



(51) International Patent Classification:

C07D 401/04 (2006.01) A61K 31/437 (2006.01)

C07D 471/04 (2006.01) A61P 35/00 (2006.01)

A61K 31/4439 (2006.01)

(21) International Application Number:

PCT/IB2018/056806

(22) International Filing Date:

06 September 2018 (06.09.2018)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/555,164 07 September 2017 (07.09.2017) US

62/587,004 16 November 2017 (16.11.2017) US

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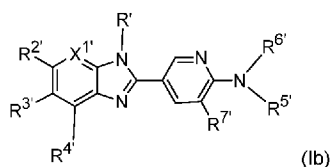
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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,

(54) Title: 5-(1 H-BENZO[D]IMIDAZO-2-YL)-PYRIDIN-2-AMINE AND 5-(3H-IMIDAZO[4,5-B]PYRIDIN-6-YL)-PYRIDIN-2-AMINE DERIVATIVES AS C-MYC AND P300/CBP HISTONE ACETYLTRANSFERASE INHIBITORS FOR TREATING CANCER



(57) Abstract: The invention is directed to substituted 5-(1H-benzo[d]imidazo-2-yl)-pyridin-2-amine and 5-(3H-imidazo[4,5-b]pyridin-6-yl)-pyridin-2-amine derivatives. Specifically, the invention is directed to compounds according to Formula (Ib) wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, and X¹ are as defined herein; or a salt thereof including a pharmaceutically acceptable salt thereof. The compounds of the invention decrease MYC protein (c-MYC) in cells and/or inhibit p300/CBP histone acetyltransferase and can be useful in the treatment of cardiac hypertrophy, diabetes, obesity & nonalcoholic fatty liver disease, HIV, polycystic kidney disease, inflammatory diseases, ankylosing spondylitis, psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease, multiple sclerosis, cancer and pre-cancerous syndromes, and diseases associated with dysregulation of Myc or inhibition of p300/CBP histone acetyltransferase. Accordingly, the invention is further directed to pharmaceutical compositions comprising a compound of the invention. The invention still further discloses methods of reducing MYC protein (c-MYC) in cells and inhibiting p300/CBP histone acetyltransferase activity, and treatment of disorders associated therewith using a compound of the invention or a pharmaceutical composition comprising a compound of the invention.



TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
- *of inventorship (Rule 4.17(iv))*

Published:

- *with international search report (Art. 21(3))*
- *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

5-(1 H-BENZO[D]IMIDAZO-2-YL)-PYRIDIN-2-AMINE AND 5-(3H-IMIDAZO[4,5-B]PYRIDIN-6-YL)-PYRIDIN-2-AMINE
DERIVATIVES AS C-MYC AND P300/CBP HISTONE ACETYLTRANSFERASE INHIBITORS FOR TREATING
CANCER

FIELD OF THE INVENTION

5 The present invention relates to substituted benzimidazole derivatives that decrease MYC protein (c-MYC) in cells and inhibit p300/CBP histone acetyltransferase. The present invention also relates to pharmaceutical compositions comprising such compounds, processes for preparing such compounds and methods of using such compounds for example in the treatment of cardiac hypertrophy, diabetes, obesity & nonalcoholic fatty liver
10 disease, HIV, polycystic kidney disease, inflammatory diseases, ankylosing spondylitis, psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease, multiple sclerosis, cancer and pre-cancerous syndromes.

BACKGROUND OF THE INVENTION

15 The transcription factor Myc plays a role in regulating cell proliferation, the cell cycle, cell growth, angiogenesis, apoptosis, and oncogenesis. Myc's levels can increase in tumors as a consequence of gene amplification chromosomal
20 rearrangements, increased expression, or mutations, (see, *e.g.*, Nesbit, *et al.* (1999) *Oncogene* 18:3004-3016; Zeller, *et al.* (2001) *J. Biol. Chem.* 276:48285-48291; He, *et al.* (1998) *Science* 281:1509-1512; McMahon, *et al.* (1998) *Cell* 94:363-374; Erisman, *et al.* (1985) *Mol. Cell Biol.* 5:1969-1976; Rochlitz, *et al.* (1996). *Oncology* 53:448-454). Increased Myc levels have been found, for example, in breast cancer and
25 prostate cancer (Liao, *et al.* (2000) *Endocrine-Related Cancer* 7:143-164; Jenkins, *et al.* (1997) *Cancer Res.* 57:524-531).

 When Myc acts as a cell cycle regulator, it can promote entry of a cell into the cell cycle (Trump, *et al.* (2001) *Nature* 414:768-773; Holzel, *et al.* (2001) *EMBO Reports* 21: 1125-1132; Bouchard, *et al.* (2001) *Genes Devel.* 15:2042-2047). Myc has been found to act in certain phases of the cell cycle, where cell cycle genes, *e.g.*, cyclins and protein kinases, may be directly or indirectly regulated by Myc. Myc also regulates growth, as it plays a role in regulating genes required for protein synthesis, *e.g.*, genes encoding transcription factors and ribosomal proteins (Greasley, *et al.*
35 (2000) *Nucleic Acids Res.* 28:446-453; Zeller, *et al.* (2001) *supra*; Menssen, *et al.* (2002) *Proc. Natl. Acad. Sci. USA* 99:6274-6279). Myc regulates apoptosis, which

can be impaired in cancer cells. Myc has been shown to regulate key apoptosis pathway proteins (Nesbitt *et al.* (1998) *Blood* 92: 1003-1010).

Many diseases are associated with abnormal cell signaling triggered by Myc-mediated events described above, including proliferative diseases (e.g., cancer) and cardiovascular diseases. Accordingly, there is a need to identify Myc inhibitors useful as therapeutic agents and research tools.

It is an object of the instant invention to provide novel compounds that decrease MYC protein (c-MYC) in cells.

It is also an object of the present invention to provide pharmaceutical compositions that comprise a pharmaceutical carrier and compounds useful in the methods of the invention.

It is also an object of the present invention to provide a method for treating cancer, and pre-cancerous syndromes that comprises administering such compounds that decrease MYC protein (c-MYC) in cells.

Histone acetyltransferases (HATs) catalyze the acetylation (transfer of an acetyl group) on a ϵ -amino group of a target lysine side chain within a substrate histone. The reversible acetylation of histones and other proteins is one of the most abundant post-translational modifications in eukaryotic cells and is a major mechanism of cellular regulation. HATs are categorized into four major families based on primary sequence homology, shared structural features, and functional roles: Gcn5/PCAF (General control nonrepressed protein 5 and p300 and CBP associated factor); MYST (named for the founding members MOZ, Ybf2/Sas3, Sas2, and Tip60); p300/CBP (protein of 300kDa and CREB Binding Protein); and Rtt 109 (Regulator of Ty 1 Transposition gene production 109).

Paralog HATs p300 (KATB) and CBP (referred to as p300/CBP) have 61% sequence identity and are conserved in metazoans. In addition to the enzymatic HAT domain, p300/CBP has 30 multiple domains including three cysteine-histidine rich domains (CHI, CH2, and CH3), a KIX domain, a bromodomain, and a steroid receptor coactivator interaction domain (SRC-1 interaction domain). P300 and CBP were originally discovered as binding partners of E1A adenoviral protein and cAMP-regulated enhancer binding

proteins, respectively (Yee and Branton, 1985, *Virology* 147: 142-153; Harlow et al., 1986, *Mol. Cell Biol.* 6: 1579-1589; Chrivia et al., 1993, *Nature* 365:855-859). P300/CBP was later found to have intrinsic HAT activity (Ogryzko et al., 1996, *Cell* 5 87:953-959; Bannister and Kouzarides, 1996, *Nature* 384:641-643). In addition to acetylating multiple lysines on

5 all four core histones (H2A, H2B, H3 and H4), P300/CBP has been shown to have promiscuous acetyltransferase activity towards >70 substrates (Wang et al., 2008, *Curr. Opin. Struct. Biol.* 18:741-747), including, for example, p53 (Gu et al., 1997, *Cell* 90:595-606), MyoD (Polesskaya et al., 2002, *J. Biol. Chem.* 275:34359-64), STAT3 (Yuan et al., 2005, *Science* 10 307:269-73) and NFkB (Chen et al., 2002, *EMBO J.* 21:6539-48).

10 Besides acting as an acetyltransferase, p300 also acts as a scaffold for transcription factors or a bridge to connect the transcription factors and the basal transcriptional machinery to activate transcription (Chan and Thangue, 2001, *J. Cell Sci.* 114:2363-2373; Chen and Li, 2011, *Epigenetics* 6:957-961). P300/CBP proteins are involved in many cellular processes, including cell growth, proliferation, and differentiation (Chan and Thangue, *supra*).

15

Aberrant p300/CBP activity or mutations has been associated with various diseases. High p300 expression has been observed in prostate cancer (Heemers et al., 2008, *Adv. Exp. Med. Biol.* 617:535-40; Isharwa1 et al., 2008, *Prostate* 68: 1097-104), liver cancer (Yokomizo et al., 2011, *Cancer Lett.* 310: 1407; Li et al., 2011, *J. Transl. Med.* 9:5), and

20 breast cancer (Fermento et al., 2010, *Exp. Mol. Pathol.* 88:256-64). Mutations in p300/CBP genes have been found in human tumors (Petrij et al., 1995, *Nature* 376:348-51; Muraoka et al, 1996, *Oncogene* 12:1565-69; Sobu10 et al., 1997, *Proc. Nati. Acad. Sci. USA* 94:8732-37; Gayther et al., 2000, *Nat. Genet.* 24:300-304). P300 missense mutations and truncations have been found in solid tumors and B-cell lymphoma, suggesting a role

25 as a tumor suppressor (Iyer et al., 2004, *Oncogene* 23:4225-31; Pasqualucci et al., 2011, *nature* 471: 189-95). Inhibition of p300/CBP has therapeutic potential in cancer (Iyer et al., 2004, *Proc. Nati. Acad. Sci. USA* 101:7386-7391; Stimson et al., 2005, *Mol. Cancer Ther.* 4: 1521-1532; Zheng et al., 2004, *Methods Enzymol.* 376: 188-199), cardiac disease (Davidson et al., 2005, *Chembiochem.* 6: 162-170); diabetes mellitus (Zhou et al., 2004,

30 *Nat. Med.* 10:633-637), and HIV (Varier and Kundu, 2006, *Curro Pharm. Des.* 12:1975-1993). Heterozygous germline mutations in CBP or p300 have also been described in Rubinstein-Taybi syndrome, an autosomal dominant disease characterized by mental retardation, skeletal abnormalities, and a high incidence of neoplasia (Petrij et al., 1995, *Nature* 376:348-51; Petrij et al., 2000, *Am. J. Med. Genet.* 92:47-52). P300/CBP is also

35 involved in regulating inflammatory mediators (Deng et al., 2004, *Blood* 103:2135-42; Turner-Brannen et al., 2011, *J. Immunol.* 186:7127-7135). P300/CBP has also been linked

to other diseases, such as fibrosis (Ghosh and Varga, 2007, *J. Cell. Physiol.* 213:663-671), metabolic syndrome (Bricambert et al., 2010, *J. Clin. Invest.* 120:4316-4331), and progressive neurodegenerative diseases, such as Huntington Disease (Cong et al., 2005, *Mol. Cell. Neurosci.* 5 30: 12-23), Kennedy's disease (Lieberman et al., 2002, *Hum. Mol. Genet.* 11: 1967-76), and Alzheimer's disease (Francis et al., 2007, *Neurosci. Lett.* 413:137-140).

Additional disease states associated with increased p300/CBP activity or mutations include: thrombocytopenia (Kauppi, M.; Murphy, J. M.; de Graaf, C. A.; Hyland, C. D.; Greig, K. T.; Metcalf, D.; Hilton, A. A.; Nicola, N. A.; Kile, B. T.; Hilton, D. J.; Alexander, W. S. *Blood* 2008, 112, 3148. Hilton, D. J.; Kile, B. T.; Alexander, W. S. *Blood* 2009, 113, 5599); cardiac hypertrophy (Gusterson, R. J.; Jazrawi, E.; Adcock, I. M.; Latchman, D. S. *J. Biol. Chem.* 2003, 278, 6838); diabetes (Zhou, X. Y.; Shibusawa, N.; Naik, K.; Porras, D.; Temple, K.; Ou, H.; Kaihara, K.; Roe, M. W.; Brady, M. J.; Wondisford, F. E. *Nat. Med.* 2004, 10, 633); obesity & nonalcoholic fatty liver disease (Bricambert, J.; Miranda, J.; Benhamed, F.; Girard, J.; Postic, C.; Dentin, R. J. *Clin. Invest.* 2010, 120, 4316). HIV treatment (Zou, W.; Wang, Z.; Liu, Y.; Fan, Y.; Zhou, B. Y.; Yang, X. F.; He, J. J. *Glia* 2010, 58, 1640); polycystic kidney disease (Merrick D, Chapin H, Baggs JE, Yu Z, Somlo S, Sun Z, Hogenesch JB, Caplan MJ. *Dev Cell.* 2012 Jan 17;22(1):197-210); and Inflammatory diseases, including ankylosing spondylitis, psoriasis and psoriatic arthritis, rheumatoid arthritis, Crohn's disease, and multiple sclerosis (Hammitzsch A, Tallant C, Fedorov O, O'Mahony A, Brennan PE, Hay DA, Martinez FO, Al-Mossawi MH, de Wit J, Vecellio M, Wells C, Wordsworth P, Müller S, Knapp S, Bowness P. *Proc Natl Acad Sci U S A.* 2015 Aug 25;112(34):10768-73).

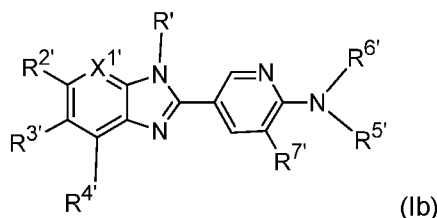
The association of p300/CBP activity in disease pathogenesis suggests potential utility of p300/CBP as a therapeutic target. However, the identification of potent, specific histone acetyltransferase inhibitors has been challenging (Cole, 2008, *Nat. Chem. Biol.* 4:590-97). Recently, selective p300/CBP HAT inhibitors were disclosed (International Publication Number WO 2016/044770 having International Publication Date March 24, 2016).

Accordingly, while progress has been made in this field, there remains a need in the art for improved compounds that decrease MYC protein (c-MYC) in cells and inhibit p300/CBP histone acetyltransferase. The present invention fulfills this need and provides further related advantages.

SUMMARY OF THE INVENTION

5

In one aspect, the invention is directed to substituted benzimidazole derivatives, specifically, to compounds according to Formula Ib:



wherein R', R²', R³', R⁴', R⁵', R⁶', R⁷', and X¹' are as defined below; or a salt thereof
10 including a pharmaceutically acceptable salt thereof.

The present invention also relates to the discovery that the compounds of Formula (Ib) decrease MYC protein (c-MYC) in cells.

15 The present invention also relates to the discovery that the compounds of Formula (Ib) prevent the transcription and function of c-MYC.

The present invention also relates to the discovery that the compounds of Formula (Ib) are active as inhibitors of p300/CBP histone acetyltransferase activity.
20

This invention also relates to a method of treating cancer and pre-cancerous syndromes, which comprises administering to a subject in need thereof an effective amount of a compound of Formula (Ib).

25 This invention also relates to a method of treating a disease state selected from: cardiac hypertrophy, diabetes, obesity & nonalcoholic fatty liver disease, HIV, polycystic kidney disease, inflammatory diseases, ankylosing spondylitis, psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease, and multiple sclerosis which comprises administering to a subject in need thereof an effective amount of a compound of Formula (Ib).

30

In a further aspect of the invention there is provided novel processes and novel intermediates useful in preparing the presently invented compounds.

Included in the present invention are pharmaceutical compositions that comprise a pharmaceutical carrier and compounds useful in the methods of the invention.

The invention also relates to a compound of Formula (Ib) or a pharmaceutically acceptable salt thereof for use in therapy.

The invention also relates to a compound of Formula (Ib) or a pharmaceutically acceptable salt thereof for use in the treatment of cancer and pre-cancerous syndromes.

The invention also relates to the use of a compound of Formula (Ib) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of a disease state selected from: cardiac hypertrophy, diabetes, obesity & nonalcoholic fatty liver disease, HIV, polycystic kidney disease, inflammatory diseases, ankylosing spondylitis, psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease, and multiple sclerosis.

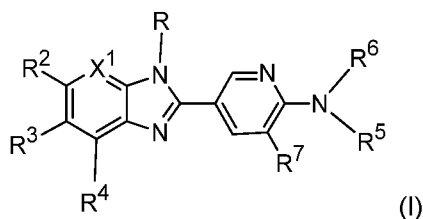
The invention also relates to the use of a compound of Formula (Ib) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of cancer and pre-cancerous syndromes.

The invention also relates to a pharmaceutical composition as defined above for use in therapy.

Also included in the present invention are methods of co-administering the presently invented compounds with further active ingredients.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to novel compounds of Formula (I):



where:

R is C₁₋₆alkyl, substituted with from 1 to 3 substituents independently selected from:

fluoro,

oxo,

aryl substituted by heteroaryl,

5 heterocyclyl,

heterocyclyl substituted with from 1 to 4 substituents independently selected from:

fluoro,

chloro,

10 bromo,

heteroaryl,

C₁₋₆alkyl, and

C₁₋₆alkyl substituted with from 1 to 5 substituents independently selected from: fluoro, chloro,

15 bromo, iodo, oxo, -CN, -OH and -NH₂,

heteroaryl,

heteroaryl substituted with from 1 to 4 substituents independently selected from:

fluoro,

20 chloro,

bromo,

heteroaryl,

C₁₋₆alkyl, and

C₁₋₆alkyl substituted with from 1 to 5 substituents independently selected from: fluoro, chloro,

25 bromo, iodo, oxo, -CN, -OH and -NH₂,

C₁₋₆alkoxy,

C₁₋₆alkoxy substituted with from 1 to 9 substituents independently selected from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and

30 -N(CH₃)₂,

-Ocycloalkyl, and

-Ocycloalkyl substituted with from 1 to 4 substituents independently selected from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and -N(CH₃)₂;

X^1 is selected from: CR^1 and N ,

where,

R^1 is selected from:

5 hydrogen,
fluoro,
chloro,
bromo,
10 iodo,
-OH,
-CN,
C1-4alkoxy,
C1-4alkoxy substituted with from 1 to 7 substituents independently selected
from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and -N(CH₃)₂,
15 C1-6alkyl,
C1-6alkyl substituted with from 1 to 7 substituents independently selected
from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH, -OC1-5alkyl,
-COOH, -S(O)₂H, -S(O)₂R^X where R^X is selected from C1-3alkyl and
C1-3alkyl substituted from one to 3 times by fluoro, heterocyclyl,
20 and -NR^aR^b,
where R^a and R^b are independently selected from:
hydrogen,
C1-5alkoxy,
C1-5alkoxy substituted with from 1 to 4 substituents
25 independently selected from: fluoro, oxo, -OH,
-OC1-5alkyl, cycloalkyl, -COOH, -NH₂, and
-S(O)₂H,
C1-5alkyl,
C1-5alkyl substituted with from 1 to 4 substituents
30 independently selected from: fluoro, oxo, -OH,
-OC1-5alkyl, cycloalkyl, -COOH, -NH₂,

-S(O)₂H, and -S(O)₂R^x where R^x is selected from C₁-3alkyl and C₁-3alkyl substituted from one to 3 times by fluoro, cycloalkyl, and cycloalkyl substituted with from 1 to 4 substituents independently selected from: fluoro, oxo, -OH, -O₁-5alkyl, -COOH, and -NH₂, heteroaryl, and heteroaryl substituted with from 1 to 4 substituents independently selected from: fluoro, chloro, C₁-6alkyl, and C₁-6alkyl substituted with from 1 to 5 substituents independently selected from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH and -NH₂;

R², R³, and R⁴ are independently selected from: hydrogen, fluoro, chloro, bromo, iodo, -OH, boronic acid, 1,3,6,2-dioxazaborocane-4,8-dione, -CN, -NR^cR^d, where R^c and R^d are independently selected from: hydrogen, C₁-5alkyl, C₁-5alkyl substituted with from 1 to 4 substituents independently selected from: fluoro, oxo, -OH,

- OC₁₋₅alkyl, cycloalkyl, -COOH, -NH₂,
 -S(O)₂H, and -S(O)₂R^X where R^X is selected
 from C₁₋₃alkyl and C₁₋₃alkyl substituted from
 one to 3 times by fluoro,
 5 aryl,
 aryl, substituted with from 1 to 4 substituents
 independently selected from: fluoro, oxo, -OH,
 -O₁₋₅alkyl, -COOH, and -NH₂,
 heteroaryl,
 10 heteroaryl, substituted with from 1 to 4 substituents
 independently selected from: fluoro, oxo, -OH,
 -O₁₋₅alkyl, -COOH, and -NH₂,
 heterocyclyl,
 heterocyclyl, substituted with from 1 to 4 substituents
 15 independently selected from: fluoro, oxo, -OH,
 -O₁₋₅alkyl, -COOH, and -NH₂,
 cycloalkyl, and
 cycloalkyl substituted with from 1 to 4 substituents
 independently selected from: fluoro, oxo, -OH,
 20 -O₁₋₅alkyl, -COOH, and -NH₂,
 C₁₋₄alkoxy,
 C₁₋₄alkoxy substituted with from 1 to 7 substituents independently selected
 from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and -N(CH₃)₂,
 C₁₋₆alkyl,
 25 C₁₋₆alkyl substituted with from 1 to 7 substituents independently selected
 from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH, -OC₁₋₅alkyl,
 heterocyclyl, -COOH, -S(O)₂H, -S(O)₂R^X where R^X is selected from
 C₁₋₃alkyl and C₁₋₃alkyl substituted from one to 3 times by fluoro,
 and -NR^aR^b,
 30 where R^a and R^b are independently selected from:

- hydrogen,
- C1-5alkyl,
- C1-5alkyl substituted with from 1 to 4 substituents
independently selected from: fluoro, oxo, -OH,
5 -OC1-5alkyl, cycloalkyl, -COOH, -NH₂,
-S(O)₂H, and -S(O)₂R^X where R^X is selected
from C1-3alkyl and C1-3alkyl substituted from
one to 3 times by fluoro,
- aryl,
- 10 aryl, substituted with from 1 to 4 substituents
independently selected from: fluoro, oxo, -OH,
-O1-5alkyl, -COOH, and -NH₂,
- heteroalkyl,
- heteroalkyl, substituted with from 1 to 4 substituents
15 independently selected from: fluoro, oxo, -OH,
-O1-5alkyl, -COOH, and -NH₂,
- heterocycle,
- heteroalkyl, substituted with from 1 to 4 substituents
independently selected from: fluoro, oxo, -OH,
20 -O1-5alkyl, -COOH, and -NH₂,
- cycloalkyl, and
- cycloalkyl substituted with from 1 to 4 substituents
independently selected from: fluoro, oxo, -OH,
-O1-5alkyl, -COOH, and -NH₂,
- 25 aryl,
- aryl substituted with from 1 to 4 substituents independently selected
from:
- fluoro,
- chloro,
- 30 C1-6alkyl, and
- C1-6alkyl substituted with from 1 to 5 substituents independently

- selected from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH and
-NH₂,
cycloalkyl,
cycloalkyl substituted with from 1 to 4 substituents independently selected
from:
- 5 fluoro,
chloro,
C₁-6alkyl, and
C₁-6alkyl substituted with from 1 to 5 substituents independently
selected from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH and
10 -NH₂,
heterocycle,
heterocycle substituted with from 1 to 4 substituents independently selected
from:
- 15 fluoro,
chloro,
C₁-6alkyl, and
C₁-6alkyl substituted with from 1 to 5 substituents independently
selected from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH and
20 -NH₂,
heteroaryl, and
heteroaryl substituted with from 1 to 4 substituents independently selected
from:
- 25 fluoro,
chloro,
C₁-6alkyl, and
C₁-6alkyl substituted with from 1 to 5 substituents independently
selected from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH and
-NH₂,
30 or 2 adjacent members of R¹, R², R³, and R⁴ are taken together to form a
non aromatic ring containing 3 to 6 member atoms independently

selected from: carbon, nitrogen, sulphur, oxygen and boron, to form an oxaborolyl, heterocyclyl, cycloalkyl, or heteroaryl, in which each of said oxaborolyl, heterocyclyl, cycloalkyl, and heteroaryl is optionally substituted with from 1 to 3 substituents independently
 5 selected from: fluoro, chloro, -OH, oxo, C1-6alkyl, and -NH₂;

R⁵ and R⁶ are independently selected from:

C1-4alkyl,
 C1-4alkyl substituted with from 1 to 6 substituents
 10 independently selected from: fluoro, oxo, -NH₂, C1-4alkoxy, and -OH,
 cycloalkyl,
 cycloalkyl substituted with from 1 to 5 substituents independently selected from:
 15 fluoro,
 chloro,
 -OH, and
 C1-6alkyl,
 or R⁵ and R⁶ are taken together with the nitrogen to which they are
 20 attached, and optionally from 1 to 3 additional heteroatoms, to form a heterocyclyl, which is optionally substituted with from 1 to 5 substituents independently selected from:
 fluoro,
 chloro,
 25 C1-6alkyl,
 C1-6alkyl substituted with from 1 to 9 substituents
 independently selected from: fluoro, chloro,
 C1-4alkoxy, oxo, -OH, -NH₂, -N(H)C1-4alkyl,
 -N(C1-4alkyl)₂, and -CN,
 30 C1-4alkoxy,

C1-4alkoxy substituted with from 1 to 4 substituents
independently selected from: fluoro, oxo, -OH,
-COOH, -NH₂, and -CN,
5 oxo,
 -NH₂,
 -N(H)C1-4alkyl, and
 -N(C1-4alkyl)₂; and

R⁷ is selected from: hydrogen and fluoro,
10 or one of R⁵ and R⁶ is taken together with R⁷, and optionally from 1 to 3
 additional heteroatoms, to form a heterocyclyl, which is optionally
 substituted with from 1 to 5 substituents independently selected from:
 fluoro, chloro, -OH, oxo, C1-4alkyl, C1-4alkoxy, and -NH₂;
15 or a pharmaceutically acceptable salt thereof.

For compounds of Formula (I), suitably X¹ is N. For compounds of Formula (1),
suitably X¹ is CR⁷.

For compounds of Formula (I), suitably R is C1-2alkyl substituted by:
20 pyrazolyl,
 pyrazolyl substituted by C1-3alkyl,
 oxazolyl,
 oxazolyl substituted by C1-3alkyl,
 imidazolyl,
25 imidazolyl substituted by C1-3alkyl,
 triazolyl,
 triazolyl substituted by C1-3alkyl,
 thiazolyl,
 thiazolyl substituted by C1-3alkyl,
30 -Ocyclopentyl,
 C1-6alkoxy,
 C1-6alkoxy substituted with from 1 to 6 times by fluoro,
 tetrahydrofuran,

pyridyl,
pyridyl substituted by bromo, or
pyridyl substituted by pyrimidinyl.

5 For compounds of Formula (I), suitably R¹, is selected from:

	hydrogen,
	fluoro,
	chloro,
	bromo,
10	-OH,
	-CN,
	-C(O)NHCH ₃ ,
	-C(O)NHCH ₂ CH ₂ OH,
	-C(O)NHCH ₂ CH ₂ SO ₂ CH ₃ ,
15	-C(O)NHCH ₃ ,
	-C(O)NH ₂ ,
	-C(O)OCH ₃ ,
	-C(O)NHCH ₂ cyclopropyl,
	-C(O)NHcyclobutyl, optionally substituted by hydroxy,
20	-CH ₂ morpholinyl,
	-CH ₂ OH,
	-CH ₂ NHCH ₂ CF ₃ ,
	-CH ₂ NHCH ₂ CH ₂ SO ₂ CH ₃ ,
	-CH ₂ SO ₂ CH ₃ ,
25	-CH(OH)CF ₃ ,
	-CH ₃ ,
	-CF ₃ ,
	-OCH ₃ ,
	pyrazolyl,
30	oxazolyl, and
	oxazolyl substituted once or twice by methyl,

For compounds of Formula (I), suitably R^2 , R^3 , and R^4 are independently selected from:

35	hydrogen, fluoro, chloro, bromo, -OH,
40	boronic acid,

- 1,3,6,2-dioxazaborocane-4,8-dione,
 -CN,
 -C(O)NHCH₃,
 -C(O)NHCH₂CH₂OH,
 5 -C(O)NHCH₂CH₂SO₂CH₃,
 -C(O)NHOCH₃,
 -C(O)NH₂,
 -C(O)OCH₃,
 -C(O)NHCH₂cyclopropyl,
 10 -C(O)NHcyclobutyl, optionally substituted by hydroxy,
 -CH₂morpholinyl,
 -CH₂OH,
 -CH₂NHCH₂CF₃,
 -CH₂NHCH₂CH₂SO₂CH₃,
 15 -CH₂SO₂CH₃,
 -CH(OH)CF₃,
 -CH₃,
 -CF₃,
 -OCH₃,
 20 -NHC(O)CH₃,
 -NH₂,
 -NHSO₂CH₃,
 morpholinyl
 pyrazolyl,
 25 oxazolyl, and
 oxazolyl substituted once or twice by methyl,

or R³ and R⁴ are taken together with the carbon atoms to which they are
 attached to form oxaborolyl, optionally substituted by hydroxyl.

30

For compounds of Formula (I), suitably R⁵ and R⁶ are independently selected from:

- C1-3alkyl,
 C1-3alkyl substituted from 1 to 3 times by fluoro, and
 cyclopropyl,

35

or R⁵ and R⁶ are taken together with the nitrogen to which they are

attached to form:

pyrrolidinyl,

which is optionally substituted one or two times by:

C1-3alkyl.

5

For compounds of Formula (I), suitably R^7 is selected from: hydrogen and fluoro;

or one of R^5 and R^6 is taken together with R^7 , and optionally 1 additional heteroatom, to form:

10

pyrrolidinyl, or

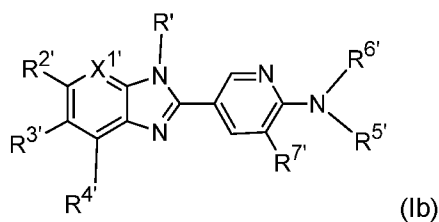
morpholinyl,

each of which are optionally substituted from 1 to 4 times by

C1-3alkyl.

15

This invention relates to novel compounds of Formula (Ib):



where:

20

R' is C1-6alkyl, substituted with from 1 to 3 substituents independently selected from:

fluoro,

oxo,

aryl substituted by heteroaryl,

25

heterocyclyl,

heterocyclyl substituted with from 1 to 4 substituents independently selected from:

fluoro,

chloro,

30

bromo,

oxo,

-OH,

- heteroaryl,
C1-6alkyl, and
C1-6alkyl substituted with from 1 to 5 substituents
independently selected from: fluoro, chloro,
5 bromo, iodo, oxo, -CN, -OH and -NH₂,
heteroaryl,
heteroaryl substituted with from 1 to 4 substituents independently
selected from:
10 fluoro,
chloro,
bromo,
-OH,
heteroaryl,
C1-6alkyl, and
15 C1-6alkyl substituted with from 1 to 5 substituents
independently selected from: fluoro, chloro,
bromo, iodo, oxo, -CN, -OH and -NH₂,
C1-6alkoxy,
C1-6alkoxy substituted with from 1 to 9 substituents independently
20 selected from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and
-N(CH₃)₂,
-Ocycloalkyl, and
-Ocycloalkyl substituted with from 1 to 4 substituents independently
selected from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and
25 -N(CH₃)₂;
X^{1'} is selected from: CR^{1'} and N,
where,
R^{1'} is selected from:
30 hydrogen,
fluoro,
chloro,
bromo,
iodo,
35 -OH,

- NH₂,
 -NHCH₃,
 -N(CH₃)₂,
 -CN,
 5 C1-4alkoxy,
 C1-4alkoxy substituted with from 1 to 7 substituents independently selected
 from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and -N(CH₃)₂,
 C1-6alkyl,
 C1-6alkyl substituted with from 1 to 7 substituents independently selected
 10 from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH, -OC1-5alkyl,
 heterocyclyl, -COOH, -S(O)₂H, -S(O)₂R^x where R^x is selected from
 C1-3alkyl and C1-3alkyl substituted from one to 3 times by fluoro,
 heterocyclyl, and -NR^aR^b,
 where R^a and R^b are independently selected form:
 15 hydrogen,
 C1-5alkoxy,
 C1-5alkoxy substituted with from 1 to 4 substituents
 independently selected from: fluoro, oxo, -OH,
 -OC1-5alkyl, cycloalkyl, cycloalkyl substituted
 20 by -OH, -COOH, -NH₂, -S(O)₂H, and
 -S(O)₂CH₃,
 C1-5alkyl,
 C1-5alkyl substituted with from 1 to 4 substituents
 independently selected from: fluoro, oxo, -OH,
 25 -OC1-5alkyl, cycloalkyl, cycloalkyl substituted
 by -OH, -COOH, -NH₂, -S(O)₂H, and
 -S(O)₂R^x where R^x is selected from C1-3alkyl
 and C1-3alkyl substituted from one to 3 times

by fluoro,
 cycloalkyl, and
 cycloalkyl substituted with from 1 to 4 substituents
 independently selected from: fluoro, oxo, -OH,
 5 -O₁-5alkyl, -COOH, and -NH₂,
 heteroaryl, and
 heteroaryl substituted with from 1 to 4 substituents independently selected
 from:
 fluoro,
 10 chloro,
 C₁-6alkyl, and
 C₁-6alkyl substituted with from 1 to 5 substituents independently
 selected from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH and
 -NH₂;
 15
 R^{2'}, R^{3'}, and R^{4'} are independently selected from:
 hydrogen,
 fluoro,
 chloro,
 20 bromo,
 iodo,
 -OH
 boronic acid,
 1,3,6,2-dioxazaborocane-4,8-dione,
 25 -CN,
 -NR^cR^d,
 where R^c and R^d are independently selected from:
 hydrogen,
 C₁-5alkyl,
 30 C₁-5alkyl substituted with from 1 to 4 substituents
 independently selected from: fluoro, oxo, -OH,
 -OC₁-5alkyl, cycloalkyl, -COOH, -NH₂,
 -N(H)C₁-4alkyl, -N(C₁-4alkyl)₂, -N(H)C₁-4alkyl where

- alkyl is substituted from one to 3 times by fluoro,
 $N(C_{1-4}alkyl)_2$ where each alkyl is substituted from
 one to 3 times by fluoro, $-S(O)_2H$, and $-S(O)_2R^X$
 where R^X is selected from $C_{1-3}alkyl$ and $C_{1-3}alkyl$
 5 substituted from one to 3 times by fluoro,
 $-S(O)_2H$,
 $-S(O)_2R^{X'}$ where $R^{X'}$ is selected from $C_{1-3}alkyl$ and $C_{1-3}alkyl$
 substituted from one to 3 times by fluoro,
 aryl,
 10 aryl, substituted with from 1 to 4 substituents
 independently selected from: fluoro, oxo, $-OH$,
 $-O_{1-5}alkyl$, $-COOH$, and $-NH_2$,
 heteroaryl,
 heteroaryl, substituted with from 1 to 4 substituents
 15 independently selected from: fluoro, oxo, $-OH$,
 $-O_{1-5}alkyl$, $-COOH$, and $-NH_2$,
 heterocyclyl,
 heterocyclyl, substituted with from 1 to 4 substituents
 independently selected from: fluoro, oxo, $-OH$,
 20 $-O_{1-5}alkyl$, $-COOH$, and $-NH_2$,
 cycloalkyl, and
 cycloalkyl substituted with from 1 to 4 substituents
 independently selected from: fluoro, oxo, $-OH$,
 $-O_{1-5}alkyl$, $-COOH$, and $-NH_2$,
 25 heterocyclyl,
 $C_{1-4}alkoxy$,
 $C_{1-4}alkoxy$ substituted with from 1 to 7 substituents independently selected
 from: fluoro, chloro, oxo, $-OH$, $-NH_2$, $-NHCH_3$, and $-N(CH_3)_2$,
 $C_{1-6}alkyl$,
 30 $C_{1-6}alkyl$ substituted with from 1 to 7 substituents independently selected
 from: fluoro, chloro, bromo, iodo, oxo, $-CN$, $-OH$, $-OC_{1-5}alkyl$,

heterocyclyl, $-\text{COOH}$, $-\text{S(O)}_2\text{H}$, $-\text{S(O)}_2\text{R}^{\text{X}}$ where R^{X} is selected from
 C1-3alkyl and C1-3alkyl substituted from one to 3 times by fluoro,
 and $-\text{NR}^{\text{a}}\text{R}^{\text{b}}$,

where R^{a} and R^{b} are independently selected form:

5

hydrogen,

C1-5alkyl,

C1-5alkyl substituted with from 1 to 4 substituents

independently selected from: fluoro, oxo, $-\text{OH}$,

$-\text{OC1-5alkyl}$, cycloalkyl, $-\text{COOH}$, $-\text{NH}_2$,

10

$-\text{S(O)}_2\text{H}$, and $-\text{S(O)}_2\text{R}^{\text{X}}$ where R^{X} is selected

from C1-3alkyl and C1-3alkyl substituted from
 one to 3 times by fluoro,

aryl,

aryl, substituted with from 1 to 4 substituents

15

independently selected from: fluoro, oxo, $-\text{OH}$,

$-\text{O1-5alkyl}$, $-\text{COOH}$, and $-\text{NH}_2$,

heteroalkyl,

heteroalkyl, substituted with from 1 to 4 substituents

independently selected from: fluoro, oxo, $-\text{OH}$,

20

$-\text{O1-5alkyl}$, $-\text{COOH}$, and $-\text{NH}_2$,

heterocycle,

heteroalkyl, substituted with from 1 to 4 substituents

independently selected from: fluoro, oxo, $-\text{OH}$,

$-\text{O1-5alkyl}$, $-\text{COOH}$, and $-\text{NH}_2$,

25

cycloalkyl, and

cycloalkyl substituted with from 1 to 4 substituents

independently selected from: fluoro, oxo, $-\text{OH}$,

$-\text{O1-5alkyl}$, $-\text{COOH}$, and $-\text{NH}_2$,

aryl,

30

aryl substituted with from 1 to 4 substituents independently selected

- from:
fluoro,
chloro,
C1-6alkyl, and
- 5 C1-6alkyl substituted with from 1 to 5 substituents independently
selected from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH and
-NH₂,
cycloalkyl,
cycloalkyl substituted with from 1 to 4 substituents independently selected
10 from:
fluoro,
chloro,
C1-6alkyl, and
C1-6alkyl substituted with from 1 to 5 substituents independently
15 selected from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH and
-NH₂,
heterocycle,
heterocycle substituted with from 1 to 4 substituents independently selected
20 from:
fluoro,
chloro,
C1-6alkyl, and
C1-6alkyl substituted with from 1 to 5 substituents independently
25 selected from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH and
-NH₂,
heteroaryl, and
heteroaryl substituted with from 1 to 4 substituents independently selected
30 from:
fluoro,
chloro,
C1-6alkyl, and

C1-6alkyl substituted with from 1 to 5 substituents independently

selected from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH and
-NH₂,

or 2 adjacent members of R^{1'}, R^{2'}, R^{3'}, and R^{4'} are taken together to form a

5 non-aromatic ring containing 3 to 6 member atoms independently
selected from: carbon, nitrogen, sulphur, oxygen and boron, to form
an oxaborolyl, heterocyclyl, cycloalkyl, or heteroaryl, in which each
of said oxaborolyl, heterocyclyl, cycloalkyl, and heteroaryl is
optionally substituted with from 1 to 3 substituents independently

10 selected from: fluoro, chloro, -OH, oxo, C1-6alkyl, and -NH₂;

R^{5'} and R^{6'} are independently selected from:

C1-4alkyl,

C1-4alkyl substituted with from 1 to 6 substituents

15 independently selected from: fluoro, oxo, -NH₂, C1-4alkoxy, and
-OH,

cycloalkyl,

cycloalkyl substituted with from 1 to 5 substituents independently

selected from:

20 fluoro,
chloro,
-OH, and
C1-6alkyl,

R^{5'} and R^{6'} are taken together with the nitrogen to which they are

25 attached, and optionally from 1 to 3 additional heteroatoms, to form
a heterocyclyl, which is optionally substituted with from 1 to 5
substituents independently selected from:

fluoro,
chloro,

30 C1-6alkyl,

C1-6alkyl substituted with from 1 to 9 substituents

- independently selected from: fluoro, chloro,
C1-4alkoxy, oxo, -OH, -NH₂, -N(H)C1-4alkyl,
-N(C1-4alkyl)₂, and -CN,
C1-4alkoxy,
- 5 C1-4alkoxy substituted with from 1 to 4 substituents
independently selected from: fluoro, oxo, -OH,
-COOH, -NH₂, and -CN,
oxo,
-NH₂,
- 10 -N(H)C1-4alkyl, and
-N(C1-4alkyl)₂, or
one of R^{5'} and R^{6'} is taken together with R^{7'}, and optionally from 1 to 3
additional heteroatoms, to form a heterocyclyl, which is optionally
substituted with from 1 to 5 substituents independently selected from:
- 15 fluoro, chloro, -OH, oxo, C1-4alkyl, C1-4alkoxy, and -NH₂; and
- R^{7'} is selected from: hydrogen and fluoro,
or one of R^{5'} and R^{6'} is taken together with R^{7'}, and optionally from 1 to 3
additional heteroatoms, to form a heterocyclyl, which is optionally
substituted with from 1 to 5 substituents independently selected from:
- 20 fluoro, chloro, -OH, oxo, C1-4alkyl, C1-4alkoxy, and -NH₂;
- or a pharmaceutically acceptable salt thereof.
- 25 For compounds of Formula (Ib), suitably X^{1'} is N. For compounds of Formula (1b),
suitably X^{1'} is CR^{7'}.
- For compounds of Formula (Ib), suitably R¹ is C1-2alkyl substituted by:
phenyl substituted by pyrimidinyl,
30 pyrazolyl,

- pyrazolyl substituted by C1-3alkyl,
 pyrazinyl,
 pyrazinyl substituted by C1-3alkyl,
 piperazinyl,
 5 piperazinyl substituted by oxo,
 piperazinyl substituted by C1-3alkyl,
 oxazolyl,
 oxazolyl substituted by C1-3alkyl,
 imidazolyl,
 10 imidazolyl substituted by C1-3alkyl,
 morpholinyl,
 morpholinyl substituted 1 or 2 times by C1-3alkyl,
 morpholinyl substituted by oxo,
 dioxanyl,
 15 dioxanyl substituted by C1-3alkyl,
 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine;
 triazolyl,
 triazolyl substituted by C1-3alkyl,
 thiazolyl,
 20 thiazolyl substituted by C1-3alkyl,
 -Ocyclopentyl,
 C1-6alkoxy,
 C1-6alkoxy substituted from 1 to 6 times by fluoro,
 C1-6alkoxy substituted by hydroxy,
 25 tetrahydrofuran,
 pyridyl,
 pyridyl substituted by bromo, or
 pyridyl substituted by pyrimidinyl.
- 30 For compounds of Formula (Ib), suitably $R^{2'}$, $R^{3'}$, and $R^{4'}$ are independently
 selected from:
 hydrogen,
 fluoro,
 chloro,
 35 bromo,
 -OH,
 boronic acid,
 1,3,6,2-dioxazaborocane-4,8-dione,
 -CN,
 40 -C(O)NHCH₃,

-C(O)NHCH₂CH₃,
-C(O)NHCH₂CF₂H,
-C(O)NHCH₂CH₂OH,
-C(O)NHCH₂CH₂SO₂CH₃,
5 -C(O)NHOCH₃,
-C(O)NH₂,
-C(O)OCH₃,
-C(O)NHCH₂cyclopropyl,
-C(O)NHcyclobutyl, optionally substituted by hydroxy,
10 -CH₂morpholinyl,
-CH₂OH,
-CH₂NHCH₂CF₃,
-CH₂NHCH₂CH₂SO₂CH₃,
-CH₂SO₂CH₃,
15 -CH(OH)CF₃,
-CH₃,
-CF₃,
-OCH₃,
methoxy-d₃,
20 -NHC(O)CH₃,
-NH₂,
-NHSO₂CH₃,
morpholinyl
pyrazolyl,
25 oxazolyl, and
oxazolyl substituted once or twice by methyl,
or R^{3'} and R^{4'} are taken together with the carbon atoms to which they
are attached to form oxaborolyl, optionally substituted by hydroxy.

30 For compounds of Formula (Ib), suitably R^{5'} and R^{6'} are independently selected from:

C1-3alkyl,
C1-3alkyl substituted from 1 to 3 times by fluoro, and
cyclopropyl,
R^{5b'} and R^{6b'} are taken together with the nitrogen to which they are
attached to form:

azetidinyl,

pyrrolidinyl,

each of which is optionally substituted one or two times by:

C1-3alkyl or C1-3alkyl substituted from 1 to 3 times by fluoro,

5

or

one of R^{5b'} and R^{6b'} is taken together with R^{7b'}, and optionally 1

additional heteroatom, to form:

pyrrolidinyl, or

morpholinyl,

10

each of which are optionally substituted from 1 to 4 times by

C1-3alkyl.

For compounds of Formula (Ib), suitably R^{7'} is selected from: hydrogen and fluoro;

15

or one of R^{5'} and R^{6'} is taken together with R^{7'}, and optionally 1

additional heteroatom, to form:

pyrrolidinyl, or

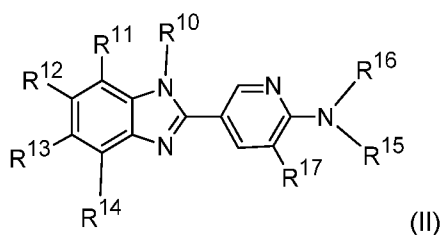
morpholinyl,

each of which are optionally substituted from 1 to 4 times by

20

C1-3alkyl.

Included in the compounds of the invention and used in the methods of the invention are compounds of Formula (II):



25

where:

R¹⁰ is C1-4alkyl, substituted with from 1 to 3 substituents independently selected from:

30

oxo,

- phenyl substituted by pyrimidinyl,
heterocyclyl,
heterocyclyl substituted with from 1 to 4 substituents independently
selected from:
- 5 fluoro,
 chloro,
 bromo,
 heteroaryl,
 C1-6alkyl, and
- 10 C1-6alkyl substituted with from 1 to 5 substituents
 independently selected from: fluoro, chloro,
 bromo, iodo, oxo, -CN, -OH and -NH₂,
heteroaryl,
heteroaryl substituted with from 1 to 4 substituents independently
selected from:
- 15 fluoro,
 chloro,
 bromo,
 heteroaryl,
 C1-6alkyl, and
- 20 C1-6alkyl substituted with from 1 to 5 substituents
 independently selected from: fluoro, chloro,
 bromo, iodo, oxo, -CN, -OH and -NH₂,
C1-6alkoxy,
C1-6alkoxy substituted with from 1 to 9 substituents independently
selected from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and
-N(CH₃)₂,
-Ocycloalkyl, and
-Ocycloalkyl substituted with from 1 to 4 substituents independently
selected from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and
30 -N(CH₃)₂;

R¹¹ is selected from:
hydrogen,

- 5 fluoro,
chloro,
bromo,
iodo,
-OH,
-CN,
C1-4alkoxy,
C1-4alkoxy substituted with from 1 to 7 substituents independently selected
from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and -N(CH₃)₂,
- 10 C1-6alkyl,
C1-6alkyl substituted with from 1 to 7 substituents independently selected
from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH, -OC1-5alkyl,
heterocyclyl, -COOH, -S(O)₂H, -S(O)₂R^{x1} where R^{x1} is selected
from C1-3alkyl and C1-3alkyl substituted from one to 3 times by
15 fluoro, and -NR^{a1}R^{b1},
where R^{a1} and R^{b1} are independently selected form:
hydrogen,
C1-5alkoxy,
C1-5alkyl,
- 20 C1-5alkyl substituted with from 1 to 4 substituents
independently selected from: fluoro, oxo, -OH,
-OC1-5alkyl, cycloalkyl, cycloalkyl substituted
by -OH, , -COOH, -NH₂, -S(O)₂H, and
-S(O)₂CH₃;
- 25 cycloalkyl, and
cycloalkyl substituted with from 1 to 4 substituents
independently selected from: fluoro, oxo, -OH,
-O1-5alkyl, -COOH, and -NH₂;
- 30 heteroaryl, and
heteroaryl substituted with from 1 to 4 substituents independently selected
from:

fluoro,
chloro,
C1-6alkyl, and

C1-6alkyl substituted with from 1 to 5 substituents independently

5 selected from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH and
-NH₂,

R¹², R¹³, and R¹⁴ are independently selected from:

10 hydrogen,
fluoro,
chloro,
bromo,
iodo,
-OH,
15 boronic acid,
1,3,6,2-dioxazaborocane-4,8-dione,
-CN,
-NR^{c1}R^{d1},

where R^{c1} and R^{d1} are independently selected from:

20 hydrogen,
C1-5alkyl,

C1-5alkyl substituted with from 1 to 4 substituents

independently selected from: fluoro, oxo, -OH,

-OC1-5alkyl, cycloalkyl, -COOH, -NH₂, and

25 -S(O)₂H,

heterocyclyl,

C1-4alkoxy,

C1-4alkoxy substituted with from 1 to 7 substituents independently selected
from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and -N(CH₃)₂,

30 C1-6alkyl,

C1-6alkyl substituted with from 1 to 7 substituents independently selected

from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH, -OC1-5alkyl,

heterocyclyl, -COOH, -S(O)₂H, -S(O)₂R^{x1} where R^{x1} is selected

from C1-3alkyl and C1-3alkyl substituted from one to 3 times by
fluoro, and $-NR^{a1}R^{b1}$,

where R^{a1} and R^{b1} are independently selected from:

hydrogen,

5 C1-5alkoxy,

C1-5alkyl,

C1-5alkyl substituted with from 1 to 4 substituents

independently selected from: fluoro, oxo, -OH,

-OC1-5alkyl, cycloalkyl, -COOH, -NH₂,

10 -S(O)₂H, and -S(O)₂R^{X1} where R^{X1} is

selected from C1-3alkyl and C1-3alkyl

substituted from one to 3 times by fluoro;

cycloalkyl, and

cycloalkyl substituted with from 1 to 4 substituents

15 independently selected from: fluoro, oxo, -OH,

-O1-5alkyl, -COOH, and -NH₂;

heteroaryl, and

heteroaryl substituted with from 1 to 3 substituents independently selected
from:

20 fluoro,

chloro,

C1-6alkyl, and

C1-6alkyl substituted with from 1 to 5 substituents independently

selected from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH and

25 -NH₂,

or 2 adjacent members of R¹², R¹³, and R¹⁴ are taken together to form

a non-aromatic ring containing 3 to 6 member atoms independently
selected from: carbon, nitrogen, sulphur, oxygen and boron, to form

an oxaborolyl, heterocyclyl, cycloalkyl, or heteroaryl, in which each

30 of said oxaborolyl, heterocyclyl, cycloalkyl, and heteroaryl is

optionally substituted with from 1 to 3 substituents independently
selected from: fluoro, chloro, -OH, oxo, C1-6alkyl, and -NH₂;

R¹⁵ and R¹⁶ are independently selected from:

- 5 C1-4alkyl,
C1-4alkyl substituted with from 1 to 6 substituents
independently selected from: fluoro, oxo, -NH₂, C1-4alkoxy, and
-OH,
cycloalkyl, and
10 cycloalkyl substituted with from 1 to 5 substituents independently
selected from:
fluoro,
chloro,
-OH, and
15 C1-6alkyl,
or R¹⁵ and R¹⁶ are taken together with the nitrogen to which they are
attached, and optionally from 1 to 3 additional heteroatoms, to form
a heterocyclyl, which is optionally substituted with from 1 to 5
substituents independently selected from:
20 fluoro,
chloro,
C1-6alkyl,
C1-6alkyl substituted with from 1 to 9 substituents
independently selected from: fluoro, chloro,
25 C1-4alkoxy, oxo, -OH, -NH₂, -N(H)C1-4alkyl,
-N(C1-4alkyl)₂, and -CN,
C1-4alkoxy,
C1-4alkoxy substituted with from 1 to 4 substituents
independently selected from: fluoro, oxo, -OH,
30 -COOH, -NH₂, and -CN,

oxo,
-NH₂,
-N(H)C₁₋₄alkyl, and
-N(C₁₋₄alkyl)₂; and

5

R¹⁷ is selected from: hydrogen and fluoro,
or one of R¹⁵ and R¹⁶ is taken together with R¹⁷, and optionally from 1 to 3
additional heteroatoms, to form a heterocyclyl, which is
optionally substituted with from 1 to 3 substituents independently
10 selected from: fluoro, chloro, -OH, oxo, C₁₋₄alkyl, C₁₋₄alkoxy, and
-NH₂;

or a pharmaceutically acceptable salt thereof.

