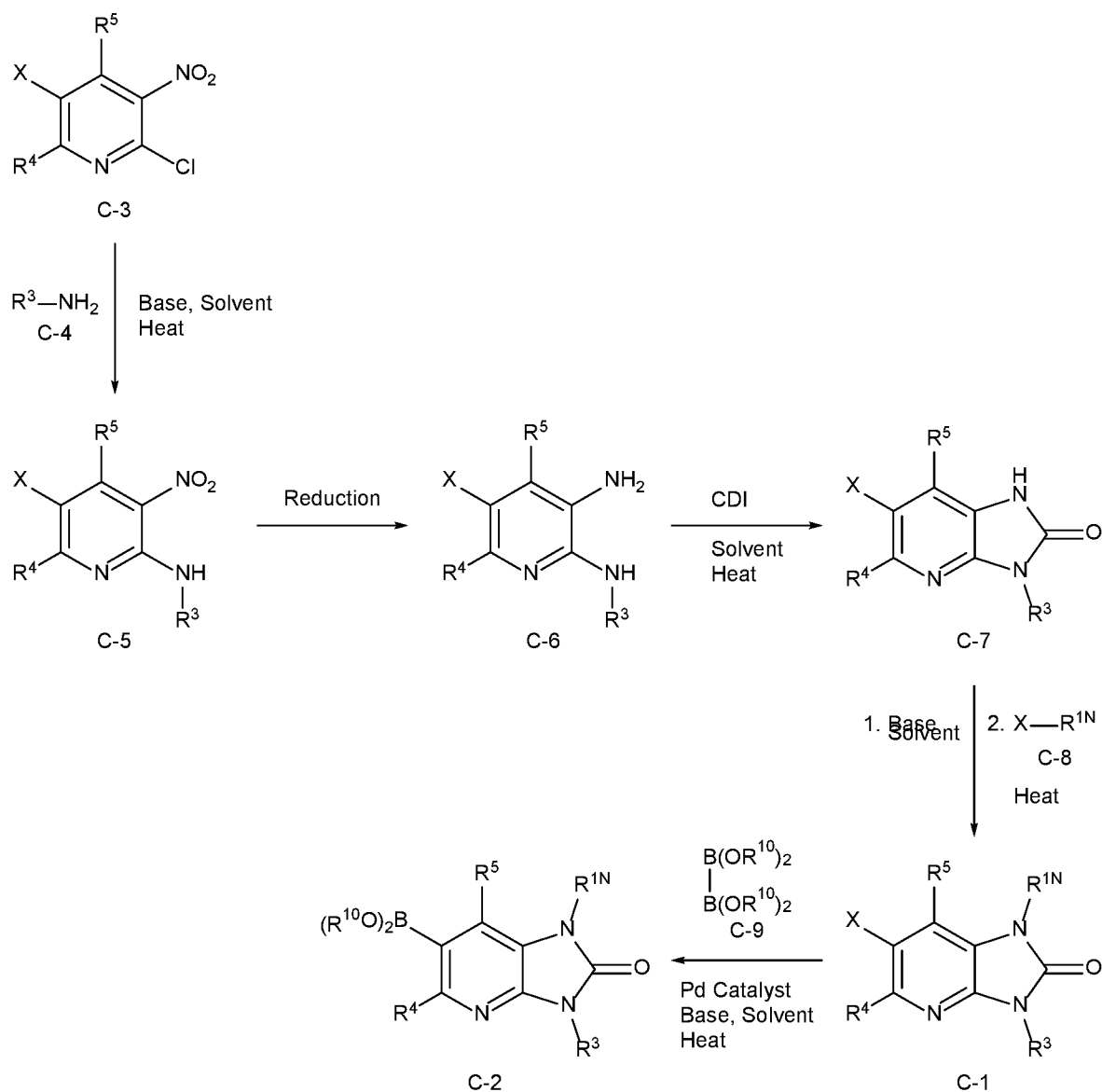
[0140] Alternatively, as shown in Scheme B, a heteroaromatic boronic acid or ester (B-1) is reacted with an aromatic (or heteroaromatic) halide (B-2), in the presence of a palladium catalyst, base and solvent as noted above for Scheme A. Like Scheme A, the cross-coupling reaction in Scheme B gives the compound of Formula 1 directly or indirectly.



Scheme B

[0141] Scheme C shows a general method for preparing heteroaromatic halide (C-1) and heteroaromatic boronic acid or ester (C-2) which correspond, respectively, to compounds (A-1) and (B-1) when α is a single bond, β is a double bond, X¹ is NR^{1N}, and R² is oxo. In accordance with the method, a 2-halo-3-nitropyridine (C-3) is reacted with an R³-substituted amine (C-4) in the presence of a base (e.g., DIPEA) and solvent (e.g., ACN, DMSO, etc.) at elevated temperature (e.g., 80°C) to give a 3-nitropyridin-2-amine (C-5). The amine (C-5) is subsequently reduced (via e.g., catalytic hydrogenation, treatment with iron metal and NH₄Cl in EtOH and water, etc.) to provide a pyridine-2,3-diamine (C-6). The diamine (C-6) is

reacted with CDI in a polar solvent (e.g., THF) and at elevated temperature (e.g., 60-75°C) to afford the desired pyrido-fused imidazolidinone (C-7). The imidazolidinone (C-7) is treated with base (e.g., NaH, K₂CO₃, etc.) in solvent (e.g., DMF, ACN, etc.) and then reacted with an alkyl halide (C-8, R^{1N} is optionally substituted alkyl, X is Br, I, etc.) at elevated temperature (80-130°C) to give the heteroaromatic halide (C-1). If desired, the halide (C-1) may be reacted with diboronic acid or ester (C-9) in the presence of a palladium catalyst (e.g., Pd(dppf)Cl₂, Pd(dppf)Cl₂.CH₂Cl₂, etc.), base (KOAc, potassium phenoxide, etc.) and solvent (e.g., dioxane) at elevated temperature (e.g., 80-100°C) to provide the heteroaromatic boronic acid or ester (C-2).

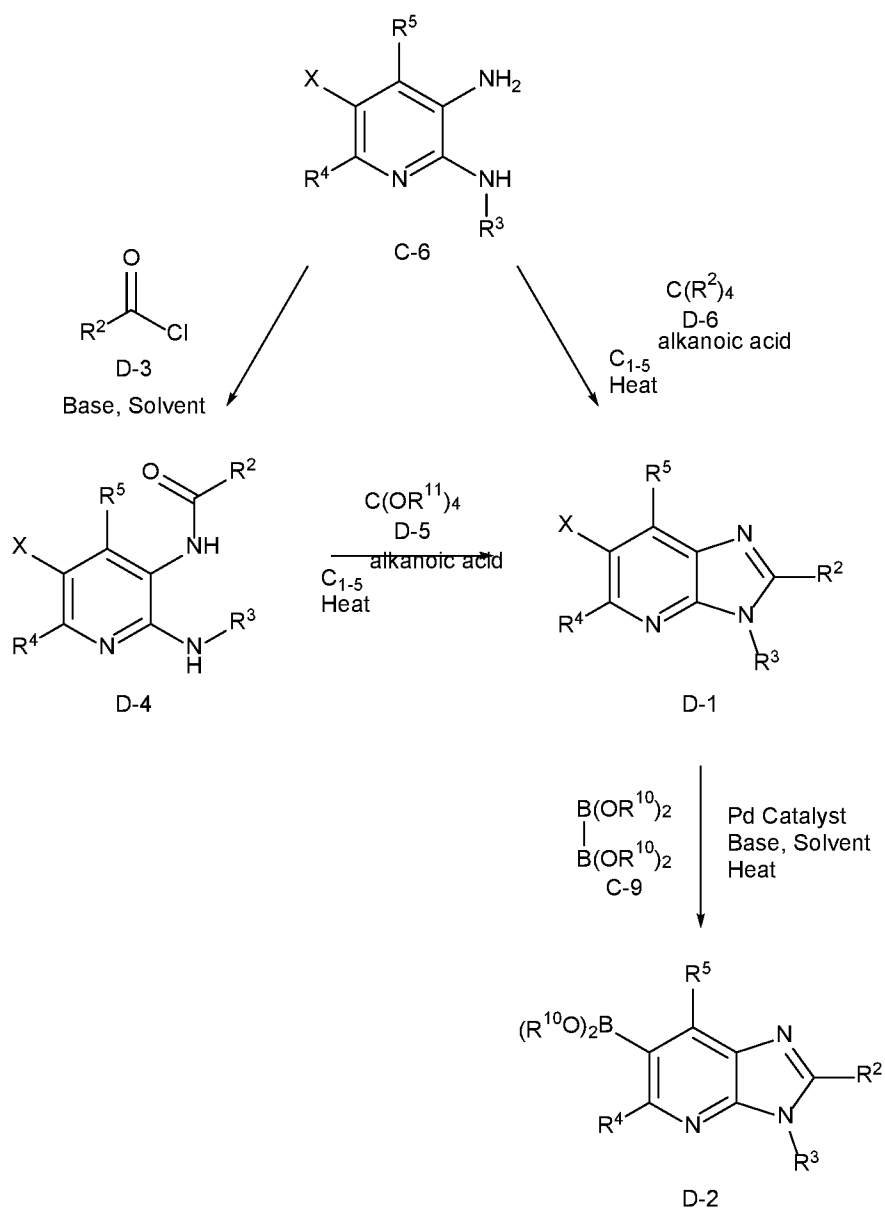


Scheme C

[0142] Scheme D shows a general method for preparing heteroaromatic halide (D-1) and heteroaromatic boronic acid or ester (D-2) which correspond, respectively, to compounds (A-

1) and (B-1) when α is a double bond, β is a single bond, and X^1 is N. In accordance with the method, pyridine-2,3-diamine (C-6) is reacted with an acid chloride (D-3, R^2 is C_{1-4} alkyl) in the presence of a non-nucleophilic base (e.g., DIPEA) and a polar solvent (THF) with cooling (e.g., 0-15°C) to obtain an *N*-(pyridin-3-yl)alkylamide (D-4). The amide (D-4) is subsequently treated with a tetraalkyl orthocarbonate (D-5, each R^{11} is, e.g., methyl) and C_{1-5} alkanolic acid (HOAc, propionic acid, butanoic acid, etc.) at elevated temperature (e.g., 100-120°C) to afford the heteroaromatic halide (D-1, R^2 is C_{1-4} alkyl). Alternatively, the pyridine-2,3-diamine (C-6) may be reacted with tetraalkyl orthocarbonate (D-6, each R^2 is C_{1-4} alkoxy) and C_{1-5} alkanolic acid (HOAc, propionic acid, butanoic acid, etc.) at elevated temperature (e.g., 100-120°C) to afford the heteroaromatic halide (D-1, R^2 is C_{1-4} alkoxy). Though not shown, when R^2 is H, the diamine (C-6) may be reacted with an orthoester ($HC(OR^{11})_3$) in the presence of a C_{1-5} alkanolic acid (e.g., HOAc) at elevated temperature (e.g., 80°C) to give the heteroaromatic halide (D-1, R^2 is H). If desired, the halide (D-1) may be reacted with diboronic acid or ester (C-9) in the presence of a palladium catalyst (e.g., $Pd(dppf)Cl_2$, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, etc.), base (e.g., KOAc, potassium phenoxide, etc.) and solvent (e.g., dioxane) at elevated temperature (e.g., 80-100°C) to provide the heteroaromatic boronic acid or ester (D-2).

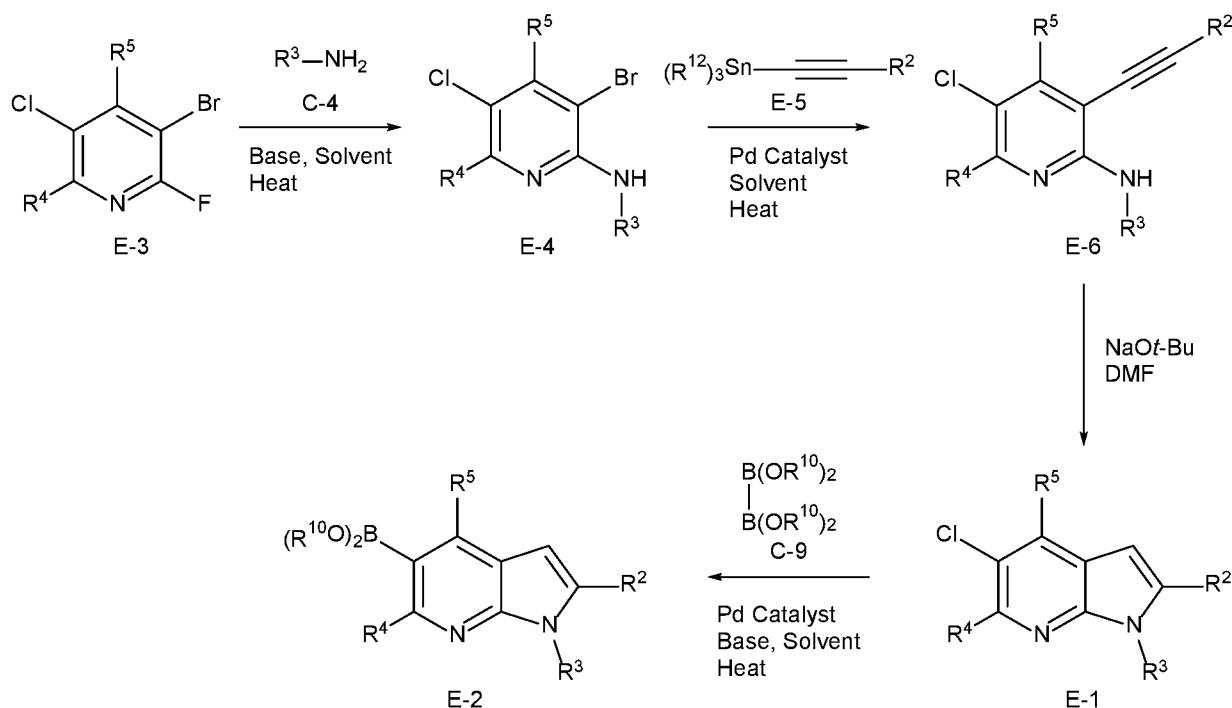
[0143] Scheme E shows a general method for preparing heteroaromatic halide (E-1) and boronic acid or ester (E-2) which correspond, respectively, to compounds (A-1) and (B-1) when α is a double bond, β is a single bond, X^1 is CR^{1C} , and R^{1C} is hydrogen. In accordance with the method, a 3-bromo-5-chloro-2-fluoropyridine (E-3) is reacted with an R^3 -substituted amine (C-4) in the presence of a base (e.g., DIPEA) and solvent (e.g., ACN, DMSO, etc.) at elevated temperature (e.g., 80°C) to give a 3-bromo-5-chloropyridin-2-amine (E-4). The amine (C-5) is subsequently reacted with an organostannane (E-5, R^{12} is, e.g., butyl) in the presence of a palladium catalyst (e.g., $Pd(PPh_3)_4$) and nonpolar solvent (e.g., toluene) at elevated temperature (e.g., 100°C). The resulting 5-chloro-3-ethynylpyridin-2-amine (E-6) is treated with a strong base (e.g., $NaOt-Bu$, $KOt-Bu$, etc.) in a polar solvent (DMF) at RT or above (e.g., 60°C) to give the heteroaromatic halide (E-1). If desired, the halide (E-1) may be reacted with diboronic acid or ester (C-9) in the presence of a palladium catalyst (e.g., $Pd(dppf)Cl_2$, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, etc.), base (e.g., KOAc, potassium phenoxide, etc.) and solvent (e.g., dioxane) at elevated temperature (e.g., 80-100°C) to provide the heteroaromatic boronic acid or ester (E-2).



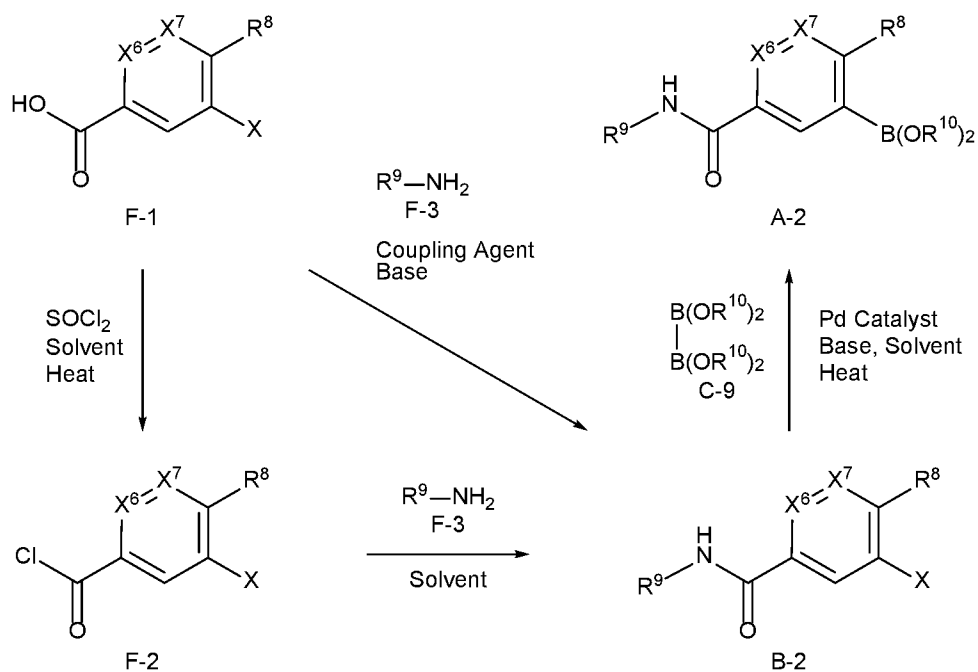
Scheme D

[0144] Scheme F shows a general method for preparing aromatic (or heteroaromatic) boronic acid or ester (A-2) or halide (B-2). In accordance with the method, a carboxylic acid (F-1) is treated with thionyl chloride in a solvent (e.g., DMF) at elevated temperature (e.g., 60-80°C). The resulting acid chloride (F-2) is reacted with an R^9 -substituted amine (F-3) in a solvent (e.g., DCM) with cooling (0-15°C) to give the aromatic halide (B-2). Alternatively, the carboxylic acid (F-1) may be reacted with the amine (F-3) using an amide coupling agent (e.g., HATU, DCC, EDC hydrochloride, T3P or 2-chloro-1-methylpyridin-1-ium iodide) in the presence of a non-nucleophilic base (e.g., Et_3N , DIPEA) and one or more compatible polar solvents (e.g. DCM, DMA, DMF, THF). The amide coupling may be carried out at temperatures which range from room temperature to about 80°C. HOBt may be used to

facilitate the reaction. If desired, the halide (B-2) may be reacted with diboronic acid or ester (C-9) in the presence of a palladium catalyst (e.g., Pd(dppf)Cl₂, Pd(dppf)Cl₂.CH₂Cl₂, etc.), base (e.g., KOAc, potassium phenoxide, etc.) and solvent (e.g., dioxane) at elevated temperature (e.g., 80-100°C) to provide the heteroaromatic boronic acid or ester (A-2).



Scheme E



Scheme F

[0145] The methods depicted in the schemes may be varied as desired. For example, protecting groups may be added or removed, and intermediates or products may be further elaborated via, for example, alkylation, acylation, halogenation, hydrolysis, oxidation, reduction, amidation, sulfonation, alkynylation, transition metal catalyzed cross-coupling reactions, and the like to give the desired final product. Furthermore, any intermediate or final product which comprises mixture of stereoisomers may be optionally purified by chiral column chromatography (e.g., supercritical fluid chromatography) or by derivatization with optically-pure reagents as described above to give a desired stereoisomer.

[0146] Compounds of Formula 1, which include compounds named above, and their pharmaceutically acceptable complexes, salts, solvates and hydrates, should be assessed for their biopharmaceutical properties, such as solubility and solution stability across pH, permeability, and the like, to select an appropriate dosage form and route of administration. Compounds that are intended for pharmaceutical use may be administered as crystalline or amorphous products, and may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, evaporative drying, microwave drying, or radio frequency drying.

[0147] Compounds of Formula 1 may be administered alone or in combination with one another or with one or more pharmacologically active compounds which are different than the compounds of Formula 1. Generally, one or more of these compounds are administered as a pharmaceutical composition (a formulation) in association with one or more pharmaceutically acceptable excipients. The choice of excipients depends on the mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form, among other things. Useful pharmaceutical compositions and methods for their preparation may be found, for example, in A. R. Gennaro (ed.), *Remington: The Science and Practice of Pharmacy* (20th ed., 2000).

[0148] Compounds of Formula 1 may be administered orally. Oral administration may involve swallowing in which case the compound enters the bloodstream via the gastrointestinal tract. Alternatively, or additionally, oral administration may involve mucosal administration (e.g., buccal, sublingual, supralingual administration) such that the compound enters the bloodstream through the oral mucosa.

[0149] Formulations suitable for oral administration include solid, semi-solid and liquid systems such as tablets; soft or hard capsules containing multi- or nano-particulates, liquids, or powders; lozenges which may be liquid-filled; chews; gels; fast dispersing dosage forms;

films; ovules; sprays; and buccal or mucoadhesive patches. Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules (made, e.g., from gelatin or hydroxypropylmethylcellulose) and typically comprise a carrier (e.g., water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil) and one or more emulsifying agents, suspending agents or both. Liquid formulations may also be prepared by the reconstitution of a solid (e.g., from a sachet).

[0150] Compounds of Formula 1 may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Liang and Chen, *Expert Opinion in Therapeutic Patents* (2001) 11(6):981-986.

[0151] For tablet dosage forms, depending on dose, the active pharmaceutical ingredient (API) may comprise from about 1 wt% to about 80 wt% of the dosage form or more typically from about 5 wt% to about 60 wt% of the dosage form. In addition to the API, tablets may include one or more disintegrants, binders, diluents, surfactants, glidants, lubricants, anti-oxidants, colorants, flavoring agents, preservatives, and taste-masking agents. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, C₁₋₆ alkyl-substituted hydroxypropylcellulose, starch, pregelatinized starch, and sodium alginate. Generally, the disintegrant will comprise from about 1 wt% to about 25 wt% or from about 5 wt% to about 20 wt% of the dosage form.

[0152] Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinized starch, hydroxypropylcellulose and hydroxypropylmethylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

[0153] Tablets may also include surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from about 0.2 wt% to about 5 wt% of the tablet, and glidants may comprise from about 0.2 wt% to about 1 wt% of the tablet.

[0154] Tablets may also contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium

lauryl sulfate. Lubricants may comprise from about 0.25 wt% to about 10 wt% or from about 0.5 wt% to about 3 wt% of the tablet.

[0155] Tablet blends may be compressed directly or by roller compaction to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tableting. If desired, prior to blending one or more of the components may be sized by screening or milling or both. The final dosage form may comprise one or more layers and may be coated, uncoated, or encapsulated. Exemplary tablets may contain up to about 80 wt% of API, from about 10 wt% to about 90 wt% of binder, from about 0 wt% to about 85 wt% of diluent, from about 2 wt% to about 10 wt% of disintegrant, and from about 0.25 wt% to about 10 wt% of lubricant. For a discussion of blending, granulation, milling, screening, tableting, coating, as well as a description of alternative techniques for preparing drug products, see A. R. Gennaro (ed.), *Remington: The Science and Practice of Pharmacy* (20th ed., 2000); H. A. Lieberman et al. (ed.), *Pharmaceutical Dosage Forms: Tablets, Vol. 1-3* (2d ed., 1990); and D. K. Parikh & C. K. Parikh, *Handbook of Pharmaceutical Granulation Technology, Vol. 81* (1997).

[0156] Consumable oral films for human or veterinary use are pliable water-soluble or water-swallowable thin film dosage forms which may be rapidly dissolving or mucoadhesive. In addition to the API, a typical film includes one or more film-forming polymers, binders, solvents, humectants, plasticizers, stabilizers or emulsifiers, viscosity-modifying agents, and solvents. Other film ingredients may include anti-oxidants, colorants, flavorants and flavor enhancers, preservatives, salivary stimulating agents, cooling agents, co-solvents (including oils), emollients, bulking agents, anti-foaming agents, surfactants, and taste-masking agents. Some components of the formulation may perform more than one function.

[0157] In addition to dosing requirements, the amount of API in the film may depend on its solubility. If water soluble, the API would typically comprise from about 1 wt% to about 80 wt% of the non-solvent components (solutes) in the film or from about 20 wt% to about 50 wt% of the solutes in the film. A less soluble API may comprise a greater proportion of the composition, typically up to about 88 wt% of the non-solvent components in the film.

[0158] The film-forming polymer may be selected from natural polysaccharides, proteins, or synthetic hydrocolloids and typically comprises from about 0.01 wt% to about 99 wt% or from about 30 wt% to about 80 wt% of the film.

[0159] Film dosage forms are typically prepared by evaporative drying of thin aqueous films coated onto a peelable backing support or paper, which may be carried out in a drying

oven or tunnel (e.g., in a combined coating-drying apparatus), in lyophilization equipment, or in a vacuum oven.

[0160] Useful solid formulations for oral administration may include immediate release formulations and modified release formulations. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted-, and programmed-release. For a general description of suitable modified release formulations, see US Patent No. 6,106,864. For details of other useful release technologies, such as high energy dispersions and osmotic and coated particles, see Verma et al, *Pharmaceutical Technology On-line* (2001) 25(2):1-14.

[0161] Compounds of Formula 1 may also be administered directly into the blood stream, muscle, or an internal organ of the subject. Suitable techniques for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial, and subcutaneous administration. Suitable devices for parenteral administration include needle injectors, including microneedle injectors, needle-free injectors, and infusion devices.

[0162] Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (e.g., pH of from about 3 to about 9). For some applications, however, compounds of Formula 1 may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water. The preparation of parenteral formulations under sterile conditions (e.g., by lyophilization) may be readily accomplished using standard pharmaceutical techniques.

[0163] The solubility of compounds which are used in the preparation of parenteral solutions may be increased through appropriate formulation techniques, such as the incorporation of solubility-enhancing agents. Formulations for parenteral administration may be formulated to be immediate or modified release. Modified release formulations include delayed, sustained, pulsed, controlled, targeted, and programmed release. Thus, compounds of Formula 1 may be formulated as a suspension, a solid, a semi-solid, or a thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and semi-solids and suspensions comprising drug-loaded poly(DL-lactic-co-glycolic)acid (PLGA) microspheres.

[0164] Compounds of Formula 1 may also be administered topically, intradermally, or transdermally to the skin or mucosa. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films,

skin patches, wafers, implants, sponges, fibers, bandages and microemulsions. Liposomes may also be used. Typical carriers may include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Topical formulations may also include penetration enhancers. See, e.g., Finnin and Morgan, *J. Pharm. Sci.* 88(10):955-958 (1999).

[0165] Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (e.g. Powderject™ and Bioject™) injection. Formulations for topical administration may be formulated to be immediate or modified release as described above.

[0166] Compounds of Formula 1 may also be administered intranasally or by inhalation, typically in the form of a dry powder, an aerosol spray, or nasal drops. An inhaler may be used to administer the dry powder, which comprises the API alone, a powder blend of the API and a diluent, such as lactose, or a mixed component particle that includes the API and a phospholipid, such as phosphatidylcholine. For intranasal use, the powder may include a bioadhesive agent, e.g., chitosan or cyclodextrin. A pressurized container, pump, sprayer, atomizer, or nebulizer, may be used to generate the aerosol spray from a solution or suspension comprising the API, one or more agents for dispersing, solubilizing, or extending the release of the API (e.g., EtOH with or without water), one or more solvents (e.g., 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane) which serve as a propellant, and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid. An atomizer using electrohydrodynamics may be used to produce a fine mist.

[0167] Prior to use in a dry powder or suspension formulation, the drug product is usually comminuted to a particle size suitable for delivery by inhalation (typically 90% of the particles, based on volume, having a largest dimension less than 5 microns). This may be achieved by any appropriate size reduction method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing, high pressure homogenization, or spray drying.

[0168] Capsules, blisters and cartridges (made, for example, from gelatin or hydroxypropylmethyl cellulose) for use in an inhaler or insufflator may be formulated to contain a powder mixture of the active compound, a suitable powder base such as lactose or starch, and a performance modifier such as L-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or monohydrated. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose, and trehalose.

[0169] A suitable solution formulation for use in an atomizer using electrohydrodynamics to produce a fine mist may contain from about 1 μg to about 20 mg of the API per actuation and the actuation volume may vary from about 1 μL to about 100 μL . A typical formulation may comprise one or more compounds of Formula 1, propylene glycol, sterile water, EtOH, and NaCl. Alternative solvents, which may be used instead of propylene glycol, include glycerol and polyethylene glycol.

[0170] Formulations for inhaled administration, intranasal administration, or both, may be formulated to be immediate or modified release using, for example, PGLA. Suitable flavors, such as menthol and levomenthol, or sweeteners, such as saccharin or sodium saccharin, may be added to formulations intended for inhaled/intranasal administration.

[0171] In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve that delivers a metered amount. Units are typically arranged to administer a metered dose or “puff” containing from about 10 μg to about 1000 μg of the API. The overall daily dose will typically range from about 100 μg to about 10 mg which may be administered in a single dose or, more usually, as divided doses throughout the day.

[0172] The active compounds may be administered rectally or vaginally, e.g., in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate. Formulations for rectal or vaginal administration may be formulated to be immediate or modified release as described above.

[0173] Compounds of Formula 1 may also be administered directly to the eye or ear, typically in the form of drops of a micronized suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, gels, biodegradable implants (e.g. absorbable gel sponges, collagen), non-biodegradable implants (e.g. silicone), wafers, lenses, and particulate or vesicular systems, such as niosomes or liposomes. The formulation may include one or more polymers and a preservative, such as benzalkonium chloride. Typical polymers include cross-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, cellulosic polymers (e.g., hydroxypropylmethylcellulose, hydroxyethylcellulose, methyl cellulose), and heteropolysaccharide polymers (e.g., gelatin gum). Such formulations may also be delivered by iontophoresis. Formulations for ocular or aural administration may be formulated to be immediate or modified release as described above.

[0174] To improve their solubility, dissolution rate, taste-masking, bioavailability, or stability, compounds of Formula 1 may be combined with soluble macromolecular entities,

including cyclodextrin and its derivatives and polyethylene glycol-containing polymers. For example, API-cyclodextrin complexes are generally useful for most dosage forms and routes of administration. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the API, the cyclodextrin may be used as an auxiliary additive, i.e. as a carrier, diluent, or solubilizer. Alpha-, beta- and gamma-cyclodextrins are commonly used for these purposes. See, e.g., WO 91/11172, WO 94/02518, and WO 98/55148.

[0175] As noted above, one or more compounds of Formula 1, including compounds specifically named above, and their pharmaceutically active complexes, salts, solvates and hydrates, may be combined with each other or with one or more other active pharmaceutically active compounds to treat various diseases, conditions and disorders. In such cases, the active compounds may be combined in a single dosage form as described above or may be provided in the form of a kit which is suitable for coadministration of the compositions. The kit comprises (1) two or more different pharmaceutical compositions, at least one of which contains a compound of Formula 1; and (2) a device for separately retaining the two pharmaceutical compositions, such as a divided bottle or a divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets or capsules. The kit is suitable for administering different types of dosage forms (e.g., oral and parenteral) or for administering different pharmaceutical compositions at separate dosing intervals, or for titrating the different pharmaceutical compositions against one another. To assist with patient compliance, the kit typically comprises directions for administration and may be provided with a memory aid.

[0176] For administration to human patients, the total daily dose of the claimed and disclosed compounds is typically in the range of about 0.1 mg to about 3000 mg depending on the route of administration. For example, oral administration may require a total daily dose of from about 1 mg to about 3000 mg, while an intravenous dose may only require a total daily dose of from about 0.1 mg to about 300 mg. The total daily dose may be administered in single or divided doses and, at the physician's discretion, may fall outside of the typical ranges given above. Although these dosages are based on an average human subject having a mass of about 60 kg to about 70 kg, the physician will be able to determine the appropriate dose for a patient (e.g., an infant) whose mass falls outside of this weight range.

[0177] As noted above, the compounds of Formula 1 may be used to treat diseases, disorders or conditions for which inhibition of RIPK2 is indicated. Such diseases, disorders

or conditions generally relate to any unhealthy or abnormal state in a subject for which the inhibition of RIPK2 provides a therapeutic benefit. More particularly, such diseases, disorders or conditions may involve the immune system and inflammation, including Type I hypersensitivity (allergic) reactions (allergic rhinitis, allergic asthma, and atopic dermatitis); autoimmune diseases (rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, psoriasis, lupus nephritis, immune thrombocytopenic purpura, Sjögren's syndrome, ankylosing spondylitis, and Behcet's disease); inflammatory bowel disease; inflammation of the lung (chronic obstructive pulmonary disease), atherosclerosis, thrombosis, and myocardial infarction. The compounds of Formula 1 may also be used to treat diseases, disorders or conditions related to abnormal cell growth, including hematological malignancies, such as acute myeloid leukemia, B-cell chronic lymphocytic leukemia, B-cell lymphoma (e.g., mantle cell lymphoma), T-cell lymphoma (e.g., peripheral T-cell lymphoma), and multiple myeloma, as well as epithelial cancers (i.e., carcinomas), such as lung cancer (small cell lung cancer and non-small cell lung cancer), pancreatic cancer, and colon cancer.

[0178] In addition to the hematological malignancies and epithelial cancers noted above, the compounds of Formula 1 may also be used to treat other types of cancer, including leukemia (chronic myelogenous leukemia and chronic lymphocytic leukemia); breast cancer, genitourinary cancer, skin cancer, bone cancer, prostate cancer, and liver cancer; brain cancer; cancer of the larynx, gall bladder, rectum, parathyroid, thyroid, adrenal, neural tissue, bladder, head, neck, stomach, bronchi, and kidneys; basal cell carcinoma, squamous cell carcinoma, metastatic skin carcinoma, osteosarcoma, Ewing's sarcoma, veticulum cell sarcoma, and Kaposi's sarcoma; myeloma, giant cell tumor, islet cell tumor, acute and chronic lymphocytic and granulocytic tumors, hairy-cell tumor, adenoma, medullary carcinoma, pheochromocytoma, mucosal neuromas, intestinal ganglioneuromas, hyperplastic corneal nerve tumor, marfanoid habitus tumor, Wilms' tumor, seminoma, ovarian tumor, leiomyomater tumor, cervical dysplasia, neuroblastoma, retinoblastoma, myelodysplastic syndrome, rhabdomyosarcoma, astrocytoma, non-Hodgkin's lymphoma, malignant hypercalcemia, polycythemia vera, adenocarcinoma, glioblastoma multiforma, glioma, lymphomas, and malignant melanomas, among others.

[0179] In addition to cancer, the compounds of Formula 1 may also be used to treat other diseases, disorders or conditions related to abnormal cell growth, including non-malignant proliferative diseases such as benign prostatic hypertrophy, restinosis, hyperplasia, synovial

proliferation disorder, idiopathic plasmacytic lymphadenopathy, retinopathy or other neovascular disorders of the eye, among others.

[0180] The compounds of Formula 1 may also be used to treat autoimmune diseases, disorders or conditions in addition to those listed above. Such diseases, disorders or conditions include Crohn's disease, dermatomyositis, diabetes mellitus type 1, Goodpasture's syndrome, Graves' disease, Guillain-Barré syndrome, Hashimoto's disease, mixed connective tissue damage, myasthenia gravis, narcolepsy, pemphigus vulgaris, pernicious anemia, polymyositis, primary biliary cirrhosis, temporal arteritis, ulcerative colitis, vasculitis, and Wegener's granulomatosis, among others.

[0181] The compounds of Formula 1 may be used to treat inflammatory diseases, disorders or conditions including asthma, chronic inflammation, chronic prostatitis, glomerulonephritis, hypersensitivities, inflammatory bowel diseases (ulcerative colitis in addition to Crohn's disease), pelvic inflammatory disease, reperfusion injury, transplant rejection, vasculitis, and systemic inflammatory response syndrome.

[0182] The compounds of Formula 1 may also be used to treat specific diseases or conditions that may fall within one or more general disorders described above, including arthritis. In addition to rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, SLE in children and adolescents, compounds of Formula 1 may also be used to treat other arthritis diseases, including ankylosing spondylitis, avascular necrosis, Behcet's disease, bursitis, calcium pyrophosphate dihydrate crystal deposition disease (pseudo gout), carpal tunnel syndrome, Ehlers-Danlos syndrome, fibromyalgia, Fifth disease, giant cell arteritis, gout, juvenile dermatomyositis, juvenile rheumatoid arthritis, juvenile spondyloarthropathy, Lyme disease, Marfan syndrome, myositis, osteoarthritis, osteogenesis imperfect, osteoporosis, Paget's disease, psoriatic arthritis, Raynaud's phenomenon, reactive arthritis, reflex sympathetic dystrophy syndrome, scleroderma, spinal stenosis, Still's disease, and tendinitis, among others.

[0183] The claimed and disclosed compounds may be combined with one or more other pharmacologically active compounds or therapies for the treatment of one or more diseases, disorders or conditions for which RIPK2 is indicated, including those involving the immune system, inflammation, and abnormal cell growth. For example, compounds of Formula 1, which include compounds specifically named in the examples, and their pharmaceutically acceptable complexes, salts, solvates and hydrates, may be administered simultaneously, sequentially or separately in combination with one or more compounds or therapies for

treating arthritis, including rheumatoid arthritis and osteoarthritis, or for treating cancer, including hematological malignancies, such as acute myeloid leukemia, B-cell chronic lymphocytic leukemia, B-cell lymphoma, T-cell lymphoma, multiple myeloma, and carcinomas, such as lung cancer, pancreatic cancer, and colon cancer. Such combinations may offer significant therapeutic advantages, including fewer side effects, improved ability to treat underserved patient populations, or synergistic activity.

[0184] For example, when used to treat arthritis, the compounds of Formula 1 may be combined with one or more nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, corticosteroids, biological response modifiers, and protein-A immunoabsorption therapy. Alternatively, or additionally, when treating rheumatoid arthritis, the compounds of Formula 1 may be combined with one or more disease modifying antirheumatic drugs (DMARDs), and when treating osteoarthritis, the compounds of Formula 1 may be combined with one or more osteoporosis agents.

[0185] Representative NSAIDs include apazone, aspirin, celecoxib, diclofenac (with and without misoprostol), diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate sodium, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, choline and magnesium salicylates, salsalate, and sulindac. Representative analgesics include acetaminophen and morphine sulfate, as well as codeine, hydrocodone, oxycodone, propoxyphene, and tramadol, all with or without acetaminophen. Representative corticosteroids include betamethasone, cortisone acetate, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, and prednisone. Representative biological response modifiers include TNF- α inhibitors, such as adalimumab, etanercept, and infliximab; selective B-cell inhibitors, such as rituximab; IL-1 inhibitors, such as anakinra, and selective costimulation modulators, such as abatacept.

[0186] Representative DMARDs include auranofin (oral gold), azathioprine, chlorambucil, cyclophosphamide, cyclosporine, gold sodium thiomalate (injectable gold), hydroxychloroquine, leflunomide, methotrexate, minocycline, myophenolate mofetil, penicillamine, sulfasalazine, and JAK3 inhibitor (e.g., tofacitinib). Representative osteoporosis agents include bisphosphonates, such as alendronate, ibandronate, risedronate, and zoledronic acid; selective estrogen receptor modulators, such as droloxifene, lasofoxifene, and raloxifene; hormones, such as calcitonin, estrogens, and parathyroid hormone; and immunosuppressant agents such as azathioprine, cyclosporine, and rapamycin.

[0187] Particularly useful combinations for treating rheumatoid arthritis include a compound of Formula 1 and methotrexate; a compound of Formula 1 and one or more biological response modifiers, such as leflunomide, etanercept, adalimumab, and infliximab; or a compound of Formula 1, methotrexate, and one or more biological response modifiers, such as leflunomide, etanercept, adalimumab, and infliximab.

[0188] For the treatment of thrombosis and restenosis, the compounds of Formula 1 may be combined with one or more cardiovascular agents such as calcium channel blockers, statins, fibrates, beta-blockers, ACE inhibitors, and platelet aggregation inhibitors.

[0189] The compounds of Formula 1 may also be combined with one or more compounds or therapies for treating cancer. These include chemotherapeutic agents (i.e., cytotoxic or antineoplastic agents) such as alkylating agents, antibiotics, antimetabolic agents, plant-derived agents, and topoisomerase inhibitors, as well as molecularly targeted drugs which block the growth and spread of cancer by interfering with specific molecules involved in tumor growth and progression. Molecularly targeted drugs include both small molecules and biologics.

[0190] Representative alkylating agents include bischloroethylamines (nitrogen mustards, e.g., chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, and uracil mustard); aziridines (e.g., thiotepa); alkyl alkane sulfonates (e.g., busulfan); nitrosoureas (e.g., carmustine, lomustine, and streptozocin); nonclassical alkylating agents (e.g., altretamine, dacarbazine, and procarbazine); and platinum compounds (e.g., carboplatin, cisplatin, nedaplatin, oxaliplatin, satraplatin, and triplatin tetranitrate).

[0191] Representative antibiotic agents include anthracyclines (e.g., aclarubicin, amrubicin, daunorubicin, doxorubicin, epirubicin, idarubicin, pirarubicin, valrubicin, and zorubicin); anthracenediones (e.g., mitoxantrone and pixantrone); and streptomyces (e.g., actinomycin, bleomycin, dactinomycin, mitomycin C, and plicamycin).

[0192] Representative antimetabolic agents include dihydrofolate reductase inhibitors (e.g., aminopterin, methotrexate, and pemetrexed); thymidylate synthase inhibitors (e.g., raltitrexed and pemetrexed); folinic acid (e.g., leucovorin); adenosine deaminase inhibitors (e.g., pentostatin); halogenated/ribonucleotide reductase inhibitors (e.g., cladribine, clofarabine, and fludarabine); thiopurines (e.g., thioguanine and mercaptopurine); thymidylate synthase inhibitors (e.g., fluorouracil, capecitabine, tegafur, carmofur, and floxuridine); DNA polymerase inhibitors (e.g., cytarabine); ribonucleotide reductase inhibitors (e.g.,

gemcitabine); hypomethylating agent (e.g., azacitidine and decitabine); and ribonucleotide reductase inhibitor (e.g., hydroxyurea); and an asparagine depleter (e.g., asparaginase)

[0193] Representative plant-derived agents include vinca alkaloids (e.g., vincristine, vinblastine, vindesine, vinzolidine, and vinorelbine), podophyllotoxins (e.g., etoposide and teniposide), and taxanes (e.g., docetaxel, larotaxel, ortataxel, paclitaxel, and tesetaxel).

[0194] Representative type I topoisomerase inhibitors include camptothecins, such as belotecan, irinotecan, rubitecan, and topotecan. Representative type II topoisomerase inhibitors include amsacrine, etoposide, etoposide phosphate, and teniposide, which are derivatives of epipodophyllotoxins.

[0195] Molecularly targeted therapies include biologic agents such as cytokines and other immune-regulating agents. Useful cytokines include interleukin-2 (IL-2, aldesleukin), interleukin 4 (IL-4), interleukin 12 (IL-12), and interferon, which includes more than 23 related subtypes. Other cytokines include granulocyte colony stimulating factor (CSF) (e.g., filgrastim) and granulocyte macrophage colony stimulating factor (GM-CSF or CSF2) (e.g., sargramostim, namimulab). Other immuno-modulating agents include bacillus Calmette-Guerin, levamisole, and octreotide; monoclonal antibodies against tumor antigens, such as trastuzumab and rituximab; and cancer vaccines, which induce an immune response to tumors.

[0196] In addition, molecularly targeted drugs that interfere with specific molecules involved in tumor growth and progression include inhibitors of epidermal growth factor (EGF), transforming growth factor- α (TGF_{α}), TGF_{β} , heregulin, insulin-like growth factor (IGF), fibroblast growth factor (FGF), keratinocyte growth factor (KGF), colony stimulating factor (CSF), erythropoietin (EPO), interleukin-2 (IL-2), nerve growth factor (NGF), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), angiopoietin, epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), HER4, insulin-like growth factor 1 receptor (IGF1R), IGF2R, fibroblast growth factor 1 receptor (FGF1R), FGF2R, FGF3R, FGF4R, vascular endothelial growth factor receptor (VEGFR), tyrosine kinase with immunoglobulin-like and epidermal growth factor-like domains 2 (Tie-2), platelet-derived growth factor receptor (PDGFR), Abl, Bcr-Abl, Raf, FMS-like tyrosine kinase 3 (FLT3), c-Kit, Src, protein kinase c (PKC), tropomyosin receptor kinase (Trk), Ret, mammalian target of rapamycin (mTOR), Aurora kinase, polo-like kinase (PLK), mitogen activated protein kinase (MAPK), mesenchymal-epithelial transition factor (c-MET), cyclin-dependant kinase (CDK), Akt,

extracellular signal-regulated kinases (ERK), poly(ADP) ribose polymerase (PARP), and the like.

[0197] Specific molecularly targeted drugs include selective estrogen receptor modulators, such as tamoxifen, toremifene, fulvestrant, and raloxifene; antiandrogens, such as bicalutamide, nilutamide, megestrol, and flutamide; and aromatase inhibitors, such as exemestane, anastrozole, and letrozole. Other specific molecularly targeted drugs include agents which inhibit signal transduction, such as imatinib, dasatinib, nilotinib, trastuzumab, gefitinib, erlotinib, cetuximab, lapatinib, panitumumab, and temsirolimus; agents that induce apoptosis, such as bortezomib; agents that block angiogenesis, such as bevacizumab, sorafenib, and sunitinib; agents that help the immune system destroy cancer cells, such as rituximab and alemtuzumab; and monoclonal antibodies which deliver toxic molecules to cancer cells, such as gemtuzumab, ozogamicin, tositumomab, ¹³¹I-tositumomab, and ibritumomab tiuxetan.

[0198] BIOLOGICAL ACTIVITY

[0199] One may determine the activity of the compounds of Formula 1 using a variety of methods, including *in vitro* and *in vivo* methods. A LanthaScreen® Eu Kinase Binding Assay (Invitrogen®) is optimized to screen the compounds of Formula 1 for RIPK2 inhibition. LanthaScreen® Eu Kinase Binding Assays are based on the binding and displacement of a proprietary ATP-competitive kinase inhibitor scaffold (kinase-199 tracer) to a kinase of interest. In this case, the assay detects binding of the Kinase Tracer-199, which is labeled with Alexa Fluor® 647, to RIPK2 using a europium-labeled anti-tag antibody, which binds to the RIPK2 kinase. Simultaneous binding of both the tracer and the antibody to RIPK2 results in a high degree of fluorescence resonance energy transfer (FRET) from the europium (Eu) donor fluorophore to the Alexa Fluor® 647 acceptor fluorophore on the kinase tracer. Binding of a test compound to RIPK2 competes for binding with the tracer, resulting in a loss of FRET.

[0200] The compound screening assay is carried out using Complete Binding Assay Buffer: 50 mM HEPES, 100 mM NaCl, 1 mM DTT, 10 mM MgCl₂, 1.15 mM CHEGA11, 0.1 mg/mL BSA, 2 nM RIPK2, 50nM Kinase Tracer-199, and 2nM Eu-Anti-His Antibody at pH 7.3. The Eu-Anti-His Antibody and Kinase Tracer-199 are purchased from Invitrogen, and human RIPK2 protein (8-317 aa, N-terminal His-tag, R171C, 38.3KDa) may be obtained as described below.

[0201] RIPK2 DNA encoding residues 8-317 of the human protein is cloned into pFastBac vector (Invitrogen®) which incorporates a 6-histidine tag at the N-terminus followed by a rTEV cleavage site. A R171C mutant is generated by site-directed mutagenesis. Recombinant baculovirus incorporating the RIPK2 construct is generated by transposition using the Bac-to-Bac system (Invitrogen®). High-titer viral stock is generated by infection of *Spodoptera frugiperda* Sf9 cells; the expression of recombinant protein is carried out by infection of *Spodoptera frugiperda* Sf9 (Invitrogen®) for 48 hours in a wave bag.

[0202] Recombinant RIPK2 protein is isolated from cellular extracts by binding with Probond Nickel resin (Life Technology®). The resin is washed with buffer containing 25 mM HEPES pH 7.6, 0.5 M NaCl and 20 mM imidazole, and then eluted with the elution buffer 50 mM HEPES pH 7.6, 250 mM imidazole, 150 mM NaCl, 5% glycerol and 0.5 mM TCEP. Partially purified protein is then dephosphorylated by adding 0.05 mM MnCl₂ and λ-phosphatase and incubating in room temperature for 4 hours. The dephosphorylated RIPK2 protein is then purified through a Superdex® 75 column in the buffer containing 10 mM HEPES pH 7.5, 150 mM NaCl, 5% glycerol, 2 mM DTT, 1 mM TCEP, 5 mM L-Arg, and 5 mM L-Glu. The protein is stored at -80°C in small aliquots.

[0203] The compounds of Formula 1 are tested for RIPK2 inhibition as follows. Test compounds are prepared in 100% DMSO and are dispensed in duplicate to individual wells of a multiplate, starting at 10 μM with 2.5 x series dilution. Next 10 μL of Complete Binding Assay Buffer is added to each of the test compounds using a Multidrop™ Combi Reagent Dispenser. The wells are covered with aluminum sealer, shaken for 2 minutes at 900 rpm, spun down for 10 seconds at 1000 rpm, incubated at RT for 60 minutes, shaken for 2 minutes at 900 rpm, and spun down for 10 seconds at 1000 rpm before reading. Samples are read on an instrument capable of measuring fluorescent polarization. The ratio 665 nM/620 nM is determined using a PHERAstar plate reader. Test compound inhibition is expressed as percent (%) inhibition of internal assay controls. For concentration response experiments, normalized data are fit and pIC₅₀s determined using conventional techniques. The pIC₅₀s are averaged to determine a mean value for a minimum of two experiments.

EXAMPLES

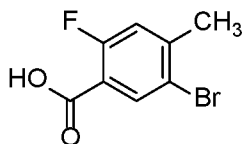
[0204] The following examples are intended to be illustrative and non-limiting and represent specific embodiments of the present invention.

[0205] ¹H Nuclear magnetic resonance (NMR) spectra were obtained for many of the compounds in the following examples. Characteristic chemical shifts (δ) are given in parts-

per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks, including s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). The following abbreviations are used for common solvents: CDCl_3 (deuteriochloroform), $\text{DMSO}-d_6$ (deuterodimethylsulfoxide), CD_3OD (deuteromethanol), CD_3CN (deuteroacetonitrile), and $\text{THF}-d_8$ (deuterotetrahydrofuran). The mass spectra (m/z for $[\text{M}+\text{H}]^+$) were recorded using either electrospray ionization (ESI-MS) or atmospheric pressure chemical ionization (APCI-MS) mass spectrometry.

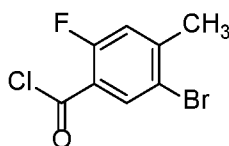
[0206] Where indicated, products of certain preparations and examples are purified by mass-triggered HPLC, flash chromatography, preparative TLC or SFC. Reverse phase chromatography is typically carried out on a column (e.g., Gemini™ 5 μm C18 110Å, Axia™, 30 x 75 mm, 5 μm) under acidic conditions (“acid mode”) eluting with ACN and water mobile phases containing 0.035% and 0.05% trifluoroacetic acid (TFA), respectively, or under basic conditions (“basic mode”) eluting with water and 20/80 (v/v) water/acetonitrile mobile phases, both containing 10 mM NH_4HCO_3 . Preparative TLC is typically carried out on silica gel 60 F₂₅₄ plates. The preparations and examples may employ SFC to separate enantiomers. After isolation by chromatography, the solvent is removed and the product is obtained by drying in a centrifugal evaporator (e.g., GeneVac™), rotary evaporator, evacuated flask, etc. Reactions in an inert (e.g., nitrogen) or reactive (e.g., H_2) atmosphere are typically carried out at a pressure of about 1 atmosphere (14.7 psi).

[0207] PREPARATION 1: 5-bromo-2-fluoro-4-methylbenzoic acid



[0208] To a solution of 2-fluoro-4-methylbenzoic acid (50 g, 324.38 mmol) in H_2SO_4 (300 mL) was added NBS (63.51 g, 356.82 mmol). The mixture was stirred at 0°C for 2 hours and then poured into ice water and filtered. The filter cake was dried under reduce pressure to give the title compound as a white solid (140 g, crude). ESI-MS m/z $[\text{M}+\text{H}]^+ = 234.1$.

[0209] PREPARATION 2: 5-bromo-2-fluoro-4-methylbenzoyl chloride



[0210] To a solution of 5-bromo-2-fluoro-4-methylbenzoic acid (70 g, 300.39 mmol) in toluene (300 mL) was added SOCl_2 (108.95 mL, 1.50 mol) and DMF (2.31 mL, 30.04 mmol).

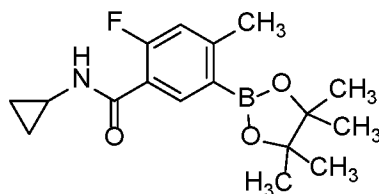
The resulting mixture was stirred at 70°C for 5 hours and then concentrated under reduce pressure to give the title compound as a yellow oil (70 g, crude).

[0211] PREPARATION 3: 5-bromo-*N*-cyclopropyl-2-fluoro-4-methylbenzamide



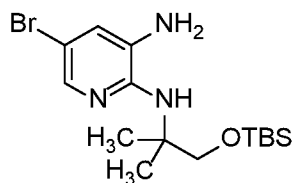
[0212] To a solution of cyclopropanamine (20.16 g, 353.1 mmol) in DCM (300 mL) was added Et₃N (163.83 mL, 1.18 mol). The mixture was stirred at 0°C for 0.5 hours. A solution of 5-bromo-2-fluoro-4-methylbenzoyl chloride (74 g, 294.26 mmol) in DCM (200 mL) was added drop-wise and the mixture was stirred at 0°C for 2 hours. The reaction mixture was then diluted with DCM, washed with water and brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was triturated with ethyl acetate (15%) in petroleum ether to give the title compound as a yellow solid (80 g, 100%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.46 - 0.59 (m, 2 H) 0.64 - 0.75 (m, 2 H) 2.37 (s, 3 H) 2.76 - 2.89 (m, 1 H) 7.35 (d, *J*=11.2 Hz, 1 H) 7.71 (d, *J*=11.2 Hz, 1 H) 8.38 (s, 1 H).

[0213] PREPARATION 4: *N*-cyclopropyl-2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

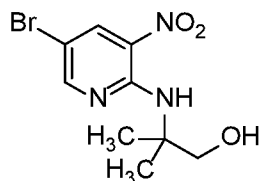


[0214] To a solution of 5-bromo-*N*-cyclopropyl-2-fluoro-4-methylbenzamide (67 g, 246.22 mmol) in dioxane (500 mL) were added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (65.65 g, 258.53 mmol), KOAc (72.49 g, 738.66 mmol) and Pd(dppf)Cl₂ (1.80 g, 2.46 mmol). The mixture was degassed and purged with N₂ (3 x) and then stirred at 90°C for 12 hours and filtered. The filtrate was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated under reduce pressure. The crude product was triturated with EtOAc (10%) in petroleum ether to give the title compound as a yellow solid (41 g, 52%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.51 - 0.58 (m, 2 H) 0.65 - 0.74 (m, 2 H) 1.31 (s, 12 H) 2.49 (s, 3 H) 2.60 - 2.82 (m, 1 H) 7.10 (d, *J*=12.0 Hz, 1 H) 7.82 (d, *J*=8.4 Hz, 1 H) 8.25 (s, 1 H); ESI-MS *m/z* [M+H]⁺ = 320.3.

[0215] PREPARATION 5: 5-bromo-*N*'-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)pyridine-2,3-diamine

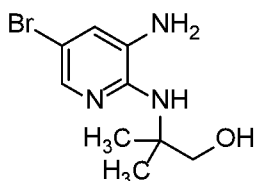


[0216] STEP 1: 2-((5-bromo-3-nitropyridin-2-yl)amino)-2-methylpropan-1-ol



[0217] A solution of 5-bromo-2-chloro-3-nitropyridine (25 g, 105.29 mmol), 2-amino-2-methylpropan-1-ol (18.77 g, 210.6 mmol) and DIPEA (40.82 g, 315.87 mmol) in acetonitrile (500 mL) was stirred at 80°C for 12 hours under nitrogen. The mixture was then concentrated. Water was added and the mixture was extracted with EtOAc. The organic layers were combined, washed with brine, and concentrated under reduced pressure. The concentrate was extracted with 1 M HCl aqueous solution. The organic layers were dried over Na₂SO₄ and concentrated to give the title compound as a yellow oil (30 g, crude).

[0218] STEP 2: 2-((3-amino-5-bromopyridin-2-yl)amino)-2-methylpropan-1-ol



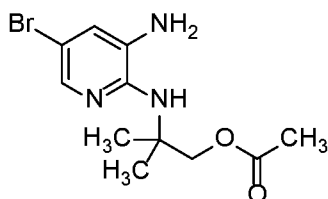
[0219] A mixture of 2-((5-bromo-3-nitropyridin-2-yl)amino)-2-methylpropan-1-ol (30 g, 103.41 mmol), Fe (28.87 g, 517.04 mmol) and NH₄Cl (22.13 g, 413.63 mmol) in EtOH (300 mL) and water (50 mL) was stirred at 80°C for 1 hour. The mixture was filtered, and the filtrate concentrated. Water was added and the mixture was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to give the title compound as a black oil (25 g, crude).

[0220] STEP 3: 5-bromo-*N*²-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)pyridine-2,3-diamine

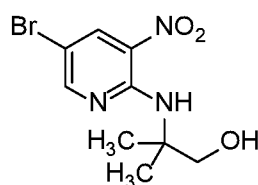
[0221] A mixture of 2-((3-amino-5-bromopyridin-2-yl)amino)-2-methylpropan-1-ol (50 g, 192.21 mmol), imidazole (26.17 g, 384.4 mmol) and TBSCl (43.46 g, 288.32 mmol) in DCM (500 mL) was stirred at 15°C for 12 hours under nitrogen. The mixture was extracted with water. The organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by preparative HPLC to give the title compound

as a purple oil (48 g, 67%). ^1H NMR (400 MHz, CDCl_3) δ ppm 0.17 (s, 6 H) 0.73 (s, 9 H) 1.27 (s, 6 H) 3.10 (s, 2 H) 3.52 (s, 2 H) 4.42 (s, 1 H) 6.91 (d, $J=2.40$ Hz, 1 H) 7.73 (d, $J=2.40$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 376.2$.

[0222] PREPARATION 6: 2-((3-amino-5-bromopyridin-2-yl)amino)-2-methylpropyl acetate

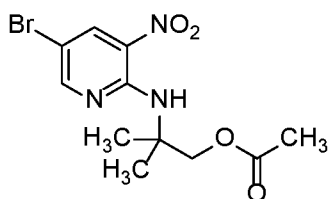


[0223] STEP 1: 2-((5-bromo-3-nitropyridin-2-yl)amino)-2-methylpropan-1-ol



[0224] To a solution of 5-bromo-2-chloro-3-nitropyridine (3 g, 12.63 mmol) and 2-amino-2-methylpropan-1-ol (2.41 mL, 25.27 mmol) in acetonitrile (20 mL) was added DIPEA (11.00 mL, 63.17 mmol). The reaction mixture was stirred at 80°C for 16 hours and was then quenched by the addition of water. The aqueous phase was separated and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography, eluting with a gradient of 3-30% EtOAc in petroleum ether to give the title compound as a yellow solid (3 g, 82%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.42 (s, 6 H) 3.50 (d, $J=5.6$ Hz, 2 H) 5.25 (s, 1 H) 8.53 (s, 1 H) 8.54-8.59 (m, 2 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 291.9$.

[0225] STEP 2: 2-((5-bromo-3-nitropyridin-2-yl)amino)-2-methylpropyl acetate



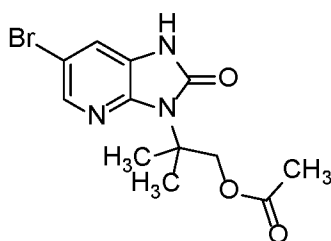
[0226] To a solution of 2-((5-bromo-3-nitropyridin-2-yl)amino)-2-methylpropan-1-ol (1.5 g, 5.2 mmol) in pyridine (15 mL) was added acetic anhydride (0.969 mL, 10.34 mmol). The mixture was stirred at 80°C for 4 hours and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with a gradient of 0-3% EtOAc in petroleum ether to give the title compound as a yellow oil (1.6 g, 93%). ^1H NMR

(400 MHz, CDCl₃) δ ppm 2.08 (s, 3 H) 4.41 (s, 2 H) 8.31 (s, 1 H) 8.42 (d, $J=2.4$ Hz, 1 H) 8.55 (d, $J=2.4$ Hz, 1 H); ESI-MS m/z $[M+H]^+ = 334.0$.

[0227] STEP 3: 2-((3-amino-5-bromopyridin-2-yl)amino)-2-methylpropyl acetate

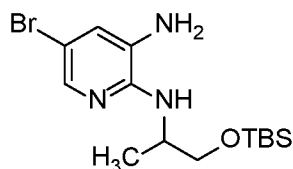
[0228] To a solution of 2-((5-bromo-3-nitropyridin-2-yl)amino)-2-methylpropyl acetate (1.6 g, 4.82 mmol) in EtOH (20 mL) and water (2 mL) were added Fe (1.35 g, 24.09 mmol) and NH₄Cl (2.58 g, 48.17 mmol). The reaction mixture was stirred at 80°C for 2 hours and then filtered. The filtrate was concentrated *in vacuo*. Water was added and the aqueous phase was extracted with EtOAc. The organic phase was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography, eluting with a gradient of 3-10% EtOAc in petroleum ether to give the title compound as a brown oil (1.2 g, 82%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.47 (s, 6 H) 2.08 (s, 3 H) 3.22 (s, 2 H) 4.19 (s, 1 H) 4.37 (s, 2 H) 6.95 (d, $J=2.0$ Hz, 1 H) 7.72 (d, $J=2.0$ Hz, 1 H).