15 For compounds of Formula (II), suitably R¹⁰ is C₁₋₂alkyl substituted by:
pyrazolyl,
pyrazolyl substituted by C₁₋₃alkyl,
oxazolyl,
oxazolyl substituted by C₁₋₃alkyl,
20 imidazolyl,
imidazolyl substituted by C₁₋₃alkyl,
triazolyl,
triazolyl substituted by C₁₋₃alkyl,
thiazolyl,
25 thiazolyl substituted by C₁₋₃alkyl,
-Ocyclopentyl,
C₁₋₆alkoxy,
C₁₋₆alkoxy substituted with from 1 to 6 times by fluoro,
tetrahydrofuran,
30 pyridyl,
pyridyl substituted by bromo, or
pyridyl substituted by pyrimidinyl.

For compounds of Formula (II), suitably R¹¹, R¹², R¹³, and R¹⁴ are independently selected
35 from:
hydrogen,

- 5 fluoro,
chloro,
bromo,
-OH,
boronic acid,
1,3,6,2-dioxazaborocane-4,8-dione,
-CN,
-C(O)NHCH₃,
-C(O)NHCH₂CH₂OH,
10 -C(O)NHCH₂CH₂SO₂CH₃,
-C(O)NHOCH₃,
-C(O)NH₂,
-C(O)OCH₃,
-C(O)NHCH₂cyclopropyl,
15 -C(O)NHcyclobutyl, optionally substituted by hydroxy,
-CH₂morpholinyl,
-CH₂OH,
-CH₂NHCH₂CF₃,
-CH₂NHCH₂CH₂SO₂CH₃,
20 -CH₂SO₂CH₃,
-CH(OH)CF₃,
-CH₃,
-CF₃,
-OCH₃,
25 pyrazolyl,
oxazolyl, and
oxazolyl substituted once or twice by methyl,
- 30 or R¹³ and R¹⁴ are taken together with the carbon atoms to which they are
attached to form oxaborolyl, optionally substituted by hydroxyl.

For compounds of Formula (II), suitably R¹⁵ and R¹⁶ are independently selected from:

- C1-3alkyl,
C1-3alkyl substituted from 1 to 3 times by fluoro, and
35 cyclopropyl,

or R¹⁵ and R¹⁶ are taken together with the nitrogen to which they are
attached to form:

pyrrolidinyl,

which is optionally substituted one or two times by:

C1-3alkyl.

5 For compounds of Formula (II), suitably R^{17} is selected from: hydrogen and fluoro;

or one of R^{15} and R^{16} is taken together with R^{17} , and optionally 1 additional heteroatom, to form:

pyrrolidinyl, or

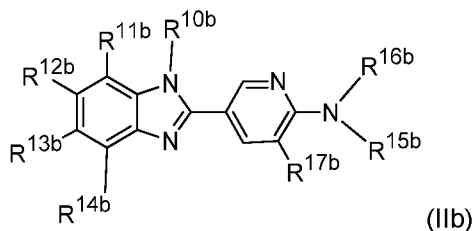
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morpholinyl,

each of which are optionally substituted from 1 to 4 times by

C1-3alkyl.

15 Included in the compounds of the invention and used in the methods of the invention are compounds of Formula (IIb):



where:

20

R^{10b} is C1-4alkyl, substituted with from 1 to 3 substituents independently selected from:

oxo,

phenyl substituted by pyrimidinyl,

25

heterocyclyl,

heterocyclyl substituted with from 1 to 4 substituents independently selected from:

fluoro,

chloro,

30

bromo,

oxo,

heteroaryl,

- C1-6alkyl, and
- C1-6alkyl substituted with from 1 to 5 substituents
independently selected from: fluoro, chloro,
bromo, iodo, oxo, -CN, -OH and -NH₂,
- 5 heteroaryl,
heteroaryl substituted with from 1 to 4 substituents independently
selected from:
fluoro,
chloro,
10 bromo,
heteroaryl,
C1-6alkyl, and
C1-6alkyl substituted with from 1 to 5 substituents
independently selected from: fluoro, chloro,
15 bromo, iodo, oxo, -CN, -OH and -NH₂,
- C1-6alkoxy,
C1-6alkoxy substituted with from 1 to 9 substituents independently
selected from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and
-N(CH₃)₂,
20 -Ocycloalkyl, and
-Ocycloalkyl substituted with from 1 to 4 substituents independently
selected from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and
-N(CH₃)₂;
- 25 R^{11b} is selected from:
hydrogen,
fluoro,
chloro,
bromo,
30 iodo,
-OH,
-NH₂,
-CN,
C1-4alkoxy,
35 C1-4alkoxy substituted with from 1 to 7 substituents independently selected

from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and -N(CH₃)₂,
C₁-6alkyl,

C₁-6alkyl substituted with from 1 to 7 substituents independently selected

5 from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH, -OC₁-5alkyl,
heterocyclyl, -COOH, -S(O)₂H, -S(O)₂R^{X1'} where R^{X1'} is selected
from C₁-3alkyl and C₁-3alkyl substituted from one to 3 times by
fluoro, and -NR^{a1'}R^{b1'},

where R^{a1'} and R^{b1'} are independently selected from:

10 hydrogen,

C₁-5alkoxy,

C₁-5alkyl,

C₁-5alkyl substituted with from 1 to 4 substituents

15 independently selected from: fluoro, oxo, -OH,
-OC₁-5alkyl, cycloalkyl, cycloalkyl substituted
by -OH, -COOH, -NH₂, -S(O)₂H, and
-S(O)₂CH₃,

cycloalkyl, and

20 cycloalkyl substituted with from 1 to 4 substituents
independently selected from: fluoro, oxo, -OH,
-O₁-5alkyl, -COOH, and -NH₂,

heteroaryl, and

heteroaryl substituted with from 1 to 4 substituents independently selected

from:

25 fluoro,

chloro,

C₁-6alkyl, and

C₁-6alkyl substituted with from 1 to 5 substituents independently

selected from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH and
-NH₂;

R^{12b} , R^{13b} , and R^{14b} are independently selected from:

5 hydrogen,
fluoro,
chloro,
bromo,
iodo,
-OH,
boronic acid,
10 1,3,6,2-dioxazaborocane-4,8-dione,
-CN,
-NR^{c1'}R^{d1'},

where R^{c1'} and R^{d1'} are independently selected from:

hydrogen,
15 C1-5alkyl,
C1-5alkyl substituted with from 1 to 4 substituents
independently selected from: fluoro, oxo, -OH,
-OC1-5alkyl, cycloalkyl, -COOH, -NH₂,
-N(H)C1-4alkyl, -N(H)C1-4alkyl where alkyl is
20 substituted from one to 3 times by fluoro, and
-S(O)₂H,
-S(O)₂H,
-S(O)₂C1-3alkyl,

heterocyclyl,
25 C1-4alkoxy,
C1-4alkoxy substituted with from 1 to 7 substituents independently selected
from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and -N(CH₃)₂,
C1-6alkyl,

C1-6alkyl substituted with from 1 to 7 substituents independently selected
30 from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH, -OC1-5alkyl,
heterocyclyl, -COOH, -S(O)₂H, -S(O)₂R^{x1'} where R^{x1'} is selected
from C1-3alkyl and C1-3alkyl substituted from one to 3 times by

fluoro, and $-NR^{a1'}R^{b1'}$,

where $R^{a1'}$ and $R^{b1'}$ are independently selected from:

hydrogen,

C1-5alkoxy,

5

C1-5alkyl,

C1-5alkyl substituted with from 1 to 4 substituents

independently selected from: fluoro, oxo, -OH,

-OC1-5alkyl, cycloalkyl, -COOH, -NH₂,

-S(O)₂H, and -S(O)₂R^{x1'} where R^{x1'} is

10

selected from C1-3alkyl and C1-3alkyl

substituted from one to 3 times by fluoro;

cycloalkyl, and

cycloalkyl substituted with from 1 to 4 substituents

independently selected from: fluoro, oxo, -OH,

15

-O1-5alkyl, -COOH, and -NH₂,

heteroaryl, and

heteroaryl substituted with from 1 to 3 substituents independently selected from:

fluoro,

20

chloro,

C1-6alkyl, and

C1-6alkyl substituted with from 1 to 5 substituents independently

selected from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH and

-NH₂,

25

or 2 adjacent members of R^{12b}, R^{13b}, and R^{14b} are taken together to form

a non-aromatic ring containing 3 to 6 member atoms independently

selected from: carbon, nitrogen, sulphur, oxygen and boron, to form

an oxaborolyl, heterocyclyl, cycloalkyl, or heteroaryl, in which each

of said oxaborolyl, heterocyclyl, cycloalkyl, and heteroaryl is

30

optionally substituted with from 1 to 3 substituents independently

selected from: fluoro, chloro, -OH, oxo, C1-6alkyl, and -NH₂;

R^{15b} and R^{16b} are independently selected from:

- C1-4alkyl,
- 5 C1-4alkyl substituted with from 1 to 6 substituents
- independently selected from: fluoro, oxo, -NH₂, C1-4alkoxy, and
- OH,
- cycloalkyl, and
- cycloalkyl substituted with from 1 to 5 substituents independently
- 10 selected from:
- fluoro,
- chloro,
- OH, and
- C1-6alkyl,
- 15 R^{15b} and R^{16b} are taken together with the nitrogen to which they are
- attached, and optionally from 1 to 3 additional heteroatoms, to form
- a heterocyclyl, which is optionally substituted with from 1 to 5
- substituents independently selected from:
- fluoro,
- 20 chloro,
- C1-6alkyl,
- C1-6alkyl substituted with from 1 to 9 substituents
- independently selected from: fluoro, chloro,
- C1-4alkoxy, oxo, -OH, -NH₂, -N(H)C1-4alkyl,
- 25 -N(C1-4alkyl)₂, and -CN,
- C1-4alkoxy,
- C1-4alkoxy substituted with from 1 to 4 substituents
- independently selected from: fluoro, oxo, -OH,
- COOH, -NH₂, and -CN,

oxo,
 -NH₂,
 -N(H)C₁₋₄alkyl, and
 -N(C₁₋₄alkyl)₂, or

5 one of R^{15b} and R^{16b} is taken together with R^{17b}, and optionally from 1 to 3 additional heteroatoms, to form a heterocyclyl, which is optionally substituted with from 1 to 3 substituents independently selected from: fluoro, -OH, C₁₋₄alkyl, and C₁₋₄alkoxy; and

10 R^{17b} is selected from: hydrogen and fluoro,
 or one of R^{15b} and R^{16b} is taken together with R^{17b}, and optionally from 1 to 3 additional heteroatoms, to form a heterocyclyl, which is optionally substituted with from 1 to 3 substituents independently selected from: fluoro, -OH, C₁₋₄alkyl, and C₁₋₄alkoxy;

15 or a pharmaceutically acceptable salt thereof.

For compounds of Formula (IIb), suitably R^{10b} is C₁₋₂alkyl substituted by:

20 phenyl substituted by pyrimidinyl,
 pyrazolyl,
 pyrazolyl substituted by C₁₋₃alkyl,
 pyrazinyl,
 pyrazinyl substituted by C₁₋₃alkyl,
 piperazinyl,
 25 piperazinyl substituted by oxo,
 piperazinyl substituted by C₁₋₃alkyl,
 oxazolyl,
 oxazolyl substituted by C₁₋₃alkyl,
 imidazolyl,
 30 imidazolyl substituted by C₁₋₃alkyl,
 morpholinyl,
 morpholinyl substituted 1 or 2 times by C₁₋₃alkyl,
 morpholinyl substituted by oxo,
 dioxanyl,
 35 dioxanyl substituted by C₁₋₃alkyl,

- 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine;
 triazolyl,
 triazolyl substituted by C₁-3alkyl,
 thiazolyl,
 thiazolyl substituted by C₁-3alkyl,
 -Ocyclopentyl,
 C₁-6alkoxy,
 C₁-6alkoxy substituted from 1 to 6 times by fluoro,
 C₁-6alkoxy substituted by hydroxy,
 tetrahydrofuran,
 pyridyl,
 pyridyl substituted by bromo, or
 pyridyl substituted by pyrimidinyl.
- For compounds of Formula (IIb), suitably R^{12b}, R^{13b}, and R^{14b} are independently selected from:
- hydrogen,
 fluoro,
 chloro,
 bromo,
 -OH,
 boronic acid,
 1,3,6,2-dioxazaborocane-4,8-dione,
 -CN,
 -C(O)NHCH₃,
 -C(O)NHCH₂CH₃,
 -C(O)NHCH₂CF₂H,
 -C(O)NHCH₂CH₂OH,
 -C(O)NHCH₂CH₂SO₂CH₃,
 -C(O)NHCH₂CH₂SO₂CH₃,
 -C(O)NHCH₂cyclopropyl,
 -C(O)NHcyclobutyl, optionally substituted by hydroxy,
 -CH₂morpholinyl,
 -CH₂OH,
 -CH₂NHCH₂CF₃,
 -CH₂NHCH₂CH₂SO₂CH₃,
 -CH₂SO₂CH₃,

5 -CH(OH)CF₃,
 -CH₃,
 -CF₃,
 -OCH₃,
 methoxy-d₃,
 -NHC(O)CH₃,
 -NH₂,
 -NHSO₂CH₃,
 10 morpholinyl
 pyrazolyl,
 oxazolyl, and
 oxazolyl substituted once or twice by methyl,
 or R^{13b} and R^{14b} are taken together with the carbon atoms to which they
 15 are attached to form oxaborolyl, optionally substituted by hydroxy.

For compounds of Formula (IIb), suitably R^{15b} and R^{16b} are independently selected from:

C1-3alkyl,
 C1-3alkyl substituted from 1 to 3 times by fluoro, and
 cyclopropyl,
 20 R^{15b} and R^{16b} are taken together with the nitrogen to which they are
 attached to form:
 azetidinyl,
 pyrrolidinyl,
 each of which is optionally substituted one or two times by:
 25 C1-3alkyl or C1-3alkyl substituted from 1 to 3 times by fluoro,
 or
 one of R^{15b} and R^{16b} is taken together with R^{17b}, and optionally 1
 additional heteroatom, to form:
 pyrrolidinyl, or
 30 morpholinyl,
 each of which are optionally substituted from 1 to 4 times by
 C1-3alkyl.

For compounds of Formula (IIb), suitably R^{17b} is selected from: hydrogen and fluoro;

or one of R^{15b} and R^{16b} is taken together with R^{17b} , and optionally 1 additional heteroatom, to form:

5

pyrrolidinyl, or

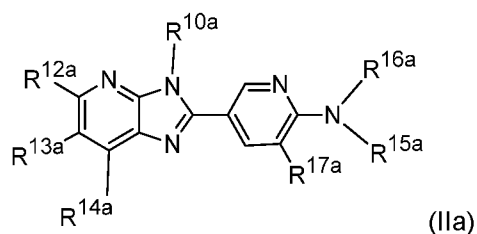
morpholinyl,

each of which are optionally substituted from 1 to 4 times by

C1-3alkyl.

10

Included in the compounds of the invention and used in the methods of the invention are compounds of Formula (IIa):



where:

15

R^{10a} is C1-4alkyl, substituted with from 1 to 3 substituents independently selected from:

oxo,

phenyl substituted by pyrimidinyl,

20

heterocyclyl,

heterocyclyl substituted with from 1 to 4 substituents independently selected from:

fluoro,

chloro,

25

bromo,

heteroaryl,

C1-6alkyl, and

C1-6alkyl substituted with from 1 to 5 substituents

independently selected from: fluoro, chloro,

30

bromo, iodo, oxo, -CN, -OH and -NH₂,

heteroaryl,

heteroaryl substituted with from 1 to 4 substituents independently
selected from:

fluoro,
chloro,
bromo,
heteroaryl,
C1-6alkyl, and

C1-6alkyl substituted with from 1 to 5 substituents

independently selected from: fluoro, chloro,
bromo, iodo, oxo, -CN, -OH and -NH₂,

C1-6alkoxy,

C1-6alkoxy substituted with from 1 to 9 substituents independently
selected from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and
-N(CH₃)₂,

-Ocycloalkyl, and

-Ocycloalkyl substituted with from 1 to 4 substituents independently
selected from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and
-N(CH₃)₂;

R^{12a}, R^{13a}, and R^{14a} are independently selected from:

hydrogen,
fluoro,
chloro,
bromo,
iodo,
-OH,
boronic acid,
1,3,6,2-dioxazaborocane-4,8-dione,
-CN,
-NR^{c1a}R^{d1a},

where R^{c1a} and R^{d1a} are independently selected from:

hydrogen,
C1-5alkyl,

C1-5alkyl substituted with from 1 to 4 substituents

independently selected from: fluoro, oxo, -OH,

- OC₁₋₅alkyl, cycloalkyl, -COOH, -NH₂, and
 -S(O)₂H,
 heterocyclyl,
 C₁₋₄alkoxy,
 5 C₁₋₄alkoxy substituted with from 1 to 7 substituents independently selected
 from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and -N(CH₃)₂,
 C₁₋₆alkyl,
 C₁₋₆alkyl substituted with from 1 to 7 substituents independently selected
 from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH, -OC₁₋₅alkyl,
 10 heterocyclyl, -COOH, -S(O)₂H, -S(O)₂R^{x1a} where R^{x1a} is selected
 from C₁₋₃alkyl and C₁₋₃alkyl substituted from one to 3 times by
 fluoro, and -NR^{a1a}R^{b1a},
 where R^{a1a} and R^{b1a} are independently selected from:
 hydrogen,
 15 C₁₋₅alkoxy,
 C₁₋₅alkyl,
 C₁₋₅alkyl substituted with from 1 to 4 substituents
 independently selected from: fluoro, oxo, -OH,
 -OC₁₋₅alkyl, cycloalkyl, -COOH, -NH₂,
 20 -S(O)₂H, and -S(O)₂R^{x1a} where R^{x1a} is
 selected from C₁₋₃alkyl and C₁₋₃alkyl
 substituted from one to 3 times by fluoro;
 cycloalkyl, and
 cycloalkyl substituted with from 1 to 4 substituents
 25 independently selected from: fluoro, oxo, -OH,
 -O₁₋₅alkyl, -COOH, and -NH₂;
 heteroaryl, and
 heteroaryl substituted with from 1 to 3 substituents independently selected
 from:

- fluoro,
chloro,
C1-6alkyl, and
C1-6alkyl substituted with from 1 to 5 substituents independently
5 selected from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH and
-NH₂,
or 2 adjacent members of R^{12a}, R^{13a}, and R^{14a} are taken together to form
a non-aromatic ring containing 3 to 6 member atoms independently
selected from: carbon, nitrogen, sulphur, oxygen and boron, to form
10 an oxaborolyl, heterocyclyl, cycloalkyl, or heteroaryl, in which each
of said oxaborolyl, heterocyclyl, cycloalkyl, and heteroaryl is
optionally substituted with from 1 to 3 substituents independently
selected from: fluoro, chloro, -OH, oxo, C1-6alkyl, and -NH₂;
- 15 R^{15a} and R^{16a} are independently selected from:
C1-4alkyl,
C1-4alkyl substituted with from 1 to 6 substituents
independently selected from: fluoro, oxo, -NH₂, C1-4alkoxy, and
-OH,
20 cycloalkyl, and
cycloalkyl substituted with from 1 to 5 substituents independently
selected from:
fluoro,
chloro,
25 -OH, and
C1-6alkyl,
or R^{15a} and R^{16a} are taken together with the nitrogen to which they are
attached, and optionally from 1 to 3 additional heteroatoms, to form
a heterocyclyl, which is optionally substituted with from 1 to 5
30 substituents independently selected from:
fluoro,

- chloro,
C1-6alkyl,
C1-6alkyl substituted with from 1 to 9 substituents
independently selected from: fluoro, chloro,
5 C1-4alkoxy, oxo, -OH, -NH₂, -N(H)C1-4alkyl,
-N(C1-4alkyl)₂, and -CN,
C1-4alkoxy,
C1-4alkoxy substituted with from 1 to 4 substituents
independently selected from: fluoro, oxo, -OH,
10 -COOH, -NH₂, and -CN,
oxo,
-NH₂,
-N(H)C1-4alkyl, and
-N(C1-4alkyl)₂; and
15
R^{17a} is selected from: hydrogen and fluoro,
or one of R^{15a} and R^{16a} is taken together with R^{17a}, and optionally from 1 to
3 additional heteroatoms, to form a heterocyclyl, which is
optionally substituted with from 1 to 3 substituents independently
20 selected from: fluoro, chloro, -OH, oxo, C1-4alkyl, C1-4alkoxy, and
-NH₂;
or a pharmaceutically acceptable salt thereof.
25 For compounds of Formula (IIa), suitably R^{10a} is C1-2alkyl substituted by:
pyrazolyl,
pyrazolyl substituted by C1-3alkyl,
oxazolyl,
oxazolyl substituted by C1-3alkyl,
30 imidazolyl,
imidazolyl substituted by C1-3alkyl,

- 5 triazolyl,
 triazolyl substituted by C1-3alkyl,
 thiazolyl,
 thiazolyl substituted by C1-3alkyl,
 -Ocyclopentyl,
 C1-6alkoxy,
 C1-6alkoxy substituted with from 1 to 6 times by fluoro,
 tetrahydrofuran,
 pyridyl,
 10 pyridyl substituted by bromo, or
 pyridyl substituted by pyrimidinyl.

For compounds of Formula (IIa), suitably R^{12a} , R^{13a} , and R^{14a} are independently selected from:

- 15 hydrogen,
 fluoro,
 chloro,
 bromo,
 -OH,
 20 boronic acid,
 1,3,6,2-dioxazaborocane-4,8-dione,
 -CN,
 -C(O)NHCH₃,
 -C(O)NHCH₂CH₂OH,
 25 -C(O)NHCH₂CH₂SO₂CH₃,
 -C(O)NHCH₃,
 -C(O)NH₂,
 -C(O)OCH₃,
 -C(O)NHCH₂cyclopropyl,
 30 -C(O)NHcyclobutyl, optionally substituted by hydroxy,
 -CH₂morpholinyl,
 -CH₂OH,
 -CH₂NHCH₂CF₃,
 -CH₂NHCH₂CH₂SO₂CH₃,
 35 -CH₂SO₂CH₃,
 -CH(OH)CF₃,
 -CH₃,
 -CF₃,
 -OCH₃,

pyrazolyl,
 oxazolyl, and
 oxazolyl substituted once or twice by methyl,

5 or R^{13a} and R^{14a} are taken together with the carbon atoms to which they are attached to form oxaborolyl, optionally substituted by hydroxyl.

For compounds of Formula (IIa), suitably R^{15a} and R^{16a} are independently selected from:
 C1-3alkyl,

10 C1-3alkyl substituted from 1 to 3 times by fluoro, and
 cyclopropyl,

or R^{15a} and R^{16a} are taken together with the nitrogen to which they are attached to form:

15 pyrrolidinyl,
 which is optionally substituted one or two times by:
 C1-3alkyl.

For compounds of Formula (IIa), suitably R^{17a} is selected from: hydrogen and fluoro;

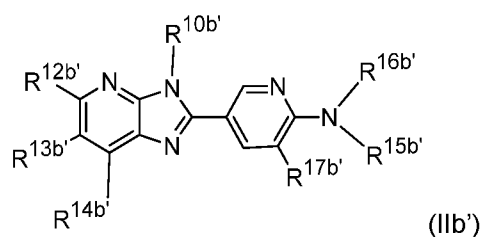
20 or one of R^{15a} and R^{16a} is taken together with R^{17a}, and optionally 1
 additional heteroatom, to form:

pyrrolidinyl, or
 morpholinyl,

25 each of which are optionally substituted from 1 to 4 times by
 C1-3alkyl.

Included in the compounds of the invention and used in the methods of the invention are compounds of Formula (IIb'):

30



where:

R^{10b'} is C₁₋₄alkyl, substituted with from 1 to 3 substituents independently selected from:

5

OXO,

phenyl substituted by pyrimidinyl,

heterocyclyl,

heterocyclyl substituted with from 1 to 4 substituents independently
selected from:

10

fluoro,

chloro,

bromo,

OXO,

heteroaryl,

15

C1-6alkyl, and

C1-6alkyl substituted with from 1 to 5 substituents

independently selected from: fluoro, chloro,

bromo, iodo, oxo, -CN, -OH and -NH₂,

heteroaryl,

20

heteroaryl substituted with from 1 to 4 substituents independently

selected from:

fluoro,

chloro,

bromo,

25

heteroaryl,

C1-6alkyl, and

C1-6alkyl substituted with from 1 to 5 substituents

independently selected from: fluoro, chloro,

bromo, iodo, oxo, -CN, -OH and -NH₂.

30

C1-6alkoxy,

C1-6alkoxy substituted with from 1 to 9 substituents independently

selected from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and

$$-\text{N}(\text{CH}_3)_2,$$

-Ocycloalkyl, and

-Ocycloalkyl substituted with from 1 to 4 substituents independently selected from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and -N(CH₃)₂;

5 R^{12b'}, R^{13b'}, and R^{14b'} are independently selected from:

hydrogen,
fluoro,
chloro,
bromo,
10 iodo,
-OH,
boronic acid,
1,3,6,2-dioxazaborocane-4,8-dione,
-CN,
15 -NR^{c1b}R^{d1b},

where R^{c1b} and R^{d1b} are independently selected from:

hydrogen,

C1-5alkyl,

C1-5alkyl substituted with from 1 to 4 substituents

20 independently selected from: fluoro, oxo, -OH,

-OC1-5alkyl, cycloalkyl, -COOH, -NH₂,

-N(H)C1-4alkyl, -N(H)C1-4alkyl where alkyl is

substituted from one to 3 times by fluoro, and

-S(O)₂H,

25 -S(O)₂H,

-S(O)₂C1-3alkyl,

heterocyclyl,

C1-4alkoxy,

C1-4alkoxy substituted with from 1 to 7 substituents independently selected

30 from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and -N(CH₃)₂,

C1-6alkyl,

C1-6alkyl substituted with from 1 to 7 substituents independently selected

from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH, -OC1-5alkyl,

heterocyclyl, $-\text{COOH}$, $-\text{S(O)}_2\text{H}$, $-\text{S(O)}_2\text{R}^{\text{x1a}}$ where R^{x1a} is selected from C1-3alkyl and C1-3alkyl substituted from one to 3 times by fluoro, and $-\text{NR}^{\text{a1b}}\text{R}^{\text{b1b}}$,

where R^{a1b} and R^{b1b} are independently selected from:

5

hydrogen,

C1-5alkoxy,

C1-5alkyl,

C1-5alkyl substituted with from 1 to 4 substituents

independently selected from: fluoro, oxo, $-\text{OH}$,

10

$-\text{OC1-5alkyl}$, cycloalkyl, $-\text{COOH}$, $-\text{NH}_2$,

$-\text{S(O)}_2\text{H}$, and $-\text{S(O)}_2\text{R}^{\text{x1b}}$ where R^{x1b} is

selected from C1-3alkyl and C1-3alkyl

substituted from one to 3 times by fluoro;

cycloalkyl, and

15

cycloalkyl substituted with from 1 to 4 substituents

independently selected from: fluoro, oxo, $-\text{OH}$,

$-\text{O1-5alkyl}$, $-\text{COOH}$, and $-\text{NH}_2$,

heteroaryl, and

heteroaryl substituted with from 1 to 3 substituents independently selected

20

from:

fluoro,

chloro,

C1-6alkyl, and

C1-6alkyl substituted with from 1 to 5 substituents independently

25

selected from: fluoro, chloro, bromo, iodo, oxo, $-\text{CN}$, $-\text{OH}$ and

$-\text{NH}_2$,

or 2 adjacent members of $\text{R}^{\text{12b'}}$, $\text{R}^{\text{13b'}}$, and $\text{R}^{\text{14b'}}$ are taken together to form

a non-aromatic ring containing 3 to 6 member atoms independently

selected from: carbon, nitrogen, sulphur, oxygen and boron, to form

an oxaborolyl, heterocyclyl, cycloalkyl, or heteroaryl, in which each of said oxaborolyl, heterocyclyl, cycloalkyl, and heteroaryl is optionally substituted with from 1 to 3 substituents independently selected from: fluoro, chloro, -OH, oxo, C1-6alkyl, and -NH₂;

5

R^{15b'} and R^{16b'} are independently selected from:

C1-4alkyl,

C1-4alkyl substituted with from 1 to 6 substituents

independently selected from: fluoro, oxo, -NH₂, C1-4alkoxy, and

10

-OH,

cycloalkyl, and

cycloalkyl substituted with from 1 to 5 substituents independently

selected from:

fluoro,

15

chloro,

-OH, and

C1-6alkyl,

R^{15b'} and R^{16b'} are taken together with the nitrogen to which they are

attached, and optionally from 1 to 3 additional heteroatoms, to form

20

a heterocyclyl, which is optionally substituted with from 1 to 5

substituents independently selected from:

fluoro,

chloro,

C1-6alkyl,

25

C1-6alkyl substituted with from 1 to 9 substituents

independently selected from: fluoro, chloro,

C1-4alkoxy, oxo, -OH, -NH₂, -N(H)C1-4alkyl,

-N(C1-4alkyl)₂, and -CN,

C1-4alkoxy,

30

C1-4alkoxy substituted with from 1 to 4 substituents

- independently selected from: fluoro, oxo, -OH,
-COOH, -NH₂, and -CN,
oxo,
-NH₂,
5 -N(H)C₁₋₄alkyl, and
-N(C₁₋₄alkyl)₂, or
one of R^{15b'} and R^{16b'} is taken together with R^{17b'}, and optionally from 1 to
3 additional heteroatoms, to form a heterocyclyl, which is optionally
substituted with from 1 to 3 substituents independently selected from:
10 fluoro, -OH, C₁₋₄alkyl, and C₁₋₄alkoxy; and
- R^{17b'} is selected from: hydrogen and fluoro,
or one of R^{15b'} and R^{16b'} is taken together with R^{17b'}, and optionally from 1
to 3 additional heteroatoms, to form a heterocyclyl, which is
15 optionally substituted with from 1 to 3 substituents independently
selected from: fluoro, -OH, C₁₋₄alkyl, and C₁₋₄alkoxy;
- or a pharmaceutically acceptable salt thereof.
- 20 For compounds of Formula (IIb'), suitably R^{10b'} is C₁₋₂alkyl substituted by:
phenyl substituted by pyrimidinyl,
pyrazolyl,
pyrazolyl substituted by C₁₋₃alkyl,
pyrazinyl,
25 pyrazinyl substituted by C₁₋₃alkyl,
piperazinyl,
piperazinyl substituted by oxo,
piperazinyl substituted by C₁₋₃alkyl,
oxazolyl,
30 oxazolyl substituted by C₁₋₃alkyl,
imidazolyl,
imidazolyl substituted by C₁₋₃alkyl,
morpholinyl,
morpholinyl substituted 1 or 2 times by C₁₋₃alkyl,

- 5 morpholinyl substituted by oxo,
dioxanyl,
dioxanyl substituted by C1-3alkyl,
4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine;
triazolyl,
triazolyl substituted by C1-3alkyl,
thiazolyl,
thiazolyl substituted by C1-3alkyl,
-Ocyclopentyl,
10 C1-6alkoxy,
C1-6alkoxy substituted from 1 to 6 times by fluoro,
C1-6alkoxy substituted by hydroxy,
tetrahydrofuran,
pyridyl,
15 pyridyl substituted by bromo, or
pyridyl substituted by pyrimidinyl.

For compounds of Formula (IIb'), suitably $R^{12b'}$, $R^{13b'}$, and $R^{14b'}$ are independently selected from:

- 20 hydrogen,
fluoro,
chloro,
bromo,
-OH,
25 boronic acid,
1,3,6,2-dioxazaborocane-4,8-dione,
-CN,
-C(O)NHCH₃,
-C(O)NHCH₂CH₃,
30 -C(O)NHCH₂CF₂H,
-C(O)NHCH₂CH₂OH,
-C(O)NHCH₂CH₂SO₂CH₃,
-C(O)NHCH₃,
-C(O)NH₂,
35 -C(O)OCH₃,
-C(O)NHCH₂cyclopropyl,
-C(O)NHcyclobutyl, optionally substituted by hydroxy,
-CH₂morpholinyl,
-CH₂OH,

- 5 -CH₂NHCH₂CF₃,
 -CH₂NHCH₂CH₂SO₂CH₃,
 -CH₂SO₂CH₃,
 -CH(OH)CF₃,
 -CH₃,
 -CF₃,
 -OCH₃,
 methoxy-d₃,
 -NHC(O)CH₃,
 10 -NH₂,
 -NHSO₂CH₃,
 morpholinyl
 pyrazolyl,
 oxazolyl, and
 15 oxazolyl substituted once or twice by methyl,
 or R^{13b'} and R^{14b'} are taken together with the carbon atoms to which they
 are attached to form oxaborolyl, optionally substituted by hydroxy.

For compounds of Formula (IIb'), suitably R^{15b'} and R^{16b'} are independently selected from:

- 20 C1-3alkyl,
 C1-3alkyl substituted from 1 to 3 times by fluoro, and
 cyclopropyl,
 R^{15b'} and R^{16b'} are taken together with the nitrogen to which they are
 attached to form:
 25 azetidinyl,
 pyrrolidinyl,
 each of which is optionally substituted one or two times by:
 C1-3alkyl or C1-3alkyl substituted from 1 to 3 times by fluoro,
 or
 30 one of R^{15b'} and R^{16b'} is taken together with R^{17b'}, and optionally 1
 additional heteroatom, to form:
 pyrrolidinyl, or
 morpholinyl,

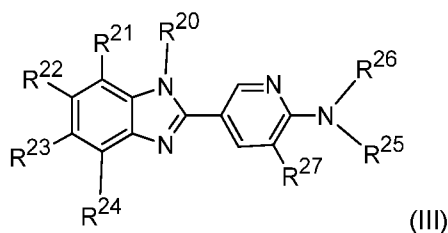
each of which are optionally substituted from 1 to 4 times by
C1-3alkyl.

For compounds of Formula (IIb'), suitably $R^{17b'}$ is selected from: hydrogen and
fluoro;
or one of $R^{15b'}$ and $R^{16b'}$ is taken together with $R^{17b'}$, and optionally 1
additional heteroatom, to form:

pyrrolidinyl, or
morpholinyl,

each of which are optionally substituted from 1 to 4 times by
C1-3alkyl.

Included in the compounds of the invention and used in the methods of the invention
are compounds of Formula (III):



where:

R^{20} is C1-2alkyl substituted by:

phenyl substituted by pyrimidinyl,
pyrazolyl,
pyrazolyl substituted by C1-3alkyl,
oxazolyl,
oxazolyl substituted by C1-3alkyl,
imidazolyl,
imidazolyl substituted by C1-3alkyl,
triazolyl,
triazolyl substituted by C1-3alkyl,
thiazolyl,
thiazolyl substituted by C1-3alkyl,
-Ocyclopentyl,
C1-6alkoxy,

5 C1-6alkoxy substituted with from 1 to 6 times by fluoro,
tetrahydrofuran,
pyridyl,
pyridyl substituted by bromo, or
pyridyl substituted by pyrimidinyl;

R²¹ is selected from:
hydrogen,
fluoro,
10 chloro,
bromo,
-OH,
-CN,
-C(O)NHCH₃,
15 -C(O)NHCH₂CH₂OH,
-C(O)NHCH₂CH₂SO₂CH₃,
-C(O)NHCH₃,
-C(O)NH₂,
-C(O)OCH₃,
20 -C(O)NHCH₂cyclopropyl,
-C(O)NHcyclobutyl, optionally substituted by hydroxy,
-CH₂morpholinyl,
-CH₂OH,
-CH₂NHCH₂CF₃,
25 -CH₂NHCH₂CH₂SO₂CH₃,
-CH₂SO₂CH₃,
-CH(OH)CF₃,
-CH₃,
-CF₃,
30 -OCH₃,
pyrazolyl,
oxazolyl, and
oxazolyl substituted once or twice by methyl,

35 R²², R²³, and R²⁴ are independently selected from:
hydrogen,
fluoro,
chloro,
bromo,
40 -OH,

- boronic acid,
 1,3,6,2-dioxazaborocane-4,8-dione,
 -CN,
 -C(O)NHCH₃,
 5 -C(O)NHCH₂CH₂OH,
 -C(O)NHCH₂CH₂SO₂CH₃,
 -C(O)NHOCH₃,
 -C(O)NH₂,
 -C(O)OCH₃,
 10 -C(O)NHCH₂cyclopropyl,
 -C(O)NHcyclobutyl, optionally substituted by hydroxy,
 -CH₂morpholinyl,
 -CH₂OH,
 -CH₂NHCH₂CF₃,
 15 -CH₂NHCH₂CH₂SO₂CH₃,
 -CH₂SO₂CH₃,
 -CH(OH)CF₃,
 -CH₃,
 -CF₃,
 20 -OCH₃,
 -NHC(O)CH₃,
 -NH₂,
 -NHSO₂CH₃,
 morpholinyl
 25 pyrazolyl,
 oxazolyl, and
 oxazolyl substituted once or twice by methyl,
 or R²³ and R²⁴ are taken together with the carbon atoms to which they are
 30 attached to form oxaborolyl, optionally substituted by hydroxy;

R²⁵ and R²⁶ are independently selected from:

- C1-3alkyl,
 C1-3alkyl substituted from 1 to 3 times by fluoro, and
 35 cyclopropyl,

or R²⁵ and R²⁶ are taken together with the nitrogen to which they are

attached to form:

pyrrolidinyl,

which is optionally substituted one or two times by:

C1-3alkyl; and

5

R^{27} is selected from: hydrogen and fluoro;

or one of R^{25} and R^{26} is taken together with R^{27} , and optionally 1 additional heteroatom, to form:

10

pyrrolidinyl, or

morpholinyl,

each of which are optionally substituted from 1 to 4 times by

C1-3alkyl;

15 or a pharmaceutically acceptable salt thereof.

For compounds of Formula (III), suitably R^{20} is C1-2alkyl substituted by:

pyrazolyl,

pyrazolyl substituted by C1-3alkyl,

20

oxazolyl,

oxazolyl substituted by C1-3alkyl,

imidazolyl,

imidazolyl substituted by C1-3alkyl,

triazolyl,

25

triazolyl substituted by C1-3alkyl,

thiazolyl,

thiazolyl substituted by C1-3alkyl,

C1-6alkoxy,

C1-6alkoxy substituted with from 1 to 6 times by fluoro,

30

tetrahydrofuran,

pyridyl,

pyridyl substituted by bromo, or

pyridyl substituted by pyrimidinyl.

35 For compounds of Formula (III), suitably R^{21} is selected from:

hydrogen,

fluoro,

- chloro,
bromo,
-OH,
boronic acid,
5 1,3,6,2-dioxazaborocane-4,8-dione,
-CN,
-C(O)NHCH₃,
-C(O)NHCH₂CH₂OH,
-C(O)NHCH₂CH₂SO₂CH₃,
10 -C(O)NHOCH₃,
-C(O)NH₂,
-C(O)OCH₃,
-C(O)NHCH₂cyclopropyl,
-C(O)NHcyclobutyl, optionally substituted by hydroxy,
15 -CH₂morpholinyl,
-CH₂OH,
-CH₂NHCH₂CF₃,
-CH₂NHCH₂CH₂SO₂CH₃,
-CH₂SO₂CH₃,
20 -CH(OH)CF₃,
-CH₃,
-CF₃,
-OCH₃,
pyrazolyl,
25 oxazolyl, and
oxazolyl substituted once or twice by methyl,

or R²³ and R²⁴ are taken together with the carbon atoms to which they are
attached to form oxaborolyl, optionally substituted by hydroxyl.
30

For compounds of Formula (III), suitably R²², R²³, and R²⁴ are independently selected from:

- hydrogen,
fluoro,
35 chloro,
bromo,
-OH,
boronic acid,
1,3,6,2-dioxazaborocane-4,8-dione,
40 -CN,

- 5 -C(O)NHCH₃,
 -C(O)NHCH₂CH₂OH,
 -C(O)NHCH₂CH₂SO₂CH₃,
 -C(O)NHOCH₃,
 -C(O)NH₂,
 -C(O)OCH₃,
 -C(O)NHCH₂cyclopropyl,
 -C(O)NHcyclobutyl, optionally substituted by hydroxy,
 -CH₂morpholinyl,
 10 -CH₂OH,
 -CH₂NHCH₂CF₃,
 -CH₂NHCH₂CH₂SO₂CH₃,
 -CH₂SO₂CH₃,
 -CH(OH)CF₃,
 15 -CH₃,
 -CF₃,
 -OCH₃,
 -NHC(O)CH₃,
 -NH₂,
 20 -NHSO₂CH₃,
 morpholinyl
 pyrazolyl,
 oxazolyl, and
 oxazolyl substituted once or twice by methyl,
 25 or R²³ and R²⁴ are taken together with the carbon atoms to which they are
 attached to form oxaborolyl, optionally substituted by hydroxyl.

For compounds of Formula (III), suitably R²⁵ and R²⁶ are independently selected from:

- 30 C1-3alkyl,
 C1-3alkyl substituted from 1 to 3 times by fluoro, and
 cyclopropyl,
 or R²⁵ and R²⁶ are taken together with the nitrogen to which they are
 35 attached to form:
 pyrrolidinyl,

which is optionally substituted one or two times by:

C1-3alkyl.

For compounds of Formula (III), suitably R^{27} is selected from: hydrogen and fluoro;

or one of R^{25} and R^{26} is taken together with R^{27} , and optionally 1 additional heteroatom, to form:

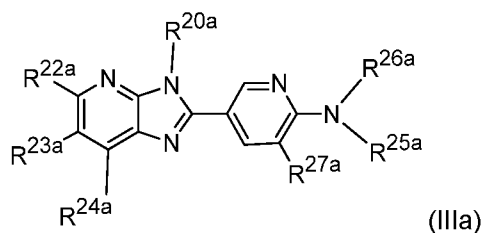
pyrrolidinyl, or

morpholinyl,

each of which are optionally substituted from 1 to 4 times by

C1-3alkyl.

Included in the compounds of the invention and used in the methods of the invention are compounds of Formula (IIIa):



where:

R^{20a} is C1-2alkyl substituted by:

phenyl substituted by pyrimidinyl,

pyrazolyl,

pyrazolyl substituted by C1-3alkyl,

oxazolyl,

oxazolyl substituted by C1-3alkyl,

imidazolyl,

imidazolyl substituted by C1-3alkyl,

triazolyl,

triazolyl substituted by C1-3alkyl,

thiazolyl,

thiazolyl substituted by C1-3alkyl,

-Ocyclopentyl,

C1-6alkoxy,

5 C1-6alkoxy substituted with from 1 to 6 times by fluoro,
 tetrahydrofuran,
 pyridyl,
 pyridyl substituted by bromo, or
 pyridyl substituted by pyrimidinyl;

10 R^{22a} , R^{23a} , and R^{24a} are independently selected from:
 hydrogen,
 fluoro,
 chloro,
 bromo,
 -OH,
 boronic acid,
 1,3,6,2-dioxazaborocane-4,8-dione,
 15 -CN,
 -C(O)NHCH₃,
 -C(O)NHCH₂CH₂OH,
 -C(O)NHCH₂CH₂SO₂CH₃,
 -C(O)NHOCH₃,
 20 -C(O)NH₂,
 -C(O)OCH₃,
 -C(O)NHCH₂cyclopropyl,
 -C(O)NHcyclobutyl, optionally substituted by hydroxy,
 -CH₂morpholinyl,
 25 -CH₂OH,
 -CH₂NHCH₂CF₃,
 -CH₂NHCH₂CH₂SO₂CH₃,
 -CH₂SO₂CH₃,
 -CH(OH)CF₃,
 30 -CH₃,
 -CF₃,
 -OCH₃,
 -NHC(O)CH₃,
 -NH₂,
 35 -NHSO₂CH₃,
 morpholinyl
 pyrazolyl,
 oxazolyl, and
 oxazolyl substituted once or twice by methyl,
 40

or R^{23a} and R^{24a} are taken together with the carbon atoms to which they are attached to form oxaborolyl, optionally substituted by hydroxy;

R^{25a} and R^{26a} are independently selected from:

5 C1-3alkyl,

C1-3alkyl substituted from 1 to 3 times by fluoro, and
cyclopropyl,

10 or R^{25a} and R^{26a} are taken together with the nitrogen to which they are
attached to form:

pyrrolidinyl,

which is optionally substituted one or two times by:

C1-3alkyl; and

15 R^{27a} is selected from: hydrogen and fluoro;

or one of R^{25a} and R^{26a} is taken together with R^{27a} , and optionally 1
additional heteroatom, to form:

20 pyrrolidinyl, or

morpholinyl,

each of which are optionally substituted from 1 to 4 times by

C1-3alkyl;

or a pharmaceutically acceptable salt thereof.

25

For compounds of Formula (IIIa), suitably R^{20a} is C1-2alkyl substituted by:

pyrazolyl,

pyrazolyl substituted by C1-3alkyl,

oxazolyl,

30 oxazolyl substituted by C1-3alkyl,

imidazolyl,

imidazolyl substituted by C1-3alkyl,

triazolyl,

triazolyl substituted by C1-3alkyl,

35

thiazolyl,

thiazolyl substituted by C1-3alkyl,
 C1-6alkoxy,
 C1-6alkoxy substituted with from 1 to 6 times by fluoro,
 tetrahydrofuran,
 5 pyridyl,
 pyridyl substituted by bromo, or
 pyridyl substituted by pyrimidinyl.

For compounds of Formula (IIIa), suitably R^{22a} , R^{23a} , and R^{24a} are independently selected
 10 from:

hydrogen,
 fluoro,
 chloro,
 bromo,
 15 -OH,
 boronic acid,
 1,3,6,2-dioxazaborocane-4,8-dione,
 -CN,
 -C(O)NHCH₃,
 20 -C(O)NHCH₂CH₂OH,
 -C(O)NHCH₂CH₂SO₂CH₃,
 -C(O)NHCH₃,
 -C(O)NH₂,
 -C(O)OCH₃,
 25 -C(O)NHCH₂cyclopropyl,
 -C(O)NHcyclobutyl, optionally substituted by hydroxy,
 -CH₂morpholinyl,
 -CH₂OH,
 -CH₂NHCH₂CF₃,
 30 -CH₂NHCH₂CH₂SO₂CH₃,
 -CH₂SO₂CH₃,
 -CH(OH)CF₃,
 -CH₃,
 -CF₃,
 35 -OCH₃,
 -NHC(O)CH₃,
 -NH₂,
 -NHSO₂CH₃,
 morpholinyl

pyrazolyl,
oxazolyl, and
oxazolyl substituted once or twice by methyl,

- 5 or R^{23a} and R^{24a} are taken together with the carbon atoms to which they are attached to form oxaborolyl, optionally substituted by hydroxyl.

For compounds of Formula (IIIa), suitably R^{25a} and R^{26a} are independently selected from:

C1-3alkyl,

- 10 C1-3alkyl substituted from 1 to 3 times by fluoro, and
cyclopropyl,

or R^{25a} and R^{26a} are taken together with the nitrogen to which they are
attached to form:

- 15 pyrrolidinyl,
which is optionally substituted one or two times by:
C1-3alkyl.

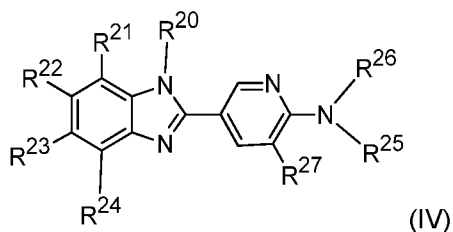
For compounds of Formula (IIIa), suitably R^{27a} is selected from: hydrogen and
20 fluoro;

or one of R^{25a} and R^{26a} is taken together with R^{27a}, and optionally 1
additional heteroatom, to form:

- 25 pyrrolidinyl, or
morpholinyl,
each of which are optionally substituted from 1 to 4 times by
C1-3alkyl.

30

Included in the compounds of the invention and used in the methods of the invention are compounds of Formula (IV):



5 where:

R^{20} is C1-2alkyl substituted by:

- phenyl substituted by pyrimidinyl,
- pyrazolyl,
- 10 pyrazolyl substituted by C1-3alkyl,
- oxazolyl,
- oxazolyl substituted by C1-3alkyl,
- imidazolyl,
- imidazolyl substituted by C1-3alkyl,
- 15 morpholiny,
- morpholiny substituted 1 or 2 times by C1-3alkyl,
- triazolyl,
- triazolyl substituted by C1-3alkyl,
- thiazolyl,
- 20 thiazolyl substituted by C1-3alkyl,
- Ocyclopentyl,
- C1-6alkoxy,
- C1-6alkoxy substituted with from 1 to 6 times by fluoro,
- tetrahydrofuran,
- 25 pyridyl,
- pyridyl substituted by bromo, or
- pyridyl substituted by pyrimidinyl;

R^{21} is selected from:

- 30 hydrogen,
- fluoro,
- chloro,
- bromo,
- OH,
- 35 -CN,
- C(O)NHCH₃,

- 5
- C(O)NHCH₂CH₂OH,
 - C(O)NHCH₂CH₂SO₂CH₃,
 - C(O)NHOCH₃,
 - C(O)NH₂,
 - C(O)OCH₃,
 - C(O)NHCH₂cyclopropyl,
 - C(O)NHcyclobutyl, optionally substituted by hydroxy,
 - CH₂morpholinyl,
- 10
- CH₂OH,
 - CH₂NHCH₂CF₃,
 - CH₂NHCH₂CH₂SO₂CH₃,
 - CH₂SO₂CH₃,
 - CH(OH)CF₃,
 - CH₃,
- 15
- CF₃,
 - OCH₃,
 - pyrazolyl,
 - oxazolyl, and
 - oxazolyl substituted once or twice by methyl,
- 20
- R²², R²³, and R²⁴ are independently selected from:
- hydrogen,
- fluoro,
- chloro,
- 25
- bromo,
- OH,
- boronic acid,
- 1,3,6,2-dioxazaborocane-4,8-dione,
- CN,
- 30
- C(O)NHCH₃,
 - C(O)NHCH₂CH₃,
 - C(O)NHCH₂CH₂OH,
 - C(O)NHCH₂CH₂SO₂CH₃,
 - C(O)NHOCH₃,
- 35
- C(O)NH₂,
 - C(O)OCH₃,
 - C(O)NHCH₂cyclopropyl,
 - C(O)NHcyclobutyl, optionally substituted by hydroxy,
 - CH₂morpholinyl,

- 5 -CH₂OH,
 -CH₂NHCH₂CF₃,
 -CH₂NHCH₂CH₂SO₂CH₃,
 -CH₂SO₂CH₃,
 -CH(OH)CF₃,
 -CH₃,
 -CF₃,
 -OCH₃,
 -NHC(O)CH₃,
 10 -NH₂,
 -NHSO₂CH₃,
 morpholinyl
 pyrazolyl,
 oxazolyl, and
 15 oxazolyl substituted once or twice by methyl,

 or R²³ and R²⁴ are taken together with the carbon atoms to which they are
 attached to form oxaborolyl, optionally substituted by hydroxy;
 20 R²⁵ and R²⁶ are independently selected from:

 C1-3alkyl,

 C1-3alkyl substituted from 1 to 3 times by fluoro, and
 cyclopropyl,

 25 or R²⁵ and R²⁶ are taken together with the nitrogen to which they are
 attached to form:
 azetidinyl,
 pyrrolidinyl,
 each of which is optionally substituted one or two times by:
 30 C1-3alkyl; and

 R²⁷ is selected from: hydrogen and fluoro;

 or one of R²⁵ and R²⁶ is taken together with R²⁷, and optionally 1 additional
 35 heteroatom, to form:

pyrrolidinyl, or
morpholinyl,
each of which are optionally substituted from 1 to 4 times by
C1-3alkyl;

5

or a pharmaceutically acceptable salt thereof.

For compounds of Formula (IV), suitably R²⁰ is C1-2alkyl substituted by:

pyrazolyl,
10 pyrazolyl substituted by C1-3alkyl,
oxazolyl,
oxazolyl substituted by C1-3alkyl,
imidazolyl,
imidazolyl substituted by C1-3alkyl,
15 morpholinyl,
morpholinyl substituted 1 or 2 times by C1-3alkyl,
triazolyl,
triazolyl substituted by C1-3alkyl,
thiazolyl,
20 thiazolyl substituted by C1-3alkyl,
C1-6alkoxy,
C1-6alkoxy substituted with from 1 to 6 times by fluoro,
tetrahydrofuran,
pyridyl,
25 pyridyl substituted by bromo, or
pyridyl substituted by pyrimidinyl.

For compounds of Formula (IV), suitably R²¹ is selected from:

hydrogen,
30 fluoro,
chloro,
bromo,
-OH,
boronic acid,
35 1,3,6,2-dioxazaborocane-4,8-dione,
-CN,
-C(O)NHCH₃,
-C(O)NHCH₂CH₂OH,
-C(O)NHCH₂CH₂SO₂CH₃,

- 5 -C(O)NHOCH₃,
 -C(O)NH₂,
 -C(O)OCH₃,
 -C(O)NHCH₂cyclopropyl,
 -C(O)NHcyclobutyl, optionally substituted by hydroxy,
 -CH₂morpholinyl,
 -CH₂OH,
 -CH₂NHCH₂CF₃,
 -CH₂NHCH₂CH₂SO₂CH₃,
 10 -CH₂SO₂CH₃,
 -CH(OH)CF₃,
 -CH₃,
 -CF₃,
 -OCH₃,
 15 pyrazolyl,
 oxazolyl, and
 oxazolyl substituted once or twice by methyl,

 20 or R²³ and R²⁴ are taken together with the carbon atoms to which they are
 attached to form oxaborolyl, optionally substituted by hydroxyl.

For compounds of Formula (IV), suitably R²², R²³, and R²⁴ are independently selected from:

- 25 hydrogen,
 fluoro,
 chloro,
 bromo,
 -OH,
 boronic acid,
 30 1,3,6,2-dioxazaborocane-4,8-dione,
 -CN,
 -C(O)NHCH₃,
 -C(O)NHCH₂CH₃,
 -C(O)NHCH₂CH₂OH,
 35 -C(O)NHCH₂CH₂SO₂CH₃,
 -C(O)NHOCH₃,
 -C(O)NH₂,
 -C(O)OCH₃,
 -C(O)NHCH₂cyclopropyl,

- 5 -C(O)NHcyclobutyl, optionally substituted by hydroxy,
 -CH₂morpholinyl,
 -CH₂OH,
 -CH₂NHCH₂CF₃,
 -CH₂NHCH₂CH₂SO₂CH₃,
 -CH₂SO₂CH₃,
 -CH(OH)CF₃,
 -CH₃,
 -CF₃,
 10 -OCH₃,
 -NHC(O)CH₃,
 -NH₂,
 -NHSO₂CH₃,
 15 morpholinyl
 pyrazolyl,
 oxazolyl, and
 oxazolyl substituted once or twice by methyl,
 20 or R²³ and R²⁴ are taken together with the carbon atoms to which they are
 attached to form oxaborolyl, optionally substituted by hydroxy.

For compounds of Formula (IV), suitably R²⁵ and R²⁶ are independently selected from:

- C1-3alkyl,
 C1-3alkyl substituted from 1 to 3 times by fluoro, and
 25 cyclopropyl,
 or R²⁵ and R²⁶ are taken together with the nitrogen to which they are
 attached to form:
 azetidinyl,
 30 pyrrolidinyl,
 each of which is optionally substituted one or two times by:
 C1-3alkyl.

For compounds of Formula (IV), suitably R²⁷ is selected from: hydrogen and fluoro;

or one of R²⁵ and R²⁶ is taken together with R²⁷, and optionally 1 additional heteroatom, to form:

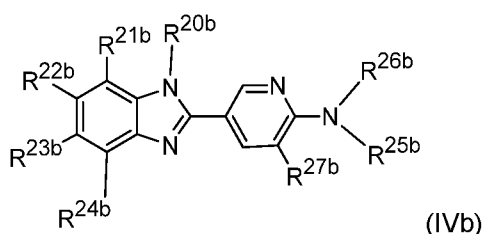
5 pyrrolidinyl, or

morpholiny],

each of which are optionally substituted from 1 to 4 times by

C₁₋₃alkyl.

10 Included in the compounds of the invention and used in the methods of the invention
are compounds of Formula (IVb):



where:

15

R^{20b} is C₁-2alkyl substituted by:

phenyl substituted by pyrimidinyl,

pyrazolyl,

pyrazolyl substituted by C1-3alkyl,

20 pyrazinyl,

pyrazinyl substituted by C₁-3alkyl,

piperazinyl,

piperazinyl substituted by oxo,

piperazinyl substituted by C₁₋₃alkyl,

25 oxazolyl,

oxazolyl substituted by C₁-3alkyl,

imidazolyl,

imidazolyl substituted by C₁-3alkyl,

morpholinyl,

30 morpholinyl substituted 1 or 2 times by C1-3alkyl,

morpholiny] substituted by oxo,

dioxanyl,

dioxanyl substituted by C₁₋₃alkyl,

4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine;
 triazolyl,
 triazolyl substituted by C₁-3alkyl,
 thiazolyl,
 thiazolyl substituted by C₁-3alkyl,
 -Ocyclopentyl,
 C₁-6alkoxy,
 C₁-6alkoxy substituted from 1 to 6 times by fluoro,
 C₁-6alkoxy substituted by hydroxy,
 tetrahydrofuran,
 pyridyl,
 pyridyl substituted by bromo, or
 pyridyl substituted by pyrimidinyl;

R^{21b} is selected from:

hydrogen,
 fluoro,
 chloro,
 bromo,
 -OH,
 -CN,
 -NH₂,
 -C(O)NHCH₃,
 -C(O)NHCH₂CH₂OH,
 -C(O)NHCH₂CH₂SO₂CH₃,
 -C(O)NHOCH₃,
 -C(O)NH₂,
 -C(O)OCH₃,
 -C(O)NHCH₂cyclopropyl,
 -C(O)NHcyclobutyl, optionally substituted by hydroxy,
 -CH₂morpholinyl,
 -CH₂OH,
 -CH₂NHCH₂CF₃,
 -CH₂NHCH₂CH₂SO₂CH₃,
 -CH₂SO₂CH₃,
 -CH(OH)CF₃,
 -CH₃,
 -CF₃,
 -OCH₃,

methoxy-d3,
pyrazolyl,
oxazolyl, and
oxazolyl substituted once or twice by methyl;

5

R^{22b} , R^{23b} , and R^{24b} are independently selected from:

hydrogen,
fluoro,
chloro,
bromo,
-OH,
boronic acid,
1,3,6,2-dioxazaborocane-4,8-dione,
-CN,

10

15

- C(O)NHCH₃,
- C(O)NHCH₂CH₃,
- C(O)NHCH₂CF₂H,
- C(O)NHCH₂CH₂OH,
- C(O)NHCH₂CH₂SO₂CH₃,
- C(O)NHOCH₃,
- C(O)NH₂,
- C(O)OCH₃,
- C(O)NHCH₂cyclopropyl,
- C(O)NHcyclobutyl, optionally substituted by hydroxy,
- CH₂morpholinyl,
- CH₂OH,
- CH₂NHCH₂CF₃,
- CH₂NHCH₂CH₂SO₂CH₃,
- CH₂SO₂CH₃,
- CH(OH)CF₃,
- CH₃,
- CF₃,
- OCH₃,

20

25

30

35

methoxy-d3,
-NHC(O)CH₃,
-NH₂,
-NHSO₂CH₃,
morpholinyl
pyrazolyl,

oxazolyl, and
oxazolyl substituted once or twice by methyl,
or R^{23b} and R^{24b} are taken together with the carbon atoms to which they
are attached to form oxaborolyl, optionally substituted by hydroxy;

5

R^{25b} and R^{26b} are independently selected from:

C1-3alkyl,

C1-3alkyl substituted from 1 to 3 times by fluoro, and

cyclopropyl,

10

R^{25b} and R^{26b} are taken together with the nitrogen to which they are
attached to form:

azetidinyl,

pyrrolidinyl,

each of which is optionally substituted one or two times by:

15

C1-3alkyl or C1-3alkyl substituted from 1 to 3 times by fluoro,

or

one of R^{25b} and R^{26b} is taken together with R^{27b} , and optionally 1
additional heteroatom, to form:

pyrrolidinyl, or

20

morpholinyl,

each of which are optionally substituted from 1 to 4 times by

C1-3alkyl; and

R^{27b} is selected from: hydrogen and fluoro;

or one of R^{25b} and R^{26b} is taken together with R^{27b} , and optionally 1

25

additional heteroatom, to form:

pyrrolidinyl, or

morpholinyl,

each of which are optionally substituted from 1 to 4 times by

C1-3alkyl;

30

or a pharmaceutically acceptable salt thereof.

For compounds of Formula (IVb), suitably R^{20b} is C1-2alkyl substituted by:

- phenyl substituted by pyrimidinyl,
- pyrazolyl,
- pyrazolyl substituted by C1-3alkyl,
- 5 pyrazinyl,
- pyrazinyl substituted by C1-3alkyl,
- piperazinyl,
- piperazinyl substituted by oxo,
- piperazinyl substituted by C1-3alkyl,
- 10 oxazolyl,
- oxazolyl substituted by C1-3alkyl,
- imidazolyl,
- imidazolyl substituted by C1-3alkyl,
- morpholinyl,
- 15 morpholinyl substituted 1 or 2 times by C1-3alkyl,
- morpholinyl substituted by oxo,
- dioxanyl,
- dioxanyl substituted by C1-3alkyl,
- 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine;
- 20 triazolyl,
- triazolyl substituted by C1-3alkyl,
- thiazolyl,
- thiazolyl substituted by C1-3alkyl,
- Ocyclopentyl,
- 25 C1-6alkoxy,
- C1-6alkoxy substituted from 1 to 6 times by fluoro,
- C1-6alkoxy substituted by hydroxy,
- tetrahydrofuran,
- pyridyl,
- 30 pyridyl substituted by bromo, or
- pyridyl substituted by pyrimidinyl.

For compounds of Formula (IVb), suitably R^{21b} is selected from:

- hydrogen,
- 35 fluoro,
- chloro,
- bromo,
- OH,
- CN,
- 40 -NH₂,

- 5 -C(O)NHCH₃,
 -C(O)NHCH₂CH₂OH,
 -C(O)NHCH₂CH₂SO₂CH₃,
 -C(O)NHOCH₃,
 -C(O)NH₂,
 -C(O)OCH₃,
 -C(O)NHCH₂cyclopropyl,
 -C(O)NHcyclobutyl, optionally substituted by hydroxy,
 -CH₂morpholinyl,
 10 -CH₂OH,
 -CH₂NHCH₂CF₃,
 -CH₂NHCH₂CH₂SO₂CH₃,
 -CH₂SO₂CH₃,
 -CH(OH)CF₃,
 15 -CH₃,
 -CF₃,
 -OCH₃,
 methoxy-d₃,
 pyrazolyl,
 20 oxazolyl, and
 oxazolyl substituted once or twice by methyl,

For compounds of Formula (IVb), suitably R^{22b}, R^{23b}, and R^{24b} are independently selected from:

- 25 hydrogen,
 fluoro,
 chloro,
 bromo,
 -OH,
 30 boronic acid,
 1,3,6,2-dioxazaborocane-4,8-dione,
 -CN,
 -C(O)NHCH₃,
 -C(O)NHCH₂CH₃,
 35 -C(O)NHCH₂CF₂H,
 -C(O)NHCH₂CH₂OH,
 -C(O)NHCH₂CH₂SO₂CH₃,
 -C(O)NHOCH₃,
 -C(O)NH₂,

- 5 -C(O)OCH₃,
 -C(O)NHCH₂cyclopropyl,
 -C(O)NHcyclobutyl, optionally substituted by hydroxy,
 -CH₂morpholinyl,
 -CH₂OH,
 -CH₂NHCH₂CF₃,
 -CH₂NHCH₂CH₂SO₂CH₃,
 -CH₂SO₂CH₃,
 -CH(OH)CF₃,
 10 -CH₃,
 -CF₃,
 -OCH₃,
 methoxy-d₃,
 -NHC(O)CH₃,
 15 -NH₂,
 -NHSO₂CH₃,
 morpholinyl
 pyrazolyl,
 oxazolyl, and
 20 oxazolyl substituted once or twice by methyl,
 or R^{23b} and R^{24b} are taken together with the carbon atoms to which they
 are attached to form oxaborolyl, optionally substituted by hydroxy.

For compounds of Formula (IVb), suitably R^{25b} and R^{26b} are independently selected from:

- 25 C1-3alkyl,
 C1-3alkyl substituted from 1 to 3 times by fluoro, and
 cyclopropyl,
 R^{25b} and R^{26b} are taken together with the nitrogen to which they are
 attached to form:
 30 azetidinyl,
 pyrrolidinyl,
 each of which is optionally substituted one or two times by:
 C1-3alkyl or C1-3alkyl substituted from 1 to 3 times by fluoro,
 or
 35 one of R^{25b} and R^{26b} is taken together with R^{27b}, and optionally 1

additional heteroatom, to form:

pyrrolidinyl, or

morpholinyl,

each of which are optionally substituted from 1 to 4 times by

5

C1-3alkyl.

For compounds of Formula (IVb), suitably R^{27b} is selected from: hydrogen and fluoro;

or one of R^{25b} and R^{26b} is taken together with R^{27b} , and optionally 1

10

additional heteroatom, to form:

pyrrolidinyl, or

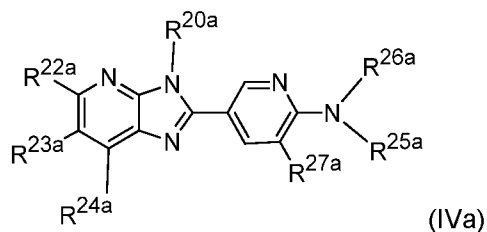
morpholinyl,

each of which are optionally substituted from 1 to 4 times by

C1-3alkyl.

15

Included in the compounds of the invention and used in the methods of the invention are compounds of Formula (IVa):



20 where:

R^{20a} is C1-2alkyl substituted by:

phenyl substituted by pyrimidinyl,

pyrazolyl,

25

pyrazolyl substituted by C1-3alkyl,

oxazolyl,

oxazolyl substituted by C1-3alkyl,

imidazolyl,

imidazolyl substituted by C1-3alkyl,

30

morpholinyl,

morpholinyl substituted 1 or 2 times by C1-3alkyl,

triazolyl,

triazolyl substituted by C1-3alkyl,
 thiazolyl,
 thiazolyl substituted by C1-3alkyl,
 -Ocyclopentyl,
 5 C1-6alkoxy,
 C1-6alkoxy substituted with from 1 to 6 times by fluoro,
 tetrahydrofuran,
 pyridyl,
 pyridyl substituted by bromo, or
 10 pyridyl substituted by pyrimidinyl;

R^{22a} , R^{23a} , and R^{24a} are independently selected from:

hydrogen,
 fluoro,
 15 chloro,
 bromo,
 -OH,
 boronic acid,
 1,3,6,2-dioxazaborocane-4,8-dione,
 20 -CN,
 -C(O)NHCH₃,
 -C(O)NHCH₂CH₃,
 -C(O)NHCH₂CH₂OH,
 -C(O)NHCH₂CH₂SO₂CH₃,
 25 -C(O)NHOCH₃,
 -C(O)NH₂,
 -C(O)OCH₃,
 -C(O)NHCH₂cyclopropyl,
 -C(O)NHcyclobutyl, optionally substituted by hydroxy,
 30 -CH₂morpholinyl,
 -CH₂OH,
 -CH₂NHCH₂CF₃,
 -CH₂NHCH₂CH₂SO₂CH₃,
 -CH₂SO₂CH₃,
 35 -CH(OH)CF₃,
 -CH₃,
 -CF₃,
 -OCH₃,
 -NHC(O)CH₃,

- 5 -NH₂,
 -NHSO₂CH₃,
 morpholinyl
 pyrazolyl,
 oxazolyl, and
 oxazolyl substituted once or twice by methyl,

 or R^{23a} and R^{24a} are taken together with the carbon atoms to which they are
 attached to form oxaborolyl, optionally substituted by hydroxy;
10 R^{25a} and R^{26a} are independently selected from:

 C1-3alkyl,

 C1-3alkyl substituted from 1 to 3 times by fluoro, and
 cyclopropyl,
15 or R^{25a} and R^{26a} are taken together with the nitrogen to which they are
 attached to form:
 azetidinyl,
 pyrrolidinyl,
20 each of which is optionally substituted one or two times by:
 C1-3alkyl; and

 R^{27a} is selected from: hydrogen and fluoro;

25 or one of R^{25a} and R^{26a} is taken together with R^{27a}, and optionally 1
 additional heteroatom, to form:
 pyrrolidinyl, or
 morpholinyl,
 each of which are optionally substituted from 1 to 4 times by
30 C1-3alkyl;

 or a pharmaceutically acceptable salt thereof.

 For compounds of Formula (IVa), suitably R^{20a} is C1-2alkyl substituted by:
35 pyrazolyl,

pyrazolyl substituted by C1-3alkyl,
oxazolyl,
oxazolyl substituted by C1-3alkyl,
imidazolyl,
5 imidazolyl substituted by C1-3alkyl,
morpholinyl,
morpholinyl substituted 1 or 2 times by C1-3alkyl,
triazolyl,
triazolyl substituted by C1-3alkyl,
10 thiazolyl,
thiazolyl substituted by C1-3alkyl,
C1-6alkoxy,
C1-6alkoxy substituted with from 1 to 6 times by fluoro,
tetrahydrofuran,
15 pyridyl,
pyridyl substituted by bromo, or
pyridyl substituted by pyrimidinyl.

For compounds of Formula (IVa), suitably R^{22a} , R^{23a} , and R^{24a} are independently selected from:

	hydrogen,
	fluoro,
	chloro,
	bromo,
25	-OH,
	boronic acid,
	1,3,6,2-dioxazaborocane-4,8-dione,
	-CN,
	-C(O)NHCH ₃ ,
30	-C(O)NHCH ₂ CH ₃ ,
	-C(O)NHCH ₂ CH ₂ OH,
	-C(O)NHCH ₂ CH ₂ SO ₂ CH ₃ ,
	-C(O)NHOCH ₃ ,
	-C(O)NH ₂ ,
35	-C(O)OCH ₃ ,
	-C(O)NHCH ₂ cyclopropyl,
	-C(O)NHcyclobutyl, optionally substituted by hydroxy,
	-CH ₂ morpholinyl,
	-CH ₂ OH,

- 5 -CH₂NHCH₂CF₃,
 -CH₂NHCH₂CH₂SO₂CH₃,
 -CH₂SO₂CH₃,
 -CH(OH)CF₃,
 -CH₃,
 -CF₃,
 -OCH₃,
 -NHC(O)CH₃,
 -NH₂,
 10 -NHSO₂CH₃,
 morpholinyl
 pyrazolyl,
 oxazolyl, and
 oxazolyl substituted once or twice by methyl,
 15 or R^{23a} and R^{24a} are taken together with the carbon atoms to which they are
 attached to form oxaborolyl, optionally substituted by hydroxy.

For compounds of Formula (IVa), suitably R^{25a} and R^{26a} are independently selected from:

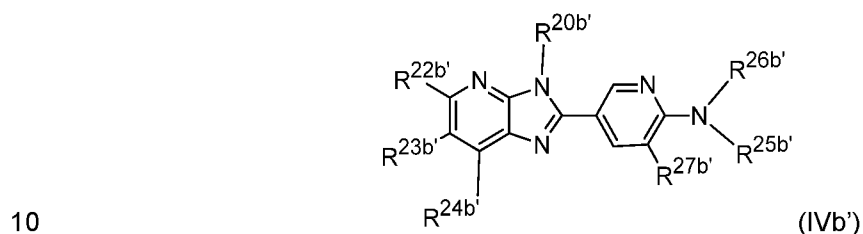
- 20 C1-3alkyl,
 C1-3alkyl substituted from 1 to 3 times by fluoro, and
 cyclopropyl,
 or R^{25a} and R^{26a} are taken together with the nitrogen to which they are
 25 attached to form:
 azetidinyl, or
 pyrrolidinyl,
 each of which is optionally substituted one or two times by:
 C1-3alkyl.

- 30 For compounds of Formula (IVa), suitably R^{27a} is selected from: hydrogen and
 fluoro;
 or one of R^{25a} and R^{26a} is taken together with R^{27a}, and optionally 1
 35 additional heteroatom, to form:

pyrrolidinyl, or
morpholinyl,
each of which are optionally substituted from 1 to 4 times by
C1-3alkyl.

5

Included in the compounds of the invention and used in the methods of the invention
are compounds of Formula (IVb'):



where:

R^{20b'} is C1-2alkyl substituted by:

15 phenyl substituted by pyrimidinyl,
pyrazolyl,
pyrazolyl substituted by C1-3alkyl,
pyrazinyl,
pyrazinyl substituted by C1-3alkyl,
piperazinyl,
20 piperazinyl substituted by oxo,
piperazinyl substituted by C1-3alkyl,
oxazolyl,
oxazolyl substituted by C1-3alkyl,
imidazolyl,
25 imidazolyl substituted by C1-3alkyl,
morpholinyl,
morpholinyl substituted 1 or 2 times by C1-3alkyl,
morpholinyl substituted by oxo,
dioxanyl,
30 dioxanyl substituted by C1-3alkyl,
4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine;
triazolyl,
triazolyl substituted by C1-3alkyl,
thiazolyl,

- thiazolyl substituted by C1-3alkyl,
 -Ocyclopentyl,
 C1-6alkoxy,
 C1-6alkoxy substituted from 1 to 6 times by fluoro,
 C1-6alkoxy substituted by hydroxy,
 tetrahydrofuran,
 pyridyl,
 pyridyl substituted by bromo, or
 pyridyl substituted by pyrimidinyl;
- $R^{22b'}$, $R^{23b'}$, and $R^{24b'}$ are independently selected from:
- hydrogen,
 fluoro,
 chloro,
 bromo,
 -OH,
 boronic acid,
 1,3,6,2-dioxazaborocane-4,8-dione,
 -CN,
 -C(O)NHCH₃,
 -C(O)NHCH₂CH₃,
 -C(O)NHCH₂CF₂H,
 -C(O)NHCH₂CH₂OH,
 -C(O)NHCH₂CH₂SO₂CH₃,
 -C(O)NHCH₂CH₂SO₂CH₃,
 -C(O)NHCH₂cyclopropyl,
 -C(O)NHcyclobutyl, optionally substituted by hydroxy,
 -CH₂morpholinyl,
 -CH₂OH,
 -CH₂NHCH₂CF₃,
 -CH₂NHCH₂CH₂SO₂CH₃,
 -CH₂SO₂CH₃,
 -CH(OH)CF₃,
 -CH₃,
 -CF₃,
 -OCH₃,
 methoxy-d₃,

- 5 -NHC(O)CH₃,
 -NH₂,
 -NHSO₂CH₃,
 morpholinyl
 pyrazolyl,
 oxazolyl, and
 oxazolyl substituted once or twice by methyl,
 or R^{23b'} and R^{24b'} are taken together with the carbon atoms to which they
 are attached to form oxaborolyl, optionally substituted by hydroxy;
- 10 R^{25b'} and R^{26b'} are independently selected from:
- C1-3alkyl,
- C1-3alkyl substituted from 1 to 3 times by fluoro, and
 cyclopropyl,
- 15 R^{25b'} and R^{26b'} are taken together with the nitrogen to which they are
 attached to form:
 azetidinyl,
 pyrrolidinyl,
 each of which is optionally substituted one or two times by:
- 20 C1-3alkyl or C1-3alkyl substituted from 1 to 3 times by fluoro,

 or
 one of R^{25b'} and R^{26b'} is taken together with R^{27b'}, and optionally 1
 additional heteroatom, to form:
 pyrrolidinyl, or
25 morpholinyl,
 each of which are optionally substituted from 1 to 4 times by
 C1-3alkyl; and
- 30 R^{27b'} is selected from: hydrogen and fluoro;
 or one of R^{25b'} and R^{26b'} is taken together with R^{27b'}, and optionally 1
 additional heteroatom, to form:
 pyrrolidinyl, or
 morpholinyl,

each of which are optionally substituted from 1 to 4 times by
C1-3alkyl;

or a pharmaceutically acceptable salt thereof.

5

For compounds of Formula (IVb'), suitably R^{20b'} is C1-2alkyl substituted by:

phenyl substituted by pyrimidinyl,
pyrazolyl,
pyrazolyl substituted by C1-3alkyl,
10 pyrazinyl,
pyrazinyl substituted by C1-3alkyl,
piperazinyl,
piperazinyl substituted by oxo,
piperazinyl substituted by C1-3alkyl,
15 oxazolyl,
oxazolyl substituted by C1-3alkyl,
imidazolyl,
imidazolyl substituted by C1-3alkyl,
morpholinyl,
20 morpholinyl substituted 1 or 2 times by C1-3alkyl,
morpholinyl substituted by oxo,
dioxanyl,
dioxanyl substituted by C1-3alkyl,
4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine;
25 triazolyl,
triazolyl substituted by C1-3alkyl,
thiazolyl,
thiazolyl substituted by C1-3alkyl,
-Ocyclopentyl,
30 C1-6alkoxy,
C1-6alkoxy substituted from 1 to 6 times by fluoro,
C1-6alkoxy substituted by hydroxy,
tetrahydrofuran,
pyridyl,
35 pyridyl substituted by bromo, or
pyridyl substituted by pyrimidinyl.

For compounds of Formula (IVb'), suitably R^{22b'}, R^{23b'}, and R^{24b'} are independently selected from:

- hydrogen,
 fluoro,
 chloro,
 bromo,
 5 -OH,
 boronic acid,
 1,3,6,2-dioxazaborocane-4,8-dione,
 -CN,
 -C(O)NHCH₃,
 10 -C(O)NHCH₂CH₃,
 -C(O)NHCH₂CF₂H,
 -C(O)NHCH₂CH₂OH,
 -C(O)NHCH₂CH₂SO₂CH₃,
 -C(O)NHOCH₃,
 15 -C(O)NH₂,
 -C(O)OCH₃,
 -C(O)NHCH₂cyclopropyl,
 -C(O)NHcyclobutyl, optionally substituted by hydroxy,
 -CH₂morpholinyl,
 20 -CH₂OH,
 -CH₂NHCH₂CF₃,
 -CH₂NHCH₂CH₂SO₂CH₃,
 -CH₂SO₂CH₃,
 -CH(OH)CF₃,
 25 -CH₃,
 -CF₃,
 -OCH₃,
 methoxy-d₃,
 -NHC(O)CH₃,
 30 -NH₂,
 -NHSO₂CH₃,
 morpholinyl
 pyrazolyl,
 oxazolyl, and
 35 oxazolyl substituted once or twice by methyl,

or R^{23b'} and R^{24b'} are taken together with the carbon atoms to which they are attached to form oxaborolyl, optionally substituted by hydroxy.

For compounds of Formula (IVb'), suitably $R^{25b'}$ and $R^{26b'}$ are independently selected from:

C1-3alkyl,

C1-3alkyl substituted from 1 to 3 times by fluoro, and

cyclopropyl,

5 $R^{25b'}$ and $R^{26b'}$ are taken together with the nitrogen to which they are attached to form:

azetidinyl,

pyrrolidinyl,

each of which is optionally substituted one or two times by:

10 C1-3alkyl or C1-3alkyl substituted from 1 to 3 times by fluoro,

or

one of $R^{25b'}$ and $R^{26b'}$ is taken together with $R^{27b'}$, and optionally 1 additional heteroatom, to form:

pyrrolidinyl, or

15 morpholinyl,

each of which are optionally substituted from 1 to 4 times by

C1-3alkyl.

20 For compounds of Formula (IVb'), suitably $R^{27b'}$ is selected from: hydrogen and fluoro;

or one of $R^{25b'}$ and $R^{26b'}$ is taken together with $R^{27b'}$, and optionally 1 additional heteroatom, to form:

pyrrolidinyl, or

25 morpholinyl,

each of which are optionally substituted from 1 to 4 times by

C1-3alkyl.

30 Included in the compounds of Formula (Ib) are:

N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;

- 5-(1-((1-Ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-dipropylpyridin-2-amine;
- N-Ethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N-propylpyridin-2-amine;
- 5 1-((1-Ethyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;
- N-Ethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N-isopropylpyridin-2-amine;
- 2-(6-(Diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 10 (S)-1-((1-Ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5R)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 15 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-(Cyclopropyl(ethyl)amino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-(Diethylamino)-5-fluoropyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 20 (S)-1-((1-Ethyl-1H-pyrazol-3-yl)methyl)-2-(5-fluoro-6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)-5-fluoropyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 25 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-(2-hydroxyethyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- (S)-1-((1-Ethyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide;
- 30 1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5R)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 5-(4-Chloro-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 35 N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-4-methyl-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;

- 4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole;
- 5-(7-Chloro-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 5 5-Bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole;
- (2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-(1H-pyrazol-3-yl)-1H-benzo[d]imidazole;
- 10 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-(1H-pyrazol-4-yl)-1H-benzo[d]imidazole;
- 5-(4,5-Dichloro-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 15 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-fluoro-1H-benzo[d]imidazole;
- N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-methoxy-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-6-methyl-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 20 2-(6-(Diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-7-carbonitrile;
- 2-(6-(Diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carbonitrile;
- 25 2-(6-(Diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-4-carbonitrile;
- 2-(6-(Diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-4-carboxamide;
- N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-methyl-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 30 5-(5-Chloro-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-7-methyl-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 35 N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-4-methoxy-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;

- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-4-(trifluoromethyl)-1H-benzo[d]imidazole;
- (2-(6-(Diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 5 (S)-1-(2-(Tert-butoxy)ethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;
- 1-(2-(Tert-butoxy)ethyl)-2-(6-((2S,5R)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;
- Methyl 1-(2-(tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylate;
- 10 1-(2-(Tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide;
- 1-(2-(Tert-butoxy)ethyl)-N-(cyclopropylmethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide;
- 15 1-(2-(Tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-N-(2-hydroxyethyl)-1H-benzo[d]imidazole-5-carboxamide;
- 5-(1-(2-(Tert-butoxy)ethyl)-4-chloro-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 5-(1-(2-(Tert-butoxy)ethyl)-4-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 20 5-(5-Bromo-1-(2-(tert-butoxy)ethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- (1-(2-(Tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 25 5-(1-(2-(Tert-butoxy)ethyl)-5-(1H-pyrazol-3-yl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 5-(1-(2-(tert-butoxy)ethyl)-5-fluoro-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 5-(1-(2-(Tert-butoxy)ethyl)-4-fluoro-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 30 1-(2-(Tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazole-4-carbonitrile;
- 1-(2-(Tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazole-4-carboxamide;
- 35 N,N-Diethyl-5-(1-(2-isopropoxyethyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;

- 5-(4-Chloro-1-(2-isopropoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 2-(6-(Diethylamino)pyridin-3-yl)-1-(2-isopropoxyethyl)-1H-benzo[d]imidazole-5-carboxamide;
- 5 (S)-1-(2-Isopropoxyethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide;
- (S)-1-(2-Isopropoxyethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide;
- 4-Chloro-2-(6-(diethylamino)pyridin-3-yl)-1-(2-isopropoxyethyl)-1H-benzo[d]imidazole-5-carboxamide;
- 10 5-(4-Chloro-1-(2-isopropoxyethyl)-5-(morpholinomethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole;
- 15 2-(6-((2S,5R)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole;
- (S)-1-(2-Ethoxyethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;
- 1-(2-Ethoxyethyl)-2-(1-ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-benzo[d]imidazole;
- 20 7-(1-(2-Ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-4-ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine;
- 5-(1-(2-Ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N-ethyl-N-(2,2,2-trifluoroethyl)pyridin-2-amine;
- 25 5-(4-Chloro-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- (2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-4-methyl-1H-benzo[d]imidazol-5-yl)boronic acid;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-3H-[1,2]oxaborolo[4',3':3,4]benzo[1,2-d]imidazol-6(8H)-ol;
- 30 4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-5-fluoro-1H-benzo[d]imidazole;
- 35 5-(5-Bromo-4-chloro-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;

- (4-Chloro-2-(6-(diethylamino)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 5-Bromo-4-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole;
- 5 (4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 5-(5-Bromo-4-chloro-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethyl-3-fluoropyridin-2-amine;
- (4-Chloro-2-(6-(diethylamino)-5-fluoropyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 10 (2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-4-(trifluoromethyl)-1H-benzo[d]imidazole;
- 5-(5-Bromo-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 15 (2-(6-(Diethylamino)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- (S)-(1-(2-Ethoxyethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 5-Bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole;
- 20 (2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-5,6-difluoro-1H-benzo[d]imidazole;
- 25 (S)-1-(2-Ethoxyethyl)-4-fluoro-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;
- Methyl 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole-5-carboxylate;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 30 (S)-1-(2-Ethoxyethyl)-6-fluoro-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;
- 5-(3-(2-Ethoxyethyl)-3H-imidazo[4,5-b]pyridin-2-yl)-N,N-diethylpyridin-2-amine;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-N-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 35

- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-7-methyl-3H-imidazo[4,5-b]pyridine;
- (2-(6-(Diethylamino)pyridin-3-yl)-3-(2-ethoxyethyl)-3H-imidazo[4,5-b]pyridin-6-yl)boronic acid;
- 5 (2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-3H-imidazo[4,5-b]pyridin-6-yl)boronic acid;
- (2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-7-methyl-3H-imidazo[4,5-b]pyridin-6-yl)boronic acid;
- 10 5-(4-Chloro-1-(2-propoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 5-(4-Chloro-1-(2-(cyclopentyloxy)ethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 5-Bromo-4-chloro-1-(2-(2,2-difluoroethoxy)ethyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;
- 15 (4-Chloro-1-(2-(2,2-difluoroethoxy)ethyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 4-Chloro-1-(2-(2,2-difluoroethoxy)ethyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;
- N,N-Diethyl-5-(1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-
- 20 amine;
- 4-Ethyl-7-(1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine;
- 4-Ethyl-7-(1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine;
- 25 2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)-4-ethyloxazole;
- 4-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)-2-ethyloxazole;
- 2-(4-Ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-1-((2-ethyloxazol-4-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 30 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 35 (2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-5-yl)metanol;

- N-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-5-yl)methyl)-2,2,2-trifluoroethanamine;
- (S)-1-((1-Methyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;
- 5 N,N-Diethyl-5-(1-((2-ethyl-1H-imidazol-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyl-1H-imidazol-4-yl)methyl)-1H-benzo[d]imidazole;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((4-ethyl-1H-imidazol-2-yl)methyl)-1H-benzo[d]imidazole;
- 10 N,N-Diethyl-5-(1-((3-ethyl-1H-1,2,4-triazol-5-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- N,N-Diethyl-5-(1-((2-ethylthiazol-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 15 N,N-Diethyl-5-(1-(oxazol-2-ylmethyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 20 2-(4-Ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(4-Ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 25 1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(1-Ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(1-Ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 30 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-methyl-1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-N-methyl-1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 35 4-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;

- 5-Bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-4-fluoro-1H-benzo[d]imidazole;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-4-fluoro-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 5 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)methanol;
- 2-(6-(Diethylamino)pyridin-3-yl)-N-methyl-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-methyl-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 10 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 2-(1-Ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-methyl-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 15 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((3-ethyl-1H-1,2,4-triazol-5-yl)methyl)-1H-benzo[d]imidazole;
- 4-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-5-((methylsulfonyl)methyl)-1H-benzo[d]imidazol-1-yl)methyl)-2-ethyloxazole;
- 2-(4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione;
- 20 1-(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-5-yl)-2,2,2-trifluoroethanol;
- N-(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)acetamide;
- 25 (R)-2-(4-ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-N-methyl-3-((2-methyloxazol-4-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-methyl-3-((2-methyloxazol-4-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- (4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 30 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-N-((1r,3S)-3-hydroxycyclobutyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-N-methoxy-1H-benzo[d]imidazole-5-carboxamide;
- 35 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-N-(2-hydroxyethyl)-1H-benzo[d]imidazole-5-carboxamide;

- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-N-(2-(methylsulfonyl)ethyl)-1H-benzo[d]imidazole-5-carboxamide;
- N-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)methyl)-2-(methylsulfonyl)ethanamine;
- 5 4-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)methyl)morpholine;
- (4-Chloro-1-(2-ethoxyethyl)-2-(4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 5-(1-(2-Ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 10 5-(1-(2-Ethoxyethyl)-7-methoxy-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- N,N-Diethyl-5-(1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 15 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-amine;
- N-(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)methanesulfonamide;
- 4-(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridin-6-yl)morpholine;
- 20 (R)-2-(4-Ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-N-methyl-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 25 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((2-methyloxazol-4-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 2-(4-Ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-N-methyl-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- (4-Chloro-2-(4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 30 (4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 35 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;

- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((2-methyl-1H-imidazol-4-yl)methyl)-3H-imidazo[4,5-b]pyridine;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-6-fluoro-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine;
- 5 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine;
- 2-(6-(Diethylamino)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-(Diethylamino)pyridin-3-yl)-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 10 N,N-Diethyl-5-(1-((tetrahydrofuran-2-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- (S)-N,N-Diethyl-5-(1-((tetrahydrofuran-2-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 15 N,N-Diethyl-5-(1-(3-(pyrimidin-5-yl)benzyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 2-(6-(Diethylamino)pyridin-3-yl)-N-methyl-1-(3-(pyrimidin-5-yl)benzyl)-1H-benzo[d]imidazole-5-carboxamide;
- (S)-2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine;
- 20 (S)-2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-4-methylmorpholine;
- (S)-2-((4-Fluoro-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine;
- 25 (S)-2-((2-(6-((2S,4S)-2,4-Dimethylazetidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1-(((S)-4-methylmorpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-N-methyl-1-(((S)-4-methylmorpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 30 4-methylmorpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-ethyl-7-methoxy-1-(((S)-morpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-ethyl-7-methoxy-1-(((S)-4-methylmorpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 35 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-1-(((S)-morpholin-2-yl)methyl)-1H-benzo[d]imidazol-7-ol;

- (S)-2-((4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine;
- (S)-2-((4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)-4-methylmorpholine;
- 5 (S)-2-((7-Methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl);
- (S)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine;
- (2S,6S)-2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-6-methylmorpholine;
- 10 (2S,6S)-2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-4,6-dimethylmorpholine;
- 1-(((2S,6S)-4,6-Dimethylmorpholin-2-yl)methyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-N-methyl-1H-benzo[d]imidazole-5-
- 15 carboxamide;
- 1-(((2S,6S)-4,6-Dimethylmorpholin-2-yl)methyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazole-5-carboxamide;
- (S)-2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-fluoro-1H-benzo[d]imidazol-1-yl)methyl)morpholine;
- 20 (S)-2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-fluoro-1H-benzo[d]imidazol-1-yl)methyl)-4-methylmorpholine;
- (S)-2-((4-Chloro-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine;
- 2-((6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-ethyl-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 25 N-(2,2-Difluoroethyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 1-(((R)-1,4-Dioxan-2-yl)methyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-(methoxy-d3)-1H-benzo[d]imidazole;
- 30 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-(methoxy-d3)-1-(pyrazin-2-yl)methyl)-1H-benzo[d]imidazole;
- N-Ethyl-7-methoxy-1-(((S)-4-methylmorpholin-2-yl)methyl)-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide;
- 1-(2-Ethoxyethyl)-2-(6-(ethyl(2,2,2-trifluoroethyl)amino)pyridin-3-yl)-7-methoxy-1H-
- 35 benzo[d]imidazole-5-carboxamide;

- 1-(2-Ethoxyethyl)-2-(6-(ethyl(2,2,2-trifluoroethyl)amino)pyridin-3-yl)-7-methoxy-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 1-(2-Ethoxyethyl)-2-(6-(ethyl(2,2,2-trifluoroethyl)amino)pyridin-3-yl)-7-hydroxy-1H-benzo[d]imidazole-5-carboxamide;
- 5 1-(2-Ethoxyethyl)-2-(6-(ethyl(2,2,2-trifluoroethyl)amino)pyridin-3-yl)-7-hydroxy-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- N,N-Diethyl-5-(5-methoxy-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 2-(6-(Diethylamino)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-5-ol;
- 10 4-(2-(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1H-benzo[d]imidazol-1-yl)ethyl)piperazin-2-one;
- 4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(((S)-morpholin-2-yl)methyl)-1H-benzo[d]imidazol-7-ol;
- 15 (R)-6-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholin-3-one;
- 2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine;
- (R)-7-Methoxy-1-((1-methyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-(trifluoromethyl)pyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;
- 20 (R)-1-((1-Methyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-(trifluoromethyl)pyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-7-ol;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-ethyl-4-fluoro-7-methoxy-1-(((S)-morpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 25 N-ethyl-4-fluoro-7-methoxy-1-(((S)-4-methylmorpholin-2-yl)methyl)-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide;
- 1-(((R)-1,4-Dioxan-2-yl)methyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 4-(2-(4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)ethyl)piperazin-2-one;
- 30 N-Ethyl-4-fluoro-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1-(((S)-morpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 3-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine;
- 35 (R)-7-Methoxy-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-(trifluoromethyl)pyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide;

- (S)-2-(6-(4,4-Difluoro-2-methylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole;
- 2-(6-((2S,4S)-4-Fluoro-2-methylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole;
- 5 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole;
- 4-(2-(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)ethyl)morpholine;
- 2-(2-(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)ethoxy)ethan-1-ol;
- 10 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-7-amine;
- 4-Fluoro-7-methoxy-1-(((S)-4-methylmorpholin-2-yl)methyl)-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide;
- 15 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1-(2-morpholinoethyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-N-methyl-1-(2-morpholinoethyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1-(((S)-4-methylmorpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide; and
- 20 N,N-Diethyl-5-(1-((6-(pyrimidin-5-yl)pyridin-2-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- or a pharmaceutically acceptable salt thereof.
- 25

Included in the compounds of Formula (I) are:

- N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 30 5-(1-((1-Ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-dipropylpyridin-2-amine;
- N-Ethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N-propylpyridin-2-amine;
- 35 1-((1-Ethyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;

- N-Ethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N-isopropylpyridin-2-amine;
- 2-(6-(Diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 5 (S)-1-((1-Ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5R)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 10 2-(6-(Cyclopropyl(ethyl)amino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-(Diethylamino)-5-fluoropyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 15 (S)-1-((1-Ethyl-1H-pyrazol-3-yl)methyl)-2-(5-fluoro-6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)-5-fluoropyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-(2-hydroxyethyl)-1H-benzo[d]imidazole-5-carboxamide;
- 20 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- (S)-1-((1-Ethyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide;
- 25 2-(6-((2S,5R)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 5-(4-Chloro-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-4-methyl-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 30 4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole;
- 5-(7-Chloro-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 35 5-Bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole;

- (2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-(1H-pyrazol-3-yl)-1H-benzo[d]imidazole;
- 5 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-(1H-pyrazol-4-yl)-1H-benzo[d]imidazole;
- 5-(4,5-Dichloro-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-fluoro-1H-benzo[d]imidazole;
- 10 N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-methoxy-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-6-methyl-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 15 2-(6-(Diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-7-carbonitrile;
- 2-(6-(Diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carbonitrile;
- 2-(6-(Diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-4-carbonitrile;
- 20 2-(6-(Diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-4-carboxamide;
- N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-methyl-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 25 5-(5-Chloro-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-7-methyl-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-4-methoxy-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 30 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-4-(trifluoromethyl)-1H-benzo[d]imidazole;
- (2-(6-(Diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 35 (S)-1-(2-(Tert-butoxy)ethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;

- 1-(2-(Tert-butoxy)ethyl)-2-(6-((2S,5R)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;
- Methyl 1-(2-(tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylate;
- 5 1-(2-(Tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide;
- 1-(2-(Tert-butoxy)ethyl)-N-(cyclopropylmethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide;
- 10 1-(2-(Tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-N-(2-hydroxyethyl)-1H-benzo[d]imidazole-5-carboxamide;
- 5-(1-(2-(Tert-butoxy)ethyl)-4-chloro-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 5-(1-(2-(Tert-butoxy)ethyl)-4-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 15 5-(5-Bromo-1-(2-(tert-butoxy)ethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- (1-(2-(Tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 5-(1-(2-(Tert-butoxy)ethyl)-5-(1H-pyrazol-3-yl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 20 5-(1-(2-(tert-butoxy)ethyl)-5-fluoro-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 5-(1-(2-(Tert-butoxy)ethyl)-4-fluoro-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 25 1-(2-(Tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazole-4-carbonitrile;
- 1-(2-(Tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazole-4-carboxamide;
- N,N-Diethyl-5-(1-(2-isopropoxyethyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 30 5-(4-Chloro-1-(2-isopropoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 2-(6-(Diethylamino)pyridin-3-yl)-1-(2-isopropoxyethyl)-1H-benzo[d]imidazole-5-carboxamide;
- (S)-1-(2-Isopropoxyethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide;
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- (S)-1-(2-Isopropoxyethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide;
- 4-Chloro-2-(6-(diethylamino)pyridin-3-yl)-1-(2-isopropoxyethyl)-1H-benzo[d]imidazole-5-carboxamide;
- 5 5-(4-Chloro-1-(2-isopropoxyethyl)-5-(morpholinomethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole;
- 2-(6-((2S,5R)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole;
- 10 (S)-1-(2-Ethoxyethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;
- 1-(2-Ethoxyethyl)-2-(1-ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-benzo[d]imidazole;
- 15 7-(1-(2-Ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-4-ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine;
- 5-(1-(2-Ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N-ethyl-N-(2,2,2-trifluoroethyl)pyridin-2-amine;
- 5-(4-Chloro-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 20 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-4-methyl-1H-benzo[d]imidazol-5-yl)boronic acid;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-3H-[1,2]oxaborolo[4',3':3,4]benzo[1,2-d]imidazol-6(8H)-ol;
- 25 4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-5-fluoro-1H-benzo[d]imidazole;
- 5-(5-Bromo-4-chloro-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 30 (4-Chloro-2-(6-(diethylamino)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 5-Bromo-4-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole;
- 35 (4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)boronic acid;

- 5-(5-Bromo-4-chloro-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethyl-3-fluoropyridin-2-amine;
- (4-Chloro-2-(6-(diethylamino)-5-fluoropyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 5 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-4-(trifluoromethyl)-1H-benzo[d]imidazole;
- 5-(5-Bromo-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- (2-(6-(Diethylamino)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 10 (S)-(1-(2-Ethoxyethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 5-Bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole;
- 15 (2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-5,6-difluoro-1H-benzo[d]imidazole;
- (S)-1-(2-Ethoxyethyl)-4-fluoro-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;
- 20 Methyl 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole-5-carboxylate;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 25 (S)-1-(2-Ethoxyethyl)-6-fluoro-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;
- 5-(3-(2-Ethoxyethyl)-3H-imidazo[4,5-b]pyridin-2-yl)-N,N-diethylpyridin-2-amine;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-N-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 30 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-7-methyl-3H-imidazo[4,5-b]pyridine;
- (2-(6-(Diethylamino)pyridin-3-yl)-3-(2-ethoxyethyl)-3H-imidazo[4,5-b]pyridin-6-yl)boronic acid;
- (2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-3H-imidazo[4,5-b]pyridin-6-yl)boronic acid;
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- (2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-7-methyl-3H-imidazo[4,5-b]pyridin-6-yl)boronic acid;
- 5-(4-Chloro-1-(2-propoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 5 5-(4-Chloro-1-(2-(cyclopentyloxy)ethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 5-Bromo-4-chloro-1-(2-(2,2-difluoroethoxy)ethyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;
- (4-Chloro-1-(2-(2,2-difluoroethoxy)ethyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 10 4-Chloro-1-(2-(2,2-difluoroethoxy)ethyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;
- N,N-Diethyl-5-(1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 15 4-Ethyl-7-(1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine;
- 4-Ethyl-7-(1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)-4-ethyloxazole;
- 20 4-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)-2-ethyloxazole;
- 2-(4-Ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-1-(2-ethyloxazol-4-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 25 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethyloxazol-4-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- (2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-5-yl)metanol;
- 30 N-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-5-yl)methyl)-2,2,2-trifluoroethanamine;
- (S)-1-((1-Methyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;
- 35 N,N-Diethyl-5-(1-((2-ethyl-1H-imidazol-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;

- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyl-1H-imidazol-4-yl)methyl)-1H-benzo[d]imidazole;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((4-ethyl-1H-imidazol-2-yl)methyl)-1H-benzo[d]imidazole;
- 5 N,N-Diethyl-5-(1-((3-ethyl-1H-1,2,4-triazol-5-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- N,N-Diethyl-5-(1-((2-ethylthiazol-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- N,N-Diethyl-5-(1-(oxazol-2-ylmethyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 10 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(4-Ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 15 ((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(4-Ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 20 2-(1-Ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(1-Ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-methyl-1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 25 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-N-methyl-1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 30 5-Bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-4-fluoro-1H-benzo[d]imidazole;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-4-fluoro-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)methanol;
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- 2-(6-(Diethylamino)pyridin-3-yl)-N-methyl-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-methyl-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 5 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 2-(1-Ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-methyl-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((3-ethyl-1H-1,2,4-triazol-5-yl)methyl)-1H-benzo[d]imidazole;
- 10 4-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-5-((methylsulfonyl)methyl)-1H-benzo[d]imidazol-1-yl)methyl)-2-ethyloxazole;
- 2-(4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione;
- 15 1-(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-5-yl)-2,2,2-trifluoroethanol;
- N-(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)acetamide;
- (R)-2-(4-ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-N-methyl-3-((2-methyloxazol-4-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 20 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-methyl-3-((2-methyloxazol-4-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- (4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 25 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-N-((1R,3S)-3-hydroxycyclobutyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-N-methoxy-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-N-(2-hydroxyethyl)-1H-benzo[d]imidazole-5-carboxamide;
- 30 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-N-(2-(methylsulfonyl)ethyl)-1H-benzo[d]imidazole-5-carboxamide;
- N-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)methyl)-2-(methylsulfonyl)ethanamine;
- 35 4-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)methyl)morpholine;

- (4-Chloro-1-(2-ethoxyethyl)-2-(4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 5-((1-(2-Ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 5-((1-(2-Ethoxyethyl)-7-methoxy-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 5-((1-((6-Bromopyridin-2-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- N,N-Diethyl-5-((1-((6-(pyrimidin-5-yl)pyridin-2-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 10 N,N-Diethyl-5-((1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 2-((6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-amine;
- N-((2-((6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)methanesulfonamide;
- 15 4-((2-((6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridin-6-yl)morpholine;
- (R)-2-((4-Ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-N-methyl-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 20 2-((6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-((6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((2-methyloxazol-4-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 2-((4-Ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-N-methyl-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;;
- 25 (4-Chloro-2-((4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- (4-Chloro-2-((6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 30 2-((6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-((6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-((6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((2-methyl-1H-imidazol-4-yl)methyl)-3H-imidazo[4,5-b]pyridine;
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- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-6-fluoro-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine;
- 5 2-(6-(Diethylamino)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-(Diethylamino)pyridin-3-yl)-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- N,N-Diethyl-5-(1-((tetrahydrofuran-2-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-
- 10 amine;
- (S)-N,N-Diethyl-5-(1-((tetrahydrofuran-2-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- N,N-Diethyl-5-(1-(3-(pyrimidin-5-yl)benzyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 15 2-(6-(Diethylamino)pyridin-3-yl)-N-methyl-1-(3-(pyrimidin-5-yl)benzyl)-1H-benzo[d]imidazole-5-carboxamide;
- (S)-2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine;
- 20 (S)-2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-4-methylmorpholine;
- (S)-2-((4-Fluoro-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine;
- (S)-2-((2-(6-((2S,4S)-2,4-Dimethylazetidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-
- 25 1H-benzo[d]imidazol-1-yl)methyl)morpholine;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1-(((S)-4-methylmorpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-N-methyl-1-(((S)-4-methylmorpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 30 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-ethyl-7-methoxy-1-(((S)-morpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-ethyl-7-methoxy-1-(((S)-4-methylmorpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-1-(((S)-morpholin-2-
- 35 yl)methyl)-1H-benzo[d]imidazol-7-ol;

- (S)-2-((4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine;
- (S)-2-((4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)-4-methylmorpholine;
- 5 (S)-2-((7-Methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl);
- (S)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine;
- (2S,6S)-2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-6-methylmorpholine;
- 10 (2S,6S)-2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-4,6-dimethylmorpholine;;
- 1-(((2S,6S)-4,6-Dimethylmorpholin-2-yl)methyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-N-methyl-1H-benzo[d]imidazole-5-
- 15 carboxamide;
- 1-(((2S,6S)-4,6-Dimethylmorpholin-2-yl)methyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazole-5-carboxamide;
- (S)-2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-fluoro-1H-benzo[d]imidazol-1-yl)methyl)morpholine;
- 20 (S)-2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-fluoro-1H-benzo[d]imidazol-1-yl)methyl)-4-methylmorpholine; and
- (S)-2-((4-Chloro-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine;
- 25 or a pharmaceutically acceptable salt thereof.