[0229] PREPARATION 7: 2-(6-bromo-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate



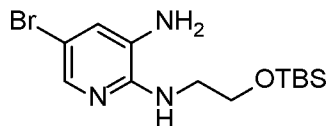
[0230] A mixture of 2-((3-amino-5-bromopyridin-2-yl)amino)-2-methylpropyl acetate (0.5 g, 1.65 mmol) and CDI (402.46 mg, 2.48 mmol) in THF (60 mL) was stirred at 70°C for 16 hours and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with a gradient of 3-20% EtOAc in petroleum ether to give the title compound as a white solid (400 mg, 73.7%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.60 (s, 3 H) 1.86 (s, 6 H) 1.99 (s, 3 H) 4.71 (s, 2 H) 7.39 (d, $J=2.0$ Hz, 1 H) 8.06 (d, $J=2.0$ Hz, 1 H) 9.37 (s, 1 H); ESI-MS m/z $[M+H]^+ = 330.0$.

[0231] PREPARATION 8: 5-bromo-*N*²-(1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)pyridine-2,3-diamine



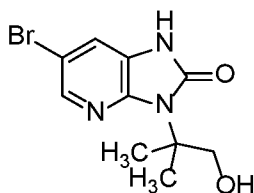
[0232] The title compound was prepared like PREPARATION 5, starting with 2-aminopropan-1-ol (379.60 mg, 5.05 mmol, 1.2 eq) in place of 2-amino-2-methylpropan-1-ol and proceeding through intermediates 2-((5-bromo-3-nitropyridin-2-yl)amino)propan-1-ol and 2-((3-amino-5-bromopyridin-2-yl)amino)propan-1-ol. The title compound was obtained as a black oil (1 g, 76% STEP 3). ESI-MS m/z $[M+H]^+ = 362.1$.

[0233] PREPARATION 9: 5-bromo-*N*²-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)pyridine-2,3-diamine



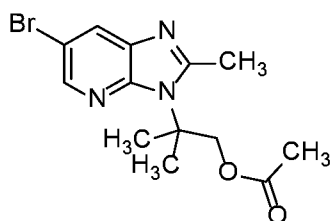
[0234] The title compound was prepared like PREPARATION 5, starting with 2-aminoethanol (282.98 mg, 4.63 mmol, 1.1 eq) in place of 2-amino-2-methylpropan-1-ol and proceeding through intermediates 2-((5-bromo-3-nitropyridin-2-yl)amino)ethan-1-ol and 2-((3-amino-5-bromopyridin-2-yl)amino)ethan-1-ol. The title compound was obtained as a purple solid (600 mg, 50.3% STEP 3). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.00 (s, 6H) - 0.08 - 0.06 (m, 1 H) 0.84 (s, 9 H) 3.39 - 3.39 (m, 3 H) 3.35 - 3.47 (m, 1 H) 3.68 (t, $J=6.4$ Hz, 2 H) 5.01 (s, 2 H) 5.78 (br t, $J=5.6$ Hz, 1 H) 6.78 (d, $J=2.0$ Hz, 1 H) 7.35 (d, $J=2.0$ Hz, 1 H); ESI-MS m/z $[M+H]^+ = 346.1$.

[0235] PREPARATION 10: 6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one



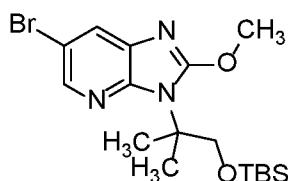
[0236] To a solution of 2-(6-bromo-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (38 g, 115.80 mmol) in MeOH (200 mL) was added K_2CO_3 (48.01 g, 347.39). The reaction mixture was stirred at 65°C for 3 hours, then filtered and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography, eluting with EtOAc, then triturated with EtOAc/petroleum ether (1:5, 60 mL) and filtered to give the title compound as an off-white solid (16 g, 47%). ^1H NMR (400 MHz, DMSO- d_6) δ 1.65 (s, 6H) 3.84 (d, $J=6.0$ Hz, 2H) 4.85 (t, $J=6.0$ Hz, 1H) 7.41 (d, $J=2.0$ Hz, 1H) 8.00 (d, $J=2.0$ Hz, 1H) 11.21 (s, 1H); ESI-MS m/z $[M+H]^+ = 288.0$ $[M+2]^+$.

[0237] PREPARATION 11: 2-(6-bromo-2-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate



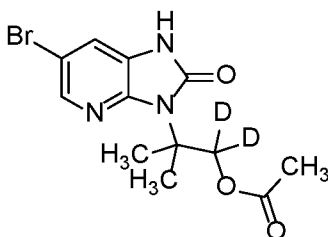
[0238] To a solution of 5-bromo-*N*²-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)pyridine-2,3-diamine (500 mg, 1.34 mmol) in HOAc (5 mL) was added tetramethoxymethane (181.82 mg, 1.34 mmol). The reaction mixture was heated to 120°C and stirred for 12 hours under nitrogen. The mixture was then concentrated *in vacuo* to remove HOAc. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 6-20% EtOAc in petroleum ether to give the title compound as a light-yellow oil (61 mg, 14%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.92 (s, 6 H) 1.94 (s, 3 H) 2.81 (s, 3 H) 4.77 (s, 2 H) 8.01 (d, *J*=2.00 Hz, 1 H) 8.31 (d, *J*=2.40 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 326.1.

[0239] PREPARATION 12: 6-bromo-3-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-2-methoxy-3*H*-imidazo[4,5-*b*]pyridine

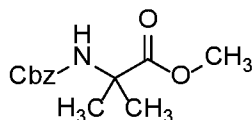


[0240] A mixture of 5-bromo-*N*²-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)pyridine-2,3-diamine (200 mg, 534 μmol), tetramethoxymethane (218.19 mg, 1.60 mmol), and propionic acid (118.72 mg, 1.60 mmol) was degassed and purged with N₂ (3 x) and then stirred at 100°C for 6 hours under N₂ atmosphere. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (SiO₂) eluting with a gradient of 0-5% EtOAc in petroleum ether to give the title compound as a light-blue oil (130 mg, 58.7%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.20 (d, *J*=2.8 Hz, 6 H) 0.73 (t, *J*=2.8 Hz, 9 H) 1.80 (s, 6 H) 4.01 (s, 2 H) 4.14 (s, 3 H) 7.81 (d, *J*=2.0 Hz, 1 H) 8.15 (d, *J*=2.4 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 416.2.

[0241] PREPARATION 13: 2-(6-bromo-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1-*d*₂ acetate

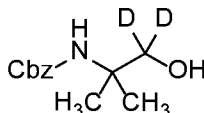


[0242] STEP 1: methyl 2-(((benzyloxy)carbonyl)amino)-2-methylpropanoate



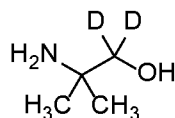
[0243] To a stirred solution of methyl 2-amino-2-methyl-propanoate (1 g, 8.54 mmol, HCl) in water (15 mL) at 10°C was added Na₂CO₃ (3.17 g, 29.88 mmol) followed by a solution of benzyl carbonochloridate (1.53 g, 8.96 mmol) in dioxane (20 mL). The resulting white suspension was stirred at 25°C for 2 hours under nitrogen. The mixture was diluted with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 0-30% EtOAc in petroleum ether to give the title compound as a yellow solid (860 mg, 40.1%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.35 (s, 6H) 3.58 (s, 3H) 5.00 (s, 2H) 7.28 - 7.42 (m, 5H) 7.73 (s, 1H); ESI-MS *m/z* [M+H]⁺ = 252.1.

[0244] STEP 2: benzyl (1-hydroxy-2-methylpropan-2-yl-1,1-*d*₂)carbamate



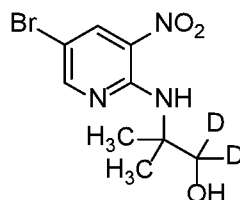
[0245] To a solution of LiAlD₄ (151.05 mg, 3.98 mmol) in THF (10 mL) was added methyl 2-(((benzyloxy)carbonyl)amino)-2-methylpropanoate (500 mg, 1.99 mmol) and the resulting mixture was stirred at 10°C for 1 hour under nitrogen. The reaction mixture was quenched with aq saturated NH₄Cl solution and water and was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 10-30% EtOAc in petroleum ether to give the title compound as a white oil (340 mg, 75.9%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.16 (s, 6 H) 4.65 (s, 1 H) 4.97 (s, 2 H) 6.69 (s, 1 H) 7.31 - 7.36 (m, 5 H).

[0246] STEP 3: 2-amino-2-methylpropan-1,1-*d*₂-1-ol



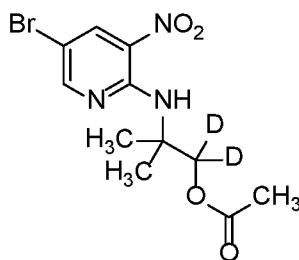
[0247] A mixture of benzyl (1-hydroxy-2-methylpropan-2-yl-1,1-*d*₂)carbamate (340 mg, 1.51 mmol) and Pd/C (50 mg, 10% purity) in MeOH (5 mL) was stirred at 15°C for 2 hours under H₂ (15 psi). The mixture was filtered, and the filtrate was concentrated to give the title compound as a white oil (150 mg, crude). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.946 (s, 6H).

[0248] STEP 4: 2-((5-bromo-3-nitropyridin-2-yl)amino)-2-methylpropan-1,1-*d*₂-1-ol



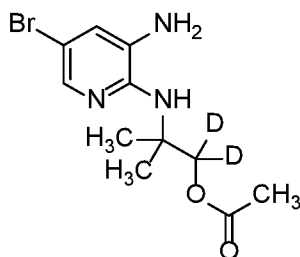
[0249] A solution of 2-amino-2-methylpropan-1,1-*d*₂-1-ol (138.20 mg, 1.52 mmol), 5-bromo-2-chloro-3-nitro-pyridine (300 mg, 1.26 mmol) and DIPEA (326.59 mg, 2.53 mmol, 440.14 μL) in acetonitrile (5 mL) was stirred at 80°C for 12 hours under nitrogen. The reaction mixture was then diluted with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 5-20% EtOAc in petroleum ether to give the title compound as a yellow solid (160 mg, 43.3%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.48 (s, 6 H) 4.19 (s, 1 H) 8.37 – 8.47 (m, 2 H) 8.60 (d, *J*=2.4 Hz, 1 H).

[0250] STEP 5: 2-((5-bromo-3-nitropyridin-2-yl)amino)-2-methylpropyl-1,1-*d*₂ acetate



[0251] A solution of 2-((5-bromo-3-nitropyridin-2-yl)amino)-2-methylpropan-1,1-*d*₂-1-ol (160 mg, 547.71 μmol) and acetic anhydride (111.83 mg, 1.10 mmol) in pyridine (3 mL) was stirred at 80°C for 3 hours under nitrogen. The mixture was concentrated, and the resulting residue was washed with 1M HCl. The organic layer was evaporated to give the title compound as a yellow solid (200 mg, crude). ESI-MS *m/z* [M+H]⁺ = 333.9.

[0252] STEP 6: 2-((3-amino-5-bromopyridin-2-yl)amino)-2-methylpropyl-1,1-*d*₂ acetate

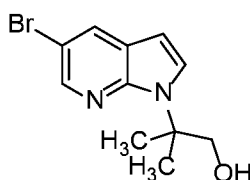


[0253] A mixture of 2-((5-bromo-3-nitropyridin-2-yl)amino)-2-methylpropyl-1,1-*d*₂ acetate (183 mg, 548 μ mol), Fe (152.91 mg, 2.74 mmol) and NH₄Cl (117.18 mg, 2.19 mmol) in EtOH (2 mL) and water (0.5 mL) was stirred at 80°C for 1 hour under nitrogen. The mixture was filtered, and the filtrate was concentrated. The resulting residue was dispersed in water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to give the title compound as a brown solid (160 mg, crude). ESI-MS *m/z* [M+H]⁺ = 304.0.

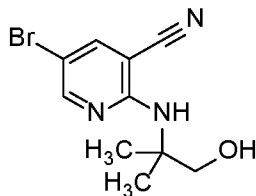
[0254] STEP 7: [2-(6-bromo-2-oxo-1H-imidazo[4,5-*b*]pyridin-3-yl)-1,1-dideuterio-2-methyl-propyl] acetate

[0255] A solution 2-((3-amino-5-bromopyridin-2-yl)amino)-2-methylpropyl-1,1-*d*₂ acetate (160 mg, 526.01 μ mol) and CDI (127.94 mg, 789.01 μ mol) in THF (3 mL) was stirred at 70°C for 5 hours under nitrogen. The mixture was diluted with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 0-30% EtOAc in petroleum to give the title compound as a yellow solid (130 mg, 74.9%). ESI-MS *m/z* [M+H]⁺ = 330.1.

[0256] PREPARATION 14: 2-(5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-2-methylpropan-1-ol



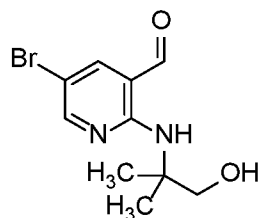
[0257] STEP 1: 5-bromo-2-((1-hydroxy-2-methylpropan-2-yl)amino)nicotinonitrile



[0258] To a solution of 5-bromo-2-chloronicotinonitrile (5 g, 22.99 mmol) and 2-amino-2-methylpropan-1-ol (4.10 g, 45.99 mmol, 4.39 mL) in acetonitrile (50 mL) was added Cs₂CO₃

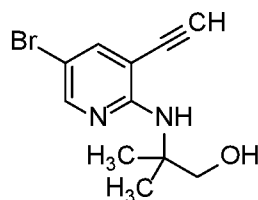
(14.98 g, 45.99 mmol). The mixture was stirred at 85°C for 15 hours and was then quenched by the addition of water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 9-17% EtOAc in petroleum ether to give the title compound as a yellow solid (2 g, 32%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.42 (s, 6 H) 3.66 (s, 2 H) 7.92 (d, *J*=2.40 Hz, 1 H) 8.29 (d, *J*=2.40 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 271.0.

[0259] STEP 2: 5-bromo-2-((1-hydroxy-2-methylpropan-2-yl)amino)nicotinaldehyde



[0260] To a solution of 5-bromo-2-((1-hydroxy-2-methylpropan-2-yl)amino)nicotinonitrile (2 g, 7.40 mmol) in pyridine (20 mL), water (10 mL) and HOAc (10 mL) were added Raney-Ni (2.22 g, 25.91 mmol) and NaH₂PO₂ (3.18 g, 37.02 mmol). The mixture was stirred at 25°C for 12 hours under nitrogen, then filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 4-5% EtOAc in petroleum ether to give the title compound as a yellow solid (750 mg, 35.2%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.43 (s, 6 H) 3.68 (s, 2 H) 5.73 (s, 1 H) 7.86 (d, *J*=2.40 Hz, 1 H) 8.25 (d, *J*=2.40 Hz, 1 H) 8.63 (s, 1 H) 9.74 (s, 1 H); ESI-MS *m/z* [M+H]⁺ = 274.0.

[0261] STEP 3: 2-((5-bromo-3-ethynylpyridin-2-yl)amino)-2-methylpropan-1-ol



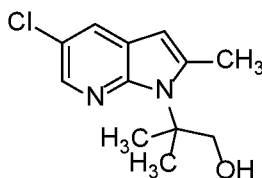
[0262] To a solution of 5-bromo-2-((1-hydroxy-2-methylpropan-2-yl)amino)nicotinaldehyde (750 mg, 2.75 mmol) and dimethyl (1-diazo-2-oxopropyl)phosphonate (633.96 mg, 3.30 mmol) in MeOH (10 mL) was added K₂CO₃ (760.13 mg, 5.50 mmol). The mixture was stirred at 25°C for 15 hours, then concentrated under reduced pressure. The concentrate was adjusted to pH=8 using aq saturated NaHCO₃ solution and then extracted with EtOAc. The organic layers were combined, dried over Na₂SO₄, filtered and concentrated. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 4-6% EtOAc in petroleum ether and then

by preparative HPLC to give the title compound as a yellow oil (510 mg, crude). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.38 (s, 6 H) 3.52 (s, 1 H) 3.65 (s, 2 H) 4.02 (s, 1 H) 5.36 (s, 1 H) 6.20 (s, 1 H) 7.64 (d, $J=2.40$ Hz, 1 H) 8.02 (d, $J=2.40$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{Na}]^+ = 291.0$.

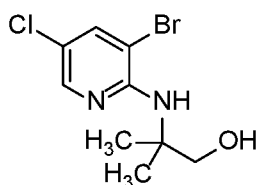
[0263] STEP 4: 2-(5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-2-methylpropan-1-ol

[0264] To a solution of 2-((5-bromo-3-ethynylpyridin-2-yl)amino)-2-methylpropan-1-ol (510 mg, 1.89 mmol) in DMF (5 mL) was added KO^tBu (425.27 mg, 3.79 mmol). The reaction mixture was stirred at 25°C for 15 hours and was then quenched by the addition of water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2) eluting with a gradient of 0-5% EtOAc in petroleum ether to give the title compound as a yellow oil (360 mg, 70.6%). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.66 (s, 6 H) 4.03 (s, 2 H) 6.13 (s, 1 H) 6.43 (d, $J=4.00$ Hz, 1 H) 7.40 (d, $J=3.60$ Hz, 1 H) 8.05 (d, $J=2.00$ Hz, 1 H) 8.27 (d, $J=2.00$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 269.0$.

[0265] PREPARATION 15: 2-(5-chloro-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-2-methylpropan-1-ol

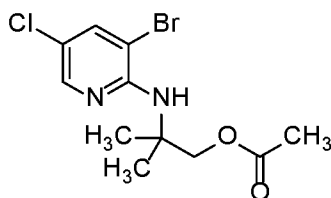


[0266] STEP 1: 2-((3-bromo-5-chloropyridin-2-yl)amino)-2-methylpropan-1-ol



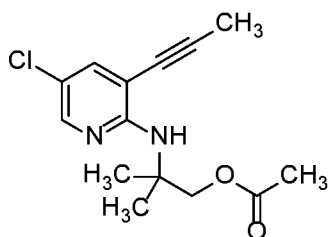
[0267] To a mixture of 3-bromo-5-chloro-2-fluoropyridine (5 g, 24 mmol) and 2-amino-2-methylpropan-1-ol (3.18 g, 35.6 mmol, 3.40 mL) in DMSO (50 mL) was added DIPEA (6.14 g, 47.52 mmol) in one portion under N_2 . The reaction mixture was stirred at 150°C for 6 hours, then quenched with water (50 mL) and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2) eluting with a gradient of 5-20% EtOAc in petroleum ether to give the title compound as a colorless oil (2.8 g, 41%). ESI-MS m/z $[\text{M}+\text{H}]^+ = 281.0$.

[0268] STEP 2: 2-((3-bromo-5-chloropyridin-2-yl)amino)-2-methylpropyl acetate



[0269] To a mixture of 2-((3-bromo-5-chloropyridin-2-yl)amino)-2-methylpropan-1-ol (2.8 g, 9.7 mmol) in pyridine (10 mL) was added acetic anhydride (1.98 g, 19.4 mmol, 1.82 mL) in one portion under N₂. The reaction mixture was stirred at 80°C for 3 hours, then diluted with water, and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 0-5% EtOAc in petroleum ether to give the title compound as a colorless oil (3.0 g, 95%). ESI-MS m/z [M+H]⁺ = 323.0.

[0270] STEP 3: 2-((5-chloro-3-(prop-1-yn-1-yl)pyridin-2-yl)amino)-2-methylpropyl acetate



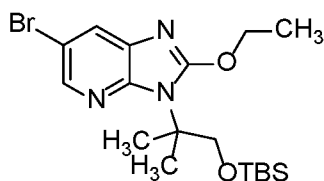
[0271] To a mixture of 2-((3-bromo-5-chloropyridin-2-yl)amino)-2-methylpropyl acetate (1 g, 3.07 mmol) and tributyl(prop-1-yn-1-yl)stannane (1.21 g, 3.68 mmol) in toluene (10 mL) was added Pd(PPh₃)₄ (177.32 mg, 153.45 μmol) in one portion under N₂. The reaction mixture was stirred at 100°C for 12 hours and then concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 0-20% EtOAc in petroleum ether to give the title compound as a yellow oil (600 mg, 67.6%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.46 (s, 6 H) 2.08 (s, 3 H) 2.13 (s, 3 H) 4.36 (s, 2 H) 5.25 (s, 1 H) 7.35 (d, *J*=2.6 Hz, 1 H) 7.91 (d, *J*=2.6 Hz, 1 H); ESI-MS m/z [M+H]⁺ = 281.1.

[0272] STEP 4: 2-(5-chloro-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-2-methylpropan-1-ol

[0273] To a mixture of 2-((5-chloro-3-(prop-1-yn-1-yl)pyridin-2-yl)amino)-2-methylpropyl acetate (500 mg, 1.73 mmol) in DMF (10 mL) was added NaOt-Bu (498.56 mg, 5.19 mmol) in one portion under N₂. The reaction mixture was stirred at 60°C for 12 hours, then diluted with water, and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 2-10% EtOAc in

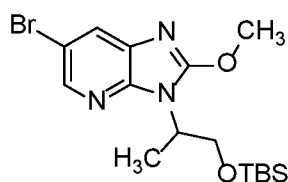
petroleum ether to give the title compound as a light-yellow oil (250 mg, 60.0%). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.65 (s, 6 H) 2.68 (s, 3 H) 4.17 (s, 2 H) 6.23 (s, 1 H) 6.34 (s, 1 H) 7.73 (d, $J=2.4$ Hz, 1 H) 8.08 (d, $J=2.4$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 239.1$.

[0274] PREPARATION 16: 6-bromo-3-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-2-ethoxy-3*H*-imidazo[4,5-*b*]pyridine



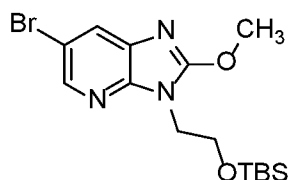
[0275] A mixture of tetraethoxymethane (2.57 g, 13.35 mmol), propionic acid (593.59 mg, 8.01 mmol) and 5-bromo-*N*²-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)pyridine-2,3-diamine (2 g, 5.34 mmol) was degassed and purged with N_2 (3 x) then stirred at 100°C for 6 hours under nitrogen and concentrated. The crude product was purified by column chromatography, eluting with a gradient of 0-20% EtOAc in petroleum ether to give the title compound as a purple oil (1.2 g, 52%). ESI-MS m/z $[\text{M}+\text{H}]^+ = 430.1$.

[0276] PREPARATION 17: 6-bromo-3-(1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-2-methoxy-3*H*-imidazo[4,5-*b*]pyridine



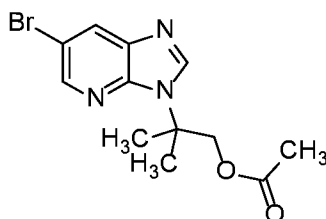
[0277] To a solution of 5-bromo-*N*²-(1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)pyridine-2,3-diamine (400 mg, 1.11 mmol) in propionic acid (123.34 mg, 1.66 mmol) was added tetramethoxymethane (377.80 mg, 2.77 mmol). The reaction mixture was stirred at 100°C for 5 hours, then concentrated under reduced pressure and diluted with EtOAc and water. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2) eluting with a gradient of 0-40% EtOAc in petroleum ether to give the title compound as a yellow oil (300 mg, 67.5%). ESI-MS m/z $[\text{M}+\text{H}]^+ = 402.0$.

[0278] PREPARATION 18: 6-bromo-3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-methoxy-3*H*-imidazo[4,5-*b*]pyridine



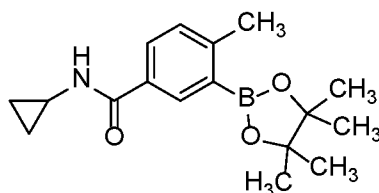
[0279] To a solution of 5-bromo-*N*²-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)pyridine-2,3-diamine (300 mg, 866.21 μ mol) in propionic acid (96.25 mg, 1.30 mmol, 96.93 μ L) was added tetramethoxymethane (294.83 mg, 2.17 mmol). The reaction mixture was stirred at 100°C for 7 hours, then poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated under reduce pressure. The crude product was purified by column chromatography (SiO₂) eluting with a gradient of 8-30% EtOAc in petroleum ether to give the title compound as a yellow oil (200 mg, 59.8%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.23 (s, 6 H) 0.68 (s, 9 H) 3.89 - 3.93 (m, 2 H) 4.13 (s, 3 H) 4.14 - 4.16 (m, 2 H) 8.04 (d, *J*=2.0 Hz, 1 H) 8.21 (d, *J*=2.0 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 388.0.

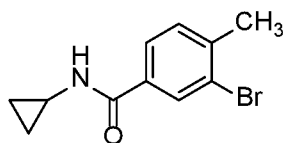
[0280] PREPARATION 19: 2-(6-bromo-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate



[0281] To a solution of 2-((3-amino-5-bromopyridin-2-yl)amino)-2-methylpropyl acetate (2.8 g, 9.27 mmol) in HOAc (10 mL) was added triethoxymethane (6.87 g, 46.33 mmol). The reaction mixture was stirred at 80°C for 15 hours, then concentrated under reduced pressure, and purified by column chromatography (SiO₂) eluting with a gradient of 15-25% EtOAc in petroleum ether to give the title compound as a brown oil (2.4 g, 83%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.84 (s, 6 H) 1.94 (s, 3 H) 4.69 (s, 2 H) 8.10 (s, 1 H) 8.19 (d, *J*=1.6 Hz, 1 H) 8.41 (d, *J*=2.0 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 311.8.

[0282] PREPARATION 20: *N*-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

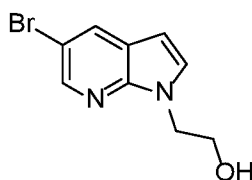


[0283] STEP 1: 3-bromo-*N*-cyclopropyl-4-methylbenzamide

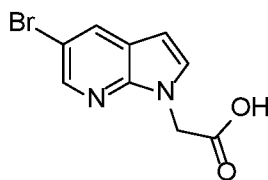
[0284] To a solution of 3-bromo-4-methylbenzoic acid (3.6 g, 16.74 mmol) and cyclopropanamine (955.80 mg, 16.74 mmol) in DMF (20 mL) were added HATU (7.00 g, 18.41 mmol) and Et₃N (5.08 g, 50.22 mmol). The reaction mixture was stirred at 30°C for 16 hours and then diluted with water (40 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography, eluting with a gradient of 10-30% EtOAc in petroleum ether to give the title compound as a white solid (4.7 g, 99%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.63 (dd, *J*=1.6, 3.6 Hz, 2 H) 0.85 (dd, *J*=1.6, 3.6 Hz, 2 H) 2.43 (s, 3 H) 2.86 - 2.92 (m, 1 H) 6.23 (s, 1 H) 7.27 (s, 1 H) 7.58 (dd, *J*=1.6, 8.0 Hz, 1 H) 7.90 (d, *J*=1.6 Hz, 1 H).

[0285] STEP 2: *N*-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

[0286] A mixture of 3-bromo-*N*-cyclopropyl-4-methylbenzamide (4.8 g, 18.89 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (5.04 g, 19.83 mmol), KOAc (5.56 g, 56.67 mmol), Pd(dppf)Cl₂ (829.26 mg, 1.13 mmol) in dioxane (80 mL) was degassed and purged with N₂ (3 x). The mixture was stirred at 80°C for 1 hour under N₂ atmosphere and then diluted with water (40 mL). The organic layer was separated, and the aqueous phase extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography, eluting with a gradient of 10-30% EtOAc in petroleum ether, then triturated with 10% EtOAc in petroleum ether (30 mL) and filtered to give the title compound as a white solid (5.5 g, 97%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.55 - 0.70 (m, 2 H) 0.73 - 0.94 (m, 2 H), 1.28 - 1.43 (m, 12 H) 2.51 - 2.60 (m, 3 H) 2.87 (td, *J*=3.6, 7.2 Hz, 1 H) 6.31 - 6.55 (m, 1 H) 7.17 - 7.24 (m, 1 H) 7.77 - 7.85 (m, 1 H) 7.98 (s, 1 H).

[0287] PREPARATION 21: 2-(5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)ethan-1-ol

[0288] STEP 1: 2-(5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)acetic acid

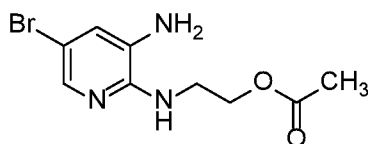


[0289] To a solution of 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (500 mg, 2.54 mmol) in DMF (5 mL) were added methyl 2-bromoacetate (465.84 mg, 3.05 mmol) and Cs₂CO₃ (4.13 g, 12.69 mmol). The reaction mixture was stirred at 80°C for 16 hours, then poured into water and adjusted pH 3 with aq HCl (1M). The acidified mixture was extracted with EtOAc and the organic layer was washed with brine and dried over Na₂SO₄. The crude product was dried under reduce pressure to give a yellow solid, which was triturated with petroleum ether/EtOAc (10:1) and isolated by filtration. The filter cake was dried under reduce pressure to give the title compound as a yellow solid (500 mg, 74.9%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 5.03 (s, 2 H) 6.50 (d, *J*=3.6 Hz, 1 H) 7.62 (d, *J*=3.6 Hz, 1 H) 8.24 (d, *J*=2.0 Hz, 1 H) 8.30 (d, *J*=2.0 Hz, 1 H) 12.64 - 13.48 (s, 1 H); ESI-MS *m/z* [M+H]⁺ = 256.9.

[0290] STEP 2: 2-(5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)ethan-1-ol

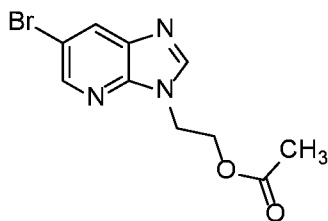
[0291] To a solution of 2-(5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)acetic acid (100 mg, 392.05 μmol) in DCM (10 mL) was added BH₃-Me₂S (10 M, 196.03 μL) at 0°C. The reaction mixture was stirred at 20°C for 12 hours, then poured into water and extracted with DCM. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated under reduce pressure. The crude product was purified by preparative TLC (SiO₂) eluting with 50% EtOAc in petroleum ether to give the title compound as a yellow oil (50 mg, 53%). ESI-MS *m/z* [M+H]⁺ = 243.0.

[0292] PREPARATION 22: 2-((3-amino-5-bromopyridin-2-yl)amino)ethyl acetate



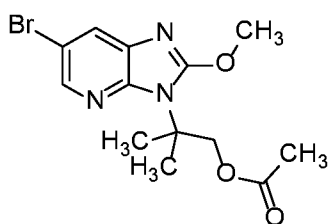
[0293] The title compound was prepared like PREPARATION 6, starting with 2-aminoethanol (257.26 mg, 4.21 mmol, 2 eq) in place of 2-amino-2-methylpropan-1-ol and proceeding through intermediates 2-((5-bromo-3-nitropyridin-2-yl)amino)ethan-1-ol and 2-((5-bromo-3-nitropyridin-2-yl)amino)ethyl acetate. The title compound was obtained as a red solid (430 mg, crude). ESI-MS *m/z* [M+H]⁺ = 276.1.

[0294] PREPARATION 23: 2-(6-bromo-3*H*-imidazo[4,5-*b*]pyridin-3-yl)ethyl acetate



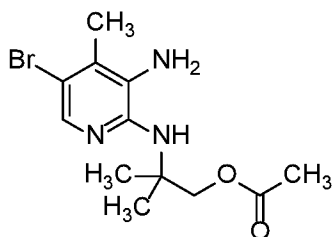
[0295] To a solution of 2-((3-amino-5-bromopyridin-2-yl)amino)ethyl acetate (200 mg, 729.62 μmol) and HOAc (3 mL) was added trimethoxymethane (193.57 mg, 1.82 mmol). The mixture was stirred at 80°C for 2 hours and then concentrated under reduced pressure to remove HOAc. The residue was dissolved in EtOAc and the mixture washed with water. The organic layer was dried, concentrated, and purified by preparative TLC, eluting with EtOAc to give the title compound as a brown solid (178 mg, 85.8% yield). ESI-MS m/z $[M+H]^+ = 286.0$.

[0296] PREPARATION 24: 2-(6-bromo-2-methoxy-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate

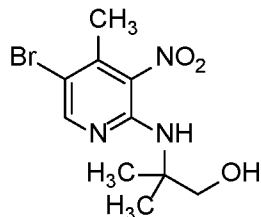


[0297] To a solution of 2-((3-amino-5-bromopyridin-2-yl)amino)-2-methylpropyl acetate (150 mg, 496.41 μmol) in tetramethoxymethane (405.51 mg, 2.98 mmol) was added propionic acid (36.77 mg, 496.41 μmol). The reaction mixture was stirred at 100°C for 2 hours. Acetonitrile (1 mL) was added, and the mixture was stirred at 90°C for 16 hours at which time additional propionic acid (147.09 mg, 1.99 mmol) was added. The reaction mixture was stirred at 100°C for 48 hours, then concentrated *in vacuo*, and purified by silica gel column chromatography, eluting with a gradient of 5-30% petroleum ether in EtOAc to give the title compound as a blue solid (165 mg, 97.1%). ^1H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.85 (s, 6 H) 1.96 (s, 3 H) 4.20 (s, 3 H) 4.67 (s, 2 H) 7.85 (d, $J=2.0$ Hz, 1 H) 8.17 (d, $J=2.0$ Hz, 1 H).

[0298] PREPARATION 25: 2-((3-amino-5-bromo-4-methylpyridin-2-yl)amino)-2-methylpropyl acetate

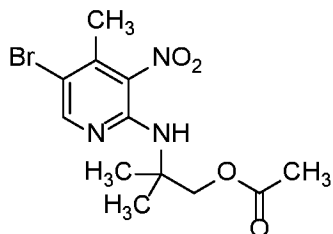


[0299] STEP 1: 2-((5-bromo-4-methyl-3-nitropyridin-2-yl)amino)-2-methylpropan-1-ol



[0300] A solution of 5-bromo-2-chloro-4-methyl-3-nitropyridine (3 g, 11.9 mmol) in 2-amino-2-methylpropan-1-ol (11.4 mL, 119 mmol) was heated to 100°C for 2 hours under N₂, then diluted with water and extracted with EtOAc. The organic phase was separated, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 5-20% EtOAc in petroleum ether to give the title compound as an orange solid (2.5 g, 67%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.39 (s, 6 H) 2.48 (s, 3 H) 3.68 (d, *J*=6.0 Hz, 2 H) 4.81 - 4.85 (m, 1 H) 6.63 (s, 1 H) 8.29 (s, 1 H); ESI-MS *m/z* [M+H]⁺ = 304.2.

[0301] STEP 2: 2-((5-bromo-4-methyl-3-nitropyridin-2-yl)amino)-2-methylpropyl acetate

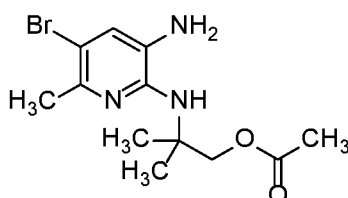


[0302] To a solution of 2-((5-bromo-4-methyl-3-nitropyridin-2-yl)amino)-2-methylpropan-1-ol (1 g, 3.19 mmol) in pyridine (10 mL) was added acetic anhydride (0.597 mL, 6.38 mmol). The reaction mixture was stirred at 90°C for 4 hours and then concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with 10% EtOAc in petroleum ether to give the title compound as an orange oil (1.1 g, crude). ¹H NMR (400 MHz, CDCl₃) δ ppm 2.10 (s, 6 H) 2.68 (s, 3 H) 3.10 (s, 3 H) 4.98 (s, 2 H) 7.99 (s, 1 H) 8.92 (s, 1 H); ESI-MS *m/z* [M+H]⁺ = 346.1.

[0303] STEP 3: 2-((3-amino-5-bromo-4-methylpyridin-2-yl)amino)-2-methylpropyl acetate

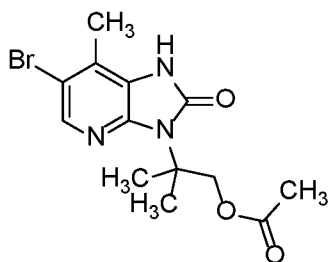
To a solution of 2-((5-bromo-4-methyl-3-nitropyridin-2-yl)amino)-2-methylpropyl acetate (1.1 g, 3.18 mmol) in EtOH (15 mL) and water (1.5 mL) were added Fe (887 mg, 15.9 mmol) and NH₄Cl (1.70 g, 31.8 mmol). The reaction mixture was stirred at 80°C for 2 hours and then concentrated under reduced pressure. The concentrate was diluted with water and extracted with EtOAc (40 mL). The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound as a brown oil (0.8 g, crude). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.45 (s, 6 H) 2.06 (s, 3 H) 2.24 (s, 3 H) 3.28 (s, 2 H) 4.36 (s, 2 H) 7.79 (s, 1 H); ESI-MS m/z [M+H]⁺ = 318.2.

[0304] PREPARATION 26: 2-((3-amino-5-bromo-6-methylpyridin-2-yl)amino)-2-methylpropyl acetate



[0305] The title compound was prepared like PREPARATION 25, starting with 3-bromo-6-chloro-2-methyl-5-nitropyridine (1.5 g, 5.97 mmol, 1 eq) in place of 5-bromo-2-chloro-4-methyl-3-nitropyridine and proceeding through intermediates 2-((5-bromo-6-methyl-3-nitropyridin-2-yl)amino)-2-methylpropan-1-ol (2.11 g, crude) and 2-((5-bromo-6-methyl-3-nitropyridin-2-yl)amino)-2-methylpropyl acetate (2.4 g, 85%). The title compound was obtained as a yellow liquid (0.98 g, 82%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.47 (s, 6 H) 1.87 (s, 3 H) 2.06 (s, 3 H) 3.06 (s, 2 H) 4.40 (s, 2 H) 6.96 (s, 1 H); ESI-MS m/z [M+H]⁺ = 316.2.

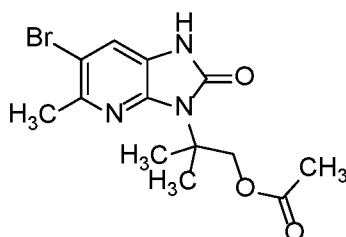
[0306] PREPARATION 27: 2-(6-bromo-7-methyl-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate



[0307] To a solution of 2-((3-amino-5-bromo-4-methylpyridin-2-yl)amino)-2-methylpropyl acetate (0.5 g, 1.58 mmol) in THF (60 mL) was added CDI (385 mg, 2.37 mmol). The mixture was stirred at 70°C for 16 hours. Additional CDI (0.2 g) and THF (20 mL) were added. The reaction mixture was stirred at 75°C for 3 hours and then concentrated under

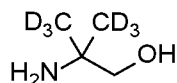
reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 10-50% EtOAc in petroleum ether to give the title compound as a white solid (0.35 g, 65%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.85 (s, 6 H) 1.98 (s, 3 H) 2.41 (s, 3 H) 4.71 (s, 2 H) 8.09 (s, 1 H) 10.69 (s, 1 H); ESI-MS m/z [M+Na]⁺ = 364.2.

[0308] PREPARATION 28: 2-(6-bromo-5-methyl-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate

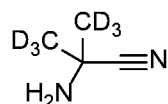


[0309] To a solution of 2-((3-amino-5-bromo-6-methylpyridin-2-yl)amino)-2-methylpropyl acetate (0.98 g, 2.85 mmol) in THF (120 mL) was added CDI (693 mg, 4.27 mmol). The mixture was stirred at 75°C for 19 hours, then diluted with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography, eluting with a gradient of 30-50% EtOAc in petroleum ether to give the title compound as a yellow solid (1 g, 92%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.85 (s, 6 H) 2.00 (s, 3 H) 2.58 (s, 3 H) 4.73 (s, 2 H) 7.37 (s, 1 H) 8.95 (s, 1 H); ESI-MS m/z [M+H]⁺ = 342.2.

[0310] PREPARATION 29: 2-amino-2-(methyl-*d*₃)propan-3,3,3-*d*₃-1-ol

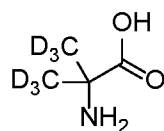


[0311] STEP 1: 2-amino-2-(methyl-*d*₃)propanenitrile-3,3,3-*d*₃



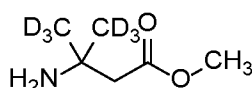
[0312] To a solution of NH₄Cl (11.01 g, 205.88 mmol) and NaCN (10.09 g, 205.88 mmol) in DCM (60 mL) and water (120 mL) was added propan-2-one-*d*₆ (11 g, 171.56 mmol) at 15°C. The reaction mixture was stirred at 15°C for 24 hours in a sealed vessel, then extracted with DCM. The organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to give the title compound as a yellow oil (11.5 g, crude).

[0313] STEP 2: 2-amino-2-(methyl-*d*₃)propanoic-3,3,3-*d*₃ acid



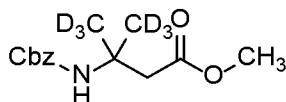
[0314] To a solution of 2-amino-2-(methyl-*d*₃)propanenitrile-3,3,3-*d*₃ (11.5 g, 90.82 mmol, HCl) was added aq HCl (12 M, 70 mL). The mixture was stirred at 100°C for 4 hours and then concentrated *in vacuo*. Ethanol was added and the mixture was filtered through a Buchner funnel. The crude product was purified by recrystallization from THF to give an HCl salt of the title compound as a white solid (12 g, 91%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.61 (d, *J*=6.4 Hz, 1 H) 8.61 (s, 2 H).

[0315] STEP 3: methyl 3-amino-3-(methyl-*d*₃)butanoate-4,4,4-*d*₃



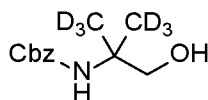
[0316] To a solution of SOCl₂ (24.60 g, 206.77 mmol) in MeOH (80 mL) at 0°C was added a solution of 2-amino-2-(methyl-*d*₃)propanoic-3,3,3-*d*₃ acid (12 g, 97.42 mmol, HCl) in MeOH (40 mL) at 0°C. The reaction mixture was stirred at 70°C for 3 hours under N₂ and then concentrated *in vacuo* to give an HCl salt of the title compound as a yellow solid (15.1 g, crude). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.73 (s, 2 H) 4.56 (s, 3 H) 8.82 (s, 2 H); ESI-MS *m/z* [M+H]⁺ = 174.1.

[0317] STEP 4: methyl 3-(((benzyloxy)carbonyl)amino)-3-(methyl-*d*₃)butanoate-4,4,4-*d*₃



[0318] To a mixture of methyl 3-amino-3-(methyl-*d*₃)butanoate-4,4,4-*d*₃ (5.1 g, 29.37 mmol, HCl) and Na₂CO₃ (9.34 g, 88.10 mmol) in water (30 mL) and dioxane (85 mL) was added benzyl carbonochloridate (6.01 g, 35.24 mmol) in dioxane (15 mL) dropwise at 15°C. The reaction mixture was stirred at 15°C for 3 hours, then diluted with EtOAc and water. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 0-20% EtOAc in petroleum ether to give the title compound as a yellow solid (2 g, 25%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.59 (s, 3 H) 5.01 (s, 2 H) 7.32 - 7.40 (m, 5 H) 7.72 (s, 1 H).

[0319] STEP 5: benzyl (2-(hydroxymethyl)propan-2-yl-1,1,1,3,3,3-*d*₆)carbamate

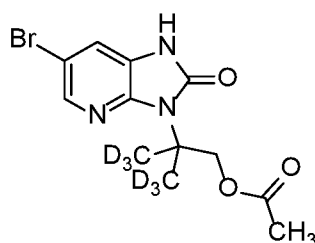


[0320] To a mixture of LiAlH_4 (590.01 mg, 15.55 mmol) in THF (30 mL) was added methyl 3-(((benzyloxy)carbonyl)amino)-3-(methyl- d_3)butanoate-4,4,4- d_3 (2 g, 7.77 mmol) in THF (15 mL) dropwise during a 5-minute period at 15°C. The reaction mixture was stirred at 15°C for 2 hours, then adjusted to pH 7 with aq saturated NH_4Cl solution. The aqueous phase was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give the title compound as a yellow solid (1.2 g, 67%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.18 (t, $J=7.2$ Hz, 1 H) 2.00 (s, 1 H) 4.01 - 4.07 (m, 1 H) 4.70 (t, $J=6.0$ Hz, 1 H) 5.00 (s, 2 H) 6.70 (s, 1 H) 7.29 - 7.33 (m, 1 H) 7.36 (s, 2 H) 7.37 (d, $J=2.8$ Hz, 1 H).

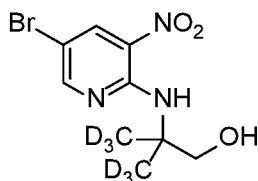
[0321] STEP 6: 2-amino-2-(methyl- d_3)propan-3,3,3- d_3 -1-ol

[0322] A mixture of benzyl (2-(hydroxymethyl)propan-2-yl-1,1,1,3,3,3- d_6)carbamate (1.2 g, 5.23 mmol), Pd/C (300 mg, 10% purity) in MeOH (20 mL) was degassed and purged with H_2 (3 x). The reaction mixture was stirred at 15°C for 2 hours under H_2 (15 psi) atmosphere, then poured into MeOH, and filtered through a pad of Celite®. The filtrate was concentrated *in vacuo* to give the title compound as a white oil (480 mg, crude). ESI-MS m/z $[\text{M}+\text{H}]^+ = 96.1$.

[0323] PREPARATION 30: 2-(6-bromo-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-(methyl- d_3)propyl-3,3,3- d_3 acetate



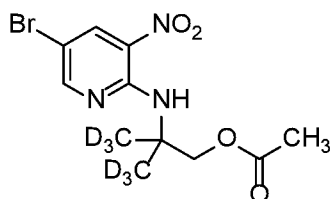
[0324] STEP 1: 2-((5-bromo-3-nitropyridin-2-yl)amino)-2-(methyl- d_3)propan-3,3,3- d_3 -1-ol



[0325] A mixture of 2-amino-2-(methyl- d_3)propan-3,3,3- d_3 -1-ol (480 mg, 5.04 mmol), 5-bromo-2-chloro-3-nitro-pyridine (1.09 g, 4.58 mmol), and DIPEA (1.19 g, 9.17 mmol) in acetonitrile (10 mL) was degassed and purged with N_2 (3 x). The reaction mixture was stirred at 80°C for 12 hours under N_2 atmosphere and then diluted with EtOAc and water. The

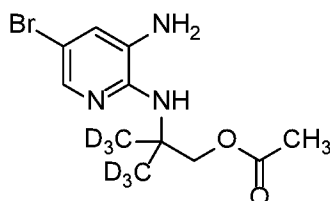
organic layer was separated, and the aqueous phase was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 0-20% EtOAc in petroleum ether to give the title compound as a yellow solid (850 mg, 62.6%).

[0326] STEP 2: 2-((5-bromo-3-nitropyridin-2-yl)amino)-2-(methyl-*d*₃)propyl-3,3,3-*d*₃ acetate



[0327] To a solution of 2-((5-bromo-3-nitropyridin-2-yl)amino)-2-(methyl-*d*₃)propan-3,3,3-*d*₃-1-ol (850 mg, 2.87 mmol) in pyridine (10 mL) was added acetic anhydride (586.02 mg, 5.74 mmol). The reaction mixture was stirred at 80°C for 3 hours, then diluted with EtOAc and water. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound as a yellow solid (950 mg, crude).

[0328] STEP 3: 2-((3-amino-5-bromopyridin-2-yl)amino)-2-(methyl-*d*₃)propyl-3,3,3-*d*₃ acetate

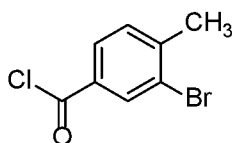


[0329] A mixture of 2-((5-bromo-3-nitropyridin-2-yl)amino)-2-(methyl-*d*₃)propyl-3,3,3-*d*₃ acetate (950 mg, 2.81 mmol), Fe (784.37 mg, 14.05 mmol) and NH₄Cl (601.05 mg, 11.24 mmol) in EtOH (10 mL) and water (2 mL) was degassed and purged with N₂ (3 x). The reaction mixture was stirred at 80°C for 1 hour under N₂ atmosphere, then poured into EtOH, and filtered through a pad of Celite®. The filtrate was concentrated *in vacuo* to give the title compound as a black oil (800 mg, crude).

[0330] STEP 4: 2-(6-bromo-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-(methyl-*d*₃)propyl-3,3,3-*d*₃ acetate

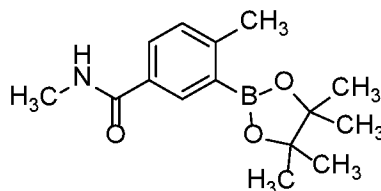
[0331] A solution of 2-((3-amino-5-bromopyridin-2-yl)amino)-2-(methyl-*d*₃)propyl-3,3,3-*d*₃ acetate (800 mg, 2.60 mmol) and CDI (631.33 mg, 3.89 mmol) in THF (10 mL) was stirred at 70°C for 5 hours under N₂. Ethyl acetate and water were added. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 0-30% EtOAc in petroleum ether to give the title compound as a brown solid (800 mg, 92.2%). ¹H NMR (400 MHz, CDCl₃) δ ppm 2.00 (s, 3 H) 4.72 (s, 2 H) 7.42 (d, *J*=2.0 Hz, 1 H) 8.08 (d, *J*=2.0 Hz, 1 H).

[0332] PREPARATION 31: 3-bromo-4-methylbenzoyl chloride

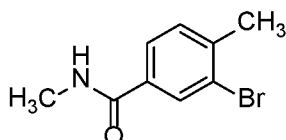


[0333] To a solution of 3-bromo-4-methylbenzoic acid (2 g, 9.30 mmol) in toluene (20 mL) were added SOCl₂ (3.32 g, 27.90 mmol) and DMF (6.80 mg, 93.00 μmol). The mixture was stirred at 70 °C for 3 hours and then concentrated under reduced pressure to give the title compound as a yellow solid (2.1 g, 96.7%).

[0334] PREPARATION 32: *N*,4-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide



[0335] STEP 1: 3-bromo-*N*,4-dimethylbenzamide

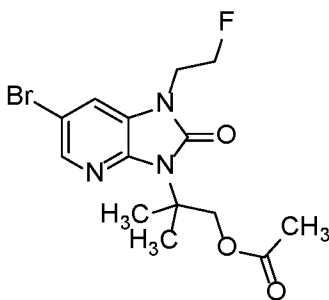


[0336] To a solution of methanamine (2 M, 12.85 mL) and DIPEA (3.71 g, 28.71 mmol) was slowly added 3-bromo-4-methylbenzoyl chloride (2 g, 8.57 mmol) in DCM (5 mL) at 0°C. The reaction mixture was stirred at 15°C for 1.5 hours and then diluted with water. The aqueous layer was extracted with EtOAc. The organic layers were combined, washed with saturated aq NaCl, dried over Na₂SO₄, and concentrated to give the title compound as a white solid (1.8 g, crude).

[0337] STEP 2: *N*,4-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

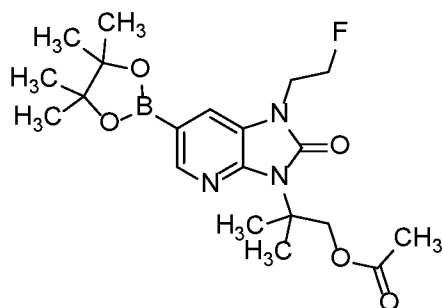
[0338] A mixture of 3-bromo-*N*,4-dimethylbenzamide (1 g, 4.38 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.34 g, 5.26 mmol), KOAc (1.29 g, 13.15 mmol), and Pd(dppf)Cl₂ (192.48 mg, 263.06 μmol) in dioxane (20 mL) was degassed and purged with N₂ (3 x). The reaction mixture was stirred at 90°C for 16 hours under N₂ atmosphere and then diluted with water. The aqueous phase was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography, eluting with a gradient of 10-30% EtOAc in petroleum ether to give the title compound as a white solid (600 mg, 49.7%). ESI-MS *m/z* [M+H]⁺ = 276.2.

[0339] PREPARATION 33: 2-(6-bromo-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate



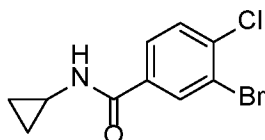
[0340] To a solution of 2-(6-bromo-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (6.3 g, 19 mmol) in acetonitrile (50 mL) were added 1-bromo-2-fluoroethane (7.31 g, 57.6 mmol) and K₂CO₃ (5.31 g, 38.4 mmol) at 15°C. The mixture was stirred at 80°C for 12 hours and then filtered. The filtrate was concentrated under reduced pressure and was purified by column chromatography, eluting with a gradient of 3-30% EtOAc in petroleum ether to give the title compound as a purple solid (6.6 g). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.84 (s, 9 H) 1.98 (s, 3 H) 4.07 - 4.15 (m, 2 H) 4.64 (t, *J*=4.4 Hz, 1 H) 4.69 (s, 2 H) 4.76 (t, *J*=4.4 Hz, 1 H) 7.36 (t, *J*=1.6 Hz, 1 H) 8.04 (t, *J*=6.0 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 374.0.

[0341] PREPARATION 34: 2-(1-(2-fluoroethyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate



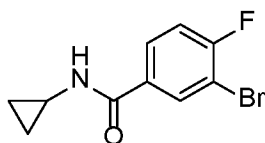
[0342] A mixture of 2-(6-bromo-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)-2-methylpropyl acetate (5 g, 12.4 mmol), KOAc (3.67 g, 37.4 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (3.31 g, 13.0 mmol), and Pd(dppf)Cl₂ (980 mg, 1.34 mmol) in dioxane (40 mL) was degassed and purged with N₂ (3 x) and stirred at 90°C for 5 hours under N₂ atmosphere. The reaction mixture was filtered, and the filtrate concentrated. The resulting residue was purified by column chromatography, eluting with a gradient of 0.3-20% EtOAc in petroleum ether to give the title compound as a yellow solid (5.5 g, crude). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.31 (s, 12 H) 1.78 (s, 6 H) 1.88 (s, 3 H) 4.10 – 4.30 (m, 2 H) 4.55 - 4.65 (m, 3 H) 4.72 (m, *J*=3.6 Hz 1 H) 7.63 (s, 1 H) 8.20 (s, 1 H). ESI-MS *m/z* [M+H]⁺ = 422.2.

[0343] PREPARATION 35: 3-bromo-4-chloro-*N*-cyclopropylbenzamide



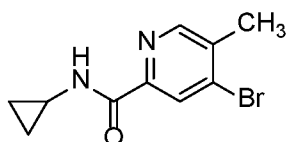
[0344] To a solution of 3-bromo-4-chlorobenzoic acid (500 mg, 2.12 mmol) in DCM (6 mL) was added HATU (888 mg, 2.34 mmol) and DIPEA (1.11 mL, 6.37 mmol). The mixture was stirred at 10°C for 30 minutes. Cyclopropanamine (0.147 mL, 2.12 mmol) was added, and the reaction mixture was stirred for 16 hours at 30°C, then diluted with water and extracted with EtOAc. The organic layers were combined, washed with water, dried over Na₂SO₄, concentrated *in vacuo*, and purified by column chromatography, eluting with a gradient of 0-2.5% EtOAc in petroleum ether, to give the title compound as a yellow oil (473 mg, 77.1%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.58 - 0.64 (m, 2 H) 0.86 - 0.92 (m, 2 H) 2.86 - 2.92 (m, 1 H) 6.28 (s, 1 H) 7.51 (d, *J*=8.4 Hz, 1 H) 7.8 (d, *J*=2.8 Hz, 1 H) 8.22 (dd, *J*₁=2.0 Hz, *J*₂=6.4 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 276.0.

[0345] PREPARATION 36: 3-bromo-*N*-cyclopropyl-4-fluorobenzamide



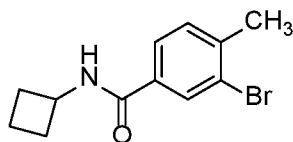
[0346] To a solution of 3-bromo-4-fluorobenzoic acid (500 mg, 2.28 mmol) and Et₃N (0.953 mL, 6.85 mmol) in DMF (3 mL) was added HATU (868 mg, 2.28 mmol). The mixture was stirred at 10°C for 30 minutes. Cyclopropanamine (0.158 mL, 2.28 mmol) was added. The reaction mixture was stirred at 10°C for 14 hours, and then water (20 mL) was added, forming a precipitate. The solids were isolated by filtration. The filter cake was triturated with a mixture of petroleum ether (5 mL) and EtOAc (50 mL) to give the title compound as a yellow solid (550 mg, 93.3%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.61 - 0.65 (m, 2 H) 0.84 - 0.91 (m, 2 H) 2.87 - 2.91 (m, 1 H) 6.33 (d, *J*=72.8 Hz, 1 H) 7.14 - 7.27 (m, 1 H) 7.71 - 7.68 (m, 1 H) 7.95 - 7.98 (m, 1 H).

[0347] PREPARATION 37: 4-bromo-*N*-cyclopropyl-5-methylpicolinamide



[0348] To a solution of 4-bromo-5-methylpicolinic acid (100 mg, 0.463 mmol) and cyclopropanamine (0.032 mL, 0.463 mmol) in DCM (5 mL) was added HATU (194 mg, 0.509 mmol) and Et₃N (0.193 mL, 1.39 mmol). The reaction mixture was stirred at 15°C for 2 hours, then concentrated and purified by preparative TLC (SiO₂) eluting with 50% EtOAc in petroleum ether to give the title compound as a yellow solid (100 mg, 78.8%). ESI-MS *m/z* [M+H]⁺ = 255.0.

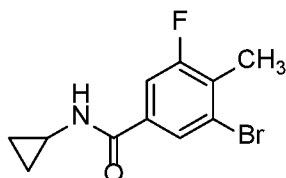
[0349] PREPARATION 38: 3-bromo-*N*-cyclobutyl-4-methylbenzamide



[0350] To a solution of cyclobutanamine (85.99 mg, 1.21 mmol) in DCM (5 mL) was added Et₃N (282.33 mg, 2.79 mmol) at 0°C. Next 3-bromo-4-methylbenzoyl chloride (217.16 mg, 930.04 μmol) in DCM (4 mL) was added dropwise. The reaction mixture was stirred at 15°C for 15 minutes, then poured into water and extracted with DCM. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the title compound as a white solid (230 mg, 92.2%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.60 - 1.74 (m, 2 H) 1.98 - 2.13 (m, 2 H) 2.15 - 2.26 (m, 2 H) 2.38 (s, 3 H) 4.39 (t, *J*=8.0

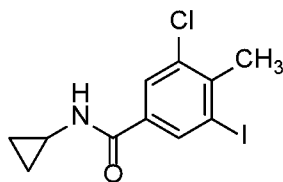
Hz, 1 H) 7.44 (d, $J=8.0$ Hz, 1 H) 7.76 (dd, $J_1 = 8.0$, $J_1 = 1.6$ Hz, 1 H) 8.06 (d, $J=1.6$ Hz, 1 H) 8.65 (d, $J=7.2$ Hz, 1 H).

[0351] PREPARATION 39: 3-bromo-*N*-cyclopropyl-5-fluoro-4-methylbenzamide

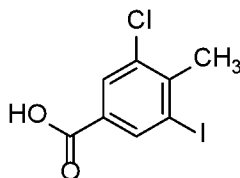


[0352] To a solution of 3-bromo-5-fluoro-4-methylbenzoic acid (0.20 g, 0.858 mmol) in DCM (1 mL) was added HATU (359 mg, 0.944 mmol,) and DIPEA (0.45 mL, 2.57 mmol,) at 15°C. The mixture was stirred at 15°C for 30 minutes after which cyclopropanamine (49 mg, 0.858 mmol) was added. The reaction mixture was stirred at 30°C for 12 hours, then diluted with water and extracted with DCM. The organic layer was concentrated under reduce pressure, and the resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 1-1.25% EtOAc in petroleum ether to give the title compound (200 mg, 79.8%). ESI-MS m/z $[M+H]^+ = 272.0$.

[0353] PREPARATION 40: 3-chloro-*N*-cyclopropyl-5-iodo-4-methylbenzamide

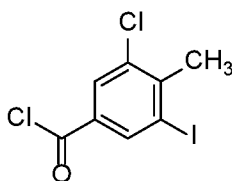


[0354] STEP 1: 3-chloro-5-iodo-4-methylbenzoic acid



[0355] To a solution of 3-chloro-4-methylbenzoic acid (0.2 g, 1.17 mmol) in H₂SO₄ (4 mL) was added NIS (290.14 mg, 1.29 mmol) at 0°C. The reaction mixture was stirred at 15°C for 1 hour and then added to ice water (10 mL) forming a solid precipitate. The mixture was filtered to isolate the precipitate, which was washed with n-hexane and dried under reduce pressure to give the title compound as a light-pink solid (130 mg, 37.4%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.57 (s, 3 H) 7.89 (d, $J=1.2$ Hz, 1 H) 8.26 (s, 1 H); ESI-MS m/z $[M+H]^+ = 297.0$.

[0356] STEP 2: 3-chloro-5-iodo-4-methylbenzoyl chloride

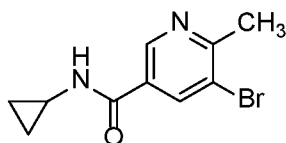


[0357] To a solution of 3-chloro-5-iodo-4-methylbenzoic acid (76 mg, 0.256 mmol) in THF (2 mL) was added SOCl_2 (0.056 mL, 0.769 mmol) followed by DMF (1.52 mL, 19.8 mmol) at 0°C. The reaction mixture was stirred at 15°C for 1 hour and then concentrated under reduce pressure to give the title compound as a yellow solid (80.7 mg, 100%).

[0358] STEP 3: 3-chloro-*N*-cyclopropyl-5-iodo-4-methylbenzamide

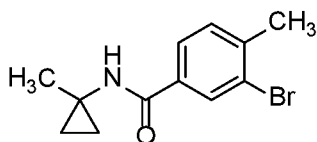
[0359] To a solution of cyclopropanamine (0.018 mL, 0.256 mmol) and Et_3N (0.107 mL, 769.02 μmol) in THF (1 mL) was added 3-chloro-5-iodo-4-methylbenzoyl chloride (80.7 mg, 0.256 μmol) in THF (1 mL) under N_2 at 0°C. The reaction mixture was stirred at 15°C for 3 hours, then diluted with water (15 mL) and extracted with EtOAc. The organic layer was washed with 1 M HCl (3 mL) and concentrated under reduce pressure to give the title compound as a yellow solid (86 mg, 96%). ESI-MS m/z $[\text{M}+\text{H}]^+ = 336.0$.

[0360] PREPARATION 41: 5-bromo-*N*-cyclopropyl-6-methylnicotinamide



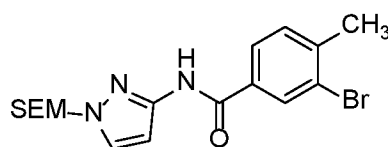
[0361] To a solution of 5-bromo-6-methylnicotinic acid (400 mg, 1.85 mmol) in DMF (3 mL) was added HATU (704 mg, 1.85 mmol) and DIPEA (0.968 mL, 5.55 mmol) at 30°C. The mixture was stirred for 30 minutes at which time cyclopropanamine (0.128 mL, 1.85 mmol) was added. The reaction mixture was stirred for 4 hours at 30°C, then diluted with water and extracted with DCM. The organic layers were combined, washed with water, dried over Na_2SO_4 , and concentrated *in vacuo*. The crude product was triturated with EtOAc (10 mL) at 8°C for 30 minutes to give the title compound as a yellow oil (400 mg, 81%). ^1H NMR (400 MHz, CDCl_3) δ ppm 0.63 - 0.69 (m, 2 H) 0.85 - 0.92 (m, 2 H) 2.70 (s, 3 H) 2.88 - 2.94 (m, 1 H) 6.50 (s, 1 H) 8.22 (d, $J=2.0$ Hz, 1 H) 8.73 (d, $J=1.6$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 256.8$.

[0362] PREPARATION 42: 3-bromo-4-methyl-*N*-(1-methylcyclopropyl)benzamide

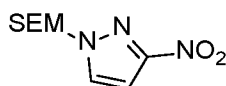


[0363] To a solution 1-methylcyclopropan-1-amine (110.58 mg, 1.03 mmol, HCl) in Et₃N (2 mL) was added a mixture of 3-bromo-4-methylbenzoyl chloride (200 mg, 856.57 μ mol) in DCM (2 mL) at 0°C. The reaction mixture was stirred at 15°C for 2 hours and then diluted with water. The aqueous phase was extracted with EtOAc, and the organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by preparative TLC, eluting with a mixture of petroleum ether and EtOAc (3:1) to give the title compound as a white solid (196 mg, 85.3%). ESI-MS *m/z* [M+H]⁺ = 269.2.

[0364] PREPARATION 43: 3-bromo-4-methyl-*N*-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)benzamide

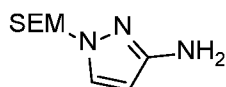


[0365] STEP 1: 3-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole



[0366] To a solution of 3-nitro-1*H*-pyrazole (1 g, 8.84 mmol) in DMF (5 mL) was added SEM-Cl (1.77 g, 10.61 mmol) and Cs₂CO₃ (8.64 g, 26.53 mmol). The reaction mixture was stirred at 15°C for 3 hours and then poured into water. The aqueous phase was extracted with EtOAc, and the organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 5-10% EtOAc in petroleum ether to give the title compound as a brown oil (1.35 g, 62.7%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.00 - 0.03 (m, 9 H), 0.95 - 0.90 (m, 2 H), 3.67 - 3.58 (m, 2 H), 5.50 (s, 2 H), 6.98 (d, *J*=2.4 Hz, 1 H) 7.68 - 7.65 (m, 1 H).

[0367] STEP 2: 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-amine

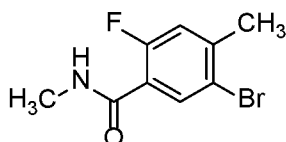


[0368] To a solution of 3-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (1.35 g, 5.55 mmol) in MeOH (10 mL) was added Pd/C (102 mg, 5.55 mmol). The reaction mixture was stirred under H₂ at 15°C for 3 hours and then filtered. The filtrate was concentrated to give the title compound as a brown oil (1.0 g, 84%). ESI-MS *m/z* [M+H]⁺ = 214.1.

[0369] STEP 3: 3-bromo-4-methyl-*N*-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)benzamide

[0370] To a solution of 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-amine (164.47 mg, 770.91 μ mol) in pyridine (2 mL) was added a mixture of 3-bromo-4-methylbenzoyl chloride (150 mg, 642.43 μ mol) in DCM (2 mL) at 0°C. The reaction mixture was stirred at 15°C for 3 hours and then diluted with water. The aqueous phase was extracted with EtOAc, and the organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO₂) eluting with a gradient of 6-10% EtOAc in petroleum ether to give the title compound as a yellow oil (230 mg, 87.2%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.00 - 0.02 (m, 9 H) 0.88 - 0.97 (m, 2 H) 2.46 (s, 3 H) 3.50 - 3.60 (m, 2 H) 5.32 (s, 2 H) 6.92 (d, *J*=2.4 Hz, 1 H) 7.34 (d, *J*=8.0 Hz, 1 H) 7.50 (d, *J*=2.4 Hz, 1 H) 7.70 (dd, *J*₁=1.6 Hz, *J*₂=7.6 Hz, 1 H) 8.07 (d, *J*=1.6 Hz, 1 H) 8.35 (s, 1 H); ESI-MS *m/z* [M+H]⁺ = 411.2.

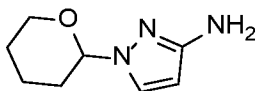
[0371] PREPARATION 44: 5-bromo-2-fluoro-*N*,4-dimethylbenzamide



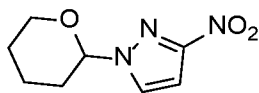
[0372] A mixture of 5-bromo-2-fluoro-4-methylbenzoic acid (500 mg, 2.15 mmol), EDCI (616.98 mg, 3.22 mmol), HOBt (289.92 mg, 2.15 mmol) and DIPEA (693.26 mg, 5.36 mmol) in DMF (10 mL) was stirred for 30 minutes at 20°C. Methanamine hydrochloride (173.84 mg, 2.57 mmol) was added, and the reaction mixture was stirred for 15 hours at 20°C under N₂. Ethyl acetate (50 mL) and water (50 mL) were added, and the aqueous and organic layers were separated. The aqueous layer was extracted with EtOAc, and the organic layers were combined, washed successively with 1N HCl, saturated aq NaHCO₃ and brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the title compound as a white solid (480 mg, 81%). ESI-MS *m/z* [M]⁺ = 246.1.

¹H NMR (400 MHz, CDCl₃) δ ppm 2.42 (s, 3 H), 3.02 – 3.03 (m, 3 H), 6.69 (s, 1 H), 7.01 (d, *J*=12.34 Hz, 1 H), 8.26 (d, *J*=7.46 Hz, 1 H).

[0373] PREPARATION 45: 1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-amine



[0374] STEP 1: 3-nitro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole

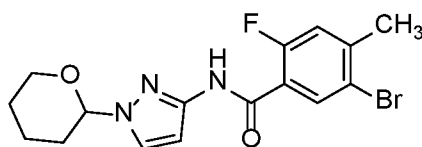


[0375] To a solution of 3-nitro-1*H*-pyrazole (0.6 g, 5.31 mmol) in THF (5 mL) was added 3,4-dihydro-2*H*-pyran (669.51 mg, 7.96 mmol) and *p*-toluenesulfonic acid (91.37 mg, 530.62 μ mol). The reaction mixture was stirred at 65°C for 5 hours and then poured into water. The aqueous phase was extracted with EtOAc, and the organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 4-6% EtOAc in petroleum ether to give the title compound as a yellow oil (935 mg, 89.4%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.62 - 1.71 (m, 3 H) 1.95 - 2.08 (m, 2 H) 2.11 - 2.22 (m, 1 H) 3.67 - 3.76 (m, 1 H) 4.02 - 4.09 (m, 1 H) 5.45 (dd, *J*₁=2.80 Hz, *J*₂=8.80 Hz, 1 H) 6.92 (d, *J*=2.80 Hz, 1 H) 7.70 (d, *J*=2.40 Hz, 1 H).

[0376] STEP 2: 1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-amine

[0377] To a solution of 3-nitro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole (600 mg, 3.04 mmol) in MeOH (6 mL) was added Pd/C (60 mg, 3.04 mmol, 10% purity) in one portion at 20°C. The suspension was degassed under vacuum and purged with H₂ four times. The reaction mixture was stirred at 20°C for 5 hours under H₂ (15 psi) and then filtered. The filtrate was concentrated under reduced pressure to give the title compound as a light-yellow oil (450 mg, crude). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.52 - 1.67 (m, 4 H) 1.97 - 2.03 (m, 2 H) 3.66 (dd, *J*₁=2.40 Hz, *J*₂=8.00 Hz, 1 H) 4.03 - 4.07 (m, 1 H) 5.11 (dd, *J*₁=2.40 Hz, *J*₂=8.00 Hz, 1 H) 5.65 (d, *J*=2.40 Hz, 1 H) 7.32 (d, *J*=2.40 Hz, 1 H).

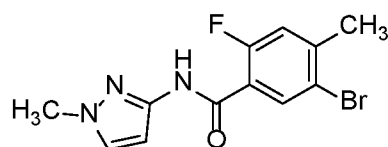
[0378] PREPARATION 46: 5-bromo-2-fluoro-4-methyl-*N*-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)benzamide



[0379] To a solution of 5-bromo-2-fluoro-4-methylbenzoic acid (250 mg, 1.07 mmol) in DMF (5 mL) were added EDCI (308.49 mg, 1.61 mmol), HOBt (217.44 mg, 1.61 mmol), and DIPEA (554.61 mg, 4.29 mmol) at 20°C. The mixture was degassed under vacuum and purged with nitrogen (3 x) and then stirred at 20°C for 30 minutes under nitrogen. Intermediate 1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-amine (233.20 mg, 1.39 mmol) was added at 20°C. The reaction mixture was degassed under vacuum and purged with nitrogen (3 x) and then stirred at 20°C for another 12 hours under nitrogen. The mixture was

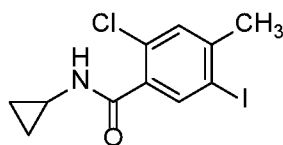
subsequently diluted with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO₂) eluting with a gradient of 9-11% EtOAc in petroleum ether to give the title compound as a light-yellow oil (227 mg, 47.3%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.59 - 1.74 (m, 4 H) 2.05 (s, 2 H) 2.45 (s, 3 H) 4.01 - 4.19 (m, 2 H) 5.27 (d, *J*=9.60 Hz, 1 H) 6.90 (s, 1 H) 7.54 (s, 1 H) 8.33 (d, *J*=7.20 Hz, 1 H) 8.90 (d, *J*=14.80 Hz, 1 H); ESI-MS *m/z* [M+Na]⁺= 404.9.

[0380] PREPARATION 47: 5-bromo-2-fluoro-4-methyl-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide

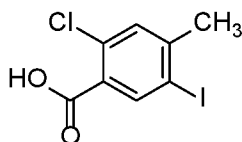


[0381] A mixture of 5-bromo-2-fluoro-4-methylbenzoic acid (1.25 g, 4.29 mmol), 1-methyl-1*H*-pyrazol-3-amine (458.3 mg, 4.72 mmol), EDCI (1.23 g, 6.44 mmol), HOBT (869.52 mg, 6.44 mmol) and DIPEA (2.99 mL, 17.16 mmol) in DMF (15 mL) was degassed and purged with N₂ (3 x). The reaction mixture was stirred at 15°C for 2 hours under N₂ atmosphere and then diluted with EtOAc and water. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 20-30% EtOAc in petroleum ether to give the title compound as a white solid (850 mg, 63.5%). ¹H NMR (400 MHz, CDCl₃) δ ppm 2.46 (s, 3 H) 3.85 (s, 3 H) 6.82 (d, *J*=2.0 Hz, 1 H) 7.09 (d, *J*=12.0 Hz, 1 H) 7.31 (d, *J*=2.4 Hz, 1 H) 8.34 (d, *J*=7.6 Hz, 1 H) 8.85 (d, *J*=14.4 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 312.1.

[0382] PREPARATION 48: 2-chloro-*N*-cyclopropyl-5-iodo-4-methylbenzamide



[0383] STEP 1: 2-chloro-5-iodo-4-methylbenzoic acid

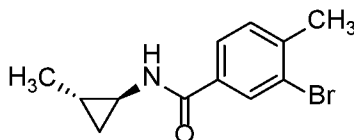


[0384] To a solution of 2-chloro-4-methylbenzoic acid (500 mg, 2.93 mmol) in DCM (20 mL) at 0°C were added H₂SO₄ (6.49 mL, 123 mmol) and NIS (692.39 mg, 3.08 mmol) portion-wise during a 10-minute period. The reaction mixture was stirred at 20°C for 30 minutes, then quenched with ice and with water, and extracted with EtOAc. The aqueous and organic layers were separated, and the aqueous layer was washed with EtOAc. The organic layers were combined, washed with aq Na₂SO₃ (10%), dried over MgSO₄ and concentrated *in vacuo* to give the title compound as a brown solid (800 mg, 92%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.39 (s, 3 H) 7.54 (s, 1 H) 8.17 (s, 1 H) 13.44 (s, 3 H).

[0385] STEP 2: 2-chloro-*N*-cyclopropyl-5-iodo-4-methylbenzamide

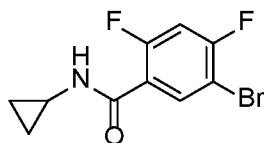
[0386] To a mixture of cyclopropanamine (0.10 mL, 1.48 mmol) and 2-chloro-5-iodo-4-methylbenzoic acid (400 mg, 1.35 mmol) in DMF (6 mL) were added EDCI (310 mg, 1.62 mmol), HOBT (219 mg, 1.62 mmol) and Et₃N (0.28 mL, 2.02 mmol). The reaction mixture was stirred at 20°C for 13 hours, then diluted with water and extracted with EtOAc. The organic layers were combined and concentrated under reduce pressure. The crude product was triturated with petroleum ether to give the title compound as a white solid (300 mg, 66.3%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.51 - 0.54 (m, 2 H) 0.65 - 0.69 (m, 2 H) 2.36 (s, 3 H) 2.75 - 2.80 (m, 1 H) 7.47 (s, 1 H) 7.77 (s, 1 H) 8.45 (d, *J*=3.6 Hz, 1 H).

[0387] PREPARATION 49: 3-bromo-4-methyl-*N*-((1*S*,2*S*)-2-methylcyclopropyl)benzamide



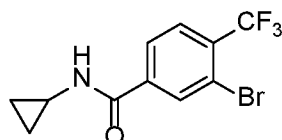
[0388] To a solution of 3-bromo-4-methylbenzoic acid (149.92 mg, 697.15 μmol) and (1*S*,2*S*)-2-methylcyclopropan-1-amine (49.58 mg, 697.15 μmol, HCl) in DMF (3 mL) were added EDCI (200.47 mg, 1.05 mmol), HOBT (141.30 mg, 1.05 mmol) and DIPEA (540.61 mg, 4.18 mmol). The reaction mixture was stirred overnight, then diluted with water and extracted with EtOAc. The organic layer was dried over Na₂SO₄, filtered and concentrated. The resulting residue was purified by the preparative TLC (SiO₂) eluting with 10% EtOAc in petroleum ether to give the title compound as a colorless oil (135 mg, 72.2%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.64 - 0.66 (m, 1 H), 0.74 - 0.75 (m, 1 H), 0.76 - 0.78 (m, 1 H), 0.98 - 1.16 (m, 3 H), 2.43 (s, 3 H), 2.58 - 2.60 (m, 1 H), 6.14 (s, 1 H), 7.26 - 7.27 (m, 1 H), 7.58 (d, *J*=8.00 Hz, 1 H), 7.89 (d, *J*=2.0 Hz, 1 H); ESI-MS *m/z* [M]⁺ = 268.1.

[0389] PREPARATION 50: 5-bromo-*N*-cyclopropyl-2,4-difluorobenzamide



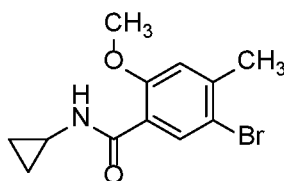
[0390] To a solution of 5-bromo-2,4-difluorobenzoic acid (500 mg, 2.11 mmol) in DMF (5 mL) were added cyclopropanamine (180.68 mg, 3.16 mmol, 219.27 μ L), EDCI (606.66 mg, 3.16 mmol), HOBt (313.58 mg, 2.32 mmol) and DIPEA (1.09 g, 8.44 mmol, 1.47 mL). The reaction mixture was stirred at 15°C for 12 hours, then poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 , and concentrated under reduce pressure. The crude product was purified by column chromatography (SiO_2) eluting with a gradient of 10-80% EtOAc in petroleum ether to give the title compound as a white solid (350 mg, 60.1%). ESI-MS m/z $[\text{M}+\text{H}]^+ = 276.1$.

[0391] PREPARATION 51: 3-bromo-*N*-cyclopropyl-4-(trifluoromethyl)benzamide

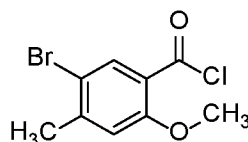


[0392] To a solution of 3-bromo-4-(trifluoromethyl)benzoic acid (200 mg, 743.45 μ mol) in DMF (3 mL) was added HOBt (120.55 mg, 892.14 μ mol), EDCI (213.78 mg, 1.12 mmol), DIPEA (384.34 mg, 2.97 mmol, 517.98 μ L) and cyclopropanamine (63.67 mg, 1.12 mmol, 77.27 μ L). The reaction mixture was stirred at 15°C for 12 hours, then poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 , and concentrated under reduce pressure. The crude product was purified by column chromatography (SiO_2) eluting with a gradient of 10-80% EtOAc in petroleum ether to give the title compound as a yellow solid (80 mg, 35%). ESI-MS m/z $[\text{M}+\text{H}]^+ = 308.1$.

[0393] PREPARATION 52: 5-bromo-*N*-cyclopropyl-2-methoxy-4-methylbenzamide



[0394] STEP 1: 5-bromo-2-methoxy-4-methylbenzoyl chloride

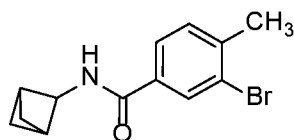


[0395] To a solution of 5-bromo-2-methoxy-4-methylbenzoic acid (100 mg, 408.05 μmol) in toluene (1 mL) was added SOCl_2 (242.73 mg, 2.04 mmol) and DMF (1.49 mg, 20.40 μmol). The reaction mixture was stirred at 70°C for 2 hours, then dried *in vacuo* to give the title compound as a yellow solid (100 mg, 93%).

STEP 2: 5-bromo-*N*-cyclopropyl-2-methoxy-4-methylbenzamide

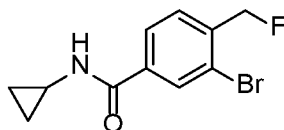
[0396] To a solution of cyclopropanamine (21.67 mg, 379.48 μmol) in DCM (1 mL) was added Et_3N (192.00 mg, 1.90 mmol). The mixture was stirred at 0°C for 30 minutes. A solution of 5-bromo-2-methoxy-4-methylbenzoyl chloride (100 mg, 379.48 μmol) in DCM (1 mL) was added. The reaction mixture was stirred at 0°C for 1 hour, then poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 , and concentrated under reduce pressure to give the title compound as a yellow solid (100 mg, 93%). ESI-MS m/z $[\text{M}+\text{H}]^+ = 284.0$.

[0397] PREPARATION 53: *N*-(bicyclo[1.1.1]pentan-2-yl)-3-bromo-4-methylbenzamide

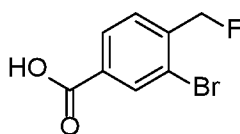


[0398] To a solution of 3-bromo-4-methylbenzoyl chloride (150 mg, 1.25 mmol, HCl) in pyridine (494.38 mg, 6.25 mmol) was added dropwise bicyclo[1.1.1]pentan-2-amine (291.86 mg, 1.25 mmol) in DCM (5 mL). The mixture was stirred at 0°C for 2 hours, then concentrated under reduced pressure. The resulting residue was diluted with 1M HCl and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give the title compound as an off-white solid (240 mg, 69%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 2.21 (s, 6 H), 2.45 (s, 3 H), 6.46 (s, 1 H), 7.28 (s, 2 H), 7.60 (dd, $J_1=1.6$, $J_2=8.0$ Hz, 1 H), 7.93 - 7.90 (m, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 281.9$.

[0399] PREPARATION 54: 3-bromo-*N*-cyclopropyl-4-(fluoromethyl)benzamide



[0400] STEP 1: 3-bromo-4-(fluoromethyl)benzoic acid

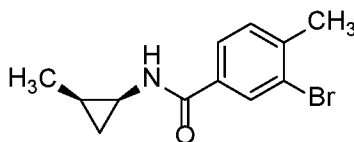


[0401] To a mixture of 3-bromo-4-methylbenzoic acid (322.57 mg, 1.5 mmol), sodium peroxydisulfate (178.58 mg, 750 μ mol) and Selectfluor® (1.59 g, 4.50 mmol) in acetonitrile (0.75 mL) and water (0.75 mL) was added AgNO₃ (25.48 mg, 150 μ mol) at -78°C under nitrogen. The reaction mixture was heated to 80°C for 5 hours and then filtered through a pad of Celite®. The filtrate was adjusted to pH 4 with HCl (1M). The aqueous phase was extracted with EtOAc, and the organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by preparative HPLC to give the title compound as a white solid (50 mg, 14%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 5.44 - 5.69 (m, 2 H) 7.66 (d, *J*=8.0 Hz, 1 H) 7.99 (d, *J*=8.0 Hz, 1 H) 8.12 (s, 1 H) 13.38 (s, 1 H); ESI-MS *m/z* [M+H]⁺ = 234.1.

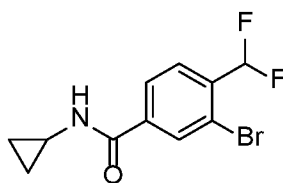
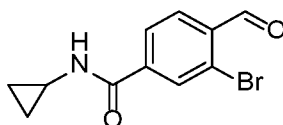
[0402] STEP 2: 3-bromo-*N*-cyclopropyl-4-(fluoromethyl)benzamide

[0403] To a solution of 3-bromo-4-(fluoromethyl)benzoic acid (30.00 mg, 128.74 μ mol) and cyclopropanamine (8.82 mg, 154.48 μ mol) in DMF (2 mL) were added HATU (73.42 mg, 193.10 μ mol) and DIPEA (49.91 mg, 386.21 μ mol). The reaction mixture was stirred at 15°C for 2 hours and then diluted with water. The aqueous phase was extracted with EtOAc, and the organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the title compound (30 mg, crude). ESI-MS *m/z* [M+H]⁺ = 273.0.

[0404] PREPARATION 55: 3-bromo-4-methyl-*N*-((1*S*,2*R*)-2-methylcyclopropyl)benzamide



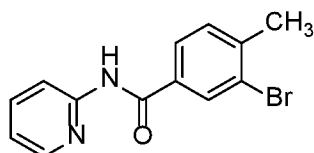
[0405] To a solution of 2-methylcyclopropan-1-amine (1 g, 14.06 mmol) and Et₃N (4.27 g, 42.18 mmol) in DCM (20 mL) was added a solution of 3-bromo-4-methylbenzoyl chloride (3.28 g, 14.06 mmol) in DCM (10 mL). The reaction mixture was stirred at 0-15°C for 1 hour, then diluted with EtOAc, washed with water and with brine, dried over Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure and purified by reversed-phase HPLC and preparative TLC (SiO₂) eluting with 15% EtOAc in petroleum ether to give the title compound as a yellow oil (80 mg, 2%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.41 (q, *J*=4.8 Hz, 1 H) 0.94 - 1.03 (m, 1 H) 1.03 - 1.11 (m, 4 H) 3.46 (s, 3 H) 2.79 - 2.85 (m, 1 H) 7.40 (d, *J*=8.0 Hz, 1 H) 7.72 (dd, *J*=1.6, 8.0 Hz, 1 H) 8.03 (d, *J*=1.6 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 270.0.

[0406] PREPARATION 56: 3-bromo-*N*-cyclopropyl-4-(difluoromethyl)benzamide**[0407]** STEP 1: 3-bromo-*N*-cyclopropyl-4-formylbenzamide

[0408] To a solution of 3-bromo-4-formylbenzoic acid (500 mg, 2.18 mmol) and cyclopropanamine (162.04 mg, 2.84 mmol) in DMF (3 mL) were added EDCI (627.77 mg, 3.27 mmol), HOBt (294.99 mg, 2.18 mmol) and DIPEA (846.47 mg, 6.55 mmol). The reaction mixture was stirred at 15°C for 3 hours, then poured into water and extracted with EtOAc. The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 5-33% EtOAc in petroleum ether to give the title compound as a yellow solid (325 mg, 55.5%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.56 - 0.63 (m, 2 H) 0.69 - 0.75 (m, 2 H) 2.81 - 2.93 (m, 1 H) 7.89 - 7.97 (m, 2 H) 8.16 (d, *J*=1.2 Hz, 1 H) 8.63 - 8.80 (m, 1 H) 10.24 (s, 1 H); ESI-MS *m/z* [M+H]⁺ = 268.0.

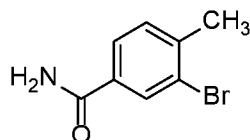
[0409] STEP 2: 3-bromo-*N*-cyclopropyl-4-(difluoromethyl)benzamide

[0410] To a solution of 3-bromo-*N*-cyclopropyl-4-formylbenzamide (100 mg, 372.99 μmol) in DCM (10 mL) was added DAST (240.49 mg, 1.49 mmol) at -40°C, followed by EtOH (2 mg, 43.41 μmol). The reaction mixture was warmed to 10°C and was stirred for 2 hours, then poured into water (20 mL) and extracted with DCM (20 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by preparative TLC (SiO₂) eluting with 60% EtOAc in petroleum ether to give the title compound as a white solid (27 mg, 25%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.56 - 0.61 (m, 2 H), 0.68 - 0.74 (m, 2 H), 2.86 (d, *J*₁=4.0, *J*₂=8.0 Hz, 1 H), 7.01 - 7.33 (m, 1 H), 7.76 (d, *J*=8.0 Hz, 1 H), 7.91 - 7.98 (m, 1 H), 8.11 - 8.17 (m, 1 H), 8.68 (d, *J*=3.6 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 292.0.

[0411] PREPARATION 57: 3-bromo-4-methyl-*N*-(pyridin-2-yl)benzamide

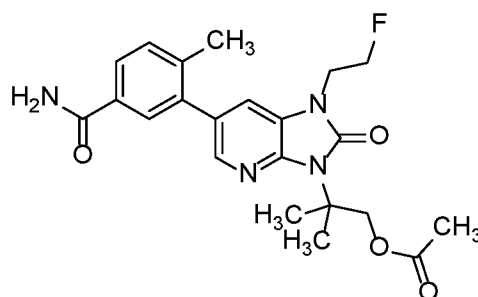
[0412] To a solution of pyridin-2-amine (120.92 mg, 1.28 mmol) in pyridine (2 mL) was added 3-bromo-4-methylbenzoyl chloride (300 mg, 1.28 mmol) in DCM (1 mL) at 0°C. The reaction mixture was stirred at 20°C for 1 hour and then concentrated. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 0-30% EtOAc in petroleum ether to give the title compound as a light-yellow solid (248 mg, 60.5%). ¹H NMR (400 MHz, CD₃OD) δ ppm 2.40 - 2.48(m, 3 H), 7.15 - 7.19(m, 1 H), 7.39 - 7.47 (m, 1 H), 7.81 - 7.91 (m, 2 H), 8.14 - 8.20 (m, 2 H), 8.35 (dd, J₁=0.8 Hz and J₂=4.8 Hz, 1 H); ESI-MS m/z [M+H]⁺ = 291.01.

[0413] PREPARATION 58: 3-bromo-4-methylbenzamide



[0414] A mixture of 3-bromo-4-methylbenzoic acid (1 g, 4.65 mmol), NH₄Cl (298.50 mg, 5.58 mmol), DIPEA (1.80 g, 13.95 mmol), EDCI (1.34 g, 6.98 mmol) and HOBT (628.35 mg, 4.65 mmol) in DMF (4 mL) was degassed and purged with N₂ (3 x). The reaction mixture was stirred at 20°C for 2 hours under N₂ atmosphere, then poured into water and filtered. The filter cake was dried *in vacuo* to give the title compound as a yellow solid (700 mg, 70%). ¹H NMR (400 MHz, CDCl₃) δ ppm 2.46 (s, 3 H) 5.67 – 5.97 (m, 2 H) 7.32 (d, J=8.0 Hz, 1 H) 7.65 (d, J=7.6 Hz, 1 H) 8.00 (s, 1 H).

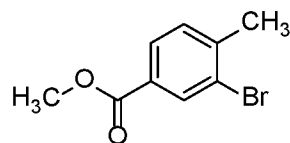
[0415] PREPARATION 59: 2-(6-(5-carbamoyl-2-methylphenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)-2-methylpropyl acetate



[0416] A mixture of 3-bromo-4-methylbenzamide (300 mg, 1.40 mmol), 2-(1-(2-fluoroethyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)-2-methylpropyl acetate (648.76 mg, 1.54 mmol), Na₂CO₃ (445.15 mg, 4.20 mmol) and Pd(dppf)Cl₂ (102.44 mg, 140.00 μmol) in dioxane (10 mL) and water (1 mL) was degassed and purged with N₂ (3 x). The reaction mixture was stirred at 90°C for 5 hours under N₂ atmosphere, then concentrated *in vacuo* and purified by column

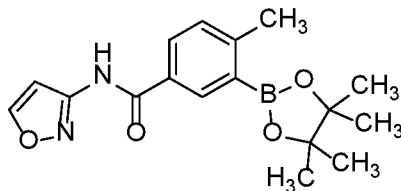
chromatography (SiO₂) eluting with a gradient of 33-50% EtOAc in petroleum ether to give the title compound as a yellow solid (550 mg, 92%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.91 (s, 6 H) 2.01 (s, 3 H) 2.34 (s, 3 H) 4.10 - 4.20 (m, 2 H) 4.76 (s, 2 H) 4.65 - 4.79 (m, 2 H) 5.84 - 6.17 (m, 2 H) 7.21 (s, 1 H) 7.37 (d, *J* = 7.6 Hz, 1 H) 7.70 - 7.74 (m, 2 H) 7.95 (d, *J* = 2.0 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 429.1.

[0417] PREPARATION 60: methyl 3-bromo-4-methylbenzoate

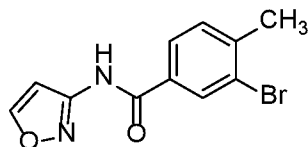


[0418] To a solution of 3-bromo-4-methylbenzoic acid (300 mg, 1.40 mmol) in MeOH (5 mL) was added H₂SO₄ (13.68 mg, 139.51 μmol). The reaction mixture was stirred at 60°C for 1 hour under N₂ and then concentrated. The resulting residue was diluted with water and extracted with EtOAc. The organic layers were combined, concentrated and purified by column chromatography, eluting with a gradient of 0-50% EtOAc in petroleum ether to give the title compound as a white solid (310 mg, 95%). ¹H NMR (400 MHz, CDCl₃) δ ppm 2.4 (s, 3 H) 3.86 (s, 3 H) 7.23 (d, *J* = 10.40 Hz, 1 H) 7.82 (dd, *J*₁ = 1.6 Hz and *J*₂ = 8.0 Hz, 1 H) 8.15 (d, *J* = 1.6 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 228.98.

[0419] PREPARATION 61: *N*-(isoxazol-3-yl)-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide



[0420] STEP 1: 3-bromo-*N*-(isoxazol-3-yl)-4-methylbenzamide



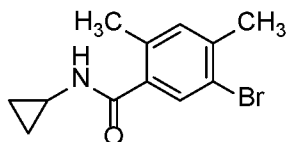
[0421] To a mixture of isoxazol-3-amine (327.35 mg, 3.89 mmol) in pyridine (8 mL) at 0°C was added 3-bromo-4-methylbenzoyl chloride (1.0 g, 4.28 mmol) in DCM (2 mL). The reaction mixture was stirred at 15°C for 1 hour, then concentrated under reduced pressure. The resulting residue was dissolved in EtOAc, washed with water, dried and concentrated. The concentrate was triturated with EtOAc in petroleum ether (5:1, 15 mL) and filtered to give the title compound as a white solid (800 mg, 73%). ¹H NMR (400 MHz, DMSO-*d*₆) δ

ppm 2.42 (s, 3H) 7.03 (d, $J=1.6$ Hz, 1H) 7.52 (d, $J=8.0$ Hz, 1H) 7.94 (dd, $J_1=1.6$ Hz, $J_2=8.0$ Hz, 1H) 8.25 (d, $J=1.6$ Hz, 1H) 8.86 (d, $J=1.6$ Hz, 1H) 11.50 (s, 1H).

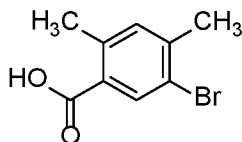
[0422] STEP 2: *N*-(isoxazol-3-yl)-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

[0423] To a solution of 3-bromo-*N*-(isoxazol-3-yl)-4-methylbenzamide (1.2 g, 4.27 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.30 g, 5.12 mmol) in dioxane (5 mL) were added potassium acetate (1.26 g, 12.81 mmol) and Pd(dppf)Cl₂ (312.36 mg, 426.89 μ mol). The reaction mixture was stirred at 90°C for 3 hours under N₂ and then diluted with water. The aqueous phase was extracted with EtOAc and the organic layers were combined, washed with brine, dried over Na₂SO₄, filtered, concentrated *in vacuo*. The crude product was purified by column chromatography (SiO₂) eluting with a gradient of 10-20% EtOAc in petroleum ether, then triturated with petroleum ether and EtOAc (10:1, 15mL) and filtered to give the title compound as a light-yellow solid (1.15 g, 82.1%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.32 (s, 12 H) 2.53 (s, 3 H) 7.03 (d, $J=1.6$ Hz, 1 H) 7.33 (d, $J=8.0$ Hz, 1 H) 7.99 (dd, $J_1=2.0$ Hz, $J_2=8.0$ Hz, 1 H) 8.25 (d, $J=2.0$ Hz, 1 H) 8.84 (d, $J=1.6$ Hz, 1 H) 11.44 (s, 1 H); ESI-MS m/z [M+H]⁺ = 329.1.

[0424] PREPARATION 62: 5-bromo-*N*-cyclopropyl-2,4-dimethylbenzamide



[0425] STEP 1: 5-bromo-2,4-dimethylbenzoic acid



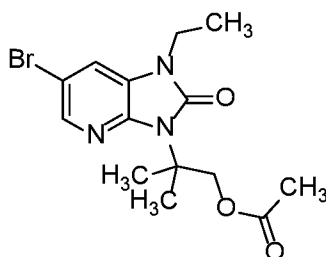
[0426] To a solution of 2,4-dimethylbenzoic acid (0.8 g, 5.33 mmol) in TFA (16.00 mL, 216 mmol) was added NBS (1.42 g, 7.99 mmol) at 10°C. The reaction mixture was stirred at 50°C for 12 hours and then concentrated *in vacuo*. The resulting residue was purified by column chromatography, eluting with a gradient of 0-2% EtOAc in petroleum ether to give the title compound as a white solid (0.6 g, 47%). ¹H NMR (400 MHz, CDCl₃) δ ppm 2.43 (s, 3 H) 2.58 (s, 3 H) 7.15 (s, 1 H) 8.24 (s, 1 H).

[0427] STEP 2: 5-bromo-*N*-cyclopropyl-2,4-dimethylbenzamide

[0428] To a solution of cyclopropanamine (0.172 mL, 2.49 mmol) in DCM (20 mL) were added HATU (1.04 g, 2.74 mmol) and DIPEA (1.30 mL, 7.46 mmol) at 10°C during a 30-

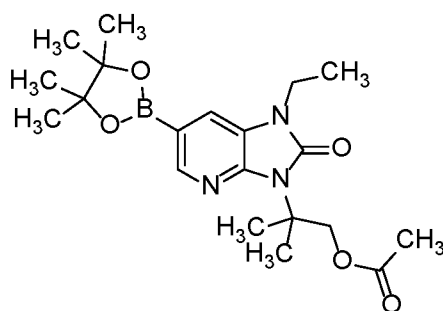
minute period. Next, 5-bromo-2,4-dimethylbenzoic acid (600 mg, 2.49 mmol) was added. The reaction mixture was stirred for 16 hours at 30°C and then washed with water. The organic layers were combined, dried over Na₂SO₄, and concentrated *in vacuo*. The product was triturated with EtOAc (20 mL) at 10°C for 30 minutes to give the title compound as a white solid (500 mg, 75%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.60 - 0.63 (m, 2 H) 0.85 - 0.88 (m, 2 H) 2.36 (s, 6 H) 2.84 - 2.91 (m, 1 H) 5.87 (s, 1 H) 7.08 (s, 1 H) 7.45 (s, 1 H); ESI-MS m/z [M+H]⁺ = 269.8.

[0429] PREPARATION 63: 2-(6-bromo-1-ethyl-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate



[0430] A mixture of 2-(6-bromo-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (50 mg, 152.36 μmol), iodoethane (47.53 mg, 304.73 μmol), and K₂CO₃ (42.12 mg, 304.73 μmol) in DMF (2 mL) was degassed and purged with N₂ (3 x). The reaction mixture was stirred at 90°C for 16 hours under N₂ atmosphere and then diluted with water. The aqueous phase was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The resulting residue was purified by preparative TLC (SiO₂) eluting with 60% EtOAc in petroleum ether to give the title compound as a yellow oil (50 mg, 92%). ESI-MS m/z [M+H]⁺ = 356.1.

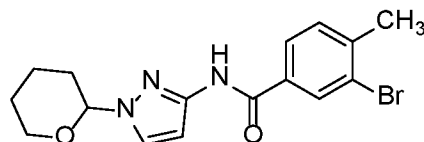
[0431] PREPARATION 64: 2-(1-ethyl-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate



[0432] To a solution of 2-(6-bromo-1-ethyl-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (2.17 g, 6.09 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-

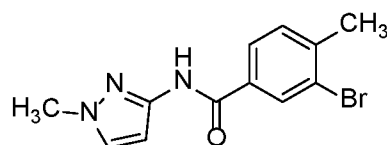
bi(1,3,2-dioxaborolane) (1.70 g, 6.70 mmol) in dioxane (30 mL) were added potassium acetate (1.49 g, 15.23 mmol) and Pd(dppf)Cl₂ (222.87 mg, 304.59 μmol). The reaction mixture was stirred at 80 to 90°C for 3 hours under N₂ and then concentrated *in vacuo*. The resulting residue was purified by column chromatography, eluting with a gradient of 10-30% EtOAc in petroleum ether to give the title compound as a white solid (2.55 g, crude). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.30-1.34 (m, 3 H) 1.36 (s, 12 H) 1.86 (s, 6 H) 1.96 (s, 3 H) 3.86 -3.92 (m, 2 H) 4.74 (s, 2 H) 7.45 (s, 1 H) 8.38 (s, 1 H); ESI-MS m/z [M+H]⁺ = 404.2.

[0433] PREPARATION 65: 3-bromo-4-methyl-*N*-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)benzamide



[0434] To a solution of 3-bromo-4-methylbenzoic acid (100 mg, 465.02 μmol) in DMF (3 mL) was added EDCI (133.72 mg, 697.53 μmol), HOBt (94.25 mg, 697.53 μmol) and DIPEA (240.40 mg, 1.86 mmol) at 20°C. The mixture was degassed under vacuum and purged with nitrogen (3 x) and stirred at 20°C for 30 minutes under nitrogen. Next, 1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-amine (101.08 mg, 604.53 μmol) was added. The mixture was degassed under vacuum and purged with nitrogen (3 x) and stirred at 20°C for another 12 hours under nitrogen. The mixture was then diluted with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by preparative TLC (SiO₂) eluting with 67% EtOAc in petroleum ether to give the title compound as a yellow oil (119 mg, 62.3%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.56 - 1.75 (m, 6 H) 2.47 (s, 3 H) 4.10 - 4.15 (m, 2 H) 5.25 (dd, J₁=2.00 Hz, J₂=8.00 Hz, 1 H) 6.90 (d, J=2.40 Hz, 1 H) 7.32 - 7.36 (m, 1 H) 7.53 - 7.55 (m, 1 H) 7.69 (dd, J₁=2.00 Hz, J₂=8.00 Hz, 1 H) 8.07 (d, J=2.40 Hz, 1 H) 8.40 (s, 1 H); ESI-MS m/z [M+H]⁺ = 365.0.

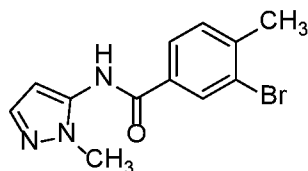
[0435] PREPARATION 66: 3-bromo-4-methyl-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



[0436] To a solution of 3-bromo-4-methylbenzoic acid (1 g, 4.65 mmol) in DMF (15 mL) were added EDCI (1.34 g, 6.98 mmol), HOBt (942.53 mg, 6.98 mmol) and DIPEA (3.61 g, 27.90 mmol), followed by 1-methyl-1*H*-pyrazol-3-amine (496.78 mg, 5.12 mmol). The

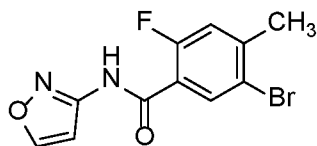
reaction mixture was stirred at 15°C for 12 hours, then washed with water and extracted with EtOAc. The organic layer was dried over Na₂SO₄, filtered and concentrated. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 10-50% EtOAc in petroleum ether to give the title compound as a yellow oil (1.22 g, 89.2%). ¹H NMR (400 MHz, CDCl₃) δ ppm 2.46 (s, 3 H) 3.77 (s, 3 H) 6.83 (d, *J*=2.0 Hz, 1 H) 7.30 (d, *J*=2.0 Hz, 1 H) 7.33 (d, *J*=8.4 Hz, 1 H) 7.68 – 7.71 (m, 1 H) 8.06 (s, 1 H) 8.73 (s, 1 H); ESI-MS *m/z* [M+H]⁺ = 294.1.

[0437] PREPARATION 67: 3-bromo-4-methyl-*N*-(1-methyl-1*H*-pyrazol-5-yl)benzamide



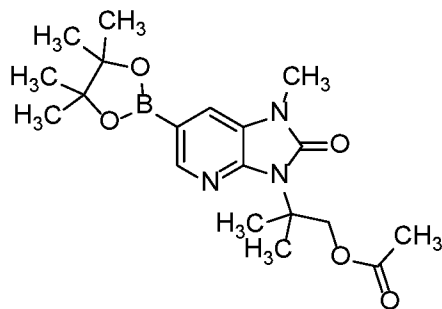
[0438] To a mixture of 3-bromo-4-methylbenzoic acid (0.1 g, 0.465 mmol) and 1-methyl-1*H*-pyrazol-5-amine (45.2 mg, 0.465 mmol) in DMF (3 mL) were added HOBt (75.4 mg, 0.558 mmol), EDCI (134 mg, 0.698 mmol) and DIPEA (0.243 mL, 1.40 mmol). The reaction mixture was stirred at 25°C for 12 hours and then concentrated under reduced pressure. The resulting residue was purified by preparative TLC, eluting with 60% EtOAc in petroleum ether to give the title compound as a light-yellow solid. ESI-MS *m/z* [M+H]⁺ = 294.0.

[0439] PREPARATION 68: 5-bromo-2-fluoro-*N*-(isoxazol-3-yl)-4-methylbenzamide

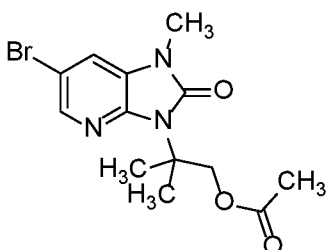


[0440] To a mixture of isoxazol-3-amine (303.93 mg, 3.61 mmol) in pyridine (5 mL) was added 5-bromo-2-fluoro-4-methylbenzoyl chloride (1 g, 3.98 mmol) in DCM (1 mL). The reaction mixture was stirred at 20°C for 1 hour and then EtOAc and water were added. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 5-25% EtOAc in petroleum ether. The product-containing fractions were combined and dried under reduced pressure to give the title compound as a white solid (900 mg, 83.2%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.37 (s, 1 H) 2.40 (s, 3 H) 7.00 (s, 1 H) 7.41-7.43 (d, *J*=10.8 Hz, 1 H) 7.88 – 7.90 (d, *J*=6.8 Hz, 1 H) 8.86 (s, 1 H) 11.52 (s, 1 H); ESI-MS *m/z* [M+H]⁺ = 300.9.

[0441] PREPARATION 69: 2-methyl-2-(1-methyl-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)propyl acetate



[0442] STEP 1: 2-(6-bromo-1-methyl-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate



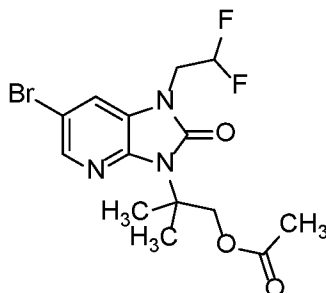
[0443] To a solution of 2-(6-bromo-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (200 mg, 609.46 μ mol) and iodomethane (173.01 mg, 1.22 mmol) in DMF (2 mL) was added K_2CO_3 (168.46 mg, 1.22 mmol). The reaction mixture was stirred at 15°C for 16 hours and then filtered. The organic layer was concentrated *in vacuo* and purified by column chromatography (SiO_2) eluting with a gradient of 5-20% EtOAc in petroleum ether to give the title compound as a colorless oil (240 mg, crude). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.83 (s, 6 H) 1.98 (s, 3 H) 3.35 (s, 3 H) 4.70 (s, 2 H) 7.24 (d, $J=2.0$ Hz, 1 H) 8.04 (d, $J=2.4$ Hz, 1 H); ESI-MS m/z $[M+H]^+ = 344.0$.

[0444] STEP 2: 2-methyl-2-(1-methyl-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)propyl acetate

[0445] To a solution of 2-(6-bromo-1-methyl-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (208.5 mg, 609.31 μ mol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (170.20 mg, 670.25 μ mol) in dioxane (8 mL) was added $Pd(dppf)Cl_2$ (22.29 mg, 30.47 μ mol) and potassium acetate (149.50 mg, 1.52 mmol). The reaction mixture was stirred at 80 to 90°C for 3 hours under N_2 and then concentrated *in vacuo*. The resulting residue was purified by column chromatography (SiO_2) eluting with a gradient of 5-20% EtOAc in petroleum ether to give the title compound as a colorless oil (150 mg, 63.2%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.36 (s, 12 H) 1.86 (s, 6 H) 1.97 (s, 3 H)

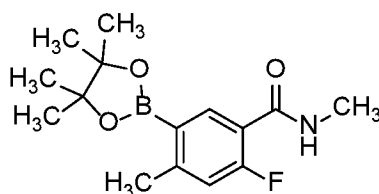
3.37 (s, 3 H) 4.75 (s, 2 H) 7.45 (d, $J=1.6$ Hz, 1 H) 8.40 (d, $J=1.6$ Hz, 1 H); ESI-MS m/z $[M+H]^+ = 390.2$.

[0446] PREPARATION 70: 2-(6-bromo-1-(2,2-difluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate



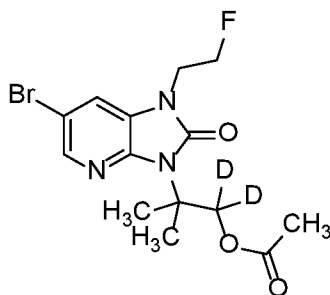
[0447] A mixture of 2-(6-bromo-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (150 mg, 457.09 μmol), 1,1-difluoro-2-iodoethane (96.51 mg, 502.80 μmol), and K_2CO_3 (75.81 mg, 548.51 μmol) in DMF (2 mL) was degassed and purged with N_2 (3 x). The reaction mixture was stirred at 15°C for 16 hours under N_2 atmosphere and then diluted with water. The aqueous phase was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was purified by preparative TLC, eluting with EtOAc in petroleum ether (1:2) to give the title compound as a yellow oil (75 mg, crude). ESI-MS m/z $[M+H]^+ = 392.2$.

[0448] PREPARATION 71: 2-fluoro-*N*,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide



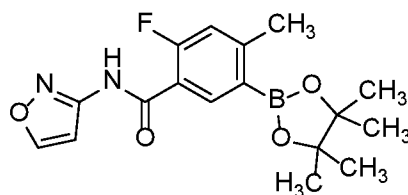
[0449] A mixture of 5-bromo-2-fluoro-*N*,4-dimethylbenzamide (250 mg, 904.19 μmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (252.57 mg, 994.61 μmol), potassium acetate (221.85 mg, 2.26 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (66.16 mg, 90.42 μmol) in dioxane (10 mL) was heated to 100°C and stirred for 15 hours under N_2 . The reaction mixture was concentrated *in vacuo* and purified by column chromatography on silica gel, eluting with a gradient of 20-100% EtOAc in petroleum ether. The title compound was obtained as a white solid (110 mg, 34%). ESI-MS m/z $[M+H]^+ = 294.2$.

[0450] PREPARATION 72: 2-(6-bromo-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1- d_2 acetate



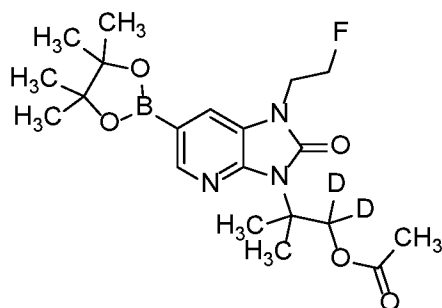
[0451] To a solution of 2-(6-bromo-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1-*d*₂ acetate (130 mg, 393.73 μ mol) and 1-bromo-2-fluoroethane (74.98 mg, 590.60 μ mol) in DMF (2 mL) was added K₂CO₃ (108.83 mg, 787.46 μ mol). The reaction mixture was stirred at 15°C for 12 hours under nitrogen and was then diluted with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 0-30% EtOAc in petroleum ether to give the title compound as a brown oil (110 mg, 74.3%). ESI-MS *m/z* [M+H]⁺ = 376.0.

[0452] PREPARATION 73: 2-fluoro-*N*-(isoxazol-3-yl)-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide



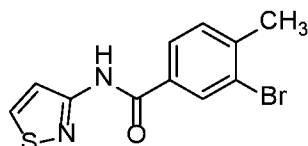
[0453] A mixture of 5-bromo-2-fluoro-*N*-(isoxazol-3-yl)-4-methylbenzamide (0.2 g, 668.68 μ mol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (203.76 mg, 802.42 μ mol), potassium acetate (131.25 mg, 1.34 mmol) and Pd(dppf)Cl₂ (48.93 mg, 66.87 μ mol) in dioxane (5 mL) was degassed and purged with N₂ (3 x). The reaction mixture was stirred at 90°C for 6 hours under N₂ atmosphere and then concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 2-20% EtOAc in petroleum ether to give the title compound as a white solid (0.11 g, 48%). ESI-MS *m/z* [M+H]⁺ = 347.1.

[0454] PREPARATION 74: 2-(1-(2-fluoroethyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1-*d*₂ acetate



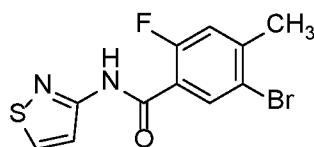
[0455] A mixture of 2-(6-bromo-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3H-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1-*d*₂ acetate (500 mg, 1.33 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (371.24 mg, 1.46 mmol), Pd(dppf)Cl₂.CH₂Cl₂ (54.27 mg, 66.45 μmol) and potassium acetate (391.29 mg, 3.99 mmol) in dioxane (10 mL) was degassed and purged with N₂ (3 x). The reaction mixture was stirred at 80°C for 2 hours under N₂ atmosphere, then diluted with EtOAc and water. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 0-40% EtOAc in petroleum ether to give the title compound as a white oil (460 mg, 81.8%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.30 (s, 12 H) 1.78 (s, 6 H) 1.88 (s, 3 H) 4.14 - 4.24 (m, 2 H) 4.58 - 4.72 (m, 2 H) 7.63 (s, 1 H) 8.21 (d, *J*=1.2 Hz, 1 H).

[0456] PREPARATION 75: 3-bromo-*N*-(isothiazol-3-yl)-4-methylbenzamide

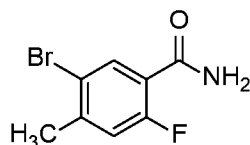


[0457] To a solution of 3-bromo-4-methylbenzamide (78.30 mg, 365.80 μmol) in dioxane (2 mL) were added 3-bromoisothiazole (50 mg, 304.83 μmol), CuI (11.61 mg, 60.97 μmol), (1*R*,2*R*)-cyclohexane-1,2-diamine (6.96 mg, 60.97 μmol) and K₂CO₃ (84.26 mg, 609.67 μmol). The reaction mixture was stirred at 120°C for 12 hours, then poured into water extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated under reduce pressure. The crude product was purified by column chromatography (SiO₂) eluting with a gradient of 5-10% EtOAc in petroleum ether to give the title compound as a yellow solid (40 mg, 44%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.43 (s, 3 H) 7.51 (d, *J*=8.0 Hz, 1 H) 7.87 (d, *J*=4.8 Hz, 1 H) 7.96 (dd, *J*₁ = 8.0, *J*₂ = 2.0 Hz, 1 H) 8.18 - 8.38 (m, 1 H) 9.07 (d, *J*=4.8 Hz, 1 H) 11.55 (s, 1 H); ESI-MS *m/z* [M+H]⁺=297.0.

[0458] PREPARATION 76: 5-bromo-2-fluoro-*N*-(isothiazol-3-yl)-4-methylbenzamide



[0459] STEP 1: 5-bromo-2-fluoro-4-methylbenzamide

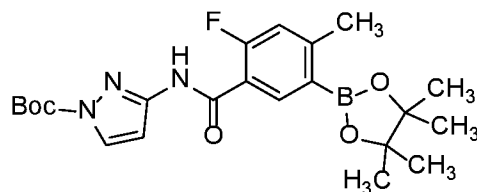


[0460] A mixture of 5-bromo-2-fluoro-4-methylbenzoic acid (1 g, 4.29 mmol), NH_4Cl (275.45 mg, 5.15 mmol), DIPEA (1.66 g, 12.87 mmol), EDCI (1.23 g, 6.44 mmol) and HOBt (579.83 mg, 4.29 mmol) in DMF (10 mL) was degassed and purged with N_2 (3 x). The reaction mixture was stirred at 15°C for 16 hours under N_2 atmosphere and then poured into water and filtered. The filter cake was collected and dried under reduce pressure to give the title compound as a white solid (860 mg, 86.4%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 2.35 (s, 3 H) 7.26 - 7.39 (m, 1 H) 7.69 (d, $J=12.4$ Hz, 2 H) 7.80 (d, 6.8 Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 231.7$.

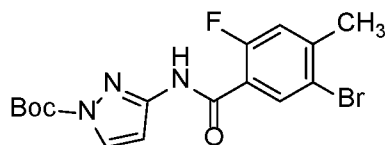
[0461] STEP 2: 5-bromo-2-fluoro-*N*-(isothiazol-3-yl)-4-methylbenzamide

[0462] A mixture of 5-bromo-2-fluoro-4-methylbenzamide (300 mg, 1.29 mmol), 3-bromoisothiazole (212.05 mg, 1.29 mmol), CuI (49.24 mg, 258.57 μmol), K_2CO_3 (357.35 mg, 2.59 mmol) and (1*R*,2*R*)-cyclohexane-1,2-diamine (29.53 mg, 258.57 μmol) in dioxane (4 mL) was degassed and purged with N_2 (3 x). The reaction mixture was stirred at 120°C for 16 hours under N_2 atmosphere and then diluted with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2) eluting with a gradient of 0-20% EtOAc in petroleum ether to give the title compound as a white solid (150 mg, 37%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 2.47 (s, 3 H) 7.12 (d, $J=12.4$ Hz, 1 H) 8.03 (d, $J=4.8$ Hz, 1 H) 8.34 (d, $J=7.6$ Hz, 1 H) 8.67 (d, $J=4.8$ Hz, 1 H) 9.32 (d, $J=13.6$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 314.8$.

[0463] PREPARATION 77: *tert*-butyl 3-(2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)-1*H*-pyrazole-1-carboxylate



[0464] STEP 1: *tert*-butyl 3-(5-bromo-2-fluoro-4-methylbenzamido)-1*H*-pyrazole-1-carboxylate

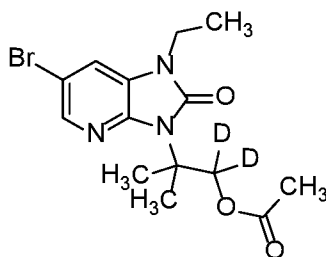


[0465] To a mixture of *tert*-butyl 3-amino-1*H*-pyrazole-1-carboxylate (728.52 mg, 3.98 mmol) in pyridine (3 mL) was added 5-bromo-2-fluoro-4-methylbenzoyl chloride (1.0 g, 3.98 mmol) in DCM (1.5 mL) at 0°C. The reaction mixture was stirred at 20°C for 2 hours and then diluted with water. The aqueous phase was extracted with EtOAc, and the organic layers were combined, washed with brine, dried over Na₂SO₄, and filtered. The filtrate was concentrated *in vacuo* and purified by column chromatography (SiO₂) eluting with a gradient of 0-5% EtOAc in petroleum ether to give the title compound as a white solid (1.06 g, 66.9%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.57 (s, 9 H) 2.39 (s, 3 H) 6.93 (s, 1 H) 7.40 (d, *J*=11.0 Hz, 1 H) 7.85 (d, *J*=6.7 Hz, 1 H) 8.23 (d, *J*=2.4 Hz, 1 H) 11.44 (s, 1 H); ESI-MS *m/z* [M+H]⁺ = 398.1.

[0466] STEP 2: *tert*-butyl 3-(2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)-1*H*-pyrazole-1-carboxylate

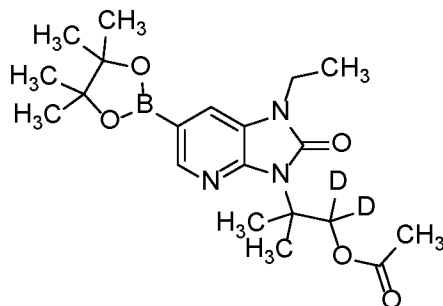
[0467] To a solution of *tert*-butyl 3-(5-bromo-2-fluoro-4-methylbenzamido)-1*H*-pyrazole-1-carboxylate (1.05 g, 2.64 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (803.47 mg, 3.16 mmol) in dioxane (10 mL) were added potassium acetate (776.31 mg, 7.91 mmol) and Pd(dppf)Cl₂ (192.93 mg, 263.67 μmol). The reaction mixture was stirred at 90°C for 3 hours under N₂ and then diluted with water. The aqueous phase was extracted with ethyl acetate, and the organic layers were combined, washed with brine, dried over Na₂SO₄ and filtered. The filtrate was concentrated *in vacuo* and purified by column chromatography (SiO₂) eluting with a gradient of 10-30% EtOAc in petroleum ether to give the title compound as a light-yellow solid (1.0 g, 85%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.33 (s, 12 H) 1.65 (s, 9 H) 2.58 (s, 3 H) 6.97 (d, *J*=13.2 Hz, 1 H) 7.11 - 7.16 (m, 1 H) 8.00 (d, *J*=2.8 Hz, 1 H) 8.52 (d, *J*=9.2 Hz, 1 H) 9.09 (d, *J*=12.8 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 446.5.

[0468] PREPARATION 78: 2-(6-bromo-1-ethyl-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1-*d*₂ acetate



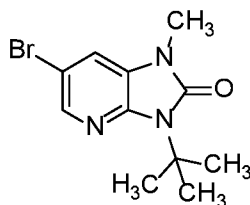
[0469] To a solution of 2-(6-bromo-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1-*d*₂ acetate (1 g, 3.03 mmol) and 1-iodopropane (772.28 mg, 4.54 mmol) in DMF (10 mL) was added K₂CO₃ (837.20 mg, 6.06 mmol). The reaction mixture was stirred at 15°C for 12 hours under nitrogen and then diluted with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 10-30% EtOAc in petroleum ether to give the title compound as a brown oil (1 g, 92%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.17 (t, *J*=7.2 Hz, 3 H) 1.75 (s, 6 H) 1.89 (s, 3 H) 3.83 (q, *J*=7.2 Hz, 2 H) 7.85 (d, *J*=2.0 Hz, 1 H) 8.04 (d, *J*=2.0 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 358.0.

[0470] PREPARATION 79: 2-(1-ethyl-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1-*d*₂ acetate

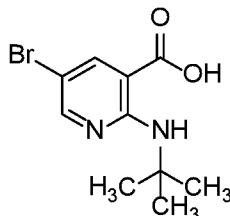


[0471] To a solution of 2-(6-bromo-1-ethyl-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1-*d*₂ acetate (300 mg, 837.46 μmol) in dioxane (3 mL) were added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (233.93 mg, 921.20 μmol), potassium acetate (246.57 mg, 2.51 mmol) and Pd(dppf)Cl₂ (61.28 mg, 83.75 μmol). The reaction mixture was stirred at 90°C under N₂ for 6 hours, then poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated under reduce pressure. The crude product was purified by column chromatography (SiO₂) eluting with a gradient of 5-10% EtOAc in petroleum to give the title compound as a yellow solid (270 mg, 80%). ESI-MS *m/z* [M+H]⁺ = 406.1.

[0472] PREPARATION 80: 6-bromo-3-(*tert*-butyl)-1-methyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

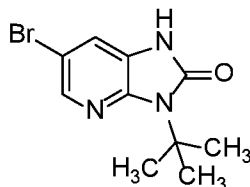


[0473] STEP 1: 5-bromo-2-(*tert*-butylamino)nicotinic acid



[0474] To a solution of 5-bromo-2-fluoronicotinic acid (1 g, 4.55 mmol) in DMSO (2 mL) was added 2-methylpropan-2-amine (0.665 g, 9.09 mmol) at room temperature. The reaction mixture was stirred at 140°C for 2 hours in a microwave reactor, then poured into water. The resulting solid was collected by filtration and dried *in vacuo* to give the title compound (672 mg, 54.1 %). ESI-MS m/z $[M+H]^+ = 273.2$.

[0475] STEP 2: 6-bromo-3-(*tert*-butyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one



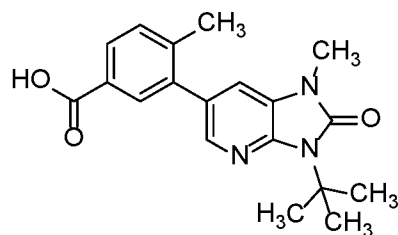
[0476] To a solution of 5-bromo-2-(*tert*-butylamino)nicotinic acid (627 mg, 2.296 mmol) and Et₃N (0.352 mL, 2.53 mmol) in dioxane (10 mL) was added diphenyl phosphorazidate (0.543 mL, 2.53 mmol) at room temperature. The reaction mixture was heated at 100°C for 2 hours, then concentrated *in-vacuo* and purified by chromatography (ISCO Gold® 40 g column) eluting with a gradient of 0-100% EtOAc in hexanes. The product-containing fractions were collected, concentrated and dried *in-vacuo* to give the title compound as an off-white solid (562 mg, 91%).