The skilled artisan will appreciate that salts, including pharmaceutically acceptable salts, of the compounds according to Formula (Ib) may be prepared. Indeed, in certain embodiments of the invention, salts including pharmaceutically-acceptable salts of the compounds according to Formula (Ib) may be preferred over the respective free or unsalted compound. Accordingly, the invention is further directed to salts, including pharmaceutically-acceptable salts, of the compounds according to Formula (Ib).

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The salts, including pharmaceutically acceptable salts, of the compounds of the invention are readily prepared by those of skill in the art.

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Typically, the salts of the present invention are pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention.

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Representative pharmaceutically acceptable acid addition salts include, but are not limited to, 4-acetamidobenzoate, acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate (besylate), benzoate, bisulfate, bitartrate, butyrate, calcium edetate, camphorate, camphorsulfonate (camsylate), caprate (decanoate), caproate (hexanoate),
 10 caprylate (octanoate), cinnamate, citrate, cyclamate, digluconate, 2,5-dihydroxybenzoate, disuccinate, dodecylsulfate (estolate), edetate (ethylenediaminetetraacetate), estolate (lauryl sulfate), ethane-1,2-disulfonate (edisylate), ethanesulfonate (esylate), formate, fumarate, galactarate (mucate), gentisate (2,5-dihydroxybenzoate), glucoheptonate (gluceptate), gluconate, glucuronate, glutamate, glutarate, glycerophosphate, glycolate,
 15 hexylresorcinate, hippurate, hydrabamine (*N,N'*-di(dehydroabietyl)-ethylenediamine), hydrobromide, hydrochloride, hydroiodide, hydroxynaphthoate, isobutyrate, lactate, lactobionate, laurate, malate, maleate, malonate, mandelate, methanesulfonate (mesylate), methylsulfate, mucate, naphthalene-1,5-disulfonate (napadisylate), naphthalene-2-sulfonate (napsylate), nicotinate, nitrate, oleate, palmitate, *p*-aminobenzenesulfonate, *p*-aminosalicylate, pamoate (embonate), pantothenate, pectinate, persulfate, phenylacetate,
 20 phenylethylbarbiturate, phosphate, polygalacturonate, propionate, *p*-toluenesulfonate (tosylate), pyroglutamate, pyruvate, salicylate, sebacate, stearate, subacetate, succinate, sulfamate, sulfate, tannate, tartrate, teoclate (8-chlorotheophyllinate), thiocyanate, triethiodide, undecanoate, undecylenate, and valerate.

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Representative pharmaceutically acceptable base addition salts include, but are not limited to, aluminium, 2-amino-2-(hydroxymethyl)-1,3-propanediol (TRIS, tromethamine), arginine, benethamine (*N*-benzylphenethylamine), benzathine (*N,N'*-dibenzylethylenediamine), *bis*-(2-hydroxyethyl)amine, bismuth, calcium, chlorprocaine,
 30 choline, clemizole (1-*p* chlorobenzyl-2-pyrrolidine-1'-ylmethylbenzimidazole), cyclohexylamine, dibenzylethylenediamine, diethylamine, diethyltriamine, dimethylamine, dimethylethanolamine, dopamine, ethanolamine, ethylenediamine, L-histidine, iron, isoquinoline, lepidine, lithium, lysine, magnesium, meglumine (*N*-methylglucamine), piperazine, piperidiny, potassium, procaine, quinine, quinoline, sodium, strontium, *t*-butylamine, and zinc.

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The compounds according to Formula Ib may contain one or more asymmetric centers (also referred to as a chiral center) and may, therefore, exist as individual enantiomers, diastereomers, or other stereoisomeric forms, or as mixtures thereof. Chiral centers, such as chiral carbon atoms, may be present in a substituent such as an alkyl group. Where the stereochemistry of a chiral center present in a compound of Formula Ib, or in any chemical structure illustrated herein, if not specified the structure is intended to encompass all individual stereoisomers and all mixtures thereof. Thus, compounds according to Formula Ib containing one or more chiral centers may be used as racemic mixtures, enantiomerically or diastereomerically enriched mixtures, or as enantiomerically or diastereomerically pure individual stereoisomers.

The compounds according to Formula (Ib) and pharmaceutically acceptable salts thereof may contain isotopically-labelled compounds, which are identical to those recited in Formula (Ib) and following, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of such isotopes include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulphur, fluorine, iodine, and chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , ^{123}I and ^{125}I .

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Isotopically-labelled compounds, for example those into which radioactive isotopes such as ^3H or ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritium, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. ^{11}C and ^{18}F isotopes are particularly useful in PET (positron emission tomography), and ^{125}I isotopes are particularly useful in SPECT (single photon emission computerized tomography), both are useful in brain imaging. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds can generally be prepared by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent. Suitably, a deuterated substituent for use herein is methoxy-d3.

The compounds according to Formula (Ib) may also contain double bonds or other centers of geometric asymmetry. Where the stereochemistry of a center of geometric

asymmetry present in Formula (Ib), or in any chemical structure illustrated herein, is not specified, the structure is intended to encompass the trans (E) geometric isomer, the cis (Z) geometric isomer, and all mixtures thereof. Likewise, all tautomeric forms are also included in Formula (Ib) whether such tautomers exist in equilibrium or predominately in one form.

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The compounds of the invention may exist in solid or liquid form. In solid form, compound of the invention 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 the 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').

20 The compounds of the invention may have the ability to crystallize in more than one form, a characteristic, which is known as polymorphism ("polymorphs"). Polymorphism generally can occur as a response to changes in temperature or pressure or both and can also result from variations in the crystallization process. Polymorphs can be distinguished by various physical characteristics known in the art such as x-ray diffraction patterns, solubility and melting point.

The compounds of Formula (Ib) may exist in solvated and unsolvated forms. As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of Formula (Ib) or a salt) and a solvent. Such solvents, for the purpose of the invention, may not interfere with the biological activity of the solute. The skilled artisan will appreciate that pharmaceutically acceptable solvates may be formed for crystalline compounds wherein solvent molecules are incorporated into the crystalline lattice during crystallization. The incorporated solvent molecules may be water molecules or non-aqueous such as ethanol, isopropanol, DMSO, acetic acid, ethanolamine, and ethyl acetate molecules. Crystalline lattice structures incorporated with water molecules are

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typically referred to as “hydrates”. Hydrates include stoichiometric hydrates as well as compositions containing variable amounts of water.

It is also noted that the compounds of Formula (Ib) may form tautomers. ‘Tautomers’ refer to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of π electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. It is understood that all tautomers and mixtures of tautomers of the compounds of the present invention are included within the scope of the compounds of the present invention.

While aspects for each variable have generally been listed above separately for each variable this invention includes those compounds in which several or each aspect in Formula (Ib) is selected from each of the aspects listed above. Therefore, this invention is intended to include all combinations of aspects for each variable.

Definitions

It will be appreciated that the following definitions apply to each of the aforementioned formulae and to all instances of these terms, unless the context dictates otherwise.

“**Alkyl**”, and derivatives thereof, refer to a hydrocarbon chain having the specified number of “carbon atoms”. For example, C₁-C₆ alkyl refers to an alkyl group having from 1 to 6 carbon atoms. Alkyl groups may be saturated or unsaturated, straight or branched. Representative branched alkyl groups have one, two, or three branches. Alkyl includes but is not limited to: methyl, methylene, ethyl, ethylene, propyl (n-propyl and isopropyl), butene, butyl (n-butyl, isobutyl, and t-butyl), pentyl and hexyl.

“**Alkoxy**” refers to an -O-alkyl group wherein “alkyl” is as defined herein. For example, C₁-C₄alkoxy refers to an alkoxy group having from 1 to 4 carbon member atoms. Examples of such groups include but is not limited to: methoxy, ethoxy, propoxy, isopropoxy, butoxy, and t-butoxy.

“**Aryl**” refers to an aromatic hydrocarbon ring systems. Aryl groups are monocyclic, fused-bicyclic, and fused-tricyclic ring systems having a total of five to fourteen ring member atoms, wherein at least one ring system is aromatic and wherein each ring in the system contains 3 to 7 member atoms, such as phenyl, naphthalene and tetrahydronaphthalene. Suitably aryl is phenyl.

“**Cycloalkyl**” refers to a saturated or unsaturated non aromatic hydrocarbon ring having the specified number of member atoms. Cycloalkyl groups are monocyclic ring systems. For example, C₃-C₇ cycloalkyl refers to a cycloalkyl group having from 3 to 7 member atoms. Examples of cycloalkyl as used herein includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclobutenyl, cyclopentenyl and cyclohexenyl. Suitably cycloalkyl is cyclopropyl.

“**Halo**” refers to the halogen radicals fluoro, chloro, bromo, and iodo.

“**Heteroaryl**” refers to a monocyclic aromatic 5 to 8 membered ring containing from 1 to 7 ring member carbon atoms and containing from 1 to 4 ring member heteroatoms, provided that when the number of carbon atoms is 3, the aromatic ring contains at least two heteroatoms. Heteroaryl groups containing more than one heteroatom may contain different heteroatoms. Heteroaryl includes: pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, triazolyl, thiazolyl, isothiazolyl, furanyl, furazanyl, thienyl, triazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, tetrazinyl. Suitably, “heteroaryl” includes: pyrazolyl, oxazolyl, triazolyl, thiazolyl, pyridinyl, and pyrimidinyl.

“**Heterocyclyl**” refers to a saturated or unsaturated non-aromatic ring containing 4 to 12 member atoms, of which 1 to 11 are carbon atoms and from 1 to 6 are heteroatoms. Heterocycloalkyl groups containing more than one heteroatom may contain different heteroatoms. Heterocycloalkyl groups are monocyclic ring systems or a monocyclic ring fused with an aryl ring or to a heteroaryl ring having from 3 to 6 member atoms. In certain embodiments, heterocyclyl is saturated. In other embodiments, heterocyclyl is unsaturated but not aromatic. Heterocyclyl includes pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, pyranal, tetrahydropyranal, dihydropyranal, tetrahydrothienyl, pyrazolidinyl, oxazolidinyl,

oxetanyl, thiazolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, thiamorpholinyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-oxathiolanyl, 1,3-oxathianyl, 1,3-dithianyl, 1,3-oxazolidin-2-one, hexahydro-1H-azepin, 4,5,6,7-tetrahydro-1H-benzimidazol, piperidinyl, 1,2,3,6-tetrahydro-pyridinyl and azetidiny.

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Suitably “**Heterocyclyl**” includes: pyrrolidinyl and morpholinyl.

Suitably “**Heterocyclyl**” includes: dioxanyl, 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine,

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“**Heteroatom**” refers to a nitrogen, sulphur or oxygen atom.

“**Pharmaceutically acceptable**” refers to those compounds, materials, compositions, and dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

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As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the *Journal of the American Chemical Society* or the *Journal of Biological Chemistry*. Standard single-letter or three-letter abbreviations are generally used to designate amino acid residues, which are assumed to be in the L-configuration unless otherwise noted. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Specifically, the following abbreviations may be used in the examples and throughout the specification:

20

25

Ac (acetyl);

Ac₂O (acetic anhydride);

ACN (acetonitrile);

30 AIBN (azobis(isobutyronitrile));

ATP (adenosine triphosphate);

- Bis-pinacolatodiboron (4,4,4',4',5,5,5',5'-Octamethyl-2,2'-bi-1,3,2-dioxaborolane);
- BSA (bovine serum albumin);
- BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl);
- BMS (borane - dimethyl sulphide complex);
- 5 Bn (benzyl);
- Boc (tert-Butoxycarbonyl);
- Boc₂O (di-*tert*-butyl dicarbonate);
- BOP (Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate);
- C18 (refers to 18-carbon alkyl groups on silicon in HPLC stationary phase);
- 10 CH₃CN (acetonitrile);
- Cy (cyclohexyl);
- CAN (ceric ammonium nitrate);
- Cbz (benzyloxycarbonyl);
- CSi (chlorosulfonyl isocyanate);
- 15 DABCO (1,4-Diazabicyclo[2.2.2]octane);
- DAST ((Diethylamino)sulfur trifluoride);
- DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene);
- DCC (Dicyclohexyl Carbodiimide);
- DCE (1,2-dichloroethane);
- 20 DDQ (2,3-Dichloro-5,6-dicyano-1,4-benzoquinone);
- DCM (dichloromethane);
- DIEA (Hünig's base, diisopropylethyl amine, N-ethyl-N-(1-methylethyl)-2-propanamine);
- DIPEA (Hünig's base, diisopropylethyl amine, N-ethyl-N-(1-methylethyl)-2-propanamine);
- 25 DMAP (4-dimethylaminopyridine);
- DME (1,2-dimethoxyethane);
- DMF (*N,N*-dimethylformamide);
- DMSO (dimethylsulfoxide);

- DPPA (diphenyl phosphoryl azide);
- EDC (N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide);
- EDTA (ethylenediaminetetraacetic acid);
- EtOAc (ethyl acetate);
- 5 EtOH (ethanol);
- Et₂O (diethyl ether);
- HEPES (4-(2-hydroxyethyl)-1-piperazine ethane sulfonic acid);
- HATU (O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate);
- HOAt (1-hydroxy-7-azabenzotriazole);
- 10 HOBt (1-hydroxybenzotriazole);
- HOAc (acetic acid);
- HPLC (high pressure liquid chromatography);
- HMDS (hexamethyldisilazide);
- Hunig's Base (N,N-Diisopropylethylamine);
- 15 IPA (isopropyl alcohol);
- Indoline (2,3-dihydro-1H-indole) ;
- KHMDS (potassium hexamethyldisilazide) ;
- LAH (lithium aluminum hydride) ;
- LDA (lithium diisopropylamide) ;
- 20 LHMDS (lithium hexamethyldisilazide)
- MeOH (methanol);
- MTBE (methyl tert-butyl ether);
- mCPBA (m-chloroperbenzoic acid);
- NaHMDS (sodium hexamethyldisilazide);
- 25 NBS (N-bromosuccinimide);
- PE (petroleum ether);
- Pd₂(dba)₃ (Tris(dibenzylideneacetone)dipalladium(0));

- Pd(dppf)Cl₂ ([1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II));
PyBOP (benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate);
PyBrOP (bromotripyrrolidinophosphonium hexafluorophosphate);
RPHPLC (reverse phase high pressure liquid chromatography);
5 RuPhos (2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl);
SFC (supercritical fluid chromatography);
SGC (silica gel chromatography);
T3P® (propane phosphonic acid anhydride);
TEA (triethylamine);
10 TEMPO (2,2,6,6-Tetramethylpiperidine 1-oxyl, free radical);
TFA (trifluoroacetic acid); and
THF (tetrahydrofuran)
- All references to ether are to diethyl ether and brine refers to a saturated aqueous solution
15 of NaCl.

Compound Preparation

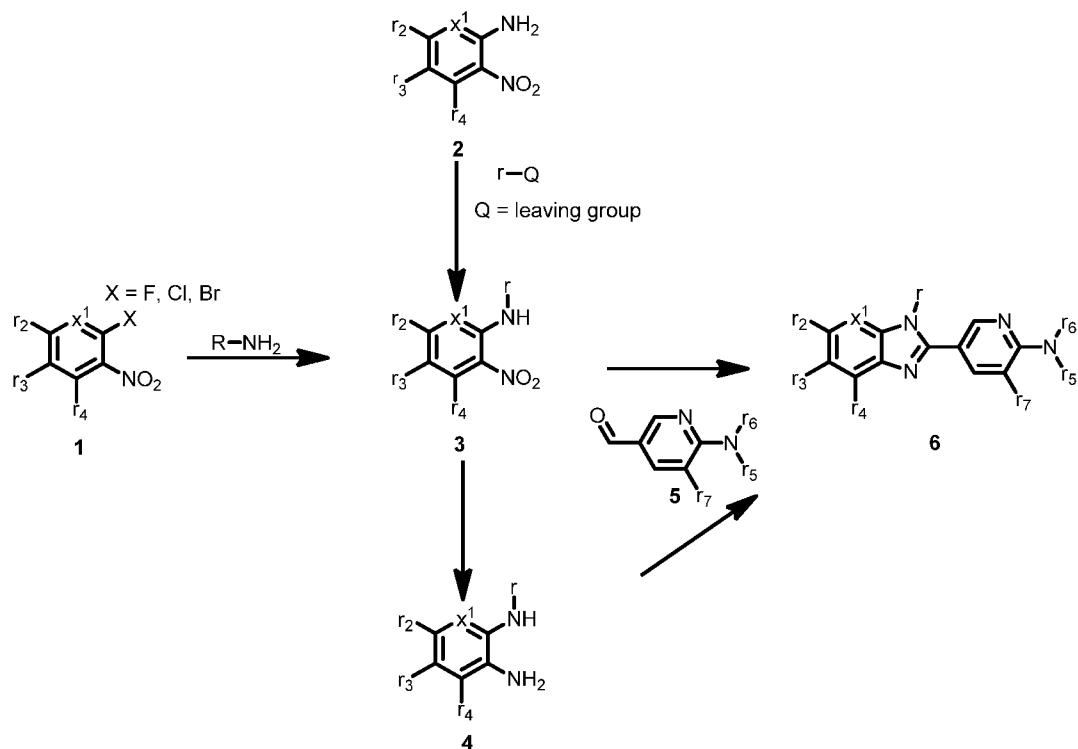
- The compounds according to Formula (Ib) are prepared using conventional organic synthetic methods. A suitable synthetic route is depicted below in the following general
20 reaction schemes. All of the starting materials are commercially available or are readily prepared from commercially available starting materials by those of skill in the art.

- The skilled artisan will appreciate that if a substituent described herein is not compatible with the synthetic methods described herein, the substituent may be protected
25 with a suitable protecting group that is stable to the reaction conditions. The protecting group may be removed at a suitable point in the reaction sequence to provide a desired intermediate or target compound. Suitable protecting groups and the methods for protecting and de-protecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which may be found in T. Greene and P.
30 Wuts, Protecting Groups in Organic Synthesis (4th ed.), John Wiley & Sons, NY (2006). In some instances, a substituent may be specifically selected to be reactive under the reaction

conditions used. Under these circumstances, the reaction conditions convert the selected substituent into another substituent that is either useful as an intermediate compound or is a desired substituent in a target compound.

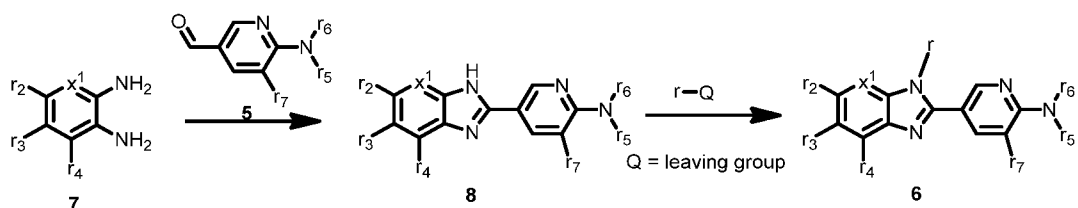
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Scheme 1



As shown in Scheme 1, intermediate **3** may be synthesized using techniques well known in the art. For instance, reaction of intermediate **1**, which is commercially available or readily available by established methods, with a suitable primary amine under reaction conditions well known in the art provides intermediate **3**. Alternatively, intermediate **3** may be prepared from intermediate **2**, which is as well commercially available or readily available by established methods. Alkylation of intermediate **2** with a suitable electrophile under appropriate S_N2 reaction conditions provides intermediate **3**. Final product **6** may be synthesized from intermediate **3** using techniques well known in the art. Reduction of the nitro group to the corresponding aniline provides intermediate **4** which can then be reacted with aldehyde **5** under oxidative conditions to provide the desired product **6**. Alternatively, final product **6** may be prepared directly in one step from nitro intermediate **3** and aldehyde intermediate **5** in the presence of a suitable reagent such as sodium dithionite in a suitable solvent such as EtOH or DMSO mixed with water at elevated temperatures.

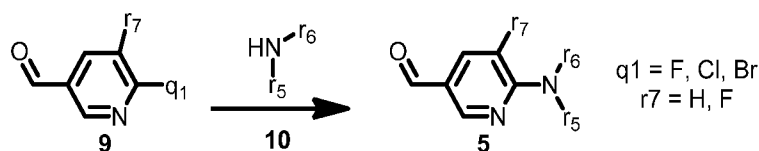
Scheme 2



- 5 An alternative method for preparing final product **6** is illustrated in Scheme 2. Dianilines **7** are commercially available or can be synthesized using techniques well known in the art. Reaction of intermediate **7** with aldehyde **5** using a suitable reagent such as sodium metabisulfite in a suitable solvent such as DMF at a suitable temperature (from about 80 to 100 °C) provides intermediate **8**. Alkylation of intermediate **8** with a suitable electrophile under appropriate S_N2 reaction conditions provides final product **3**.

The skilled artisan will appreciate that if further manipulation of functionality present in the substituents is necessary, it may be performed at different stages during the synthesis of final product **6**. Highlighted in the schemes below are the syntheses of selected aminopyridines **5** used in the examples.

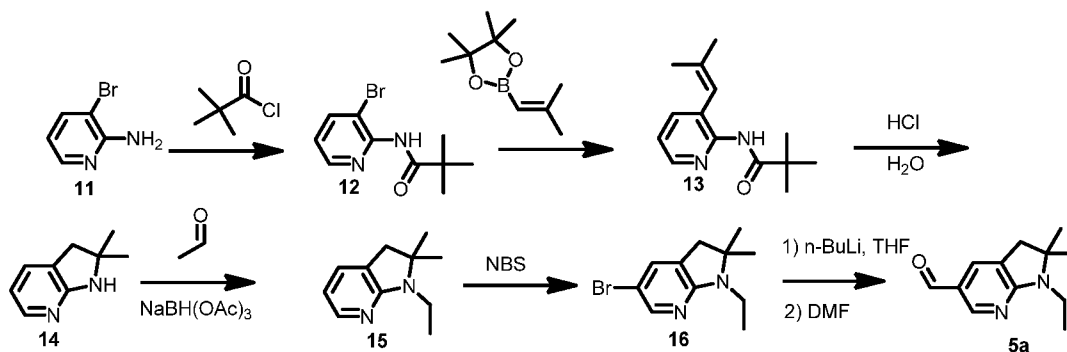
Scheme 3



- 20 Scheme 3 illustrates the synthesis of 5-F and 5-H 6-aminopyridines **5** from intermediate **9** which is commercially available or can be synthesized using techniques well known in the art. Reaction of intermediate **9** with a suitable amine in a suitable solvent such as DMSO and a suitable base such as K₂CO₃ or N,N-diisopropylethylamine at a suitable temperature (typically from about room temperature to about 100 °C) provides intermediate **5**.

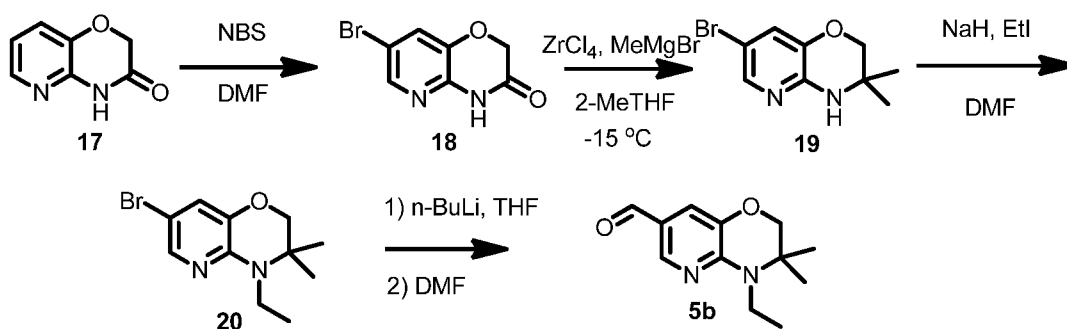
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Scheme 4



Commercially available aminopyridine **5** can be acylated with pivaloyl chloride by techniques well known in the art to afford intermediate **12**. Suzuki coupling of intermediate **12** with a suitable vinylboron species such as the one shown in Scheme 4 under suitable reaction conditions using a palladium catalyst such as $\text{Pd}_2(\text{dba})_3$ in the presence of $(t\text{-Bu})_3\text{PHBF}_4$ and a suitable base such as K_3PO_4 in a suitable solvent such as 1,4-dioxane at an elevated temperature (about 85 to 90 °C) affords intermediate **13**. Reaction of intermediate **13** with aqueous HCl at an elevated temperature (about 110 °C) provides intermediate **14**. Ethylation of intermediate **14** under reductive amination conditions well known in the art using acetaldehyde and a suitable reducing agent such as $\text{NaBH}(\text{OAc})_3$ affords the corresponding ethylated intermediate **15**. Bromination of intermediate **15** with NBS using conditions well known in the art provides bromo intermediate **16** which can then be converted to the desired intermediate **5a**. Reaction of intermediate **16** with $n\text{-BuLi}$ followed by quenching with DMF provides the desired aminopyridine aldehyde **5a**.

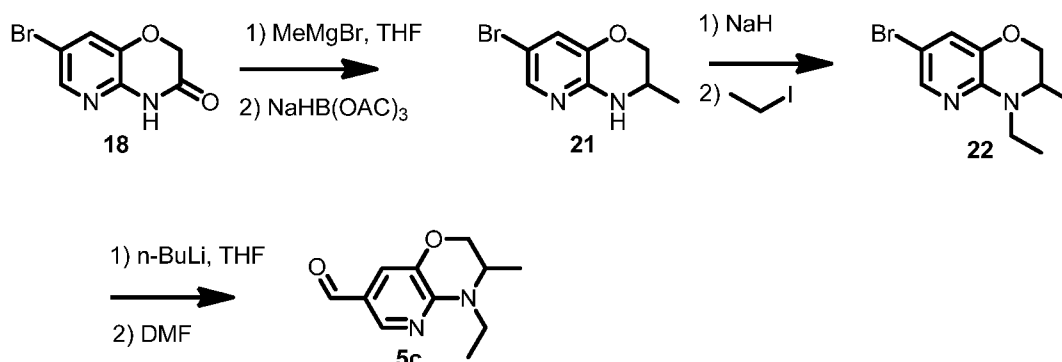
Scheme 5



Intermediate **18** is commercially available or may be prepared from commercially available intermediate **17** by bromination reaction using techniques well known in the art such as brominating agent NBS in a suitable solvent such as DMF. Reaction of intermediate **18** with

methyl magnesium bromide in the presence of ZrCl_4 in a suitable solvent such as 2-MeTHF at a suitable temperature (from about -15°C to room temperature) provides intermediate **19**. Ethylation of intermediate **19** with a suitable ethylating agent such as ethyl iodide using a suitable base such as NaH in a suitable solvent such as DMF affords ethylated intermediate **20**. Conversion of bromo intermediate **20** to desired aldehyde **5b** may be accomplished following a similar protocol to the described previously for the synthesis of **5a**.

Scheme 6

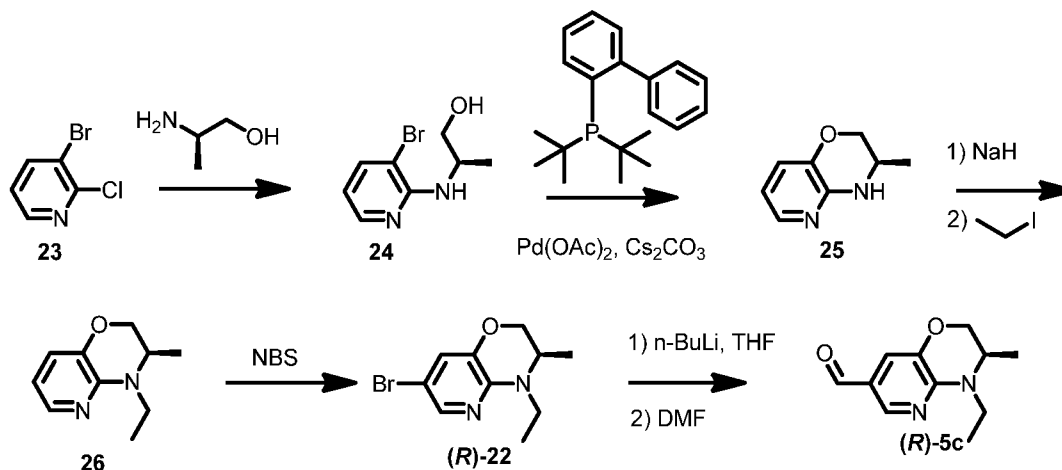


10

Racemic intermediate **5c** was prepared as described in Scheme 6. Treatment of intermediate **18** with MeMgBr followed by NaHB(OAc)₃ provides intermediate **21**. Ethylation of intermediate **21** with a suitable ethylating agent such as ethyl iodide using a suitable base such as NaH in a suitable solvent such as DMF affords ethylated intermediate **22**. Conversion of bromo intermediate **22** to desired racemic aldehyde **5c** may be accomplished following a similar protocol to the described previously for the syntheses of **5a** and **5b**.

15

Scheme 7



Alternatively, optically pure (**R**)-**5c** can be prepared as described in Scheme 7. Intermediate **24** can be readily prepared from commercially available starting materials **23** and (*R*)-2-aminopropan-1-ol by techniques well known in the art. Palladium catalysed cyclization provides intermediate **25** which can then be converted to aldehyde (**R**)-**5c** by the methods previously described.

Methods of Use

The compounds according to Formula Ib and pharmaceutically acceptable salts thereof decrease MYC protein (c-MYC) in cells and inhibit p300/CBP histone acetyltransferase.

These compounds are potentially useful in the treatment of conditions wherein the underlying pathology is attributable to (but not limited to) the dysregulation of Myc, for example, cancer and pre-cancerous syndromes.

The compounds according to Formula Ib and pharmaceutically acceptable salts thereof are inhibitors of p300/CBP histone acetyltransferase activity. These compounds are potentially useful in the treatment of conditions wherein the underlying pathology is attributable to (but not limited to) the dysregulation of p300/CBP histone acetyltransferase activity, for example, cancer, pre-cancerous syndromes, thrombocytopenia, cardiac hypertrophy, diabetes, obesity & nonalcoholic fatty liver disease, HIV, polycystic kidney disease, inflammatory diseases, ankylosing spondylitis, psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease, and multiple sclerosis.

Suitably, the present invention relates to a method for treating breast cancer, including inflammatory breast cancer, ductal carcinoma, and lobular carcinoma.

Suitably the present invention relates to a method for treating colon cancer.

Suitably the present invention relates to a method for treating pancreatic cancer, including insulinomas, adenocarcinoma, ductal adenocarcinoma, adenosquamous carcinoma, acinar cell carcinoma, and glucagonoma.

Suitably the present invention relates to a method for treating skin cancer, including melanoma and metastatic melanoma.

Suitably the present invention relates to a method for treating lung cancer including small cell lung cancer, non-small cell lung cancer, squamous cell carcinoma, adenocarcinoma, and large cell carcinoma.

5

Suitably the present invention relates to a method for treating cancers selected from the group consisting of brain (gliomas), glioblastomas, astrocytomas, glioblastoma multiforme, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, Wilm's tumor, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, head and neck, kidney, liver, melanoma, ovarian, pancreatic, adenocarcinoma, ductal adenocarcinoma, adenosquamous carcinoma, acinar cell carcinoma, glucagonoma, insulinoma, prostate, sarcoma, osteosarcoma, giant cell tumor of bone, thyroid, lymphoblastic T cell leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic neutrophilic leukemia, acute lymphoblastic T cell leukemia, plasmacytoma, Immunoblastic large cell leukemia, mantle cell leukemia, multiple myeloma, megakaryoblastic leukemia, multiple myeloma, acute megakaryocytic leukemia, promyelocytic leukemia, erythroleukemia, malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma, neuroblastoma, bladder cancer, urothelial cancer, vulval cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharyngeal cancer, buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor) and testicular cancer.

25 Suitably the present invention relates to a method for treating pre-cancerous syndromes in a mammal, including a human, wherein the pre-cancerous syndrome is selected from: cervical intraepithelial neoplasia, monoclonal gammopathy of unknown significance (MGUS), myelodysplastic syndrome, aplastic anemia, cervical lesions, skin nevi (pre-melanoma), prostatic intraepithelial (intraductal) neoplasia (PIN), Ductal Carcinoma in situ (DCIS), colon polyps and severe hepatitis or cirrhosis.

Suitably the present invention relates to a method for treating additional diseases associated with inhibition of p300/CBP histone acetyltransferase, for example including: Type 1 diabetes, Alzheimer's disease, stroke, Parkinson disease, Huntington's disease, amyotrophic lateral sclerosis, myocardial infarction, cardiovascular disease, atherosclerosis, and arrhythmias.

c-MYC inhibition has been shown to abrogate angiogenesis which is implicated in the treatment of ocular diseases. *Nature Reviews Drug Discovery* 4, 711-712 (September 2005). Suitably the present invention relates to a method for treating ocular diseases/angiogenesis. In embodiments of methods according to the invention, the disorder of ocular diseases, including vascular leakage can be: edema or neovascularization for any occlusive or inflammatory retinal vascular disease, such as rubeosis irides, neovascular glaucoma, pterygium, vascularized glaucoma filtering blebs, conjunctival papilloma; choroidal neovascularization, such as neovascular age-related macular degeneration (AMD), myopia, prior uveitis, trauma, or idiopathic; macular edema, such as post surgical macular edema, macular edema secondary to uveitis including retinal and/or choroidal inflammation, macular edema secondary to diabetes, and macular edema secondary to retinovascular occlusive disease (i.e. branch and central retinal vein occlusion); retinal neovascularization due to diabetes, such as retinal vein occlusion, uveitis, ocular ischemic syndrome from carotid artery disease, ophthalmic or retinal artery occlusion, sickle cell retinopathy, other ischemic or occlusive neovascular retinopathies, retinopathy of prematurity, or Eale's Disease; and genetic disorders, such as VonHippel-Lindau syndrome.

In some embodiments, the neovascular age-related macular degeneration is wet age-related macular degeneration. In other embodiments, the neovascular age-related macular degeneration is dry age-related macular degeneration and the patient is characterized as being at increased risk of developing wet age-related macular degeneration.

25

The methods of treatment of the invention comprise administering an effective amount of a compound according to Formula Ib or a pharmaceutically acceptable salt, thereof to a patient in need thereof.

The invention also provides a compound according to Formula Ib or a pharmaceutically-acceptable salt thereof for use in medical therapy, and particularly in cancer therapy. Thus, in further aspect, the invention is directed to the use of a compound according to Formula Ib or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a disorder characterized by dysregulation of Myc, such as cancer.

35

The methods of treatment of the invention comprise administering an effective amount of a compound according to Formula (Ib) or a pharmaceutically acceptable salt, thereof to a patient in need thereof.

5 By the term "treating" and derivatives thereof as used herein, in reference to a condition means: (1) to ameliorate the condition or one or more of the biological manifestations of the condition, (2) to interfere with (a) one or more points in the biological cascade that leads to or is responsible for the condition or (b) one or more of the biological manifestations of the condition, (3) to alleviate one or more of the symptoms or effects
10 associated with the condition, or (4) to slow the progression of the condition or one or more of the biological manifestations of the condition.

The term "treating" and derivatives thereof refers to therapeutic therapy. Therapeutic therapy is appropriate to alleviate symptoms or to treat at early signs of
15 disease or its progression.

The skilled artisan will appreciate that "prevention" is not an absolute term. In medicine, "prevention" is understood to refer to the prophylactic administration of a drug to substantially diminish the likelihood or severity of a condition or biological manifestation
20 thereof, or to delay the onset of such condition or biological manifestation thereof.

Prophylactic therapy is appropriate when a subject has, for example, a strong family history of cancer or is otherwise considered at high risk for developing cancer, or when a subject has been exposed to a carcinogen.
25

As used herein, the term "effective amount" and derivatives thereof means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" and derivatives thereof
30 means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

As used herein, "patient" or "subject" refers to a human or other animal. Suitably the patient or subject is a human.

5 The compounds of Formula Ib or pharmaceutically acceptable salts thereof may be administered by any suitable route of administration, including systemic administration. Systemic administration includes oral administration, and parenteral administration. Parenteral administration refers to routes of administration other than enteral, transdermal, or by inhalation, and is typically by injection or infusion. Parenteral administration includes intravenous, intramuscular, intraperitoneal injection, and subcutaneous injection or infusion.

10

The compounds of Formula Ib or pharmaceutically acceptable salts thereof may be administered once or according to a dosing regimen wherein a number of doses are administered at varying intervals of time for a given period of time. For example, doses may be administered one, two, three, or four times per day. Doses may be administered until the desired therapeutic effect is achieved or indefinitely to maintain the desired therapeutic effect. Suitable dosing regimens for a compound of the invention depend on the pharmacokinetic properties of that compound, such as absorption, distribution, and half-life, which can be determined by the skilled artisan. In addition, suitable dosing regimens, including the duration such regimens are administered, for a compound of the invention depend on the condition being treated, the severity of the condition being treated, the age and physical condition of the patient being treated, the medical history of the patient to be treated, the nature of concurrent therapy, the desired therapeutic effect, and like factors within the knowledge and expertise of the skilled artisan. It will be further understood by such skilled artisans that suitable dosing regimens may require adjustment given an individual patient's response to the dosing regimen or over time as individual patient needs change.

Typical daily dosages may vary depending upon the particular route of administration chosen. Typical dosages for oral administration range from 1 mg to 1000 mg per person per dose. Preferred dosages are 1 – 500 mg once daily or BID per person.

35 Additionally, the compounds of Formula Ib or pharmaceutically-acceptable salts thereof may be administered as prodrugs. As used herein, a "prodrug" of a compound of the invention is a functional derivative of the compound which, upon administration to a patient, eventually liberates the compound of the invention in vivo. Administration of a

compound of the invention as a prodrug may enable the skilled artisan to do one or more of the following: (a) modify the onset of the compound in vivo; (b) modify the duration of action of the compound in vivo; (c) modify the transportation or distribution of the compound in vivo; (d) modify the solubility of the compound in vivo; and (e) overcome or overcome a side effect or other difficulty encountered with the compound. Where a -COOH or -OH group is present, pharmaceutically acceptable esters can be employed, for example methyl, ethyl, and the like for -COOH, and acetate maleate and the like for -OH, and those esters known in the art for modifying solubility or hydrolysis characteristics.

10 The compounds of Formula (Ib) and pharmaceutically acceptable salts thereof may be co-administered with at least one other active agent known to be useful in the treatment of cancer or pre-cancerous syndromes.

15 By the term "co-administration" as used herein is meant either simultaneous administration or any manner of separate sequential administration of a c-MYC inhibiting compound, as described herein, and a further active agent or agents, known to be useful in the treatment of cancer, including chemotherapy and radiation treatment. The term further active agent or agents, as used herein, includes any compound or therapeutic agent known to or that demonstrates advantageous properties when administered to a patient in need of treatment for cancer. Preferably, if the administration is not simultaneous, the compounds are administered in a close time proximity to each other. Furthermore, it does not matter if the compounds are administered in the same dosage form, e.g. one compound may be administered by injection and another compound may be administered orally.

25 Examples of a further active ingredient or ingredients (anti-neoplastic agent) for use in combination or co-administered with the presently invented combinations are indicated below. This list is non-limiting. Additional anti-neoplastic agents are contemplated for use with the presently invented compounds.

30 Typically, any anti-neoplastic agent that has activity versus a susceptible tumor being treated may be co-administered in the treatment of cancer in the present invention. Examples of such agents can be found in Cancer Principles and Practice of Oncology by V.T. Devita and S. Hellman (editors), 6th edition (February 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Typical anti-neoplastic agents useful in the present invention

include, but are not limited to, anti-microtubule agents such as diterpenoids and vinca alkaloids; platinum coordination complexes; alkylating agents such as nitrogen mustards, oxazaphosphorines, alkylsulfonates, nitrosoureas, and triazenes; antibiotic agents such as anthracyclins, actinomycins and bleomycins; topoisomerase II inhibitors such as
5 epipodophyllotoxins; antimetabolites such as purine and pyrimidine analogues and anti-folate compounds; topoisomerase I inhibitors such as camptothecins; hormones and hormonal analogues; signal transduction pathway inhibitors; non-receptor tyrosine kinase angiogenesis inhibitors; immunotherapeutic agents; proapoptotic agents; cell cycle signaling inhibitors; proteasome inhibitors; and inhibitors of cancer metabolism.

10 Examples of a further active ingredient or ingredients (anti-neoplastic agent) for use in combination or co-administered with the presently invented compounds are chemotherapeutic agents.

15 Anti-microtubule or anti-mitotic agents are phase specific agents active against the microtubules of tumor cells during M or the mitosis phase of the cell cycle. Examples of anti-microtubule agents include, but are not limited to, diterpenoids and vinca alkaloids.

20 Diterpenoids, which are derived from natural sources, are phase specific anti-cancer agents that operate at the G₂/M phases of the cell cycle. It is believed that the diterpenoids stabilize the β -tubulin subunit of the microtubules, by binding with this protein. Disassembly of the protein appears then to be inhibited with mitosis being arrested and cell death following. Examples of diterpenoids include, but are not limited to, paclitaxel and its analog docetaxel.

25 Paclitaxel, 5 β ,20-epoxy-1,2 α ,4,7 β ,10 β ,13 α -hexa-hydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine; is a natural diterpene product isolated from the Pacific yew tree *Taxus brevifolia* and is commercially available as an injectable solution TAXOL®. It is a member of the taxane family of terpenes. It was first isolated in 1971 by Wani et al. J. Am. Chem. Soc., 93:2325. 1971), who
30 characterized its structure by chemical and X-ray crystallographic methods. One mechanism for its activity relates to paclitaxel's capacity to bind tubulin, thereby inhibiting cancer cell growth. Schiff et al., Proc. Natl. Acad. Sci. USA, 77:1561-1565 (1980); Schiff et al., Nature, 277:665-667 (1979); Kumar, J. Biol. Chem, 256: 10435-10441 (1981). For a review of synthesis and anticancer activity of some paclitaxel derivatives see: D. G. I.
35 Kingston et al., Studies in Organic Chemistry vol. 26, entitled "New trends in Natural

Products Chemistry 1986", Attaur-Rahman, P.W. Le Quesne, Eds. (Elsevier, Amsterdam, 1986) pp 219-235.

Paclitaxel has been approved for clinical use in the treatment of refractory ovarian
5 cancer in the United States (Markman et al., Yale Journal of Biology and Medicine, 64:583,
1991; McGuire et al., Ann. Intern. Med., 111:273,1989) and for the treatment of breast
cancer (Holmes et al., J. Nat. Cancer Inst., 83:1797,1991.) It is a potential candidate for
treatment of neoplasms in the skin (Einzig et. al., Proc. Am. Soc. Clin. Oncol., 20:46) and
head and neck carcinomas (Forastire et. al., Sem. Oncol., 20:56, 1990). The compound
10 also shows potential for the treatment of polycystic kidney disease (Woo et. al., Nature,
368:750. 1994), lung cancer and malaria. Treatment of patients with paclitaxel results in
bone marrow suppression (multiple cell lineages, Ignoff, R.J. et. al, Cancer Chemotherapy
Pocket Guide, 1998) related to the duration of dosing above a threshold concentration
(50nM) (Kearns, C.M. et. al., Seminars in Oncology, 3(6) p.16-23, 1995).

15

Docetaxel, (2R,3S)- N-carboxy-3-phenylisoserine,N-*tert*-butyl ester, 13-ester with
5 β -20-epoxy-1,2 α ,4,7 β ,10 β ,13 α -hexahydroxytax-11-en-9-one 4-acetate 2-benzoate,
trihydrate; is commercially available as an injectable solution as TAXOTERE®. Docetaxel
is indicated for the treatment of breast cancer. Docetaxel is a semisynthetic derivative of
20 paclitaxel *q.v.*, prepared using a natural precursor, 10-deacetyl-baccatin III, extracted from
the needle of the European Yew tree. The dose limiting toxicity of docetaxel is neutropenia.

Vinca alkaloids are phase specific anti-neoplastic agents derived from the periwinkle
plant. Vinca alkaloids act at the M phase (mitosis) of the cell cycle by binding specifically
25 to tubulin. Consequently, the bound tubulin molecule is unable to polymerize into
microtubules. Mitosis is believed to be arrested in metaphase with cell death following.
Examples of vinca alkaloids include, but are not limited to, vinblastine, vincristine, and
vinorelbine.

30 Vinblastine, vincalukoblastine sulfate, is commercially available as VELBAN® as
an injectable solution. Although, it has possible indication as a second line therapy of
various solid tumors, it is primarily indicated in the treatment of testicular cancer and various
lymphomas including Hodgkin's Disease; and lymphocytic and histiocytic lymphomas.
Myelosuppression is the dose limiting side effect of vinblastine.

35

Vincristine, vincaleukoblastine, 22-oxo-, sulfate, is commercially available as ONCOVIN® as an injectable solution. Vincristine is indicated for the treatment of acute leukemias and has also found use in treatment regimens for Hodgkin's and non-Hodgkin's malignant lymphomas. Alopecia and neurologic effects are the most common side effect of vincristine and to a lesser extent myelosuppression and gastrointestinal mucositis effects occur.

Vinorelbine, 3',4'-didehydro -4'-deoxy-C'-norvincaleukoblastine [R-(R*,R*)-2,3-dihydroxybutanedioate (1:2)(salt)], commercially available as an injectable solution of vinorelbine tartrate (NAVELBINE®), is a semisynthetic vinca alkaloid. Vinorelbine is indicated as a single agent or in combination with other chemotherapeutic agents, such as cisplatin, in the treatment of various solid tumors, particularly non-small cell lung, advanced breast, and hormone refractory prostate cancers. Myelosuppression is the most common dose limiting side effect of vinorelbine.

Platinum coordination complexes are non-phase specific anti-cancer agents, which are interactive with DNA. The platinum complexes enter tumor cells, undergo a quaternization and form intra- and interstrand crosslinks with DNA causing adverse biological effects to the tumor. Examples of platinum coordination complexes include, but are not limited to, cisplatin and carboplatin.

Cisplatin, cis-diamminedichloroplatinum, is commercially available as PLATINOL® as an injectable solution. Cisplatin is primarily indicated in the treatment of metastatic testicular and ovarian cancer and advanced bladder cancer. The primary dose limiting side effects of cisplatin are nephrotoxicity, which may be controlled by hydration and diuresis, and ototoxicity.

Carboplatin, platinum, diammine [1,1-cyclobutane-dicarboxylate(2-)-O,O'], is commercially available as PARAPLATIN® as an injectable solution. Carboplatin is primarily indicated in the first and second line treatment of advanced ovarian carcinoma. Bone marrow suppression is the dose limiting toxicity of carboplatin.

Alkylating agents are non-phase anti-cancer specific agents and strong electrophiles. Typically, alkylating agents form covalent linkages, by alkylation, to DNA through nucleophilic moieties of the DNA molecule such as phosphate, amino, sulfhydryl,

hydroxyl, carboxyl, and imidazole groups. Such alkylation disrupts nucleic acid function leading to cell death. Examples of alkylating agents include, but are not limited to, nitrogen mustards such as cyclophosphamide, melphalan, and chlorambucil; alkyl sulfonates such as busulfan; nitrosoureas such as carmustine; and triazenes such as dacarbazine.

5

Cyclophosphamide, 2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate, is commercially available as an injectable solution or tablets as CYTOXAN®. Cyclophosphamide is indicated as a single agent or in combination with other chemotherapeutic agents, in the treatment of malignant lymphomas, multiple myeloma, and leukemias. Alopecia, nausea, vomiting and leukopenia are the most common dose limiting side effects of cyclophosphamide.

10

Melphalan, 4-[bis(2-chloroethyl)amino]-L-phenylalanine, is commercially available as an injectable solution or tablets as ALKERAN®. Melphalan is indicated for the palliative treatment of multiple myeloma and non-resectable epithelial carcinoma of the ovary. Bone marrow suppression is the most common dose limiting side effect of melphalan.

15

Chlorambucil, 4-[bis(2-chloroethyl)amino]benzenebutanoic acid, is commercially available as LEUKERAN® tablets. Chlorambucil is indicated for the palliative treatment of chronic lymphatic leukemia, and malignant lymphomas such as lymphosarcoma, giant follicular lymphoma, and Hodgkin's disease. Bone marrow suppression is the most common dose limiting side effect of chlorambucil.

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Busulfan, 1,4-butanediol dimethanesulfonate, is commercially available as MYLERAN® TABLETS. Busulfan is indicated for the palliative treatment of chronic myelogenous leukemia. Bone marrow suppression is the most common dose limiting side effects of busulfan.

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Carmustine, 1,3-[bis(2-chloroethyl)-1-nitrosourea, is commercially available as single vials of lyophilized material as BiCNU®. Carmustine is indicated for the palliative treatment as a single agent or in combination with other agents for brain tumors, multiple myeloma, Hodgkin's disease, and non-Hodgkin's lymphomas. Delayed myelosuppression is the most common dose limiting side effects of carmustine.

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Dacarbazine, 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide, is commercially available as single vials of material as DTIC-Dome®. Dacarbazine is indicated for the treatment of metastatic malignant melanoma and in combination with other agents for the second line treatment of Hodgkin's Disease. Nausea, vomiting, and anorexia are the most common dose limiting side effects of dacarbazine.

Antibiotic anti-neoplastics are non-phase specific agents, which bind or intercalate with DNA. Typically, such action results in stable DNA complexes or strand breakage, which disrupts ordinary function of the nucleic acids, leading to cell death. Examples of antibiotic anti-neoplastic agents include, but are not limited to, actinomycins such as dactinomycin, anthracyclins such as daunorubicin and doxorubicin; and bleomycins.

Dactinomycin, also known as Actinomycin D, is commercially available in injectable form as COSMEGEN®. Dactinomycin is indicated for the treatment of Wilm's tumor and rhabdomyosarcoma. Nausea, vomiting, and anorexia are the most common dose limiting side effects of dactinomycin.

Daunorubicin, (8S-cis-)-8-acetyl-10-[(3-amino-2,3,6-trideoxy- α -L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12 naphthacenedione hydrochloride, is commercially available as a liposomal injectable form as DAUNOXOME® or as an injectable as CERUBIDINE®. Daunorubicin is indicated for remission induction in the treatment of acute nonlymphocytic leukemia and advanced HIV associated Kaposi's sarcoma. Myelosuppression is the most common dose limiting side effect of daunorubicin.

Doxorubicin, (8S, 10S)-10-[(3-amino-2,3,6-trideoxy- α -L-lyxo-hexopyranosyl)oxy]-8-glycoloyl, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12 naphthacenedione hydrochloride, is commercially available as an injectable form as RUBEX® or ADRIAMYCIN RDF®. Doxorubicin is primarily indicated for the treatment of acute lymphoblastic leukemia and acute myeloblastic leukemia, but is also a useful component in the treatment of some solid tumors and lymphomas. Myelosuppression is the most common dose limiting side effect of doxorubicin.

Bleomycin, a mixture of cytotoxic glycopeptide antibiotics isolated from a strain of *Streptomyces verticillus*, is commercially available as BLENOXANE®. Bleomycin is

indicated as a palliative treatment, as a single agent or in combination with other agents, of squamous cell carcinoma, lymphomas, and testicular carcinomas. Pulmonary and cutaneous toxicities are the most common dose limiting side effects of bleomycin.

5 Topoisomerase II inhibitors include, but are not limited to, epipodophyllotoxins.

Epipodophyllotoxins are phase specific anti-neoplastic agents derived from the mandrake plant. Epipodophyllotoxins typically affect cells in the S and G₂ phases of the cell cycle by forming a ternary complex with topoisomerase II and DNA causing DNA strand
10 breaks. The strand breaks accumulate and cell death follows. Examples of epipodophyllotoxins include, but are not limited to, etoposide and teniposide.

Etoposide, 4'-demethyl-epipodophyllotoxin 9[4,6-O-(R)-ethylidene-β-D-glucopyranoside], is commercially available as an injectable solution or capsules as
15 VePESID® and is commonly known as VP-16. Etoposide is indicated as a single agent or in combination with other chemotherapy agents in the treatment of testicular and non-small cell lung cancers. Myelosuppression is the most common side effect of etoposide. The incidence of leucopenia tends to be more severe than thrombocytopenia.

20 Teniposide, 4'-demethyl-epipodophyllotoxin 9[4,6-O-(R)-thenylidene-β-D-glucopyranoside], is commercially available as an injectable solution as VUMON® and is commonly known as VM-26. Teniposide is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia in children. Myelosuppression is the most common dose limiting side effect of teniposide. Teniposide
25 can induce both leucopenia and thrombocytopenia.

Antimetabolite neoplastic agents are phase specific anti-neoplastic agents that act at S phase (DNA synthesis) of the cell cycle by inhibiting DNA synthesis or by inhibiting purine or pyrimidine base synthesis and thereby limiting DNA synthesis. Consequently, S
30 phase does not proceed and cell death follows. Examples of antimetabolite anti-neoplastic agents include, but are not limited to, fluorouracil, methotrexate, cytarabine, mecaptopurine, thioguanine, and gemcitabine.

5-fluorouracil, 5-fluoro-2,4- (1H,3H) pyrimidinedione, is commercially available as
35 fluorouracil. Administration of 5-fluorouracil leads to inhibition of thymidylate synthesis and

is also incorporated into both RNA and DNA. The result typically is cell death. 5-fluorouracil is indicated as a single agent or in combination with other chemotherapy agents in the treatment of carcinomas of the breast, colon, rectum, stomach and pancreas. Myelosuppression and mucositis are dose limiting side effects of 5-fluorouracil. Other
5 fluoropyrimidine analogs include 5-fluoro deoxyuridine (floxuridine) and 5-fluorodeoxyuridine monophosphate.

Cytarabine, 4-amino-1- β -D-arabinofuranosyl-2 (1H)-pyrimidinone, is commercially available as CYTOSAR-U® and is commonly known as Ara-C. It is believed that cytarabine
10 exhibits cell phase specificity at S-phase by inhibiting DNA chain elongation by terminal incorporation of cytarabine into the growing DNA chain. Cytarabine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. Other cytidine analogs include 5-azacytidine and 2',2'-difluorodeoxycytidine (gemcitabine). Cytarabine induces leucopenia, thrombocytopenia, and mucositis.

15 Mercaptopurine, 1,7-dihydro-6H-purine-6-thione monohydrate, is commercially available as PURINETHOL®. Mercaptopurine exhibits cell phase specificity at S-phase by inhibiting DNA synthesis by an as of yet unspecified mechanism. Mercaptopurine is indicated as a single agent or in combination with other chemotherapy agents in the
20 treatment of acute leukemia. Myelosuppression and gastrointestinal mucositis are expected side effects of mercaptopurine at high doses. A useful mercaptopurine analog is azathioprine.

Thioguanine, 2-amino-1,7-dihydro-6H-purine-6-thione, is commercially available as
25 TABLOID®. Thioguanine exhibits cell phase specificity at S-phase by inhibiting DNA synthesis by an as of yet unspecified mechanism. Thioguanine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. Myelosuppression, including leucopenia, thrombocytopenia, and anemia, is the most common dose limiting side effect of thioguanine administration. However, gastrointestinal
30 side effects occur and can be dose limiting. Other purine analogs include pentostatin, erythrohydroxynonyladenine, fludarabine phosphate, and cladribine.

Gemcitabine, 2'-deoxy-2', 2'-difluorocytidine monohydrochloride (β -isomer), is commercially available as GEMZAR®. Gemcitabine exhibits cell phase specificity at S-
35 phase and by blocking progression of cells through the G1/S boundary. Gemcitabine is

indicated in combination with cisplatin in the treatment of locally advanced non-small cell lung cancer and alone in the treatment of locally advanced pancreatic cancer. Myelosuppression, including leucopenia, thrombocytopenia, and anemia, is the most common dose limiting side effect of gemcitabine administration.

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Methotrexate, N-[4[[[(2,4-diamino-6-pteridiny) methyl]methylamino] benzoyl]-L-glutamic acid, is commercially available as methotrexate sodium. Methotrexate exhibits cell phase effects specifically at S-phase by inhibiting DNA synthesis, repair and/or replication through the inhibition of dihydrofolate reductase which is required for synthesis of purine nucleotides and thymidylate. Methotrexate is indicated as a single agent or in combination with other chemotherapy agents in the treatment of choriocarcinoma, meningeal leukemia, non-Hodgkin's lymphoma, and carcinomas of the breast, head, neck, ovary and bladder. Myelosuppression (leucopenia, thrombocytopenia, and anemia) and mucositis are expected side effect of methotrexate administration.

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Camptothecins, including, camptothecin and camptothecin derivatives are available or under development as Topoisomerase I inhibitors. Camptothecins cytotoxic activity is believed to be related to its Topoisomerase I inhibitory activity. Examples of camptothecins include, but are not limited to irinotecan, topotecan, and the various optical forms of 7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20-camptothecin described below.

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Irinotecan HCl, (4S)-4,11-diethyl-4-hydroxy-9-[(4-piperidinopiperidino) carbonyloxy]-1H-pyrano[3',4',6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione hydrochloride, is commercially available as the injectable solution CAMPTOSAR®.

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Irinotecan is a derivative of camptothecin which binds, along with its active metabolite SN-38, to the topoisomerase I – DNA complex. It is believed that cytotoxicity occurs as a result of irreparable double strand breaks caused by interaction of the topoisomerase I : DNA : irinotecan or SN-38 ternary complex with replication enzymes. Irinotecan is indicated for treatment of metastatic cancer of the colon or rectum. The dose limiting side effects of irinotecan HCl are myelosuppression, including neutropenia, and GI effects, including diarrhea.

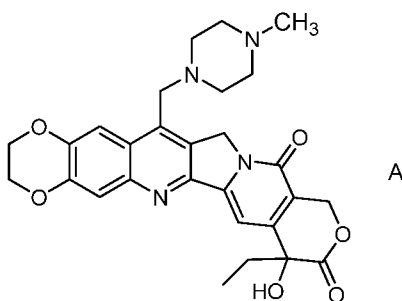
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Topotecan HCl, (S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3',4',6,7]indolizino[1,2-b]quinoline-3,14-(4H,12H)-dione monohydrochloride, is commercially available as the injectable solution HYCAMTIN®. Topotecan is a derivative

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of camptothecin which binds to the topoisomerase I – DNA complex and prevents religation of single strand breaks caused by Topoisomerase I in response to torsional strain of the DNA molecule. Topotecan is indicated for second line treatment of metastatic carcinoma of the ovary and small cell lung cancer. The dose limiting side effect of topotecan HCl is myelosuppression, primarily neutropenia.

Also of interest, is the camptothecin derivative of Formula A following, including the racemic mixture (R,S) form as well as the R and S enantiomers:



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known by the chemical name “7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20(R,S)-camptothecin (racemic mixture) or “7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20(R)-camptothecin (R enantiomer) or “7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20(S)-camptothecin (S enantiomer). Such compound as well as related compounds are described, including methods of making, in U.S. Patent Nos. 6,063,923; 5,342,947; 5,559,235; 5,491,237 and pending U.S. patent Application No. 08/977,217 filed November 24, 1997.

Hormones and hormonal analogues are useful compounds for treating cancers in which there is a relationship between the hormone(s) and growth and/or lack of growth of the cancer. Examples of hormones and hormonal analogues useful in cancer treatment include, but are not limited to, adrenocorticosteroids such as prednisone and prednisolone which are useful in the treatment of malignant lymphoma and acute leukemia in children; aminoglutethimide and other aromatase inhibitors such as anastrozole, letrozole, vorazole, and exemestane useful in the treatment of adrenocortical carcinoma and hormone dependent breast carcinoma containing estrogen receptors; progestins such as megestrol acetate useful in the treatment of hormone dependent breast cancer and endometrial carcinoma; estrogens, androgens, and anti-androgens such as flutamide, nilutamide, bicalutamide, cyproterone acetate and 5 α -reductases such as finasteride and dutasteride,

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useful in the treatment of prostatic carcinoma and benign prostatic hypertrophy; anti-estrogens such as tamoxifen, toremifene, raloxifene, droloxifene, idoxifene, as well as selective estrogen receptor modulators (SERMS) such those described in U.S. Patent Nos. 5,681,835, 5,877,219, and 6,207,716, useful in the treatment of hormone dependent breast carcinoma and other susceptible cancers; and gonadotropin-releasing hormone (GnRH) and analogues thereof which stimulate the release of leutinizing hormone (LH) and/or follicle stimulating hormone (FSH) for the treatment prostatic carcinoma, for instance, LHRH agonists and antagagonists such as goserelin acetate and luprolide.

10 Signal transduction pathway inhibitors are those inhibitors, which block or inhibit a chemical process which evokes an intracellular change. As used herein this change is cell proliferation or differentiation. Signal tranduction inhibitors useful in the present invention include inhibitors of receptor tyrosine kinases, non-receptor tyrosine kinases, SH2/SH3 domain blockers, serine/threonine kinases, phosphatidylinositol-3 kinases, myo-inositol
15 signaling, and Ras oncogenes.

Several protein tyrosine kinases catalyse the phosphorylation of specific tyrosyl residues in various proteins involved in the regulation of cell growth. Such protein tyrosine kinases can be broadly classified as receptor or non-receptor kinases.

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Receptor tyrosine kinases are transmembrane proteins having an extracellular ligand binding domain, a transmembrane domain, and a tyrosine kinase domain. Receptor tyrosine kinases are involved in the regulation of cell growth and are generally termed growth factor receptors. Inappropriate or uncontrolled activation of many of these kinases, i.e. aberrant kinase growth factor receptor activity, for example by over-expression or
25 mutation, has been shown to result in uncontrolled cell growth. Accordingly, the aberrant activity of such kinases has been linked to malignant tissue growth. Consequently, inhibitors of such kinases could provide cancer treatment methods. Growth factor receptors include, for example, epidermal growth factor receptor (EGFr), platelet derived growth factor receptor (PDGFr), erbB2, erbB4, vascular endothelial growth factor receptor (VEGFr), tyrosine kinase with immunoglobulin-like and epidermal growth factor homology domains (TIE-2), insulin growth factor -I (IGFI) receptor, macrophage colony stimulating factor (cfms), BTK, ckit, cmet, fibroblast growth factor (FGF) receptors, Trk receptors (TrkA, TrkB, and TrkC), ephrin (eph) receptors, and the RET protooncogene. Several inhibitors of
30 growth receptors are under development and include ligand antagonists, antibodies, tyrosine kinase inhibitors and anti-sense oligonucleotides. Growth factor receptors and

agents that inhibit growth factor receptor function are described, for instance, in Kath, John C., Exp. Opin. Ther. Patents (2000) 10(6):803-818; Shawver et al DDT Vol 2, No. 2 February 1997; and Lofts, F. J. et al, "Growth factor receptors as targets", New Molecular Targets for Cancer Chemotherapy, ed. Workman, Paul and Kerr, David, CRC press 1994, 5 London.

Suitably, the pharmaceutically active compounds of the invention are used in combination with a VEGFR inhibitor, suitably 5-[[4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide, or a pharmaceutically acceptable salt, suitably the monohydrochloride salt thereof, which is disclosed and claimed 10 in International Application No. PCT/US01/49367, having an International filing date of December 19, 2001, International Publication Number WO02/059110 and an International Publication date of August 1, 2002, the entire disclosure of which is hereby incorporated by reference, and which is the compound of Example 69. 5-[[4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide can be prepared as 15 described in International Application No. PCT/US01/49367.

Suitably, 5-[[4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide is in the form of a monohydrochloride salt. This salt form can 20 be prepared by one of skill in the art from the description in International Application No. PCT/US01/49367, having an International filing date of December 19, 2001.

5-[[4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide is sold commercially as the monohydrochloride salt and is 25 known by the generic name pazopanib and the trade name Votrient®.

Pazopanib is implicated in the treatment of cancer and ocular diseases/angiogenesis. Suitably the present invention relates to the treatment of cancer and ocular diseases/angiogenesis, suitably age-related macular degeneration, which 30 method comprises the administration of a compound of Formula (Ib) alone or in combination with pazopanib.

Tyrosine kinases, which are not growth factor receptor kinases are termed non-receptor tyrosine kinases. Non-receptor tyrosine kinases for use in the present invention, 35 which are targets or potential targets of anti-cancer drugs, include cSrc, Lck, Fyn, Yes, Jak, cAbl, FAK (Focal adhesion kinase), Brutons tyrosine kinase, and Bcr-Abl. Such non-

receptor kinases and agents which inhibit non-receptor tyrosine kinase function are described in Sinh, S. and Corey, S.J., (1999) *Journal of Hematotherapy and Stem Cell Research* 8 (5): 465 – 80; and Bolen, J.B., Brugge, J.S., (1997) *Annual review of Immunology*, 15: 371-404.

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SH2/SH3 domain blockers are agents that disrupt SH2 or SH3 domain binding in a variety of enzymes or adaptor proteins including, PI3-K p85 subunit, Src family kinases, adaptor molecules (Shc, Crk, Nck, Grb2) and Ras-GAP. SH2/SH3 domains as targets for anti-cancer drugs are discussed in Smithgall, T.E. (1995), *Journal of Pharmacological and Toxicological Methods*, 34(3) 125-32.

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Inhibitors of Serine/Threonine Kinases including MAP kinase cascade blockers which include blockers of Raf kinases (rafk), Mitogen or Extracellular Regulated Kinase (MEKs), and Extracellular Regulated Kinases (ERKs); and Protein kinase C family member blockers including blockers of PKCs (alpha, beta, gamma, epsilon, mu, lambda, iota, zeta). Ikb kinase family (IKKa, IKKb), PKB family kinases, akt kinase family members, PDK1 and TGF beta receptor kinases. Such Serine/Threonine kinases and inhibitors thereof are described in Yamamoto, T., Taya, S., Kaibuchi, K., (1999), *Journal of Biochemistry*, 126 (5) 799-803; Brodt, P, Samani, A., and Navab, R. (2000), *Biochemical Pharmacology*, 60, 1101-1107; Massague, J., Weis-Garcia, F. (1996) *Cancer Surveys*, 27:41-64; Philip, P.A., and Harris, A.L. (1995), *Cancer Treatment and Research*, 78: 3-27, Lackey, K. et al *Bioorganic and Medicinal Chemistry Letters*, (10), 2000, 223-226; U.S. Patent No. 6,268,391; Pearce, L.R et al. *Nature Reviews Molecular Cell Biology* (2010) 11, 9-22. and Martinez-lacaci, L., et al, *Int. J. Cancer* (2000), 88(1), 44-52.

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Suitably, the pharmaceutically active compounds of the invention are used in combination with a MEK inhibitor. Suitably, N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide, or a pharmaceutically acceptable salt or solvate, suitably the dimethyl sulfoxide solvate, thereof, which is disclosed and claimed in International Application No. PCT/JP2005/011082, having an International filing date of June 10, 2005; International Publication Number WO 2005/121142 and an International Publication date of December 22, 2005, the entire disclosure of which is hereby incorporated by reference. N-{3-[3-cyclopropyl-5-(2-fluoro-4-iodo-phenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro-2H-pyrido[4,3-d]pyrimidin-1-yl]phenyl}acetamide, can be prepared as described in United

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States Patent Publication No. US 2006/0014768, Published January 19, 2006, the entire disclosure of which is hereby incorporated by reference.

Suitably, the pharmaceutically active compounds of the invention are used in
5 combination with a B-Raf inhibitor. Suitably, *N*-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide, or a pharmaceutically acceptable salt thereof, which is disclosed and claimed, in International Application No. PCT/US2009/042682, having an International filing date of May 4, 2009, the entire disclosure of which is hereby incorporated by reference. *N*-{3-[5-(2-Amino-4-
10 pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide can be prepared as described in International Application No. PCT/US2009/042682.

Suitably, the pharmaceutically active compounds of the invention are used in
15 combination with an Akt inhibitor. Suitably, *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide or a pharmaceutically acceptable salt thereof, which is disclosed and claimed in International Application No. PCT/US2008/053269, having an International filing date of February 7, 2008; International Publication Number WO 2008/098104 and an
20 International Publication date of August 14, 2008, the entire disclosure of which is hereby incorporated by reference. *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide is the compound of example 224 and can be prepared as described in International Application No. PCT/US2008/053269.

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Suitably, the pharmaceutically active compounds of the invention are used in combination with an Akt inhibitor. Suitably, *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide or a pharmaceutically acceptable salt thereof, which is disclosed
30 and claimed in International Application No. PCT/US2008/053269, having an International filing date of February 7, 2008; International Publication Number WO 2008/098104 and an International Publication date of August 14, 2008, the entire disclosure of which is hereby incorporated by reference. *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide is the compound of example 96
35 and can be prepared as described in International Application No. PCT/US2008/053269. Suitably, *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-

1*H*-pyrazol-5-yl)-2-thiophenecarboxamide is in the form of a hydrochloride salt. The salt form can be prepared by one of skill in the art from the description in International Application No. PCT/US2010/022323, having an International filing date of January 28, 2010.

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Inhibitors of Phosphatidylinositol-3 Kinase family members including blockers of PI3-kinase, ATM, DNA-PK, and Ku may also be useful in the present invention. Such kinases are discussed in Abraham, R.T. (1996), *Current Opinion in Immunology*. 8 (3) 412-8; Canman, C.E., Lim, D.S. (1998), *Oncogene* 17 (25) 3301-3308; Jackson, S.P. (1997),
10 *International Journal of Biochemistry and Cell Biology*. 29 (7):935-8; and Zhong, H. et al, *Cancer res*, (2000) 60(6), 1541-1545.

Also of interest in the present invention are Myo-inositol signaling inhibitors such as phospholipase C blockers and Myo-inositol analogues. Such signal inhibitors are described
15 in Powis, G., and Kozikowski A., (1994) *New Molecular Targets for Cancer Chemotherapy* ed., Paul Workman and David Kerr, CRC press 1994, London.

Another group of signal transduction pathway inhibitors are inhibitors of Ras Oncogene. Such inhibitors include inhibitors of farnesyltransferase, geranyl-geranyl
20 transferase, and CAAX proteases as well as anti-sense oligonucleotides, ribozymes and immunotherapy. Such inhibitors have been shown to block ras activation in cells containing wild type mutant ras, thereby acting as antiproliferation agents. Ras oncogene inhibition is discussed in Scharovsky, O.G., Rozados, V.R., Gervasoni, S.I. Matar, P. (2000), *Journal of Biomedical Science*. 7(4) 292-8; Ashby, M.N. (1998), *Current Opinion in Lipidology*. 9 (2)
25 99 – 102; and *BioChim. Biophys. Acta*, (1989) 1423(3):19-30.

As mentioned above, antibody antagonists to receptor kinase ligand binding may also serve as signal transduction inhibitors. This group of signal transduction pathway inhibitors includes the use of humanized antibodies to the extracellular ligand binding
30 domain of receptor tyrosine kinases. For example Imclone C225 EGFR specific antibody (see Green, M.C. et al, *Monoclonal Antibody Therapy for Solid Tumors*, *Cancer Treat. Rev.*, (2000), 26(4), 269-286); Herceptin ® erbB2 antibody (see *Tyrosine Kinase Signalling in Breast cancer:erbB Family Receptor Tyrosine Kinases*, *Breast cancer Res.*, 2000, 2(3), 176-183); and 2CB VEGFR2 specific antibody (see Brekken, R.A. et al, *Selective Inhibition*
35 *of VEGFR2 Activity by a monoclonal Anti-VEGF antibody blocks tumor growth in mice*, *Cancer Res.* (2000) 60, 5117-5124).

Non-receptor kinase angiogenesis inhibitors may also be useful in the present invention. Inhibitors of angiogenesis related VEGFR and TIE2 are discussed above in regard to signal transduction inhibitors (both receptors are receptor tyrosine kinases).

5 Angiogenesis in general is linked to erbB2/EGFR signaling since inhibitors of erbB2 and EGFR have been shown to inhibit angiogenesis, primarily VEGF expression. Accordingly, non-receptor tyrosine kinase inhibitors may be used in combination with the compounds of the present invention. For example, anti-VEGF antibodies, which do not recognize VEGFR (the receptor tyrosine kinase), but bind to the ligand; small molecule inhibitors of integrin

10 ($\alpha_v\beta_3$) that will inhibit angiogenesis; endostatin and angiostatin (non-RTK) may also prove useful in combination with the disclosed compounds. (See Bruns CJ et al (2000), Cancer Res., 60: 2926-2935; Schreiber AB, Winkler ME, and Derynck R. (1986), Science, 232: 1250-1253; Yen L et al. (2000), Oncogene 19: 3460-3469).

15 Agents used in immunotherapeutic regimens may also be useful in combination with the compounds of Formula (Ib). There are a number of immunologic strategies to generate an immune response. These strategies are generally in the realm of tumor vaccinations. The efficacy of immunologic approaches may be greatly enhanced through combined inhibition of signaling pathways using a small molecule inhibitor. Discussion of the

20 immunologic/tumor vaccine approach against erbB2/EGFR are found in Reilly RT et al. (2000), Cancer Res. 60: 3569-3576; and Chen Y, Hu D, Eling DJ, Robbins J, and Kipps TJ. (1998), Cancer Res. 58: 1965-1971.

Agents used in proapoptotic regimens (e.g., bcl-2 antisense oligonucleotides) may

25 also be used in the combination of the present invention. Members of the Bcl-2 family of proteins block apoptosis. Upregulation of bcl-2 has therefore been linked to chemoresistance. Studies have shown that the epidermal growth factor (EGF) stimulates anti-apoptotic members of the bcl-2 family (i.e., mcl-1). Therefore, strategies designed to downregulate the expression of bcl-2 in tumors have demonstrated clinical benefit and are

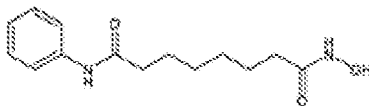
30 now in Phase II/III trials, namely Genta's G3139 bcl-2 antisense oligonucleotide. Such proapoptotic strategies using the antisense oligonucleotide strategy for bcl-2 are discussed in Water JS et al. (2000), J. Clin. Oncol. 18: 1812-1823; and Kitada S et al. (1994), Antisense Res. Dev. 4: 71-79.

35 Cell cycle signalling inhibitors inhibit molecules involved in the control of the cell cycle. A family of protein kinases called cyclin dependent kinases (CDKs) and their

interaction with a family of proteins termed cyclins controls progression through the eukaryotic cell cycle. The coordinate activation and inactivation of different cyclin/CDK complexes is necessary for normal progression through the cell cycle. Several inhibitors of cell cycle signalling are under development. For instance, examples of cyclin dependent
 5 kinases, including CDK2, CDK4, and CDK6 and inhibitors for the same are described in, for instance, Rosania et al, *Exp. Opin. Ther. Patents* (2000) 10(2):215-230. Further, p21WAF1/CIP1 has been described as a potent and universal inhibitor of cyclin-dependent kinases (Cdks) (Ball et al., *Progress in Cell Cycle Res.*, 3: 125 (1997)). Compounds that are known to induce expression of p21WAF1/CIP1 have been implicated in the suppression
 10 of cell proliferation and as having tumor suppressing activity (Richon et al., *Proc. Nat Acad. Sci. U.S.A.* 97(18): 10014-10019 (2000)), and are included as cell cycle signaling inhibitors. Histone deacetylase (HDAC) inhibitors are implicated in the transcriptional activation of p21WAF1/CIP1 (Vigushin et al., *Anticancer Drugs*, 13(1): 1-13 (Jan 2002)), and are suitable cell cycle signaling inhibitors for use in combination herein.
 15 Examples of such HDAC inhibitors include:

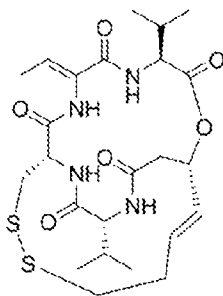
1. Vorinostat, including pharmaceutically acceptable salts thereof. Marks et al., *Nature Biotechnology* 25, 84 to 90 (2007); Stenger, *Community Oncology* 4, 384-386 (2007). Vorinostat has the following chemical structure and name:

20



N-hydroxy-N'-phenyl-octanediamide

2. Romidepsin, including pharmaceutically acceptable salts thereof.
 25 Vinodhkumar et al., *Biomedicine & Pharmacotherapy* 62 (2008) 85-93.
 Romidepsin, has the following chemical structure and name:

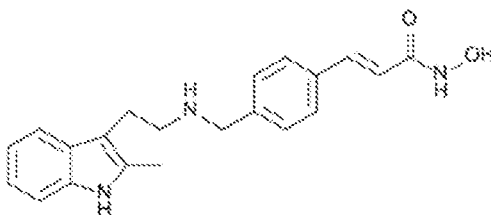


- (1S,4S,7Z,10S,16E,21R)-7-ethylidene-4,21-di(propan-2-yl)-2-oxa-12,13-dithia-5,8,20,23-tetrazabicyclo[8.7.6]tricos-16-ene-3,6,9,19,22-pentone

30

3. Panobinostat, including pharmaceutically acceptable salts thereof. *Drugs of the Future* 32(4): 315-322 (2007).

Panobinostat, has the following chemical structure and name:

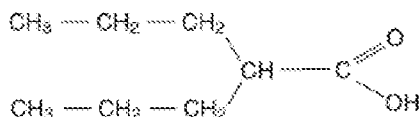


5

(2E)-N-hydroxy-3-[4-({[2-(2-methyl-1H-indol-3-yl)ethyl]amino}methyl)phenyl]acrylamide

4. Valproic acid, including pharmaceutically acceptable salts thereof. Gottlicher, et al., *EMBO J.* 20(24): 6969-6978 (2001).

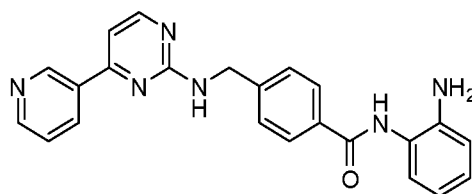
10 Valproic acid, has the following chemical structure and name:



2-propylpentanoic acid

15 5. Mocetinostat (MGCD0103), including pharmaceutically acceptable salts thereof. Balasubramanian et al., *Cancer Letters* 280: 211-221 (2009).

Mocetinostat, has the following chemical structure and name:

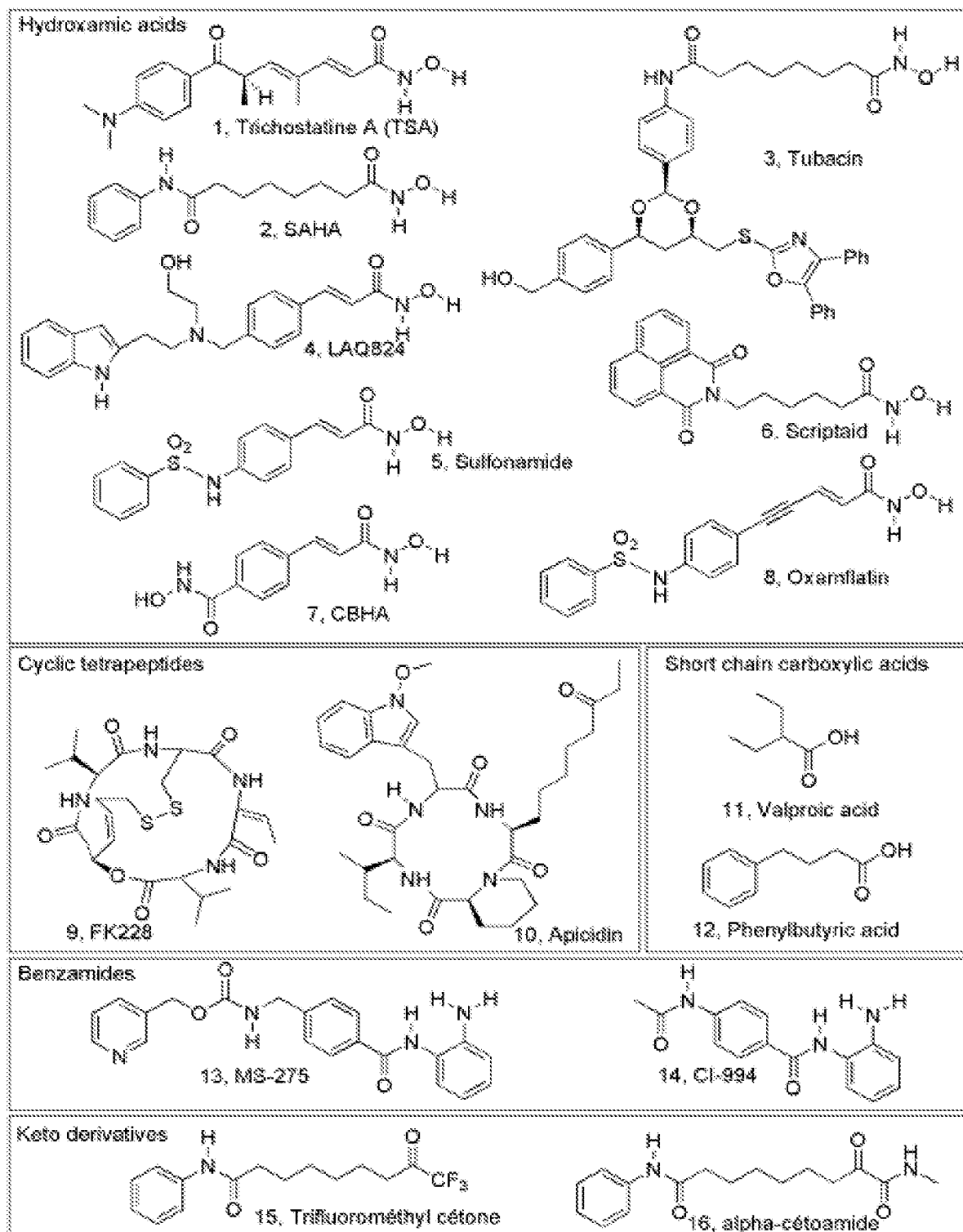


20

N-(2-Aminophenyl)-4-[[[4-pyridin-3-yl]pyrimidin-2-yl]amino]methyl] benzamide

Further examples of such HDAC inhibitors are included in Bertrand *European Journal of Medicinal Chemistry* 45, (2010) 2095-2116, particularly the compounds of table 3 therein as indicated below.

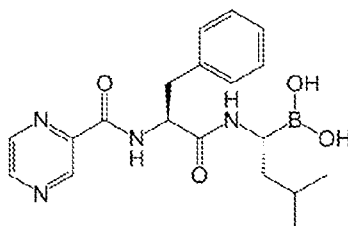
25



Proteasome inhibitors are drugs that block the action of proteasomes, cellular
5 complexes that break down proteins, like the p53 protein. Several proteasome inhibitors

are marketed or are being studied in the treatment of cancer. Suitable proteasome inhibitors for use in combination herein include:

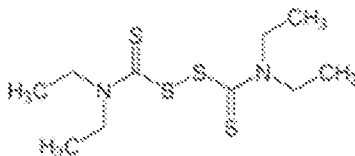
1. Bortezomib (Velcade®), including pharmaceutically acceptable salts thereof.
- 5 Adams J, Kauffman M (2004), *Cancer Invest* **22** (2): 304–11.
Bortezomib has the following chemical structure and name.



[(1*R*)-3-methyl-1-({(2*S*)-3-phenyl-2-[(pyrazin-2-ylcarbonyl)amino]propanoyl}amino)butyl]boronic acid

10

2. Disulfiram, including pharmaceutically acceptable salts thereof.
- Bouma et al. (1998). *J. Antimicrob. Chemother.* **42** (6): 817–20.
Disulfiram has the following chemical structure and name.

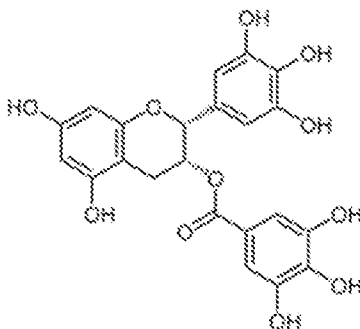


15

1,1',1'',1'''-[disulfanediy]bis(carbonothioylnitrilo)]tetraethane

3. Epigallocatechin gallate (EGCG), including pharmaceutically acceptable salts thereof. Williamson et al., (December 2006), *The Journal of Allergy and Clinical Immunology* **118** (6): 1369–74.

20 Epigallocatechin gallate has the following chemical structure and name.

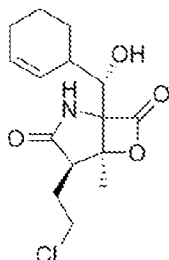


[(2*R*,3*R*)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl]3,4,5-trihydroxybenzoate

4. Salinosporamide A, including pharmaceutically acceptable salts thereof.

Feling et al., (2003), *Angew. Chem. Int. Ed. Engl.* **42** (3): 355–7.

Salinosporamide A has the following chemical structure and name.



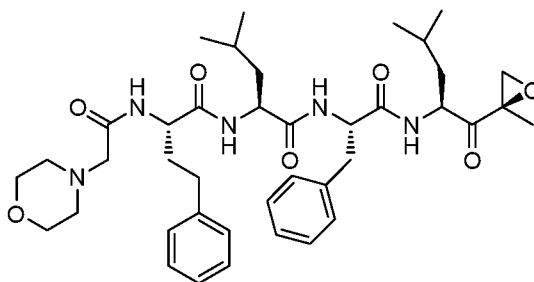
5

(4R,5S)-4-(2-chloroethyl)-1-((1S)-cyclohex-2-enyl(hydroxy)methyl)-5-methyl-6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione

5. Carfilzomib, including pharmaceutically acceptable salts thereof. Kuhn DJ, et al,

10 Blood, 2007, 110:3281-3290.

Carfilzomib has the following chemical structure and name.



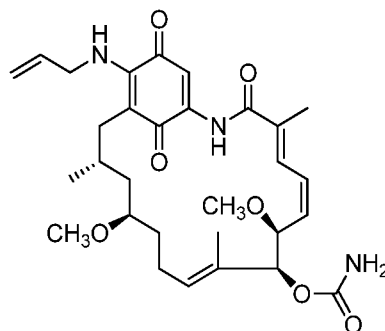
- 15 (S)-4-methyl-N-(((S)-1-(((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)pentanamide

20 The 70 kilodalton heat shock proteins (Hsp70s) and 90 kilodalton heat shock proteins (Hsp90s) are a families of ubiquitously expressed heat shock proteins. Hsp70s and Hsp90s are over expressed certain cancer types. Several Hsp70s and Hsp90s inhibitors are being studied in the treatment of cancer. Suitable Hsp70s and Hsp90s inhibitors for use in combination herein include:

25

1. 17-AAG(Geldanamycin), including pharmaceutically acceptable salts thereof. Jia W et al. Blood. 2003 Sep 1;102(5):1824-32.

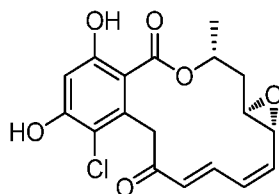
17-AAG(Geldanamycin) has the following chemical structure and name.



17-(Allylamino)-17-demethoxygeldanamycin

2. Radicicol, including pharmaceutically acceptable salts thereof. (Lee et al., Mol Cell Endocrinol. 2002, 188,47-54)

Radicicol has the following chemical structure and name.



(1aR,2Z,4E,14R,15aR)-8-chloro-9,11-dihydroxy-14-methyl-15,15a-dihydro-1aH-benzo[c]oxireno[2,3-k][1]oxacyclotetradecine-6,12(7H,14H)-dione

Inhibitors of cancer metabolism - Many tumor cells show a markedly different metabolism from that of normal tissues. For example, the rate of glycolysis, the metabolic process that converts glucose to pyruvate, is increased, and the pyruvate generated is reduced to lactate, rather than being further oxidized in the mitochondria via the tricarboxylic acid (TCA) cycle. This effect is often seen even under aerobic conditions and is known as the Warburg Effect.

Lactate dehydrogenase A (LDH-A), an isoform of lactate dehydrogenase expressed in muscle cells, plays a pivotal role in tumor cell metabolism by performing the reduction of

pyruvate to lactate, which can then be exported out of the cell. The enzyme has been shown to be upregulated in many tumor types. The alteration of glucose metabolism described in the Warburg effect is critical for growth and proliferation of cancer cells and knocking down LDH-A using RNA-i has been shown to lead to a reduction in cell proliferation and tumor growth in xenograft models.

D. A. Tennant et. al., Nature Reviews, 2010, 267.

P. Leder, et. al., Cancer Cell, 2006, 9, 425.

High levels of fatty acid synthase (FAS) have been found in cancer precursor lesions. Pharmacological inhibition of FAS affects the expression of key oncogenes involved in both cancer development and maintenance.

Alli et al. *Oncogene* (2005) 24, 39–46. doi:10.1038

Inhibitors of cancer metabolism, including inhibitors of LDH-A and inhibitors of fatty acid biosynthesis (or FAS inhibitors), are suitable for use in combination with the compounds of this invention.

In one embodiment, the cancer treatment method of the claimed invention includes the co-administration a compound of Formula (Ib) and/or a pharmaceutically acceptable salt thereof and at least one anti-neoplastic agent, such as one selected from the group consisting of anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, hormones and hormonal analogues, signal transduction pathway inhibitors, non-receptor tyrosine kinase angiogenesis inhibitors, immunotherapeutic agents, proapoptotic agents, cell cycle signaling inhibitors; proteasome inhibitors; and inhibitors of cancer metabolism.

In one embodiment, a compound of Formula (Ib) is used as a chemosensitizer to enhance tumor cell killing.

30

In one embodiment, a compound of Formula (Ib) is used in combination as a chemosensitizer to enhance tumor cell killing.

In one embodiment, a compound of Formula (Ib) is used in combination with a compound that inhibits the activity of protein kinase R (PKR)-like ER kinase, PERK (PERK inhibitor).

35

Suitably, the compounds of Formula (Ib) and pharmaceutically acceptable salts thereof may be co-administered with at least one other active agent known to be inhibitors of PERK kinase (EIF2K3) for treating or lessening the severity of neurodegenerative diseases/injury, such as Alzheimer's disease, spinal cord injury, *traumatic brain injury*, ischemic stroke, stroke, diabetes, Parkinson disease, Huntington's disease, Creutzfeldt-Jakob Disease, and related prion diseases, progressive supranuclear palsy, amyotrophic lateral sclerosis, myocardial infarction, cardiovascular disease, inflammation, fibrosis, chronic and acute diseases of the liver, chronic and acute diseases of the lung, chronic and acute diseases of the kidney, chronic traumatic encephalopathy (CTE), neurodegeneration, dementia, traumatic brain injury, cognitive impairment, atherosclerosis, ocular diseases, arrhythmias, in organ transplantation and in the transportation of organs for transplantation.

"Chemotherapeutic" or "chemotherapeutic agent" is used in accordance with its plain ordinary meaning and refers to a chemical composition or compound having antineoplastic properties or the ability to inhibit the growth or proliferation of cells.

Additionally, the compounds described herein can be co-administered with conventional immunotherapeutic agents including, but not limited to, immunostimulants (e.g., Bacillus Calmette-Guerin (BCG), levamisole, interleukin-2, alpha-interferon, etc.), monoclonal antibodies (e.g., anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (e.g., anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22 monoclonal antibody-pseudomonas exotoxin conjugate, etc.), and radioimmunotherapy (e.g., anti-CD20 monoclonal antibody conjugated to ^{111}In , ^{90}Y , or ^{131}I , etc.).

In a further embodiment, the compounds described herein can be co-administered with conventional radiotherapeutic agents including, but not limited to, radionuclides such as ^{47}Sc , ^{64}Cu , ^{67}Cu , ^{89}Sr , ^{86}Y , ^{87}Y , and ^{212}Bi , optionally conjugated to antibodies directed against tumor antigens.

Additional examples of a further active ingredient or ingredients (anti-neoplastic agent) for use in combination or co-administered with the presently invented ATF4 pathway inhibiting compounds are anti-PD-L1 agents.

Anti-PD-L1 antibodies and methods of making the same are known in the art.

5 Such antibodies to PD-L1 may be polyclonal or monoclonal, and/or recombinant, and/or humanized.

Exemplary PD-L1 antibodies are disclosed in:

US Patent No. 8,217,149; 12/633,339;
US Patent No. 8,383,796; 13/091,936;
10 US Patent No 8,552,154; 13/120,406;
US patent publication No. 20110280877; 13/068337;
US Patent Publication No. 20130309250; 13/892671;
WO2013019906;
WO2013079174;
15 US Application No. 13/511,538 (filed August 7, 2012), which is the
US National Phase of International Application No. PCT/US10/58007 (filed 2010);
and
US Application No. 13/478,511 (filed May 23, 2012).

Additional exemplary antibodies to PD-L1 (also referred to as CD274 or B7-H1) and
20 methods for use are disclosed in US Patent No. 7,943,743; US20130034559,
WO2014055897, US Patent No. 8,168,179; and US Patent No. 7,595,048. PD-L1
antibodies are in development as immuno-modulatory agents for the treatment of cancer.

In one embodiment, the antibody to PD-L1 is an antibody disclosed in US Patent
No. 8,217,149. In another embodiment, the anti-PD-L1 antibody comprises the CDRs of
25 an antibody disclosed in US Patent No. 8,217,149.

In another embodiment, the antibody to PD-L1 is an antibody disclosed in US
Application No. 13/511,538. In another embodiment, the anti-PD-L1 antibody comprises the
CDRs of an antibody disclosed in US Application No. 13/511,538.

In another embodiment, the antibody to PD-L1 is an antibody disclosed in
30 Application No. 13/478,511. In another embodiment, the anti-PD-L1 antibody comprises
the CDRs of an antibody disclosed in US Application No. 13/478,511.

In one embodiment, the anti-PD-L1 antibody is BMS-936559 (MDX-1105). In
another embodiment, the anti-PD-L1 antibody is MPDL3280A (RG7446). In another
embodiment, the anti-PD-L1 antibody is MEDI4736.

35

Additional examples of a further active ingredient or ingredients (anti-neoplastic agent) for use in combination or co-administered with the presently invented ATF4 pathway inhibiting compounds are PD-1 antagonist.

"PD-1 antagonist" means any chemical compound or biological molecule that blocks
5 binding of PD-L1 expressed on a cancer cell to PD-1 expressed on an immune cell (T cell, B cell or NKT cell) and preferably also blocks binding of PD-L2 expressed on a cancer cell to the immune-cell expressed PD-1. Alternative names or synonyms for PD-1 and its ligands include: PDCD1, PD1, CD279 and SLEB2 for PD-1; PDCD1L1, PDL1, B7H1, B7-4, CD274 and B7-H for PD-L1; and PDCD1L2, PDL2, B7-DC, Btdc and CD273
10 for PD-L2. In any embodiments of the aspects or embodiments of the present invention in which a human individual is to be treated, the PD-1 antagonist blocks binding of human PD-L1 to human PD-1, and preferably blocks binding of both human PD-L1 and PD-L2 to human PD-1. Human PD-1 amino acid sequences can be found in NCBI Locus No.: NP_005009. Human PD-L1 and PD-L2 amino acid sequences can be found in NCBI
15 Locus No.: NP_054862 and NP_079515, respectively.

PD-1 antagonists useful in the any of the aspects of the present invention include a monoclonal antibody (mAb), or antigen binding fragment thereof, which specifically binds to PD-1 or PD-L1, and preferably specifically binds to human PD-1 or human PD-L1. The mAb may be a human antibody, a humanized antibody or a chimeric antibody, and
20 may include a human constant region. In some embodiments, the human constant region is selected from the group consisting of IgG1, IgG2, IgG3 and IgG4 constant regions, and in preferred embodiments, the human constant region is an IgG1 or IgG4 constant region. In some embodiments, the antigen binding fragment is selected from the group consisting of Fab, Fab'-SH, F(ab')₂, scFv and Fv fragments.

25 Examples of mAbs that bind to human PD-1, and useful in the various aspects and embodiments of the present invention, are described in US7488802, US7521051, US8008449, US8354509, US8168757, WO2004/004771, WO2004/072286, WO2004/056875, and US2011/0271358.

Specific anti-human PD-1 mAbs useful as the PD-1 antagonist in any of the aspects
30 and embodiments of the present invention include: MK-3475, a humanized IgG4 mAb with the structure described in *WHO Drug Information*, Vol. 27, No. 2, pages 161-162 (2013) and which comprises the heavy and light chain amino acid sequences shown in Figure 6; nivolumab, a human IgG4 mAb with the structure described in *WHO Drug*

Information, Vol. 27, No. 1, pages 68-69 (2013) and which comprises the heavy and light chain amino acid sequences shown in Figure 7; the humanized antibodies h409A11, h409A16 and h409A17, which are described in WO2008/156712, and AMP-514, which is being developed by Medimmune.

5 Other PD-1 antagonists useful in the any of the aspects and embodiments of the present invention include an immunoadhesin that specifically binds to PD-1, and preferably specifically binds to human PD-1, e.g., a fusion protein containing the extracellular or PD-1 binding portion of PD-L1 or PD-L2 fused to a constant region such as an Fc region of an immunoglobulin molecule. Examples of immunoadhesion molecules that specifically
10 bind to PD-1 are described in WO2010/027827 and WO2011/066342. Specific fusion proteins useful as the PD-1 antagonist in the treatment method, medicaments and uses of the present invention include AMP-224 (also known as B7-DCIg), which is a PD-L2-FC fusion protein and binds to human PD-1.

Other examples of mAbs that bind to human PD-L1, and useful in the treatment
15 method, medicaments and uses of the present invention, are described in WO2013/019906, W02010/077634 A1 and US8383796. Specific anti-human PD-L1 mAbs useful as the PD-1 antagonist in the treatment method, medicaments and uses of the present invention include MPDL3280A, BMS-936559, MEDI4736, MSB0010718C.

KEYTRUDA/pembrolizumab is an anti-PD-1 antibody marketed for the treatment of
20 lung cancer by Merck. The amino acid sequence of pembrolizumab and methods of using are disclosed in US Patent No. 8,168,757.

Opdivo/nivolumab is a fully human monoclonal antibody marketed by Bristol Myers Squibb directed against the negative immunoregulatory human cell surface receptor PD-1 (programmed death-1 or programmed cell death-1/PCD-1) with immunopotential activity.
25 Nivolumab binds to and blocks the activation of PD-1, an Ig superfamily transmembrane protein, by its ligands PD-L1 and PD-L2, resulting in the activation of T-cells and cell-mediated immune responses against tumor cells or pathogens. Activated PD-1 negatively regulates T-cell activation and effector function through the suppression of P13k/Akt pathway activation. Other names for nivolumab include: BMS-936558, MDX-
30 1106, and ONO-4538. The amino acid sequence for nivolumab and methods of using and making are disclosed in US Patent No. US 8,008,449.

Additional examples of a further active ingredient or ingredients (anti-neoplastic agent) for use in combination or co-administered with the presently invented ATF4 pathway inhibiting compounds are immuno-modulators.

As used herein "immuno-modulators" refer to any substance including monoclonal
5 antibodies that affects the immune system. The ICOS binding proteins of the present invention can be considered immune-modulators. Immuno-modulators can be used as anti-neoplastic agents for the treatment of cancer. For example, immune-modulators include, but are not limited to, anti-CTLA-4 antibodies such as ipilimumab (YERVOY) and anti-PD-1 antibodies (Opdivo/nivolumab and Keytruda/pembrolizumab). Other immuno-modulators
10 include, but are not limited to, OX-40 antibodies, PD-L1 antibodies, LAG3 antibodies, TIM-3 antibodies, 41BB antibodies and GITR antibodies.

Yervoy (ipilimumab) is a fully human CTLA-4 antibody marketed by Bristol Myers Squibb. The protein structure of ipilimumab and methods are using are described in US Patent Nos. 6,984,720 and 7,605,238.

15

Compositions

The pharmaceutically active compounds within the scope of this invention are useful in decreasing MYC protein (c-MYC) in cells and inhibiting p300/CBP histone acetyltransferase in mammals, particularly humans, in need thereof.

20

The present invention therefore provides a method of treating cancer, arthritis and other conditions requiring reduced c-MYC levels; p300/CBP histone acetyltransferase inhibition which comprises administering an effective amount of a compound of Formula (Ib) or a pharmaceutically acceptable salt thereof. The compounds of Formula (Ib) also
25 provide for a method of treating the above indicated disease states because of their demonstrated ability to decrease MYC protein (c-MYC) in cells and inhibit p300/CBP histone acetyltransferase. The drug may be administered to a patient in need thereof by any conventional route of administration, including, but not limited to, intravenous, intramuscular, oral, subcutaneous, intradermal, and parenteral.

30

The pharmaceutically active compounds of the present invention are incorporated into convenient dosage forms such as capsules, tablets, or injectable preparations. Solid or liquid pharmaceutical carriers are employed. Solid carriers include, starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium

stearate, and stearic acid. Liquid carriers include syrup, peanut oil, olive oil, saline, and water. Similarly, the carrier or diluent may include any prolonged release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies widely but, preferably, will be from about 25 mg to about 1 g per dosage unit.

- 5 When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampoule, or an aqueous or nonaqueous liquid suspension.

- 10 When referring to a pharmaceutical compositions, the term carrier and excipient are used interchangeably herein.

As used herein the terms "disease" and "disease state" are considered to refer to the same condition. These terms are used interchangeably herein.

- 15 The pharmaceutical compositions are made following conventional techniques of a pharmaceutical chemist involving mixing, granulating, and compressing, when necessary, for tablet forms, or mixing, filling and dissolving the ingredients, as appropriate, to give the desired oral or parenteral products.

- 20 Doses of the presently invented pharmaceutically active compounds in a pharmaceutical dosage unit as described above will be an efficacious quantity preferably selected from the range of 0.001 - 100 mg/kg of active compound, preferably 0.001 - 50 mg/kg. When treating a human patient in need of reduced c-MYC levels and/or inhibit p300/CBP histone acetyltransferase activity, the selected dose is administered preferably
25 from 1-6 times daily, orally or parenterally. Preferred forms of parenteral administration include topically, rectally, transdermally, by injection and continuously by infusion. Oral dosage units for human administration preferably contain from 0.05 to 3500 mg of active compound. Oral administration, which uses lower dosages, is preferred. Parenteral administration, at high dosages, however, also can be used when safe and convenient for
30 the patient.

- Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular inhibitor in use, the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors
35 depending on the particular patient being treated will result in a need to adjust dosages, including patient age, weight, diet, and time of administration.

The method of this invention of inducing p300/CBP histone acetyltransferase inhibitory activity in mammals, including humans, comprises administering to a subject in need of such activity an effective p300/CBP histone acetyltransferase inhibiting amount of
5 a pharmaceutically active compound of the present invention.

The method of this invention of reducing cellular c-MYC levels in mammals, including humans, comprises administering to a subject in need of such activity an effective c-MYC reducing amount of a pharmaceutically active compound of the present invention.
10

The invention also provides for the use of a compound of Formula (Ib) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in decreasing MYC protein (c-MYC) in cells.

15 The invention also provides for the use of a compound of Formula (Ib) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use as a p300/CBP histone acetyltransferase inhibitor.

20 The invention also provides for the use of a compound of Formula (Ib) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in therapy.

25 The invention also provides for the use of a compound of Formula (Ib) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in treating cancer.

30 The invention also provides for a pharmaceutical composition for use in reducing cellular c-MYC protein levels which comprises a compound of Formula (Ib) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The invention also provides for a pharmaceutical composition for use as a p300/CBP histone acetyltransferase inhibitor which comprises a compound of Formula (Ib) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The invention also provides for a pharmaceutical composition for use in the treatment of cancer which comprises a compound of Formula (Ib) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

5 In addition, the pharmaceutically active compounds of the present invention can be co-administered with further active ingredients, such as other compounds known to treat cancer, or compounds known to have utility when used in combination with a compound that decreases cellular c-MYC protein.