[0477] STEP 3: 6-bromo-3-(*tert*-butyl)-1-methyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

[0478] To a solution of 6-bromo-3-(*tert*-butyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (250 mg, 0.925 mmol) and iodomethane (0.174 mL, 2.78 mmol) in DMF (2 mL) was added cesium carbonate (1206 mg, 3.70 mmol). The reaction mixture was stirred at room

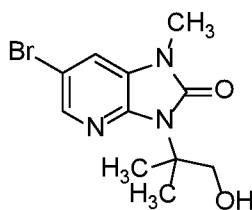
temperature and then diluted with water. The resulting solid was collected by filtration, rinsed with water, and dried *in-vacuo* to give the title compound (243 mg, 92%). ESI-MS m/z $[M+H]^+ = 286.2$.

[0479] PREPARATION 81: 3-(3-(*tert*-butyl)-1-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzoic acid



[0480] To a microwave vial equipped for stirring was added 6-bromo-3-(*tert*-butyl)-1-methyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (243 mg, 0.855 mmol), 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (336 mg, 1.283 mmol), and dioxane (8 mL). The solution was stirred at room temperature for 5 minutes, then sodium bicarbonate (431 mg, 5.13 mmol) and Pd(dppf)Cl₂ (188 mg, 0.257 mmol) were added. The solution was heated to 110°C in a microwave reactor for 15 minutes and then concentrated *in-vacuo*. Next 1 N NaOH was added and the mixture was filtered. The filtrate was acidified to pH 3-4 with 1 N HCl and the resulting solid was collected by vacuum filtration to give the title compound (310 mg). ESI-MS m/z $[M+H]^+ = 340.4$.

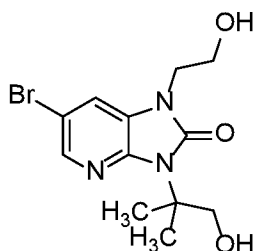
[0481] PREPARATION 82: 6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1-methyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one



[0482] To a solution of 6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (188 mg, 0.657 mmol) in DMF (1 mL) was added NaH (28.9 mg, 0.723 mmol) at 25°C, and the mixture was stirred for 15 minutes. Iodomethane (0.041 mL, 0.657 mmol) was added and the reaction mixture was stirred at 25°C for 20 minutes, then poured into water and extracted with EtOAc. The organic layers were combined, washed with saturated aq NaCl, dried over Na₂SO₄ and filtered. The filtrate was concentrated, dried *in vacuo* and purified by column (ISCO Gold® 24 g column) eluting with a gradient of 0-100% EtOAc in hexanes. The product-containing fractions were collected and then concentrated

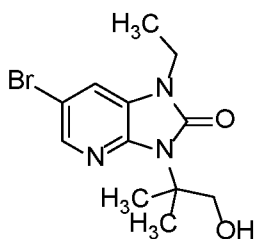
and dried *in vacuo* to give the title compound as a white solid (126 mg, 63.9%). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.66 - 1.67 (m, 6 H) 3.27 - 3.29 (m, 3 H) 3.85 (d, $J=6.33$ Hz, 2 H) 4.81 - 4.86 (m, 1 H) 7.76 (s, 1 H) 8.01 - 8.07 (m, 1 H). ESI-MS m/z $[\text{M}+\text{H}]^+ = 300.2$.

[0483] PREPARATION 83: 6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxyethyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one



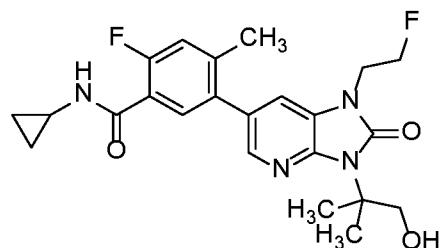
[0484] To a mixture of 6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (1.8 g, 6.29 mmol) and 2-bromoethan-1-ol (1.179 g, 9.44 mmol) in DMF (25 mL) was added K_2CO_3 (1.739 g, 12.58 mmol). The reaction mixture was stirred at 90°C for 3 hours, then cooled to RT, diluted with EtOAc and washed with brine. The organic phase was dried over Na_2SO_4 , filtered and concentrated to give the title compound (1.92 g, 92%) which was used without further purification. ESI-MS m/z $[\text{M}+\text{H}]^+ = 332.2$.

[0485] PREPARATION 84: 6-bromo-1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

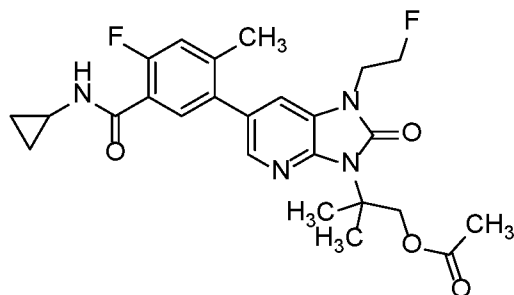


[0486] To a solution of 6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (247 mg, 0.863 mmol) in DMF (2 mL) was added NaH (38.0 mg, 0.950 mmol) at 25°C. The mixture was stirred at 25°C for 15 minutes. Iodoethane (0.069 mL, 0.863 mmol) was added. The reaction mixture was stirred at 25°C overnight and then diluted with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated and dried *in-vacuo*. The crude product was purified by silica column to give the title compound (100 mg, 37%). ESI-MS m/z $[\text{M}+\text{H}]^+ = 316.3$.

[0487] EXAMPLE 1: *N*-cyclopropyl-2-fluoro-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



[0488] STEP 1: 2-(6-(5-(cyclopropylcarbamoyl)-4-fluoro-2-methylphenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)-2-methylpropyl acetate

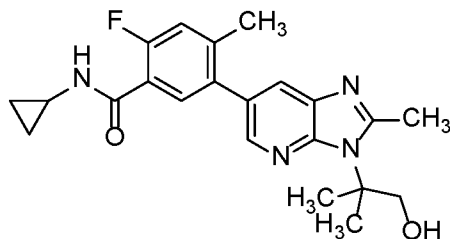


[0489] A mixture of 5-bromo-N-cyclopropyl-2-fluoro-4-methylbenzamide (100 mg, 367 μ mol), 2-(1-(2-fluoroethyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)-2-methylpropyl acetate (155 mg, 0.367 mmol), K_2CO_3 (152 mg, 1.10 mmol), and XPhos Pd G3 (15.6 mg, 0.018 mmol) in water (0.5 mL) and dioxane (10 mL) was degassed and purged with N_2 (3 x) and then stirred at 100°C for 6 hours under N_2 atmosphere. The reaction mixture was filtered on silica. The organic layers were concentrated *in vacuo* to give the title compound as a yellow gum (150 mg, crude). ESI-MS m/z $[M+H]^+ = 487.1$.

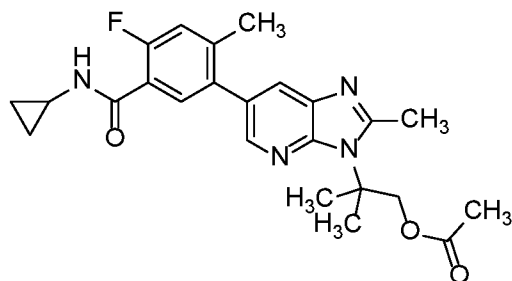
[0490] STEP 2: N-cyclopropyl-2-fluoro-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-6-yl)-4-methylbenzamide

[0491] To a solution of 2-(6-(5-(cyclopropylcarbamoyl)-4-fluoro-2-methylphenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)-2-methylpropyl acetate (150 mg, 0.308 mmol) in MeOH (10 mL) was added K_2CO_3 (128 mg, 0.925 mmol). The mixture was stirred at 80°C for 14 hours and then concentrated *in vacuo*. The resulting residue was purified by preparative HPLC to give the title compound as a white solid (40 mg). ^1H NMR (400 MHz, $DMSO-d_6$) δ ppm 0.52 -0.57 (m, 2 H) 0.66 -0.72 (m, 2 H) 1.72 (s, 6 H) 2.30 (s, 3 H) 2.80 - 2.85 (m, 1 H) 3.92 (d, $J=6.4$ Hz, 2 H) 4.16 - 4.24 (m, 2 H) 4.62 (t, $J=4.8$ Hz, 1 H) 4.74 (t, $J=4.8$ Hz, 1 H) 4.99 (t, $J=6.4$ Hz, 1 H) 7.27 (d, $J=11.2$ Hz, 1 H) 7.42 (d, $J=7.6$ Hz, 1 H) 7.57 (d, $J=0.8$ Hz, 1 H) 7.96 (d, $J=0.8$ Hz, 1 H) 8.30 (d, $J=4.0$ Hz, 1 H); ESI-MS m/z $[M+H]^+ = 445.2$.

[0492] EXAMPLE 2: *N*-cyclopropyl-2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



[0493] STEP 1: 2-(6-(5-(cyclopropylcarbamoyl)-4-fluoro-2-methylphenyl)-2-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate



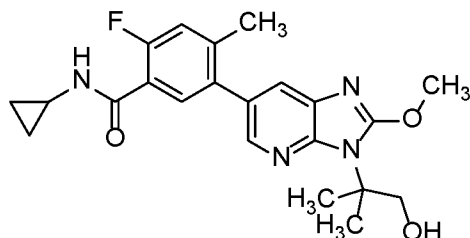
[0494] To a solution of 2-(6-bromo-2-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (61 mg, 187.01 μ mol) and *N*-cyclopropyl-2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (71.63 mg, 224.41 μ mol) in dioxane (2 mL) and water (0.2 mL) were added Na_2CO_3 (59.46 mg, 561.03 μ mol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (6.84 mg, 9.35 μ mol) at 20°C. The suspension was degassed under vacuum and purged with nitrogen (3 x). The reaction mixture was stirred at 90°C for 12 hours under nitrogen and was then quenched by the addition of water and extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure and purified by preparative TLC (SiO_2) eluting with EtOAc to give the title compound as a yellow oil (30 mg, 37%). ^1H NMR (400 MHz, CDCl_3) δ ppm 0.60 - 0.67 (m, 2 H) 0.87 - 0.90 (m, 2 H) 1.98 (d, $J=2.80$ Hz, 9 H) 2.30 (s, 3 H) 2.85 (s, 3 H) 2.92 - 2.99 (m, 1 H) 4.85 (s, 2 H) 6.83 (d, $J=13.60$ Hz, 1 H) 7.05 (d, $J=12.80$ Hz, 1 H) 7.79 (d, $J=2.00$ Hz, 1 H) 8.01 (d, $J=8.00$ Hz, 1 H) 8.19 (d, $J=2.00$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 439.2$.

[0495] STEP 2: *N*-cyclopropyl-2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

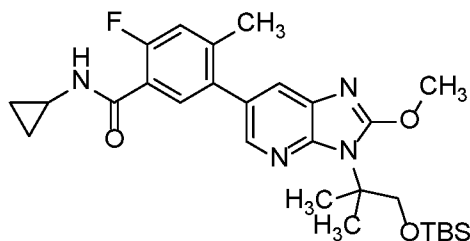
[0496] To a solution of 2-(6-(5-(cyclopropylcarbamoyl)-4-fluoro-2-methylphenyl)-2-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (80 mg, 182 μ mol) in MeOH (2 mL) was added K_2CO_3 (25.21 mg, 182 μ mol) at 20°C. The reaction mixture was stirred at 50°C for 0.5 hours under nitrogen and then filtered. The filtrate was purified by preparative

HPLC to give the title compound as a white solid (28.5 mg, 71.6 μ mol). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 0.50 - 0.57 (m, 2 H) 0.64 - 0.72 (m, 2 H) 1.83 (s, 6 H) 2.28 (s, 3 H) 2.77 (s, 3 H) 2.79 - 2.86 (m, 1 H) 4.01 (s, 2 H) 5.09 (s, 1 H) 7.27 (d, $J=11.20$ Hz, 1 H) 7.42 (d, $J=7.60$ Hz, 1 H) 7.88 (d, $J=2.00$ Hz, 1 H) 8.21 (d, $J=2.00$ Hz, 1 H) 8.32 (d, $J=4.00$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 397.2$.

[0497] EXAMPLE 3: *N*-cyclopropyl-2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-2-methoxy-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



[0498] STEP 1: 5-(3-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-2-methoxy-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-cyclopropyl-2-fluoro-4-methylbenzamide

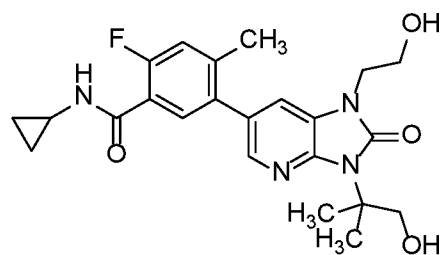


[0499] A mixture of 6-bromo-3-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-2-methoxy-3*H*-imidazo[4,5-*b*]pyridine (160 mg, 386.09 μ mol), *N*-cyclopropyl-2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (123.23 mg, 386.09 μ mol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (28.25 mg, 38.61 μ mol), Na_2CO_3 (102.30 mg, 965.22 μ mol) in dioxane (5 mL) and water (0.5 mL) was degassed and purged with N_2 (3 x) and then stirred at 95°C for 4 hours under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (SiO_2) eluting with a gradient of 0-25% EtOAc in petroleum ether to give the title compound as a yellow oil (160 mg, 78.7). ^1H NMR (400 MHz, CDCl_3) δ ppm 0.21 (s, 6 H) 0.61 - 0.66 (m, 2 H) 0.72 (s, 9 H) 0.86 - 0.91 (m, 2 H) 1.86 (s, 6 H) 2.28 (s, 3 H) 2.92 - 2.99 (m, 1 H) 4.08 (s, 2 H) 4.17 (s, 3 H) 6.83 (d, $J=11.2$ Hz, 1 H) 7.05 (d, $J=12.4$ Hz, 1 H) 7.60 (d, $J=2.0$ Hz, 1 H) 7.98 (d, $J=8.0$ Hz, 1 H) 8.01 (d, $J=2.4$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 527.3$.

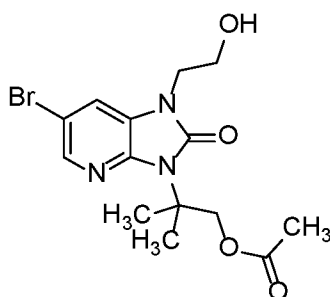
[0500] STEP 2: *N*-cyclopropyl-2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-2-methoxy-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

[0501] To a solution of 5-(3-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-2-methoxy-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-cyclopropyl-2-fluoro-4-methylbenzamide (160 mg, 304 μ mol) was added tetrabutylammonium fluoride (1 M, 2.43 mL). The mixture was stirred at 15°C for 3 hours and then NH_4Cl was added and the mixture extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by reversed-phase HPLC to give the title compound as a white solid (61.4 mg, 47%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 0.29 - 0.24 (m, 2 H) 0.15 - 0.10 (m, 2 H) 0.92 (s, 6 H) 1.47 (s, 3 H) 1.98 - 2.05 (m, 1 H) 3.13 (d, $J=5.6$ Hz, 2 H) 3.31 (s, 3 H) 4.33 (t, $J=6.0$ Hz, 1 H) 6.45 (d, $J=11.2$ Hz, 1 H) 6.60 (d, $J=7.6$ Hz, 1 H) 6.95 (d, $J=2.0$ Hz, 1 H) 7.24 (d, $J=2.0$ Hz, 1 H) 7.48 (d, $J=4.0$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 413.3$.

[0502] EXAMPLE 4: *N*-cyclopropyl-2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxyethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

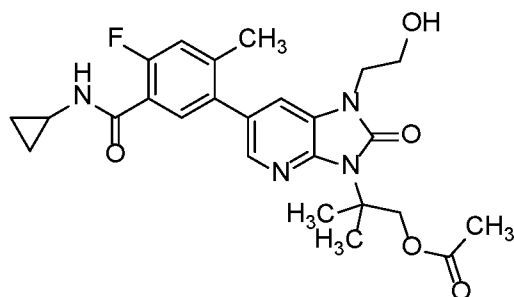


[0503] STEP 1: 2-(6-bromo-1-(2-hydroxyethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate



[0504] A reaction mixture of 2-(6-bromo-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (0.2 g, 0.6 mmol), 2-iodoethanol (0.095 mL, 1.2 mmol) and K_2CO_3 (0.168 mg, 1.22 mmol) in DMF (5 mL) was stirred at 25°C for 10 hours. The mixture was then diluted with water and extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give the title compound as a gray oil (0.22 g, crude). ESI-MS m/z $[\text{M}+\text{H}]^+ = 374.0$.

[0505] STEP 2: 2-(6-(5-(cyclopropylcarbamoyl)-4-fluoro-2-methylphenyl)-1-(2-hydroxyethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate

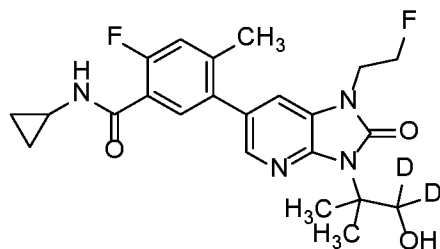


[0506] A mixture of 2-(6-bromo-1-(2-hydroxyethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (0.22 g, 0.59 mmol), *N*-cyclopropyl-2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (208 mg, 0.650 mmol), Na₂CO₃ (125 mg, 1.18 mmol), Pd(dppf)Cl₂ (43.3 mg, 0.059 mmol) in dioxane (10 mL) and water (2 mL) was degassed and purged with N₂ (3 x) and then stirred at 90°C for 6 hours under N₂ atmosphere. The mixture was concentrated under reduced pressure and purified by column chromatography (SiO₂) eluting with a gradient of 20-50% EtOAc in petroleum ether to give the title compound as a yellow solid (0.25 g, 87%). ESI-MS *m/z* [M+H]⁺ = 485.2.

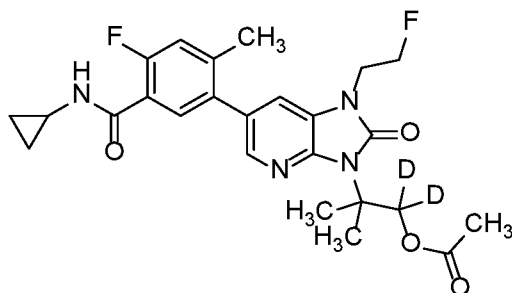
[0507] STEP 3: *N*-cyclopropyl-2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxyethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

[0508] A mixture of 2-(6-(5-(cyclopropylcarbamoyl)-4-fluoro-2-methylphenyl)-1-(2-hydroxyethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (0.25 g, 0.52 mmol) and K₂CO₃ (143 mg, 1.03 mmol) in MeOH (3 mL) was stirred at 50°C for 1 hour. The reaction mixture was purified by preparative HPLC to give the title compound as an off-white solid (136 mg, 59.1%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.60 - 0.66 (m, 2 H) 0.85 - 0.92 (m, 2 H) 1.73 (s, 6 H) 2.31 (s, 3 H) 2.56 - 2.62 (m, 1 H) 2.90 - 2.97 (m, 1 H) 3.95 - 4.00 (m, 2 H) 4.02 - 4.06 (m, 4 H) 5.62 (t, *J*=8.0 Hz, 1 H) 6.85 (d, *J*=12.8 Hz, 1 H) 7.05 (d, *J*=12.8 Hz, 1 H) 7.28 (d, *J*=2.0 Hz, 1 H) 7.92 (d, *J*=2.0 Hz, 1 H) 7.96 (d, *J*=8.0 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 443.3.

[0509] EXAMPLE 5: *N*-cyclopropyl-2-fluoro-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-1,1-*d*₂)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



[0510] STEP 1: 2-(6-(5-(cyclopropylcarbamoyl)-4-fluoro-2-methylphenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1-*d*₂ acetate

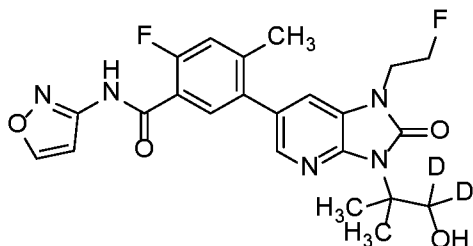


[0511] To a mixture of 2-(6-bromo-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1-*d*₂ acetate (320 mg, 850.57 μ mol), *N*-cyclopropyl-2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (298.63 mg, 935.63 μ mol) and K₂CO₃ (235.12 mg, 1.70 mmol) in dioxane (6 mL) and water (1 mL) was added Pd(dppf)Cl₂ (62.24 mg, 85.06 μ mol). The mixture was stirred at 90°C for 3 hours under nitrogen, then diluted with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to give the title compound as a brown oil (400 mg, crude). ESI-MS *m/z* [M+H]⁺ = 489.3.

[0512] STEP 2: *N*-cyclopropyl-2-fluoro-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl-1,1-*d*₂)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

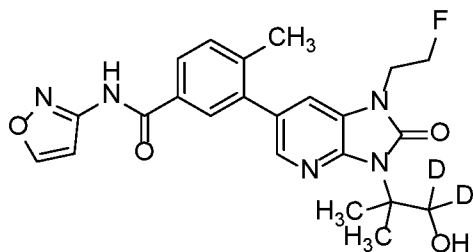
[0513] A mixture of 2-(6-(5-(cyclopropylcarbamoyl)-4-fluoro-2-methylphenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1-*d*₂ acetate (400 mg, 818.80 μ mol) and LiOH.H₂O (171.80 mg, 4.09 mmol) in THF (5 mL), DMF (1 mL) and water (1 mL) was stirred at 50°C for 2 hours under nitrogen. The mixture was then diluted with aq saturated NH₄Cl solution and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The resulting residue was purified by preparative HPLC to give the title compound as a white solid (54.55 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.48 - 0.59 (m, 2 H) 0.62 - 0.75 (m, 2 H) 1.71 (s, 6 H) 2.29 (s, 3 H) 2.80 - 2.86 (m, 1H) 4.08 - 4.28 (m, 2 H) 4.62 (t, *J*=4.8 Hz, 1 H) 4.74 (t, *J*=4.8 Hz, 1 H) 4.94 (s, 1 H) 7.27 (d, *J*=11.6 Hz, 1 H) 7.42 (d, *J*=7.6 Hz, 1 H) 7.57 (d, *J*=1.6 Hz, 1 H) 7.95 (d, *J*=1.6 Hz, 1 H) 8.22 - 8.35 (m, 1 H); ESI-MS *m/z* [M+H]⁺ = 447.2.

[0514] EXAMPLE 6: 2-fluoro-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl-1,1- d_2)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-(isoxazol-3-yl)-4-methylbenzamide

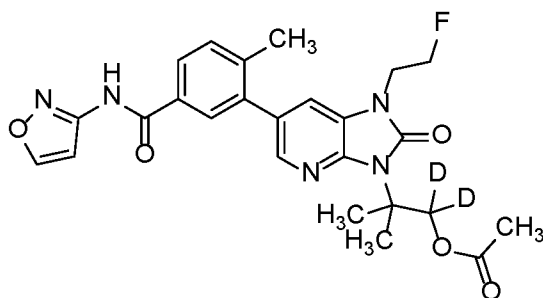


[0515] The title compound was prepared like EXAMPLE 5, starting with 2-fluoro-*N*-(isoxazol-3-yl)-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide in place of *N*-cyclopropyl-2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide, and proceeding through intermediate 2-(6-(4-fluoro-5-(isoxazol-3-ylcarbamoyl)-2-methylphenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1- d_2 acetate. The title compound was obtained as a white solid (6.52 mg). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.74 (s, 6 H) 2.37 (s, 3 H) 4.13 - 4.26 (m, 2 H) 4.65 - 4.83 (m, 2 H) 5.49 (s, 1 H) 7.14 - 7.22 (m, 2 H) 7.96 (d, $J=2.0$ Hz, 1 H) 8.03 (d, $J=8.0$ Hz, 1 H) 8.36 (d, $J=1.2$ Hz, 1 H) 9.11 (d, $J=14.8$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 474.2$.

[0516] EXAMPLE 7: 3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl-1,1- d_2)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-(isoxazol-3-yl)-4-methylbenzamide



[0517] STEP 1: 2-(1-(2-fluoroethyl)-6-(5-(isoxazol-3-ylcarbamoyl)-2-methylphenyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1- d_2 acetate



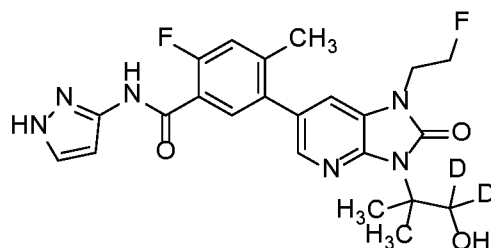
[0518] To a solution of 2-(6-bromo-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1- d_2 acetate (412.71 mg, 1.10 mmol) and *N*-(isoxazol-3-yl)-

4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (300 mg, 914.16 μmol) in dioxane (3 mL) and water (0.3 mL) were added Na_2CO_3 (290.67 mg, 2.74 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (66.89 mg, 91.42 μmol). The reaction mixture was stirred at 90°C for 5 hours under N_2 and then diluted with water. The aqueous phase was extracted with EtOAc, and the organic layers were combined, washed with brine, dried over Na_2SO_4 , and filtered. The filtrate was concentrated *in vacuo* and purified by column chromatography (SiO_2) eluting with a gradient of 20-50% EtOAc in petroleum ether to give the title compound as a light-yellow solid (350 mg, 77%). ESI-MS m/z $[\text{M}+\text{H}]^+ = 498.2$.

[0519] STEP 2: 3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl-1,1- d_2)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-(isoxazol-3-yl)-4-methylbenzamide

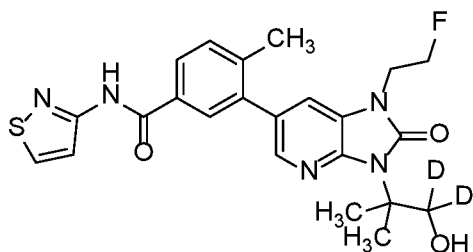
[0520] To a solution of 2-(1-(2-fluoroethyl)-6-(5-(isoxazol-3-ylcarbamoyl)-2-methylphenyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1- d_2 acetate (350 mg, 703.50 μmol) in MeOH (5 mL) was added K_2CO_3 (97.23 mg, 703.50 μmol). The reaction mixture was stirred at 50°C for 15 minutes and then adjusted to pH 3 with aq HCl (1M). Water was added and the aqueous phase was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and purified by preparative HPLC, followed by successive re-crystallizations from EtOH (10 mL) and THF/MeOH (2:1, 2 mL). The solids were collected by filtration to give a first batch of the title compound as a white solid (22.9 mg) as white solid, and the filtrate was concentrated and purified by preparative HPLC to give a second batch of the title compound as a white solid (100 mg, 74.5% purity). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.73 (s, 6 H) 2.37 (s, 3 H) 4.14-4.26 (m, 2 H) 4.60 - 4.77 (m, 2 H) 4.97 (s, 1 H) 7.06 (d, $J=1.6$ Hz, 1 H) 7.50 (d, $J=8.0$ Hz, 1 H) 7.65 (s, 1 H) 7.92 - 8.00 (m, 2 H) 8.06 (d, $J=1.6$ Hz, 1 H) 8.84 (d, $J=1.6$ Hz, 1 H) 11.43 (s, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 456.2$.

[0521] EXAMPLE 8: 2-fluoro-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl-1,1- d_2)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-(1*H*-pyrazol-3-yl)benzamide

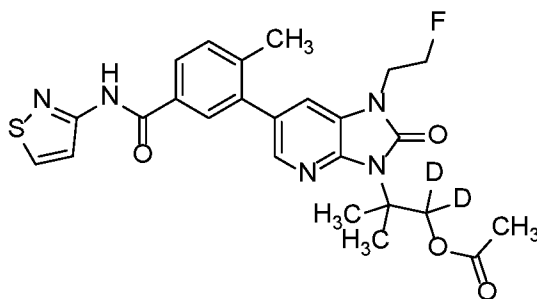


[0522] The title compound was prepared like EXAMPLE 7, starting with *tert*-butyl 3-(2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)-1*H*-pyrazole-1-carboxylate in place of *N*-(isoxazol-3-yl)-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide, and proceeding through intermediate 2-(6-(5-((1*H*-pyrazol-3-yl)carbamoyl)-4-fluoro-2-methylphenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1-*d*₂ acetate. The title compound was obtained as white solid (10 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.72 (s, 6 H) 2.33 (s, 3 H) 4.12 - 4.25 (m, 2 H) 4.60 - 4.77 (m, 2 H) 4.96 (s, 1 H) 6.62 (s, 1 H) 7.32 (d, *J*=11.2 Hz, 1 H) 7.55 (d, *J*=7.6 Hz, 1 H) 7.61 (s, 1 H) 7.66 (s, 1 H) 8.02 (s, 1 H) 10.73 (s, 1 H) 12.43 (s, 1 H); ESI-MS *m/z* [M+H]⁺ = 473.2.

[0523] EXAMPLE 9: 3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl-1,1-*d*₂)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-(isothiazol-3-yl)-4-methylbenzamide



[0524] STEP 1: 2-(1-(2-fluoroethyl)-6-(5-(isothiazol-3-ylcarbamoyl)-2-methylphenyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1-*d*₂ acetate



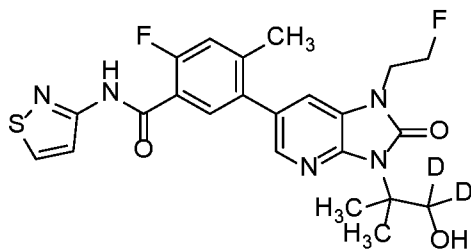
[0525] A mixture of 3-bromo-*N*-(isothiazol-3-yl)-4-methylbenzamide (60 mg, 201.90 μmol), 2-(1-(2-fluoroethyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1-*d*₂ acetate (102.55 mg, 242.28 μmol), Pd(dppf)Cl₂.CH₂Cl₂ (16.49 mg, 20.19 μmol) and Na₂CO₃ (42.80 mg, 403.81 μmol) in dioxane (1.5 mL) and water (0.3 mL) was degassed and purged with N₂ (3 x). The reaction mixture was stirred at 90°C for 6 hours under N₂ atmosphere and then diluted with EtOAc and water. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered

and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 0-40% EtOAc in petroleum ether to give the title compound as a white oil (50 mg, 48%). ESI-MS m/z $[M+H]^+ = 514.2$.

[0526] STEP 2: 3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl-1,1-*d*₂)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-(isothiazol-3-yl)-4-methylbenzamide

[0527] A mixture of 2-(1-(2-fluoroethyl)-6-(5-(isothiazol-3-ylcarbamoyl)-2-methylphenyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1-*d*₂ acetate (50 mg, 97.36 μ mol) and K₂CO₃ (13.46 mg, 97.36 μ mol) in MeOH (1.5 mL) was degassed and purged with N₂ (3 x). The reaction mixture was stirred at 50°C for 15 minutes under N₂ atmosphere and then diluted with EtOAc and water. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by preparative HPLC to give the title compound as a white solid (21.73 mg, 47%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.73 (s, 6 H) 2.37 (s, 3 H) 4.16 - 4.18 (m, 1 H) 4.23 - 4.25 (m, 1 H) 4.62 - 4.64 (m, 1 H) 4.74 - 4.76 (m, 1 H) 4.98 (s, 1 H) 7.48 (d, $J=7.6$ Hz, 1 H) 7.65 (s, 1 H) 7.89 (d, $J=4.8$ Hz, 1 H) 7.96 (d, $J=8.0$ Hz, 1 H) 7.98 (s, 1 H) 8.07 (s, 1 H) 9.04 (d, $J=4.8$ Hz, 1 H) 11.48 (s, 1 H); ESI-MS m/z $[M+H]^+ = 472.2$.

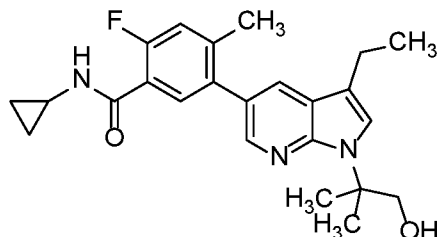
[0528] EXAMPLE 10: 2-fluoro-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl-1,1-*d*₂)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-(isothiazol-3-yl)-4-methylbenzamide



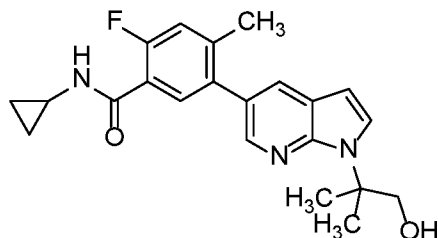
[0529] The title compound was prepared like EXAMPLE 9, starting with 5-bromo-2-fluoro-*N*-(isothiazol-3-yl)-4-methylbenzamide in place of 3-bromo-*N*-(isothiazol-3-yl)-4-methylbenzamide, and proceeding through intermediate 2-(6-(4-fluoro-5-(isothiazol-3-ylcarbamoyl)-2-methylphenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1-*d*₂ acetate. The title compound was obtained as a white solid (5.42 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.72 (s, 6 H) 2.34 (s, 3 H) 4.16 - 4.24 (m, 2 H) 4.61 - 4.76 (m, 2 H) 4.96 (s, 1 H) 7.34 (d, $J=11.6$ Hz, 1 H) 7.58 (s, 1 H) 7.60 (d,

$J=5.2$ Hz, 1 H) 7.85 (d, $J=4.8$ Hz, 1 H) 8.02 (d, $J=1.6$ Hz, 1 H) 9.05 (d, $J=4.8$ Hz, 1 H) 11.47 (s, 1 H); ESI-MS m/z $[M+H]^+ = 490.2$.

[0530] EXAMPLE 11: *N*-cyclopropyl-5-(3-ethyl-1-(1-hydroxy-2-methylpropan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-fluoro-4-methylbenzamide

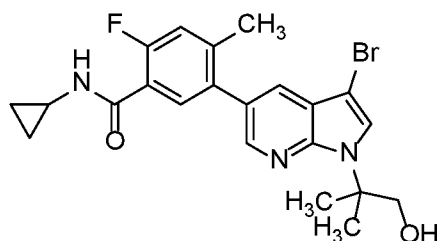


[0531] STEP 1: *N*-cyclopropyl-2-fluoro-5-(1-(1-hydroxy-2-methylpropan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide



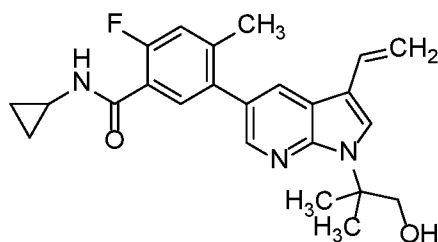
[0532] To a solution of 2-(5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-2-methylpropan-1-ol (345 mg, 1.28 mmol) and *N*-cyclopropyl-2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (470.52 mg, 1.47 mmol) in dioxane (3.6 mL) and water (0.6 mL) were added K_2CO_3 (354.33 mg, 2.56 mmol) and $Pd(dppf)Cl_2$ (93.80 mg, 128.19 μ mol) at 25°C. The suspension was degassed under vacuum and purged with nitrogen (3 x). The reaction mixture was heated to 90°C for 12 hours under nitrogen, then diluted with brine and EtOAc, and filtered. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2) eluting with a gradient of 6-33% EtOAc in petroleum ether to give the title compound as a yellow oil (340 mg, 69.6%). ESI-MS m/z $[M+H]^+ = 382.2$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.62 - 0.66 (m, 2 H) 0.86 - 0.90 (m, 2 H) 1.26 - 1.29 (m, 1 H) 1.70 (s, 6 H) 2.32 (s, 3 H) 2.90 - 3.00 (m, 1 H) 3.95 - 4.20 (m, 2 H) 6.51 (d, $J=3.20$ Hz, 1 H) 6.79 - 6.87 (m, 1 H) 7.05 (d, $J=12.80$ Hz, 1 H) 7.45 (d, $J=3.60$ Hz, 1 H) 7.86 (s, 1 H) 8.00 (d, $J=8.00$ Hz, 1 H) 8.16 (s, 1 H).

[0533] STEP 2: 5-(3-bromo-1-(1-hydroxy-2-methylpropan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-*N*-cyclopropyl-2-fluoro-4-methylbenzamide



[0534] To a solution of *N*-cyclopropyl-2-fluoro-5-(1-(1-hydroxy-2-methylpropan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide (340 mg, 891.35 μmol) in DCM (10 mL) was added NBS (166.58 mg, 935.92 μmol) at 0°C. The mixture was stirred at 0°C for 45 minutes and then concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2) eluting with a gradient of 6-14% EtOAc in petroleum ether to give the title compound as a yellow oil (360 mg, 87.7%). ^1H NMR (400 MHz, CDCl_3) δ ppm 0.63 - 0.66 (m, 2 H) 0.87 - 0.91 (m, 2 H) 1.69 (s, 6 H) 2.77 (s, 3 H) 2.92 - 2.99 (m, 1 H) 4.06 (s, 2 H) 6.85 (d, $J=12.80$ Hz, 1 H) 7.04 - 7.09 (m, 1 H) 7.47 (s, 1 H) 7.82 (d, $J=1.60$ Hz, 1 H) 8.00 - 8.04 (m, 1 H) 8.21 (d, $J=1.60$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 461.1$.

[0535] STEP 3: *N*-cyclopropyl-2-fluoro-5-(1-(1-hydroxy-2-methylpropan-2-yl)-3-vinyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide



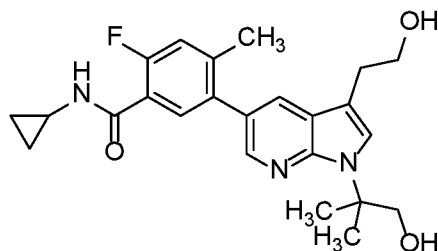
[0536] To a solution of 5-(3-bromo-1-(1-hydroxy-2-methylpropan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-*N*-cyclopropyl-2-fluoro-4-methylbenzamide (320 mg, 695.14 μmol), potassium trifluoro(vinyl)borate (121.05 mg, 903.68 μmol) and K_2CO_3 (192.15 mg, 1.39 mmol) in dioxane (4 mL) and water (0.4 mL) was added $\text{PdCl}_2(\text{dtbpf})$ (22.65 mg, 34.76 μmol) at 20°C. The mixture was heated and stirred at 100°C for 3 hours under nitrogen. Brine and EtOAc were added. The mixture was stirred for 10 minutes and filtered. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2) eluting with a gradient of gradient of 9-25% EtOAc in petroleum ether to give the title compound as a yellow oil (110 mg, 38.8%). ^1H NMR (400 MHz, CDCl_3) δ ppm 0.64 - 0.66 (m, 2 H) 0.88 - 0.90 (m, 2 H) 1.70 (s, 6 H) 2.33 (s, 3 H) 2.93 - 2.97 (m, 1 H) 4.05 (s, 2 H) 5.21 (d, $J=12.00$ Hz, 1 H) 5.64 (d, $J=18.00$ Hz, 1 H) 6.79 - 6.87 (m, 2 H) 7.07 (d, $J=12.80$ Hz, 1 H) 7.48 (s, 1 H) 8.03 (d,

$J=8.40$ Hz, 1 H) 8.10 (d, $J=2.00$ Hz, 1 H) 8.18 (d, $J=2.00$ Hz, 1 H); ESI-MS m/z $[M+H]^+ = 408.1$.

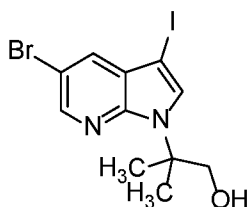
[0537] STEP 4: *N*-cyclopropyl-5-(3-ethyl-1-(1-hydroxy-2-methylpropan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-fluoro-4-methylbenzamide

[0538] To a solution of *N*-cyclopropyl-2-fluoro-5-(1-(1-hydroxy-2-methylpropan-2-yl)-3-vinyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide (20 mg, 49 μ mol) in MeOH (1 mL) was added Pd/C (70 mg, 10% purity) at 25°C. The suspension was degassed under vacuum and purged with H₂ (3 x) and stirred under H₂ (15 psi) at 25°C for 20 minutes. The mixture was filtered, concentrated under reduced pressure, and purified by preparative HPLC to give the title compound as a white solid (5.17 mg). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.61 - 0.68 (m, 2 H) 0.85 - 0.94 (m, 2 H) 1.24 - 1.36 (m, 4 H) 1.66 (s, 6 H) 2.32 (s, 3 H) 2.70 - 2.80 (m, 2 H) 2.92 - 3.00 (m, 1 H) 4.04 (s, 2 H) 6.84 (d, $J=12.40$ Hz, 1 H) 7.05 (d, $J=12.80$ Hz, 1 H) 7.20 (s, 1 H) 7.82 (d, $J=2.00$ Hz, 1 H) 8.02 (d, $J=8.00$ Hz, 1 H) 8.13 (d, $J=2.00$ Hz, 1 H); ESI-MS m/z $[M+H]^+ = 410.2$.

[0539] EXAMPLE 12: *N*-cyclopropyl-2-fluoro-5-(1-(1-hydroxy-2-methylpropan-2-yl)-3-(2-hydroxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide



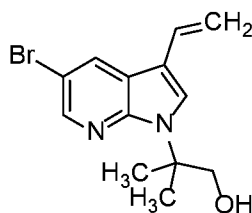
[0540] STEP 1: 2-(5-bromo-3-iodo-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-2-methylpropan-1-ol



[0541] To a solution of 2-(5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-2-methylpropan-1-ol (842 mg, 3.13 mmol) in DCM (10 mL) was added NIS (703.87 mg, 3.13 mmol) at 0°C. The reaction mixture was stirred at 25°C for 1 hour and was then quenched by the addition of water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by preparative TLC, eluting with 30% EtOAc in petroleum ether to give the title compound as a yellow solid (900 mg, 72.8%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.67 (s, 6

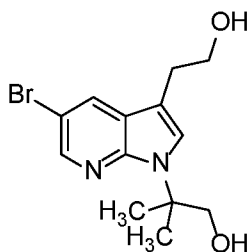
H) 4.03 (d, $J=3.6$ Hz, 2 H) 5.60 (s, 1 H) 7.49 (s, 1 H) 7.90 (d, $J=2.4$ Hz, 1 H) 8.30 (d, $J=2.0$ Hz, 1 H); ESI-MS m/z $[M+H]^+ = 394.8$.

[0542] STEP 2: 2-(5-bromo-3-vinyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-2-methylpropan-1-ol



[0543] To a solution of 2-(5-bromo-3-iodo-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-2-methylpropan-1-ol (400 mg, 1.01 mmol) and potassium trifluoro(vinyl)borate (149.20 mg, 1.11 mmol) in dioxane (5 mL) and water (0.5 mL) was added K_2CO_3 (279.90 mg, 2.03 mmol) and $Pd(dppf)Cl_2$ (74.09 mg, 101.26 μ mol). The mixture was stirred at 80°C for 3 hours and then filtered and concentrated under reduced pressure. The resulting residue was purified by preparative TLC, eluting with 25% EtOAc in petroleum ether to give the title compound as a yellow oil (200 mg, 66.9%). ^1H NMR (400MHz, $CDCl_3$) δ ppm 1.66 (s, 6 H) 4.03 (s, 2 H) 5.24 (dd, $J=1.2, 11.6$ Hz, 1 H) 5.64 (dd, $J=0.8, 18.0$ Hz, 1 H) 6.76 (dd, $J=11.6, 18.0$ Hz, 1 H) 8.30 (s, 2 H) 7.43 (s, 1 H); ESI-MS m/z $[M+H]^+ = 295.0$.

[0544] STEP 3: 2-(5-bromo-3-(2-hydroxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-2-methylpropan-1-ol

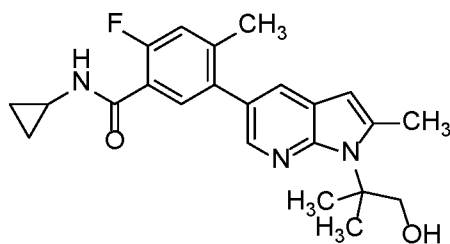


[0545] A solution of 2-(5-bromo-3-vinyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-2-methylpropan-1-ol (200 mg, 678 μ mol) in THF (1 mL) was admixed with $BH_3 \cdot Me_2S$ (10 M, 203.27 μ L) at 0°C and stirred for 1 hour. Next, NaOH (1 M, 2.03 mL) and H_2O_2 (209.52 mg, 2.03 mmol, 177.56 μ L, 33% purity) were added at 0°C. The reaction mixture was stirred at 25°C for 2 hours, then quenched by the addition of MeOH, washed with aq sodium sulfite solution, and concentrated under reduced pressure. The resulting residue was purified by preparative TLC, eluting with 50% EtOAc in petroleum ether to give the title compound as a yellow oil (40 mg, 19%). ESI-MS m/z $[M+H]^+ = 313.0$.

[0546] STEP 4: *N*-cyclopropyl-2-fluoro-5-(1-(1-hydroxy-2-methylpropan-2-yl)-3-(2-hydroxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide

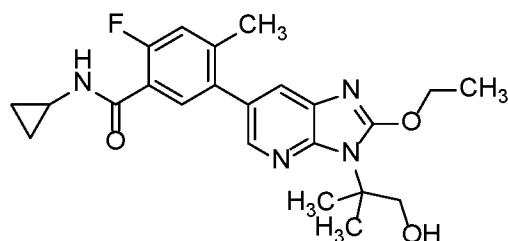
[0547] To a solution of 2-(5-bromo-3-(2-hydroxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-2-methylpropan-1-ol (40 mg, 128 μ mol) and *N*-cyclopropyl-2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (48.92 mg, 153.3 μ mol) in dioxane (1.8 mL) and water (0.3 mL) were added K_2CO_3 (35.30 mg, 255.4 μ mol) and $Pd(dppf)Cl_2$ (9.35 mg, 12.8 μ mol). The mixture was stirred at 90°C for 12 hours, then filtered and concentrated under reduced pressure. The resulting residue was purified by preparative HPLC to give the title compound as a white solid (22.06 mg, 38.97%). ^1H NMR (400 MHz, $DMSO-d_6$) δ ppm 0.57 - 0.51 (m, 2 H) 0.72 - 0.66 (m, 2 H) 2.30 (s, 3 H) 1.68 (s, 6 H) 2.84 (t, $J=6.8$ Hz, 3 H) 3.73 - 3.57 (m, 2 H) 3.97 (d, $J=5.2$ Hz, 2 H) 4.65 (br t, $J=5.6$ Hz, 1 H) 4.65 (br t, $J=5.6$ Hz, 1 H) 5.09 (t, $J=5.6$ Hz, 1 H) 7.27 (d, $J=11.6$ Hz, 1 H) 7.46 - 7.39 (m, 2 H) 7.91 (d, $J=2.0$ Hz, 1 H) 8.17 (d, $J=2.0$ Hz, 1 H) 8.33 (d, $J=3.2$ Hz, 1 H); ESI-MS $[M+H]^+ = 426.1$.

[0548] EXAMPLE 13: *N*-cyclopropyl-2-fluoro-5-(1-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide

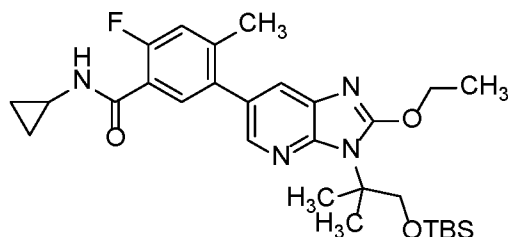


[0549] To a mixture of 2-(5-chloro-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-2-methylpropan-1-ol (549 mg, 2.30 mmol) and *N*-cyclopropyl-2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (807.46 mg, 2.53 mmol) in dioxane (5 mL) and water (1 mL) were added K_2CO_3 (635.70 mg, 4.60 mmol) and XPhos Pd G3 (97.33 mg, 114.99 μ mol) in one portion under N_2 . The reaction mixture was stirred at 90°C for 12 hours, then diluted with water, and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2) eluting with a gradient of 20-50% EtOAc in petroleum ether, followed by preparative HPLC, to give the title compound as a white solid (400 mg, 46.0%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.60 - 0.67 (m, 2 H) 0.85 - 0.93 (m, 2 H) 1.69 (s, 6 H) 2.31 (s, 3 H) 2.72 (s, 3 H) 2.95 (m, 1 H) 4.21 (s, 2 H) 6.32 (s, 1 H) 6.83 (d, $J=13.4$ Hz, 1 H) 7.01 - 7.09 (m, 2 H) 7.70 (d, $J=2.2$ Hz, 1 H) 8.00 (d, $J=8.4$ Hz, 1 H) 8.07 (d, $J=2.2$ Hz, 1 H); ESI-MS m/z $[M+H]^+ = 396.1$.

[0550] EXAMPLE 14: *N*-cyclopropyl-5-(2-ethoxy-3-(1-hydroxy-2-methylpropan-2-yl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-2-fluoro-4-methylbenzamide



[0551] STEP 1: 5-(3-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-2-ethoxy-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-cyclopropyl-2-fluoro-4-methylbenzamide



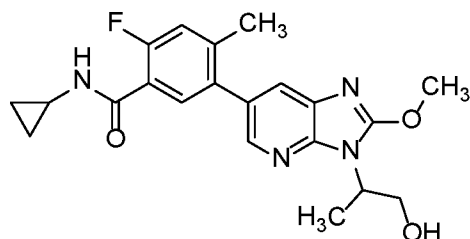
[0552] A mixture of 6-bromo-3-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-2-ethoxy-3*H*-imidazo[4,5-*b*]pyridine (1.2 g, 2.80 mmol), *N*-cyclopropyl-2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (1.07 g, 3.36 mmol), K₂CO₃ (774.19 mg, 5.60 mmol) and Pd(dppf)Cl₂ (102.47 mg, 140.04 μmol) in dioxane (10 mL) and water (2 mL) was stirred at 90°C for 4 hours under nitrogen, then diluted with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The resulting residue was purified by column chromatography, eluting with a gradient of 0-20% petroleum ether in EtOAc to give the title compound as a purple oil (400 mg, 26.4%). ESI-MS *m/z* [M+H]⁺ = 541.3.

[0553] STEP 2: *N*-cyclopropyl-5-(2-ethoxy-3-(1-hydroxy-2-methylpropan-2-yl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-2-fluoro-4-methylbenzamide

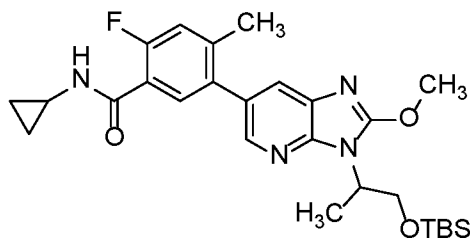
[0554] A mixture of 5-(3-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-2-ethoxy-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-cyclopropyl-2-fluoro-4-methylbenzamide (400 mg, 740 μmol) and tetrabutylammonium fluoride (1 M, 3.70 mL, 5 *eq*) was stirred at 15°C for 12 hours under nitrogen, then diluted with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The resulting residue was purified by column chromatography, eluting with a gradient of 0-30% petroleum ether in EtOAc. A resulting precipitate was triturated in petroleum ether and EtOAc (5:1), collected by filtration and purified by preparative HPLC. The product was re-crystallized from EtOH and then from EtOH and THF (10:1) to give the title compound as a white solid (50 mg, 16%). ¹H NMR (400 Hz, DMSO-*d*₆) δ ppm 0.50 - 0.56 (m, 2% H) 0.63 - 0.75 (m, 2 H) 1.43 (t, *J*=7.2 Hz, 3 H) 1.73 (s, 6 H) 2.28 (s, 3 H) 2.74 -

2.89 (m, 1 H) 3.95 (d, $J=6.4$ Hz, 2 H) 4.56 (q, $J=6.8$ Hz, 2 H) 5.17 (t, $J=6.4$ Hz, 1 H) 7.26 (d, $J=11.6$ Hz, 1 H) 7.40 (d, $J=7.2$ Hz, 1 H) 7.75 (s, 1 H) 8.04 (s, 1 H) 8.31 (d, $J=3.2$ Hz, 1 H); ESI-MS m/z $[M+H]^+ = 427.1$.

[0555] EXAMPLE 15: *N*-cyclopropyl-2-fluoro-5-(3-(1-hydroxypropan-2-yl)-2-methoxy-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



[0556] STEP 1: 5-(3-(1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-2-methoxy-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-cyclopropyl-2-fluoro-4-methylbenzamide



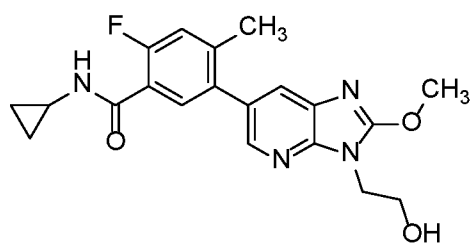
[0557] A mixture of 6-bromo-3-(1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-2-methoxy-3*H*-imidazo[4,5-*b*]pyridine (300 mg, 749 μ mol), *N*-cyclopropyl-2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (263.07 mg, 824.21 μ mol), Na_2CO_3 (158.83 mg, 1.50 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (54.83 mg, 74.93 μ mol) in dioxane (3 mL) and water (0.6 mL) was degassed and purged with N_2 (3 x). The reaction mixture was stirred at 90°C for 6 hours under N_2 atmosphere and then EtOAc and water were added. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2) eluting with a gradient of 0-50% EtOAc in petroleum ether to give the title compound as a yellow solid (360 mg, 93.7%). ESI-MS m/z $[M+H]^+ = 513.3$.

[0558] STEP 2: *N*-cyclopropyl-2-fluoro-5-(3-(1-hydroxypropan-2-yl)-2-methoxy-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

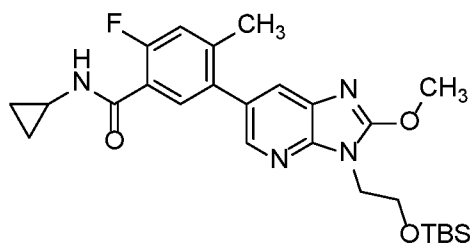
[0559] To a solution of 5-(3-(1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-2-methoxy-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-cyclopropyl-2-fluoro-4-methylbenzamide (360 mg, 702 μ mol) in tetrabutylammonium fluoride (1 M, 3.51 mL). The mixture was stirred at 20°C for 2 hours, then concentrated under reduced pressure, and diluted with EtOAc and water. The organic

layer was separated, and the aqueous phase was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by preparative HPLC to give the title compound as a white solid (125.61 mg, 44.9%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.52 - 0.56 (m, 1 H) 0.66 - 0.71 (m, 1 H) 1.49 (d, *J*=6.8 Hz, 3 H) 2.27 (s, 3 H) 2.81 - 2.85 (m, 1 H) 3.70 - 3.74 (m, 1 H) 4.01 (t, *J*=10.0 Hz, 1 H) 4.14 (s, 3 H) 4.62 - 4.67 (m, 1 H) 4.99 (s, 1 H) 7.28 (d, *J*=11.2 Hz, 1 H) 7.42 (d, *J*=7.6 Hz, 1 H) 7.78 (d, *J*=2.0 Hz, 1 H) 8.06 (d, *J*=2.0 Hz, 1 H) 8.32 (d, *J*=4.0 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 399.2.

[0560] EXAMPLE 16: *N*-cyclopropyl-2-fluoro-5-(3-(2-hydroxyethyl)-2-methoxy-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



[0561] STEP 1: 5-(3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-methoxy-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-cyclopropyl-2-fluoro-4-methylbenzamide



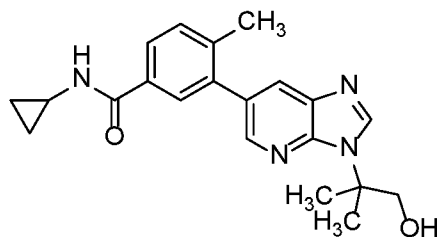
[0562] To a solution of 6-bromo-3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-methoxy-3*H*-imidazo[4,5-*b*]pyridine (200 mg, 518 μmol) in dioxane (2 mL) and water (0.7 mL) were added *N*-cyclopropyl-2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (181.75 mg, 569.42 μmol), Na₂CO₃ (164.60 mg, 1.55 mmol) and Pd(dppf)Cl₂ (37.88 mg, 51.77 μmol). The reaction mixture was stirred at 90°C for 6 hours, then poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated under reduce pressure. The crude product was purified by column chromatography (SiO₂) eluting with a gradient of 15-50% EtOAc in petroleum ether to give the title compound as a yellow oil (150 mg, 58.1%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.21 (s, 6 H) 0.51 - 0.58 (m, 3 H) 0.67 (br s, 2 H) 1.07 (s, 9 H) 1.05 - 1.10 (m, 1 H) 2.25 (s, 3 H) 2.72 - 2.83 (m, 1 H) 3.92 - 3.99 (m, 3 H) 4.15 (s, 3 H) 4.20 (t, *J*=4.8 Hz, 2 H) 7.19 - 7.31

(m, 1 H) 7.40 (d, $J=7.6$ Hz, 1 H) 7.78 (d, $J=2.0$ Hz, 1 H) 8.06 (d, $J=2.0$ Hz, 1 H) 8.28 - 8.39 (m, 1 H); ESI-MS m/z $[M+H]^+ = 499.2$.

[0563] STEP 2: *N*-cyclopropyl-2-fluoro-5-(3-(2-hydroxyethyl)-2-methoxy-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

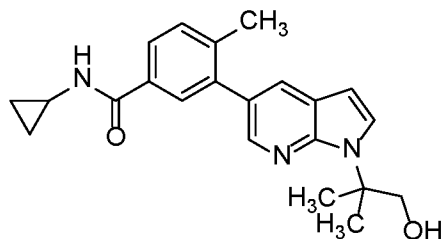
[0564] A solution of 5-(3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-methoxy-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-cyclopropyl-2-fluoro-4-methylbenzamide (150 mg, 301 μ mol) and tetrabutylammonium fluoride (1 M, 1.50 mL) was stirred at 30 °C for 2 hours, then poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 , and concentrated under reduce pressure. The crude product was purified by preparative HPLC to give the title compound (45 mg, 39%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 0.51 - 0.59 (m, 2 H) 0.64 - 0.73 (m, 2 H) 2.27 (s, 3 H) 2.78 - 2.83 (m, 1 H) 3.68 - 3.77 (m, 2 H) 4.13 (t, $J=5.6$ Hz, 2 H) 4.16 (s, 3 H) 4.96 (br t, $J=5.6$ Hz, 1 H) 7.28 (d, $J=12$ Hz, 1 H) 7.41 (d, $J=7.6$ Hz, 1 H) 7.79 (d, $J=2.0$ Hz, 1 H) 8.07 (d, $J=2.0$ Hz, 1 H) 8.34 (br d, $J=4.0$ Hz, 1 H); ESI-MS m/z $[M+H]^+ = 385.2$.

[0565] EXAMPLE 17: *N*-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



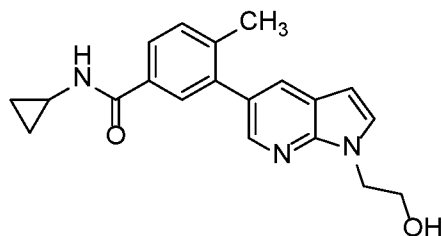
[0566] A mixture of 2-(6-bromo-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (400 mg, 1.28 mmol), *N*-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (463.12 mg, 1.54 mmol), Na_2CO_3 (407.44 mg, 3.84 mmol), $\text{PdCl}_2(\text{dtbpf})$ (83.51 mg, 128.14 μ mol) and water (1 mL) in 1,4-dioxane (10 mL) was degassed and purged with N_2 (3 x). The reaction mixture was stirred at 90°C for 15 hours under N_2 atmosphere, then diluted with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2) eluting with a gradient of 0-100% EtOAc in petroleum ether, and then further purified by preparative HPLC to give the title compound as a white solid (73.2 mg, 15.7%). ^1H NMR (400 MHz, CD_3OD) δ ppm 0.62-0.65 (m, 2 H) 0.78-0.82 (m, 2 H) 1.84 (s, 6 H) 2.32 (s, 3 H) 2.82-2.87 (m, 1 H), 4.16 (s, 2 H) 7.42 (d, $J=8.0$ Hz, 1 H) 7.72 (d, $J=2.0$ Hz, 1 H) 7.75 (d, $J=8.0$ Hz, 1 H) 7.99 (s, 1 H) 8.37 (s, 1 H) 8.47 (s, 1 H); ESI-MS m/z $[M+H]^+ = 365.1$.

[0567] EXAMPLE 18: *N*-cyclopropyl-3-(1-(1-hydroxy-2-methylpropan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide



[0568] A mixture of 2-(5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-2-methylpropan-1-ol (50 mg, 185.78 μmol), *N*-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (67.15 mg, 222.93 μmol), Na_2CO_3 (39.38 mg, 371.56 μmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (13.59 mg, 18.58 μmol), and water (0.4 mL) in 1,4-dioxane (2 mL) was degassed and purged with N_2 (3 x). The reaction mixture was stirred at 90°C for 10 hours under N_2 atmosphere, then diluted with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by preparative HPLC to give the title compound as a gray solid (23.08 mg, 34.2%). ^1H NMR (400 MHz, CD_3OD) δ ppm 0.63-0.64 (m, 2 H) 0.77-0.81 (m, 2 H) 1.75 (s, 6 H) 2.33 (s, 3 H) 2.82-2.87 (m, 1 H) 4.15 (s, 2 H), 6.50 (d, $J=3.6$ Hz, 1 H) 7.40 (d, $J=7.6$ Hz, 1 H) 7.59 (d, $J=4.0$ Hz, 1 H) 7.71-7.73 (m, 2 H) 7.91 (d, $J=2.0$ Hz, 1 H) 8.19 (d, $J=2.0$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 364.1$.