10 In addition, the pharmaceutically active compounds of the present invention can be co-administered with further active ingredients, such as other compounds known to treat cancer, or compounds known to have utility when used in combination with a p300/CBP histone acetyltransferase inhibitor.

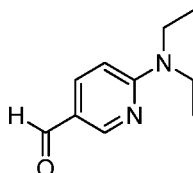
15 The invention also provides novel processes and novel intermediates useful in preparing the presently invented compounds.

 The invention also provides a pharmaceutical composition comprising from 0.5 to 1,000 mg of a compound of Formula (Ib) or pharmaceutically acceptable salt thereof and
20 from 0.5 to 1,000 mg of a pharmaceutically acceptable excipient.

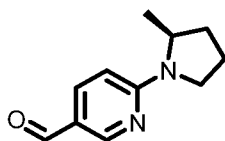
 Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following Examples are, therefore, to be construed as merely illustrative and not a limitation of the
25 scope of the present invention in any way.

EXAMPLES

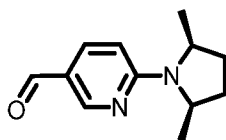
30 The following examples illustrate the invention. These examples are not intended to limit the scope of the present invention, but rather to provide guidance to the skilled artisan to prepare and use the compounds, compositions, and methods of the present invention. While particular embodiments of the present invention are described, the skilled artisan will appreciate that various changes and modifications can be made without
35 departing from the spirit and scope of the invention.

Intermediate 16-(Diethylamino)nicotinaldehyde

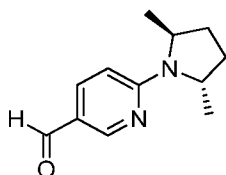
To 6-bromonicotinaldehyde (10.01 g, 53.8 mmol) in DMSO (5 mL) were added diethylamine
5 (8.43 mL, 81 mmol) and K_2CO_3 (11.16 g, 81 mmol), and the reaction mixture was heated
overnight at 60 °C. The reaction was quenched with water (30 mL) and extracted with EtOAc
(4 X 30 mL). The organic extracts were combined and washed with brine, dried ($MgSO_4$),
filtered and concentrated. Purification by flash chromatography on SiO_2 (gradient from 0 to
25% EtOAc/hexanes) afforded 6-(diethylamino)nicotinaldehyde (7.99 g) as a light yellow
10 solid. LC-MS (ES) m/z = 179 $[M+H]^+$. ^1H NMR (400 MHz, $DMSO-d_6$): δ 1.14 (t, J = 7.1 Hz,
6H), 3.59 (q, J = 6.9 Hz, 4H), 6.73 (d, J = 9.1 Hz, 1H), 7.84 (dd, J = 9.1, 2.3 Hz, 1H), 8.56
(d, J = 2.3 Hz, 1H), 9.70 (s, 1H).

Intermediate 215 (S)-6-(2-Methylpyrrolidin-1-yl)nicotinaldehyde

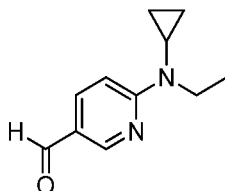
A mixture of 6-bromonicotinaldehyde (1.552 g, 8.35 mmol), (S)-2-methylpyrrolidine (1.067
g, 13.5 mmol), and K_2CO_3 (1.732 g, 13 mmol) in DMSO (40 mL) was heated at 80 °C for 16
hours. The reaction was poured onto water and extracted with CH_2Cl_2 . The organic extract
20 was washed with water, dried over $MgSO_4$, filtered, and concentrated. The resulting residue
was purified via silica gel chromatography (0% to 50% (3:1 EtOAc:EtOH)/hexanes) to afford
(S)-6-(2-methylpyrrolidin-1-yl)nicotinaldehyde (1.26 g) as a oil. LC-MS (ES) m/z = 191
 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 9.75 (s, 1H), 8.55 (d, J = 2.0 Hz, 1H), 7.89 (dd, J =
2.3, 8.9 Hz, 1H), 6.42 (d, J = 9.1 Hz, 1H), 4.31 (br. s., 1H), 3.34 - 3.79 (m, 2H), 1.99 - 2.32
25 (m, 3H), 1.80 (dd, J = 4.1, 5.8 Hz, 1H), 1.27 (d, J = 6.3 Hz, 3H).

Intermediate 36-((2S,5R)-2,5-Dimethylpyrrolidin-1-yl)nicotinaldehyde

A mixture of 6-bromonicotinaldehyde (2.91 g, 15.64 mmol), (2R,5S)-2,5-dimethylpyrrolidine
 5 hydrochloride (3.18 g, 23.47 mmol), and N,N-diisopropylethylamine (9.56 mL, 54.8 mmol)
 in DMSO (15 mL) was stirred at 60 °C overnight. The reaction was quenched with water
 (100 mL), and the resulting mixture was extracted with EtOAc (3 x 100 mL). The combined
 organic extracts were washed with brine (30 mL), dried over Na₂SO₄, filtered, and
 concentrated. The remaining residue was purified by silica gel chromatography (0-20%,
 10 EtOAc/hexanes) to afford the desired product (1.68 g) as a yellow solid. LC-MS (ES) m/z =
 205 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.71 (s, 1H), 8.58 (d, *J* = 2.3 Hz, 1H), 7.84
 (dd, *J* = 2.4, 9.0 Hz, 1H), 6.63 (d, *J* = 9.1 Hz, 1H), 4.00 - 4.33 (m, 2H), 2.00 - 2.18 (m, 2H),
 1.68 - 1.84 (m, 2H), 1.29 (d, *J* = 6.3 Hz, 6H).

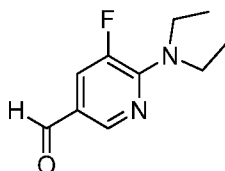
15 Intermediate 3a6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)nicotinaldehyde

To 6-fluoronicotinaldehyde (12.04 g, 96 mmol) in DMSO (150 mL) were added K₂CO₃
 (17.29 g, 125 mmol), triethylamine (16.10 mL, 115 mmol), and (2S,5S)-2,5-
 20 dimethylpyrrolidine hydrochloride (13.71 g, 101 mmol), and the reaction mixture was stirred
 overnight at room temperature. The reaction was quenched with water (100 mL) and
 extracted with EtOAc (4 x 30 mL). The organic extracts were combined and washed with
 brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂
 (gradient of 0 to 40% EtOAc/hexanes) afforded 6-((2S,5S)-2,5-dimethylpyrrolidin-1-
 25 yl)nicotinaldehyde (12.2 g) as a yellow solid. LC-MS (ES) m/z = 205 [M+H]⁺. ¹H NMR (400
 MHz, DMSO-*d*₆): δ 1.07 - 1.21 (m, 6H), 1.65 (br. s., 2H), 2.23 (br. s., 2H), 4.14 - 4.43 (m,
 2H), 6.61 (d, *J* = 9.1 Hz, 1H), 7.82 (dd, *J* = 9.1, 2.3 Hz, 1H), 8.57 (d, *J* = 2.3 Hz, 1H), 9.70
 (s, 1H).

Intermediate 46-(Cyclopropyl(ethyl)amino)nicotinaldehyde

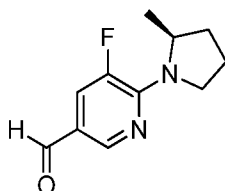
To 6-fluoronicotinaldehyde (400 mg, 3.20 mmol) in DMSO (2 mL) were added N-ethylcyclopropanamine (299 mg, 3.52 mmol) and K_2CO_3 (574 mg, 4.16 mmol), and the reaction mixture was heated overnight at 60 °C. The reaction was quenched with water, and the resulting solid was filtered. The filtrate was extracted with EtOAc (4 X 10 mL). The organic extracts were combined and washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography on SiO_2 (conditions: 2 minutes at 100% hexanes, then 2 minutes at 100% CH_2Cl_2 , then a gradient from 0 to 8% CH_3OH/CH_2Cl_2) afforded 6-(cyclopropyl(ethyl)amino)nicotinaldehyde (450 mg) as a yellow oil. LC-MS (ES) m/z = 191 $[M+H]^+$. ^1H NMR (400 MHz, $DMSO-d_6$): δ 0.69 (dd, J = 3.9, 2.15 Hz, 2H), 0.94 - 1.01 (m, 2H), 1.11 (t, J = 7.0 Hz, 3H), 2.65 - 2.73 (m, 1H), 3.70 - 3.81 (m, 2H), 7.08 (d, J = 8.9 Hz, 1H), 7.88 - 7.97 (m, 1H), 8.62 (d, J = 2.0 Hz, 1H), 9.76 (s, 1H).

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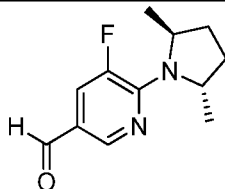
Intermediate 56-(Diethylamino)-5-fluoronicotinaldehyde

To 6-chloro-5-fluoronicotinaldehyde (200 mg, 1.254 mmol) were added DMSO (2 mL), diethylamine (0.169 mL, 1.630 mmol), and K_2CO_3 (225 mg, 1.630 mmol), and the reaction mixture was heated at 80 °C under microwave conditions for 2 hours. The reaction was then quenched with water (5 mL) and extracted with EtOAc (4 X 5 mL). The organic extracts were combined and washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography on SiO_2 (gradient from 0 to 30% EtOAc/hexanes) afforded 6-(diethylamino)-5-fluoronicotinaldehyde (225 mg) as a yellow oil. LC-MS (ES) m/z = 197 $[M+H]^+$. ^1H NMR (400 MHz, $DMSO-d_6$): δ 1.19 (t, J = 7.1 Hz, 6H), 3.62 (qd, J = 7.0, 1.9 Hz, 4H), 7.66 (dd, J = 15.0, 1.8 Hz, 1H), 8.46 (t, J = 2.0 Hz, 1H), 9.76 (d, J = 2.5 Hz, 1H).

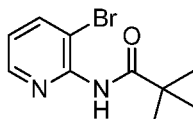
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Intermediate 6(S)-5-Fluoro-6-(2-methylpyrrolidin-1-yl)nicotinaldehyde

To 6-chloro-5-fluoronicotinaldehyde (250 mg, 1.567 mmol) in DMSO (5 mL) were added
5 (S)-2-methylpyrrolidine (173 mg, 2.037 mmol) and K_2CO_3 (282 mg, 2.037 mmol), and the reaction mixture was stirred overnight at 60 °C. The reaction was quenched with water (5 mL) and extracted with EtOAc (4 X 5 mL). The organic extracts were combined and washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography on SiO_2 (gradient from 0 to 30% EtOAc/hexanes) afforded (S)-5-fluoro-6-(2-methylpyrrolidin-1-yl)nicotinaldehyde (50 mg) as a yellow oil. LC-MS (ES) m/z = 209 $[M+H]^+$.
10 ^1H NMR (400 MHz, $DMSO-d_6$): δ 1.20 (d, J = 6.3 Hz, 3H), 1.69 (dd, J = 5.2, 2.9 Hz, 1H), 1.88 - 1.98 (m, 1H), 1.98 - 2.08 (m, 2H), 3.59 - 3.69 (m, 1H), 3.83 (m, 1H), 4.42 - 4.51 (m, 1H), 7.65 (dd, J = 14.5, 1.8 Hz, 1H), 8.46 (t, J = 1.9 Hz, 1H), 9.76 (d, J = 2.8 Hz, 1H).

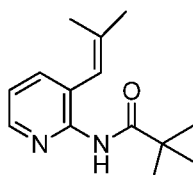
15 Intermediate 76-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)-5-fluoronicotinaldehyde

To 6-chloro-5-fluoronicotinaldehyde (250 mg, 1.567 mmol) in DMSO (5 mL) were added
(2S,5S)-2,5-dimethylpyrrolidine, hydrochloride (276 mg, 2.037 mmol), triethylamine (0.437
20 mL, 3.13 mmol), and K_2CO_3 (282 mg, 2.037 mmol), and the reaction mixture was stirred overnight at 60 °C. The reaction was quenched with water (5 mL) and then extracted with EtOAc (4 X 5 mL). The organic extracts were combined and washed with brine, dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on SiO_2 (gradient from 0 to 30% EtOAc/hexanes) afforded 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)-5-fluoronicotinaldehyde (190 mg) as a yellow oil. LC-MS (ES) m/z = 223 $[M+H]^+$. ^1H NMR (400 MHz, $DMSO-d_6$): δ 1.12 (d, J = 6.1 Hz, 6H), 1.64 (d, J = 5.8 Hz, 2H), 2.14 - 2.27 (m, 2H), 4.55 (br. s, 2H), 7.68 (dd, J = 14.5, 1.8 Hz, 1H), 8.49 (t, J = 2.0 Hz, 1H), 9.77 (d, J = 2.5 Hz, 1H).

Intermediate 8N-(3-Bromopyridin-2-yl)pivalamide

- 5 To a stirred mixture of 3-bromo-2-aminopyridine (22.50 g, 130 mmol) and N,N-diisopropylethylamine (34.1 mL, 195 mmol) in 1,4-dioxane (200 mL) in a 500 mL RBF was added pivaloyl chloride (19.20 mL, 156 mmol) quickly over a 5 minutes period, and the reaction mixture was heated in a heating block at 40 °C for 1 hour. The mixture was diluted with water (200 mL) and extracted with EtOAc (600 mL). The organic extract was washed
- 10 with saturated aqueous NaHCO₃ (120 mL) and brine (80 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The resulting brownish solid residue (33.38 g) was triturated with methyl tert-butyl ether (100 mL), and the resulting suspension was filtered. The cake was washed with methyl tert-butyl ether (40 mL) and dried at room temperature under house vacuum for 1 hour to afford the title compound (27.34 g) as an off-white powdery solid. LC-
- 15 MS m/z = 257, 259 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.24 (s, 9H), 7.27 (dd, *J* = 7.9, 4.6 Hz, 1H) 8.14 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.45 (dd, *J* = 4.6, 1.5 Hz, 1H), 9.75 (s, 1H). The mother liquor was adsorbed onto silica and purified by silica gel chromatography (0% to 100% EtOAc/hexanes) to afford another 2.96 g of the title compound as an off-white solid.

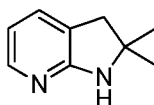
20 Intermediate 9

N-(N-(3-(2-Methylprop-1-en-1-yl)pyridin-2-yl)pivalamide

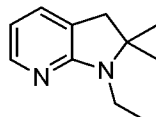
- 25 A mixture of N-(3-bromopyridin-2-yl)pivalamide (30.0 g, 117 mmol), 4,4,5,5-tetramethyl-2-(2-methylprop-1-en-1-yl)-1,3,2-dioxaborolane (25.5 g, 140 mmol), K₃PO₄ (61.9 g, 292 mmol) and Pd₂(dba)₃ (5.34 g, 5.83 mmol) in 1,4-dioxane (300 mL) and water (100 mL) in a 1 L 3-neck RBF fitted with a temperature control probe, mechanical overhead stirrer and a radiator-type condenser was stirred at room temperature and evacuated and back flushed
- 30 with N₂ (repeated 3x). To the mixture was added (t-Bu)₃PHBF₄ (3.39 g, 11.67 mmol, 0.1 equiv) in one portion, and the resulting mixture was evacuated, back flushed with N₂

(repeated 4x), and exposed to a positive nitrogen atmosphere (bubbling). The reaction mixture was then heated in a heating mantle to 87-88 °C in a gentle reflux for 24 hours. The mixture was cooled to room temperature, diluted with water (200 mL) and then filtered through celite. The cake was washed with EtOAc (700 mL total). The combined filtrate
5 organic layer was separated, and the aqueous layer was extracted with EtOAc (200 mL). The combined organic extract was dried over Na₂SO₄, filtered, and concentrated in vacuo. The resulting brownish thick slurry (49 g) was redissolved in CH₂Cl₂ and adsorbed onto silica (split into three equal portions). Purification (each) by silica gel chromatography (0% to 100% EtOAc/hexanes) afforded the desired product in two batches. The first batch
10 (27 g as a yellowish thick oil) contained pinacol type impurities. The second batch was pure title compound (9.5 g) as a pale yellowish thick oil, which turned into a waxy solid upon ageing at room temperature. LC-MS m/z = 233 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.20 (s, 9H), 1.64 (d, *J* = 1.3 Hz, 3H), 1.82 (d, *J* = 1.5 Hz, 3H), 6.03 (s, 1H), 7.27 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.63 (dd, *J* = 7.6, 1.3 Hz, 1H), 8.30 (dd, *J* = 4.8, 1.5 Hz, 1H), 9.45 (s, 1H).

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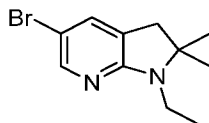
Intermediate 102,2-Dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine

20 A mixture of N-(3-(2-methylprop-1-en-1-yl)pyridin-2-yl)pivalamide (theoretical 117 mmol, 1 equiv, contained pinacol type impurities) and 6N HCl (150 mL) in a 500 mL RBF fitted with a magnetic stirrer and a radiator condenser was stirred and heated at 110 °C in a heating block insert at a gentle reflux for 16 hours. LC-MS showed the mixture was mostly 3-(2-methylprop-1-en-1-yl)pyridin-2-amine intermediate. To the mixture was added additional 6N
25 HCl (100 mL), and the mixture was heated at 120 °C for another 20 hours. The mixture was cooled in an ice bath, followed by portionwise addition of NH₄OH (120 mL) until the final pH reached 10 and solids precipitated out from the solution. The resulting chilled suspension was filtered, and the cake was washed with water (3 x 15 mL). The cake was aspirated under house vacuum at room temperature for 8 hours, followed by drying under high
30 vacuum at room temperature over P₂O₅ for 60 hours to afford the title compound (12.17 g) as a light tan-colored powdery solid. LC-MS m/z = 149 [M+H]. ¹H NMR (400 MHz, CD₃OD): δ 1.33 (s, 6H), 2.85 (s, 2H), 6.49 (dd, *J* = 7.1, 5.6 Hz, 1H), 7.28 (dq, *J* = 7.0, 1.4 Hz, 1H), 7.64 (d, *J* = 4.8 Hz, 1H).

Intermediate 111-Ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine

- 5 To a stirred mixture of 2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine (1.96 g, 13.22 mmol) and acetic acid (1.51 mL, 26.4 mmol) in CH₃OH (60 mL) at room temperature in a 500 mL 3-neck RBF fitted with magnetic stirrer and a temperature probe was added acetaldehyde (3.73 mL, 66.1 mmol) in one portion, followed by portionwise addition of NaBH(OAc)₃ (8.41 g, 39.7 mmol) over a 10 minutes period. Each hydride addition involved
- 10 addition of 5 equiv of acetaldehyde, followed with 3 equivalents of NaBH(OAc)₃ portionwise. The mixture was stirred at room temperature for 20 minutes, and then began with another hydride addition. After 6 hydride additions, the mixture was stirred at room temperature overnight. The mixture was concentrated in vacuo to give a white solid residue, which was taken up in water (100 mL). The pH was adjusted by adding 5 N NaOH solution
- 15 (140 mL). The resulting aqueous mixture was extracted with 10% CH₃OH in CH₂Cl₂ (250 mL). A middle emulsion layer was observed. The mixture was filtered through celite, and the resulting filtrate was phase separated. The aqueous layer was extracted with 10% CH₃OH in CH₂Cl₂ (5 x 125 mL). The combined organic extract was dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting yellowish gel-like oil was dissolved in
- 20 CH₂Cl₂ and adsorbed onto silica. Purification by silica gel chromatography (0% to 60% EtOAc/hexanes) afforded the title compound (1.48 g) as a light yellowish oil. LC-MS m/z = 177 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.22 (t, J = 7.1 Hz, 3H), 1.30 (s, 6H), 2.84 (s, 2H), 3.25 -3.37 (m, 2H), 6.40 (dd, J = 6.8, 5.6 Hz, 1H), 7.20 (dq, J = 6.8, 1.4 Hz, 1H), 7.66 (dd, J = 5.5, 0.9 Hz, 1H).

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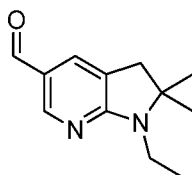
Intermediate 125-Bromo-1-ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine

- 30 To a mixture of 1-ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine (1.47 g, 8.34 mmol) in DMF (5 mL) was added NBS (1.781 g, 10.01 mmol), and the reaction mixture was heated in a heating block at 50 °C for 4 hours. The cooled mixture was diluted with water

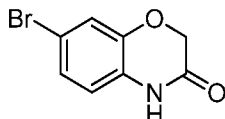
(15 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were concentrated *in vacuo*, and the resulting crude oil was purified by silica gel chromatography eluting with a gradient from 0 to 30% EtOAc/hexanes to provide 5-bromo-1-ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine (1.45 g) as a light brown oil that partially crystallized upon standing. LC-MS (ES) m/z = 255, 257 $[M+H]^+$. ^1H NMR (400MHz, $CDCl_3$): δ 7.89 - 7.85 (m, 1H), 7.20 - 7.16 (m, 1H), 3.28 (q, J = 7.1 Hz, 2H), 2.80 (s, 2H), 1.29 (s, 6H), 1.24 (t, J = 7.1 Hz, 3H).

Intermediate 13

10 1-Ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-5-carbaldehyde

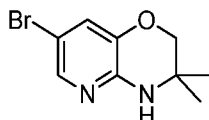


A solution of 5-bromo-1-ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine (1.7 g, 6.66 mmol) dissolved in THF (15 mL) was cooled to -78 °C in a dry ice/acetone bath for 10 minutes. n-Butyllithium (3.20 mL, 8.00 mmol) was then added dropwise at -78 °C, and the reaction was stirred at -78 °C for 1 hour. DMF (1.032 mL, 13.33 mmol) was subsequently added dropwise, the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature over 1 hour. During this time period, the reaction turned from a light yellow color to reddish orange. The reaction was then quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered, and concentrated. The resulting crude brown oil was purified by silica gel chromatography eluting with a gradient from 0 to 70% EtOAc/ CH_2Cl_2 to provide 1-ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-5-carbaldehyde (0.641 g) as a yellow solid after drying under high vacuum. LC-MS (ES) m/z = 205 $[M+H]^+$. ^1H NMR (400MHz, $CDCl_3$): δ 9.67 (s, 1H), 8.27 (d, J = 1.8 Hz, 1H), 7.58 (q, J = 1.8 Hz, 1H), 3.45 (q, J = 7.1 Hz, 2H), 2.88 (d, J = 1.0 Hz, 2H), 1.36 (s, 6H), 1.29 (t, J = 7.1 Hz, 3H).

Intermediate 147-Bromo-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one

5

To 2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one (45.0 g, 300 mmol) in DMF (360 mL) at 20 °C was added NBS (74.7 g, 420 mmol) in one portion, and the resulting brownish suspension was heated at 50 °C for 20 hours. The mixture was cooled to 25 °C, and the content was poured into stirred water (1 L) in a 3 L flask fitted with an overhead mechanical stirrer. The resulting aqueous suspension was stirred at room temperature for 30 minutes followed by filtration. The yellowish cake was washed with 10% Na₂S₂O₃ solution (100 mL) followed by water (2 x 100 mL). The cake was aspirated at room temperature under house vacuum overnight. The solids were washed with Et₂O (100 mL), aspirated under house vacuum at room temperature for 18 hours, and then dried under high vacuum at 50 °C for 72 hours to afford the title compound (65.30 g) as a light tan-colored powdery solid. LC-MS (ES) m/z = 229, 231 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 4.68 (s, 2H), 7.66 (d, *J* = 2.0 Hz, 1H), 8.02 (d, *J* = 2.0 Hz, 1H), 11.44 (br. s., 1H).

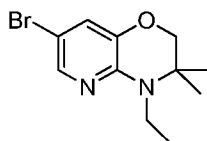
Intermediate 157-Bromo-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine

Starting material 7-bromo-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one (15.0 g, 65.5 mmol) was added to a 1 L glass reactor fitted with an overhead mechanical stirrer followed by 2-MeTHF (330 mL), and the resulting mixture was capped and swept with nitrogen (positive N₂ pressure bubbling). The resulting suspension was stirred at -15 °C for 20 minutes, and then ZrCl₄ (15.26 g, 65.5 mmol) was added as a fine powder in one portion. After stirring the suspension at -15 °C for 20 minutes under nitrogen, methylmagnesium bromide solution (3.4 M in THF, 116 mL, 393 mmol) was added via syringe over a 120 minutes period total such that the internal temperature stayed at -10 °C. The reaction mixture was stirred at -15 °C for another 20 minutes, and then it was slowly warmed up to 25 °C over a 1 hour period, and stayed at 25 °C for 2 hours. The reaction was cooled back to 0 °C and then treated

with saturated aqueous NH_4Cl (200 mL) slowly such that the internal temperature stayed below 15 °C. The mixture was then stirred at 20 °C for 20 minutes. To this mixture was added EtOAc (200 mL), which became a biphasic mixture of liquid and gel-like solid. Celite (150 mL) was added, and the resulting mixture was filtered through celite (100 mL), washing the cake with EtOAc. More celite was added to aid filtration. A total of 450 mL of celite was used in the whole process, and a total of 550 mL of EtOAc was used in washing. The filtrate was phase separated, and the aqueous layer was extracted with EtOAc (200 mL). The combined organic extract was dried over Na_2SO_4 , filtered, and concentrated in vacuo to afford a dark brownish thick oily/foamy residue (17 g). This residue was redissolved in CH_2Cl_2 and adsorbed onto silica. Purification by silica gel chromatography (0% to 40% EtOAc/hexanes) afforded the title compound (5.42 g) as a light yellowish powdery solid. LC-MS (ES) m/z = 243, 245 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.27 (s, 6H), 3.84 (s, 2H), 7.16 (d, J = 2.0 Hz, 1H), 7.61 (d, J = 2.0 Hz, 1H).

Intermediate 16

7-Bromo-4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine

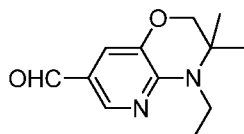


To a mixture of 7-bromo-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin (8.09 g, 33.3 mmol) in DMF (60 mL) in a 250 mL RBF and stirred at room temperature was added NaH (60% in mineral oil, 2.00 g, 49.9 mmol) portionwise over a 5 minutes period. The mixture was stirred at room temperature under nitrogen for 20 minutes, and then cooled to 5 °C (ice bath). Iodoethane (3.23 mL, 39.9 mmol) was then added dropwise/portionwise over a 20 minutes period. Upon completion of addition, the ice bath was removed, and the reaction mixture was stirred under N_2 at ambient temperature for 1 hour. The mixture was cooled in an ice bath, and saturated aqueous NH_4Cl solution (20 mL) was added followed by water (100 mL) and EtOAc (120 mL). The mixture was shaken and phase separated, and the aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic extract was washed with brine (3 x 40 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo to give 10 g of a brownish thick oil. This material was dissolved in CH_2Cl_2 and adsorbed onto silica. Purification by silica gel chromatography (0% to 25% EtOAc/hexanes) afforded the title compound (7.96 g) as a white solid. LC-MS m/z = 271, 273 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz,

DMSO- d_6): δ 1.13 (t, J = 6.8 Hz, 3H), 1.23 (s, 6H), 3.42 - 3.54 (m, 2H), 3.87 (s, 2H), 7.17 (d, J = 2.3 Hz, 1H), 7.76 (d, J = 2.3 Hz, 1H).

Intermediate 17

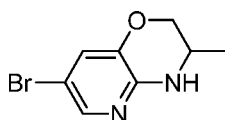
5 4-Ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-7-carbaldehyde



To a solution of 7-bromo-4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine (531 mg, 1.958 mmol) in THF (6 mL) was added n-BuLi in hexane (2.4 M, 0.979 mL, 2.350 mmol) dropwise under a nitrogen atmosphere at -78 °C, and the resulting mixture was stirred for 1 hour at -78 °C. DMF (0.303 mL, 3.92 mmol) was then added, and the reaction mixture was stirred for 1 hour at -78 °C. The mixture was warmed to room temperature and quenched with aqueous NH_4Cl solution (5 mL). Water (100 mL) was then added, and the resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic extract was dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified by silica gel chromatography (1:20 EtOAc:hexanes) to give the desired product (340 mg) as a yellow solid. LC-MS (ES) m/z = 221 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 9.75 (s, 1H), 8.21 (s, 1H), 7.34 (s, 1H), 3.85 (s, 2H), 3.69 (q, J = 7.0 Hz, 2H), 1.35 (s, 6H), 1.29 (t, J = 7.0 Hz, 3H).

20 Intermediate 18

7-Bromo-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine

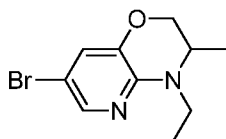


To a stirring solution of 7-bromo-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one (1.0 g, 4.37 mmol) in THF (25 mL) was added methylmagnesium bromide (1.562 g, 13.10 mmol) at 0 °C, the resulting mixture was stirred at room temperature for 2 hours. $\text{NaBH}(\text{OAc})_3$ (2.78 g, 13.10 mmol) was then added, and the reaction mixture was stirred at room temperature for 12 hours. The reaction was quenched by addition of NH_4Cl (aq. 5 mL), and the mixture was concentrated under vacuum. The residue residue was poured into water (100 mL), and extracted with EtOAc (2 x 100 mL). The combined organic extract was dried over anhydrous Na_2SO_4 , and concentrated. The resulting crude product was purified by silica gel

chromatography (1:3 EtOAc:hexanes) to give 7-bromo-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine (500 mg, 2.074 mmol) as a pale solid. LC-MS (ES) m/z = 229, 231 $[M+H]^+$.

Intermediate 19

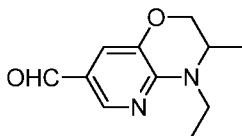
5 7-Bromo-4-ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine



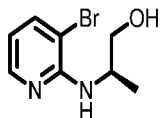
To a solution of 7-bromo-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine (2.1 g, 9.17 mmol) in DMF (30 mL) was added NaH (60%, 0.733 g, 18.33 mmol), and the mixture was stirred for 10 minutes. Iodoethane (5.72 g, 36.7 mmol) was then added, and the reaction mixture was stirred overnight at room temperature. The reaction mixture was poured onto water (100 mL), and extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 1:10 EtOAc/hexanes) to give the desired product (1.66 g) as a yellow solid. LC-MS (ES) m/z = 256, 259 $[M+H]^+$.

Intermediate 20

4-Ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-7-carbaldehyde

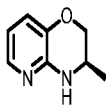


To a solution of 7-bromo-4-ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine (1.66 g, 6.46 mmol) in THF (20 mL) was added n -BuLi in hexane (2.4 M, 3.23 mL, 7.75 mmol) dropwise under a nitrogen atmosphere at $-78^\circ C$, and the resulting mixture was stirred for 1 hour at $-78^\circ C$. DMF (1.0 mL, 12.9 mmol) was then added, and the reaction was stirred for 1 hour at $-78^\circ C$. The mixture was warmed to room temperature and quenched with aqueous NH_4Cl (5 mL) solution. Water (100 mL) was added, and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic extract was dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 1:20 EtOAc/hexanes) to give the desired product (1 g) as a yellow solid. LC-MS (ES) m/z = 207 $[M+H]^+$.

Intermediate 21(R)-2-((3-Bromopyridin-2-yl)amino)propan-1-ol

ref: Tetrahedron Lett. **2010**, 51, 3886.

- 5 A solution of 3-bromo-2-chloropyridine (3.0 g, 15.59 mmol) and (R)-2-aminopropan-1-ol (2.93 g, 39.0 mmol) in pyridine (10 mL) was irradiated for 2 hours at 180 °C using a microwave reactor. The reaction mixture was then poured onto a mixture of saturated aqueous NaHCO₃ (30 mL) and CH₂Cl₂ (20 mL). The phases were separated, and the aqueous layer was further extracted with CH₂Cl₂ (2 x 25 mL). The combined organic extract
- 10 was dried over Na₂SO₄ and then concentrated under reduced pressure. The resulting dark brown oil was purified by flash chromatography on silica gel eluting with a gradient of 0 to 60% EtOAc/hexanes to provide (R)-2-((3-bromopyridin-2-yl)amino)propan-1-ol (2.76 g) as a yellow oil. LC-MS (ES) m/z = 231, 233 [M+H]⁺ ¹H NMR (400 MHz, CDCl₃): δ 7.99 (dd, J = 1.5, 5.1 Hz, 1H), 7.64 (dd, J = 1.5, 7.6 Hz, 1H), 6.49 (dd, J = 4.9, 7.7 Hz, 1H), 5.08 (d, J = 3.8 Hz, 1H), 4.64 (br. s., 1H), 4.23 - 4.15 (m, 1H), 3.78 (dd, J = 2.9, 10.8 Hz, 1H), 3.63
- 15 (dd, J = 7.4, 10.9 Hz, 1H), 1.31 (d, J = 6.6 Hz, 3H).

Intermediate 22(R)-3-Methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine

20

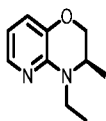
ref: Tetrahedron Lett. **2010**, 51, 3886

- A 250 mL rounded bottom flask was charged with Pd(OAc)₂ (0.597 g, 2.66 mmol), 2-(di-*t*-butylphosphino)biphenyl (1.270 g, 4.25 mmol), and Cs₂CO₃ (26.0 g, 80 mmol). The flask was evacuated, back-filled with argon, then fitted with a rubber septum. (R)-2-((3-bromopyridin-2-yl)amino)propan-1-ol (12.29 g, 53.2 mmol) and toluene (150 mL) were
- 25 added, and the flask was placed in a preheated heating block at 100 °C for 48 hours. The reaction was subsequently cooled to room temperature, diluted with Et₂O (150 mL), and then filtered through a pad of Celite. The filtrate was concentrated *in vacuo*, and the resulting residue was purified by silica gel chromatography using a gradient of 20 to 80%
- 30 EtOAc/hexanes to provide (R)-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine (1.57 g) as a yellow-brown oil. LC-MS (ES) m/z = 151 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.54

(dd, $J = 1.5, 4.8$ Hz, 1H), 7.16 (s, 1H), 6.85 (dd, $J = 1.4, 7.7$ Hz, 1H), 6.39 (dd, $J = 5.1, 7.6$ Hz, 1H), 4.02 (d, $J = 8.4$ Hz, 1H), 3.62 - 3.50 (m, 2H), 1.11 (d, $J = 6.1$ Hz, 3H).

Intermediate 23

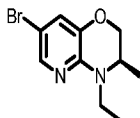
5 (R)-4-Ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine



NaH (0.399 g, 9.99 mmol, 60% dispersion in mineral oil) was added portionwise at 0 °C to an ice-cooled solution of (R)-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine (1.5 g, 9.99 mmol) in DMF (20 mL), and the resulting mixture was stirred at 0 °C for 1 hour. Iodoethane (0.888 mL, 10.99 mmol) was then added dropwise, and the reaction mixture was allowed to warm to room temperature. After 15 hours, the mixture was poured onto water and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed successively with brine, water, dried over Na₂SO₄, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography eluting with a gradient of 0 to 30% EtOAc /hexanes to provide (R)-4-ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine (1.08 g) as a white solid. LC-MS (ES) $m/z = 179$ [M+H]⁺. ¹H NMR (400MHz, CDCl₃): δ 7.78 (dd, $J = 1.5, 5.1$ Hz, 1H), 6.92 (dd, $J = 1.5, 7.6$ Hz, 1H), 6.48 (dd, $J = 5.1, 7.6$ Hz, 1H), 4.07 - 3.95 (m, 3H), 3.70 - 3.62 (m, 1H), 3.32 (dd, $J = 7.1, 14.2$ Hz, 1H), 1.28 (d, $J = 6.6$ Hz, 3H), 1.21 (t, $J = 7.1$ Hz, 3H).

Intermediate 24

(R)-7-Bromo-4-ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine

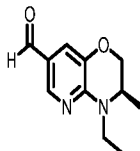


To a solution of (R)-4-ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine (1.08 g, 6.06 mmol) in DMF (20 mL) was added NBS (1.078 g, 6.06 mmol), and the reaction mixture was heated at 75 °C for 2 hours. The reaction was cooled to room temperature, and then poured onto water (100 mL) with stirring. The resulting mixture was extracted with CH₂Cl₂, and the combined organic layers were dried over Na₂SO₄ and concentrated. The crude residue was purified by silica gel chromatography eluting with a gradient from 0 to 50% EtOAc/hexanes to provide (R)-7-bromo-4-ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine (1.09 g) as a yellow solid. LC-MS (ES) $m/z = 257, 259$ [M+H]⁺. ¹H NMR

(400 MHz, CDCl₃): δ 7.79 (d, J = 2.0 Hz, 1H), 7.05 (d, J = 2.0 Hz, 1H), 4.01 (d, J = 2.8 Hz, 2H), 3.94 (qd, J = 7.1, 14.2 Hz, 1H), 3.68 - 3.60 (m, 1H), 3.29 (qd, J = 6.9, 14.1 Hz, 1H), 1.26 (d, J = 6.3 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H).

5 Intermediate 25

(R)-4-Ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-7-carbaldehyde

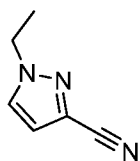


A solution of (R)-7-bromo-4-ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine (1.4 g, 5.44 mmol) in THF (10 mL) was cooled to -78 °C in a dry ice/acetone bath for 10 minutes. n-Butyllithium (2.396 mL, 5.99 mmol) was then added dropwise at -78 °C, and the reaction mixture was stirred at -78 °C for 1 hour. DMF (0.843 mL, 10.89 mmol) was then added dropwise, the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature over 1 hour. During this time period, the reaction turned from a light yellow color to reddish orange. The reaction was then quenched with saturated aqueous NH₄Cl solution, and the resulting mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The crude brown oil was purified by silica gel chromatography eluting with a gradient from 0 to 50% EtOAc/DCM to provide (R)-4-ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-7-carbaldehyde (0.75 g, 3.64 mmol, 66.8 % yield) as a yellow solid after drying under high vacuum. $[R]_D^{25} = +27.9$ (c = 1.00, CHCl₃). LC-MS (ES) m/z = 207 $[M+H]^+$. ¹H NMR (400 MHz, CDCl₃): δ 9.74 (s, 1H), 8.18 (d, J = 2.0 Hz, 1H), 7.33 (d, J = 2.0 Hz, 1H), 4.14 - 4.03 (m, 2H), 4.01 - 3.95 (m, 1H), 3.77 - 3.68 (m, 1H), 3.41 (qd, J = 7.0, 13.9 Hz, 1H), 1.33 (d, J = 6.6 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H).

25

Intermediate 26

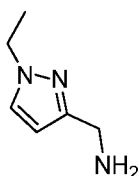
1-Ethyl-1H-pyrazole-3-carbonitrile



To a mixture of sodium hydride (60% in oil, 3.87 g, 97 mmol) in THF (50 mL) cooled in an ice bath was added a solution of 1H-pyrazole-3-carbonitrile (6.92 g, 74.3 mmol) in THF (25 mL) dropwise, and the reaction mixture was then stirred at room temperature for 1 hour. Iodoethane (3.22 mL, 39.8 mmol) was then added, and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with water (30 mL) and extracted with EtOAc (3 X 30 mL). The organic extracts were combined and washed with brine, dried (MgSO₄), filtered, and concentrated. Purification by flash chromatography on SiO₂ (gradient from 0 to 30% EtOAc/hexanes) afforded 1-ethyl-1H-pyrazole-3-carbonitrile (5.66 g) as a clear oil. LC-MS (ES) m/z = 122 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.39 (t, *J* = 7.4 Hz, 3H), 4.25 (q, *J* = 7.4 Hz, 2H), 6.96 (d, *J* = 2.3 Hz, 1H), 8.05 (d, *J* = 2.5 Hz, 1H).

Intermediate 27

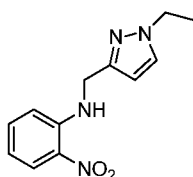
(1-Ethyl-1H-pyrazol-3-yl)methanamine



To a solution of 1-ethyl-1H-pyrazole-3-carbonitrile (5.66 g, 46.7 mmol) in Et₂O (150 mL) cooled in an ice bath was added LiAlH₄ (51.4 mL, 103 mmol, 2M in THF) slowly, and the reaction mixture was stirred overnight at room temperature. The reaction was then cooled in ice bath and treated sequentially [Caution: H₂ evolution] with water (4 mL), 15% NaOH solution (4 mL), and water (12 mL). The resulting mixture was stirred for 15 minutes, and then filtered. The filtrate was dried over MgSO₄ and concentrated to afford (1-ethyl-1H-pyrazol-3-yl)methanamine (4.60 g) as a clear oil. LC-MS (ES) m/z = 126 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.33 (t, *J* = 7.4 Hz, 3H), 1.61 (br. s., 2H), 3.61 (s, 2H), 4.00 - 4.08 (m, 2H), 6.13 (s, 1H), 7.58 (s, 1H).

Intermediate 28

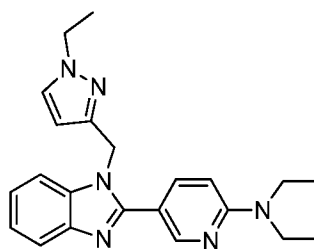
N-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline



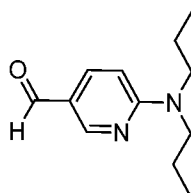
To a solution of 1-fluoro-2-nitrobenzene (500 mg, 3.54 mmol) in DMF (15 mL) were added (1-ethyl-1H-pyrazol-3-yl)methanamine (444 mg, 3.54 mmol) and K₂CO₃ (490 mg, 3.54 mmol), and the reaction mixture was stirred at 35 °C for 18 hours. The reaction was quenched with water (30 mL) and extracted with EtOAc (3x). The extract was dried (Na₂SO₄) and concentrated. The resulting residue was purified using column chromatography (silica gel, 0 to 60% EtOAc/hexanes) to give the desired product (670 mg) as a pale brown oil. LC-MS (ES) m/z = 247 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 1.55 (t, J = 7.4 Hz, 3H), 4.22 (q, J = 7.4 Hz, 2H), 4.58 (d, J = 5.1 Hz, 2H) 6.26 (d, J = 2.3 Hz, 1H), 6.71 (ddd, J = 8.5, 7.0, 1.3 Hz, 1H), 7.01 (dd, J = 8.7, 0.9 Hz, 1H), 7.41 (d, J = 2.3 Hz, 1H), 7.47 (ddd, J = 8.6, 7.1, 1.5 Hz, 1H), 8.23 (dd, J = 8.6, 1.5 Hz, 1H), 8.49 (br. s., 1H).

Example 1

N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine



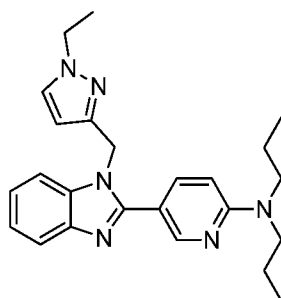
To a 20-mL microwave tube were added N-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline (180 mg, 0.731 mmol), 6-(diethylamino)nicotinaldehyde (130 mg, 0.731 mmol), sodium hydrosulfite (452 mg, 85%, 1.864 mmol), ethanol (4.5 mL), and water (3.00 mL), and the reaction mixture was heated at 135 °C for 20 minutes under microwave conditions. The reaction mixture was then concentrated, and the resulting residue was treated with CH₃OH and filtered. The filtrate was concentrated, and the resulting residue was purified using silica gel chromatography (0 to 100% EtOAc/heptane and then 0 to 50% (3:1 EtOAc:EtOH)/heptane) to give the desired product (101 mg) as a pale brown solid after lyophilization. LC-MS (ES) m/z = 375 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.24 (t, J = 7.0 Hz, 6H), 1.43 (t, J = 7.2 Hz, 3H), 3.62 (q, J = 7.1 Hz, 4H), 4.16 (q, J = 7.3 Hz, 2H), 5.47 (s, 2H), 6.06 (d, J = 2.3 Hz, 1H), 6.71 - 6.81 (m, 1 H), 7.25 - 7.33 (m, 2H), 7.45 - 7.53 (m, 1H), 7.58 (d, J = 2.3 Hz, 1H), 7.65 - 7.73 (m, 1H), 7.93 (dd, J = 9.1, 2.5 Hz, H) 8.48 - 8.55 (m, 1H).

Intermediate 296-(Dipropylamino)nicotinaldehyde

To 6-bromonicotinaldehyde (300 mg, 1.613 mmol) in DMSO (1.5 mL) were added
 5 dipropylamine (0.331 mL, 2.419 mmol) and K_2CO_3 (267 mg, 1.935 mmol), and the reaction
 mixture was heated overnight at 60 °C. The reaction was quenched with water (5 mL), and
 then extracted with EtOAc (4 x 3 mL). The organic extracts were combined and washed
 with brine, dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography on
 SiO₂ (gradient: 0 to 20% EtOAc/hexanes) afforded 6-(dipropylamino)nicotinaldehyde (300
 10 mg) as a clear oil. LC-MS (ES) m/z = 207 $[M+H]^+$. ¹H NMR (400 MHz, DMSO-*d*₆): δ 0.89 (t, J = 7.4 Hz, 6H), 1.52 - 1.65 (m, 4H), 3.50 (t, J = 7.4 Hz, 4H), 6.74 (d, J = 9.1 Hz, 1H), 7.82
 (dd, J = 9.1, 2.3 Hz, 1H), 8.55 (d, J = 2.0 Hz, 1H), 9.69 (s, 1H).

Example 2

15 5-(1-((1-Ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-
dipropylpyridin-2-amine



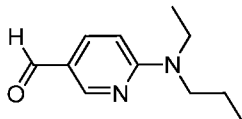
To N1-((1-ethyl-1H-pyrazol-3-yl)methyl)benzene-1,2-diamine (50 mg, 0.231 mmol) in DMF
 (2 mL) and water (2.000 mL) was added 6-(dipropylamino)nicotinaldehyde (47.7 mg, 0.231
 20 mmol) followed by oxone (92 mg, 0.150 mmol), and the reaction mixture was stirred at room
 temperature for 0.5 hours. The reaction was quenched with saturated aqueous NH_4Cl and
 extracted with EtOAc (3 x 20 mL). The organic extracts were then combined and washed
 with brine, dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography on
 SiO₂ (gradient: 0 to 75% EtOAc/hexanes) afforded 5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-
 25 1H-benzo[d]imidazol-2-yl)-N,N-dipropylpyridin-2-amine (54 mg) as a white solid after
 freeze-drying. LC-MS (ES) m/z = 403 $[M+H]^+$. ¹H NMR (400 MHz, DMSO-*d*₆): δ 0.91 (t, J

= 7.4 Hz, 6H), 1.33 (t, J = 7.2 Hz, 3H), 1.54 - 1.65 (m, 4H), 3.43 - 3.51 (m, 4H), 4.08 (q, J = 7.4 Hz, 2H), 5.40 (s, 2H), 6.07 (d, J = 2.0 Hz, 1H), 6.74 (d, J = 9.1 Hz, 1H), 7.17 - 7.22 (m, 2H), 7.48 - 7.53 (m, 1H), 7.61 - 7.66 (m, 1H), 7.68 (d, J = 2.4 Hz, 1H), 8.00 (dd, J = 9.0, 2.4 Hz, 1H), 8.56 (d, J = 2.0 Hz, 1H).

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Intermediate 30

6-(Ethyl(propyl)amino)nicotinaldehyde

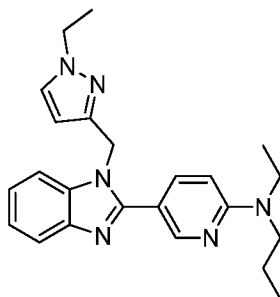


To 6-bromonicotinaldehyde (300 mg, 1.613 mmol) in DMSO (1.5 mL) were added N-ethylpropan-1-amine (211 mg, 2.419 mmol), and K_2CO_3 (267 mg, 1.935 mmol), and the reaction mixture was heated overnight at 60 °C. The reaction was then quenched with water (5 mL) and extracted with EtOAc (4 x 3 mL). The organic extracts were combined and washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography on SiO_2 (gradient: 0 to 30% EtOAc/hexanes) afforded 6-(ethyl(propyl)amino)nicotinaldehyde (195 mg) as a clear oil. LC-MS (ES) m/z = 193 $[M+H]^+$. ^1H NMR (400 MHz, $DMSO-d_6$): δ 0.90 (t, J = 7.4 Hz, 3H), 1.13 (t, J = 7.1 Hz, 3H), 1.52 - 1.65 (m, 2H), 3.49 (t, J = 7.4 Hz, 2H), 3.60 (q, J = 7.0 Hz, 2H), 6.74 (d, J = 9.1 Hz, 1H), 7.83 (dd, J = 9.1, 2.3 Hz, 1H), 8.56 (d, J = 2.0 Hz, 1H), 9.70 (s, 1H).

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Example 3

N-Ethyl-5-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N-propylpyridin-2-amine

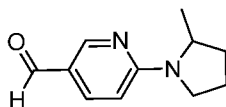


To N1-((1-ethyl-1H-pyrazol-3-yl)methyl)benzene-1,2-diamine (47 mg, 0.217 mmol) in DMF (2 mL) and water (2.000 mL) was added 6-(ethyl(propyl)amino)nicotinaldehyde (41.8 mg, 0.217 mmol) followed by oxone (87 mg, 0.141 mmol), and the reaction mixture was stirred at room temperature for 0.5 hours. The reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (3 x 20 mL). The organic extracts were combined and washed with

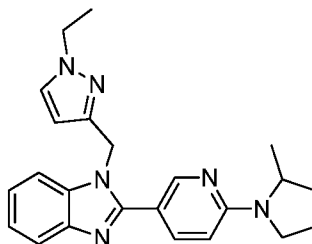
brine, dried (MgSO₄), filtered, and concentrated. The resulting material was diluted with DMSO (1.5 mL) and purified by reverse phase HPLC (two injections: 30 to 60% CH₃CN/0.1% NH₄OH in H₂O). Product fractions were combined, concentrated, and then freeze-dried. The resulting amber color was dissolved in CH₂Cl₂ and purified by chromatography on SiO₂ (gradient: 0 to 75% EtOAc/hexanes) to afford N-ethyl-5-(1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N-propylpyridin-2-amine (42 mg, 0.108 mmol) as a white solid after freeze-drying. LC-MS (ES) m/z = 389 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 0.92 (t, *J* = 7.4 Hz, 3H), 1.10 - 1.18 (m, 3H), 1.30 - 1.36 (m, 3H), 1.54 - 1.67 (m, 2H), 3.42 - 3.50 (m, 2H), 3.57 (q, *J* = 7.1 Hz, 2H), 4.08 (q, *J* = 7.2 Hz, 2H), 5.40 (s, 2H), 6.08 (d, *J* = 2.3 Hz, 1H), 6.74 (d, *J* = 9.1 Hz, 1H), 7.16 - 7.24 (m, 2H), 7.47 - 7.53 (m, 1H), 7.61 - 7.66 (m, 1H), 7.68 (d, *J* = 2.0 Hz, 1H), 8.01 (dd, *J* = 9.0, 2.4 Hz, 1H), 8.57 (d, *J* = 2.3 Hz, 1H).

Intermediate 31

6-(2-Methylpyrrolidin-1-yl)nicotinaldehyde (34.3 mg, 0.180 mmol)

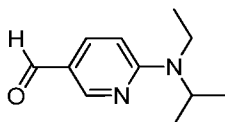


To 6-bromonicotinaldehyde (300 mg, 1.613 mmol) in DMSO (5 mL) were added 2-methylpyrrolidine (0.198 mL, 1.935 mmol) and K₂CO₃ (267 mg, 1.935 mmol), and the reaction mixture was heated at 100 °C for 1 hour under microwave conditions. The reaction was quenched with water (5 mL) and extracted with EtOAc (4 x 3 mL). The organic extracts were then combined and washed with brine, dried (MgSO₄), filtered, and concentrated. Purification by chromatography on SiO₂ (gradient: 0 to 40% EtOAc/hexanes) afforded 6-(2-methylpyrrolidin-1-yl)nicotinaldehyde (271 mg) as a clear oil. LC-MS (ES) m/z = 191 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.15 - 1.22 (m, 3H), 1.71 (d, *J* = 3.0 Hz, 1H), 1.94 - 2.12 (m, 3H), 3.39 (br. s., 1H), 3.59 (br. s., 1H), 4.29 (br. s., 1H), 6.59 (d, *J* = 8.9 Hz, 1H), 7.84 (dd, *J* = 9.0, 2.4 Hz, 1H), 8.57 (d, *J* = 2.3 Hz, 1H), 9.71 (s, 1H).

Example 4**1-((1-Ethyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole**

- 5 To N1-((1-ethyl-1H-pyrazol-3-yl)methyl)benzene-1,2-diamine (39 mg, 0.180 mmol) in DMF (2 mL) and water (2 mL) was added 6-(2-methylpyrrolidin-1-yl)nicotinaldehyde (34.3 mg, 0.180 mmol) followed by oxone (72.1 mg, 0.117 mmol), and the reaction mixture was stirred at room temperature for 0.5 hours. The reaction was quenched with saturated aqueous NH_4Cl and the pH adjusted to slightly basic with NaHCO_3 solution. The resulting mixture
- 10 was extracted with EtOAc (3 x 20 mL), and the organic extracts were then combined and washed with brine, dried (MgSO_4), filtered, and concentrated. Purification by chromatography on SiO_2 (gradient: 0 to 8% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$) afforded 1-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole (30 mg) as a white solid after freeze-drying. LC-MS (ES) $m/z = 387$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 1.19 (d, $J = 6.1$ Hz, 3H), 1.33 (t, $J = 7.4$ Hz, 3H), 1.67 - 1.74 (m, 1H), 1.93 - 2.12 (m, 3H), 3.29 - 3.38 (m, 1H), 3.51 - 3.60 (m, 1H), 4.08 (q, $J = 7.2$ Hz, 2H), 4.22 (t, $J = 6.0$ Hz, 1H), 5.40 (s, 2H), 6.08 (d, $J = 2.3$ Hz, 1H), 6.60 (d, $J = 8.6$ Hz, 1H), 7.16 - 7.23 (m, 2H), 7.49 - 7.54 (m, 1H), 7.61 - 7.66 (m, 1H), 7.68 (d, $J = 2.3$ Hz, 1H), 8.03 (dd, $J = 8.9, 2.3$ Hz, 1H), 8.59 (d, $J = 1.8$ Hz, 1H).

20

Intermediate 32**6-(Ethyl(isopropyl)amino)nicotinaldehyde**

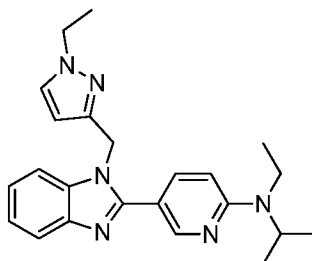
- To 6-bromonicotinaldehyde (300 mg, 1.613 mmol) in DMSO (1.5 mL) were added N-ethylpropan-2-amine (0.293 mL, 2.419 mmol) and K_2CO_3 (334 mg, 2.419 mmol), and the
- 25 reaction mixture was heated at 100 °C for 1 hour under microwave conditions. The reaction was then quenched with water (5mL) and extracted with EtOAc (4 x 3 mL). The organic extracts were combined and washed with brine, dried (MgSO_4), filtered, and concentrated. Purification by chromatography on SiO_2 (gradient: 0 to 20% EtOAc/hexanes) afforded 6-

(ethyl(isopropyl)amino)nicotinaldehyde (220 mg) as a clear oil. LC-MS (ES) m/z = 193 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 1.12 - 1.22 (m, 9H), 3.47 (q, J = 6.8 Hz, 2H), 4.82 - 5.05 (m, 1H), 6.74 (d, J = 9.1 Hz, 1H), 7.84 (dd, J = 9.1, 2.3 Hz, 1H), 8.58 (d, J = 2.0 Hz, 1H), 9.71 (s, 1H).

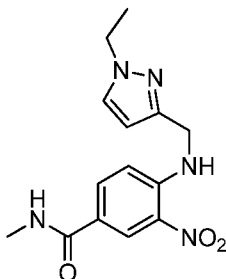
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Example 5

N-Ethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N-isopropylpyridin-2-amine

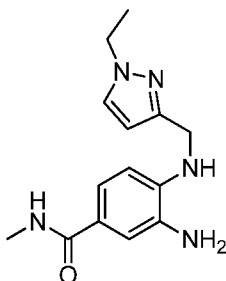


- 10 To N1-((1-ethyl-1H-pyrazol-3-yl)methyl)benzene-1,2-diamine (45 mg, 0.208 mmol) in DMF (2 mL) and water (2 mL) was added 6-(ethyl(isopropyl)amino)nicotinaldehyde (40.0 mg, 0.208 mmol) followed by oxone (83 mg, 0.135 mmol), and the reaction mixture was stirred at room temperature for 0.5 hours. The reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (3 x 20 mL). The organic extracts were combined and
- 15 washed with brine, dried ($MgSO_4$), filtered, and concentrated. The resulting material was diluted with DMSO (1.5 mL) and purified by reverse phase HPLC (two injections: 30 to 60% $CH_3CN/0.1\%$ NH_4OH in H_2O). Product fractions were combined, concentrated, and freeze-dried. The resulting amber color oil was dissolved in CH_2Cl_2 and purified by chromatography on SiO_2 (gradient: 0 to 75% EtOAc/hexanes) to afford N-ethyl-5-(1-((1-ethyl-1H-pyrazol-3-
- 20 yl)methyl)-1H-benzo[d]imidazol-2-yl)-N-isopropylpyridin-2-amine (35 mg) as a yellow oil after freeze-drying. LC-MS (ES) m/z = 389 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 1.14 - 1.21 (m, 9H), 1.33 (t, J = 7.4 Hz, 3H), 3.44 (q, J = 6.8 Hz, 2H), 4.08 (q, J = 7.4 Hz, 2H), 4.84 - 4.93 (m, 1H), 5.41 (s, 2H), 6.09 (d, J = 2.3 Hz, 1H), 6.74 (d, J = 8.9 Hz, 1H), 7.17 - 7.23 (m, 2H), 7.48 - 7.54 (m, 1H), 7.61 - 7.66 (m, 1H), 7.68 (d, J = 2.3 Hz, 1H), 8.03 (dd, J
- 25 = 9.0, 2.4 Hz, 1H), 8.59 (d, J = 2.0 Hz, 1H).

Intermediate 334-(((1-Ethyl-1H-pyrazol-3-yl)methyl)amino)-N-methyl-3-nitrobenzamide

- 5 To (1-ethyl-1H-pyrazol-3-yl)methanamine (1 g, 7.99 mmol) in DMF (15 mL) were added 4-fluoro-N-methyl-3-nitrobenzamide (1.583 g, 7.99 mmol) and K_2CO_3 (638 mg, 4.62 mmol), and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with water (40 mL) and a solid formed. The resulting mixture was stirred for 30 minutes at room temperature and then filtered. Trituration of the filtered solid from Et_2O
- 10 afforded 4-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)-N-methyl-3-nitrobenzamide (1.76 g) as a yellow solid. LC-MS (ES) $m/z = 304 [M+H]^+$. ^1H NMR (400 MHz, $DMSO-d_6$): δ 1.36 (t, $J = 7.2$ Hz, 3H), 2.76 (d, $J = 4.6$ Hz, 3H), 4.11 (q, $J = 7.27$ Hz, 2H), 4.58 (d, $J = 5.6$ Hz, 2H), 6.19 (d, $J = 2.3$ Hz, 1H), 7.16 (d, $J = 9.1$ Hz, 1H), 7.69 (d, $J = 2.3$ Hz, 1H), 7.93 - 7.98 (m, 1H), 8.46 (d, $J = 4.6$ Hz, 1H), 8.64 (d, $J = 2.0$ Hz, 1H), 8.79 (t, $J = 5.5$ Hz, 1H).

15

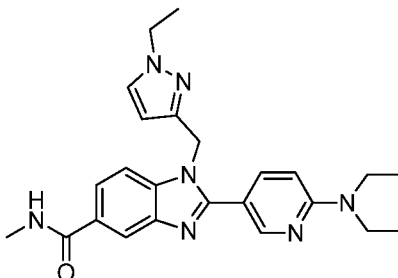
Intermediate 343-Amino-4-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)-N-methylbenzamide

- To a solution of 4-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)-N-methyl-3-nitrobenzamide (1.76 g, 5.80 mmol) in CH_3OH (100 mL) cooled in an ice bath was added $NiCl_2 \cdot 6H_2O$ (3.46 g, 14.51 mmol) followed by sodium borohydride (1.098 g, 29.0 mmol) in small portion over 15 minutes, and the reaction mixture was stirred at room temperature for 30 minutes. The reaction was then diluted with concentrated NH_4OH (40 mL) and extracted with CH_2Cl_2 (4 x 50 mL). The organic extracts were combined and washed with brine, dried ($MgSO_4$),
- 20 filtered, and concentrated. Trituration from $EtOAc$ and hexanes afforded 3-amino-4-(((1-
- 25

ethyl-1H-pyrazol-3-yl)methyl)amino)-N-methylbenzamide (1.20 g) as an off-white solid. LC-MS (ES) m/z = 274 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 1.35 (t, J = 7.4 Hz, 3H), 2.70 (d, J = 4.3 Hz, 3H), 4.03 - 4.13 (m, 2H), 4.24 (d, J = 5.8 Hz, 2H), 4.65 (s, 2H), 5.31 (t, J = 5.6 Hz, 1H), 6.14 (d, J = 2.0 Hz, 1H), 6.47 (d, J = 8.4 Hz, 1H), 7.00 (dd, J = 8.2, 1.9 Hz, 1H), 7.07 (d, J = 2.0 Hz, 1H), 7.63 (d, J = 2.3 Hz, 1H), 7.87 (d, J = 4.8 Hz, 1H).

Example 6

2-(6-(Diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide

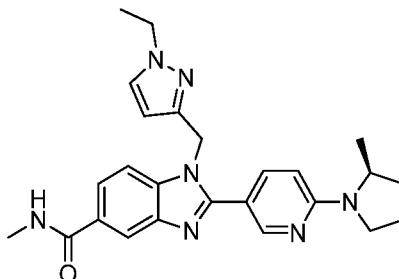


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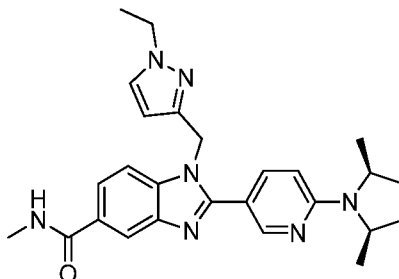
To 3-amino-4-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)-N-methylbenzamide (299 mg, 1.094 mmol) in DMF (10 mL) and water (10 mL) was added 6-(diethylamino)nicotinaldehyde (195 mg, 1.094 mmol) followed by oxone (437 mg, 0.711 mmol), and the reaction mixture was stirred at for 0.5 hour at room temperature. The reaction was quenched with saturated aqueous NH_4Cl (2 mL) followed by addition of saturated aqueous $NaHCO_3$ (3 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL), and the organic extracts were combined and washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography on SiO_2 (gradient of 0 to 8% CH_3OH in CH_2Cl_2) afforded 2-(6-(diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-

benzo[d]imidazole-5-carboxamide (348 mg) as a light brown solid after freeze drying. LC-MS (ES) m/z = 432 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 1.13 - 1.17 (m, 6H), 1.32 (t, J = 7.2 Hz, 3H), 2.81 (d, J = 4.3 Hz, 3H), 3.57 (q, J = 7.0 Hz, 4H), 4.05 (q, J = 16.3 Hz, 2H), 5.44 (s, 2H), 6.10 (d, J = 2.3 Hz, 1H), 6.75 (d, J = 8.6 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 2.3 Hz, 1H), 7.71 - 7.75 (m, 1H), 8.03 (dd, J = 9.1, 2.5 Hz, 1H), 8.15 (d, J = 1.0 Hz, 1H), 8.41 (d, J = 4.6 Hz, 1H), 8.58 (d, J = 1.8 Hz, 1H).

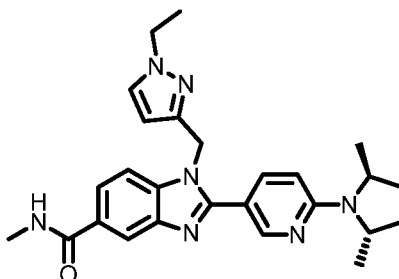
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Example 7**(S)-1-(((1-Ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide**

- 5 To 3-amino-4-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)-N-methylbenzamide (50 mg, 0.183 mmol) in DMF (2 mL) and water (2 mL) was added (S)-6-(2-methylpyrrolidin-1-yl)nicotinaldehyde (34.8 mg, 0.183 mmol) followed by oxone (73.1 mg, 0.119 mmol), and the reaction mixture was stirred at room temperature for 30 minutes. The reaction was quenched with saturated aqueous NH₄Cl followed by saturated aqueous NaHCO₃ (5 mL),
- 10 and the resulting aqueous mixture was extracted with EtOAc (3 x 20 mL). The organic extracts were combined and washed with brine, dried (MgSO₄), filtered, and concentrated. Purification by flash chromatography on SiO₂ (Conditions: 2 minutes at 100% hexanes, then 2 minutes at 100% CH₂Cl₂, then a gradient from 0 to 8% CH₃OH/CH₂Cl₂) afforded an off-white oil. CH₃CN (3mL) was then added, and the resulting precipitate was filtered to afford
- 15 (S)-1-(((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide (51 mg) as a white solid. LC-MS (ES) m/z = 444 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.20 (d, *J*=6.08 Hz, 3 H), 1.32 (t, *J* = 7.4 Hz, 3H), 1.71 (br. s., 1H), 1.94 - 2.10 (m, 4H), 2.81 (d, *J* = 4.3 Hz, 3H), 3.56 (dd, *J* = 10.3, 7.5 Hz, 1H), 4.07 (q, *J* = 7.2 Hz, 2H), 4.23 (t, *J* = 6.1 Hz, 1H), 5.43 (s, 2H), 6.09 (d, *J* = 2.3 Hz, 1H),
- 20 6.61 (d, *J* = 8.9 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 2.3 Hz, 1H), 7.73 (dd, *J* = 8.5, 1.7 Hz, 1H), 8.03 (dd, *J* = 8.9, 2.3 Hz, 1H), 8.15 (d, *J* = 1.3 Hz, 1H), 8.41 (d, *J* = 4.3 Hz, 1H), 8.59 (d, *J* = 2.3 Hz, 1H).

Example 8**2-(6-((2S,5R)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide**

- 5 To 3-amino-4-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)-N-methylbenzamide (53 mg, 0.194 mmol) in DMF (2 mL) and water (1 mL) was added 6-((2S,5R)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (39.6 mg, 0.194 mmol) followed by oxone (77 mg, 0.126 mmol), and the reaction mixture was stirred at room temperature for 30 minutes. The reaction was quenched with saturated aqueous NH₄Cl followed by saturated aqueous NaHCO₃ (5 mL),
- 10 and the resulting aqueous mixture was extracted with EtOAc (3 x 20 mL). The organic extracts were combined and washed with brine, dried (MgSO₄), filtered, and concentrated. Purification by flash chromatography on SiO₂ (Conditions: 2 minutes at 100% hexanes, then 2 minutes at 100% CH₂Cl₂, then a gradient from 0 to 10% CH₃OH/CH₂Cl₂) afforded a clear oil which was freeze-dried to afford 2-(6-((2S,5R)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-
- 15 1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide (63 mg) as a white solid. LC-MS (ES) m/z = 458 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.26 - 1.35 (m, 9H), 1.70 - 1.80 (m, 2H), 2.02 - 2.13 (m, 2H), 2.81 (d, *J* = 4.3 Hz, 3H), 4.02 - 4.16 (m, 4H), 5.44 (s, 2H), 6.10 (d, *J* = 2.3 Hz, 1H), 6.64 (d, *J* = 8.9 Hz, 1H), 7.56 (d, *J* = 8.6 Hz, 1H), 7.69 (d, *J* = 2.28 Hz, 1H), 7.73 (dd, *J* = 8.4, 1.5 Hz, 1H), 8.03 (dd, *J* = 8.9, 2.5 Hz, 1H),
- 20 8.15 (d, *J* = 1.3 Hz, 1H), 8.37 - 8.44 (m, 1H), 8.59 (s, 1H).

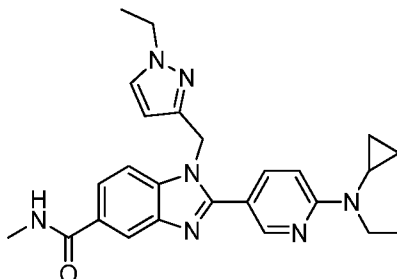
Example 9**2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide**

5 To a mixture of 3-amino-4-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)-N-methylbenzamide (84 mg, 0.307 mmol) and 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (69.1 mg, 0.338 mmol) in DMF (3 mL) and water (3 mL) was added oxone (123 mg, 0.200 mmol), and the reaction mixture was stirred at room temperature for 1 hour. The reaction was queched

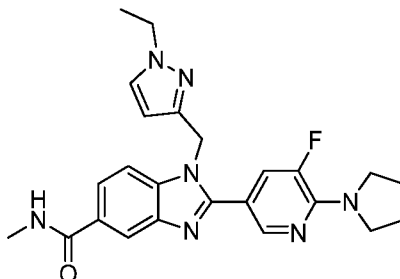
10 with saturated aqueous NH₄Cl (8 mL), and the pH was adjusted to ~ 10 with NH₄OH (10 mL). The product was extracted with CH₂Cl₂ (3 x 25 mL). The combined organic layers were washed with brine (3 mL), dried over Na₂SO₄, filtered, and concentrated. The remaining residue was taken up in CH₃OH (1.25 mL). Some solid did not dissolve and more precipitate formed in the sample. The sample was diluted with DMSO (1.2 mL) and water (5 mL), and

15 the solid was collected via filtration and then dried under high vacuum overnight to afford 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide (65 mg) as a tan solid. LC-MS (ES) m/z = 458 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.59 (d, *J* = 2.0 Hz, 1H), 8.42 (d, *J* = 4.6 Hz, 1H), 8.15 (d, *J* = 1.3 Hz, 1H), 8.01 (dd, *J* = 2.4, 9.0 Hz, 1H), 7.73 (dd, *J* = 1.52, 8.62 Hz, 1H), 7.69 (d, *J* = 2.3 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 6.63 (d, *J* = 8.6 Hz, 1H), 6.10 (d, *J* = 2.3 Hz, 1H), 5.44 (s, 2H), 4.13 - 4.39 (m, 2H), 4.07 (q, *J* = 7.4 Hz, 2H), 2.81 (d, *J* = 4.6 Hz, 3H), 2.24 (br. s., 2H), 1.65 (d, *J* = 5.3 Hz, 2H), 1.32 (t, *J* = 7.4 Hz, 3H), 1.15 (d, *J* = 6.1 Hz, 6H).

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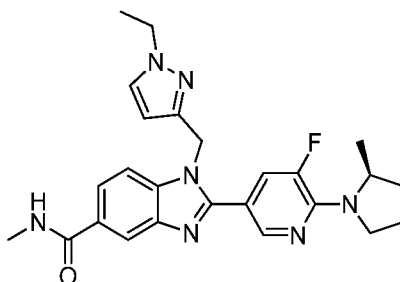
Example 10**2-(6-(Cyclopropyl(ethyl)amino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide**

- 5 To 3-amino-4-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)-N-methylbenzamide (50 mg, 0.183 mmol) in DMF (2 mL) were added 6-(cyclopropyl(ethyl)amino)nicotinaldehyde (34.8 mg, 0.183 mmol) and water (2 mL) followed by oxone (73.1 mg, 0.119 mmol), and the reaction mixture was stirred for 30 minutes at room temperature. The reaction was quenched with saturated aqueous NH_4Cl followed by saturated aqueous NaHCO_3 solution (5 mL), and the
- 10 resulting aqueous mixture was extracted with EtOAc (3 x 20 mL). The organic extracts were combined and washed with brine, dried (MgSO_4), filtered, and concentrated. Purification by flash chromatography on SiO_2 (Conditions: 2 minutes at 100% hexanes, then 2 minutes at 100% CH_2Cl_2 , then a gradient from 0 to 8% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$) afforded after freeze-drying 2-
- 15 (6-(cyclopropyl(ethyl)amino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide (65 mg) as a white solid. LC-MS (ES) $m/z = 444$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 0.63 - 0.69 (m, 2H), 0.93 - 0.99 (m, 2H), 1.11 (t, $J = 7.0$ Hz, 3H), 1.31 (t, $J = 7.4$ Hz, 3H), 2.63 (dt, $J = 6.9, 3.3$ Hz, 1H), 2.81 (d, $J = 4.3$ Hz, 3H), 3.73 (q, $J = 7.0$ Hz, 2H), 4.07 (q, $J = 7.3$ Hz, 2H), 5.44 (s, 2H), 6.10 (d, $J = 2.3$ Hz, 1H), 7.11 (d, $J = 8.9$ Hz, 1H), 7.58 (d, $J = 8.6$ Hz, 1H), 7.68 (d, $J = 2.0$ Hz, 1H), 7.74 (dd, $J = 8.6, 1.5$ Hz,
- 20 1H), 8.10 (dd, $J = 9.0, 2.4$ Hz, 1H), 8.16 (d, $J = 1.3$ Hz, 1H), 8.42 (d, $J = 4.6$ Hz, 1H), 8.63 (d, $J = 2.5$ Hz, 1H).

Example 11**2-(6-(Diethylamino)-5-fluoropyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide**

- 5 To 3-amino-4-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)-N-methylbenzamide (50 mg, 0.183 mmol) in DMF (2 mL) were added 6-(diethylamino)-5-fluoronicotinaldehyde (35.9 mg, 0.183 mmol) and water (2 mL) followed by oxone (73.1 mg, 0.119 mmol), and the reaction mixture was stirred at room temperature for 30 minutes. The reaction was quenched with saturated aqueous NH₄Cl followed by saturated aqueous NaHCO₃ (5 mL), and the resulting aqueous
- 10 mixture was extracted with EtOAc (3 x 20 mL). The organic extracts were combined and washed with brine, dried (MgSO₄), filtered, and concentrated. Purification by flash chromatography on SiO₂ (Conditions: 2 minutes at 100% hexanes, then 2 minutes at 100% CH₂Cl₂, then a gradient from 0 to 8% CH₃OH/CH₂Cl₂) afforded 2-(6-(diethylamino)-5-fluoropyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-
- 15 carboxamide (64 mg) as a white solid. LC-MS (ES) m/z = 450 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.20 (t, *J* = 7.0 Hz, 6H), 1.28 - 1.34 (m, 3H), 2.81 (d, *J* = 4.3 Hz, 3H), 3.54 - 3.63 (m, 4H), 4.07 (q, *J* = 7.4 Hz, 2H), 5.47 (s, 2H), 6.15 (d, *J* = 2.3 Hz, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.69 (d, *J* = 2.3 Hz, 1H), 7.77 (dd, *J* = 8.6, 1.52 Hz, 1H), 8.05 (dd, *J* = 15.6, 1.9 Hz, 1H), 8.17 (d, *J* = 1.3 Hz, 1H), 8.40 - 8.45 (m, 1H), 8.46 (t, *J* = 1.9 Hz, 1H).

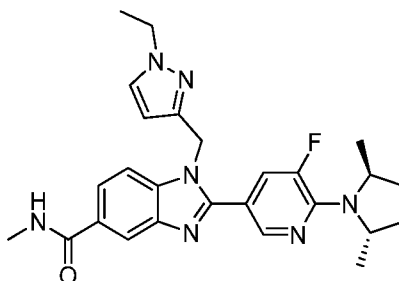
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Example 12**(S)-1-((1-Ethyl-1H-pyrazol-3-yl)methyl)-2-(5-fluoro-6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide**

To 3-amino-4-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)-N-methylbenzamide (45 mg, 0.165 mmol) in DMF (2 mL) were added (S)-5-fluoro-6-(2-methylpyrrolidin-1-yl)nicotinaldehyde (34.3 mg, 0.165 mmol) and water (2 mL) followed by oxone (65.8 mg, 0.107 mmol), and the reaction mixture was stirred at room temperature for 30 minutes. The reaction was quenched with saturated aqueous NH₄Cl followed by saturated aqueous NaHCO₃ (5 mL), and the resulting aqueous mixture was extracted with EtOAc (3 x 20 mL). The organic extracts were combined and washed with brine, dried (MgSO₄), filtered, and concentrated. Purification by flash chromatography on SiO₂ (Purification procedure was done twice; Conditions: 2 minutes at 100% hexanes, then 2 minutes at 100% CH₂Cl₂, then a gradient from 0 to 10% CH₃OH/CH₂Cl₂) afforded (S)-1-(((1-ethyl-1H-pyrazol-3-yl)methyl)-2-(5-fluoro-6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide (45 mg) as a white solid. LC-MS (ES) m/z = 462 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.19 - 1.22 (d, 3H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.64 - 1.72 (m, 1H), 1.86 - 2.11 (m, 3H), 2.81 (d, *J* = 4.6 Hz, 3H), 3.53 - 3.63 (m, 1H), 3.79 (m, 1H), 4.07 (q, *J* = 7.1 Hz, 2H), 4.41 (br. s., 1H), 5.46 (s, 2H), 6.15 (d, *J* = 2.3 Hz, 1H), 7.62 (s, 1H), 7.69 (s, 1H), 7.76 (dd, *J* = 8.6, 1.52 Hz, 1H), 8.03 (dd, *J* = 15.0, 1.8 Hz, 1H), 8.16 (d, *J* = 1.3 Hz, 1H), 8.40 - 8.48 (m, 2H).

Example 13

2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)-5-fluoropyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide

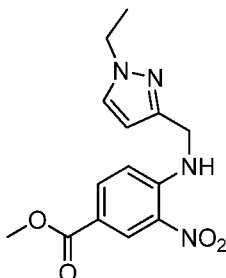


To 3-amino-4-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)-N-methylbenzamide (50 mg, 0.183 mmol) in DMF (2 mL) were added 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)-5-fluoronicotinaldehyde (40.7 mg, 0.183 mmol) and water (2 mL) followed by oxone (73.1 mg, 0.119 mmol), and the reaction was stirred at room temperature for 30 minutes. The reaction was quenched with saturated aqueous NH₄Cl followed by saturated aqueous NaHCO₃ (5 mL), and the resulting aqueous mixture was extracted with EtOAc (3 x 20 mL). The organic extracts were combined and washed with brine, dried (MgSO₄), filtered, and concentrated. Purification by flash chromatography on SiO₂ (Conditions: 2 minutes at 100% hexanes, then 2 minutes at 100% CH₂Cl₂, then a gradient from 0 to 8% CH₃OH/CH₂Cl₂) afforded 2-(6-

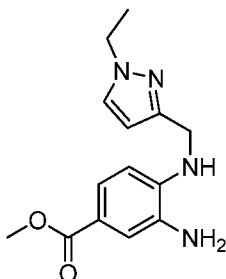
((2S,5S)-2,5-dimethylpyrrolidin-1-yl)-5-fluoropyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide (70 mg) as a white solid. LC-MS (ES) m/z = 476 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 1.12 (d, J = 6.3 Hz, 6H), 1.31 (t, J = 7.2 Hz, 3H), 1.63 (d, J = 5.6 Hz, 2H), 2.18 - 2.25 (m, 2H), 2.81 (d, J = 4.5 Hz, 3H), 4.07 (q, J = 7.4 Hz, 2H), 4.46 - 4.56 (m, 2H), 5.48 (s, 2H), 6.15 (s, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.69 (d, J = 2.3 Hz, 1H), 7.77 (dd, J = 8.5, 1.7 Hz, 1H), 8.02 - 8.08 (m, 1H), 8.17 (d, J = 1.3 Hz, 1H), 8.43 (s, 1H), 8.47 - 8.51 (m, 1H).

Intermediate 35

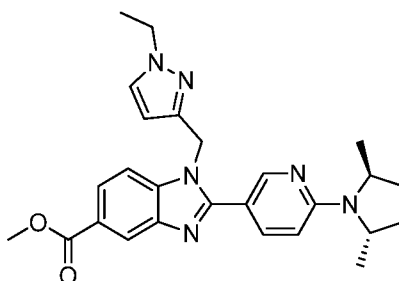
10 4-(((1-Ethyl-1H-pyrazol-3-yl)methyl)amino)-3-nitrobenzoate



To methyl 4-fluoro-3-nitrobenzoate (1.96 g, 9.84 mmol) in DMF (20 mL) were added (1-ethyl-1H-pyrazol-3-yl)methanamine (1.23 g, 9.84 mmol) and K_2CO_3 (1.496 g, 10.83 mmol), and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with water (50 mL) and extracted with EtOAc (3 x 50 mL). The organic extracts were combined and washed with brine, dried ($MgSO_4$), filtered and concentrated. Purification by chromatography on SiO_2 (gradient of 0 to 60% EtOAc/hexanes) afforded 4-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)-3-nitrobenzoate (2.14 g) as a clear oil. LC-MS (ES) m/z = 305 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 1.36 (t, J = 7.2 Hz, 3H), 3.83 (s, 3H), 4.11 (q, J = 7.4 Hz, 2H), 4.60 (d, J = 5.6 Hz, 2H), 6.19 (s, 1H), 7.20 (d, J = 9.1 Hz, 1H), 7.70 (d, J = 2.3 Hz, 1H), 7.98 (dd, J = 9.0, 1.7 Hz, 1H), 8.64 (s, 1H), 8.98 (s, 1H).

Intermediate 363-Amino-4-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)benzoate

To methyl 4-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)-3-nitrobenzoate (2.12 g, 6.97 mmol)
 5 in CH₃OH (20 mL) was added NiCl₂•6H₂O (4.15 g, 17.42 mmol) followed by sodium borohydride (1.318 g, 34.8 mmol) in small portion over 15 minutes, and the reaction mixture was stirred at room temperature for 30 minutes. The reaction was diluted with concentrated NH₄OH (20 mL) and extracted with CH₂Cl₂ (3 x 30 mL). The organic extracts were combined and washed with brine, dried (MgSO₄), filtered, and concentrated to afford methyl 3-amino-
 10 4-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)benzoate (1.74 g) as a clear oil. LC-MS (ES) m/z = 275 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.35 (t, *J* = 7.2 Hz, 3H), 3.72 (s, 3H), 4.08 (q, *J* = 7.4 Hz, 2H), 4.27 (d, *J* = 5.6 Hz, 2H), 4.79 (s, 2H), 5.66 (m, 1H), 6.14 (d, *J* = 2.3 Hz, 1H), 6.53 (d, *J* = 8.1 Hz, 1H), 7.15 - 7.20 (m, 2H), 7.63 (d, *J* = 2.3 Hz, 1H).

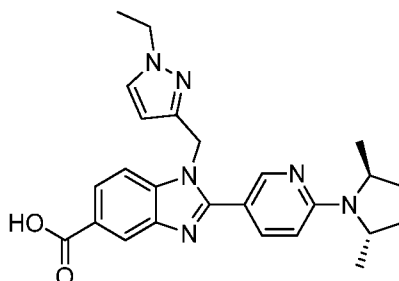
15 Intermediate 372-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylate

To methyl 3-amino-4-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)benzoate (120 mg, 0.437
 20 mmol) in DMF (3 mL) and water (3 mL) were added 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (89 mg, 0.437 mmol) and oxone (175 mg, 0.284 mmol), and the reaction mixture was stirred at room temperature for 0.5 hours. The reaction was quenched with water (20 mL) follow by saturated aqueous NaHCO₃ (5 mL). The resulting solid was isolated by filtration to afford methyl 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-
 25 ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylate (188 mg) as a light

brown solid. LC-MS (ES) m/z = 459 $[M+H]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 1.15 (d, J = 6.1 Hz, 6H), 1.29 - 1.34 (m, 3H), 1.66 (d, J = 5.6 Hz, 2H), 2.24 (br. s., 2H), 3.88 (s, 3H), 4.04 - 4.10 (m, 2H), 4.29 (br. s., 2H), 5.48 (s, 2H), 6.12 (d, J = 2.3 Hz, 1H), 6.66 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 8.6 Hz, 1H), 7.69 (d, J = 2.3 Hz, 1H), 7.86 (dd, J = 8.5, 1.7 Hz, 1H), 8.03 (d, J = 9.4 Hz, 1H), 8.23 (d, J = 1.3 Hz, 1H), 8.60 (d, J = 2.0 Hz, 1H).

Intermediate 38

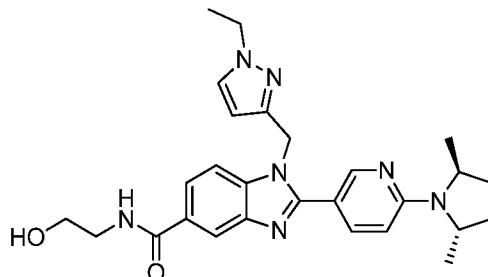
2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid



10

To methyl 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylate (188 mg, 0.410 mmol) in CH_3OH (5 mL) was added 10N NaOH (0.615 mL, 6.15 mmol), and the reaction mixture was stirred at 45 °C for 48 hours. The reaction was partly concentrated under vacuum, diluted with water (5 mL), and then neutralized by addition of 6N HCl solution until pH ~ 7. The resulting precipitate was filtered and purified by chromatography on SiO_2 (gradient of 0 to 10% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$) to afford 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid (110 mg) as a light brown solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 1.14 (d, J = 6.4 Hz, 6H), 1.31 (t, J = 7.2 Hz, 3H), 1.65 (d, J = 5.3 Hz, 2H), 2.24 (br. s., 2H), 4.07 (q, J = 7.3 Hz, 2H), 4.26 (br. s., 2H), 5.46 (s, 2H), 6.10 (d, J = 2.3 Hz, 1H), 6.63 (d, J = 8.9 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.83 (dd, J = 8.5, 1.4 Hz, 1H), 8.01 (dd, J = 8.9, 2.5 Hz, 1H), 8.20 (d, J = 1.5 Hz, 1H), 8.59 (d, J = 2.3 Hz, 1H), 12.72 (s, 1H).

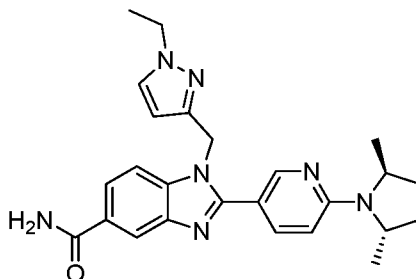
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Example 14**2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-(2-hydroxyethyl)-1H-benzo[d]imidazole-5-carboxamide**

5 To 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid (61 mg, 0.137 mmol) in DMSO (2 mL) were added 2-aminoethan-1-ol (0.012 mL, 0.192 mmol), EDC (52.6 mg, 0.274 mmol), HOBT (42.0 mg, 0.274 mmol), and N-methylmorpholine (0.091 mL, 0.823 mmol), and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with water

10 (5 mL), and the resulting solid was filtered and purified by chromatography on SiO₂ (gradient of 0 to 35% (80:20:2 CH₂Cl₂:CH₃OH:NH₄OH)/CH₂Cl₂) to afford 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-(2-hydroxyethyl)-1H-benzo[d]imidazole-5-carboxamide (52 mg) as a clear oil. LC-MS (ES) m/z = 488 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.14 (d, *J* = 6.3 Hz, 6H), 1.32 (t, *J* = 7.4 Hz, 3H), 1.65 (d, *J* = 5.3 Hz, 2H), 2.24 (br. s., 2H), 3.53 (q, *J* = 6.0 Hz, 2H), 4.07 (q, *J* = 7.2 Hz, 2H), 4.25 (br. s., 2H), 4.74 (t, *J* = 5.7 Hz, 1H), 5.44 (s, 2H), 6.08 (d, *J* = 2.3 Hz, 1H), 6.63 (d, *J* = 8.9 Hz, 1H), 7.56 (d, *J* = 8.6 Hz, 1H), 7.68 (d, *J* = 2.3 Hz, 1H), 7.75 (dd, *J* = 8.6, 1.52 Hz, 1H), 8.01 (dd, *J* = 8.9, 2.53 Hz, 1H), 8.18 (d, *J* = 1.3 Hz, 1H), 8.41 (t, *J* = 5.7 Hz, 1H), 8.59 (d, *J* = 2.3 Hz, 1H).

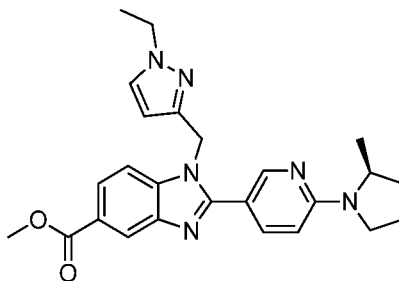
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Example 15**2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide**

To 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid (48 mg, 0.108 mmol) in DMSO (2 mL) were added NH₄Cl (10.40 mg, 0.194 mmol), EDC (41.4 mg, 0.216 mmol), HOBT (33.1 mg, 0.216 mmol), and N-methylmorpholine (0.071 mL, 0.648 mmol), and the reaction mixture
 5 was stirred overnight at room temperature. The reaction was quenched with water (5 mL), and the resulting solid was filtered and dried under vacuum oven. Purification by flash chromatography on SiO₂ (Conditions: 2 minutes at 100% Hexane, then 2 minutes at 100% CH₂Cl₂, then a gradient of 0 to 10% CH₃OH in CH₂Cl₂ over 25 minutes) afforded 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-
 10 benzo[d]imidazole-5-carboxamide (40 mg) as a white solid. LC-MS (ES) m/z = 444 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.14 (d, *J* = 6.3 Hz, 6H), 1.29 - 1.35 (m, 3H), 1.65 (d, *J* = 5.6 Hz, 2H), 2.24 (br. s., 2H), 4.07 (q, *J* = 7.4 Hz, 2H), 4.25 (br. s., 2H), 5.44 (s, 2H), 6.09 (d, *J* = 2.3 Hz, 1H), 6.63 (d, *J* = 8.9 Hz, 1H), 7.27 (br. s., 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 2.0 Hz, 1H), 7.77 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.96 (br. s., 1H), 8.01 (dd, *J* = 9.0, 2.4
 15 Hz, 1H), 8.21 (d, *J* = 1.3 Hz, 1H), 8.59 (d, *J* = 2.5 Hz, 1H).

Intermediate 39

Methyl (S)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylate

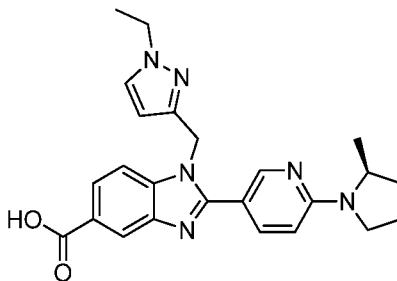


20 To methyl 3-amino-4-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)benzoate (500 mg, 1.823 mmol) in DMF (5 mL) and water (5 mL) was added (S)-6-(2-methylpyrrolidin-1-yl)nicotinaldehyde (347 mg, 1.823 mmol) followed by oxone (728 mg, 1.185 mmol), and the reaction mixture was stirred at room temperature for 0.5 hours. The reaction was quenched
 25 with saturated aqueous NH₄Cl (3 mL) followed by saturated aqueous NaHCO₃ (5 mL), and the resulting mixture was then extracted with EtOAc (3 x 20 mL). The organic extracts were then combined and washed with brine, dried (MgSO₄), filtered, and concentrated. Purification by flash chromatography on SiO₂ (Conditions: 2 minutes at 100% Hexanes, then 2 minutes at 100% CH₂Cl₂, then a gradient of 0 to 8% CH₃OH in CH₂Cl₂ over 28
 30 minutes) afforded a clear oil which was triturated with 9:1 Hexanes:EtOAc to afford methyl

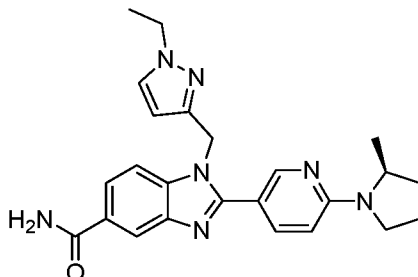
(S)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylate (416 mg) as a light brown solid. LC-MS (ES) m/z = 445 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 1.20 (d, J = 6.3 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.71 (d, J = 3.6 Hz, 1H), 1.93 - 2.13 (m, 3H), 3.53 - 3.60 (m, 1H), 3.87 (s, 3H), 4.07 (q, J = 7.4 Hz, 2H), 4.23 (br. s., 1H), 5.46 (s, 2H), 6.11 (d, J = 2.3 Hz, 1H), 6.61 (d, J = 8.9 Hz, 1H), 7.64 (d, J = 8.6 Hz, 1H), 7.69 (d, J = 2.3 Hz, 1H), 7.85 (dd, J = 8.5, 1.65 Hz, 1H), 8.03 (dd, J = 8.9, 2.53 Hz, 1H), 8.23 (d, J = 1.3 Hz, 1H), 8.60 (d, J = 2.0 Hz, 1H).

Intermediate 40

10 (S)-1-((1-Ethyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylic acid

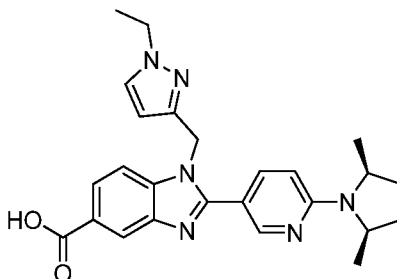


To methyl (S)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylate (53 mg, 0.119 mmol) in CH_3OH (3 mL) was added 15 10N NaOH (0.119 mL, 1.192 mmol), and the reaction mixture was stirred overnight at 40 °C. Additional 10N NaOH (0.119 mL, 1.192 mmol) was added, and the reaction mixture was stirred overnight at 40 °C. The reaction was then partly concentrated under reduced pressure. Water (5 mL) was added followed by slow addition of 6N HCl until pH of 7. The resulting solid was collected by filtration and dried in vacuum oven overnight to afford (S)-
20 1-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylic acid (40 mg) as a light brown solid. LC-MS (ES) m/z = 431 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 1.22 (d, J = 6.3 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.78 (d, J = 9.9 Hz, 1H), 2.00 - 2.16 (m, 3H), 3.46 (d, J = 6.3 Hz, 1H), 3.69 (br. s., 1H), 4.07 (q, J = 7.2 Hz, 2H), 4.35 (br. s., 1H), 5.59 (s, 2H), 6.32 (d, J = 2.0 Hz, 1H), 6.98 (br. s., 1H),
25 7.75 (d, J = 2.3 Hz, 1H), 7.86 (d, J = 8.6 Hz, 1H), 8.02 (d, J = 8.6 Hz, 1H), 8.23 - 8.30 (m, 2H), 8.68 (d, J = 2.3 Hz, 1H), 12.77 - 13.56 (br. s., 1H).

Example 16**(S)-1-((1-Ethyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide**

- 5 To (S)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylic acid (40 mg, 0.093 mmol) in DMSO (2 mL) were added NH₄Cl (8.95 mg, 0.167 mmol), EDC (35.6 mg, 0.186 mmol), HOBt (28.5 mg, 0.186 mmol), and N-methylmorpholine (0.061 mL, 0.557 mmol), and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with water (5 mL), and the
- 10 resulting solid was collected and purified by flash chromatography on SiO₂ (Conditions: 2 minutes at 100% Hexanes, then 2 minutes at 100% CH₂Cl₂, then a gradient of 0 to 10% CH₃OH in CH₂Cl₂ over 28 minutes) to afford (S)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide (18 mg) as a white solid. LC-MS (ES) m/z = 430 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.18 - 1.22 (m, 3H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.71 (br. s., 1H), 1.94 - 2.12 (m, 4H), 3.52 - 3.59 (m, 1H), 4.07 (q, *J* = 7.3 Hz, 2H), 4.23 (br. s., 1H), 5.43 (s, 2H), 6.09 (d, *J* = 2.3 Hz, 1H), 6.61 (d, *J* = 9.1 Hz, 1H), 7.27 (br. s., 1H), 7.55 (d, *J* = 8.6 Hz, 1H), 7.68 (d, *J* = 2.0 Hz, 1H), 7.77 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.96 (br. s., 1H), 8.03 (dd, *J* = 8.9, 2.5 Hz, 1H) 8.21 (d, *J* = 1.3 Hz, 1H), 8.59 (d, *J* = 2.3 Hz, 1H).

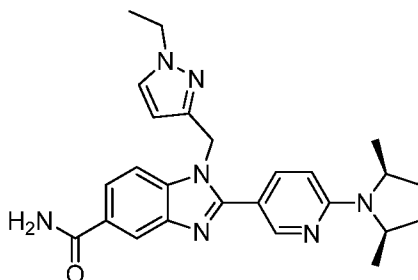
20

Intermediate 41**2-(6-((2S,5R)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid**

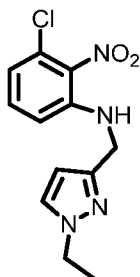
To methyl 2-(6-((2S,5R)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylate (65 mg, 0.142 mmol) in CH₃OH (2 mL) was added 10N NaOH (0.142 mL, 1.417 mmol), and the reaction mixture was stirred overnight at 40 °C. The reaction was then partly concentrated by reduced pressure. Water (5 mL) was added followed by slow addition of 6N HCl solution until pH of 7. The resulting solid was collected by filtration and dried in vacuum oven overnight to afford 2-(6-((2S,5R)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid (40 mg) as a white solid. LC-MS (ES) *m/z* = 445 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.28 - 1.35 (m, 9H), 1.71 - 1.81 (m, 2H), 2.03 - 2.14 (m, 2H), 4.03 - 4.17 (m, 4H), 5.48 (s, 2H) 6.14 (d, *J* = 2.3 Hz, 1H), 6.69 (d, *J* = 8.9 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 2.3 Hz, 1H), 7.84 - 7.89 (m, 1H), 8.06 (dd, *J* = 8.9, 2.3 Hz, 1H), 8.22 (s, 1H), 8.61 (d, *J* = 2.3 Hz, 1H), 12.80 (br. s., 1H).

Example 17

2-(6-((2S,5R)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide

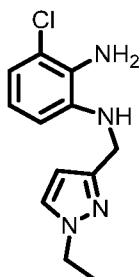


To 2-(6-((2S,5R)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid (40 mg, 0.090 mmol) in DMSO (2 mL) were added NH₄Cl (8.66 mg, 0.162 mmol), EDC (34.5 mg, 0.180 mmol), HOBt (27.6 mg, 0.180 mmol), and N-methylmorpholine (0.059 mL, 0.540 mmol), and reaction mixture was stirred at room temperature overnight. The reaction was quenched with water (5 mL), and the resulting solid was collected by filtration and dried in vacuum oven to afford 2-(6-((2S,5R)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide (30 mg) as a white solid. LC-MS (ES) *m/z* = 444 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.27 - 1.35 (m, 9H), 1.70 - 1.80 (m, 2H), 2.02 - 2.13 (m, 2H), 4.03 - 4.16 (m, 4H), 5.44 (s, 2H), 6.10 (d, *J* = 2.3 Hz, 1H), 6.64 (d, *J* = 8.9 Hz, 1H), 7.27 (br. s., 1H), 7.55 (d, *J* = 8.3 Hz, 1H), 7.69 (d, *J* = 2.3 Hz, 1H), 7.77 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.97 (br. s., 1H), 8.03 (dd, *J* = 8.9, 2.5 Hz, 1H), 8.21 (d, *J* = 1.3 Hz, 1H), 8.60 (d, *J* = 2.5 Hz, 1H).

Intermediate 423-Chloro-N-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline

5 A solution of 1-chloro-3-fluoro-2-nitrobenzene (250 mg, 1.424 mmol), (1-ethyl-1H-pyrazol-3-yl)methanamine (196 mg, 1.567 mmol) and N,N-diisopropylethylamine (0.298 mL, 1.709 mmol) in DMF (20 mL) was stirred at room temperature for 2 hours. The reaction was then heated to 60 °C for 16 hours. The reaction was concentrated, and the resulting residue was purified via silica gel chromatography (0% to 27% EtOAc/hexanes) to yield 3-chloro-N-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline (263 mg) as an oil. LC-MS (ES) m/z = 281, 283 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.39 (d, J = 2.0 Hz, 1H), 7.25 (dd, J = 7.9, 8.6 Hz, 1H), 6.86 (dd, J = 1.0, 8.6 Hz, 1H), 6.80 (dd, J = 1.3, 7.9 Hz, 1H), 6.28 (br. s., 1H), 6.21 (d, J = 2.0 Hz, 1H), 4.44 (d, J = 4.3 Hz, 2H), 4.19 (q, J = 7.3 Hz, 2H), 1.53 (t, J = 7.2 Hz, 3H).

15

Intermediate 433-Chloro-N-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline

A mixture of 3-chloro-N-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline (116 mg, 0.413 mmol) and NiCl₂•6H₂O (246 mg, 1.033 mmol) in CH₃OH (20 mL) was cooled in an ice water bath. Sodium borohydride (78 mg, 2.066 mmol) was added, and the reaction mixture was stirred in ice water bath for 10 minutes. The reaction was concentrated. NH₄OH (28% in water) was added, and the resulting mixture was extracted with CH₂Cl₂. The combined CH₂Cl₂ extract was dried over MgSO₄, filtered, and concentrated. The resulting residue was purified via silica gel column chromatography (0% to 100% EtOAc/hexanes) to afford

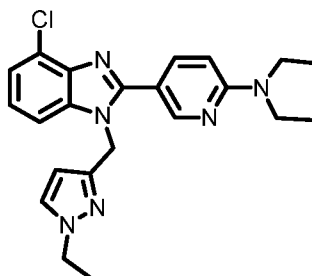
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3-chloro-N-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline (58 mg). LC-MS (ES) m/z = 251, 253 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J = 2.3 Hz, 1H), 6.86 (dd, J = 1.5, 7.9 Hz, 1H), 6.59 - 6.80 (m, 2H), 6.26 (d, J = 2.3 Hz, 1H), 4.36 (s, 2H), 4.20 (q, J = 7.4 Hz, 2H), 1.53 (t, J = 7.34 Hz, 3H).

5

Example 18

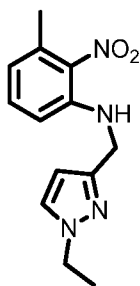
5-(4-Chloro-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine



- 10 A mixture of 3-chloro-N1-((1-ethyl-1H-pyrazol-3-yl)methyl)benzene-1,2-diamine (58 mg, 0.185 mmol), 6-(diethylamino)nicotinaldehyde (33.0 mg, 0.185 mmol), and oxone (74.0 mg, 0.120 mmol) in DMF (10 mL) and water (4 mL) was stirred at room temperature for 30 minutes. Saturated aqueous $NaHCO_3$ was added, and the resulting mixture was extracted with EtOAc. The combined EtOAc extract was washed with water, brine, dried over $MgSO_4$,
 15 filtered and concentrated. The resulting residue was purified via silica gel chromatography (0% to 100% EtOAc/hexanes) to give 5-(4-chloro-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (16 mg) as a dark brown glass/solid. LC-MS (ES) m/z = 409, 411 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, J = 1.8 Hz, 1H), 7.98 (dd, J = 2.4, 9.0 Hz, 1H), 7.26 - 7.38 (m, 3H), 7.04 - 7.21 (m, 1H), 6.59 (d, J = 9.1 Hz, 1H), 5.95 (d, J = 2.3 Hz, 1H), 5.44 (s, 2H), 4.18 (q, J = 7.4 Hz, 2H), 3.60 (q, J = 7.1 Hz, 4H),
 20 1.51 (t, J = 7.4 Hz, 3H), 1.24 (t, J = 7.1 Hz, 6H).

Intermediate 44

N-((1-Ethyl-1H-pyrazol-3-yl)methyl)-3-methyl-2-nitroaniline

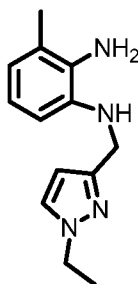


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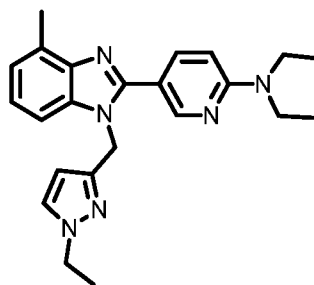
A solution of 1-fluoro-3-methyl-2-nitrobenzene (176 mg, 1.135 mmol), (1-ethyl-1H-pyrazol-3-yl)methanamine (156 mg, 1.248 mmol), and N,N-diisopropylethylamine (0.238 mL, 1.361 mmol) in DMF (15 mL) was stirred at room temperature for 16 hours. The reaction mixture was concentrated, and the resulting residue was purified via silica gel chromatography (0% to 30% EtOAc/hexanes) to give N-((1-ethyl-1H-pyrazol-3-yl)methyl)-3-methyl-2-nitroaniline (72 mg) as a yellow oil. LC-MS (ES) m/z = 261 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J = 2.3 Hz, 1H), 7.25 (dd, J = 7.6, 8.4 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 6.58 (d, J = 7.4 Hz, 1H), 6.23 (d, J = 2.3 Hz, 1H), 4.47 (s, 2H), 4.21 (q, J = 7.4 Hz, 2H), 2.51 (s, 3H), 1.54 (t, J = 7.4 Hz, 3H).