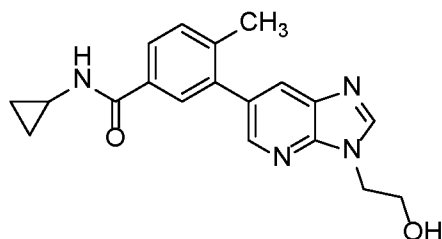
[0569] EXAMPLE 19: *N*-cyclopropyl-3-(1-(2-hydroxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide



[0570] To a solution of 2-(5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)ethan-1-ol (50 mg, 207.40 μmol) in dioxane (5 mL) and water (1 mL) were added *N*-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (68.71 mg, 228.14 μmol), K_2CO_3 (229.31 mg, 1.66 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (15.18 mg, 20.74 μmol). The reaction mixture was stirred at 90°C for 12 hours, then poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over on Na_2SO_4 , and concentrated under reduce pressure. The crude product was purified by preparative HPLC to give the title compound as a white solid (17.74 mg, 25.5%). ^1H NMR (400 MHz, CD_3OD) δ ppm 0.62 - 0.68 (m, 2 H) 0.78 -

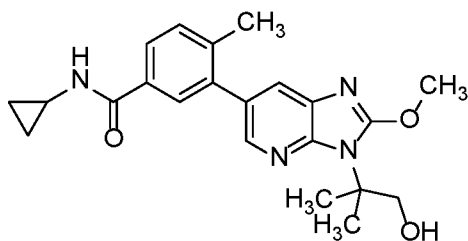
0.85 (m, 2 H) 2.34 (s, 3 H) 2.83 - 2.90 (m, 1 H) 3.97 (t, $J=5.6$ Hz, 2 H) 4.46 (t, $J=5.6$ Hz, 2 H) 4.51 - 4.68 (m, 1 H) 4.56 - 4.64 (m, 1 H) 4.61 (s, 1 H) 6.56 (d, $J=3.6$ Hz, 1 H) 7.43 (d, $J=8$ Hz, 1 H) 7.53 (d, $J=3.6$ Hz, 1 H) 7.71 - 7.79 (m, 2 H) 7.98 (d, $J=2.0$ Hz, 1 H) 8.21 (d, $J=2.0$ Hz, 1 H); ESI-MS m/z $[M+H]^+ = 336.1$.

[0571] EXAMPLE 20: *N*-cyclopropyl-3-(3-(2-hydroxyethyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

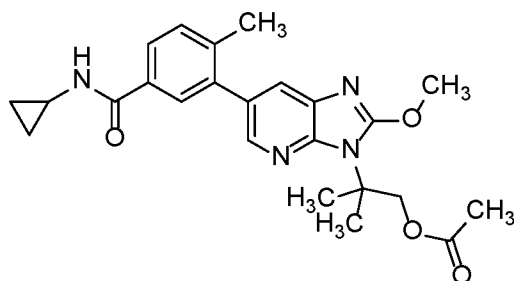


[0572] To a solution of 2-(6-bromo-3*H*-imidazo[4,5-*b*]pyridin-3-yl)ethyl acetate (175 mg, 615.96 μ mol) and *N*-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (222.62 mg, 739.15 μ mol) in dioxane (3 mL) and water (0.3 mL) were added K_2CO_3 (297.95 mg, 2.16 mmol) and $Pd(dppf)Cl_2$ (45.07 mg, 61.60 μ mol). The reaction mixture was stirred at 90°C for 5 hours and then diluted with water. The aqueous phase was extracted with EtOAc and the organic layers were combined, washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and purified by preparative HPLC to give the title compound as a white solid (65 mg, 31%). ^1H NMR (400MHz, $CDCl_3$) δ ppm 0.58 - 0.67 (m, 2 H) 0.79 - 0.91 (m, 2 H) 1.25 (s, 1 H) 2.24 (s, 3 H) 2.91 (td, $J_1=3.2$ Hz, $J_2=6.8$ Hz, 1 H) 3.31 (s, 1 H) 4.04 - 4.15 (m, 2 H) 4.42 - 4.50 (m, 2 H) 6.73 (s, 1 H) 7.33 (d, $J=8.0$ Hz, 1 H) 7.59 (s, 1 H) 7.74 - 7.67 (m, 1 H) 7.86 (s, 1 H) 8.13 (s, 1 H) 8.21 (s, 1 H); ESI-MS m/z $[M+H]^+ = 337.1$.

[0573] EXAMPLE 21: *N*-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-2-methoxy-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



[0574] STEP 1: 2-(6-(5-(cyclopropylcarbamoyl)-2-methylphenyl)-2-methoxy-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate

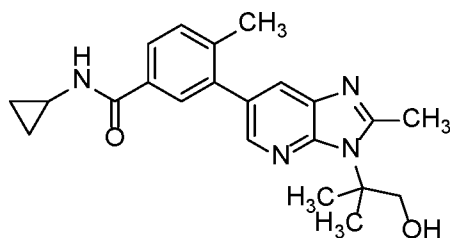


[0575] A mixture of 2-(6-bromo-2-methoxy-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (180 mg, 526.03 μmol), *N*-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (158.43 mg, 526.03 μmol), K_2CO_3 (363.50 mg, 2.63 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (38.49 mg, 52.60 μmol) in dioxane (5 mL) and water (1 mL) was degassed and purged with N_2 (3 x). The reaction mixture was stirred at 90°C for 16 hours under N_2 atmosphere and then diluted with water. The aqueous phase was extracted with EtOAc, and the organic layers were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography, eluting with EtOAc to give the title compound as a yellow oil (180 mg, 78.4%). ESI-MS m/z $[\text{M}+\text{H}]^+ = 437.3$.

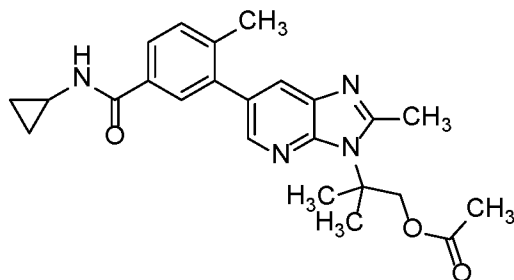
[0576] STEP 2: *N*-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-2-methoxy-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

[0577] A mixture of 2-(6-(5-(cyclopropylcarbamoyl)-2-methylphenyl)-2-methoxy-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (150 mg, 343.64 μmol) and K_2CO_3 (237.47 mg, 1.72 mmol) in MeOH (3 mL) was stirred at 70°C for 1 hour and then filtered. The filtrate was purified by preparative HPLC. The product-containing fractions were combined, concentrated and lyophilized to give the title compound as a white solid (15.67 mg, 11.6%). ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 0.56 - 0.68 (m, 2 H), 0.78 - 0.96 (m, 2 H), 1.64 (s, 6 H), 1.87 (s, 1 H), 2.32 (s, 3 H), 2.91 (dt, $J_1 = 3.2$ Hz, $J_2 = 7.2$ Hz, 1 H), 4.15 (s, 2 H), 4.27 (s, 3 H), 6.25 - 6.37 (m, 2 H), 7.36 (d, $J = 8.0$ Hz, 1 H), 7.60 (d, $J = 2.0$ Hz, 1 H), 7.64 - 7.79 (m, 1 H), 8.03 (d, $J = 2.0$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 395.2$.

[0578] EXAMPLE 22: *N*-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



[0579] STEP 1: 2-(6-(5-(cyclopropylcarbamoyl)-2-methylphenyl)-2-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate

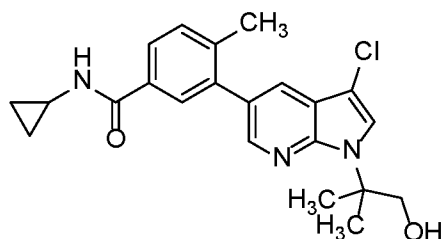


[0580] To a solution of 2-(6-bromo-2-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (70 mg, 214.60 μmol) in dioxane (4 mL), MeOH (0.1 mL) and water (1 mL) were added *N*-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (77.56 mg, 257.52 μmol), K_2CO_3 (88.98 mg, 643.80 μmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (7.85 mg, 10.73 μmol) at 20°C. The suspension was degassed under vacuum and purged with nitrogen (3 x) then heated to 90°C for 7 hours with stirring under nitrogen. The reaction mixture was subsequently diluted with water and extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure and purified by preparative HPLC to give the title compound as a light-yellow oil (55 mg, crude). ESI-MS m/z $[\text{M}+\text{H}]^+ = 421.3$.

[0581] STEP 2: *N*-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

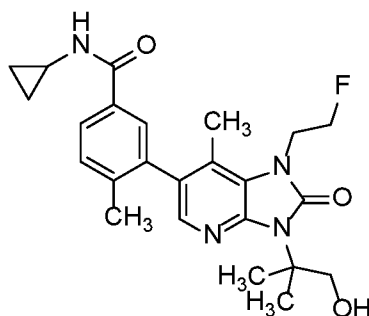
[0582] To a solution of 2-(6-(5-(cyclopropylcarbamoyl)-2-methylphenyl)-2-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (55 mg, 130.80 μmol) in MeOH (2 mL) was added K_2CO_3 (36.15 mg, 261.59 μmol) at 20°C. The mixture was heated at 50°C for 2 hours with stirring under nitrogen, then purified by preparative HPLC to give the title compound as a white solid (12 mg, 24%). ^1H NMR (400 MHz, CDCl_3) δ ppm 0.59 - 0.65 (m, 2 H) 0.84 - 0.91 (m, 2 H) 1.73 (s, 6 H) 2.32 (s, 3 H) 2.88 - 2.95 (m, 4 H) 4.25 (s, 2 H) 6.26 (s, 1 H) 7.37 (d, $J=8.00$ Hz, 1 H) 7.62 (d, $J=2.00$ Hz, 1 H) 7.69 (dd, $J_1=1.60$ Hz, $J_2=7.60$ Hz, 1 H) 7.90 (d, $J=2.00$ Hz, 1 H) 8.20 (d, $J=1.60$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 379.2$.

[0583] EXAMPLE 23: 3-(3-chloro-1-(1-hydroxy-2-methylpropan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-*N*-cyclopropyl-4-methylbenzamide

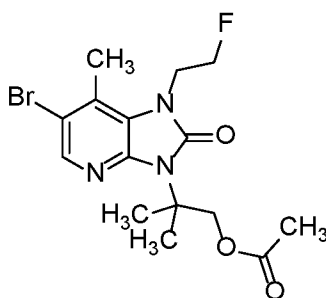


[0584] To a solution of *N*-cyclopropyl-3-(1-(1-hydroxy-2-methylpropan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide (70 mg, 0.174 mmol) in DMF (6 mL) was added NCS (30.2 mg, 0.226 mmol) at 20°C. The reaction mixture was stirred at 60°C for 10 hours, then poured into water and extracted with EtOAc. The organic layers were combined, washed with brine, and dried over Na₂SO₄. The crude product was dried under reduce pressure and purified by preparative HPLC to give a formic acid salt of the title compound as a yellow solid (23 mg, 33.2%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.55 - 0.56 (m, 2 H) 0.65 - 0.68 (m, 2 H) 1.70 (s, 6 H) 2.31 (s, 3 H) 2.83 - 2.86 (m, 1 H) 3.97 (s, 2 H) 5.05 (s, 1 H) 7.41 (d, *J*=8.0 Hz, 1 H) 7.75 - 7.78 (m, 3H) 7.87 (d, *J*=1.6 Hz, 1 H) 8.33 (d, *J*=1.6 Hz, 1 H) 8.42 (d, *J*=3.6 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 398.3.

[0585] EXAMPLE 24: *N*-cyclopropyl-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-7-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



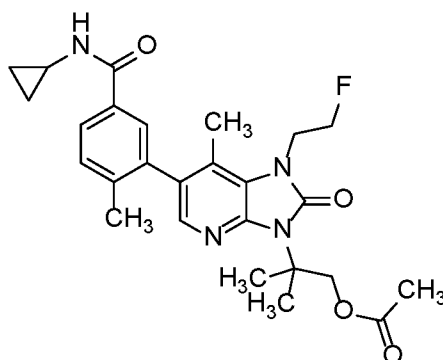
[0586] STEP 1: 2-(6-bromo-1-(2-fluoroethyl)-7-methyl-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate



[0587] To a solution of 2-(6-bromo-7-methyl-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (0.15 g, 0.438 μmol) and 1-bromo-2-fluoroethane (167 mg, 1.32 mmol) in acetonitrile (10 mL) was added K₂CO₃ (121 mg, 0.877 mmol). The

reaction mixture was stirred at 80°C for 16 hours and then concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with 10% EtOAc in petroleum ether to give the title compound as a white solid (140 mg, 80.6%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.84 (s, 6 H) 1.97 (s, 3 H) 2.62 (s, 3 H) 4.32 (t, *J*=4.8 Hz, 1 H) 4.39 (t, *J*=5.2 Hz, 1 H) 4.63 (t, *J*=5.2 Hz, 1 H) 4.69 (s, 2 H) 4.75 (t, *J*=4.8 Hz, 1 H) 8.01 (s, 1 H); ESI-MS *m/z* [M+H]⁺ = 390.3.

[0588] STEP 2: 2-(6-(5-(cyclopropylcarbamoyl)-2-methylphenyl)-1-(2-fluoroethyl)-7-methyl-2-oxo-1*H*-imidazo[4,5-*b*]pyridin-3(2*H*)-yl)-2-methylpropyl acetate



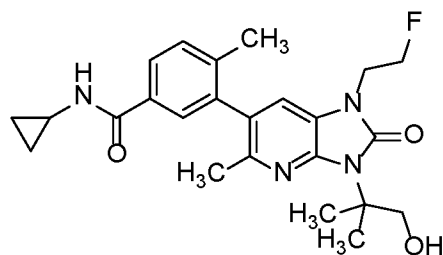
[0589] A solution of 2-(6-bromo-1-(2-fluoroethyl)-7-methyl-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (140 mg, 0.361 μmol), *N*-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (130 mg, 0.433 μmol), aq K₂CO₃ (2 M, 0.541 mL), and PdCl₂(dtbpf) (23.5 mg, 0.036 mmol) in dioxane (4 mL) was degassed and purged with N₂ (3 x). The reaction mixture was stirred at 100°C for 3 hours, then diluted with water and extracted with EtOAc. The organic phase was washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 10-50% EtOAc in petroleum ether to give the title compound as a yellow solid (110 mg, 58.1%). ESI-MS *m/z* [M+H]⁺ = 483.4.

[0590] STEP 3: *N*-cyclopropyl-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-7-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

[0591] To a solution of 2-(6-(5-(cyclopropylcarbamoyl)-2-methylphenyl)-1-(2-fluoroethyl)-7-methyl-2-oxo-1*H*-imidazo[4,5-*b*]pyridin-3(2*H*)-yl)-2-methylpropyl acetate (110 mg, 0.228 mmol) in MeOH (10 mL) was added K₂CO₃ (158 mg, 1.14 mmol). The reaction mixture was stirred at 60°C for 2 hours, then diluted with water and extracted with EtOAc. The organic phase was washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by column

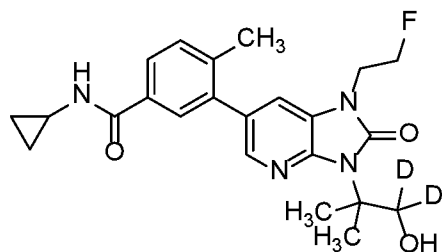
chromatography (SiO₂) eluting with a gradient of 10-50% EtOAc in petroleum ether and was further purified with preparative HPLC to give the title compound as a white solid (76.5 mg,). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.61 - 0.63 (m, 2 H) 0.85 - 0.90 (m, 2 H) 1.73 (s, 6 H) 2.21 (s, 3 H) 2.24 (s, 3 H) 2.88 - 2.92 (m, 1 H) 4.03 (s, 2 H) 4.38 (t, *J*=4.8 Hz, 1 H) 4.44 (t, *J*=4.8 Hz, 1 H) 4.67 (t, *J*=4.8 Hz, 1 H) 4.78 (d, *J*=4.8 Hz, 1 H) 5.73 (s, 1 H) 6.19 (s, 1 H) 7.36 (d, *J*=8.0 Hz, 1 H) 7.48 (d, *J*=1.6 Hz, 1 H) 7.72 (dd, *J*₁=1.6 Hz, *J*₂=2.0 Hz, 1 H) 7.77 (s, 1 H); ESI-MS *m/z* [M+H]⁺ = 441.3.

[0592] EXAMPLE 25: *N*-cyclopropyl-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-5-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

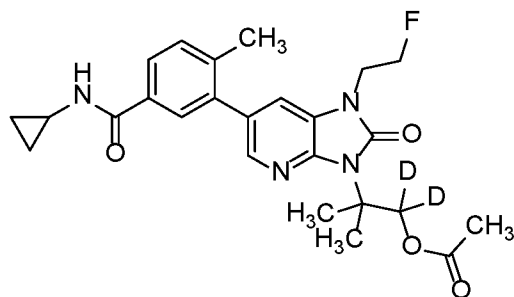


[0593] The title compound was prepared like EXAMPLE 24, starting with 2-(6-bromo-5-methyl-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (0.4 g, 1.17 mmol, 1 eq) in place of 2-(6-bromo-7-methyl-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate and proceeding through intermediates 2-(6-bromo-1-(2-fluoroethyl)-5-methyl-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate and 2-(6-(5-(cyclopropylcarbamoyl)-2-methylphenyl)-1-(2-fluoroethyl)-5-methyl-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate. The title compound was obtained as a white solid (8 mg, 5.5% STEP 3). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.60 - 0.64 (m, 2 H) 0.86 - 0.90 (m, 2 H) 1.73 (t, *J*=3.2 Hz, 6 H) 2.14 (s, 3 H) 2.23 (s, 3 H) 2.89 - 2.93 (m, 1 H) 4.03 - 4.06 (m, 1 H) 4.08 - 4.11 (m, 1 H) 4.13 - 4.18 (m, 1 H) 4.65 (t, *J*=4.4 Hz, 1 H) 4.76 (t, *J*=4.8 Hz, 1 H) 5.99 (t, *J*=6.8 Hz, 1 H) 6.19 (s, 1 H) 7.05 (d, *J*=0.8 Hz, 1 H) 7.34 (d, *J*=7.6 Hz, 1 H) 7.51 (d, *J*=1.6 Hz, 1 H) 7.65 (dd, *J*₁=2.0 Hz, *J*₂=8.0 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 441.3.

[0594] EXAMPLE 26: *N*-cyclopropyl-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-1,1-*d*₂)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



[0595] STEP 1: 2-(6-(5-(cyclopropylcarbamoyl)-2-methylphenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1-*d*₂ acetate



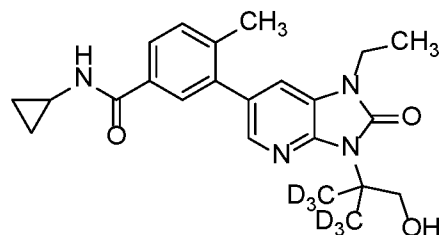
[0596] To a mixture of 2-(6-bromo-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1-*d*₂ acetate (100 mg, 265.80 μ mol), *N*-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (88.06 mg, 292.38 μ mol) and K₂CO₃ (73.47 mg, 531.61 μ mol) in dioxane (2 mL) and water (0.5 mL) was added Pd(dppf)Cl₂ (19.45 mg, 26.58 μ mol). The reaction mixture was stirred at 90°C for 3 hours under nitrogen, then diluted with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to give the title compound as a brown oil (150 mg, crude). ESI-MS *m/z* [M+H]⁺ = 471.4.

[0597] STEP 2: *N*-cyclopropyl-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-1,1-*d*₂)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

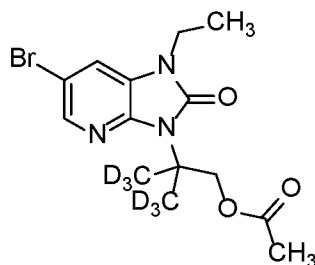
[0598] A mixture of 2-(6-(5-(cyclopropylcarbamoyl)-2-methylphenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1-*d*₂ acetate (500 mg, 1.06 mmol), LiOH (127.24 mg, 5.31 mmol) and H₂O (250 mg, 13.88 mmol) in THF (5 mL) and DMF (0.5 mL) was stirred at 50°C for 12 hours, then diluted with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 0-100% EtOAc in petroleum ether, and then by preparative HPLC to give the title compound as a white solid (81.5 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.51 - 0.59 (m, 2 H) 0.63 - 0.73 (m, 2 H) 1.72 (s, 6 H) 2.26 - 2.34 (m, 3 H) 2.81 - 2.87 (m, 1 H) 4.12 - 4.26 (m, 2 H) 4.57 - 4.78 (m, 2 H) 4.90 - 4.99 (m, 1

H) 4.90 - 4.99 (m, 1 H) 4.95 (s, 1 H) 7.40 (d, $J=8.0$ Hz, 1 H) 7.59 (d, $J=1.6$ Hz, 1 H) 7.70 - 7.78 (m, 2 H) 7.97 (d, $J=2.0$ Hz, 1 H) 8.37 (d, $J=4.0$ Hz, 1 H); ESI-MS m/z $[M+H]^+ = 429.3$.

[0599] EXAMPLE 27: *N*-cyclopropyl-3-(1-ethyl-3-(2-(hydroxymethyl)propan-2-yl)-1,1,1,3,3,3- d_6)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

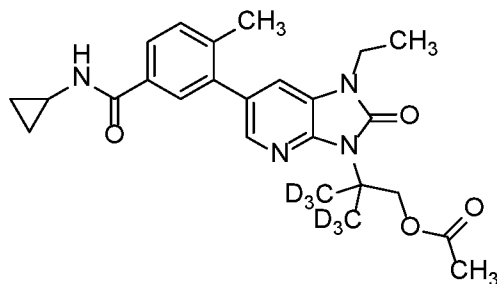


[0600] STEP 1: 2-(6-bromo-1-ethyl-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-(methyl- d_3)propyl-3,3,3- d_3 acetate



[0601] A solution of 2-(6-bromo-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-(methyl- d_3)propyl-3,3,3- d_3 acetate (200 mg, 598.45 μ mol), iodoethane (140.01 mg, 897.67 μ mol) and K_2CO_3 (165.42 mg, 1.20 mmol) in DMF (2 mL) was stirred at 15°C for 3 hours under N_2 . Ethyl acetate and water were added. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2) eluting with a gradient of 0-30% EtOAc in petroleum ether to give the title compound as a brown oil (210 mg, 96.9%). ESI-MS m/z $[M+H]^+ = 364.2$.

[0602] STEP 2: 2-(6-(5-(cyclopropylcarbamoyl)-2-methylphenyl)-1-ethyl-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-(methyl- d_3)propyl-3,3,3- d_3 acetate

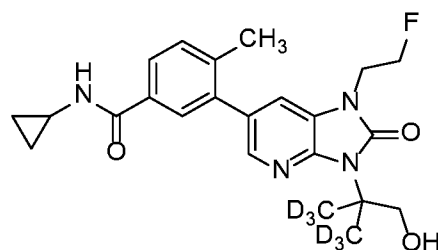


[0603] To a mixture of 2-(6-bromo-1-ethyl-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-(methyl-*d*₃)propyl-3,3,3-*d*₃ acetate (210 mg, 579.71 μ mol), *N*-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (192.06 mg, 637.68 μ mol) and K₂CO₃ (160.24 mg, 1.16 mmol) in dioxane (4 mL) and water (1 mL) was added Pd(dppf)Cl₂ (42.42 mg, 57.97 μ mol). The reaction mixture was stirred at 90°C for 2 hours under N₂. Ethyl acetate and water were added. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂) eluting with a gradient of 0-50% EtOAc in petroleum ether to give the title compound as a yellow solid (210 mg, 79.3%). ESI-MS *m/z* [M+H]⁺ = 457.4.

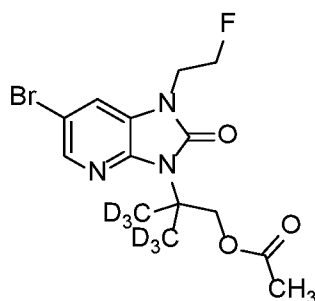
[0604] STEP 3: *N*-cyclopropyl-3-(1-ethyl-3-(2-(hydroxymethyl)propan-2-yl-1,1,1,3,3,3-*d*₆)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

[0605] A mixture of 2-(6-(5-(cyclopropylcarbamoyl)-2-methylphenyl)-1-ethyl-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-(methyl-*d*₃)propyl-3,3,3-*d*₃ acetate (210 mg, 459.96 μ mol), and K₂CO₃ (127.14 mg, 919.91 μ mol) in MeOH (5 mL) was degassed and purged with N₂ (3 x). The reaction mixture was stirred at 50°C for 2 hours under N₂ atmosphere. Ethyl acetate and water were added. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to give the title compound as a white solid (93.05 mg, 48.8%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.54 - 0.58 (m, 2 H) 0.67 - 0.71 (m, 2 H) 1.06 (t, *J*=7.0 Hz, 1 H) 1.21 (t, *J*=7.0 Hz, 3 H) 2.33 (s, 3 H) 2.82 - 2.88 (m, 1 H) 3.87 - 3.93 (m, 4 H) 5.00 (t, *J*=6.4 Hz, 1 H) 7.42 (d, *J*=8.0 Hz, 1 H) 7.61 (s, 3 H) 7.76 (t, *J*=8.8 Hz, 2 H) 7.96 (s, 1 H) 8.39 (d, *J*=4.4 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 415.2.

[0606] EXAMPLE 28: *N*-cyclopropyl-3-(1-(2-fluoroethyl)-3-(2-(hydroxymethyl)propan-2-yl-1,1,1,3,3,3-*d*₆)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

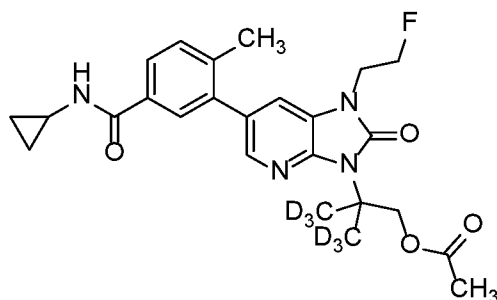


[0607] STEP 1: 2-(6-bromo-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-(methyl-*d*₃)propyl-3,3,3-*d*₃ acetate



[0608] A solution of 2-(6-bromo-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-(methyl-*d*₃)propyl-3,3,3-*d*₃ acetate (300 mg, 897.67 μ mol), K₂CO₃ (248.13 mg, 1.80 mmol) and 1-bromo-2-fluoroethane (170.95 mg, 1.35 mmol) in DMF (2 mL) was stirred at 15°C for 3 hours under N₂. Ethyl acetate and water were added. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 3-20% EtOAc in petroleum ether to give the title compound as a brown oil (320 mg, 93.8%). ESI-MS *m/z* [M+H]⁺ = 380.2.

[0609] STEP 2: 2-(6-(5-(cyclopropylcarbamoyl)-2-methylphenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-(methyl-*d*₃)propyl-3,3,3-*d*₃ acetate

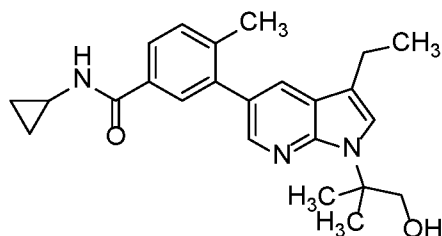


[0610] To a mixture of 2-(6-bromo-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-(methyl-*d*₃)propyl-3,3,3-*d*₃ acetate (320 mg, 841.57 μ mol), *N*-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (278.82 mg, 925.73 μ mol) and K₂CO₃ (232.62 mg, 1.68 mmol) in dioxane (4 mL) and water (0.8 mL) was added Pd(dppf)Cl₂ (61.58 mg, 84.16 μ mol). The reaction mixture was stirred at 90°C for 2 hours under N₂. Ethyl acetate and water were added. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 5-30% EtOAc in petroleum ether to give the title compound as a yellow solid (300 mg, 75.1%). ESI-MS *m/z* [M+H]⁺ = 475.4.

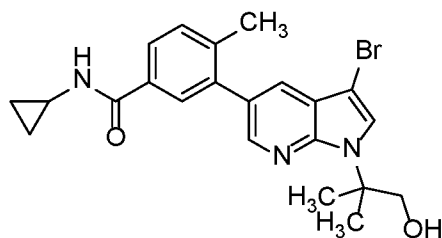
[0611] STEP 3: *N*-cyclopropyl-3-(1-(2-fluoroethyl)-3-(2-(hydroxymethyl)propan-2-yl)-1,1,1,3,3,3-*d*₆)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

[0612] A solution of 2-(6-(5-(cyclopropylcarbamoyl)-2-methylphenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-(methyl-*d*₃)propyl-3,3,3-*d*₃ acetate (300 mg, 632.17 μmol) and LiOH (75.70 mg, 3.16 mmol) in THF (5 mL), DMF (0.5 mL) and water (0.25 mL) was stirred at 50°C for 12 hours. The mixture was then diluted with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 0-100% EtOAc in petroleum ether, and then by preparative HPLC to give the title compound as a white solid (67.2 mg, 24.6%).
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.52 - 0.58 (m, 2 H) 0.65 - 0.71 (m, 2 H) 2.31 (s, 3 H) 2.82 - 2.87 (m, 1 H) 3.92 (d, *J*=6.4 Hz, 2 H) 4.17 (d, *J*=4.8 Hz, 1 H) 4.23 (t, *J*=4.8 Hz, 1 H) 4.62 (t, *J*=4.8 Hz, 1 H) 4.74 (t, *J*=4.8 Hz, 1 H) 4.98 (t, *J*=6.4 Hz, 1 H) 7.40 (d, *J*=8.0 Hz, 1 H) 7.59 (s, 1 H) 7.72 (s, 1 H) 7.76 (d, *J*=8.0 Hz, 1 H) 7.97 (d, *J*=2.0 Hz, 1 H) 8.38 (d, *J*=4.0 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 433.3.

[0613] EXAMPLE 29: *N*-cyclopropyl-3-(3-ethyl-1-(1-hydroxy-2-methylpropan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide



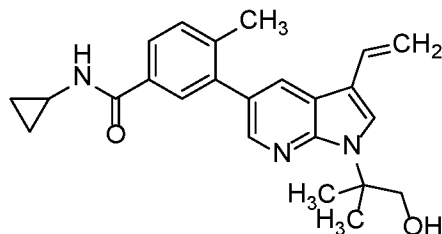
[0614] STEP 1: 3-(3-bromo-1-(1-hydroxy-2-methylpropan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-*N*-cyclopropyl-4-methylbenzamide



[0615] To a solution of *N*-cyclopropyl-3-(1-(1-hydroxy-2-methylpropan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide (500 mg, 1.24 mmol) in DCM (15 mL) was added NBS (232 mg, 1.31 mmol) at 0°C. The reaction mixture was stirred at 0°C for 0.5 hours and then concentrated. The crude product was purified by column chromatography (SiO₂) eluting with a gradient of 10-50% EtOAc in petroleum ether to give the title

compound as a yellow solid (0.48 g, 85%). ^1H NMR (400 MHz, CDCl_3) δ ppm 0.62 - 0.65 (m, 2 H) 0.85 - 0.89 (m, 2 H) 1.69 (s, 6 H) 2.33 (s, 3 H) 2.89 - 2.93 (m, 1 H) 4.05 (s, 2 H) 6.29 (s, 1 H) 6.57 (s, 1 H) 7.37 (d, $J=8.0$ Hz, 1 H) 7.47 (s, 1 H) 7.63 (d, $J=2.0$ Hz, 1 H) 7.70 (dd, $J_1=1.6$ Hz, $J_2=8.0$ Hz, 1 H) 7.83 (d, $J=2.0$ Hz, 1 H) 8.23 (d, $J=2.4$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 444.0$.

[0616] STEP 2: *N*-cyclopropyl-3-(1-(1-hydroxy-2-methylpropan-2-yl)-3-vinyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide



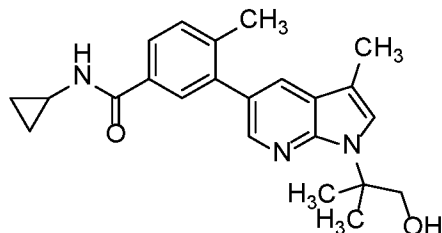
[0617] To a solution of 3-(3-bromo-1-(1-hydroxy-2-methylpropan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-*N*-cyclopropyl-4-methylbenzamide (300 mg, 0.657 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (131 mg, 0.855 mmol) and K_2CO_3 (181 mg, 1.32 mmol) in dioxane (5 mL) and water (0.5 mL) was added $\text{PdCl}_2(\text{dtbpf})$ (21.4 mg, 0.033 mmol) at 15°C . The reaction mixture was stirred at 100°C for 5 hours, then poured into water and extracted with EtOAc. The organic layers were combined, washed with brine, and dried over Na_2SO_4 . The crude product was dried under reduce pressure and purified by column chromatography (SiO_2) eluting with a gradient of 10-50% EtOAc in petroleum ether to give the title compound as a yellow solid (160 mg, 62.6%). ^1H NMR (400 MHz, CDCl_3) δ ppm 0.61 - 0.63 (m, 2 H) 0.84 - 0.90 (m, 2 H) 1.69 (s, 6 H) 2.34 (s, 3 H) 2.90 - 2.93 (m, 1 H) 4.04 (s, 2 H) 5.20 (d, $J=11.6$ Hz, 1 H) 5.64 (d, $J=18.0$ Hz, 1 H) 6.28 (s, 1 H) 6.77 - 6.82 (m, 1 H) 6.85 (s, 1 H) 7.37 (d, $J=8.0$ Hz, 1 H) 7.48 (s, 1 H) 7.63 (d, $J=1.6$ Hz, 1 H) 7.70 (dd, $J=1.6$ Hz, $J=5.6$ Hz, 1 H) 8.12 (d, $J=2.0$ Hz, 1 H) 8.20 (d, $J=2.0$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 390.4$.

[0618] STEP 3: *N*-cyclopropyl-3-(3-ethyl-1-(1-hydroxy-2-methylpropan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide

[0619] To a solution of *N*-cyclopropyl-3-(1-(1-hydroxy-2-methylpropan-2-yl)-3-vinyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide (30 mg, 0.734 mmol) in MeOH (2 mL) was added Pd/C (5 mg, 10% purity) under N_2 atmosphere. The mixture was stirred at 20°C for 2 hours under H_2 atmosphere (15 psi) and then filtered. The filtrate was concentrated and purified by preparative HPLC to give the title compound as a white solid (10 mg, 3.4%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 0.54 - 0.57 (m, 2 H) 0.66 - 0.68 (m, 2 H) 1.26 (t, $J=7.6$ Hz, 3 H) 1.68 (s, 6 H) 2.31 (s, 3 H) 2.66 - 2.75 (m, 2 H) 2.84 - 2.86 (m, 1 H) 3.97 (s, 2 H)

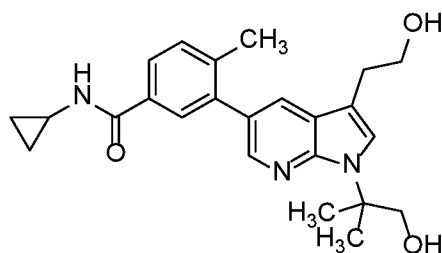
5.08 (s, 1 H) 7.39 (d, $J=9.2$ Hz, 2 H) 7.75 (d, $J=7.2$ Hz, 2 H) 7.90 (d, $J=2.0$ Hz, 1 H) 8.19 (d, $J=2.0$ Hz, 1 H) 8.38 (d, $J=4.0$ Hz, 1 H); ESI-MS m/z $[M+H]^+ = 392.1$.

[0620] EXAMPLE 30: *N*-cyclopropyl-3-(1-(1-hydroxy-2-methylpropan-2-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide

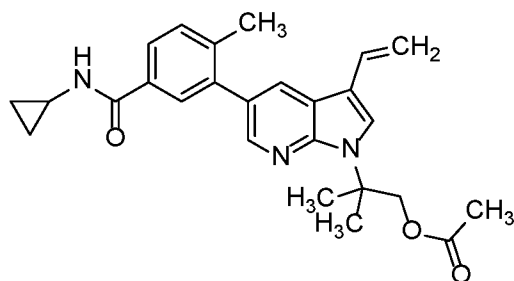


[0621] To a solution of 3-(3-bromo-1-(1-hydroxy-2-methylpropan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-*N*-cyclopropyl-4-methylbenzamide (80 mg, 175 μ mol), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (52.8 mg, 0.210 mmol) and XPhos Pd G3 (7.42 mg, 9 μ mol) in THF (1 mL) and water (0.1 mL) was added K_3PO_4 (74.4 mg, 0.350 mmol) at 15°C. The mixture was stirred at 70°C for 15 hours, then diluted with water, and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 , and concentrated under reduce pressure. The crude product was purified by preparative TLC (SiO_2) eluting with 50% EtOAc in petroleum ether to give the title compound as a white solid (17.0 mg, 26%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.61 - 0.64 (m, 2 H) 0.83 - 0.86 (m, 2 H) 1.65 (s, 6 H) 2.31 (s, 3 H) 2.33 (s, 3 H) 2.89 - 2.93 (m, 1 H) 4.03 (s, 2 H) 6.37 (s, 1 H) 7.20 (s, 1 H) 7.34 (d, $J=8.0$ Hz, 1 H) 7.64 (d, $J=2.0$ Hz, 1 H) 7.67 (dd, $J_1=2.0$ Hz, $J_2=8.0$ Hz, 1 H) 7.81 (d, $J=2.0$ Hz, 1 H) 8.14 (d, $J=2.0$ Hz, 1 H); ESI-MS m/z $[M+H]^+ = 378.0$.

[0622] EXAMPLE 31: *N*-cyclopropyl-3-(1-(1-hydroxy-2-methylpropan-2-yl)-3-(2-hydroxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide



[0623] STEP 1: 2-(5-(5-(cyclopropylcarbamoyl)-2-methylphenyl)-3-vinyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-2-methylpropyl acetate



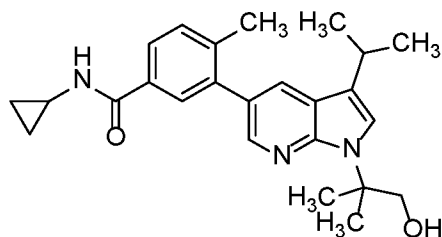
[0624] A mixture of *N*-cyclopropyl-3-(1-(1-hydroxy-2-methylpropan-2-yl)-3-vinyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide (100 mg, 0.244 mmol) and acetic anhydride (0.046 mL, 0.489 mmol) in pyridine (1 mL) was stirred at 70°C for 2 hours. The mixture was then concentrated, diluted with water, and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, and concentrated under reduce pressure to give the title compound as a yellow solid (110 mg, 96%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.61 - 0.63 (m, 2 H) 0.86 - 0.89 (m, 2 H) 1.85 (s, 6 H) 1.99 (s, 3 H) 2.35 (s, 3 H) 2.90 - 2.93 (m, 1 H) 4.82 (s, 2 H) 5.17 (d, *J*=11.6 Hz, 1 H) 5.64 (d, *J*=17.6 Hz, 1 H) 6.25 (s, 1 H) 6.78 - 6.83 (m, 1 H) 7.36 - 7.37 (m, 1 H) 7.38 (d, *J*=8.0 Hz, 1 H) 7.41 (s, 1 H) 7.61 (d, *J*=2.0 Hz, 1 H) 7.72 (dd, *J*₁=2.0 Hz, *J*₂=8.0 Hz, 1 H) 8.06 (d, *J*=2.0 Hz, 1 H) 8.23 (d, *J*=2.0 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 432.1.

[0625] STEP 2: *N*-cyclopropyl-3-(1-(1-hydroxy-2-methylpropan-2-yl)-3-(2-hydroxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide

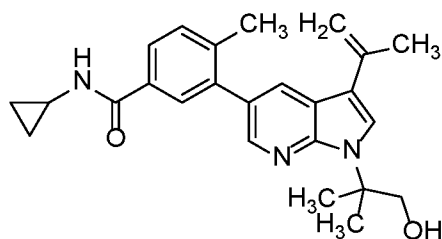
[0626] To a solution of 2-(5-(5-(cyclopropylcarbamoyl)-2-methylphenyl)-3-vinyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-2-methylpropyl acetate (90 mg, 0.196 mmol) in THF (2 mL) was added 9-borabicyclo[3.3.1]nonane (0.5 M, 1.18 mL) at 0°C. The mixture was stirred at 20°C for 20 hours, then aq NaOH (3 M, 0.45 mL) was added at 0°C, followed by H₂O₂ (0.36 mL, 6.24 mmol, 50% purity) at 0°C. The mixture was stirred at 20°C for 12 hours, then diluted with water, and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, and concentrated under reduce pressure. The resulting residue was purified by preparative TLC (SiO₂) eluting with 5% MeOH in EtOAc. The crude product was dissolved in MeOH (5 mL). The mixture was adjusted to pH to 2 with 1N HCl, then stirred at 30°C for 3 hours, and concentrated. The resulting residue was diluted with water, adjusted to pH 9 with K₂CO₃ (solid), and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, and concentrated under reduce pressure. The crude product was purified by preparative TLC (SiO₂) eluting with 10% MeOH in DCM to give the title compound as a white solid (15.74 mg, 19.7%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.61 - 0.63 (m, 2 H) 0.83 - 0.86 (m, 2 H) 1.68 (s, 6 H) 2.32 (s, 3 H) 2.90 - 2.91 (m, 1 H) 2.99 (t,

$J=6.0$ Hz, 2 H) 3.90 (s, 2 H) 4.03 (s, 2 H) 6.38 (s, 1 H) 7.06 (s, 1 H) 7.30 (d, $J=1.6$ Hz, 1 H) 7.31 - 7.35 (m, 2 H) 7.65 (dd, $J_1=2.0$ Hz, $J_2=6.0$ Hz, 1 H) 7.87 (d, $J=2.0$ Hz, 1 H) 8.16 (d, $J=2.0$ Hz, 1 H); ESI-MS m/z $[M+H]^+ = 408.3$.

[0627] EXAMPLE 32: *N*-cyclopropyl-3-(1-(1-hydroxy-2-methylpropan-2-yl)-3-isopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide



[0628] STEP 1: *N*-cyclopropyl-3-(1-(1-hydroxy-2-methylpropan-2-yl)-3-(prop-1-en-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide

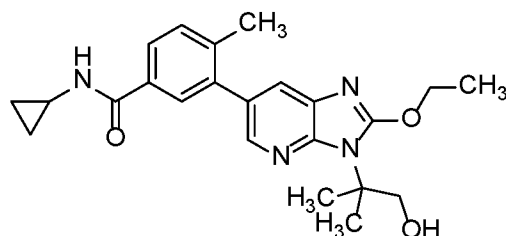


[0629] A mixture of 3-(3-bromo-1-(1-hydroxy-2-methylpropan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-*N*-cyclopropyl-4-methylbenzamide (50 mg, 0.104 mmol), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (22.7 mg, 0.135 mmol), $PdCl_2(dtbpf)$ (3.39 mg, 0.005 mmol), K_2CO_3 (2 M, 0.104 mL) in dioxane (3 mL) at $15^\circ C$ was degassed and purged with N_2 (3 x). The reaction mixture was stirred at $100^\circ C$ for 3 hours under N_2 atmosphere and then partitioned between water and EtOAc. The organic layer was separated, washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by chromatography (SiO_2) eluting with a gradient of 10-50% EtOAc in petroleum ether to give the title compound as a colorless solid (30 mg, crude). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.62 - 0.63 (m, 2 H) 0.88 (d, $J=5.6$ Hz, 2 H) 1.25 (s, 6 H) 2.21 (s, 3 H) 2.34 (s, 3 H) 2.90 - 2.94 (m, 1 H) 4.06 (s, 2 H) 5.09 (d, $J=1.6$ Hz, 1 H) 5.40 (s, 1 H) 6.22 (s, 1 H) 7.38 (d, $J=8.0$ Hz, 1 H) 7.45 (s, 1 H) 7.63 (d, $J=2.0$ Hz, 1 H) 7.70 (dd, $J_1=1.6$ Hz, $J_2=7.6$ Hz, 1 H) 8.17 (d, $J=2.0$ Hz, 1 H) 8.20 (d, $J=2.4$ Hz, 1 H); ESI-MS m/z $[M+H]^+ = 404.4$.

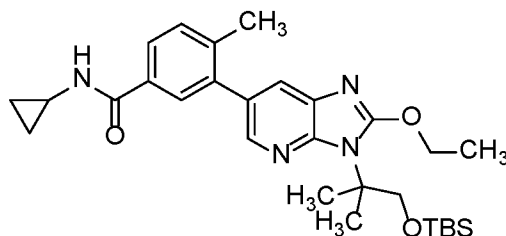
[0630] STEP 2: *N*-cyclopropyl-3-(1-(1-hydroxy-2-methylpropan-2-yl)-3-isopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide

[0631] To a solution of *N*-cyclopropyl-3-(1-(1-hydroxy-2-methylpropan-2-yl)-3-(prop-1-en-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide (25 mg, 0.047 mmol) in MeOH (5 mL) was added Pd/C (50 mg, 10% purity) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The reaction mixture was stirred under H₂ (15 psi) at 15°C for 1 hour and filtered. The filtrate was concentrated and purified by preparative HPLC to give the title compound as a white solid (8.59 mg, 45.1%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.62 - 0.63 (m, 2 H) 0.85 - 0.89 (m, 2 H) 1.36 (d, *J*=6.8 Hz, 6 H) 1.67 (s, 6 H) 2.34 (s, 3 H) 2.90 - 2.95 (m, 1 H) 3.13 - 3.20 (m, 1 H) 4.04 (s, 2 H) 6.24 (s, 1 H) 7.17 (s, 1 H) 7.37 (d, *J*=8.0 Hz, 1 H) 7.63 (d, *J*=2.0 Hz, 1 H) 7.68 (dd, *J*₁=1.6 Hz, *J*₂=2.0 Hz, 1 H) 7.89 (d, *J*=2.0 Hz, 1 H) 8.16 (d, *J*=2.0 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 406.2.

[0632] EXAMPLE 33: *N*-cyclopropyl-3-(2-ethoxy-3-(1-hydroxy-2-methylpropan-2-yl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



[0633] STEP 1: 3-(3-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-2-ethoxy-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-cyclopropyl-4-methylbenzamide



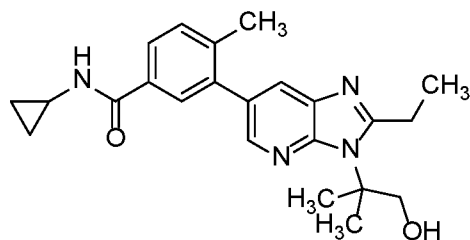
[0634] A mixture of 6-bromo-3-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-2-ethoxy-3*H*-imidazo[4,5-*b*]pyridine (190 mg, 443.47 μmol), *N*-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (140.25 mg, 465.64 μmol), Pd(dppf)Cl₂ (32.45 mg, 44.35 μmol), and K₂CO₃ (153.23 mg, 1.11 mmol) in dioxane (6 mL) and water (2 mL) was degassed and purged with N₂ (3 x). The reaction mixture was stirred at 90°C for 4 hours under N₂ atmosphere, then diluted with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 0-20% EtOAc in petroleum ether to give the title compound as a yellow solid (196 mg, 84.5%). ¹H NMR (400 MHz, CDCl₃) δ ppm

0.19 (s, 6 H) 0.59 - 0.64 (m, 2 H) 0.73 (s, 9 H) 0.84 - 0.90 (m, 2 H) 1.58 (s, 3 H) 1.88 (s, 6 H) 2.25 - 2.35 (m, 1 H) 2.31 (s, 2 H) 2.86 - 2.97 (m, 1 H) 4.08 - 4.13 (m, 2 H) 4.55 - 4.65 (dd, $J_1=2.0$ Hz, $J_2=7.2$ Hz, 2 H) 4.57 - 4.53 (m, 1 H) 6.21 (s, 1 H) 7.35 (d, $J=8.0$ Hz, 1 H) 7.59 (d, $J=2.0$ Hz, 1 H) 7.62 (d, $J=2.0$ Hz, 1 H) 7.66 - 7.69 (dd, $J_1=2.0$ Hz, $J_2=8.0$ Hz, 1 H) 8.04 (d, $J=2.0$ Hz, 1 H); ESI-MS m/z $[M+H]^+ = 523.3$.

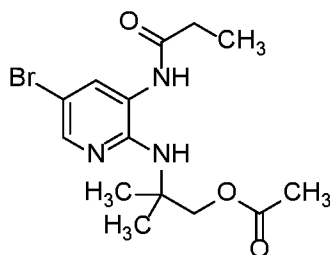
[0635] STEP 2: *N*-cyclopropyl-3-(2-ethoxy-3-(1-hydroxy-2-methylpropan-2-yl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

[0636] Intermediate 3-(3-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-2-ethoxy-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-cyclopropyl-4-methylbenzamide (50 mg, 95.65 μ mol) was added to TBAF (1 M, 1.91 mL in THF). The reaction mixture was stirred at 15°C for 2 hours and then at room temperature for 30 minutes. The reaction mixture was quenched with saturated bicarbonate solution, diluted with saturated aq NH_4Cl and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by preparative HPLC to give the title compound as a white solid (24 mg, 61%). ^1H NMR (400 MHz, $DMSO-d_6$) 0.52 - 0.59 (m, 2 H) 0.67 - 0.70 (m, 2 H) 1.43 (m, 3 H) 1.74 (s, 6 H) 2.31 (s, 3 H) 3.96 (s, 2 H) 4.57 (d, $J=8.0$ Hz, 2 H) 5.19 (s, 1 H) 7.40 (d, $J=8.0$ Hz, 1 H) 7.79 - 7.72 (m, 3 H) 8.08 (d, $J=1.6$ Hz, 1 H) 8.40 (d, $J=3.6$ Hz, 1 H); ESI-MS m/z $[M+H]^+ = 409.2$.

[0637] EXAMPLE 34: *N*-cyclopropyl-3-(2-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



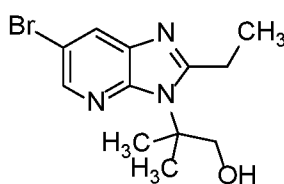
[0638] STEP 1: 2-((5-bromo-3-propionamidopyridin-2-yl)amino)-2-methylpropyl acetate



[0639] To a solution of 2-((3-amino-5-bromopyridin-2-yl)amino)-2-methylpropyl acetate (0.5 g, 1.65 mmol) and DIPEA (0.576 mL, 3.31 mmol) in THF (1 mL) was added propionyl

chloride (0.168 mg, 1.82 mmol) at 0°C. The reaction mixture was warmed to 15°C and stirred for 3 hours. The mixture was then diluted with water and extracted with EtOAc. The organic layers were combined, concentrated under reduce pressure, and purified by column chromatography (SiO₂) eluting with a gradient of 2-30% EtOAc in petroleum ether to give the title compound as a green solid (300 mg, 50.6%). ESI-MS m/z $[M+H]^+ = 358.2$.

[0640] STEP 2: 2-(6-bromo-2-ethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropan-1-ol

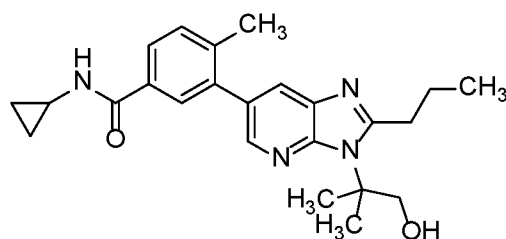


[0641] To a solution of 2-((5-bromo-3-propionamidopyridin-2-yl)amino)-2-methylpropyl acetate (200 mg, 0.558 mmol) in propionic acid (2 mL) was added tetramethoxymethane (3.80 mg, 0.028 mmol). The reaction mixture was heated to 120°C and stirred for 12 hours. The mixture was then diluted with water and extracted with EtOAc. The aqueous layer was acidified with aq NaHCO₃ (10 mL) to pH=7.0 and extracted with EtOAc. The organic layers were combined and concentrated under reduce pressure to give the title compound as a yellow solid (138 mg, 82.9%).

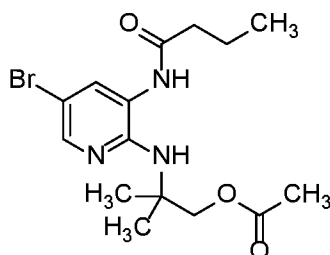
[0642] STEP 3: *N*-cyclopropyl-3-(2-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

[0643] A mixture of 2-(6-bromo-2-ethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropan-1-ol (138 mg, 0.463 mmol), *N*-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (153 mg, 0.509 mmol), Pd(dppf)Cl₂ (16.9 mg, 0.023 mmol) and K₂CO₃ (192 mg, 1.39 mmol) in dioxane (2 mL) and water (0.5 mL) was degassed and purged with N₂ (3 x). The reaction mixture was stirred at 90°C for 12 hours under N₂ atmosphere, then concentrated under reduce pressure and purified by column chromatography (SiO₂) eluting with a gradient of 2-100% EtOAc in petroleum ether. The crude product was further purified by preparative HPLC to give a formic acid salt of the title compound as a yellow solid (49.62 mg, 24.4%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.62 - 0.65 (m, 2 H) 0.84 - 0.89 (m, 2 H) 1.18 (t, $J=7.6$ Hz 3 H) 1.63 (s, 6 H) 2.35 (s, 3 H) 2.59 (q, $J=7.6$ Hz 2 H) 2.87 - 2.91 (m, 1 H) 4.32 (s, 2 H) 6.59 (s, 1 H) 7.26 (d, $J=1.2$ Hz 1 H) 7.31 (d, $J=8.8$ Hz 1 H) 7.62 - 7.63 (m, 2 H) 8.59 (d, $J=1.6$ Hz, 1 H) 8.67 (s, 1 H) 11.62 (s, 1 H); ESI-MS m/z $[M+H]^+ = 393.2$.

[0644] EXAMPLE 35: *N*-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

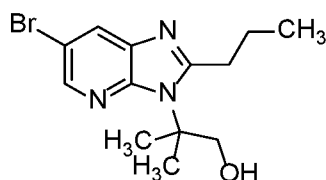


[0645] STEP 1: 2-((5-bromo-3-butylamido)pyridin-2-yl)amino)-2-methylpropyl acetate



[0646] To a solution of 2-((3-amino-5-bromopyridin-2-yl)amino)-2-methylpropyl acetate (0.5 g, 1.65 mmol) and DIPEA (0.576 mL, 3.31 mmol) in THF (10 mL) was added butyryl chloride (0.176 mL, 1.69 mmol) at 0°C. The reaction mixture was stirred at 10°C for 2 hours and then at 50°C for another 4 hours. The mixture was concentrated *in vacuo* and purified by column chromatography (SiO₂) eluting with a gradient of 3-50% EtOAc in petroleum ether to give the title compound as a black-brown solid (550 mg, 89.3%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.04 (t, *J*=7.2 Hz 2 H) 1.45 (s, 6 H) 1.75 - 1.81 (m, 2 H) 2.40 (d, *J*=7.2 Hz 2 H) 3.10 (s, 3 H) 4.29 (s, 1 H) 4.73 (s, 1 H) 6.84 (s, 1 H) 7.69 (s, 1 H) 8.02 (s, 1 H).

[0647] STEP 2: 2-(6-bromo-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropan-1-ol

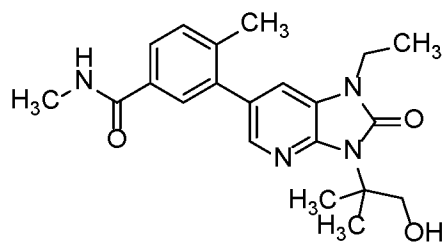


[0648] To a mixture of 2-((5-bromo-3-butylamido)pyridin-2-yl)amino)-2-methylpropyl acetate (150 mg, 0.403 mmol) in butyric acid (3 mL) was added tetramethoxymethane (2.74 mg, 0.02 mmol). The reaction mixture was stirred at 110°C for 16 hours, then warmed to 120°C and stirred for 4 hours. The mixture was acidified to pH 3 via addition of 1M HCl (30 mL) and then extracted with EtOAc. The aqueous phase was adjusted to pH 11 by adding saturated aq Na₂CO₃ and was extracted with EtOAc. The organic layers were combined, dried over Na₂SO₄ and concentrated *in vacuo* to give the title compound as a yellow solid (110 mg, 87.4%).

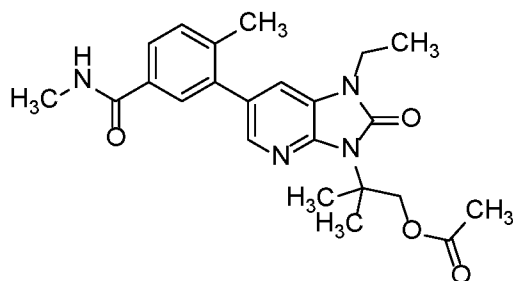
[0649] STEP 3: *N*-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

[0650] A mixture of 2-(6-bromo-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropan-1-ol (81.5 mg, 0.271 mmol), *N*-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (110 mg, 0.352 mmol), Pd(dppf)Cl₂ (9.90 mg, 0.014 mmol), and K₂CO₃ (112 mg, 0.812 mmol) in dioxane (5 mL) and water (0.5 mL) was degassed and purged with N₂ (3 x). The reaction mixture was stirred at 100°C for 4 hours under N₂ atmosphere. Additional Pd(dppf)Cl₂ (9.90 mg, 0.014 mmol) was added and the reaction mixture was stirred at 100°C for another 4 hours, then concentrated under vacuum and purified by column chromatography (SiO₂) eluting with a gradient of 2-10% MeOH in DCM to give the title compound as a black-brown solid (17.09 mg, 15.5%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.64 - 0.69 (m, 2 H) 0.79 - 0.83 (m, 2 H) 0.98 (t, *J*=4.0 Hz 3 H) 1.57 (s, 6 H) 1.66 - 1.74 (m, 2 H) 2.34 (s, 3 H) 2.58 (t, *J*=7.2 Hz 2 H) 2.84 - 2.87 (m, 1 H) 3.72 (s, 1 H) 4.33 (s, 2 H) 7.05 (s, 1 H) 7.25 - 7.28 (m, 1 H) 7.50 (s, 1 H) 7.65 - 7.70 (m, 2 H) 8.58 (s, 1 H); ESI-MS *m/z* [M+H]⁺ = 407.3.

[0651] EXAMPLE 36: 3-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*,4-dimethylbenzamide



[0652] STEP 1: 2-(1-ethyl-6-(2-methyl-5-(methylcarbamoyl)phenyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate



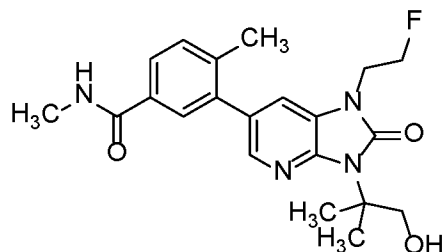
[0653] A mixture of 2-(6-bromo-1-ethyl-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (45.35 mg, 127.32 μmol), *N*,4-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (38.53 mg, 140.05 μmol), K₂CO₃ (87.98 mg, 636.58 μmol), and Pd(dppf)Cl₂ (9.32 mg, 12.73 μmol) in water (1 mL) and dioxane (5 mL) was degassed and purged with N₂ (3 x). The reaction mixture was stirred at 90°C for 5 hours under N₂ atmosphere and then diluted with water. The aqueous phase was extracted with

ethyl acetate. The organic layers were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give the title compound as a yellow solid (40 mg, crude).

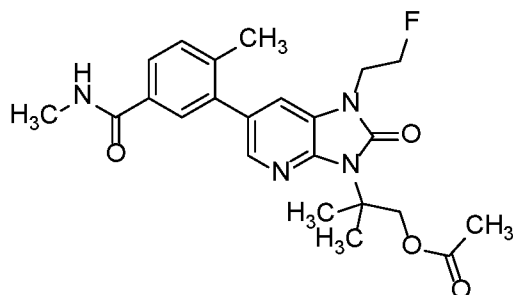
[0654] STEP 2: 3-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*,4-dimethylbenzamide

[0655] To a solution of 2-(1-ethyl-6-(2-methyl-5-(methylcarbamoyl)phenyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (40 mg, 94.23 μmol) in MeOH (5 mL) was added K_2CO_3 (39.07 mg, 282.69 μmol). The reaction mixture was stirred at 70°C for 3 hours and then filtered. The filtrate was concentrated under reduced pressure and purified by preparative HPLC. The product-containing fractions were concentrated, and the product was lyophilized to give the title compound as a white solid (12.3 mg, 34%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.36 (t, $J=7.2$ Hz, 3 H) 1.63 (s, 1 H) 1.71 - 1.77 (m, 6 H) 2.03 (s, 1 H) 2.36 (s, 3 H) 3.05 (d, $J=4.8$ Hz, 3 H) 3.95 (q, $J=7.2$ Hz, 2 H) 4.06 (s, 2 H) 5.65 - 5.80 (m, 1 H) 6.19 (s, 1 H) 7.18 (d, $J=2.0$ Hz, 1 H) 7.39 (d, $J=8.0$ Hz, 1 H) 7.68 (d, $J=8.0$ Hz, 2 H) 7.69 (s, 1 H) 7.96 (d, $J=2.0$ Hz, 1 H).

[0656] EXAMPLE 37: 3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*,4-dimethylbenzamide



[0657] STEP 1: 2-(1-(2-fluoroethyl)-6-(2-methyl-5-(methylcarbamoyl)phenyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate



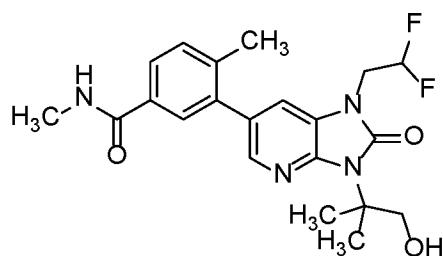
[0658] A mixture of 2-(6-bromo-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (100 mg, 267.23 μmol), *N*,4-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (80.88 mg, 293.96 μmol), K_2CO_3 (369.34

mg, 2.67 mmol), and Pd(dppf)Cl₂ (19.55 mg, 26.72 μmol) in dioxane (5 mL) and water (1 mL) was degassed and purged with N₂ (3 x). The reaction mixture was stirred at 90°C for 5 hours under N₂ atmosphere and then diluted with water. The aqueous phase was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by preparative TLC, eluting with 50% EtOAc in petroleum ether to give the title compound as a yellow oil (85 mg, 72%). ESI-MS *m/z* [M+H]⁺ = 443.3.

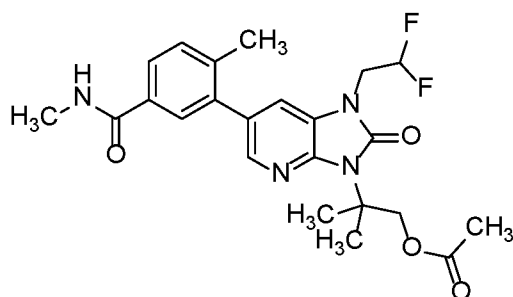
[0659] STEP 2: 3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*,4-dimethylbenzamide

[0660] To a solution of 2-(1-(2-fluoroethyl)-6-(2-methyl-5-(methylcarbamoyl)phenyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (80.00 mg, 180.80 μmol) in THF (2 mL), DMF (0.2 mL) and water (0.1 mL) was added LiOH.H₂O (37.93 mg, 903.99 μmol). The reaction mixture was stirred at 50°C for 2 hours and then diluted with water. The aqueous phase was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by preparative HPLC to give the title compound as a white solid (12 mg, 17%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.73 (s, 6 H) 2.32 (s, 3 H) 2.77 (d, *J*=4.4 Hz, 3 H) 3.93 (s, 2 H) 4.11 - 4.28 (m, 2 H) 4.57 - 4.77 (m, 2 H) 5.02 (s, 1 H) 7.41 (d, *J*=8.0 Hz, 1 H) 7.61 (d, *J*=1.6 Hz, 1 H) 7.73 - 7.79 (m, 2 H) 7.99 (d, *J*=2.0 Hz, 1 H) 8.44 (d, *J*=4.8 Hz, 1H); ESI-MS *m/z* [M+H]⁺ = 401.2.

[0661] EXAMPLE 38: 3-(1-(2,2-difluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*,4-dimethylbenzamide



[0662] STEP 1: 2-(1-(2,2-difluoroethyl)-6-(2-methyl-5-(methylcarbamoyl)phenyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate

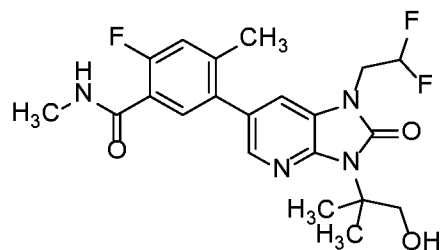


[0663] A mixture of 2-(6-bromo-1-(2,2-difluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (75 mg, 191.23 μ mol), *N*,4-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (57.88 mg, 210.35 μ mol), K_2CO_3 (264.30 mg, 1.91 mmol), and $Pd(dppf)Cl_2$ (13.99 mg, 19.12 μ mol) in dioxane (5 mL) and water (1 mL) was degassed and purged with N_2 (3 x). The reaction mixture was stirred at 90°C for 5 hours under N_2 atmosphere and then diluted with water. The aqueous phase was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was purified by preparative TLC, eluting with 50% EtOAc in petroleum ether to give the title compound as a yellow solid (60 mg, 68%).

[0664] STEP 2: 3-(1-(2,2-difluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*,4-dimethylbenzamide

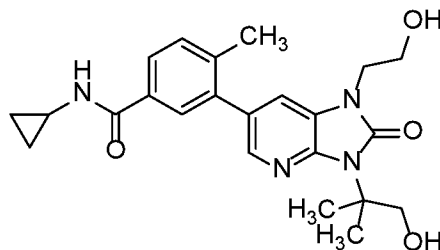
[0665] To a solution of 2-(1-(2,2-difluoroethyl)-6-(2-methyl-5-(methylcarbamoyl)phenyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (50 mg, 108.58 μ mol) in THF (2 mL), DMF (0.2 mL) and water (0.1 mL) was added $LiOH \cdot H_2O$ (22.78 mg, 542.92 μ mol). The reaction mixture was stirred at 50°C for 2 hours and then diluted with water. The aqueous phase was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was purified by preparative HPLC to give the title compound as a white solid (6 mg, 7%). ^1H NMR (400 MHz, $DMSO-d_6$) δ ppm 1.73 (s, 6 H) 2.32 (s, 3 H) 2.77 (d, $J=4.4$ Hz, 3 H) 3.93 (s, 2 H) 4.27 - 4.42 (m, 2 H) 5.00 (s, 1 H) 6.12 - 6.55 (m, 1 H) 7.42 (d, $J=8.0$ Hz, 1 H) 7.65 (s, 1 H) 7.72 - 7.80 (m, 2 H) 8.01 (d, $J=1.6$ Hz, 1 H) 8.44 (d, $J=4.8$ Hz, 1 H); ESI-MS m/z $[M+H]^+ = 419.2$.

[0666] EXAMPLE 39: 5-(1-(2,2-difluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2-fluoro-*N*,4-dimethylbenzamide

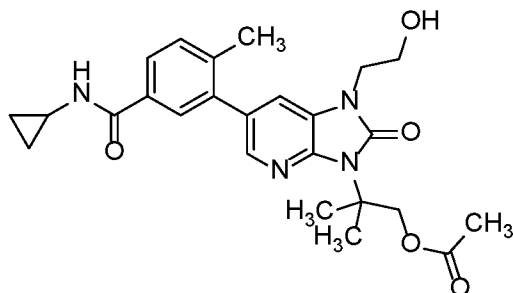


[0667] The title compound was prepared like EXAMPLE 38, starting with 2-fluoro-*N*,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide in place of *N*,4-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide, and proceeding through intermediate 2-(1-(2,2-difluoroethyl)-6-(4-fluoro-2-methyl-5-(methylcarbamoyl)phenyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate. The title compound was obtained as a white solid (7.72 mg). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.74 (s, 6 H), 2.32 (s, 3 H), 3.02 – 3.09 (m, 3 H), 4.06 (d, *J*=7.20 Hz, 2 H), 4.19 – 4.27 (m, 2 H), 5.44 (t, *J*=7.64 Hz, 1 H), 5.89 – 6.22 (m, 1 H), 6.75 (s, 1 H), 7.09 (d, *J*=12.72 Hz, 1 H), 7.25 (s, 1 H), 7.89 – 8.00 (m, 2 H); ESI-MS *m/z* [M+H]⁺ = 437.3.

[0668] EXAMPLE 40: *N*-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxyethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



[0669] STEP 1: 2-(6-(5-(cyclopropylcarbamoyl)-2-methylphenyl)-1-(2-hydroxyethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate



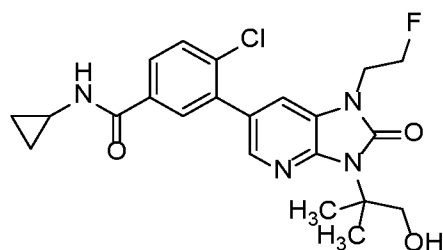
[0670] To a mixture of 2-(6-bromo-1-(2-hydroxyethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (60 mg, 161.20 μmol) and *N*-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (53.41 mg, 177.32 μmol) in dioxane (2 mL) and water (0.2 mL) was added K₂CO₃ (111.39 mg, 805.99 μmol) and Pd(dppf)Cl₂ (11.79 mg, 16.12 μmol) at 20°C. The suspension was degassed under vacuum and purged

with nitrogen (3 x) then heated to 90°C and stirred for 2.5 hours under nitrogen. The mixture was purified by column chromatography (SiO₂) eluting with a gradient of 30-80% EtOAc in petroleum ether to give the title compound as a yellow oil (44 mg, 59%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.58 - 0.65 (m, 2 H) 0.80 - 0.90 (m, 2 H) 1.92 (s, 6 H) 2.05 (s, 3 H) 2.31 (s, 3 H) 2.85 - 2.91 (m, 1 H) 3.74 (s, 1 H) 3.96 (d, *J*=3.60 Hz, 2 H) 4.00 (d, *J*=2.00 Hz, 2 H) 4.73 (s, 2 H) 6.37 (s, 1 H) 7.22 (d, *J*=2.00 Hz, 1 H) 7.32 (d, *J*=7.60 Hz, 1 H) 7.58 - 7.67 (m, 2 H) 7.92 (d, *J*=1.60 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 467.3.

[0671] STEP 2: *N*-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxyethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

[0672] To a solution of 2-(6-(5-(cyclopropylcarbamoyl)-2-methylphenyl)-1-(2-hydroxyethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (106 mg, 227.21 μmol) in MeOH (3 mL) was added K₂CO₃ (94.21 mg, 681.63 μmol) at 20°C. The reaction mixture was heated to 75°C and stirred at 75°C for 2 hours under nitrogen. The mixture was then concentrated under reduced pressure and purified by preparative HPLC to give the title compound as a white solid (32 mg, 33%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.48 - 0.60 (m, 2 H) 0.61 - 0.74 (m, 2 H) 1.72 (s, 6 H) 2.30 - 2.34 (m, 3 H) 2.80 - 2.90 (m, 1 H) 3.64 (d, *J*=4.00 Hz, 2 H) 3.82 - 3.98 (m, 4 H) 4.84 (s, 1 H) 5.03 (t, *J*=6.40 Hz, 1 H) 7.40 (d, *J*=8.40 Hz, 1 H) 7.56 (d, *J*=2.00 Hz, 1 H) 7.68 - 7.80 (m, 2 H) 7.95 (d, *J*=2.00 Hz, 1 H) 8.40 (d, *J*=4.00 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 425.1.

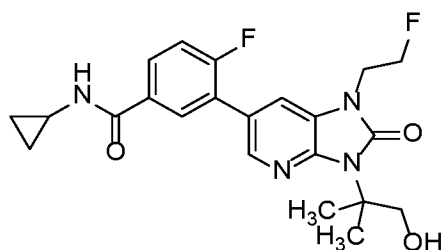
[0673] EXAMPLE 41: 4-chloro-*N*-cyclopropyl-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)benzamide



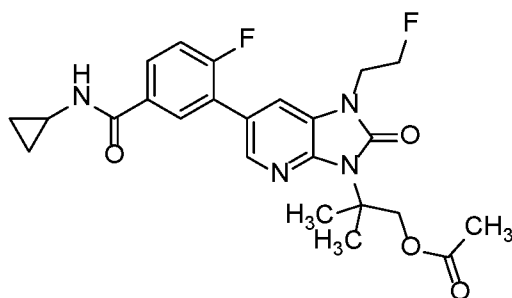
[0674] To a solution of 2-(1-(2-fluoroethyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (321 mg, 0.761 mmol), 3-bromo-4-chloro-*N*-cyclopropylbenzamide (200 mg, 0.692 mmol) and K₂CO₃ (287 mg, 2.08 mmol) in dioxane (5 mL) and water (1 mL) was added Pd(dppf)Cl₂ (15.2 mg, 0.021 mmol) under N₂. The reaction mixture was heated to 120°C for 16 hours under N₂, then concentrated *in vacuo* and purified by column chromatography, eluting with a gradient of 0-2% EtOAc in petroleum ether. The crude product was triturated with EtOAc (10

mL) at 15°C for 30 minutes to give the title compound as a white solid (115 mg, 36.4%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.55 - 0.59 (m, 2 H) 0.68 - 0.76 (m, 2 H) 1.73 (s, 6 H) 2.82 - 2.88 (m, 1 H) 3.92 (d, *J*=6.4 Hz, 2 H) 4.15 - 4.23 (m, 2 H) 4.63 (t, *J*=4.4 Hz, 1 H) 4.74 (t, *J*=4.4 Hz, 1 H) 4.97 (t, *J*=2.4 Hz, 1 H) 7.70 (t, *J*=8.0 Hz, 2 H) 7.85 (d, *J*=2.4 Hz, 1 H) 7.91 (t, *J*=3.2 Hz, 1 H) 8.06 (t, *J*=2.0 Hz, 1 H) 8.54 (t, *J*=4.0 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 446.9.

[0675] EXAMPLE 42: *N*-cyclopropyl-4-fluoro-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)benzamide



[0676] STEP 1: 2-(6-(5-(cyclopropylcarbamoyl)-2-fluorophenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate



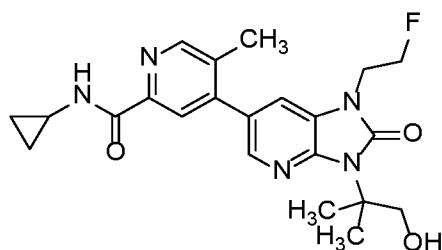
[0677] A mixture of 3-bromo-*N*-cyclopropyl-4-fluorobenzamide (300 mg, 1.16 mmol), 2-(1-(2-fluoroethyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (0.466 mg, 1.11 mmol), PdCl₂(dtbpf) (14.4 mg, 0.022 mmol), and Na₂CO₃ (0.352 mg, 3.32 mmol) in dioxane (10 mL) and water (0.5 mL) was degassed and purged with N₂ (3 x). The reaction mixture was stirred at 100°C for 14 hours under N₂ atmosphere and then concentrated *in vacuo* to give the title compound (1.42 g crude) which was used without further purification. ESI-MS *m/z* [M+H]⁺ = 473.4.

[0678] STEP 2: *N*-cyclopropyl-4-fluoro-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)benzamide

[0679] A mixture of 2-(6-(5-(cyclopropylcarbamoyl)-2-fluorophenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (590 mg, 1.25 mmol) and K₂CO₃ (518 mg, 3.75 mmol) in MeOH (10 mL) was stirred at 65°C for 4 hours and then filtered. The filtrate was concentrated *in vacuo* and purified by column

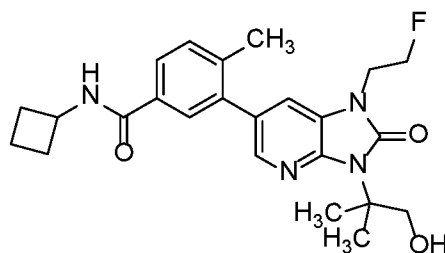
chromatography (SiO₂) eluting with a gradient of 2-50% EtOAc in petroleum ether to give the title compound as a white solid (65 mg, 12%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.56 - 0.60 (m, 2 H) 0.70 - 0.74 (m, 2 H) 1.73 (s, 6 H) 2.83 - 2.88 (m, 1 H) 3.92 (d, *J*=6.4 Hz, 2 H) 4.14 - 4.25 (m, 2 H) 4.64 (t, *J*=4.8 Hz, 1 H) 4.76 (t, *J*=4.8 Hz, 1 H) 4.95 (t, *J*=4.0 Hz, 1 H) 7.43 (dd, *J*₁=8.8 Hz, *J*₂=10.4 Hz, 1 H) 7.75 (s, 1 H) 7.87 - 7.90 (m, 1 H) 8.02 (d, *J*=2.0 Hz, 1 H) 8.19 (s, 1 H) 8.50 (d, *J*=4.0 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 431.2.

[0680] EXAMPLE 43: *N*-cyclopropyl-4-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-5-methylpicolinamide

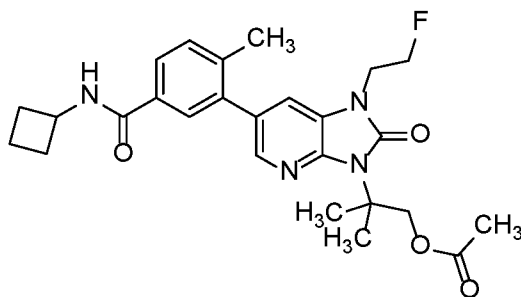


[0681] To a solution of 2-(1-(2-fluoroethyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (70 mg, 0.166 mmol) in dioxane (5 mL) and water (0.5 mL) was added K₂CO₃ (46 mg, 0.333 mmol), 4-bromo-*N*-cyclopropyl-5-methylpicolinamide (47.1 mg, 0.172 mmol), and Pd(dppf)Cl₂ (12.2 mg, 0.017 mmol) at 10°C under N₂. The reaction mixture was stirred at 110°C for 4 hours and then concentrated to a residue, which was dissolved in MeOH (5 mL) and admixed with K₂CO₃ (200 mg, 1.45 mmol) at 15°C. The mixture was heated to 80°C, stirred for 3 hours and filtered. The filtrate was concentrated and purified by column chromatography (SiO₂) eluting with a gradient of 0-1% MeOH in DCM. The product was further purified by preparative HPLC to give the title compound as a white solid (6.84 mg, 10%). ESI-MS *m/z* [M+H]⁺ = 428.2.

[0682] EXAMPLE 44: *N*-cyclobutyl-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



[0683] STEP 1: 2-(6-(5-(cyclobutylcarbamoyl)-2-methylphenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate

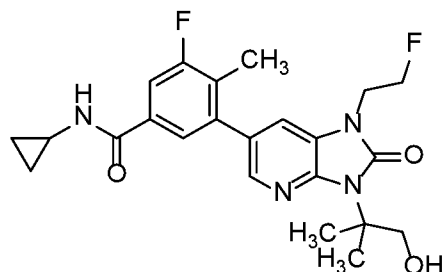


[0684] To a solution of 3-bromo-*N*-cyclobutyl-4-methylbenzamide (100 mg, 372.93 μmol) in dioxane (3 mL) and water (1 mL) was added 2-(1-(2-fluoroethyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (172.81 mg, 410.22 μmol), K_2CO_3 (154.62 mg, 1.12 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (27.29 mg, 37.29 μmol). The reaction mixture was stirred at 90°C for 12 hours, then poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 , and dried under reduce pressure to give the title compound as a brown solid (300 mg, crude). ESI-MS m/z $[\text{M}+\text{H}]^+ = 483.2$.

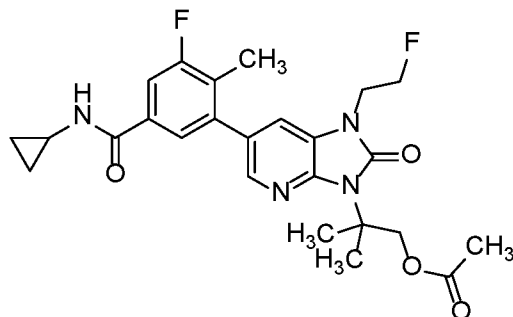
[0685] STEP 2: *N*-cyclobutyl-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

[0686] To a solution of 2-(6-(5-(cyclobutylcarbamoyl)-2-methylphenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (300 mg, 621.70 μmol) in THF (5 mL), DMF (0.5 mL) and water (0.25 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (130.44 mg, 3.11 mmol). The reaction mixture was stirred at 50°C for 4 hours, then poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 , and concentrated under reduce pressure. The crude product was purified by preparative HPLC to give a formic acid salt of the title compound as a yellow solid (33.67 mg, 12.3%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.58 - 1.69 (m, 2 H) 1.74 (s, 6 H) 1.98 - 2.12 (m, 2 H) 2.16 - 2.25 (m, 2 H) 2.32 (s, 3 H) 3.94 (s, 2 H) 4.11 - 4.19 (m, 1 H) 4.21 - 4.30 (m, 1 H) 4.32 - 4.48 (m, 1 H) 4.63 (t, $J=4.8$ Hz, 1 H) 4.75 (t, $J=4.4$ Hz, 1 H) 5.01 (s, 1 H) 7.42 (d, $J=8.0$ Hz, 1 H) 7.61 (s, 1 H) 7.73 - 7.83 (m, 2 H) 8.00 (d, $J=1.6$ Hz, 1 H) 8.47 (br s, 1 H) 8.57 (d, $J=7.6$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 4411$.

[0687] EXAMPLE 45: *N*-cyclopropyl-3-fluoro-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



[0688] STEP 1: 2-(6-(5-(cyclopropylcarbamoyl)-3-fluoro-2-methylphenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate

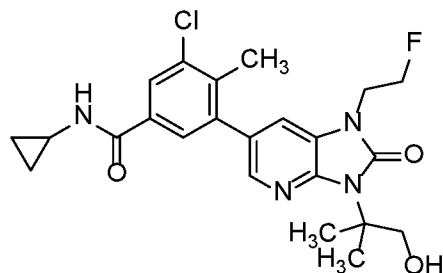


[0689] To a mixture of 3-bromo-*N*-cyclopropyl-5-fluoro-4-methylbenzamide (100 mg, 0.367 mmol), 2-(1-(2-fluoroethyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (147.44 mg, 0.35 mmol) and Na₂CO₃ (111 mg, 1.05 mmol) in dioxane (3 mL) and water (0.2 mL) was added PdCl₂(dtbpf) (22.8 mg, 0.035 mmol) under N₂. The reaction mixture was stirred at 100°C for 6 hours under N₂ atmosphere and then concentrated under reduce pressure to give the title compound as a black solid (170 mg, crude). ESI-MS *m/z* [M+H]⁺ = 487.2.

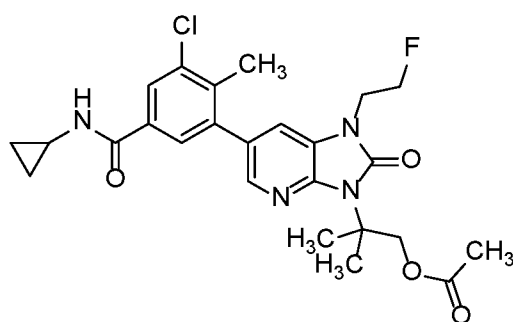
[0690] STEP 2: *N*-cyclopropyl-3-fluoro-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

[0691] To a solution of 2-(6-(5-(cyclopropylcarbamoyl)-3-fluoro-2-methylphenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (170 mg, 0.133 mmol) in MeOH (2 mL) was added K₂CO₃ (55.2 mg, 0.399 mmol) at 15°C. The reaction mixture was heated to 70°C, stirred at 70°C for 2 hours and then concentrated under reduce pressure. The resulting residue was purified by preparative HPLC to give the title compound as a white solid (11.22 mg, 19%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.55 - 0.57 (m, 2 H) 0.68 - 0.70 (m, 2 H) 1.73 (s, 6 H) 2.21 (d, *J*=1.6 Hz, 3 H) 2.83 - 2.87 (m, 1 H) 3.93 (d, *J*=6.4 Hz, 1 H) 4.16 (t, *J*=4.4 Hz, 1 H) 4.23 (t, *J*=4.0 Hz, 1 H) 4.62 (t, *J*=4.8 Hz, 1 H) 4.74 (t, *J*=4.8 Hz, 1 H) 4.98 (t, *J*=6.4 Hz, 1 H) 7.62 - 7.64 (m, 3 H) 8.00 (d, *J*=2.0 Hz, 1 H) 8.49 (d, *J*=4.0 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 445.2.

[0692] EXAMPLE 46: 3-chloro-*N*-cyclopropyl-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



[0693] STEP 1: 2-(6-(3-chloro-5-(cyclopropylcarbamoyl)-2-methylphenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate



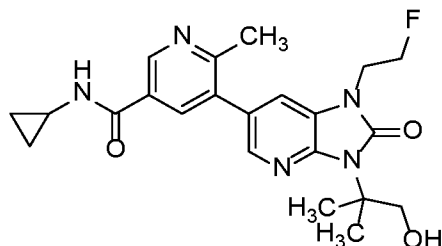
[0694] To a mixture of 3-chloro-*N*-cyclopropyl-5-iodo-4-methylbenzamide (86 mg, 0.246 μ mol) and 2-(1-(2-fluoroethyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (109 mg, 0.259 mmol) in dioxane (2 mL) and water (0.5 mL) were added K_2CO_3 (102 mg, 0.739 mmol) and $PdCl_2(dtbpf)$ (16.1 mg, 0.025 mmol) under N_2 . The reaction mixture was purged with N_2 (3 x), heated to 100°C, stirred for 12 hours and then concentrated under reduce pressure to give the title compound as a black solid (124 mg, crude). ESI-MS m/z $[M+H]^+ = 503.1$.

[0695] STEP 2: 3-chloro-*N*-cyclopropyl-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

[0696] To a solution of 2-(6-(3-chloro-5-(cyclopropylcarbamoyl)-2-methylphenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (124 mg, 0.246 mmol) in MeOH (2 mL) was added K_2CO_3 (102 mg, 0.739 mmol) at 15°C. The reaction mixture was heated to 70°C, stirred for 2 hours and then concentrated under reduce pressure. The crude product was purified by preparative HPLC to give the title compound as a white solid (21.4 mg, 18.9%). ^1H NMR (400 MHz, $DMSO-d_6$) δ ppm 0.55 - 0.58 (m, 3 H) 0.68 - 0.70 (m, 2 H) 1.73 (s, 6 H) 2.32 (s, 3 H) 2.83 - 2.87 (m, 1 H) 3.92 (d, $J=6.4$ Hz, 2 H) 4.15 - 4.16 (m, 1 H) 4.22 (t, $J=4.4$ Hz, 1 H) 4.62 (t, $J=4.4$ Hz, 1 H) 4.74 (t, $J=4.8$ Hz, 1 H)

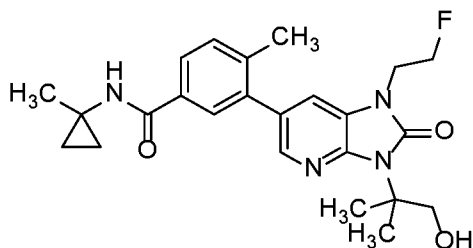
4.98 (t, $J=6.8$ Hz, 1 H) 7.61 (d, $J=1.6$ Hz, 1 H) 7.71 (d, $J=1.6$ Hz, 1 H) 7.92 (d, $J=1.6$ Hz, 1 H) 7.98 (d, $J=1.4$ Hz, 1 H) 8.53 (d, $J=4.0$ Hz, 1 H); ESI-MS m/z $[M+H]^+ = 461.2$.

[0697] EXAMPLE 47: *N*-cyclopropyl-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-6-methylnicotinamide

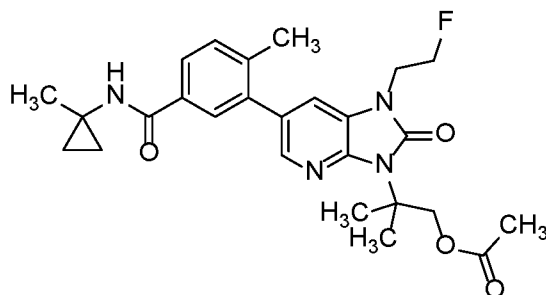


[0698] To a solution of 2-(1-(2-fluoroethyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (376 mg, 0.894 mmol), 5-bromo-*N*-cyclopropyl-6-methylnicotinamide (200 mg, 0.745 mmol) and K_2CO_3 (309 mg, 2.23 mmol) in dioxane (3 mL) and water (1 mL) was added $Pd(dppf)Cl_2$ (54.5 mg, 0.075 mmol) under N_2 . The reaction mixture was heated at $120^\circ C$ for 15 hours under N_2 , then concentrated under reduced pressure, diluted with water and extracted with EtOAc. The organic layers were combined, washed with water, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by preparative HPLC to give the title compound as a white solid (35.7 mg, 11%). ^1H NMR (400 MHz, $DMSO-d_6$) δ ppm 0.55 - 0.59 (m, 2 H) 0.68 - 0.72 (m, 2 H) 1.72 (s, 6 H) 2.52 (s, 3 H) 2.82 - 2.89 (m, 1 H) 3.92 (s, 2 H) 4.15 - 4.24 (m, 2 H) 4.60 - 4.64 (m, 1 H) 4.72 - 4.76 (m, 1 H) 7.68 (d, $J=2.0$ Hz, 1 H) 8.03 (t, $J=1.6$ Hz, 2 H) 8.58 (d, $J=4.0$ Hz, 1 H) 8.88 (d, $J=2.0$ Hz, 1 H); ESI-MS m/z $[M+H]^+ = 428.0$.

[0699] EXAMPLE 48: 3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-(1-methylcyclopropyl)benzamide



[0700] STEP 1: 2-(1-(2-fluoroethyl)-6-(2-methyl-5-((1-methylcyclopropyl)carbamoyl)phenyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate

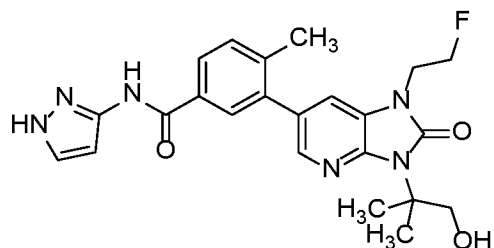


[0701] To a solution of 2-(1-(2-fluoroethyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)-2-methylpropyl acetate (100 mg, 237.38 μmol) and 3-bromo-4-methyl-N-(1-methylcyclopropyl)benzamide (76.38 mg, 284.85 μmol) in dioxane (3 mL) and water (0.3 mL) were added Na_2CO_3 (75.48 mg, 712.13 μmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (17.37 mg, 23.74 μmol). The reaction mixture was stirred at 90°C for 3 hours under N_2 and then diluted with water. The aqueous phase was extracted with EtOAc, and the organic layers were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was purified by preparative TLC, eluting with 50% EtOAc in petroleum ether to give the title compound as a light-yellow oil (124 mg, 99.5%). ESI-MS m/z $[\text{M}+\text{H}]^+ = 483.2$.

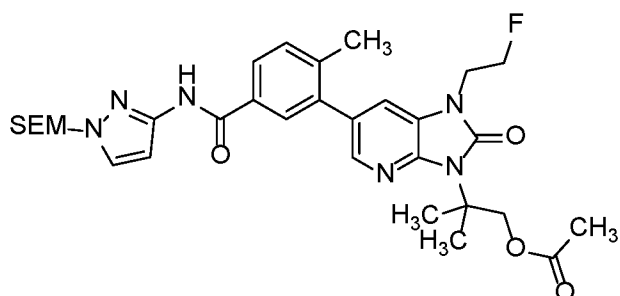
[0702] STEP 2: 3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-6-yl)-4-methyl-N-(1-methylcyclopropyl)benzamide

[0703] To a solution of 2-(1-(2-fluoroethyl)-6-(2-methyl-5-((1-methylcyclopropyl)carbamoyl)phenyl)-2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)-2-methylpropyl acetate (120 mg, 248.68 μmol) in THF (2 mL), DMF (0.2 mL) and water (0.05 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (52.17 mg, 1.24 mmol). The reaction mixture was stirred at 50°C for 5 hours and then diluted with saturated aq NH_4Cl . The aqueous phase was extracted with EtOAc, and the organic layers were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was purified by preparative HPLC to give the title compound as a white solid (36 mg, 33%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 0.53 - 0.65 (m, 2 H) 0.68 - 0.77 (m, 2 H) 1.36 (s, 3 H) 1.73 (s, 6 H) 2.30 (s, 3 H) 3.93 (d, $J=6.0$ Hz, 2 H) 4.13 - 4.27 (m, 2 H) 4.59 - 4.77 (m, 2 H) 5.00 (t, $J=6.4$ Hz, 1 H) 7.38 (d, $J=8.0$ Hz, 1 H) 7.59 (d, $J=1.6$ Hz, 1 H) 7.70 - 7.78 (m, 2 H) 7.97 (d, $J=1.6$ Hz, 1 H) 8.60 (s, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 441.2$.

[0704] EXAMPLE 49: 3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-6-yl)-4-methyl-N-(1H-pyrazol-3-yl)benzamide

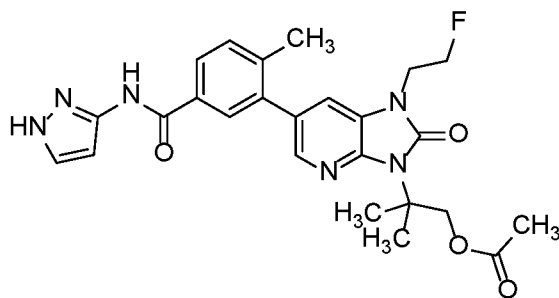


[0705] STEP 1: 2-(1-(2-fluoroethyl)-6-(2-methyl-5-((1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)carbamoyl)phenyl)-2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)-2-methylpropyl acetate



[0706] To a solution of 3-bromo-4-methyl-N-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)benzamide (150 mg, 365.51 μmol) and 2-(1-(2-fluoroethyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)-2-methylpropyl acetate (184.78 mg, 438.62 μmol) in dioxane (3 mL) and water (0.3 mL) were added Na_2CO_3 (116.22 mg, 1.10 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (26.74 mg, 36.55 μmol). The reaction mixture was stirred at 90°C for 3 hours under N_2 and then diluted with water. The aqueous phase was extracted with EtOAc, and the organic layers were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The resulting residue was purified by preparative TLC, eluting with 50% EtOAc in petroleum ether to give the title compound as a brown oil (188 mg, 78.5%). ESI-MS m/z $[\text{M}+\text{H}]^+ = 625.3$.

[0707] STEP 2: 2-(6-(5-((1H-pyrazol-3-yl)carbamoyl)-2-methylphenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)-2-methylpropyl acetate



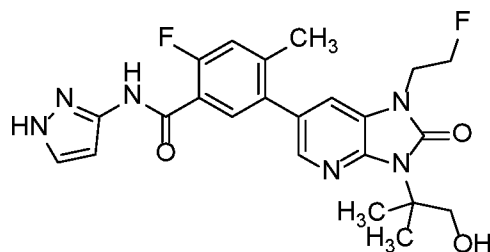
[0708] To a solution of 2-(1-(2-fluoroethyl)-6-(2-methyl-5-((1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)carbamoyl)phenyl)-2-oxo-1,2-dihydro-3H-

imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (185 mg, 296.11 μ mol) in DCM (2 mL) was added TFA (3.08 g, 27.01 mmol). The reaction mixture was stirred at 15°C for 2 hours, then concentrated under reduced pressure and poured into saturated aq NaHCO₃. The aqueous phase was extracted with EtOAc, and the organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by preparative TLC, eluting with MeOH in DCM (1:10) to give the title compound as a yellow oil (120 mg, 81.9%). ESI-MS m/z [M+H]⁺ = 495.3.

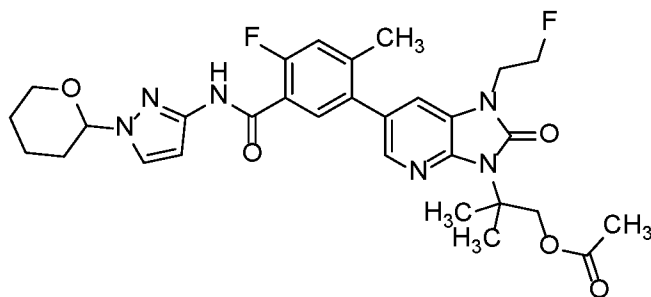
[0709] STEP 3: 3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-(1*H*-pyrazol-3-yl)benzamide

[0710] To a solution of 2-(6-(5-((1*H*-pyrazol-3-yl)carbamoyl)-2-methylphenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (120 mg, 242.66 μ mol) in THF (3 mL), DMF (0.3 mL) and water (0.05 mL) was added LiOH.H₂O (50.91 mg, 1.21 mmol). The reaction mixture was stirred at 50°C for 5 hours and then diluted with saturated aq NH₄Cl. The aqueous phase was extracted with EtOAc, and the organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by preparative HPLC to give the title compound as a white solid (7 mg, 6%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.74 (s, 6 H) 2.36 (s, 3 H) 3.94 (s, 2 H) 4.15 - 4.27 (m, 2 H) 4.62 - 4.78 (m, 2 H) 5.02 (s, 1 H) 6.62 (s, 1 H) 7.46 (d, *J*=8.0 Hz, 1 H) 7.59 - 7.67 (m, 2 H) 7.91 - 7.96 (m, 2 H) 8.07 (d, *J*=2.0 Hz, 1 H) 10.84 (s, 1 H) 12.44 (s, 1 H); ESI-MS m/z [M+H]⁺ = 453.2.

[0711] EXAMPLE 50: 2-fluoro-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-(1*H*-pyrazol-3-yl)benzamide



[0712] STEP 1: 2-(6-(4-fluoro-2-methyl-5-((1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)carbamoyl)phenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate



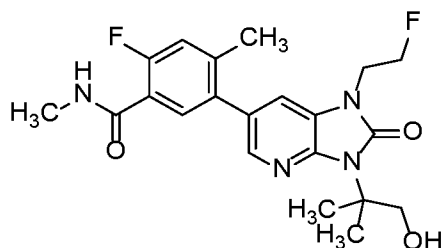
[0713] To a mixture of 5-bromo-2-fluoro-4-methyl-*N*-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)benzamide (117 mg, 261.41 μmol) and 2-(1-(2-fluoroethyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (132.15 mg, 313.69 μmol) in dioxane (3 mL) and water (0.3 mL) were added K_2CO_3 (108.39 mg, 784.23 μmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (9.56 mg, 13.07 μmol) at 20°C. The suspension was degassed under vacuum and purged with nitrogen (3 x). The reaction mixture was heated to 90°C and stirred for 7 hours under nitrogen, then diluted with water and extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and purified by preparative TLC (SiO_2) eluting with 67% EtOAc in petroleum to give the title compound as a yellow solid (115 mg, 61.9%). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.60 - 1.76 (m, 4 H) 1.91 (s, 6 H) 2.01 (s, 3 H) 2.08 - 2.27 (m, 2 H) 2.35 (s, 3 H) 4.08 - 4.21 (m, 4 H) 4.73 - 4.83 (m, 4 H) 5.28 (dd, $J_1=2.40$ Hz, $J_2=10.00$ Hz, 1 H) 6.91 (d, $J=2.40$ Hz, 1 H) 7.12 (d, $J=12.80$ Hz, 1 H) 7.20 (s, 1 H) 7.55 (d, $J=2.40$ Hz, 1 H) 7.94 (d, $J=1.60$ Hz, 1 H) 8.00 - 8.08 (m, 1 H) 8.99 (d, $J=14.40$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 597.4$.

[0714] STEP 2: 2-fluoro-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-(1*H*-pyrazol-3-yl)benzamide

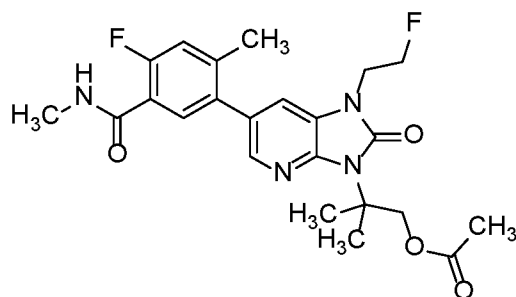
[0715] To 2-(6-(4-fluoro-2-methyl-5-((1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)carbamoyl)phenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (115 mg, 161.91 μmol) was added HCl in dioxane (4 M, 5 mL) at 20°C. The reaction mixture was stirred at 20°C for 12 hours under nitrogen, then diluted with water and adjusted to pH 7-8 via addition of saturated aq NaHCO_3 . The mixture was extracted with EtOAc, and the organic layers were combined, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and purified by preparative HPLC to give the title compound as a white solid (15.5 mg, 20.3%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.72 (s, 6 H) 2.33 (s, 3 H) 3.93 (d, $J=6.00$ Hz, 2 H) 4.16 (t, $J=5.20$ Hz, 1 H) 4.23 (t, $J=4.40$ Hz, 1 H) 4.63 (t, $J=4.80$ Hz, 1 H) 4.74 (t, $J=4.80$ Hz, 1 H) 4.99 (t, $J=6.40$ Hz, 1 H)

6.62 (s, 1 H) 7.32 (d, $J=11.20$ Hz, 1 H) 7.55 (d, $J=7.60$ Hz, 1 H) 7.61 (d, $J=1.20$ Hz, 1 H) 7.65 (s, 1 H) 8.02 (d, $J=1.60$ Hz, 1 H) 10.71 (s, 1 H) 12.43 (s, 1 H); ESI-MS m/z $[M+H]^+ = 471.2$.

[0716] EXAMPLE 51: 2-fluoro-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*,4-dimethylbenzamide



[0717] STEP 1: 2-(6-(4-fluoro-2-methyl-5-(methylcarbamoyl)phenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate



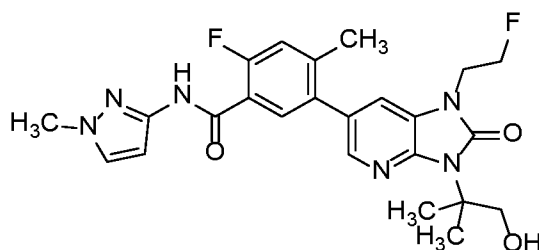
[0718] A mixture of 5-bromo-2-fluoro-*N*,4-dimethylbenzamide (60 mg, 217.01 μmol), 2-(1-(2-fluoroethyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (100.56 mg, 238.71 μmol), Pd(dppf)Cl₂ (15.88 mg, 21.70 μmol) and K₂CO₃ (89.98 mg, 651.02 μmol) in dioxane (10 mL) and water (1 mL) was heated to 100°C and stirred for 15 hours under N₂. The mixture was subsequently concentrated *in vacuo* and purified by preparative TLC, eluting with 10% MeOH in DCM to give the title compound as a yellow oil (70 mg, 64%). ESI-MS m/z $[M+H]^+ = 461.3$.

[0719] STEP 2: 2-fluoro-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*,4-dimethylbenzamide

[0720] A mixture of 2-(6-(4-fluoro-2-methyl-5-(methylcarbamoyl)phenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (70 mg, 139.86 μmol), water (1.00 g, 55.51 mmol) and LiOH.H₂O (16.75 mg, 399.16 μmol) in THF (10 mL) and DMF (1 mL) was heated to 50°C and stirred for 4 hours at 50°C under N₂. Ethyl acetate and water were added, and the aqueous and organic layers were separated. The aqueous phase was extracted with EtOAc, and the organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The resulting residue was

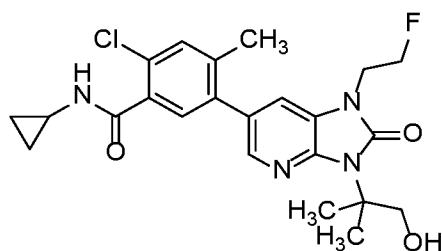
purified by preparative HPLC to give the title compound as a yellow solid (18.21 mg, 31%). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.73 (s, 6 H), 2.32 (s, 3 H), 3.05 (d, $J=4.52$ Hz, 3 H), 4.07 (s, 2 H), 4.15 (br t, $J=4.58$ Hz, 2 H), 4.22 (br t, $J=4.58$ Hz, 1 H), 4.66 (t, $J=4.58$ Hz, 1 H), 4.78 (t, $J=4.52$ Hz, 1 H), 6.82 (br d, $J=8.08$ Hz, 1 H), 7.08 (d, $J=12.84$ Hz, 1 H), 7.27 (br s, 1 H), 7.93 (d, $J=1.80$ Hz, 1 H), 7.97 (d, $J=8.08$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 419.3$.

[0721] EXAMPLE 52: 2-fluoro-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide

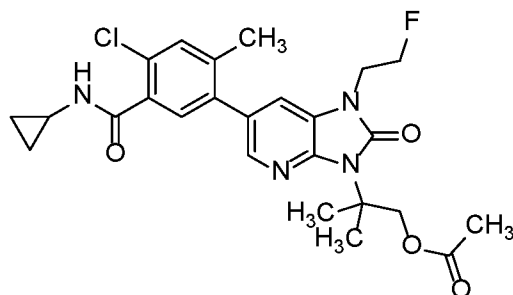


[0722] The title compound was prepared like EXAMPLE 51, starting with 5-bromo-2-fluoro-4-methyl-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide in place of 5-bromo-2-fluoro-*N*,4-dimethylbenzamide, and proceeding through intermediate 2-(6-(4-fluoro-2-methyl-5-((1-methyl-1*H*-pyrazol-3-yl)carbamoyl)phenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate. The title compound was obtained as a white solid (117.07 mg). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.72 (s, 6 H) 2.33 (s, 3 H) 3.77 (s, 3 H) 3.92 - 3.93 (d, $J= 6.4$ Hz, 2 H) 4.15 - 4.24 (m, 2 H) 4.63 (t, $J=4.4$ Hz, 1 H) 4.74 (t, $J=4.8$ Hz, 1 H) 4.97 - 5.00 (m, 1 H) 6.56 (s, 1 H) 7.30 - 7.33 (d, $J= 11.6$ Hz, 1 H) 7.53 - 7.55 (d, $J= 7.6$ Hz, 1 H) 7.60 (s, 2 H) 8.00 - 8.01 (d, $J= 2.0$ Hz, 1 H) 10.70 (s, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 485.2$.

[0723] EXAMPLE 53: 2-chloro-*N*-cyclopropyl-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



[0724] STEP 1: 2-(6-(4-chloro-5-(cyclopropylcarbamoyl)-2-methylphenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate

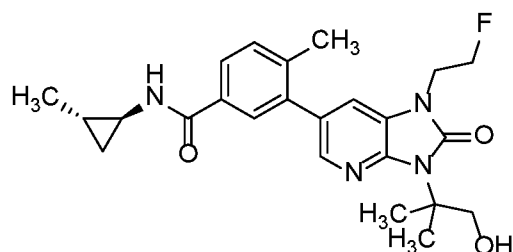


[0725] To a mixture of 2-(1-(2-fluoroethyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)-2-methylpropyl acetate (200 mg, 0.476 mmol) and 2-chloro-N-cyclopropyl-5-iodo-4-methylbenzamide (176 mg, 0.523 mmol) in THF (5 mL) and water (3 mL) were added Na_2CO_3 (75.7 mg, 0.714 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (34.8 mg, 0.048 mmol). The suspension was stirred at 70°C for 4 hours, then filtered and concentrated *in vacuo*. The resulting residue was purified by preparative TLC, eluting with 50% EtOAc in petroleum ether to give the title compound as a yellow oil (160 mg, 50.1%). ^1H NMR (400 MHz, CDCl_3) δ ppm 0.64 - 0.67 (m, 2 H) 0.87 - 0.92 (m, 2 H) 1.90 (s, 6 H) 2.01 (s, 3 H) 2.29 (s, 3 H) 2.92 - 2.95 (m, 1 H) 4.10 - 4.19 (m, 2 H) 4.65 - 4.70 (m, 1 H) 4.76 - 4.79 (m, 3 H) 6.43 (s, 1 H) 7.17 (s, 1 H) 7.33 (s, 1 H) 7.60 (s, 1 H) 7.91 (d, $J=1.6$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 503.2$.

[0726] STEP 2: 2-chloro-N-cyclopropyl-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-6-yl)-4-methylbenzamide

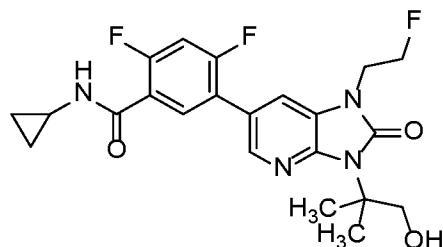
[0727] To a solution of 2-(6-(4-chloro-5-(cyclopropylcarbamoyl)-2-methylphenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)-2-methylpropyl acetate (55 mg, 0.082 mmol) in MeOH (1 mL) was added K_2CO_3 (34.00 mg, 0.246 mmol). The reaction mixture was heated to 50°C, stirred for 30 minutes, and then diluted with water and extracted with DCM. The organic layers were combined, dried over Na_2SO_4 , and concentrated under reduce pressure. The resulting residue was lyophilized to give the title compound as a white solid (77.8 mg, 98.4%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 0.46 - 0.53 (m, 2 H) 0.65 - 0.70 (m, 2 H) 1.17 (s, 6 H) 2.29 (s, 3 H) 2.77 - 2.84 (m, 1 H) 3.92 (s, 2 H) 4.16 (t, $J=4.4$ Hz, 1 H) 4.23 (t, $J=4.8$ Hz, 1 H) 4.62 (m, $J=4.8$ Hz, 1 H) 4.74 (t, $J=4.8$ Hz, 1 H) 4.95 - 5.04 (m, 1 H) 7.27 (s, 1 H) 7.48 (s, 1 H) 7.56 (d, $J=1.6$ Hz, 1 H) 7.96 (d, $J=2.0$ Hz, 1 H) 8.44 (d, $J=4.0$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 461.2$.

[0728] EXAMPLE 54: 3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-6-yl)-4-methyl-N-((1S,2S)-2-methylcyclopropyl)benzamide

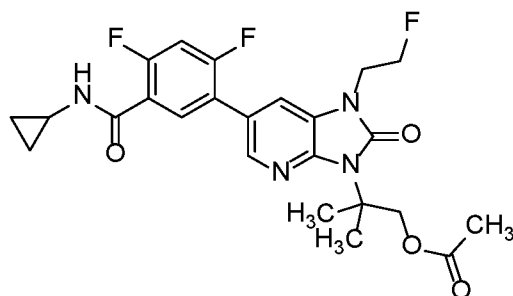


[0729] The title compound was prepared like EXAMPLE 48, starting with 3-bromo-4-methyl-*N*-((1*S*,2*S*)-2-methylcyclopropyl)benzamide in place of 3-bromo-4-methyl-*N*-(1-methylcyclopropyl)benzamide, and proceeding through intermediate 2-(1-(2-fluoroethyl)-6-(2-methyl-5-(((1*S*,2*S*)-2-methylcyclopropyl)carbamoyl)phenyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate. The title compound was obtained as a white solid (25.94 mg). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.59 - 0.80 (m, 2 H), 0.98 (d, *J*=5.98 Hz, 1 H), 1.16 (d, *J*=6.12 Hz, 3 H), 1.74 (s, 6 H), 2.32 (s, 3 H), 2.60 (dd, *J*=7.08 Hz, 1 H), 4.06 (d, *J*=4.52 Hz, 2 H), 4.12 - 4.25 (m, 2 H), 4.62 - 4.87 (m, 2 H), 5.64 (s, 1 H), 6.19 (s, 1 H), 7.28 - 7.29 (m, 1 H), 7.35 (d, *J*=8.07 Hz, 1 H), 7.58 - 7.68 (m, 2 H), 7.96 (d, *J*=1.58 Hz, 1 H). ESI-MS *m/z* [M+H]⁺ = 441.3.

[0730] EXAMPLE 55: *N*-cyclopropyl-2,4-difluoro-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)benzamide



[0731] STEP 1: 2-(6-(5-(cyclopropylcarbamoyl)-2,4-difluorophenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate



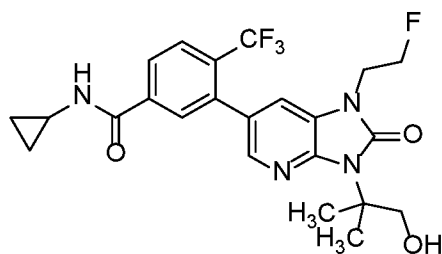
[0732] To a solution of 5-bromo-*N*-cyclopropyl-2,4-difluorobenzamide (350 mg, 1.27 mmol) in dioxane (5 mL) and water (1 mL) were added 2-(1-(2-fluoroethyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (534.07 mg, 1.27 mmol), K₂CO₃ (525.64 mg, 3.80 mmol) and

Pd(dppf)Cl_2 (92.76 mg, 126.78 μmol). The reaction mixture was stirred at 90°C for 16 hours, then poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 , and concentrated under reduce pressure. The crude product was purified by column chromatography (SiO_2) eluting with a gradient of 10-100% EtOAc in petroleum ether to give the title compound as a yellow solid (300 mg, 48.3%). ESI-MS m/z $[\text{M}+\text{H}]^+ = 491.2$.

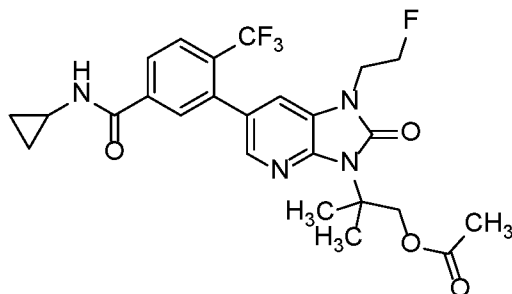
[0733] STEP 2: *N*-cyclopropyl-2,4-difluoro-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)benzamide

[0734] To a solution of 2-(6-(5-(cyclopropylcarbamoyl)-2,4-difluorophenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (300 mg, 611.65 μmol) in MeOH (3 mL) was added K_2CO_3 (84.53 mg, 611.65 μmol). The reaction mixture was stirred at 50°C for 15 minutes, then adjusted to pH 3 with HCl (1 M), poured into water, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 , and concentrated under reduce pressure. The crude product was purified by recrystallization from EtOH (5 mL) to give the title compound as a white solid (108.1 mg, 39.4%). ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 0.50 - 0.60 (m, 2 H) 0.67 - 0.80 (m, 2 H) 1.73 (s, 6 H) 2.82 - 2.86 (m, 1 H) 3.92 (d, $J=6.4$ Hz, 2 H) 4.12 - 4.32 (m, 2 H) 4.57 - 4.83 (m, 2 H) 4.90 - 4.95 (m, 1 H) 7.51 (t, $J=10.4$ Hz, 1 H) 7.67 - 7.83 (m, 2 H) 8.16 (s, 1 H) 8.45 (d, $J=4.0$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 449.3$.

[0735] EXAMPLE 56: *N*-cyclopropyl-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-(trifluoromethyl)benzamide



[0736] STEP 1: 2-(6-(5-(cyclopropylcarbamoyl)-2-(trifluoromethyl)phenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate

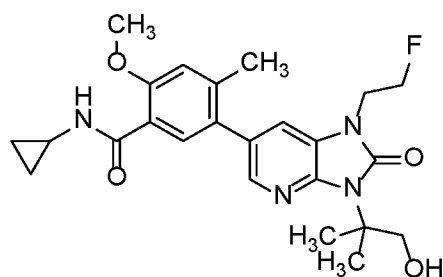


[0737] To a solution of 3-bromo-*N*-cyclopropyl-4-(trifluoromethyl)benzamide (80 mg, 259.66 μ mol) in dioxane (2 mL) and water (0.4 mL) were added 2-(1-(2-fluoroethyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (109.39 mg, 259.66 μ mol), K_2CO_3 (107.66 mg, 778.98 μ mol) and $Pd(dppf)Cl_2$ (19.00 mg, 25.97 μ mol). The reaction mixture was stirred at 90°C under N_2 for 12 hours, then poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 , concentrated under reduce pressure. The crude product was purified by column chromatography (SiO_2) eluting with a gradient of 8-50% EtOAc in petroleum ether to give the title compound as a yellow solid (100 mg, 74%). ESI-MS m/z $[M+H]^+ = 523.2$.

[0738] STEP 2: *N*-cyclopropyl-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-(trifluoromethyl)benzamide

[0739] To a solution of 2-(6-(5-(cyclopropylcarbamoyl)-2-(trifluoromethyl)phenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (100 mg, 191.39 μ mol) in MeOH (1.5 mL) was added K_2CO_3 (26.45 mg, 191.39 μ mol). The reaction mixture was stirred at 50°C for 30 minutes, then adjusted to pH 3 with HCl (1 M), poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 , and concentrated under reduce pressure. The crude product was purified by preparative HPLC to give the title compound as a white solid (27.8 mg, 30.2%). ^1H NMR (400 MHz, $DMSO-d_6$) δ ppm 0.53 - 0.62 (m, 2 H) 0.65 - 0.78 (m, 2 H) 1.74 (s, 6 H) 2.80 - 2.90 (m, 1 H) 3.93 (d, $J=5.6$ Hz, 2 H) 4.10 - 4.27 (m, 2 H) 4.56 - 4.77 (m, 2 H) 4.80 - 4.97 (m, 1 H) 7.56 (s, 1 H) 7.89 (s, 1 H) 7.93 - 8.00 (m, 2 H) 8.04 - 8.09 (m, 1 H) 8.67 (d, $J=4.0$ Hz, 1 H); ESI-MS m/z $[M+H]^+ = 481.3$.

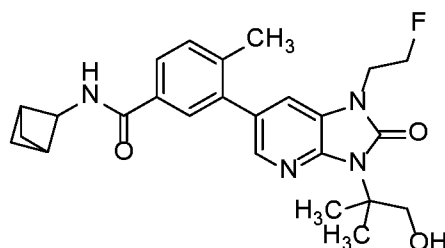
[0740] EXAMPLE 57: *N*-cyclopropyl-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2-methoxy-4-methylbenzamide



[0741] The title compound was prepared like EXAMPLE 56, starting with 5-bromo-*N*-cyclopropyl-2-methoxy-4-methylbenzamide in place of 3-bromo-*N*-cyclopropyl-4-(trifluoromethyl)benzamide, and proceeding through intermediate 2-(6-(5-

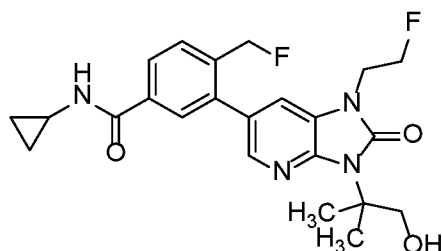
(cyclopropylcarbamoyl)-4-methoxy-2-methylphenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate. The title compound was obtained as a white solid (25 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.51 - 0.58 (m, 2 H) 0.61 - 0.80 (m, 2 H) 1.73 (s, 6 H) 2.26 - 2.36 (m, 3 H) 2.70 - 2.84 (m, 1 H) 3.86 - 3.96 (m, 5 H) 4.11 - 4.27 (m, 2 H) 4.55 - 4.78 (m, 2 H) 5.01 (br t, *J*=6.0 Hz, 1 H) 7.10 (s, 1 H) 7.52 (d, *J*=1.2 Hz, 1 H) 7.57 (s, 1 H) 7.92 (d, *J*=2.0 Hz, 1 H) 8.05 (d, *J*=4.0 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 457.3.

[0742] EXAMPLE 58: *N*-(bicyclo[1.1.1]pentan-2-yl)-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



[0743] The title compound was prepared like EXAMPLE 56, starting with *N*-(bicyclo[1.1.1]pentan-2-yl)-3-bromo-4-methylbenzamide in place of 3-bromo-*N*-cyclopropyl-4-(trifluoromethyl)benzamide, and proceeding through intermediate 2-(6-(5-(bicyclo[1.1.1]pentan-2-ylcarbamoyl)-2-methylphenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate. The title compound was obtained as a yellow solid (101.32 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.73 (s, 6 H) 2.07 (s, 6 H) 2.31 (s, 3 H) 2.45 (s, 1 H) 3.93 (d, *J*=6.4 Hz, 2 H) 4.16 (t, *J*₁=4.4 Hz, *J*₂=4.0 Hz, 1 H) 4.20 - 4.26 (m, 1 H) 4.62 (t, *J*=4.8 Hz, 1 H) 4.74 (t, *J*=4.8 Hz, 1 H) 5.01 (t, *J*=6.4 Hz, 1 H) 7.40 (d, *J*=8.0 Hz, 1 H) 7.61 (s, 1 H) 7.73 - 7.79 (m, 2 H) 7.99 (d, *J*=1.6 Hz, 1 H) 8.93 (s, 1 H); ESI-MS *m/z* [M+H]⁺ = 453.1.

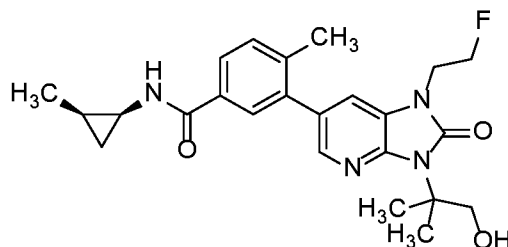
[0744] EXAMPLE 59: *N*-cyclopropyl-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-(fluoromethyl)benzamide



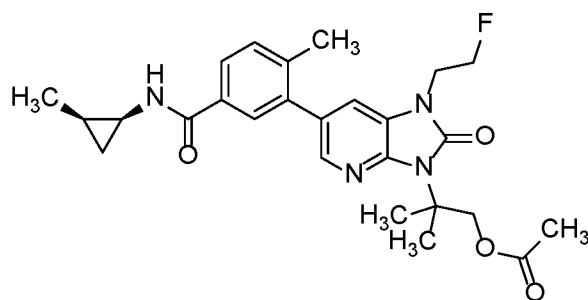
[0745] The title compound was prepared like EXAMPLE 56, starting with 3-bromo-*N*-cyclopropyl-4-(fluoromethyl)benzamide in place of 3-bromo-*N*-cyclopropyl-4-

(trifluoromethyl)benzamide, and proceeding through intermediate 2-(6-(5-(cyclopropylcarbamoyl)-2-(fluoromethyl)phenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate. The title compound was obtained as a white solid (16 mg). ESI-MS m/z $[M+H]^+ = 445.2$.

[0746] EXAMPLE 60: 3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-((1*S*,2*R*)-2-methylcyclopropyl)benzamide



[0747] STEP 1: 2-(1-(2-fluoroethyl)-6-(2-methyl-5-(((1*S*,2*R*)-2-methylcyclopropyl)carbamoyl)phenyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate



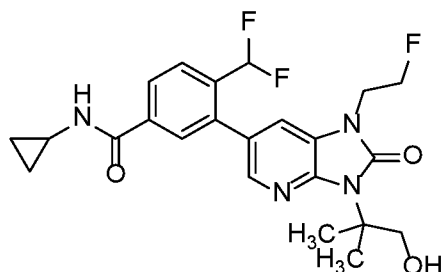
[0748] To a solution of 3-bromo-4-methyl-*N*-((1*S*,2*R*)-2-methylcyclopropyl)benzamide (80 mg, 298.34 μmol) and 2-(1-(2-fluoroethyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (138.25 mg, 328.18 μmol) in dioxane (5 mL) and water (0.5 mL) were added Na_2CO_3 (79.05 mg, 745.85 μmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (21.83 mg, 29.83 μmol) under N_2 . The reaction mixture was stirred at 90°C for 12 hours under N_2 and then diluted with EtOAc. The organic phase was washed with water and brine, dried over Na_2SO_4 , filtered, concentrated under reduced pressure and purified by preparative TLC (SiO_2) eluting with 50% EtOAc in petroleum ether to give the title compound as a yellow oil (90 mg, 63%). ^1H NMR (400 MHz, CDCl_3) δ ppm 0.23 (d, $J=4.4$ Hz, 1 H) 1.02 – 1.10 (m, 1 H) 1.13 (s, 4 H) 1.92 (s, 6 H) 2.02 (s, 3 H) 2.33 (s, 3 H) 2.94 (s, 1 H) 4.13 (t, $J=4.4$ Hz, 1 H) 4.20 (t, $J=4.4$ Hz, 1 H) 4.67 (t, $J=4.8$ Hz, 1 H) 4.77 (s, 2 H) 4.79 – 4.81 (m, 1 H) 7.21 (s, 1 H) 7.35 – 7.39 (m, 1 H) 7.63 (d, $J=2.0$ Hz, 1 H) 7.67 (dd, $J=$

2.0, 8.0 Hz, 1 H) 7.96 (d, $J=2.0$ Hz, 1 H) 8.18 (d, $J=2.0$ Hz, 1 H); ESI-MS m/z $[M+H]^+ = 483.3$.

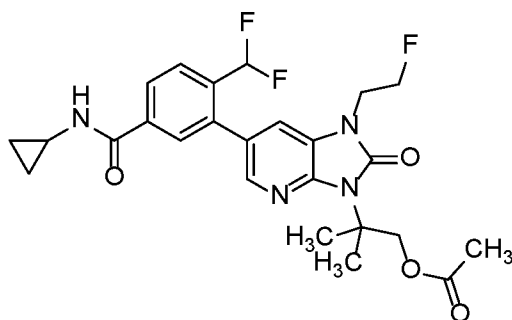
[0749] STEP 2: *N*-cyclopropyl-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-(fluoromethyl)benzamide

[0750] To a mixture of 2-(1-(2-fluoroethyl)-6-(2-methyl-5-(((1*S*,2*R*)-2-methylcyclopropyl)carbamoyl)phenyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (90 mg, 186.51 μ mol) in THF (5 mL), DMF (0.5 mL), MeOH (2 mL) and water (1 mL) were added LiOH.H₂O (39.13 mg, 932.55 μ mol) and K₂CO₃ (51.55 mg, 373.02 μ mol). The reaction mixture was stirred at 50°C for 15 minutes under N₂ and then diluted with EtOAc. The organic phase was washed with water and brine, dried over Na₂SO₄, filtered, concentrated under reduced pressure and purified by preparative HPLC to give the title compound as a white solid (39 mg, 46%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.39 (d, $J=5.2$ Hz, 1 H) 0.85 (d, $J=5.6$ Hz, 1 H) 0.94 (s, 4 H) 1.73 (s, 6 H) 2.31 (s, 3 H) 2.81 (s, 1 H) 3.93 (d, $J=6.0$ Hz, 2 H) 4.16 (t, $J=4.8$ Hz, 1 H) 4.22 (t, $J=4.4$ Hz, 1 H) 4.61 (t, $J=4.4$ Hz, 1 H) 4.73 (t, $J=4.8$ Hz, 1 H) 5.00 (t, $J=6.4$ Hz, 1 H) 7.41 (d, $J=8.0$ Hz, 1 H) 7.60 (s, 1 H) 7.75 – 7.80 (m, 2 H) 7.99 (s, 1 H) 8.22 (d, $J=3.2$ Hz, 1 H); ESI-MS m/z $[M+H]^+ = 441.2$.

[0751] EXAMPLE 61: *N*-cyclopropyl-4-(difluoromethyl)-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)benzamide



[0752] STEP 1: 2-(6-(5-(cyclopropylcarbamoyl)-2-(difluoromethyl)phenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate



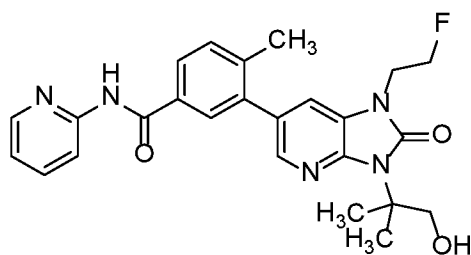
[0753] To a solution of 3-bromo-*N*-cyclopropyl-4-(difluoromethyl)benzamide (60 mg, 206.82 μ mol) and 2-(1-(2-fluoroethyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

yl)-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (104.55 mg, 248.18 μ mol) in dioxane (2 mL) and water (0.5 mL) were added Na_2CO_3 (65.76 mg, 620.46 μ mol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (7.57 mg, 10.34 μ mol). The reaction mixture was degassed and purged with N_2 (3 x), stirred at 90°C for 6 hours under N_2 atmosphere, and then poured into water and extracted with EtOAc. The organic phase was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2) eluting with EtOAc to give the title compound as a yellow oil (60 mg, 58%). ESI-MS m/z $[\text{M}+\text{H}]^+ = 505.2$.

[0754] STEP 2: *N*-cyclopropyl-4-(difluoromethyl)-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)benzamide

[0755] A solution of 2-(6-(5-(cyclopropylcarbamoyl)-2-(difluoromethyl)phenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (60 mg, 118.93 μ mol) and K_2CO_3 (16.44 mg, 118.93 μ mol) in MeOH (2 mL) was degassed and purged with N_2 (3 x) and stirred at 50°C for 10 minutes under N_2 atmosphere. The mixture was then poured into water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by preparative HPLC to give the title compound as an off-white solid (11.11 mg, 20%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 0.58-0.60 (m, 2 H) 0.71-0.76 (m, 2 H) 1.73 (s, 6 H) 2.87 (dd, $J_1=7.2, J_2=6.8$, 1 H) 3.93 (s, 2 H) 4.25 - 4.14 (m, 2 H) 4.67 - 4.52 (m, 1 H) 4.75 (s, 1 H) 4.98 (s, 1 H) 7.14 - 6.83 (m, 1 H) 7.59 (s, 1 H) 7.88 - 7.82 (m, 2 H) 8.05 - 7.94 (m, 2 H) 8.62 (d, $J=3.6$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 463.1$.

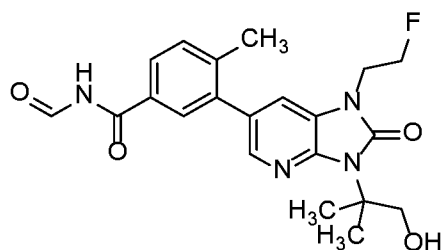
[0756] EXAMPLE 62: 3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-(pyridin-2-yl)benzamide



[0757] The title compound was prepared like EXAMPLE 56, starting with 3-bromo-4-methyl-*N*-(pyridin-2-yl)benzamide in place of 3-bromo-*N*-cyclopropyl-4-(trifluoromethyl)benzamide, and proceeding through intermediate 2-(1-(2-fluoroethyl)-6-(2-methyl-5-(pyridin-2-ylcarbamoyl)phenyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate. The title compound was obtained as a brown solid (12.9 mg,

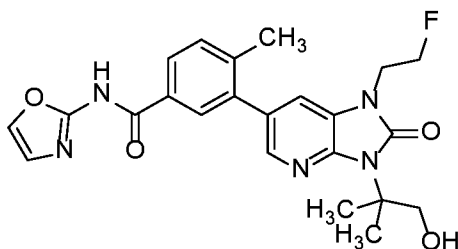
21.7%). ^1H NMR (400 MHz, CD_3OD) δ ppm 1.78 (s, 6 H), 2.38 (s, 3 H), 4.1 (s, 2 H), 4.20 - 4.29 (m, 2 H), 4.64 - 4.79 (m, 2 H), 7.15 - 7.18 (m, 1 H), 7.50 (d, $J=8.0$ Hz, 1 H), 7.55 (s, 1 H), 7.82 - 7.93 (m, 3 H), 8.06 (s, 1 H), 8.22 (d, $J=8.8$ Hz, 1 H), 8.35 (d, $J=4.8$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 464.20$.

[0758] EXAMPLE 63: 3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-formyl-4-methylbenzamide

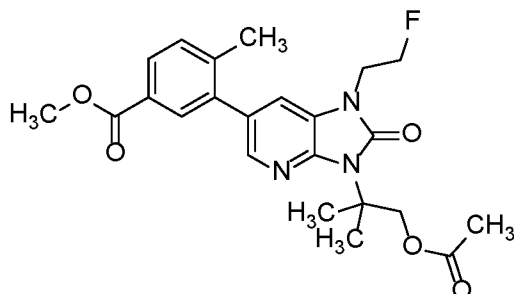


[0759] A mixture of 2-(6-(5-carbamoyl-2-methylphenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (100 mg, 233.40 μmol) and DMF-DMA (897.00 mg, 7.53 mmol, 1 mL) was stirred at 100°C for 2 hours under N_2 . The mixture was then concentrated *in vacuo* and purified by preparative HPLC to give the title compound as an off-white solid (15.47 mg, 16%). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.75 (s, 6 H) 2.38 (s, 3 H) 4.06 (s, 2 H) 4.06 - 4.24 (m, 2 H) 4.68-4.81 (m, 2 H) 5.51 (m, 1 H) 7.29 (m, 1 H) 7.48 (d, $J=7.6$ Hz, 1 H) 7.74 - 7.79 (m, 2 H) 7.97 (d, $J=2.0$ Hz, 1 H) 8.85 (s, 1 H) 9.36 (d, $J=9.6$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 415.2$.

[0760] EXAMPLE 64: 3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-(oxazol-2-yl)benzamide

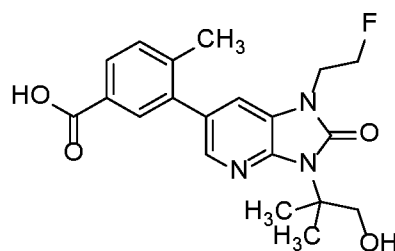


[0761] STEP 1: methyl 3-(3-(1-acetoxy-2-methylpropan-2-yl)-1-(2-fluoroethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzoate



[0762] To a solution of methyl 3-bromo-4-methylbenzoate (100 mg, 436.55 μmol) in dioxane (2 mL) and water (0.4 mL) were added 2-(1-(2-fluoroethyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (183.90 mg, 436.55 μmol), K_2CO_3 (181.00 mg, 1.31 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (31.94 mg, 43.65 μmol). The reaction mixture was stirred at 90°C for 5 hours under N_2 and then concentrated. The resulting residue was diluted with water and extracted with EtOAc. The organic layers were combined, concentrated and purified by column chromatography, eluting with a gradient of 0-20% EtOAc in petroleum ether to give the title compound as a light-yellow oil (120 mg, 62%). ^1H NMR (400 MHz, CD_3OD) δ ppm 3.90(s, 3 H) 4.17 - 4.19(m, 1 H) 4.24 - 4.26 (m, 1 H) 4.56(s, 2 H) 4.62 - 4.64 (m, 1 H) 4.74 (s, 1 H) 7.43 - 7.45 (m, 2 H) 7.88 (s, 1 H) 7.93 - 7.96 (m, 2 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 444.19$.

[0763] STEP 2: 3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzoic acid



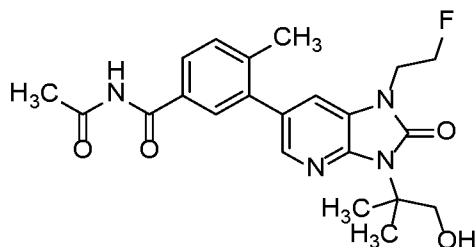
[0764] To a solution of methyl 3-(3-(1-acetoxy-2-methylpropan-2-yl)-1-(2-fluoroethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzoate (60 mg, 135.30 μmol) in THF (0.5 mL) and water (0.5 mL) was added LiOH (6.48 mg, 270.60 μmol). The reaction mixture was stirred at 25°C for 1 hour, then diluted with water, adjusted to pH 3 with aq HCl (1 M) and extracted with EtOAc. The organic layers were combined and concentrated to give the title compound as a light-yellow oil (50 mg, 95%). ^1H NMR (400 MHz, CD_3OD) δ ppm 1.78 (s, 6 H) 2.35 (s, 3 H) 4.19 - 4.28 (m, 2 H) 4.63 - 4.66 (m, 1 H) 4.75 - 4.77 (m, 2 H) 7.44 (d, $J=8.0$ Hz, 1 H) 7.49 (s, 1 H) 7.89 - 7.99 (m, 3 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 388.16$.

[0765] STEP 3: 3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-(oxazol-2-yl)benzamide

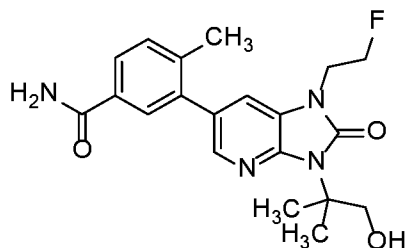
[0766] To a solution of 3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzoic acid (50 mg, 129.06 μmol) in DMF (1 mL) were added oxazol-2-amine (10.85 mg, 129.06 μmol), HOBt (19.18 mg, 141.97 μmol), Et_3N (516.26 μmol , 71.86 μL), EDCI (27.22 mg, 141.97 μmol) and DMAP (31.54 mg, 258.13 μmol). The reaction mixture was stirred at 90°C for 12 hours under N_2 , the

diluted with water and extracted with EtOAc. The organic layers were combined and concentrated. The resulting residue was purified by preparative HPLC to give the title compound as a brown solid (3 mg, 5%). ^1H NMR (400 MHz, CD_3OD) δ ppm 1.78 (s, 6H) 2.37 (s, 3H) 4.1 (s, 2 H) 4.21 - 4.29 (m, 2 H) 4.64 - 4.77 (m, 2 H) 7.18 (s, 1 H) 7.53 (s, 2 H) 7.74 (s, 1H) 7.82 - 7.92 (m, 2 H) 8.03 (s, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 454.18$.

[0767] EXAMPLE 65: *N*-acetyl-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

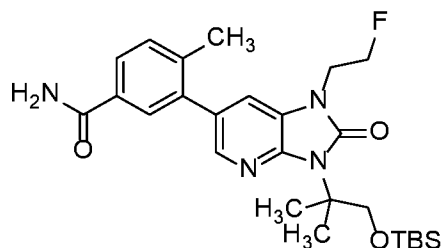


[0768] STEP 1: 3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



[0769] To a solution of 2-(6-(5-carbamoyl-2-methylphenyl)-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (100 mg, 233.40 μmol) in MeOH (1 mL) was added K_2CO_3 (32.26 mg, 233.40 μmol). The reaction mixture was stirred at 60°C for 20 minutes and then concentrated *in vacuo* to give the title compound (90 mg, crude). ESI-MS m/z $[\text{M}+\text{H}]^+ = 387.1$.

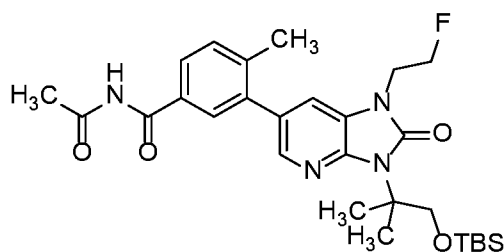
[0770] STEP 2: 3-(3-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-1-(2-fluoroethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



[0771] To a mixture of 3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide (90 mg, 232.91 μmol) and imidazole (23.78 mg, 349.36 μmol) in DCM (1 mL) was added TBSCl (42.12 mg, 279.49

μmol). The reaction mixture was stirred at 25°C for 2 hours, then poured into water and extracted with DCM. The organic layer was concentrated *in vacuo* and purified by preparative TLC to give the title compound as a white solid (90 mg, 77%). ESI-MS m/z $[M+H]^+ = 501.2$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm -0.12(s, 6 H) 0.74 (s, 9 H) 1.89 (s, 6 H) 2.32 (s, 3 H) 4.06 - 4.18 (m, 4 H) 4.63 - 4.77 (m, 2 H) 5.53 - 6.04 (m, 2 H) 7.18 (m, 1 H) 7.38 (d, $J = 8.0$ Hz, 1 H) 7.69 - 7.73 (m, 2 H) 7.95 (s, 1 H).

[0772] STEP 3: *N*-acetyl-3-(3-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-1-(2-fluoroethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

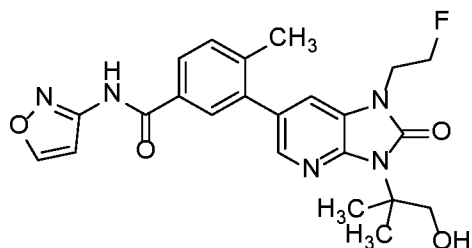


[0773] A mixture of 3-(3-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-1-(2-fluoroethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide (90 mg, 179.76 μmol) and acetic anhydride (1.09 g, 10.68 mmol) was stirred at 80°C for 12 hours, then concentrated *in vacuo* and purified by preparative TLC to give the title compound as a white solid (30 mg, 31%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm -0.12 (s, 6 H) 0.75 (s, 9 H) 1.89 (s, 6 H) 2.35 (s, 3 H) 2.63 (s, 3 H) 4.10 - 4.19 (m, 4 H) 4.63 - 4.77 (m, 2 H) 7.17 (t, $J = 1.6$ Hz, 1 H) 7.43 (d, $J = 7.6$ Hz, 1 H) 7.70 - 7.75 (m, 2 H) 7.94 (d, $J = 2.0$ Hz, 1 H) 8.50 (s, 1 H); ESI-MS m/z $[M+H]^+ = 543.3$.

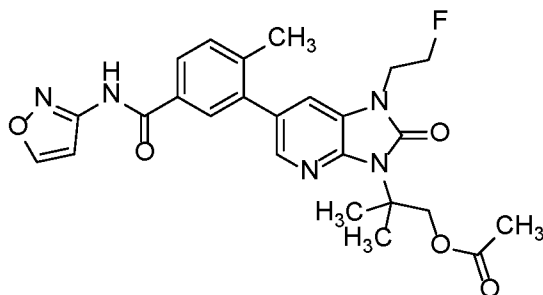
[0774] STEP 4: *N*-acetyl-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

[0775] A mixture of *N*-acetyl-3-(3-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-1-(2-fluoroethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide (10 mg, 18.43 μmol) and HCl (1 M, 0.5 mL) in THF (1 mL) was stirred at 25°C for 10 minutes, then concentrated *in vacuo* at 25°C and purified by preparative HPLC to give the title compound as a brown solid (7.59 mg, 96%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.72 (s, 6 H) 2.35 (m, 6 H) 3.92 (d, $J = 4.8$ Hz, 2 H) 4.14-4.24 (m, 2 H) 4.61 - 4.75 (m, 2 H) 5.01 (s, 1 H) 7.47 (d, $J = 8.0$ Hz, 1 H) 7.61 (d, $J = 1.2$ Hz, 1 H) 7.25 - 7.17 (m, 2 H) 7.83 - 7.86 (m, 4 H) 8.02 (d, $J = 2.0$ Hz, 1 H) 10.98 (s, 1 H); ESI-MS m/z $[M+H]^+ = 429.2$.

[0776] EXAMPLE 66: 3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-(isoxazol-3-yl)-4-methylbenzamide



[0777] STEP 1: 2-(1-(2-fluoroethyl)-6-(5-(isoxazol-3-ylcarbamoyl)-2-methylphenyl)-2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)-2-methylpropyl acetate



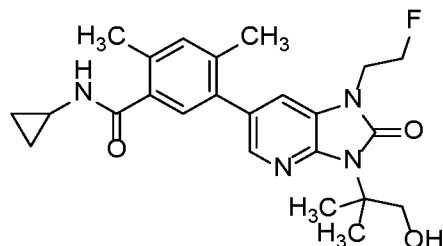
[0778] To a solution of *N*-(isoxazol-3-yl)-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (80 mg, 213.79 μmol) and 2-(6-bromo-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)-2-methylpropyl acetate (77.17 mg, 235.17 μmol) in dioxane (3 mL) and water (0.3 mL) were added Na_2CO_3 (67.98 mg, 641.36 μmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (15.64 mg, 21.38 μmol). The reaction mixture was stirred at 90°C for 2 hours under N_2 and then diluted with water. The aqueous phase was extracted with EtOAc and the organic layers were combined, washed with brine, dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by preparative TLC, eluting with EtOAc to give the title compound as a brown oil (67 mg, 63%). ESI-MS m/z $[\text{M}+\text{H}]^+ = 496.3$.

[0779] STEP 2: 3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-6-yl)-*N*-(isoxazol-3-yl)-4-methylbenzamide

[0780] To a solution of 2-(1-(2-fluoroethyl)-6-(5-(isoxazol-3-ylcarbamoyl)-2-methylphenyl)-2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)-2-methylpropyl acetate (65 mg, 131.18 μmol) in THF (3 mL), DMF (0.3 mL) and water (0.02 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (27.52 mg, 655.90 μmol). The reaction mixture was stirred at 50°C for 5 hours, then diluted with saturated aq NH_4Cl . The aqueous phase was extracted with EtOAc, and the organic layers were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was purified by preparative HPLC to give the title compound as a white solid (15 mg, 25%). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.75 (d, $J=1.6$ Hz, 6 H) 2.38 (s, 3 H) 4.07 (s, 2 H) 4.14 - 4.26 (m, 2 H) 4.66 - 4.83 (m, 2 H) 5.55 (s, 1 H)

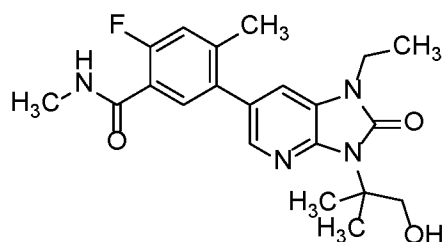
7.22 (s, 1 H) 7.30 (d, $J=1.2$ Hz, 1 H) 7.46 (d, $J=7.6$ Hz, 1 H) 7.80 - 7.89 (m, 2 H) 7.96 - 8.04 (m, 1 H) 8.32 (s, 1 H) 9.02 (s, 1 H); ESI-MS m/z $[M+H]^+ = 454.2$.

[0781] EXAMPLE 67: *N*-cyclopropyl-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2,4-dimethylbenzamide

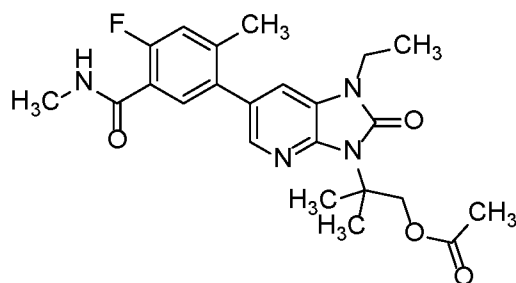


[0782] To a solution of 2-(6-bromo-1-(2-fluoroethyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (157 mg, 0.373 mmol), 5-bromo-*N*-cyclopropyl-2,4-dimethylbenzamide (100 mg, 0.373 mmol) and K_2CO_3 (155 mg, 1.12 mmol) in dioxane (3 mL) and water (1 mL) was added XPhos Pd G3 (6.31 mg, 0.007 mmol) under N_2 . The reaction mixture was heated to 120°C for 15 hours under N_2 and then concentrated under reduced pressure. The resulting residue was diluted with water and extracted with EtOAc. The organic layers were combined, washed with water, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude product was purified by preparative HPLC to give the title compound as a white solid (68.2 mg, 41.5%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.48 - 0.52 (m, 2 H) 0.64 - 0.69 (m, 2 H) 1.71 (s, 6 H) 2.26 (s, 3 H) 2.35 (s, 3 H) 2.84 - 2.79 (m, 1 H) 3.92 (s, 2 H) 4.15 - 4.24 (m, 2 H) 4.61 (t, $J=4.8$ Hz, 1 H) 4.73 (t, $J=4.8$ Hz, 1 H) 4.99 (s, 1 H) 7.18 (d, $J=3.2$ Hz, 2 H) 7.54 (d, $J=1.2$ Hz, 1 H) 7.95 (s, 1 H) 8.22 (d, $J=4.4$ Hz, 1 H); ESI-MS m/z $[M+H]^+ = 441.0$.

[0783] EXAMPLE 68: 5-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2-fluoro-*N*,4-dimethylbenzamide



[0784] STEP 1: 2-(1-ethyl-6-(4-fluoro-2-methyl-5-(methylcarbamoyl)phenyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate

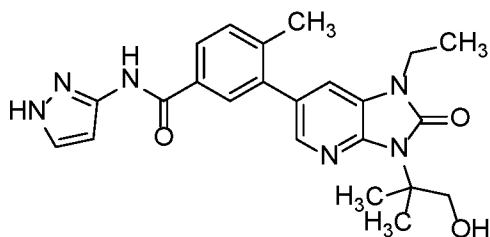


[0785] A mixture of 5-bromo-2-fluoro-*N*,4-dimethylbenzamide (60 mg, 217.01 μmol), 2-(1-ethyl-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (96.27 mg, 238.71 μmol), K_2CO_3 (74.98 mg, 542.52 μmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (15.88 mg, 21.70 μmol) in dioxane (5 mL) and water (0.5 mL) was heated to 100°C and stirred for 12 hours under N_2 . The reaction mixture was then concentrated *in vacuo* and the resulting residue purified by preparative TLC, eluting with 10% DCM in MeOH to give the title compound as a yellow oil (25 mg, 24%). ESI-MS m/z $[\text{M}+\text{H}]^+ = 443.1$.

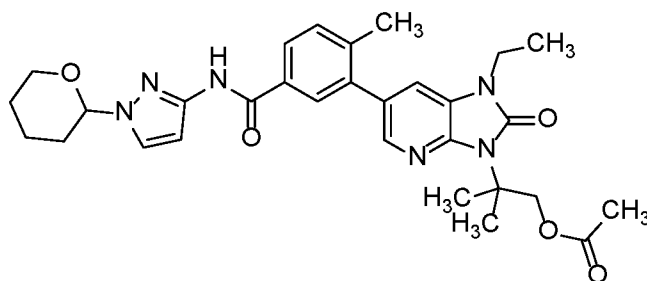
[0786] STEP 2: 5-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2-fluoro-*N*,4-dimethylbenzamide

[0787] A mixture of 2-(1-ethyl-6-(4-fluoro-2-methyl-5-(methylcarbamoyl)phenyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (25 mg, 51.41 μmol), water (500.00 mg, 27.75 mmol) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (6.16 mg, 146.79 μmol) in THF (5 mL) and DMF (0.5 mL) was heated to 50°C and stirred for 5 hours under N_2 . Ethyl acetate and water were added to the mixture and layers were separated. The aqueous layer was extracted with EtOAc, and the organic layers were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The resulting residue was purified by preparative HPLC to give the title compound as a white solid (8.93 mg, 43.4%). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.35 (t, $J=7.20$ Hz, 3 H), 1.74 (s, 6 H), 2.34 (s, 3 H), 3.06 (d, $J=4.64$ Hz, 3 H), 3.94 (q, $J=7.06$ Hz, 2 H), 4.05 (d, $J=6.10$ Hz, 2 H), 5.64 (s, 1 H), 6.75 (s, 1 H), 7.08 (d, $J=12.72$ Hz, 1 H), 7.13 (d, $J=1.58$ Hz, 1 H), 7.92 (d, $J=1.58$ Hz, 1 H), 8.01 (d, $J=8.30$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 401.3$.

[0788] EXAMPLE 69: 3-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-(1*H*-pyrazol-3-yl)benzamide



[0789] STEP 1: 2-(1-ethyl-6-(2-methyl-5-((1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)carbamoyl)phenyl)-2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)-2-methylpropyl acetate



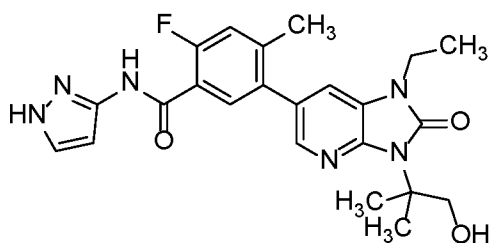
[0790] To a mixture of 3-bromo-4-methyl-N-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)benzamide (119 mg, 289.79 μmol) and 2-(1-ethyl-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)-2-methylpropyl acetate (175.30 mg, 434.69 μmol) in dioxane (3 mL) and water (0.3 mL) were added K_2CO_3 (120.16 mg, 869.38 μmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (10.60 mg, 14.49 μmol) at 20°C. The suspension was degassed under vacuum and purged with nitrogen (3 x). The reaction mixture was heated to 90°C and stirred for 7 hours under nitrogen, then diluted with water and extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by preparative TLC (SiO_2) eluting with 67% EtOAc in petroleum ether to give the title compound as a light-yellow solid (101 mg, 41.2%). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.32 - 1.36 (m, 3 H) 1.91 (s, 6 H) 1.99 - 2.02 (m, 4 H) 2.04 (s, 2 H) 2.08 (s, 3 H) 2.37 (s, 3 H) 3.90 - 3.95 (m, 2 H) 4.03 - 4.17 (m, 2 H) 4.76 - 4.77 (m, 2 H) 5.24 (dd, $J_1=2.00$ Hz, $J_2=8.40$ Hz, 1 H) 6.91 (d, $J=2.40$ Hz, 1 H) 7.10 - 7.12 (m, 1 H) 7.41 (d, $J=8.40$ Hz, 1 H) 7.54 (d, $J=2.40$ Hz, 1 H) 7.77 - 7.81 (m, 2 H) 7.95 (d, $J=2.00$ Hz, 1 H) 8.64 (s, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 561.4$.

[0791] STEP 2: 3-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-6-yl)-4-methyl-N-(1H-pyrazol-3-yl)benzamide

[0792] To 2-(1-ethyl-6-(2-methyl-5-((1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)carbamoyl)phenyl)-2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)-2-methylpropyl acetate (101 mg, 180.15 μmol) was added HCl in dioxane (4 M, 5 mL) at 20°C. The reaction

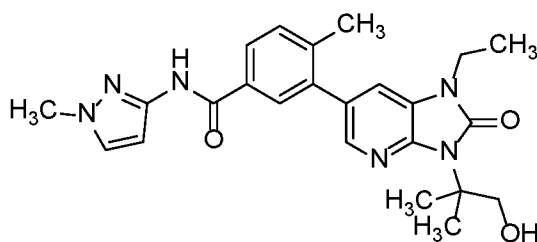
mixture was stirred at 20°C for 15 hours under nitrogen, then diluted with water, adjusted to pH 7-8 by addition of saturated aq NaHCO₃ and extracted with EtOAc. The organic layers were combined, dried over Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by preparative HPLC to give the title compound as a white solid (10 mg, 13%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.36 (t, *J*=8.00 Hz, 3 H) 1.75 (s, 6 H) 2.38 (s, 3 H) 3.91 - 3.98 (m, 2 H) 4.06 (s, 2 H) 6.86 (s, 1 H) 7.18 (d, *J*=1.60 Hz, 1 H) 7.43 (d, *J*=8.00 Hz, 1 H) 7.54 (s, 1 H) 7.79 - 7.85 (m, 2 H) 7.97 (d, *J*=1.60 Hz, 1 H) 8.74 (s, 1 H); ESI-MS *m/z* [M+H]⁺ = 435.3.

[0793] EXAMPLE 70: 5-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2-fluoro-4-methyl-*N*-(1*H*-pyrazol-3-yl)benzamide

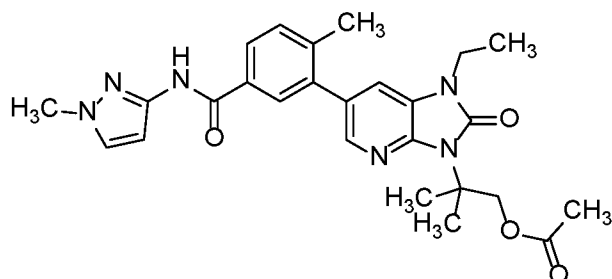


[0794] The title compound was prepared like EXAMPLE 69, starting with 5-bromo-2-fluoro-4-methyl-*N*-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)benzamide in place of 3-bromo-4-methyl-*N*-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)benzamide, and proceeding through intermediate 2-(1-ethyl-6-(4-fluoro-2-methyl-5-((1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)carbamoyl)phenyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate. The title compound was obtained as a white solid (12.20 mg). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.36 (t, *J*=7.20 Hz, 3 H) 1.74 (s, 6 H) 2.37 (s, 3 H) 3.90 - 3.98 (m, 2 H) 4.05 (s, 2 H) 5.61 (s, 1 H) 6.81 (d, *J*=2.00 Hz, 1 H) 7.13 - 7.19 (m, 2 H) 7.55 (d, *J*=2.40 Hz, 1 H) 7.94 (d, *J*=2.00 Hz, 1 H) 8.07 (d, *J*=8.00 Hz, 1 H) 9.02 (d, *J*=15.20 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 453.2.

[0795] EXAMPLE 71: 3-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



[0796] STEP 1: 2-(1-ethyl-6-(2-methyl-5-((1-methyl-1*H*-pyrazol-3-yl)carbamoyl)phenyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate

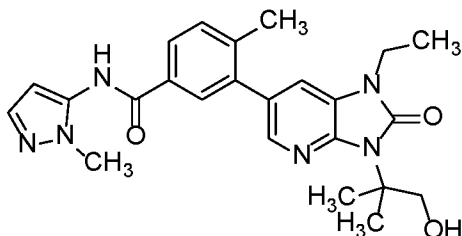


[0797] A solution of 3-bromo-4-methyl-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (100 mg, 339.97 μmol), 2-(1-ethyl-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (150.81 mg, 373.96 μmol), K_2CO_3 (140.96 mg, 1.02 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (12.44 mg, 17.00 μmol) in dioxane (5 mL) and water (0.5 mL) was stirred at 95°C for 16 hours under N_2 and then concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2) eluting with a gradient of 0-20% EtOAc in petroleum ether to give the title compound as a black solid (168 mg, crude). ESI-MS m/z $[\text{M}+\text{H}]^+ = 491.4$.

[0798] STEP 2: 3-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide

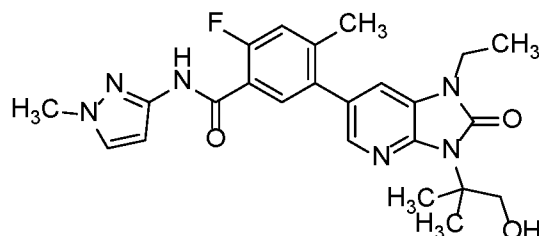
[0799] To a solution of 2-(1-ethyl-6-(2-methyl-5-((1-methyl-1*H*-pyrazol-3-yl)carbamoyl)phenyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (168 mg, 342.47 μmol) in MeOH (2 mL) was added K_2CO_3 (94.66 mg, 684.94 μmol). The reaction mixture was stirred at 50°C for 6 hours and then filtered. The filtrate was concentrated under reduced pressure and purified by preparative HPLC to give the title compound as a white solid (62.38 mg, 40.6%). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.37 (t, $J=7.2$ Hz, 3 H) 1.75 (s, 6 H) 2.38 (s, 3 H) 3.83 (s, 3 H) 3.93 – 3.98 (m, 2 H) 4.06 (s, 2 H) 5.65 (s, 1 H) 6.84 (d, $J=2.4$ Hz, 1 H) 7.18 (d, $J=2.0$ Hz, 1 H) 7.31 (d, $J=2.4$ Hz, 1 H) 7.44 (d, $J=8.4$ Hz, 1 H) 7.79 – 7.80 (m, 2 H) 7.97 (d, $J=1.6$ Hz, 1 H) 8.47 (s, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 449.3$.

[0800] EXAMPLE 72: 3-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-(1-methyl-1*H*-pyrazol-5-yl)benzamide



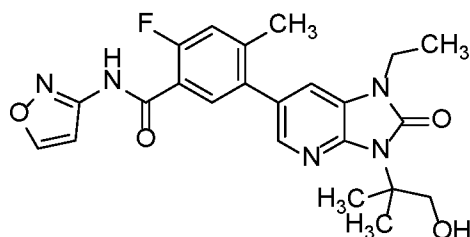
[0801] The title compound was prepared like EXAMPLE 71, starting with 3-bromo-4-methyl-*N*-(1-methyl-1*H*-pyrazol-5-yl)benzamide in place of 3-bromo-4-methyl-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide, and proceeding through intermediate 2-(1-ethyl-6-(2-methyl-5-((1-methyl-1*H*-pyrazol-5-yl)carbamoyl)phenyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate. The title compound was obtained as an off-white solid (26.08 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.22 (t, *J*=7.2 Hz, 3 H) 1.72 (s, 6 H) 2.38 (s, 3 H) 3.68 (s, 3 H) 3.84 - 3.96 (m, 4 H) 5.01 (s, 1 H) 6.21 (s, 1 H) 7.39 (d, *J*=1.6 Hz, 1 H) 7.51 (d, *J*=8.4 Hz, 1 H) 7.64 (d, *J*=1.6 Hz, 1 H) 7.87 - 7.94 (m, 2 H) 8.01 (d, *J*=1.6 Hz, 1 H) 10.28 (s, 1 H); ESI-MS *m/z* [M+H]⁺ = 449.3.

[0802] EXAMPLE 73: 5-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2-fluoro-4-methyl-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



[0803] The title compound was prepared like EXAMPLE 71, starting with 5-bromo-2-fluoro-4-methyl-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide in place of 3-bromo-4-methyl-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide, and proceeding through intermediate 2-(1-ethyl-6-(4-fluoro-2-methyl-5-((1-methyl-1*H*-pyrazol-3-yl)carbamoyl)phenyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate. The title compound was obtained as a white solid (61.97 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.21 (t, *J*= 7.2 Hz, 3 H) 1.71 (s, 6 H) 2.34 (s, 3 H) 3.77 (s, 3 H) 3.88 - 3.92 (m, 4 H), 5.00 (t, *J*= 6.4 Hz, 1 H) 6.56 (s, 1 H) 7.32 (d, *J*= 11.2 Hz, 1 H) 7.56 (d, *J*= 7.2 Hz, 1 H) 7.60 (s, 2 H) 7.98 (s, 1 H) 10.70 (s, 1 H); ESI-MS *m/z* [M+H]⁺ = 467.2.

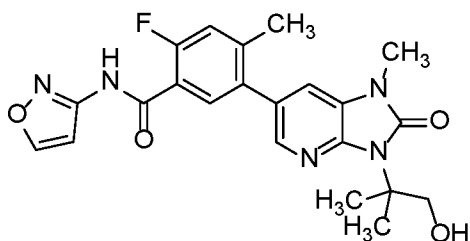
[0804] EXAMPLE 74: 5-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2-fluoro-*N*-(isoxazol-3-yl)-4-methylbenzamide



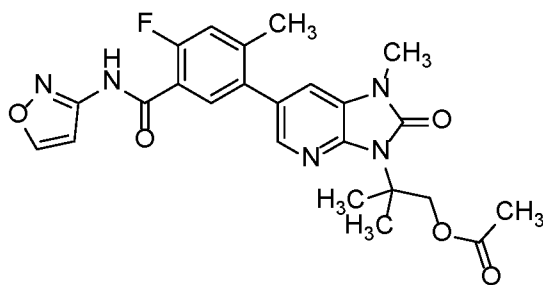
[0805] The title compound was prepared like EXAMPLE 71, starting with 5-bromo-2-fluoro-*N*-(isoxazol-3-yl)-4-methylbenzamide in place of 3-bromo-4-methyl-*N*-(1-methyl-1*H*-

pyrazol-3-yl)benzamide, and proceeding through intermediate 2-(1-ethyl-6-(4-fluoro-5-(isoxazol-3-ylcarbamoyl)-2-methylphenyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate. The title compound was obtained as a white solid (9.84 mg). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.36 (t, *J*=7.2 Hz, 3 H) 1.74 (s, 6 H) 2.39 (s, 3 H) 3.92 – 3.97 (m, 2 H) 4.06 (d, *J*=8.0 Hz, 2 H) 5.57 (t, *J*=8.0 Hz, 1 H) 7.14 (d, *J*=2.0 Hz, 1 H) 7.18 – 7.21 (m, 2 H) 7.94 (d, *J*=2.0 Hz, 1 H) 8.05 (d, *J*=8.4 Hz, 1 H) 8.36 (d, *J*=1.6 Hz, 1 H) 9.12 (d, *J*=15.2 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 454.2.

[0806] EXAMPLE 75: 2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-1-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-(isoxazol-3-yl)-4-methylbenzamide



[0807] STEP 1: 2-(6-(4-fluoro-5-(isoxazol-3-ylcarbamoyl)-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate

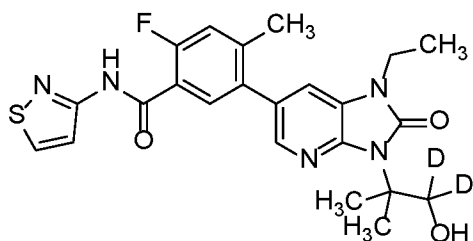


[0808] To a solution of 2-methyl-2-(1-methyl-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)propyl acetate (150 mg, 308.28 μmol) and 5-bromo-2-fluoro-*N*-(isoxazol-3-yl)-4-methylbenzamide (92.21 mg, 308.28 μmol) in dioxane (10 mL) and water (1 mL) were added K₂CO₃ (127.82 mg, 924.85 μmol) and Pd(dppf)Cl₂ (22.56 mg, 30.83 μmol). The reaction mixture was stirred at 95°C for 16 hours under N₂ and then partitioned between water and EtOAc. The organic phase was separated, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 5-50% EtOAc in petroleum ether to give the title compound as a yellow solid (70 mg, 37%). ESI-MS *m/z* [M+H]⁺ = 482.1.

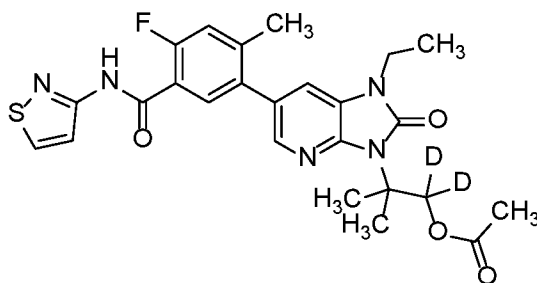
[0809] STEP 2: 2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-1-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-(isoxazol-3-yl)-4-methylbenzamide

[0810] To a solution of 2-(6-(4-fluoro-5-(isoxazol-3-ylcarbamoyl)-2-methylphenyl)-1-methyl-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl acetate (70 mg, 114.56 μ mol) in MeOH (1 mL) was added K_2CO_3 (31.67 mg, 229.13 μ mol). The reaction mixture was stirred at 50°C for 4 hours, then filtered and concentrated under reduced pressure. The resulting residue was purified by preparative HPLC to give the title compound as a yellow gum (13.16 mg, 29.9%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.74 (s, 6 H) 2.38 (s, 3 H) 3.43 (s, 3 H) 4.07 (d, $J=8.0$ Hz, 2 H) 5.55 (t, $J=8.0$ Hz, 1 H) 7.13 (d, $J=2.0$ Hz, 1 H) 7.17 – 7.21 (m, 2 H) 7.95 (d, $J=1.6$ Hz, 1 H) 8.05 (d, $J=8.0$ Hz, 1 H) 8.36 (d, $J=1.6$ Hz, 1 H) 9.12 (d, $J=5.2$ Hz, 1 H); ESI-MS m/z $[M+H]^+ = 440.2$.

[0811] EXAMPLE 76: 5-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl-1,1- d_2)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2-fluoro-*N*-(isothiazol-3-yl)-4-methylbenzamide



[0812] STEP 1: 2-(1-ethyl-6-(4-fluoro-5-(isothiazol-3-ylcarbamoyl)-2-methylphenyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1- d_2 acetate

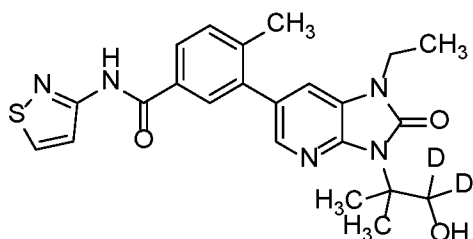


[0813] To a solution of 5-bromo-2-fluoro-*N*-isothiazol-3-yl-4-methyl-benzamide (50 mg, 158.65 μ mol) in dioxane (2 mL) and water (0.4 mL) were added 2-(1-ethyl-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1- d_2 acetate (70.73 mg, 174.51 μ mol), K_2CO_3 (65.78 mg, 475.95 μ mol) and $Pd(dppf)Cl_2$ (11.61 mg, 15.86 μ mol). The reaction mixture was stirred at 90°C under N_2 for 7 hours, then poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. The resulting residue was purified by preparative TLC (SiO_2) eluting with 50% EtOAc in petroleum ether to give the title compound as a yellow solid (30 mg, 37%). ESI-MS m/z $[M+H]^+ = 514.1$.

[0814] STEP 2: 5-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl-1,1- d_2)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2-fluoro-*N*-(isothiazol-3-yl)-4-methylbenzamide

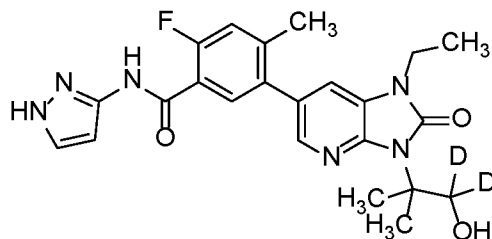
[0815] To a solution of 2-(1-ethyl-6-(4-fluoro-5-(isothiazol-3-ylcarbamoyl)-2-methylphenyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1- d_2 acetate (30 mg, 58.41 μ mol) in MeOH (1.5 mL) was added K_2CO_3 (24.22 mg, 175.24 μ mol). The reaction mixture was stirred at 50°C for 1 hour and then filtered. The filtrate was purified by preparative HPLC to give the title compound as a white solid (11.37 mg, 41.3%). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.21 (t, $J=7.2$ Hz, 3 H) 1.70 (s, 6 H) 2.35 (s, 3 H) 3.82 - 3.94 (m, 2 H) 4.97 (s, 1 H) 7.34 (d, $J=11.6$ Hz, 1 H) 7.54 - 7.65 (m, 2 H) 7.85 (d, $J=4.8$ Hz, 1 H) 8.00 (d, $J=2.0$ Hz, 1 H) 9.06 (d, $J=4.8$ Hz, 1 H) 11.47 (s, 1 H); ESI-MS m/z $[M+H]^+ = 472.2$.

[0816] EXAMPLE 77: 3-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl-1,1- d_2)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-(isothiazol-3-yl)-4-methylbenzamide

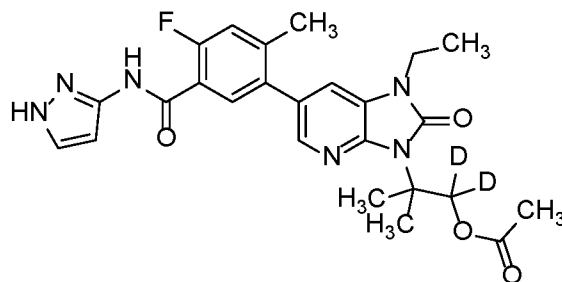


[0817] The title compound was prepared like EXAMPLE 76, starting with 3-bromo-*N*-(isothiazol-3-yl)-4-methylbenzamide in place of 5-bromo-2-fluoro-*N*-isothiazol-3-yl-4-methylbenzamide, and proceeding through intermediate 2-(1-ethyl-6-(5-(isothiazol-3-ylcarbamoyl)-2-methylphenyl)-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1- d_2 acetate. The title compound was obtained as a white solid (30 mg). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.23 (t, $J=6.8$ Hz, 3 H) 1.72 (s, 6 H) 2.39 (s, 3 H) 3.85 - 3.97 (m, 2 H) 5.00 (s, 1 H) 7.49 (d, $J=8.0$ Hz, 1 H) 7.66 (d, $J=2.0$ Hz, 1 H) 7.90 (d, $J=4.8$ Hz, 1 H) 7.96 (dd, $J_1 = 2.0$, $J_2 = 8.0$ Hz, 1 H) 8.00 (d, $J=1.6$ Hz, 1 H) 8.05 (d, $J=2.0$ Hz, 1 H) 9.05 (d, $J=4.8$ Hz, 1 H) 11.48 (s, 1 H); ESI-MS m/z $[M+H]^+ = 454.1$.

[0818] EXAMPLE 78: 5-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl-1,1- d_2)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2-fluoro-4-methyl-*N*-(1*H*-pyrazol-3-yl)benzamide



[0819] STEP 1: 2-(6-(5-((1*H*-pyrazol-3-yl)carbamoyl)-4-fluoro-2-methylphenyl)-1-ethyl-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1-*d*₂ acetate

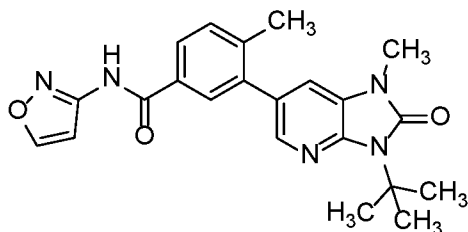


[0820] To a solution of 2-(6-bromo-1-ethyl-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1-*d*₂ acetate (600 mg, 1.67 mmol) and *tert*-butyl 3-(2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)-1*H*-pyrazole-1-carboxylate (745.82 mg, 1.67 mmol) in dioxane (6 mL) and water (0.6 mL) were added Na₂CO₃ (532.57 mg, 5.02 mmol) and Pd(dppf)Cl₂.CH₂Cl₂ (136.78 mg, 167.49 μmol). The reaction mixture was stirred at 90°C for 5 hours and then diluted with water. The aqueous phase was extracted with EtOAc, and organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography (SiO₂) eluting with a gradient of 10-50% EtOAc in petroleum ether to give the title compound as a light-yellow solid (400 mg, 48%). ESI-MS *m/z* [M+H]⁺ = 497.1. The reaction also yielded side-product *tert*-butyl 3-(5-(3-(1-acetoxy-2-methylpropan-2-yl)-1,1-*d*₂)-1-ethyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2-fluoro-4-methylbenzamido)-1*H*-pyrazole-1-carboxylate as light-yellow solid (260 mg, 26%); ESI-MS *m/z* [M+H]⁺ = 597.1.

[0821] STEP 2: 5-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-1,1-*d*₂)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2-fluoro-4-methyl-*N*-(1*H*-pyrazol-3-yl)benzamide

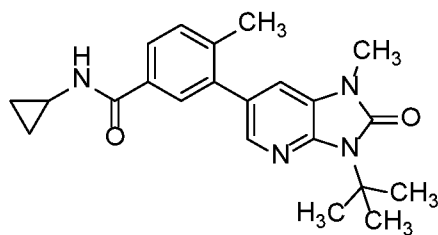
[0822] To a solution of 2-(6-(5-((1*H*-pyrazol-3-yl)carbamoyl)-4-fluoro-2-methylphenyl)-1-ethyl-2-oxo-1,2-dihydro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2-methylpropyl-1,1-*d*₂ acetate (400 mg, 805.59 μmol) in MeOH (8 mL) was added K₂CO₃ (111.34 mg, 805.59 μmol). The reaction mixture was stirred at 50°C for 20 minutes, then adjusted to pH 3 with aq HCl (1M) and concentrated *in vacuo*. The crude product was purified by preparative HPLC to give the title compound as an off-white solid (235 mg,). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.20 (t, *J*=7.2 Hz, 3 H) 1.70 (s, 6 H) 2.34 (s, 3 H) 3.88 (q, *J*=6.8 Hz, 2 H) 4.98 (s, 1 H) 6.62 (s, 1 H) 7.31 (d, *J*=11.2 Hz, 1 H) 7.55 (d, *J*=7.6 Hz, 1 H) 7.62 (d, *J*=1.6 Hz, 1 H) 7.65 (s, 1 H) 7.99 (d, *J*=1.6 Hz, 1 H) 10.74 (s, 1 H) 12.44 (s, 1 H); ESI-MS *m/z* [M+H]⁺ = 455.2.

[0823] EXAMPLE 79: 3-(3-(*tert*-butyl)-1-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-(isoxazol-3-yl)-4-methylbenzamide



[0824] To a solution of 3-(3-(*tert*-butyl)-1-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzoic acid (50 mg, 0.147 mmol) in DCM (1 mL) was added oxalyl chloride (0.019 mL, 0.221 mmol) followed by DMF (4.56 μ L, 0.059 mmol) at room temperature. The mixture was stirred for 1 hour. Next, K_2CO_3 (81 mg, 0.589 mmol) and isoxazol-3-amine (18.58 mg, 0.221 mmol) were added, and the reaction mixture was stirred at room temperature for 30 minutes at which time HATU (70 mg, 0.184 mmol) and *N*-methylmorpholine (0.1 mL, 0.91 mmol) were added. The reaction mixture was stirred overnight, then diluted with water and extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4 , concentrated, and dried *in-vacuo*. The resulting residue was purified by chromatography (ISCO Gold® 12 g column) eluting with a gradient of 0-100% EtOAc in hexanes. The product-containing fractions were collected and were concentrated and dried *in-vacuo*, then purified by SFC to give the title compound as a white film (0.8 mg, 1.3%). ^1H NMR (400 MHz, CD_3OD) δ ppm 1.87 (s, 9 H) 2.37 - 2.41 (m, 3 H) 3.39 - 3.41 (m, 3 H) 7.01 - 7.08 (m, 1 H) 7.38 - 7.45 (m, 1 H) 7.45 - 7.53 (m, 1 H) 7.82 - 7.94 (m, 2 H) 7.98 - 8.05 (m, 1 H) 8.49 - 8.60 (m, 1 H); ESI-MS m/z $[M+H]^+ = 406.4$.

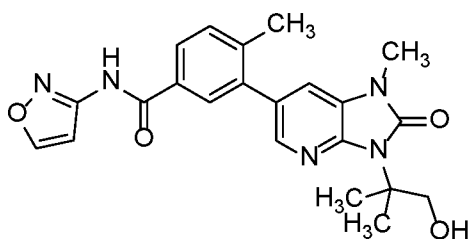
[0825] EXAMPLE 80: 3-(3-(*tert*-butyl)-1-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-cyclopropyl-4-methylbenzamide



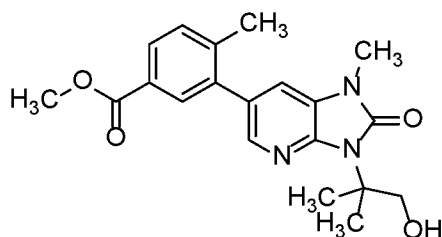
[0826] To a solution of 3-(3-(*tert*-butyl)-1-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzoic acid (40 mg, 0.118 mmol) and *N*-methyilmorpholine (0.065 mL, 0.589 mmol) in DMF (1 mL) was added cyclopropanamine (26.9 mg, 0.471 mmol) followed by HATU (58.3 mg, 0.153 mmol) at 25°C. The reaction mixture was stirred at 25°C for 3 hours and then diluted with water. The resulting solid was collected by filtration and

purified to give the title compound as a colorless film (9.2 mg, 21%). ^1H NMR (400 MHz, CD_3OD) δ ppm 0.52 - 0.59 (m, 2 H) 0.69 - 0.77 (m, 2 H) 1.79 (s, 9 H) 2.24 - 2.28 (m, 3 H) 2.74 - 2.82 (m, 1 H) 3.22 - 3.25 (m, 2 H) 4.60 - 4.82 (m, 3 H) 7.27 - 7.34 (m, 2 H) 7.61 - 7.68 (m, 2 H) 7.88 - 7.92 (m, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 379.4$.

[0827] EXAMPLE 81: 3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-(isoxazol-3-yl)-4-methylbenzamide

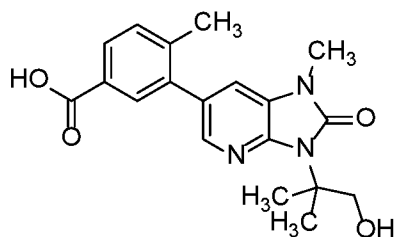


[0828] STEP 1: methyl 3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzoate



[0829] To a microwave vial equipped with stirring was added 6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1-methyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (126 mg, 0.420 mmol) and methyl 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (151 mg, 0.546 mmol). Dioxane (2 mL) was added and the solution was stirred at 25°C for 5 minutes. Next, NaHCO_3 (212 mg, 2.52 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (61.4 mg, 0.084 mmol) were added and the solution was heated to 110°C in microwave reactor for 15 minutes. LCMS indicated incomplete conversion, so the reaction mixture was heated at 120°C for 1 hour. The reaction was still incomplete, so fresh methyl 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (151 mg, 0.546 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (61.4 mg, 0.084 mmol) were added and the reaction mixture was heated at 120°C for 20 minutes. LCMS indicated the reaction was approximately 50% complete. The reaction mixture was dried over Na_2SO_4 , diluted with EtOAc, and filtered. The filtrate was concentrated *in vacuo* to give the title compound (25 mg, 16%) which was used without further purification. ESI-MS m/z $[\text{M}+\text{H}]^+ = 370.4$.

[0830] STEP 2: 3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzoic acid

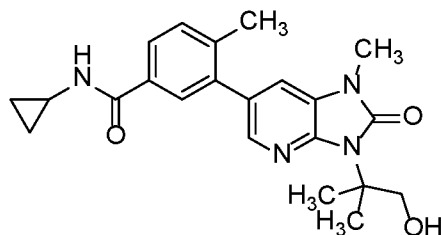


[0831] A scintillation vial was charged with methyl 3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-6-yl)-4-methylbenzoate (0.025 g, 0.068 mmol), dioxane (1 mL) and 2 N LiOH aq (0.169 mL, 0.338 mmol). The reaction mixture was stirred at room temperature for 3 days, then poured onto ice, and neutralized with 5 N aq HCl. The solid product was isolated by vacuum filtration, washing with slightly acidic water to give the title compound as an off-white solid (23 mg, 96%). ESI-MS m/z $[M+H]^+ = 356.4$.

[0832] STEP 3: 3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-6-yl)-N-(isoxazol-3-yl)-4-methylbenzamide

[0833] A scintillation vial was charged with 3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-6-yl)-4-methylbenzoic acid (0.023 g, 0.065 mmol), HATU (0.037 g, 0.097 mmol), DMA (1 mL) and DIPEA (0.034 mL, 0.194 mmol). After 10 minutes, isoxazol-3-amine (9.56 μ L, 0.129 mmol) was added. The reaction mixture reaction was stirred at room temperature overnight and then slowly poured onto ice. A resulting precipitate was isolated by vacuum filtration, washing with water. The crude solid was dissolved in DCM and purified by chromatography (ISCO® 12 g silica gel column) eluting with a gradient of 0-100% EtOAc in heptanes. The product-containing fractions were combined and dried in a stream of nitrogen to give the title compound as a white film (0.5 mg, 1.8%). ESI-MS m/z $[M+H]^+ = 422.4$.

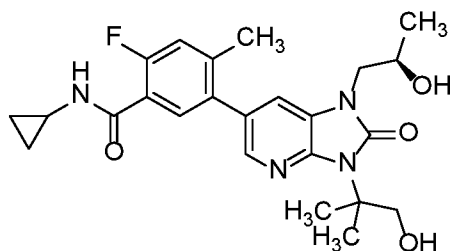
[0834] EXAMPLE 82: N-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-6-yl)-4-methylbenzamide



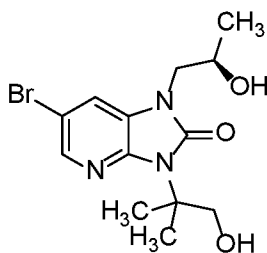
[0835] A microwave vial was charged with 6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1-methyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (0.064 g, 0.213 mmol), N-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (0.077 g,

0.256 mmol), tetrakis(triphenylphosphine)palladium(0) (0.025 g, 0.021 mmol), 2 N Na₂CO₃ aq (0.320 mL, 0.640 mmol) and DME (2 mL). The reaction mixture was degassed with nitrogen, and the vial was capped and heated in a microwave reactor at 130°C for 1 hour. Following reaction, the solvent was removed via a stream of nitrogen, and the residue was taken up in EtOAc (10 mL) and water (5 mL). The organic layer was washed with water (5 mL) and the solvent was removed via a stream of nitrogen. The residue was dispersed in DCM and purified by chromatography (ISCO® 12 g silica gel column) eluting with a gradient of 0-100% EtOAc in heptanes. The product-containing fractions were combined and dried via a stream of nitrogen to give the title compound as a white film (19 mg, 23%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.54 - 0.60 (m, 2 H) 0.65 - 0.75 (m, 2 H) 1.72 (s, 6 H) 2.27 - 2.37 (m, 4 H) 2.85 (tq, *J*=7.41, 3.92 Hz, 2 H) 3.34 (s, 3 H) 3.92 (d, *J*=6.42 Hz, 2 H) 5.00 (t, *J*=6.51 Hz, 1 H) 7.41 (d, *J*=7.98 Hz, 1 H) 7.54 (d, *J*=1.93 Hz, 1 H) 7.73 (s, 1 H) 7.77 (d, *J*=8.06 Hz, 1 H) 7.95 (d, *J*=2.02 Hz, 1 H) 8.38 (d, *J*=4.22 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ = 395.5.

[0836] EXAMPLE 83: (*R*)-*N*-cyclopropyl-2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxypropyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



[0837] STEP 1: (*R*)-6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxypropyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one



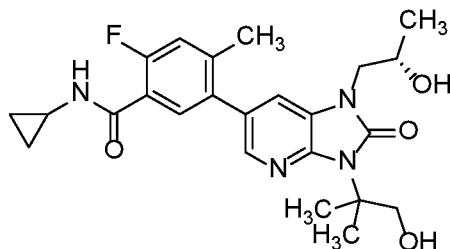
[0838] To a mixture of 6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (100 mg, 0.349 mmol) and (*R*)-1-chloropropan-2-ol (49.6 mg, 0.524 mmol) in DMF (3 mL) was added K₂CO₃ (97 mg, 0.699 mmol). The reaction mixture was stirred at 90°C for 18 hours, then cooled to RT, diluted with EtOAc and washed with brine. The organic layer was dried over Na₂SO₄, filtered and concentrated to give the title

compound (120 mg, 100%) which was used without further purification. ESI-MS m/z $[M+H]^+ = 346.3$.

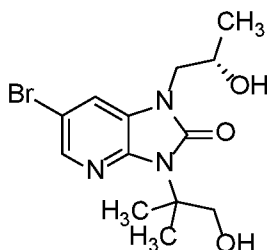
[0839] STEP 2: (*R*)-*N*-cyclopropyl-2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxypropyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

[0840] To a mixture of (*R*)-6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxypropyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (60 mg, 0.174 mmol) and *N*-cyclopropyl-2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (61.2 mg, 0.192 mmol) in 1,4-dioxane (3 mL) and water (0.300 mL) were added K_2CO_3 (120 mg, 0.872 mmol) and $Pd(dppf)Cl_2$ (12.75 mg, 0.017 mmol) at 20°C. The suspension was purged with N_2 . The reaction mixture was heated to 100°C in a microwave reactor for 2 hours, then diluted with EtOAc and washed with water and brine. The organic phase was dried over Na_2SO_4 , filtered, concentrated and purified by SFC. The product-containing fractions were combined and concentrated to give the title compound as a clear film (12 mg, 15%). ^1H NMR (400 MHz, CD_3OD) δ ppm 0.63 - 0.69 (m, 2 H) 0.84 (q, $J=6.42$ Hz, 2 H) 1.25 (d, $J=6.33$ Hz, 3 H) 1.78 (s, 7 H) 2.32 - 2.37 (m, 3 H) 2.85 - 2.93 (m, 1 H) 3.35 - 3.40 (m, 1 H) 3.77 - 3.95 (m, 2 H) 4.06 - 4.20 (m, 3 H) 7.19 (d, $J=11.65$ Hz, 1 H) 7.48 - 7.62 (m, 2 H) 7.95 - 8.00 (m, 1 H); ESI-MS m/z $[M+H]^+ = 457.5$.

[0841] EXAMPLE 84: (*S*)-*N*-cyclopropyl-2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxypropyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



[0842] STEP 1: (*S*)-6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxypropyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one



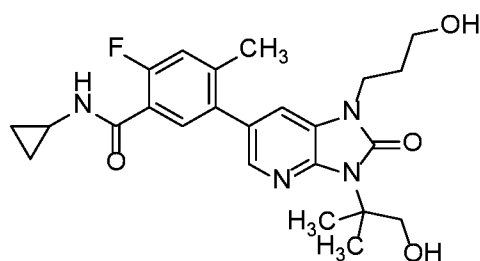
[0843] To a mixture of 6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (100 mg, 0.349 mmol) and (*S*)-1-chloropropan-2-ol (49.6 mg,

0.524 mmol) in DMF (3 mL) was added K_2CO_3 (97 mg, 0.699 mmol). The reaction mixture was stirred at 90°C for 18 hours, then cooled to RT, diluted with EtOAc and washed with brine. The organic phase was dried over Na_2SO_4 , filtered and concentrated to give the title compound (120 mg, 100%) which was used without further purification. ESI-MS m/z $[M+H]^+ = 344.3$.

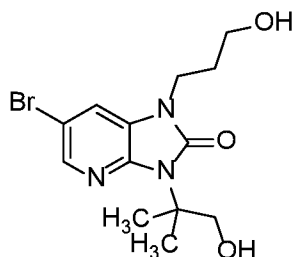
[0844] STEP 2: (*S*)-*N*-cyclopropyl-2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxypropyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

[0845] To a mixture of (*S*)-6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxypropyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (120 mg, 0.349 mmol) and *N*-cyclopropyl-2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (122 mg, 0.383 mmol) in 1,4-dioxane (3 mL) and water (0.300 mL) were added K_2CO_3 (241 mg, 1.743 mmol) and $Pd(dppf)Cl_2$ (25.5 mg, 0.035 mmol) at 20°C. The suspension was purged with N_2 . The reaction mixture was heated to 100°C in a microwave reactor for 2 hours, then diluted with EtOAc and washed with water and brine. The organic phase was dried over Na_2SO_4 , filtered, concentrated and purified by SFC. The product-containing fractions were combined and concentrated to give the title compound as a yellow film (93 mg, 58%). ^1H NMR (400 MHz, CD_3OD) δ ppm 0.61 - 0.69 (m, 2 H) 0.83 (q, $J=6.51$ Hz, 2 H) 1.25 (d, $J=6.24$ Hz, 3 H) 1.78 (s, 7 H) 2.34 (s, 3 H) 2.85 - 2.92 (m, 1 H) 3.80 - 3.97 (m, 2 H) 4.08 - 4.19 (m, 3 H) 7.19 (d, $J=11.55$ Hz, 1 H) 7.53 (s, 1 H) 7.58 (d, $J=7.43$ Hz, 1 H) 7.95 - 8.00 (m, 1 H); ESI-MS m/z $[M+H]^+ = 457.5$.

[0846] EXAMPLE 85: *N*-cyclopropyl-2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(3-hydroxypropyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



[0847] STEP 1: 6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1-(3-hydroxypropyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

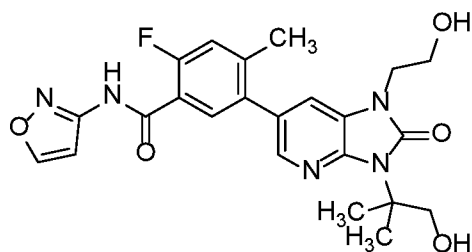


[0848] To a mixture of 6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (50 mg, 0.175 mmol) and 3-bromopropan-1-ol (36.4 mg, 0.262 mmol) in DMF (3 mL) was added K₂CO₃ (48.3 mg, 0.349 mmol). The reaction mixture was stirred at 90°C for 18 hours, then cooled to RT, diluted with EtOAc and washed with brine. The organic phase was dried over Na₂SO₄, filtered and concentrated to give the title compound (60 mg, 100%) which was used without further purification. ESI-MS *m/z* [M+H]⁺ = 346.3.

[0849] STEP 2: *N*-cyclopropyl-2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(3-hydroxypropyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

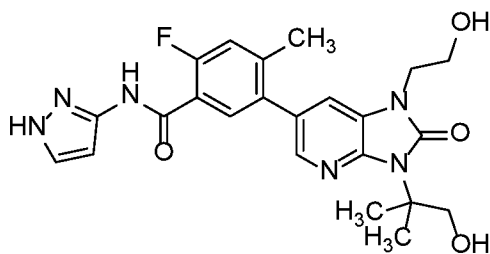
[0850] To a mixture of 6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1-(3-hydroxypropyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (60 mg, 0.174 mmol) and *N*-cyclopropyl-2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (61.2 mg, 0.192 mmol) in 1,4-dioxane (3 mL) and water (0.300 mL) were added K₂CO₃ (120 mg, 0.872 mmol) and Pd(dppf)Cl₂ (12.75 mg, 0.017 mmol) at 20°C. The suspension was purged with N₂. The reaction mixture was heated to 100°C in a microwave reactor for 2 hours, then diluted with EtOAc and washed with water and brine. The organic phase was dried over Na₂SO₄, filtered, concentrated and purified by SFC. The product-containing fractions were combined and concentrated to give the title compound as a clear film (31 mg, 39%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.61 - 0.67 (m, 2 H) 0.84 (q, *J*=6.63 Hz, 2 H) 1.78 (s, 6 H) 1.95 (quin, *J*=6.44 Hz, 2 H) 2.35 (s, 3 H) 2.84 - 2.92 (m, 1 H) 3.62 (t, *J*=6.01 Hz, 2 H) 4.03 (t, *J*=6.88 Hz, 2 H) 4.09 (s, 2 H) 7.15 - 7.23 (m, 1 H) 7.51 - 7.55 (m, 1 H) 7.59 (d, *J*=7.43 Hz, 1 H) 7.98 (s, 1 H); ESI-MS *m/z* [M+H]⁺ = 457.5.

[0851] EXAMPLE 86: 2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxyethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-(isoxazol-3-yl)-4-methylbenzamide

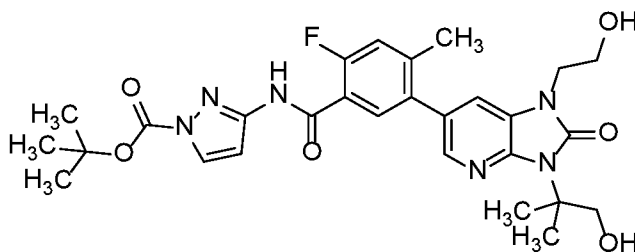


[0852] To a mixture of 6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxyethyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (45.8 mg, 0.139 mmol) and 2-fluoro-*N*-(isoxazol-3-yl)-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (48 mg, 0.139 mmol) in 1,4-dioxane (3 mL) and water (0.300 mL) were added K_2CO_3 (96 mg, 0.693 mmol) and $Pd(dppf)Cl_2$ (10.15 mg, 0.014 mmol) at 20°C. The suspension was purged with N_2 . The reaction mixture was heated to 100°C in a microwave reactor for 2 hours, then diluted with EtOAc and washed with water and brine. The organic phase was dried over Na_2SO_4 , filtered, concentrated and purified by SFC. The product-containing fractions were combined and concentrated to give the title compound as a yellow film (22 mg, 34%). ^1H NMR (400 MHz, CD_3OD) δ ppm 1.79 (s, 6 H) 2.38 (s, 3 H) 3.82 - 3.89 (m, 2 H) 4.04 (t, $J=5.09$ Hz, 2 H) 4.10 (s, 2 H) 7.06 (s, 1 H) 7.28 (d, $J=11.55$ Hz, 1 H) 7.55 (s, 1 H) 7.69 (d, $J=7.34$ Hz, 1 H) 8.00 (s, 1 H) 8.59 - 8.64 (m, 1 H); ESI-MS m/z $[M+H]^+ = 470.4$.

[0853] EXAMPLE 87: 2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxyethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-(1*H*-pyrazol-3-yl)benzamide



[0854] STEP 1: *tert*-butyl 3-(2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxyethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamido)-1*H*-pyrazole-1-carboxylate

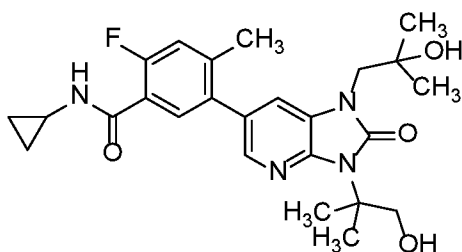


[0855] To a mixture of 6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxyethyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (89 mg, 0.269 mmol) and *tert*-butyl 3-(2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamido)-1*H*-pyrazole-1-carboxylate (120 mg, 0.269 mmol) in 1,4-dioxane (3 mL) and water (0.300 mL) was added K₂CO₃ (186 mg, 1.347 mmol) and Pd(dppf)Cl₂ (19.72 mg, 0.027 mmol) at 20°C. The suspension was purged with N₂. The reaction mixture was heated to 100°C in a microwave reactor for 2 hours, then diluted with EtOAc and washed with water and brine. The organic phase was dried over Na₂SO₄, filtered and concentrated to give the title compound (150 mg, 98%) which was used without further purification. ESI-MS *m/z* [M+H]⁺ = 569.6.

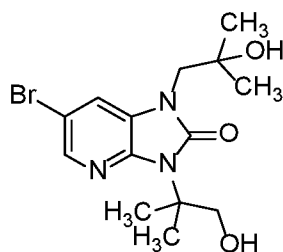
[0856] STEP 2: 2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxyethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-(1*H*-pyrazol-3-yl)benzamide

[0857] A mixture of *tert*-butyl 3-(2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxyethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamido)-1*H*-pyrazole-1-carboxylate (150 mg, 0.264 mmol) in TFA (1 mL) and DCM (1 mL) was stirred at RT for 45 minutes and then concentrated and purified by SFC. The product-containing fractions were combined and concentrated to give the title compound as a colorless film (43 mg, 35%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.79 (s, 6 H) 2.38 (s, 3 H) 3.81 - 3.89 (m, 2 H) 4.04 (t, *J*=5.00 Hz, 2 H) 4.10 (s, 2 H) 6.69 (s, 1 H) 7.27 (d, *J*=11.83 Hz, 1 H) 7.55 (s, 1 H) 7.62 (s, 1 H) 7.73 (d, *J*=7.52 Hz, 1 H) 7.98 - 8.02 (m, 1 H); ESI-MS *m/z* [M+H]⁺ = 470.4.

[0858] EXAMPLE 88: *N*-cyclopropyl-2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxy-2-methylpropyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



[0859] STEP 1: 6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxy-2-methylpropyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

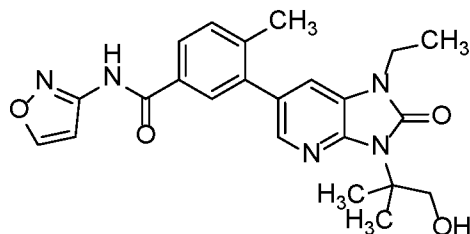


[0860] To a mixture of 6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (120 mg, 0.419 mmol) and 1-bromo-2-methylpropan-2-ol (96 mg, 0.629 mmol) in DMF (3 mL) was added K₂CO₃ (116 mg, 0.839 mmol). The reaction mixture was stirred at 80°C for 18 hours, then cooled to RT, diluted with EtOAc and washed with brine. The organic phase was dried over Na₂SO₄, filtered and concentrated to give the title compound (150 mg, crude) which was used without further purification. ESI-MS *m/z* [M+H]⁺ = 360.3.

[0861] STEP 2: *N*-cyclopropyl-2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxy-2-methylpropyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

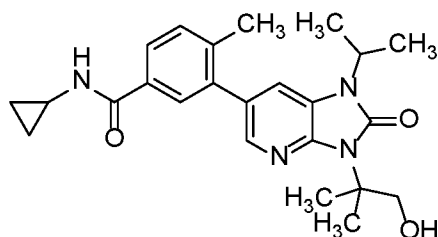
[0862] To a mixture of 6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxy-2-methylpropyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (150 mg, 0.419 mmol) and *N*-cyclopropyl-2-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (147 mg, 0.461 mmol) in 1,4-dioxane (5 mL) and water (0.5 mL) were added K₂CO₃ (289 mg, 2.094 mmol) and PdCl₂(dppf) (30.6 mg, 0.042 mmol) at 20°C. The suspension was purged with N₂. The reaction mixture was heated to 100°C in a microwave reactor for 2 hours, then diluted with EtOAc and washed with water and brine. The organic phase was dried over Na₂SO₄, filtered, concentrated and purified by SFC. The product-containing fractions were combined and concentrated to give the title compound as a white solid (113 mg, 57.4%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.60 - 0.69 (m, 2 H) 0.80 - 0.88 (m, 2 H) 1.28 (s, 6 H) 1.78 (s, 6 H) 2.34 (s, 3 H) 2.84 - 2.96 (m, 1 H) 3.88 (s, 2 H) 4.10 (s, 2 H) 7.14 - 7.25 (m, 1 H) 7.54 - 7.63 (m, 2 H) 7.97 (s, 1 H); ESI-MS *m/z* [M+H]⁺ = 471.5.

[0863] EXAMPLE 89: 3-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-(isoxazol-3-yl)-4-methylbenzamide

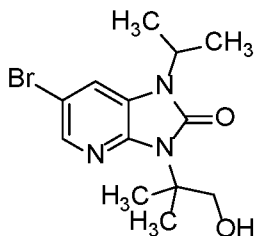


[0864] To a mixture of 6-bromo-1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (100mg, 0.318 mmol), *N*-(isoxazol-3-yl)-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (104 mg, 0.318 mmol) in 1,4-dioxane (2 mL) was added 2 N Na₂CO₃ aq (0.318 mL, 0.637 mmol). The mixture was degassed with nitrogen. Next, PdCl₂(dtbpf) (20.74 mg, 0.032 mmol) was added. The reaction mixture was heated at 130°C for 1 hour, then diluted with water and extracted by EtOAc. The organic layers were combined, dried over Na₂SO₄ and filtered. The filtrate was concentrated, dried *in-vacuo* and purified by SFC to give the title compound as a reddish-brown solid (7 mg, 5%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.28 - 1.44 (m, 9 H) 1.74 - 1.85 (m, 7 H) 2.37 - 2.45 (m, 3 H) 3.91 - 4.07 (m, 2 H) 4.07 - 4.17 (m, 2 H) 6.92 - 7.15 (m, 1 H) 7.45 - 7.60 (m, 2 H) 7.79 - 7.97 (m, 2 H) 7.99 - 8.09 (m, 1 H) 8.49 - 8.63 (m, 1 H); ESI-MS *m/z* [M+H]⁺ = 436.4.

[0865] EXAMPLE 90: *N*-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-isopropyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



[0866] STEP 1: 6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1-isopropyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

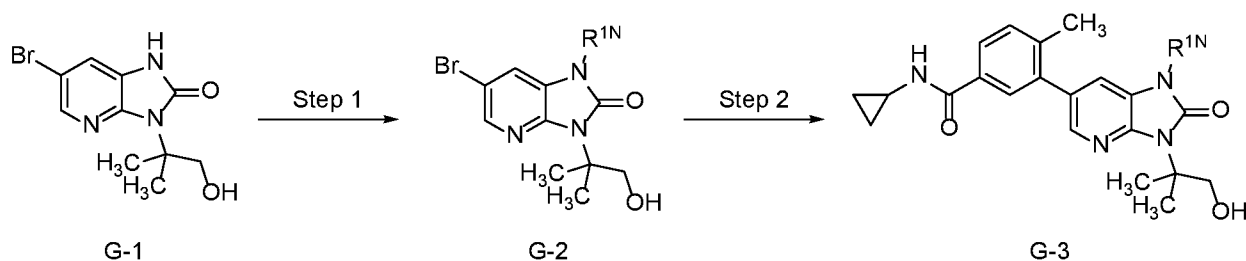


[0867] To a solution of 6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (200 mg, 0.699 mmol) in DMF (2 mL) was added NaH (30.8 mg, 0.769 mmol) at 25°C. The solution was stirred for 15 minutes and then 2-iodopropane (69.9 μL, 0.699 mmol) was added. The reaction mixture was stirred at 25°C overnight, then diluted with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by silica column chromatography to give the title compound (60 mg, 26%). ESI-MS *m/z* [M+H]⁺ = 328.2.

[0868] STEP 2: *N*-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-isopropyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

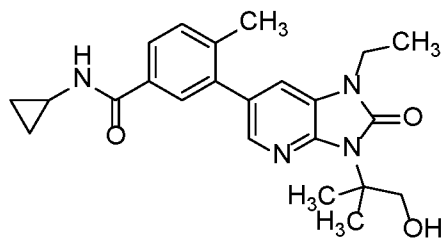
[0869] To a vial charged with 6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1-isopropyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (60 mg, 0.183 mmol) and *N*-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (55.1 mg, 0.183 mmol) in 1,4-dioxane (2 mL) was added 2 N Na₂CO₃ aq (183 μL, 0.366 mmol). The mixture was degassed with nitrogen. Next, PdCl₂(dtbpf) (11.91 mg, 0.018 mmol) was added, and the vial was capped and heated in a microwave reactor at 130°C for 1 hour. The crude product was purified by SFC to give the title compound as a brown film (28 mg, 36%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.58 - 0.72 (m, 2 H) 0.75 - 0.88 (m, 2 H) 1.26 - 1.41 (m, 1 H) 1.48 - 1.59 (m, 6 H) 1.77 (s, 6 H) 2.18 - 2.40 (m, 3 H) 2.79 - 2.94 (m, 1 H) 4.01 - 4.18 (m, 2 H) 7.35 - 7.49 (m, 1 H) 7.51 - 7.66 (m, 1 H) 7.67 - 7.81 (m, 2 H) 7.88 - 8.07 (m, 1 H); ESI-MS *m/z* [M+H]⁺ = 423.5.

[0870] Like EXAMPLE 90, each of EXAMPLES 91 to 107, below, were prepared in accordance with Scheme G in which: (Step 1) 6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (G-1) in DMF is treated with NaH and subsequently reacted with an alkyl halide (X-R^{1N}) at RT to obtain an *N*-alkylated aryl halide (G-2); and (Step 2) the *N*-alkylated aryl halide in 1,4-dioxane is reacted with *N*-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide in the presence Na₂CO₃ aq and PdCl₂(dtbpf) at 130°C in a microwave reactor to afford the title compound (G-3).



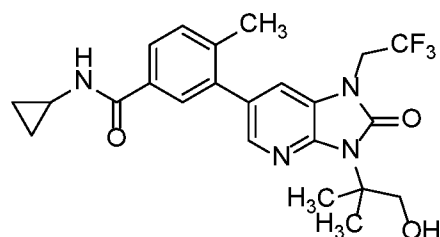
Scheme G

[0871] EXAMPLE 91: *N*-cyclopropyl-3-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



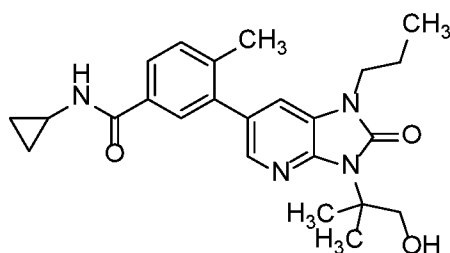
[0872] ^1H NMR (400 MHz, CD_3OD) δ ppm 0.60 - 0.71 (m, 2 H) 0.76 - 0.87 (m, 2 H) 1.33 (t, $J=7.20$ Hz, 3 H) 1.77 (s, 6 H) 2.36 (s, 3 H) 2.87 (br t, $J=3.71$ Hz, 1 H) 3.98 (q, $J=7.15$ Hz, 2 H) 4.09 (s, 2 H) 7.41 (d, $J=7.89$ Hz, 1 H) 7.50 (d, $J=1.83$ Hz, 1 H) 7.73 (s, 1 H) 7.75 (d, $J=7.83$ Hz, 1 H) 8.00 (d, $J=1.83$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 409.4$.

[0873] EXAMPLE 92: *N*-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-1-(2,2,2-trifluoroethyl)-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



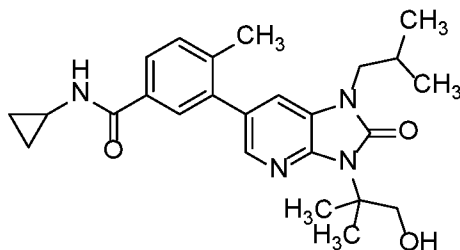
[0874] ^1H NMR (400 MHz, CD_3OD) δ ppm 0.61 - 0.69 (m, 2 H) 0.79 - 0.85 (m, 2 H) 1.80 (s, 6 H) 2.35 (s, 3 H) 2.87 (s, 1 H) 4.12 (s, 2 H) 4.71 (q, $J=8.99$ Hz, 2 H) 7.43 (d, $J=7.98$ Hz, 1 H) 7.56 (s, 1 H) 7.72 (s, 1 H) 7.76 (d, $J=7.74$ Hz, 1 H) 8.07 (d, $J=1.83$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 463.3$.

[0875] EXAMPLE 93: *N*-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-1-propyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



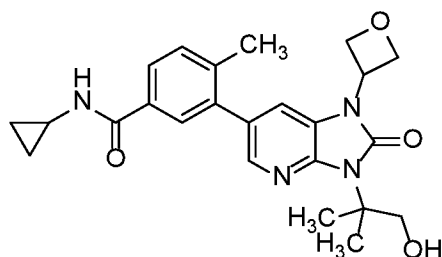
[0876] ^1H NMR (400 MHz, CD_3OD) δ ppm 0.59 - 0.72 (m, 2 H) 0.77 - 0.87 (m, 2 H) 0.98 (t, $J=7.38$ Hz, 3 H) 1.72 - 1.84 (m, 8 H) 2.36 (s, 3 H) 2.82 - 2.91 (m, 1 H) 3.91 (t, $J=7.11$ Hz, 2 H) 4.10 (s, 2 H) 7.43 (d, $J=7.98$ Hz, 1 H) 7.49 (s, 1 H) 7.72 (s, 1 H) 7.75 (d, $J=7.70$ Hz, 1 H) 8.01 (s, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 423.5$.

[0877] EXAMPLE 94: *N*-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-isobutyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



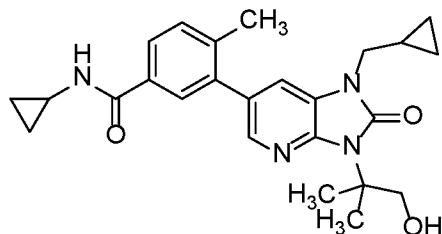
[0878] ^1H NMR (400 MHz, CD_3OD) δ ppm 0.59 - 0.72 (m, 2 H) 0.76 - 0.90 (m, 2 H) 0.98 (d, $J=6.69$ Hz, 6 H) 1.78 (s, 6 H) 2.10 - 2.26 (m, 1 H) 2.35 (s, 3 H) 2.82 - 2.92 (m, 1 H) 3.74 (d, $J=7.43$ Hz, 2 H) 4.10 (s, 2 H) 7.40 - 7.44 (m, 1 H) 7.46 - 7.49 (m, 1 H) 7.70 - 7.78 (m, 2 H) 8.00 (s, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 437.5$.

[0879] EXAMPLE 95: *N*-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(oxetan-3-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



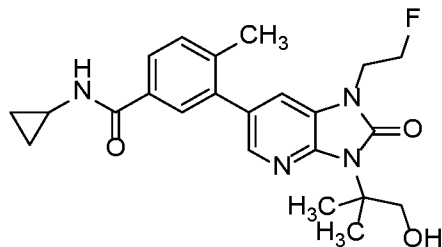
[0880] ^1H NMR (400 MHz, CD_3OD) δ ppm 0.60 - 0.74 (m, 2 H) 0.75 - 0.90 (m, 2 H) 1.76 - 1.84 (m, 6 H) 2.27 - 2.44 (m, 3 H) 2.80 - 2.95 (m, 1 H) 4.07 - 4.15 (m, 2 H) 5.07 - 5.23 (m, 4 H) 5.57 - 5.72 (m, 1 H) 7.38 - 7.52 (m, 1 H) 7.68 - 7.81 (m, 2 H) 7.81 - 7.91 (m, 1 H) 8.02 - 8.17 (m, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 437.5$.

[0881] EXAMPLE 96: *N*-cyclopropyl-3-(1-(cyclopropylmethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



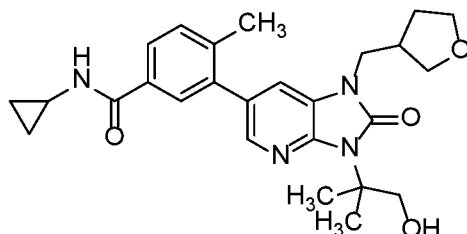
[0882] ^1H NMR (400 MHz, CD_3OD) δ ppm 0.33 - 0.49 (m, 2 H) 0.51 - 0.62 (m, 2 H) 0.62 - 0.70 (m, 2 H) 0.75 - 0.91 (m, 2 H) 1.12 - 1.37 (m, 1 H) 1.78 (s, 6 H) 2.27 - 2.48 (m, 3 H) 2.81 - 2.97 (m, 1 H) 3.71 - 3.90 (m, 2 H) 4.00 - 4.21 (m, 2 H) 7.25 - 7.48 (m, 1 H) 7.47 - 7.58 (m, 1 H) 7.68 - 7.81 (m, 2 H) 7.92 - 8.08 (m, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 435.5$.

[0883] EXAMPLE 97: *N*-cyclopropyl-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



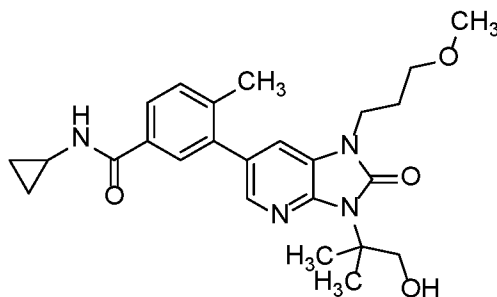
[0884] ^1H NMR (400 MHz, CD_3OD) δ ppm 0.42 - 0.52 (m, 2 H) 0.59 - 0.72 (m, 2 H) 1.56 - 1.66 (m, 6 H) 2.16 (s, 3 H) 2.64 - 2.74 (m, 1 H) 3.90 - 3.95 (m, 2 H) 3.98 - 4.18 (m, 2 H) 4.41 - 4.52 (m, 1 H) 4.57 - 4.62 (m, 1 H) 7.19 - 7.27 (m, 1 H) 7.30 - 7.36 (m, 1 H) 7.51 - 7.61 (m, 2 H) 7.80 - 7.86 (m, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 427.4$.

[0885] EXAMPLE 98: *N*-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-1-((tetrahydrofuran-3-yl)methyl)-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



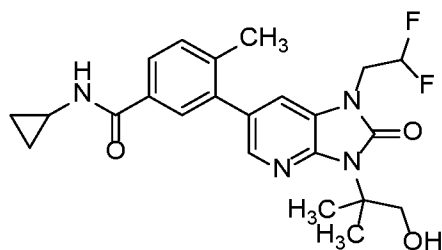
[0886] ^1H NMR (400 MHz, CD_3OD) δ ppm 0.61 - 0.70 (m, 2 H) 0.82 (br d, $J=6.05$ Hz, 2 H) 1.78 (s, 7 H) 2.05 (br d, $J=7.43$ Hz, 1 H) 2.36 (s, 3 H) 2.76 - 2.93 (m, 2 H) 3.37 (s, 1 H) 3.65 (dd, $J=8.71, 5.14$ Hz, 1 H) 3.72 - 3.81 (m, 2 H) 3.88 - 4.00 (m, 3 H) 4.10 (s, 2 H) 7.42 (d, $J=7.89$ Hz, 1 H) 7.54 (s, 1 H) 7.69 - 7.78 (m, 2 H) 8.02 (s, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 465.5$.

[0887] EXAMPLE 99: *N*-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(3-methoxypropyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



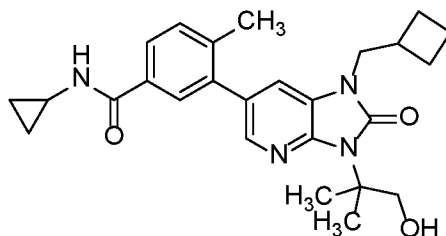
[0888] ^1H NMR (400 MHz, CD_3OD) δ ppm 0.46 - 0.70 (m, 2 H) 0.72 - 0.89 (m, 2 H) 1.77 (s, 7 H) 1.92 - 2.07 (m, 2 H) 2.17 - 2.49 (m, 4 H) 2.81 - 2.91 (m, 1 H) 3.24 - 3.29 (m, 3 H) 3.36 - 3.39 (m, 3 H) 3.39 - 3.46 (m, 3 H) 3.93 - 4.06 (m, 2 H) 4.06 - 4.12 (m, 2 H) 7.33 - 7.46 (m, 1 H) 7.64 - 7.81 (m, 2 H) 7.91 - 8.07 (m, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 453.5$.

[0889] EXAMPLE 100: *N*-cyclopropyl-3-(1-(2,2-difluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



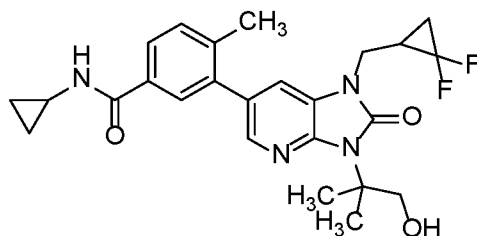
[0890] ^1H NMR (400 MHz, CD_3OD) δ ppm 0.59 - 0.71 (m, 2 H) 0.77 - 0.91 (m, 2 H) 1.79 (s, 6 H) 2.23 - 2.44 (m, 3 H) 2.79 - 2.94 (m, 1 H) 4.02 - 4.18 (m, 2 H) 4.25 - 4.45 (m, 2 H) 5.99 - 6.41 (m, 1 H) 7.34 - 7.49 (m, 1 H) 7.50 - 7.58 (m, 1 H) 7.67 - 7.80 (m, 2 H) 7.95 - 8.11 (m, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 445.4$.

[0891] EXAMPLE 101: 3-(1-(cyclobutylmethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-6-yl)-N-cyclopropyl-4-methylbenzamide



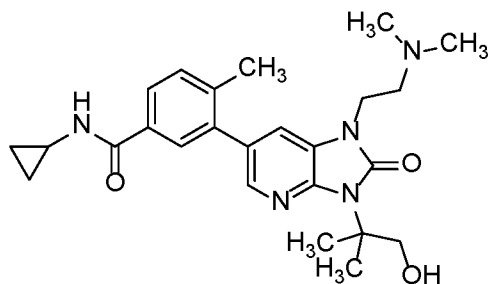
[0892] ^1H NMR (400 MHz, CD_3OD) δ ppm 0.59 - 0.72 (m, 2 H) 0.77 - 0.87 (m, 2 H) 1.77 (s, 6 H) 1.84 - 1.97 (m, 4 H) 1.98 - 2.11 (m, 2 H) 2.35 (s, 3 H) 2.78 - 2.91 (m, 2 H) 3.96 (d, $J=7.15$ Hz, 2 H) 4.09 (s, 2 H) 7.43 (d, $J=7.89$ Hz, 1 H) 7.49 (s, 1 H) 7.71 (s, 1 H) 7.75 (d, $J=7.72$ Hz, 1 H) 8.00 (s, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 449.5$.

[0893] EXAMPLE 102: N-cyclopropyl-3-(1-((2,2-difluorocyclopropyl)methyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-6-yl)-4-methylbenzamide



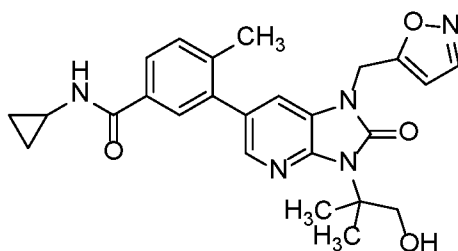
[0894] ^1H NMR (400 MHz, CD_3OD) δ ppm 0.62 - 0.69 (m, 2 H) 0.82 (q, $J=6.24$ Hz, 2 H) 1.30 - 1.49 (m, 1 H) 1.54 - 1.66 (m, 1 H) 1.79 (s, 6 H) 2.17 (br dd, $J=12.56, 5.32$ Hz, 1 H) 2.36 (s, 3 H) 2.87 (dt, $J=7.22, 3.50$ Hz, 1 H) 3.97 (dd, $J=15.13, 7.61$ Hz, 1 H) 4.08 - 4.21 (m, 3 H) 7.42 (d, $J=7.89$ Hz, 1 H) 7.52 (s, 1 H) 7.72 (s, 1 H) 7.75 (d, $J=7.80$ Hz, 1 H) 8.02 (s, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 471.5$.

[0895] EXAMPLE 103: *N*-cyclopropyl-3-(1-(2-(dimethylamino)ethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



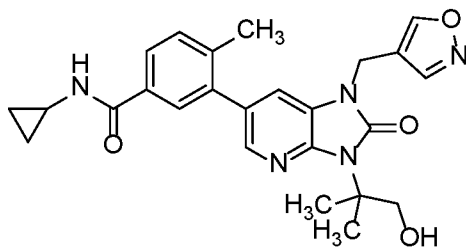
[0896] ^1H NMR (400 MHz, CD_3OD) δ ppm 0.58 - 0.74 (m, 2 H) 0.75 - 0.89 (m, 2 H) 1.73 (s, 1 H) 1.79 (s, 6 H) 2.31 - 2.38 (m, 8 H) 2.67 - 2.77 (m, 2 H) 2.88 (br d, $J=3.58$ Hz, 1 H) 4.02 - 4.13 (m, 4 H) 7.43 (d, $J=7.89$ Hz, 1 H) 7.52 (s, 1 H) 7.72 (s, 1 H) 7.75 (d, $J=8.60$ Hz, 1 H) 8.01 (s, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 452.5$.

[0897] EXAMPLE 104: *N*-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(isoxazol-5-ylmethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



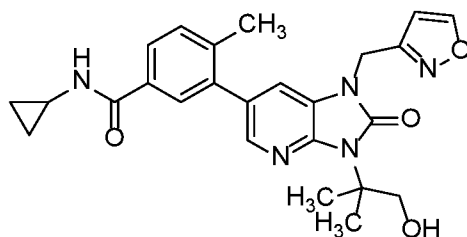
[0898] ^1H NMR (400 MHz, CD_3OD) δ ppm 0.58 - 0.72 (m, 2 H) 0.74 - 0.89 (m, 2 H) 1.80 (s, 6 H) 2.32 (s, 3 H) 2.87 (s, 1 H) 4.11 (s, 2 H) 5.33 (s, 2 H) 6.44 (s, 1 H) 7.41 (d, $J=7.98$ Hz, 1 H) 7.52 (s, 1 H) 7.69 - 7.78 (m, 2 H) 8.04 (s, 1 H) 8.35 (s, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 462.5$.

[0899] EXAMPLE 105: *N*-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(isoxazol-4-ylmethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



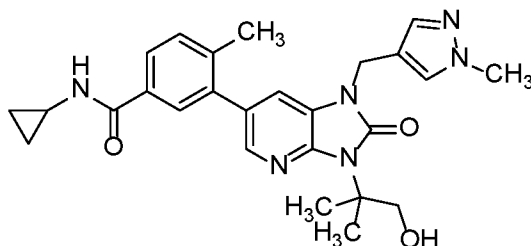
[0900] ^1H NMR (400 MHz, CD_3OD) δ ppm 0.56 - 0.71 (m, 2 H) 0.71 - 0.87 (m, 2 H) 1.80 (s, 6 H) 2.32 (s, 3 H) 2.78 - 2.98 (m, 1 H) 4.07 - 4.20 (m, 2 H) 4.99 - 5.11 (m, 2 H) 7.36 - 7.49 (m, 1 H) 7.49 - 7.60 (m, 1 H) 7.66 - 7.84 (m, 2 H) 7.93 - 8.10 (m, 1 H) 8.33 - 8.56 (m, 1 H) 8.64 - 8.89 (m, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 462.5$.

[0901] EXAMPLE 106: *N*-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(isoxazol-3-ylmethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



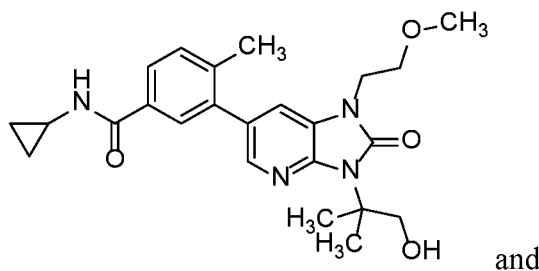
[0902] ^1H NMR (400 MHz, CD_3OD) δ ppm 0.53 - 0.72 (m, 2 H) 0.77 - 0.90 (m, 2 H) 1.79 (s, 6 H) 2.28 (s, 3 H) 2.74 - 2.95 (m, 1 H) 4.10 (s, 2 H) 5.17 - 5.38 (m, 2 H) 6.38 - 6.67 (m, 1 H) 7.28 - 7.54 (m, 2 H) 7.62 - 7.86 (m, 2 H) 7.89 - 8.12 (m, 1 H) 8.51 - 8.76 (m, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 462.5$.

[0903] EXAMPLE 107: *N*-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-((1-methyl-1*H*-pyrazol-4-yl)methyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide



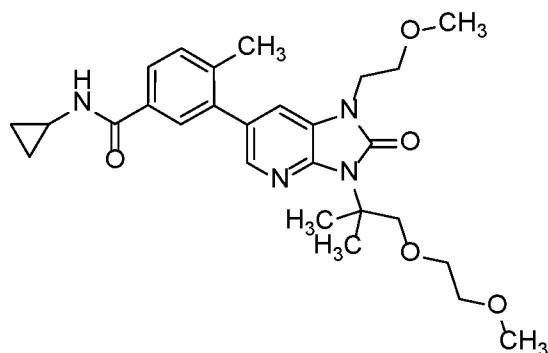
[0904] ^1H NMR (400 MHz, CD_3OD) δ ppm 0.60 - 0.71 (m, 2 H) 0.76 - 0.89 (m, 2 H) 1.79 (s, 6 H) 2.26 - 2.34 (m, 3 H) 2.79 - 2.95 (m, 1 H) 3.78 - 3.90 (m, 3 H) 4.06 - 4.18 (m, 2 H) 4.94 - 5.05 (m, 2 H) 7.38 - 7.44 (m, 1 H) 7.47 - 7.53 (m, 2 H) 7.63 - 7.72 (m, 2 H) 7.72 - 7.78 (m, 1 H) 7.96 - 8.02 (m, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+ = 475.5$.

[0905] EXAMPLE 108: *N*-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-methoxyethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

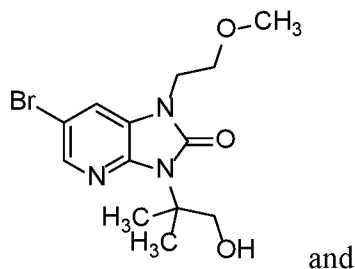


and

[0906] EXAMPLE 109: *N*-cyclopropyl-3-(3-(1-(2-methoxyethoxy)-2-methylpropan-2-yl)-1-(2-methoxyethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

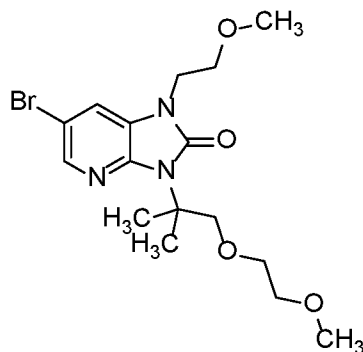


[0907] STEP 1: 6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-methoxyethyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one



and

[0908] 6-bromo-3-(1-(2-methoxyethoxy)-2-methylpropan-2-yl)-1-(2-methoxyethyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one



[0909] To a solution of 6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (165 mg, 0.577 mmol) in DMF (2 mL) was added NaH (25.4 mg, 0.634 mmol) at 25°C. The solution was stirred for 15 minutes and then 1-iodo-2-methoxyethane (322 mg, 1.730 mmol) was added. The reaction mixture was stirred at 25°C overnight, then diluted with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na₂SO₄ and filtered. The filtrate was concentrated and dried *in-vacuo* to give a crude mixture which contained 6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-methoxyethyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one, ESI-MS *m/z* [M+H]⁺ = 344.3, and 6-bromo-3-(1-(2-methoxyethoxy)-2-methylpropan-2-yl)-1-(2-methoxyethyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one, ESI-MS *m/z* [M+H]⁺ = 404.3.

[0910] STEP 2: *N*-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-methoxyethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide and *N*-cyclopropyl-3-(3-(1-(2-methoxyethoxy)-2-methylpropan-2-yl)-1-(2-methoxyethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide

[0911] A vial charged with an (assumed) equimolar mixture of 6-bromo-3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-methoxyethyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (0.199 g, 0.577 mmol) and 6-bromo-3-(1-(2-methoxyethoxy)-2-methylpropan-2-yl)-1-(2-methoxyethyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (0.232 g, 0.577 mmol), and with *N*-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (0.174 g, 0.577 mmol), 2 N Na₂CO₃ aq (0.577 mL, 1.154 mmol) and 1,4-dioxane (5 mL), was degassed with nitrogen. Next, PdCl₂(dtbpf) (0.038 g, 0.058 mmol) was added, and the vial was capped and heated in a microwave reactor at 130°C for 1 hour. The reaction mixture was then diluted with water and extracted with EtOAc. The organic phase was dried over Na₂SO₄, concentrated and purified by SFC. Compound *N*-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-methoxyethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide was obtained as a brown film (60 mg, 24%); compound *N*-cyclopropyl-3-(3-(1-(2-methoxyethoxy)-2-methylpropan-2-yl)-1-(2-methoxyethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide was obtained as a brown film (18 mg, 6%).

[0912] EXAMPLE 108: ¹H NMR (400 MHz, CD₃OD) δ ppm 0.59 - 0.69 (m, 2 H) 0.75 - 0.85 (m, 2 H) 1.76 (s, 6 H) 2.34 (s, 3 H) 2.82 - 2.89 (m, 1 H) 3.35 (s, 3 H) 3.68 (t, *J*=5.04 Hz, 2 H) 4.04 - 4.12 (m, 4 H) 7.40 (d, *J*=7.98 Hz, 1 H) 7.51 (s, 1 H) 7.70 (s, 1 H) 7.73 (d, *J*=7.80 Hz, 1 H) 7.98 (s, 1 H); ESI-MS *m/z* [M+H]⁺ = 439.5.

[0913] EXAMPLE 109: ¹H NMR (400 MHz, CD₃OD) δ ppm 0.60 - 0.72 (m, 2 H) 0.75 - 0.90 (m, 2 H) 1.88 (s, 6 H) 2.87 (s, 1 H) 3.25 (s, 3 H) 3.30 - 3.37 (m, 3 H) 3.42 - 3.50 (m, 2 H) 3.55 - 3.63 (m, 2 H) 3.68 (t, *J*=5.14 Hz, 2 H) 4.07 (t, *J*=5.09 Hz, 2 H) 4.14 (s, 2 H) 7.42 (d, *J*=7.66 Hz, 1 H) 7.46 (s, 1 H) 7.71 (s, 1 H) 7.74 (d, *J*=7.59 Hz, 1 H) 7.98 (s, 1 H); ESI-MS *m/z* [M+H]⁺ = 497.6.

[0914] TABLE 1, below, lists RIPK2 inhibition data for the compounds described in the examples, where larger pIC₅₀ values represent higher potency. The compounds were tested in accordance with the assay described in the section entitled Biological Activity, above.

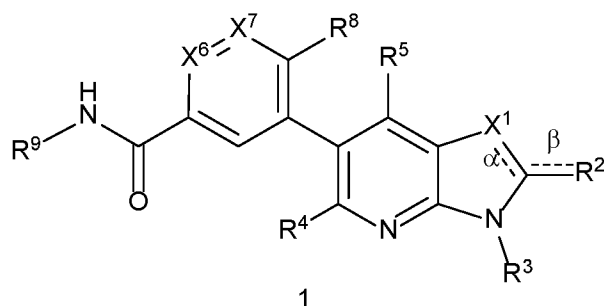
[0915] TABLE 1: RIPK2 Inhibition (pIC₅₀) for Example Compounds

Ex	pIC ₅₀	Ex	pIC ₅₀	Ex	pIC ₅₀	Ex	pIC ₅₀	Ex	pIC ₅₀
1	8.6	26	8.6	51	7.9	76	8.5	101	8.3
2	8.6	27	8.6	52	8.1	77	8.7	102	8.5
3	>8.6	28	8.6	53	8.0	78	8.5	103	6.8
4	8.5	29	8.3	54	7.9	79	6.9	104	7.5
5	8.5	30	7.5	55	8.2	80	6.9	105	7.8
6	8.4	31	8.2	56	6.0	81	7.8	106	7.7
7	8.5	32	8.5	57	6.1	82	7.7	107	7.7
8	8.6	33	>8.6	58	6.0	83	8.0	108	7.9
9	8.6	34	<5.0	59	8.2	84	8.5	109	6.4
10	8.5	35	5.5	60	6.0	85	8.4		
11	>8.6	36	7.8	61	7.5	86	8.5		
12	>8.6	37	7.8	62	7.4	87	8.3		
13	>8.6	38	7.6	63	7.4	88	8.4		
14	>8.6	39	7.9	64	8.1	89	8.5		
15	7.6	40	8.5	65	7.0	90	8.3		
16	7.6	41	8.4	66	8.8	91	8.4		
17	6.9	42	7.7	67	7.4	92	8.2		
18	7.4	43	7.4	68	7.9	93	8.4		
19	6.4	44	7.7	69	8.4	94	8.6		
20	6.4	45	8.2	70	8.4	95	7.6		
21	>8.6	46	6.5	71	8.2	96	>8.6		
22	8.1	47	7.4	72	7.1	97	8.5		
23	7.4	48	7.1	73	8.1	98	8.0		
24	7.2	49	8.3	74	8.0	99	7.7		
25	5.2	50	8.4	75	8.0	100	8.5		

[0916] As used in this specification and the appended claims, singular articles such as “a,” “an,” and “the,” may refer to a single object or to a plurality of objects unless the context clearly indicates otherwise. Thus, for example, reference to a composition containing “a compound” may include a single compound or two or more compounds. The above description is intended to be illustrative and not restrictive. Many embodiments will be apparent to those of skill in the art upon reading the above description. Therefore, the scope of the invention should be determined with reference to the appended claims and includes the full scope of equivalents to which such claims are entitled. The disclosures of all articles and references cited in the disclosure, including patents, patent applications and publications, are herein incorporated by reference in their entirety and for all purposes.

WHAT IS CLAIMED IS:

1. A compound of Formula 1,



or a pharmaceutically acceptable salt thereof in which:

α is a single bond, β is a double bond, X^1 is NR^{1N} , and R^2 is oxo; or

α is a double bond, β is a single bond, X^1 is selected from N and CR^{1C} , and R^2 is selected from hydrogen, C_{1-4} alkyl, and C_{1-4} alkoxy;

R^{1C} is selected from hydrogen, halo, and C_{1-6} alkyl which is substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, C_{1-4} alkoxy, and amino which is optionally substituted with one or two C_{1-4} alkyl;

R^{1N} is selected from C_{1-4} alkyl, C_{3-8} cycloalkyl- $(CH_2)_n$, C_{2-8} heterocyclyl- $(CH_2)_n$, and C_{1-9} heteroaryl- $(CH_2)_n$, wherein each of the C_{1-4} alkyl, C_{3-8} cycloalkyl, C_{2-8} heterocyclyl, and C_{1-9} heteroaryl moieties is substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, and amino which is optionally substituted with one or two C_{1-4} alkyl, and wherein the C_{1-4} alkyl and C_{1-4} alkoxy optional substituents are each independently substituted with from 0 to 3 optional substituents independently selected from halo;

n is selected from 0, 1, 2, and 3;

R^3 is C_{1-6} alkyl which is substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, C_{1-4} alkoxy which is optionally substituted with C_{1-4} alkoxy, and from amino which is optionally substituted with one or two C_{1-4} alkyl, wherein one or more of the hydrogen atoms on R^3 may optionally be deuterium;

R^4 and R^5 are each independently selected from hydrogen, halo, and C_{1-4} alkyl;

X^6 is selected from N and $C(R^6)$;

X^7 is selected from N and $C(R^7)$;

R^6 and R^7 are each independently from hydrogen, halo, C_{1-4} alkyl, and C_{1-4} alkoxy;

R⁸ is selected from hydrogen, halo, C₁₋₄ alkyl, and C₁₋₄ alkoxy, wherein the C₁₋₄ alkyl and C₁₋₄ alkoxy substituents are substituted with from 0 to 3 optional substituents independently selected from halo; and

R⁹ is selected from C₁₋₆ alkyl, C₃₋₈ cycloalkyl, C₂₋₈ heterocyclyl, and C₁₋₉ heteroaryl, each substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, oxo, C₁₋₄ alkyl, C₁₋₄ alkoxy, and amino which is optionally substituted with one or two C₁₋₄ alkyl, wherein the C₁₋₄ alkyl and C₁₋₄ alkoxy optional substituents are each independently substituted with from 0 to 3 optional substituents independently selected from halo; and

wherein each of the heterocyclyl and heteroaryl moieties independently has 1 to 4 ring members which are heteroatoms, each of the heteroatoms independently selected from N, O, and S.

2. The compound or pharmaceutically acceptable salt according to claim 1, wherein α is a single bond, β is a double bond, X¹ is NR^{1N}, and R² is oxo.

3. The compound or pharmaceutically acceptable salt according to any one of claims 1 and 2, wherein R^{1N} is selected from C₁₋₄ alkyl, C₃₋₆ cycloalkyl-(CH₂)_n, C₃₋₅ heterocyclyl-(CH₂)_n, and C₁₋₅ heteroaryl-(CH₂)_n, wherein each of the C₁₋₄ alkyl, C₃₋₆ cycloalkyl, C₃₋₅ heterocyclyl, and C₁₋₅ heteroaryl moieties is substituted with from 0 to 3 optional substituents as defined in claim 1.

4. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 3, wherein each of the 0 to 3 optional substituents of R^{1N} is independently selected from halo, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, and amino which is optionally substituted with one or two C₁₋₄ alkyl.

5. The compound or pharmaceutically acceptable salt according to any one of claims 1 and 2, wherein R^{1N} is C₁₋₄ alkyl which is substituted with from 0 to 3 optional substituents as defined in claim 1.

6. The compound or pharmaceutically acceptable salt according to claim 5, wherein the C₁₋₄ alkyl substituent of R^{1N} is substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, and amino which is optionally substituted with one or two C₁₋₄ alkyl.

7. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 6, wherein n is 1.
8. The compound or pharmaceutically acceptable salt according to claim 1, wherein α is a double bond, β is a single bond, X^1 is N, and R^2 is selected from hydrogen, C_{1-4} alkyl, and C_{1-4} alkoxy.
9. The compound or pharmaceutically acceptable salt according to claim 1, wherein α is a double bond, β is a single bond, X^1 is CR^{1C} , and R^2 is selected from hydrogen, C_{1-4} alkyl, and C_{1-4} alkoxy.
10. The compound or pharmaceutically acceptable salt according to claim 9, wherein R^{1C} is selected from hydrogen, halo, and C_{1-4} alkyl which is substituted with hydroxy.
11. The compound or pharmaceutically acceptable salt according to claim 9, wherein R^{1C} is hydrogen.
12. The compound or pharmaceutically acceptable salt according to any one of claims 8 to 11, wherein R^2 is selected from hydrogen, methyl, ethyl, propyl, methoxy, and ethoxy.
13. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 12, wherein R^3 is C_{1-4} alkyl which is substituted with hydroxy or C_{1-4} alkoxy which is optionally substituted with C_{1-4} alkoxy.
14. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 13, wherein R^4 and R^5 are each hydrogen.
15. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 14, wherein X^6 is $C(R^6)$ and X^7 is $C(R^7)$.
16. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 15, wherein R^6 and R^7 are each independently selected from hydrogen and fluoro.
17. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 16, wherein R^8 is methyl.
18. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 17, wherein R^9 is selected from C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-5} heterocyclyl, and

C₁₋₅ heteroaryl, each substituted with from 0 to 3 optional substituents independently selected from halo, hydroxy, cyano, oxo, C₁₋₄ alkyl, C₁₋₄ alkoxy, and amino which is optionally substituted with one or two C₁₋₄ alkyl, wherein the C₁₋₄ alkyl and C₁₋₄ alkoxy optional substituents are each independently substituted with from 0 to 3 optional substituents independently selected from halo.

19. The compound or pharmaceutically acceptable salt according to claim 18, wherein R⁹ is C₃₋₆ cycloalkyl which is substituted with from 0 to 3 optional substituents as defined in claim 1.

20. The compound according to claim 1, which is selected from the following compounds:

N-cyclopropyl-2-fluoro-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-2-methoxy-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxyethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-2-fluoro-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-1,1-*d*₂)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

2-fluoro-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-1,1-*d*₂)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-(isoxazol-3-yl)-4-methylbenzamide;

3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-1,1-*d*₂)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-(isoxazol-3-yl)-4-methylbenzamide;

2-fluoro-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-1,1-*d*₂)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-(1*H*-pyrazol-3-yl)benzamide;

3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-1,1-*d*₂)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-(isothiazol-3-yl)-4-methylbenzamide;

2-fluoro-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-1,1-*d*₂)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-(isothiazol-3-yl)-4-methylbenzamide;

N-cyclopropyl-5-(3-ethyl-1-(1-hydroxy-2-methylpropan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-2-fluoro-4-methylbenzamide;

N-cyclopropyl-2-fluoro-5-(1-(1-hydroxy-2-methylpropan-2-yl)-3-(2-hydroxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide;

N-cyclopropyl-2-fluoro-5-(1-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide;

N-cyclopropyl-5-(2-ethoxy-3-(1-hydroxy-2-methylpropan-2-yl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-2-fluoro-4-methylbenzamide;

N-cyclopropyl-2-fluoro-5-(3-(1-hydroxypropan-2-yl)-2-methoxy-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-2-fluoro-5-(3-(2-hydroxyethyl)-2-methoxy-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-3-(1-(1-hydroxy-2-methylpropan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide;

N-cyclopropyl-3-(1-(2-hydroxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide;

N-cyclopropyl-3-(3-(2-hydroxyethyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-2-methoxy-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

3-(3-chloro-1-(1-hydroxy-2-methylpropan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-*N*-cyclopropyl-4-methylbenzamide;

N-cyclopropyl-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-7-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-5-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl-1,1-*d*₂)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-3-(1-ethyl-3-(2-(hydroxymethyl)propan-2-yl-1,1,1,3,3,3-*d*₆)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-3-(1-(2-fluoroethyl)-3-(2-(hydroxymethyl)propan-2-yl-1,1,1,3,3,3-*d*₆)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-3-(3-ethyl-1-(1-hydroxy-2-methylpropan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide;

N-cyclopropyl-3-(1-(1-hydroxy-2-methylpropan-2-yl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide;

N-cyclopropyl-3-(1-(1-hydroxy-2-methylpropan-2-yl)-3-(2-hydroxyethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide;

N-cyclopropyl-3-(1-(1-hydroxy-2-methylpropan-2-yl)-3-isopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-4-methylbenzamide;

N-cyclopropyl-3-(2-ethoxy-3-(1-hydroxy-2-methylpropan-2-yl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-3-(2-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

3-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*,4-dimethylbenzamide;

3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*,4-dimethylbenzamide;

3-(1-(2,2-difluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*,4-dimethylbenzamide;

5-(1-(2,2-difluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2-fluoro-*N*,4-dimethylbenzamide;

N-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxyethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

4-chloro-*N*-cyclopropyl-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)benzamide;

N-cyclopropyl-4-fluoro-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)benzamide;

N-cyclopropyl-4-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-5-methylpicolinamide;

N-cyclobutyl-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-3-fluoro-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

3-chloro-*N*-cyclopropyl-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-6-methylnicotinamide;

3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-(1-methylcyclopropyl)benzamide;

3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-(1*H*-pyrazol-3-yl)benzamide;

2-fluoro-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-(1*H*-pyrazol-3-yl)benzamide;

2-fluoro-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*,4-dimethylbenzamide;

2-fluoro-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide;

2-chloro-*N*-cyclopropyl-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-((1*S*,2*S*)-2-methylcyclopropyl)benzamide;

N-cyclopropyl-2,4-difluoro-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)benzamide;

N-cyclopropyl-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-(trifluoromethyl)benzamide;

N-cyclopropyl-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2-methoxy-4-methylbenzamide;

N-(bicyclo[1.1.1]pentan-2-yl)-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-(fluoromethyl)benzamide;

3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-((1*S*,2*R*)-2-methylcyclopropyl)benzamide;

N-cyclopropyl-4-(difluoromethyl)-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)benzamide;

3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-(pyridin-2-yl)benzamide;

3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-formyl-4-methylbenzamide;

3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-(oxazol-2-yl)benzamide;

N-acetyl-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-(isoxazol-3-yl)-4-methylbenzamide;

N-cyclopropyl-5-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2,4-dimethylbenzamide;

5-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2-fluoro-*N*,4-dimethylbenzamide;

3-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-(1*H*-pyrazol-3-yl)benzamide;

5-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2-fluoro-4-methyl-*N*-(1*H*-pyrazol-3-yl)benzamide;

3-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide;

3-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-(1-methyl-1*H*-pyrazol-5-yl)benzamide;

5-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2-fluoro-4-methyl-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide;
5-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2-fluoro-*N*-(isoxazol-3-yl)-4-methylbenzamide;
2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-1-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-(isoxazol-3-yl)-4-methylbenzamide;
5-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl-1,1-*d*₂)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2-fluoro-*N*-(isothiazol-3-yl)-4-methylbenzamide;
3-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl-1,1-*d*₂)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-(isothiazol-3-yl)-4-methylbenzamide;
5-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl-1,1-*d*₂)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2-fluoro-4-methyl-*N*-(1*H*-pyrazol-3-yl)benzamide;
3-(3-(*tert*-butyl)-1-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-(isoxazol-3-yl)-4-methylbenzamide;
3-(3-(*tert*-butyl)-1-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-cyclopropyl-4-methylbenzamide;
3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-(isoxazol-3-yl)-4-methylbenzamide;
N-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;
(*R*)-*N*-cyclopropyl-2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxypropyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;
(*S*)-*N*-cyclopropyl-2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxypropyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;
N-cyclopropyl-2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(3-hydroxypropyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;
2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxyethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-(isoxazol-3-yl)-4-methylbenzamide;

2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxyethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methyl-*N*-(1*H*-pyrazol-3-yl)benzamide;

N-cyclopropyl-2-fluoro-5-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-hydroxy-2-methylpropyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

3-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-(isoxazol-3-yl)-4-methylbenzamide;

N-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-isopropyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-3-(1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-1-(2,2,2-trifluoroethyl)-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-1-propyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-isobutyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(oxetan-3-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-3-(1-(cyclopropylmethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-3-(1-(2-fluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-1-((tetrahydrofuran-3-yl)methyl)-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(3-methoxypropyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

N-cyclopropyl-3-(1-(2,2-difluoroethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;

3-(1-(cyclobutylmethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-cyclopropyl-4-methylbenzamide;

N-cyclopropyl-3-(1-((2,2-difluorocyclopropyl)methyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;
N-cyclopropyl-3-(1-(2-(dimethylamino)ethyl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;
N-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(isoxazol-5-ylmethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;
N-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(isoxazol-4-ylmethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;
N-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(isoxazol-3-ylmethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;
N-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-((1-methyl-1*H*-pyrazol-4-yl)methyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;
N-cyclopropyl-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-(2-methoxyethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide;
N-cyclopropyl-3-(3-(1-(2-methoxyethoxy)-2-methylpropan-2-yl)-1-(2-methoxyethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-methylbenzamide; and
 a pharmaceutically acceptable salt of any one of the compounds.

21. A pharmaceutical composition comprising:
 a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 20; and
 a pharmaceutically acceptable excipient.
22. A compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 20 for use as a medicament.
23. A compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 20 for use in treating a disease, disorder or condition selected from allergic rhinitis, asthma, atopic dermatitis, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, lupus nephritis, psoriasis, immune thrombocytopenic purpura, inflammatory bowel disease, chronic obstructive pulmonary disease, Sjögren's syndrome, ankylosing spondylitis, Behcet's disease, graft versus host disease, pemphigus vulgaris, idiopathic plasmacytic lymphadenopathy, atherosclerosis, myocardial infarction, and thrombosis.

24. A method for inhibiting RIPK2 in a subject, the method comprising administering to the subject a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 20.
25. A method of treating a disease, disorder or condition in a subject, the method comprising administering to the subject a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 20, wherein the disease, disorder or condition is associated with RIPK2.
26. A method of treating a disease, disorder or condition in a subject, the method comprising administering to the subject a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 20, wherein the disease, disorder or condition is selected from Type I hypersensitivity reactions, autoimmune diseases, and inflammatory disorders, cancer, and non-malignant proliferative disorders.
27. A method of treating a disease, disorder or condition in a subject, the method comprising administering to the subject a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 20, wherein the disease, disorder or condition is selected from allergic rhinitis, asthma, atopic dermatitis, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, lupus nephritis, psoriasis, immune thrombocytopenic purpura, inflammatory bowel disease, chronic obstructive pulmonary disease, Sjögren's syndrome, ankylosing spondylitis, Behcet's disease, graft versus host disease, pemphigus vulgaris, idiopathic plasmacytic lymphadenopathy, atherosclerosis, myocardial infarction, and thrombosis.
28. A combination comprising a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 20, and at least one additional pharmacologically active agent.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2020/023984

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D471/04 A61K31/4439 A61P37/00 A61P37/06 A61P37/08 A61P29/00 A61P35/00 A61P11/00 A61P11/02 A61P11/06 A61P17/00 A61P17/06 A61P19/00 A61P19/02 A61P25/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2018/052772 A1 (BOEHRINGER INGELHEIM INT [DE]) 22 March 2018 (2018-03-22) page 2, paragraph 3 examples page 112 - page 115; table 3 claims 1, 17, 21 -----	1-28
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents :		
"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search	Date of mailing of the international search report	
6 May 2020	15/05/2020	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Cortés Suárez, José	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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