Intermediate 45

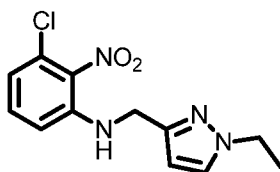
N¹-((1-Ethyl-1H-pyrazol-3-yl)methyl)-3-methylbenzene-1,2-diamine



A mixture of N-((1-ethyl-1H-pyrazol-3-yl)methyl)-3-methyl-2-nitroaniline (70 mg, 0.269 mmol) and $NiCl_2 \cdot 6H_2O$ (160 mg, 0.672 mmol) in CH_3OH (20 mL) was cooled in a ice water bath. Sodium borohydride (50.9 mg, 1.345 mmol) was added, and the reaction mixture was stirred in ice water bath for 10 minutes. The reaction mixture was concentrated. NH_4OH (28% in water) was added, and the resulting mixture was extracted with CH_2Cl_2 . The combined CH_2Cl_2 extract was dried over $MgSO_4$, filtered, and concentrated to give N¹-((1-ethyl-1H-pyrazol-3-yl)methyl)-3-methylbenzene-1,2-diamine (60 mg) as an oil. LC-MS (ES) m/z = 231 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J = 2.0 Hz, 1H), 6.64 - 6.88 (m, 3H), 6.26 (d, J = 2.0 Hz, 1H), 4.36 (s, 2H), 4.21 (q, J = 7.4 Hz, 2H), 2.26 (s, 3H), 1.42 - 1.59 (m, 3H).

Example 19**N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-4-methyl-1H-benzo[d]imidazol-2-yl)pyridin-2-amine**

- 5 A mixture of N1-((1-ethyl-1H-pyrazol-3-yl)methyl)-3-methylbenzene-1,2-diamine (60 mg, 0.208 mmol), 6-(diethylamino)nicotinaldehyde (37.1 mg, 0.208 mmol), and oxone (83 mg, 0.135 mmol) in DMF (10 mL) and water (4 mL) was stirred at room temperature for 30 minutes. Saturated aqueous NaHCO₃ was then added, and the resulting mixture was extracted with EtOAc. The organic layer was separated, washed sequentially with water and brine, dried over MgSO₄, filtered and concentrated. The resulting residue was purified via silica gel chromatography (0% to 100% EtOAc/hexanes). Further purification via reverse phase HPLC (10% CH₃CN/H₂O, 0.1% formic acid to 40% CH₃CN/H₂O, 0.1% formic acid) afforded N,N-diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-4-methyl-1H-benzo[d]imidazol-2-yl)pyridin-2-amine (32 mg) as a tar/solid. LC-MS (ES) m/z = 389 [M+H]⁺.
- 10
- 15 ¹H NMR (400 MHz, CDCl₃): δ 8.58 (d, J = 1.8 Hz, 1H), 7.95 (dd, J = 2.3, 8.9 Hz, 1H), 7.32 (d, J = 2.3 Hz, 1H), 7.21 - 7.26 (m, 1H), 7.17 (t, J = 7.5 Hz, 1H), 7.09 - 7.13 (m, 1H), 6.60 (d, J = 9.1 Hz, 1H), 5.97 (d, J = 2.3 Hz, 1H), 5.43 (s, 2H), 4.19 (q, J = 7.4 Hz, 2H), 3.61 (q, J = 7.1 Hz, 4H), 2.76 (s, 3H), 1.53 (t, J = 7.2 Hz, 3H), 1.25 (t, J = 7.1 Hz, 6H).

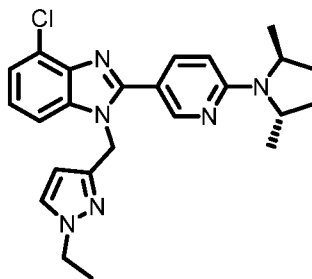
20 Intermediate 46**3-Chloro-N-((1-ethyl-1H-pyrazol-4-yl)methyl)-2-nitroaniline**

- A solution of 1-chloro-3-fluoro-2-nitrobenzene (157 mg, 0.894 mmol), (1-ethyl-1H-pyrazol-3-yl)methanamine (123 mg, 0.984 mmol), and N,N-diisopropylethylamine (0.187 mL, 1.073 mmol) in DMF (15 mL) was stirred at room temperature for 16 hours. The reaction was concentrated, and the resulting residue was purified via silica gel chromatography (0% to
- 25

35% EtOAc/hexanes) to afford 3-chloro-N-((1-ethyl-1H-pyrazol-4-yl)methyl)-2-nitroaniline (142 mg) as a orange oil. LC-MS (ES) m/z = 281, 283 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J = 2.3 Hz, 1H), 7.24 (t, J = 8.2 Hz, 1H), 6.85 (dd, J = 1.0, 8.6 Hz, 1H), 6.79 (dd, J = 1.1, 8.0 Hz, 1H), 6.29 (br. s., 1H), 6.20 (d, J = 2.3 Hz, 1H), 4.43 (d, J = 5.1 Hz, 2H), 4.18 (q, J = 7.3 Hz, 2H), 1.51 (t, J = 7.4 Hz, 3H).

Example 20

4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole

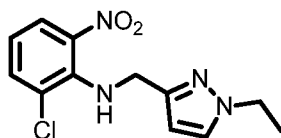


10

A mixture of 3-chloro-N-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline (142 mg, 0.506 mmol), sodium hydrosulfite (264 mg, 85%, 1.287 mmol), and 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (108 mg, 0.531 mmol) in EtOH (4 mL) and water (2mL) was heated in at 130 °C under microwave conditions for 30 minutes. The reaction was filtered and concentrated to dryness. CH_2Cl_2 was added, and the resulting mixture was filtered again. The filtrate was purified via silica gel chromatography (0% to 100% EtOAc/hexanes) to afford 4-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1Hbenzo[d]imidazole (68 mg) as a white solid. LC-MS (ES) m/z = 435 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, J = 2.3 Hz, 1H), 7.96 (dd, J = 2.3, 8.9 Hz, 1H), 7.25 - 7.35 (m, 3H), 7.09 - 7.19 (m, 1H), 6.50 (d, J = 8.9 Hz, 1H), 5.95 (d, J = 2.0 Hz, 1H), 5.45 (s, 2H), 4.28 (dd, J = 7.2, 14.6 Hz, 2H), 4.18 (q, J = 7.4 Hz, 2H), 2.21 - 2.36 (m, 2H), 1.65 - 1.80 (m, 2H), 1.51 (t, J = 7.4 Hz, 3H), 1.22 (d, J = 6.1 Hz, 6H).

25 Intermediate 47

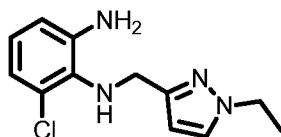
2-Chloro-N-((1-ethyl-1H-pyrazol-3-yl)methyl)-6-nitroaniline



A solution of 1-chloro-2-fluoro-3-nitrobenzene (172 mg, 0.980 mmol), (1-ethyl-1H-pyrazol-3-yl)methanamine (135 mg, 1.078 mmol), and N,N-diisopropylethylamine (0.205 mL, 1.176 mmol) in DMF (20 mL) was stirred for 16 hours. The reaction was concentrated, and the resulting residue was purified via silica gel chromatography (0% to 30% EtOAc/hexanes) to afford 2-chloro-N-((1-ethyl-1H-pyrazol-3-yl)methyl)-6-nitroaniline (194 mg) as an orange oil. LC-MS (ES) m/z = 281, 283 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 7.95 (dd, J = 1.7, 8.5 Hz, 1H), 7.56 (dd, J = 1.5, 7.9 Hz, 1H), 7.35 (d, J = 2.3 Hz, 1H), 6.82 (t, J = 8.1 Hz, 1H), 6.15 (d, J = 2.3 Hz, 1H), 4.63 (s, 2H), 4.16 (q, J = 7.2 Hz, 2H), 1.49 (t, J = 7.4 Hz, 3H).

10 Intermediate 48

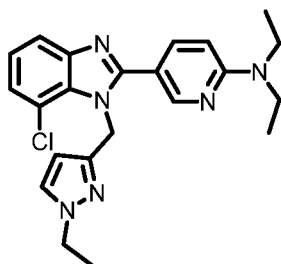
6-Chloro-N1-((1-ethyl-1H-pyrazol-3-yl)methyl)benzene-1,2-diamine



A mixture of 2-chloro-N-((1-ethyl-1H-pyrazol-3-yl)methyl)-6-nitroaniline (190 mg, 0.677 mmol) and $NiCl_2 \cdot 6H_2O$ (403 mg, 1.692 mmol) in CH_3OH (20 mL) was cooled in an ice water bath. Sodium borohydride (128 mg, 3.38 mmol) was then added, and the reaction mixture was stirred in ice water bath for 10 minutes. The reaction was concentrated. NH_4OH (28% in water) was added, and the resulting mixture was extracted with CH_2Cl_2 . The combined CH_2Cl_2 extract was dried over $MgSO_4$, filtered, and concentrated to afford 6-chloro-N1-((1-ethyl-1H-pyrazol-3-yl)methyl)benzene-1,2-diamine (160 mg) as a tan oil. LC-MS (ES) m/z = 251, 253 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, J = 2.0 Hz, 1H), 6.74 - 6.92 (m, 2H), 6.66 (dd, J = 1.5, 7.9 Hz, 1H), 6.18 (d, J = 2.3 Hz, 1H), 4.09 - 4.28 (m, 4H), 1.53 (t, J = 7.4 Hz, 3H).

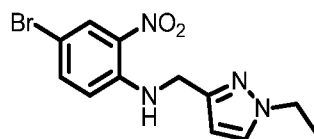
Example 21

25 5-(7-Chloro-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine



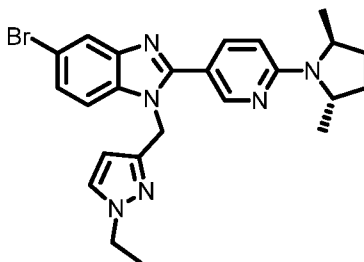
A mixture of 6-chloro-N1-((1-ethyl-1H-pyrazol-3-yl)methyl)benzene-1,2-diamine (155 mg, 0.495 mmol), 6-(diethylamino)nicotinaldehyde (88 mg, 0.495 mmol), and oxone (198 mg, 0.321 mmol) in DMF (10 mL) and water (4 mL) was stirred at room temperature for 30 minutes. Saturated aqueous NaHCO₃ was then added, and the resulting mixture was
5 extracted with EtOAc. The organic extract was washed sequentially with water and brine, dried over MgSO₄, filtered, and concentrated. Purification by reverse phase HPLC (25% CH₃CN/H₂O, 0.1% formic acid to 55% CH₃CN/H₂O, 0.1% formic acid) followed by silica gel chromatography (0% to 100% EtOAc/hexanes) afforded 5-(7-chloro-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (35 mg) as a
10 brown oil. LC-MS (ES) m/z = 409, 411 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.50 (d, J = 1.8 Hz, 1H), 7.82 (dd, J = 2.5, 9.1 Hz, 1H), 7.74 (dd, J = 3.7, 5.2 Hz, 1H), 7.32 (d, J = 2.0 Hz, 1H), 7.19 - 7.24 (m, 2H), 6.54 (d, J = 8.9 Hz, 1H), 5.88 (d, J = 2.3 Hz, 1H), 5.79 (s, 2H), 4.17 (q, J = 7.4 Hz, 2H), 3.59 (q, J = 7.1 Hz, 4H), 1.50 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.1 Hz, 6H).

15

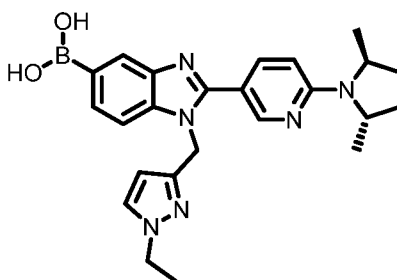
Intermediate 494-Bromo-N-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline

A solution of 4-bromo-1-fluoro-2-nitrobenzene (400 mg, 1.818 mmol), (1-ethyl-1H-pyrazol-3-yl)methanamine (228 mg, 1.818 mmol), and N,N-diisopropylethylamine (0.381 mL, 2.182 mmol) in DMF (15 mL) was stirred at room temperature for 16 hours. The reaction was concentrated, and the resulting residue was purified via silica gel chromatography (0% to 30% EtOAc/hexanes) to afford 4-bromo-N-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline (533 mg) as a orange solid. LC-MS (ES) m/z = 325, 327 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃):
20 δ 8.49 (br. s., 1H), 8.37 (d, J = 2.3 Hz, 1H), 7.52 (dd, J = 2.0, 9.1 Hz, 1H), 7.41 (d, J = 2.3 Hz, 1H), 6.94 (d, J = 9.1 Hz, 1H), 6.23 (d, J = 2.3 Hz, 1H), 4.55 (d, J = 5.3 Hz, 2H), 4.21 (q, J = 7.2 Hz, 2H), 1.54 (t, J = 7.4 Hz, 3H).

25

Example 22**5-Bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole**

- 5 A mixture of 4-bromo-N-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline (225 mg, 0.692 mmol), 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (141 mg, 0.692 mmol), and sodium hydrosulfite (120 mg, 85%, 0.588 mmol) in EtOH (4 mL) and water (2mL) was heated at 130 °C under microwave conditions for 20 minutes. The reaction mixture was filtered, and the filtrate was concentrated to dryness. CH₂Cl₂ was then added, and the
- 10 resulting mixture was filtered again. The filtrate was purified via silica gel chromatography (0% to 40% (3:1 EtOAc:EtOH)/hexanes) to afford 5-bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole (195 mg) as a white foam. LC-MS (ES) m/z = 479, 481 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.63 (br. s., 1H), 7.97 (s, 2H), 7.32 - 7.41 (m, 2H), 7.24 - 7.30 (m, 1H),
- 15 6.54 (d, J = 8.6 Hz, 1H), 6.00 (br. s., 1H), 5.45 (s, 2H), 4.39 (br.s., 2H), 4.20 (q, J = 7.4 Hz, 2H), 2.22 - 2.42 (m, 2H), 1.74 (d, J = 5.6 Hz, 2H), 1.53 (t, J = 7.4 Hz, 3H), 1.24 (d, J = 6.3 Hz, 6H).

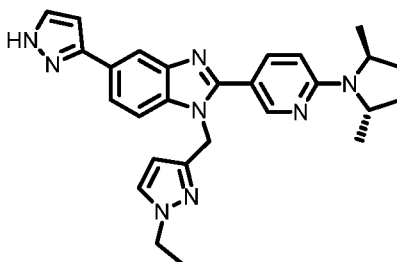
Example 23**(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-5-yl)boronic acid**

- Through a mixture of hypodiboric acid (45.4 mg, 0.507 mmol), 1,3-bis(diphenylphosphino)propane-nickel(II) chloride (9.16 mg, 0.017 mmol), 5-bromo-2-(6-
- 25 ((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-

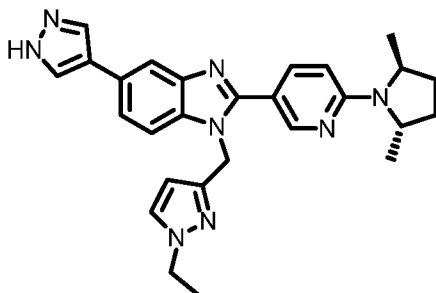
benzo[d]imidazole (162mg, 0.338 mmol), triphenylphosphine (8.86 mg, 0.034 mmol), and N,N-diisopropylethylamine (0.177 mL, 1.014 mmol) in EtOH (10 mL) was bubbled argon gas for 10 minutes, and the reaction mixture was heated at 80 °C for 16 hours. The reaction was concentrated, and the resulting residue was purified via silica gel chromatography (0% to 20% CH₃OH/CH₂Cl₂) to afford 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-5-yl)boronic acid (11 mg) as a off white solid. LC-MS (ES) m/z = 445 [M+H]⁺. ¹H NMR (400 MHz, CH₃OD): δ 8.53 (d, J = 2.0 Hz, 1H), 7.91 - 8.06 (m, 2H), 7.57 - 7.68 (m, 2H), 7.46 - 7.55 (m, 1H), 6.70 (d, J = 8.9 Hz, 1H), 6.11 (d, J = 2.3 Hz, 1H), 5.49 (s, 2H), 4.31 (br. s, 2H), 4.16 (q, J = 7.2 Hz, 2H), 2.28 - 2.45 (m, 2H), 1.75 (d, J = 5.8 Hz, 2H), 1.43 (t, J = 7.4 Hz, 3H), 1.22 (d, J = 6.1 Hz, 6H).

Example 24

2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-(1H-pyrazol-3-yl)-1H-benzo[d]imidazole



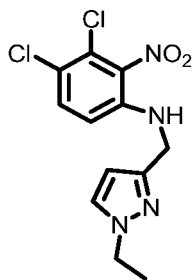
Through a mixture of 5-bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole (74 mg, 0.154 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (44.9 mg, 0.232 mmol), tetrakis(triphenylphosphine)palladium(0) (17.84 mg, 0.015 mmol), and Na₂CO₃ (40.9 mg, 0.386 mmol) in EtOH (4 mL) and water (1 mL) was bubble argon gas for 15 minutes. The reaction vial was capped, and the reaction mixture was heated at 75 °C for 6 hours. The reaction was filtered, and the filtrate was concentrated. CH₂Cl₂ was then added, and the resulting mixture was filtered again. The filtrate was purified via silica gel chromatography (0% to 100% (3:1 EtOAc:EtOH)/hexanes) to afford 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-(1H-pyrazol-3-yl)-1H-benzo[d]imidazole (35 mg) as a white solid. LC-MS (ES) m/z = 467 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.68 (d, J = 1.8 Hz, 1H), 8.19 (s, 1H), 8.07 (d, J = 6.1 Hz, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.68 (d, J = 2.0 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.37 (d, J = 2.3 Hz, 1H), 6.70 (d, J = 2.0 Hz, 1H), 6.56 (d, J = 9.1 Hz, 1H), 6.04 (d, J = 2.0 Hz, 1H), 5.51 (s, 2H), 4.32 (br. s., 2H), 4.17 - 4.26 (m, 2H), 2.32 (br. s., 2H), 1.74 (d, J = 5.8 Hz, 2H), 1.54 (t, J = 7.4 Hz, 3H), 1.25 (d, J = 6.1 Hz, 6H).

Example 25**2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-(1H-pyrazol-4-yl)-1H-benzo[d]imidazole**

5

Through a mixture of 5-bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole (74 mg, 0.154 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (68.1 mg, 0.232 mmol), tetrakis(triphenylphosphine)palladium(0) (8.92 mg, 7.72 μ mol), and Na_2CO_3 (32.7 mg, 0.309 mmol) in EtOH (4.00 mL) and water (1 mL) was bubbled argon gas for 15 minutes. The reaction vial was capped, and the mixture was heated at 95 °C for 16 hours. The reaction mixture was filtered, and the filtrate was concentrated. CH_2Cl_2 was added, and the resulting mixture was filtered again. The filtrate was purified via silica gel chromatography (0% to 20% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$) to afford 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-(1H-pyrazol-4-yl)-1H-benzo[d]imidazole (24 mg) as a white solid. LC-MS (ES) m/z = 467 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 8.64 (d, J = 2.0 Hz, 1H), 7.95 - 8.05 (m, 2H), 7.88 - 7.94 (m, 2H), 7.33 - 7.46 (m, 3H), 6.53 (d, J = 8.9 Hz, 1H), 6.01 (d, J = 2.0 Hz, 1H), 5.48 (s, 2H), 4.31 (br. s, 2H) 4.21 (q, J = 7.3 Hz, 2H), 2.25 - 2.40 (m, 2H), 1.73 (d, J = 5.6 Hz, 2H), 1.54 (t, J = 7.4 Hz, 3H), 1.24 (d, J = 6.3 Hz, 6H).

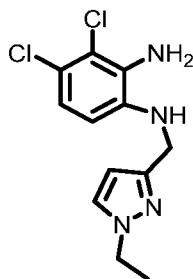
20

Intermediate 50**3,4-Dichloro-N-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline**

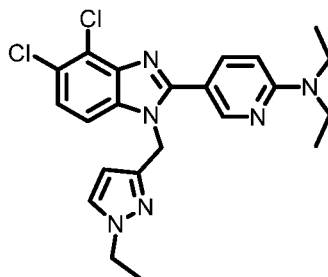
A solution of 1,2-dichloro-4-fluoro-3-nitrobenzene (200 mg, 0.952 mmol), (1-ethyl-1H-pyrazol-3-yl)methanamine (131 mg, 1.048 mmol), and N,N-diisopropylethylamine (0.200 mL, 1.143 mmol) in DMF (20 mL) was stirred for 16 hours. The reaction was concentrated, and the resulting residue was purified via silica gel chromatography (0% to 50% EtOAc/hexanes) to afford 3,4-dichloro-N-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline (185 mg) as an orange oil. LC-MS (ES) m/z = 315 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 - 7.53 (m, 2H), 6.85 (d, J = 9.4 Hz, 1H), 6.20 (d, J = 2.3 Hz, 1H), 5.98 (br. s., 1H), 4.43 (d, J = 5.1 Hz, 2H), 4.19 (q, J = 7.4 Hz, 2H), 1.53 (t, J = 7.4 Hz, 3H).

10 Intermediate 51

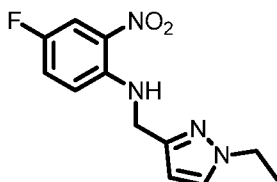
3,4-Dichloro-N1-((1-ethyl-1H-pyrazol-3-yl)methyl)benzene-1,2-diamine



A mixture of 3,4-dichloro-N-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline (185 mg, 0.587 mmol) and $NiCl_2 \cdot 6H_2O$ (349 mg, 1.468 mmol) in CH_3OH (20 mL) was cooled in a ice water bath. Sodium borohydride (111 mg, 2.94 mmol) was added, and the reaction mixture was stirred in ice water bath for 10 minutes. The reaction was concentrated. NH_4OH (28% in water) was added, and the resulting mixture was extracted with CH_2Cl_2 . The combined CH_2Cl_2 extract was dried over $MgSO_4$, filtered, and concentrated to afford 3,4-dichloro-N1-((1-ethyl-1H-pyrazol-3-yl)methyl)benzene-1,2-diamine (196 mg). LC-MS (ES) m/z = 285 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J = 2.0 Hz, 1H), 6.90 (d, J = 8.6 Hz, 1H), 6.64 (d, J = 8.6 Hz, 1H), 6.23 (d, J = 2.3 Hz, 1H), 4.33 (s, 2H), 4.20 (q, J = 7.2 Hz, 2H), 3.99 (br. s., 1H), 1.53 (t, J = 7.4 Hz, 3H).

Example 26**5-(4,5-Dichloro-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzod[imidazol-2-yl]-N,N-diethylpyridin-2-amine**

- 5 A mixture of 3,4-dichloro-N1-((1-ethyl-1H-pyrazol-3-yl)methyl)benzene-1,2-diamine (95 mg, 0.267 mmol), 6-(diethylamino)nicotinaldehyde (47.5 mg, 0.267 mmol), and oxone (106 mg, 0.173 mmol) in DMF (10 mL) and water (4 mL) was stirred for 30 minutes. Saturated aqueous NaHCO₃ was then added, and the resulting mixture was extracted with EtOAc. The combined organic extract was washed sequentially with water and brine, dried over
- 10 MgSO₄, filtered, and concentrated. Purification by reverse phase HPLC (28% CH₃CN/H₂O, 0.1% formic acid to 58% CH₃CN/H₂O, 0.1% formic acid) afforded 5-(4,5-dichloro-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (65 mg) as a white solid. LC-MS (ES) m/z = 443 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.93 (s, 1H), 8.45 (d, J = 7.9 Hz, 1H), 7.35 - 7.50 (m, 3H), 6.92 (d, J = 9.4 Hz, 1H), 6.22 (d, J = 1.8 Hz, 1H), 5.44 (s, 2H), 4.18 (q, J = 7.4 Hz, 2H), 3.76 (d, J = 6.8 Hz, 4H), 1.48 (t, J = 7.4 Hz, 3H),
- 15 1.38 (t, J = 7.1 Hz, 6H).

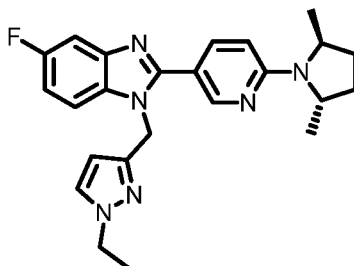
Intermediate 52**N-((1-Ethyl-1H-pyrazol-3-yl)methyl)-4-fluoro-2-nitroaniline**

- 20 A solution of 1,4-difluoro-2-nitrobenzene (310 mg, 1.949 mmol), (1-ethyl-1H-pyrazol-3-yl)methanamine (268 mg, 2.143 mmol), and N,N-diisopropylethylamine (0.408 mL, 2.338 mmol) in DMF (15 mL) was stirred at room temperature for 16 hours. The reaction was concentrated, and the resulting residue was purified via silica gel chromatography (0% to
- 25 35% EtOAc/hexanes) to afford N-((1-ethyl-1H-pyrazol-3-yl)methyl)-4-fluoro-2-nitroaniline (390 mg) as an orange solid. LC-MS (ES) m/z = 265 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.39 (br. s., 1H), 7.94 (dd, J = 2.9, 9.25 Hz, 1H), 7.41 (d, J = 2.3 Hz, 1H), 7.24 - 7.30 (m,

1H), 7.01 (dd, $J = 4.6, 9.4$ Hz, 1H), 6.24 (d, $J = 2.3$ Hz, 1H), 4.57 (d, $J = 5.3$ Hz, 2H), 4.22 (q, $J = 7.2$ Hz, 2H), 1.54 (t, $J = 7.4$ Hz, 3H).

Example 27

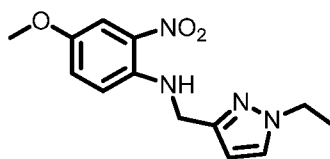
5 **2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-fluoro-1H-benzo[d]imidazole**



A mixture of N-((1-ethyl-1H-pyrazol-3-yl)methyl)-4-fluoro-2-nitroaniline (125 mg, 0.473 mmol), sodium hydrosulfite (247 mg, 85%, 1.206 mmol), and 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (101 mg, 0.497 mmol) in EtOH (4 mL) and water (2 mL) was heated at 130 °C under microwave conditions for 20 minutes. The reaction was filtered, and the filtrate was concentrated to dryness. CH₂Cl₂ was added, and the resulting mixture was filtered again. The filtrate was purified via silica gel chromatography (0% to 40% (3:1 EtOAc:EtOH)/hexanes) to afford 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-fluoro-1H-benzo[d]imidazole (114 mg) as a viscous oil. LC-MS (ES) $m/z = 419$ [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.60 (d, $J = 2.0$ Hz, 1H), 7.93 (dd, $J = 2.5, 8.9$ Hz, 1H), 7.47 (dd, $J = 2.3, 9.4$ Hz, 1H), 7.34 (d, $J = 2.3$ Hz, 1H), 7.24 - 7.32 (m, 1H), 6.98 (dt, $J = 2.3, 9.1$ Hz, 1H), 6.51 (d, $J = 8.9$ Hz, 1H), 5.98 (d, $J = 2.0$ Hz, 1H), 5.44 (s, 2H), 4.29 (br. s., 2H), 4.19 (q, $J = 7.3$ Hz, 2H), 2.30 (br. s., 2H), 1.64 - 1.81 (m, 2H), 1.52 (t, $J = 7.2$ Hz, 3H), 1.23 (d, $J = 6.1$ Hz, 6H).

Intermediate 53

N-((1-Ethyl-1H-pyrazol-3-yl)methyl)-4-methoxy-2-nitroaniline

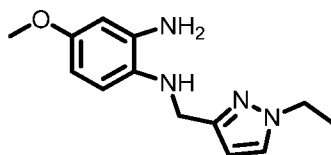


25 A solution of 1-fluoro-4-methoxy-2-nitrobenzene (151 mg, 0.882 mmol), (1-ethyl-1H-pyrazol-3-yl)methanamine (121 mg, 0.971 mmol), and N,N-diisopropylethylamine (185 μ L, 1.059 mmol) in DMF was stirred at room temperature for 16 hours. The reaction was concentrated, and the resulting residue was purified via silica gel chromatography (0% to

50% EtOAc/hexanes) to afford N-((1-ethyl-1H-pyrazol-3-yl)methyl)-4-methoxy-2-nitroaniline (76 mg) as a red oil. LC-MS (ES) m/z = 277 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.40 (br. s., 1H), 7.66 (d, J = 3.0 Hz, 1H), 7.39 (d, J = 2.3 Hz, 1H), 7.17 (dd, J = 3.0, 9.4 Hz, 1H), 6.98 (d, J = 9.4 Hz, 1H), 6.23 (d, J = 2.3 Hz, 1H), 4.56 (d, J = 5.1 Hz, 2H), 4.20 (d, J = 7.1 Hz, 2H), 3.83 (s, 3H), 1.53 (t, J = 7.4 Hz, 3H).

Intermediate 54

N1-((1-Ethyl-1H-pyrazol-3-yl)methyl)-4-methoxybenzene-1,2-diamine

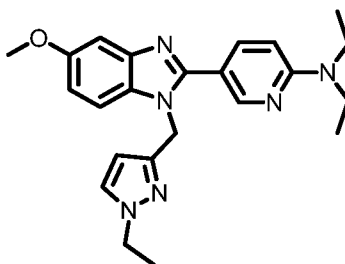


10 A mixture of N-((1-ethyl-1H-pyrazol-3-yl)methyl)-4-methoxy-2-nitroaniline (76 mg, 0.275 mmol) and $NiCl_2 \cdot 6H_2O$ (164 mg, 0.688 mmol) in CH_3OH (20 mL) was cooled in a ice water bath. Sodium borohydride (52.0 mg, 1.375 mmol) was added, and the reaction mixture was stirred in ice water bath for 10 minutes. The reaction was concentrated, NH_4OH (28% in water) was added, and the resulting mixture was extracted with CH_2Cl_2 . The combined organic extract was dried over $MgSO_4$, filtered and concentrated to afford N1-((1-ethyl-1H-pyrazol-3-yl)methyl)-4-methoxybenzene-1,2-diamine (73 mg). LC-MS (ES) m/z = 247 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, J = 2.3 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 6.32 - 6.42 (m, 2H), 6.24 (d, J = 2.3 Hz, 1H), 4.28 (s, 2H), 4.14 - 4.23 (m, 2H), 3.74 - 3.79 (m, 3H), 1.52 (t, J = 7.4 Hz, 3H).

20

Example 28

N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-methoxy-1H-benzo[d]imidazol-2-yl)pyridin-2-amine



25 A mixture of N1-((1-ethyl-1H-pyrazol-3-yl)methyl)-4-methoxybenzene-1,2-diamine (73 mg, 0.237 mmol), 6-(diethylamino)nicotinaldehyde (42.3 mg, 0.237 mmol), and oxone (95 mg, 0.154 mmol) in DMF (10 mL) and water (4 mL) was stirred at room temperature for 30 minutes. Saturated aqueous $NaHCO_3$ was added, and the resulting mixture was extracted

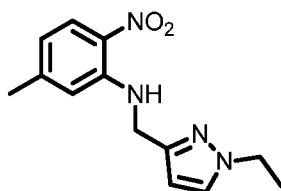
with EtOAc. The organic extract was washed sequentially with water and brine, dried over MgSO_4 , filtered, and concentrated. The resulting residue was purified via silica gel chromatography (0% to 80% EtOAc/hexanes) to afford N,N-diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-methoxy-1H-benzo[d]imidazol-2-yl)pyridin-2-amine (23 mg) as a oil.

- 5 LC-MS (ES) m/z = 405 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 8.59 (d, J = 2.0 Hz, 1H), 7.97 (dd, J = 2.4, 9.00 Hz, 1H), 7.34 (d, J = 2.0 Hz, 2H), 7.26 (d, J = 8.9 Hz, 1H), 6.90 (dd, J = 2.4, 8.7 Hz, 1H), 6.61 (d, J = 8.9 Hz, 1H), 5.99 (d, J = 2.3 Hz, 1H), 5.43 (s, 2H), 4.20 (q, J = 7.2 Hz, 2H), 3.90 (s, 3H), 3.61 (q, J = 7.1 Hz, 4H), 1.54 (t, J = 7.4 Hz, 3H), 1.26 (t, J = 7.1 Hz, 6H).

10

Intermediate 55

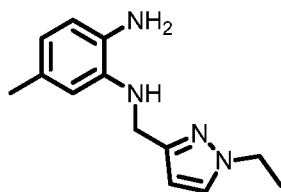
N-((1-Ethyl-1H-pyrazol-3-yl)methyl)-5-methyl-2-nitroaniline



- A solution of 2-fluoro-4-methyl-1-nitrobenzene (184 mg, 1.186 mmol), (1-ethyl-1H-pyrazol-3-yl)methanamine (163 mg, 1.305 mmol), and N,N-diisopropylethylamine (0.249 mL, 1.423 mmol) in DMF (15 mL) was stirred at room temperature for 16 hours. The reaction was concentrated, and the resulting residue was purified via silica gel chromatography (0% to 30% EtOAc/hexanes) to afford N-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-methyl-2-nitroaniline (152 mg) as a yellow solid. LC-MS (ES) m/z = 261 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 8.52 (br. s., 1H), 8.12 (d, J = 8.6 Hz, 1H), 7.41 (d, J = 2.3 Hz, 1H), 6.79 (s, 1H), 6.52 (dd, J = 1.5, 8.6 Hz, 1H), 6.25 (d, J = 2.3 Hz, 1H), 4.56 (d, J = 5.3 Hz, 2H), 4.22 (q, J = 7.4 Hz, 2H), 2.37 (s, 3H), 1.55 (t, J = 7.4 Hz, 3H).
- 20

Intermediate 56

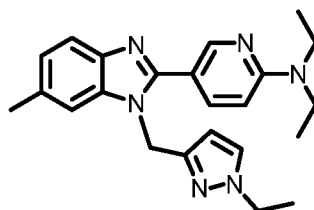
- 25 N1-((1-Ethyl-1H-pyrazol-3-yl)methyl)-5-methylbenzene-1,2-diamine



A mixture of N-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-methyl-2-nitroaniline (150 mg, 0.576 mmol) and $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (343 mg, 1.441 mmol) in CH_3OH (20 mL) was cooled in a ice water

bath. Sodium borohydride (109 mg, 2.88 mmol) was added, and the reaction mixture was stirred in ice water bath for 10 minutes. The reaction was concentrated, NH_4OH (28% in water) was added, and the resulting mixture was extracted with CH_2Cl_2 . The combined organic extract was dried over MgSO_4 , filtered, and concentrated to afford N1-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-methylbenzene-1,2-diamine (136 mg). LC-MS (ES) m/z = 231 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 7.36 (br. s., 1H), 6.56 - 6.72 (m, 2H), 6.52 (d, J = 6.8 Hz, 1H), 6.24 (br. s., 1H), 4.34 (br. s., 2H), 4.18 (q, J = 7.1 Hz, 2H), 2.29 (br. s., 3H), 1.51 (t, J = 7.1 Hz, 3H).

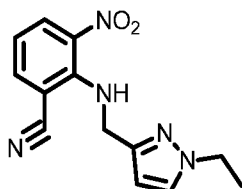
10

Example 29**N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-6-methyl-1H-benzo[d]imidazol-2-yl)pyridin-2-amine**

15 A mixture of N1-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-methylbenzene-1,2-diamine (136 mg, 0.591 mmol), 6-(diethylamino)nicotinaldehyde (105 mg, 0.591 mmol), and oxone (236 mg, 0.384 mmol) in DMF (5 mL) and water (5 mL) was stirred at room temperature for 30 minutes. Saturated aqueous NaHCO_3 was then added, and the resulting mixture was extracted with EtOAc. The combined organic extract was washed sequentially with water and brine, dried over MgSO_4 , filtered, and concentrated. The resulting residue was purified via silica gel chromatography (0% to 100% EtOAc/hexanes) to afford N,N-diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-6-methyl-1H-benzo[d]imidazol-2-yl)pyridin-2-amine (119 mg) as a solid. LC-MS (ES) m/z = 389 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 8.58 (d, J = 2.5 Hz, 1H), 7.96 (dd, J = 2.4, 9.0 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.17 (s, 1H), 7.12 (dd, J = 1.1, 8.2 Hz, 1H), 6.59 (d, J = 8.9 Hz, 1H), 5.97 (d, J = 2.3 Hz, 1H), 5.43 (s, 2H), 4.21 (q, J = 7.2 Hz, 2H), 3.60 (q, J = 7.1 Hz, 4H), 2.49 (s, 3H), 1.55 (t, J = 7.2 Hz, 3H), 1.25 (t, J = 7.0 Hz, 6H).

Intermediate 57

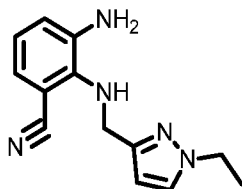
2-(((1-Ethyl-1H-pyrazol-3-yl)methyl)amino)-3-nitrobenzonitrile



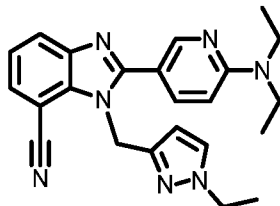
A solution of 2-fluoro-3-nitrobenzonitrile (150 mg, 0.903 mmol), (1-ethyl-1H-pyrazol-3-yl)methanamine (124 mg, 0.993 mmol), and N,N-diisopropylethylamine (0.189 mL, 1.084 mmol) in DMF (15 mL) was stirred at room temperature for 16 hours. The reaction was concentrated, and the resulting residue was purified via silica gel chromatography (0% to 50% EtOAc/hexanes) to afford 2-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)-3-nitrobenzonitrile (210 mg) as a yellow solid. LC-MS (ES) m/z = 272 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 9.03 (br. s., 1H), 8.45 (dd, J = 1.8, 8.4 Hz, 1H), 7.81 (dd, J = 1.7, 7.5 Hz, 1H), 7.44 (d, J = 2.3 Hz, 1H), 6.79 (dd, J = 7.6, 8.6 Hz, 1H), 6.30 (d, J = 2.3 Hz, 1H), 5.11 (d, J = 4.6 Hz, 2H), 4.23 (q, J = 7.4 Hz, 2H), 1.55 (t, J = 7.4 Hz, 3H).

Intermediate 58

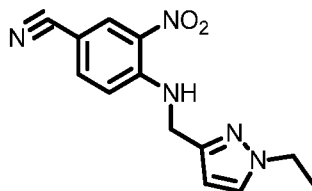
3-Amino-2-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)benzonitrile



To a solution of 2-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)-3-nitrobenzonitrile (210 mg, 0.774 mmol) in EtOH (25 mL) was added tin(II) chloride (294 mg, 1.548 mmol), and the reaction mixture was refluxed for 2 hours. The reaction was poured onto ice and treated with saturated aqueous $NaHCO_3$ until pH~9. EtOAc was then added, and the resulting mixture was filtered through celite. The organic layer was separated, and the aqueous phase was further extracted with EtOAc (3x). The combined organic extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified via silica gel chromatography (0% to 100% EtOAc/hexanes) to afford 3-amino-2-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)benzonitrile (69 mg) as a oil. LC-MS (ES) m/z = 242 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J = 2.3 Hz, 1H), 7.06 (dt, J = 1.5, 8.0 Hz, 2H), 6.86 - 6.98 (m, 1H), 6.17 (d, J = 2.3 Hz, 1H), 4.51 (s, 2H), 4.40 (s, 3H), 4.20 (q, J = 7.2 Hz, 2H), 1.50 (t, J = 7.2 Hz, 3H).

Example 30**2-(6-(Diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-7-carbonitrile**

- 5 A mixture of 3-amino-2-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)benzonitrile (69 mg, 0.229 mmol), 6-(diethylamino)nicotinaldehyde (44.9 mg, 0.252 mmol), and oxone (91 mg, 0.149 mmol) in DMF (10 mL) and water (4 mL) was stirred at room temperature for 30 minutes. Saturated aqueous NaHCO₃ was added, and the resulting mixture was extracted with EtOAc. The combined organic extract was washed sequentially with water and brine, dried
- 10 over MgSO₄, filtered, and concentrated. The resulting residue was purified via silica gel chromatography (0% to 100% EtOAc/hexanes) to afford 2-(6-(diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-7-carbonitrile (67 mg) as a tan solid. LC-MS (ES) *m/z* = 400 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.61 (br. s., 1H), 8.06 (d, *J* = 8.1 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.60 (dd, *J* = 0.8, 7.6 Hz, 1H), 7.34 - 7.45 (m, 2H), 6.58 (d, *J* = 8.9 Hz, 1H), 6.08 (br. s., 1H), 5.77 (s, 2H), 4.15 (q, *J* = 7.3 Hz, 2H), 3.62
- 15 (q, *J* = 6.7 Hz, 4H), 1.48 (t, *J* = 7.4 Hz, 3H), 1.26 (d, *J* = 13.9 Hz, 6H).

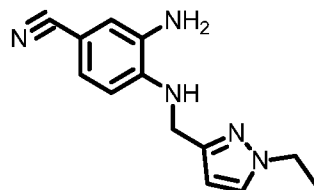
Intermediate 59**4-(((1-Ethyl-1H-pyrazol-3-yl)methyl)amino)-3-nitrobenzonitrile**

- 20 A solution of 4-fluoro-3-nitrobenzonitrile (150 mg, 0.903 mmol), (1-ethyl-1H-pyrazol-3-yl)methanamine (124 mg, 0.993 mmol), and N,N-diisopropylethylamine (0.189 mL, 1.084 mmol) in DMF (15 mL) was stirred at room temperature for 16 hours. The reaction was concentrated, and the resulting residue was purified via silica gel chromatography (0% to
- 25 50% EtOAc/hexanes) to afford 4-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)-3-nitrobenzonitrile (197 mg) as a yellow solid. LC-MS (ES) *m/z* = 272 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.89 (br. s., 1H), 8.57 (d, *J* = 2.0 Hz, 1H), 7.64 (dd, *J* = 2.0, 8.9 Hz, 1H),

7.43 (d, $J = 2.3$ Hz, 1H), 7.10 (d, $J = 8.9$ Hz, 1H), 6.25 (d, $J = 2.0$ Hz, 1H), 4.61 (d, $J = 5.1$ Hz, 2H), 4.22 (q, $J = 7.4$ Hz, 2H), 1.54 (t, $J = 7.4$ Hz, 3H).

Intermediate 60

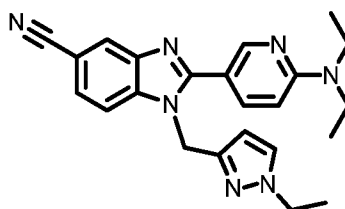
5 3-Amino-4-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)benzonitrile



To a solution of 4-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)-3-nitrobenzonitrile (192 mg, 0.708 mmol) in EtOH (30 mL) was added tin(II) chloride (268 mg, 1.416 mmol), and the reaction mixture was refluxed for 2 hours. Additional tin(II) chloride (268 mg, 1.416 mmol) was added, and the reaction mixture was refluxed for 1 hour. The reaction mixture was then stirred at room temperature for 16 hours. The reaction was poured onto ice and treated with saturated aqueous NaHCO₃ until pH~9. EtOAc was then added, and the resulting mixture was filtered through celite. The organic layer was separated, and the aqueous phase was further extracted with EtOAc (3x). The combined organic extract was washed with brine, dried over MgSO₄, filtered, and concentrated. The resulting residue was purified via silica gel chromatography (0% to 100% EtOAc/hexanes) to afford 3-amino-4-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)benzonitrile (113 mg) as a white solid. LC-MS (ES) $m/z = 242$ [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.41 (d, $J = 2.0$ Hz, 1H), 7.20 (dd, $J = 1.9, 8.2$ Hz, 1H), 6.98 (d, $J = 1.8$ Hz, 1H), 6.72 (d, $J = 8.4$ Hz, 1H), 6.24 (d, $J = 2.3$ Hz, 1H), 4.41 (s, 2H), 4.20 (q, $J = 7.4$ Hz, 2H), 1.53 (t, $J = 7.4$ Hz, 3H).

Example 31

25 2-(6-(Diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carbonitrile

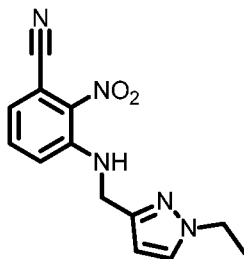


A mixture of 3-amino-4-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)benzonitrile (113 mg, 0.375 mmol), 6-(diethylamino)nicotinaldehyde (66.8 mg, 0.375 mmol), and oxone (150 mg,

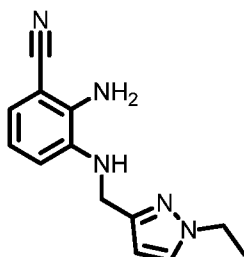
0.244 mmol) in DMF (10 mL) and water (4 mL) was stirred at room temperature for 30 minutes. Saturated aqueous NaHCO₃ was then added, and the resulting mixture was extracted with EtOAc. The combined organic extract was washed sequentially with water and brine, dried over MgSO₄, filtered, and concentrated. The resulting residue was purified via silica gel chromatography (0% to 100% EtOAc/hexanes) to afford 2-(6-(diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carbonitrile (124 mg) as a foam. LC-MS (ES) *m/z* = 400 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.64 (br. s., 1H), 8.13 (s, 1H), 7.99 (d, *J* = 7.6 Hz, 1H), 7.45 - 7.54 (m, 2H), 7.37 (d, *J* = 2.3 Hz, 1H), 6.63 (d, *J* = 8.9 Hz, 1H), 6.02 (s, 1H), 5.48 (s, 2H), 4.20 (q, *J* = 7.3 Hz, 2H), 3.63 (q, *J* = 7.1 Hz, 4H), 1.53 (t, *J* = 7.4 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 6H).

Intermediate 61

3-(((1-Ethyl-1H-pyrazol-3-yl)methyl)amino)-2-nitrobenzonitrile



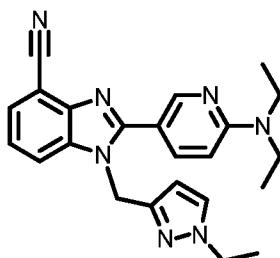
A solution of 3-fluoro-2-nitrobenzonitrile (150 mg, 0.903 mmol), (1-ethyl-1H-pyrazol-3-yl)methanamine (124 mg, 0.993 mmol), and N,N-diisopropylethylamine (0.189 mL, 1.084 mmol) in DMF (15 mL) was stirred at room temperature for 16 hours. The reaction was concentrated, and the resulting residue was purified via silica gel chromatography (0% to 50% EtOAc/hexanes) to afford 3-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)-2-nitrobenzonitrile (177 mg) as an orange solid. LC-MS (ES) *m/z* = 272 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.55 (br. s., 1H), 7.51 (dd, *J* = 7.5, 8.7 Hz, 1H), 7.43 (d, *J* = 2.0 Hz, 1H), 7.33 (d, *J* = 1.0 Hz, 1H), 7.17 (dd, *J* = 1.3, 7.1 Hz, 1H), 6.25 (d, *J* = 2.3 Hz, 1H), 4.60 (d, *J* = 5.3 Hz, 2H), 4.23 (q, *J* = 7.4 Hz, 2H), 1.55 (t, *J* = 7.4 Hz, 3H).

Intermediate 622-Amino-3-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)benzonitrile

To a solution of 3-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)-2-nitrobenzonitrile (177 mg, 0.652 mmol) in EtOH (25 mL) was added tin(II) chloride (371 mg, 1.957 mmol), and the reaction mixture was refluxed for 4 hour, then stirred for 16 hours at room temperature. Additional tin(II) chloride (371 mg, 1.957 mmol) was added, and the reaction mixture was refluxed for 4 hours. The reaction was poured onto ice and treated with saturated aqueous NaHCO₃ until pH~9. EtOAc was then added, and the resulting mixture was filtered through celite. The organic layer was separated, and the aqueous phase was extracted with additional EtOAc (3x). The combined organic extract was washed with brine, dried over MgSO₄, filtered, and concentrated. The resulting residue was purified via silica gel chromatography (0% to 100% EtOAc/hexanes) to afford 2-amino-3-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)benzonitrile (98 mg) as a yellow solid. LC-MS (ES) m/z = 242 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.40 (d, J = 2.3 Hz, 1H), 7.00 (dd, J = 1.3, 7.9 Hz, 1H), 6.95 (dd, J = 1.3, 7.9 Hz, 1H), 6.76 - 6.85 (m, 1H), 6.26 (d, J = 2.3 Hz, 1H), 4.36 (s, 2H), 4.20 (q, J = 7.4 Hz, 2H), 1.53 (t, J = 7.4 Hz, 3H).

Example 32

2-(6-(Diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-4-carbonitrile

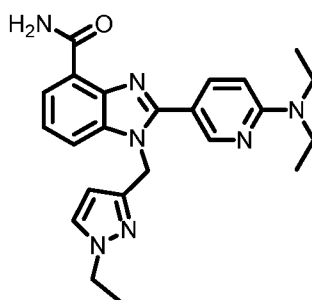


A mixture of 2-amino-3-(((1-ethyl-1H-pyrazol-3-yl)methyl)amino)benzonitrile (98 mg, 0.325 mmol), 6-(diethylamino)nicotinaldehyde (63.7 mg, 0.357 mmol), and oxone (130 mg, 0.211 mmol) in DMF (10 mL) and water (4 mL) was stirred at room temperature for 30 minutes. Saturated aqueous NaHCO₃ was then added, and the resulting mixture was extracted with

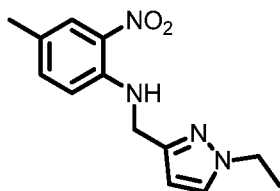
EtOAc. The combined organic extract was washed sequentially with water and brine, dried over MgSO₄, filtered, and concentrated. The resulting residue was purified via silica gel chromatography (0% to 100% EtOAc/hexanes) followed by reverse phase HPLC (15% CH₃CN/H₂O, 0.1% formic acid to 45% CH₃CN/H₂O, 0.1% formic acid) to afford 2-(6-(diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-4-carbonitrile (60 mg) as a white solid. LC-MS (ES) m/z = 400 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 8.63 (d, J = 2.3 Hz, 1H), 8.34 (dd, J = 2.2, 9.5 Hz, 1H), 7.92 (dd, J = 0.9, 8.2 Hz, 1H), 7.75 (dd, J = 0.9, 7.5 Hz, 1H), 7.64 (d, J = 2.3 Hz, 1H), 7.43 - 7.51 (m, 1H), 7.26 (d, J = 9.4 Hz, 1H), 6.28 (d, J = 2.3 Hz, 1H), 5.58 (s, 2H), 4.15 (q, J = 7.2 Hz, 2H), 3.73 (q, J = 7.1 Hz, 4H), 1.41 (t, J = 7.2 Hz, 3H), 1.34 (t, J = 7.1 Hz, 6H).

Example 33

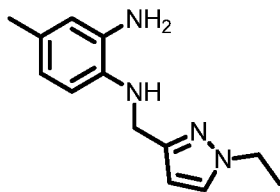
2-(6-(Diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-4-carboxamide



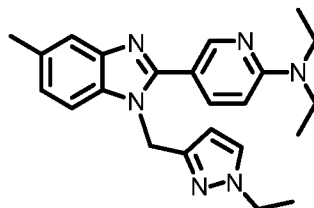
A solution of 2-(6-(diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-4-carbonitrile (40 mg, 0.100 mmol) and 1N NaOH (0.501 mL, 0.501 mmol) in water (5 mL) and EtOH (5 mL) was heated at 132 °C under microwave conditions for 100 minutes. The reaction was concentrated, and the resulting material was purified by reverse phase HPLC (10% CH₃CN/H₂O, 0.1% formic acid to 50% CH₃CN/H₂O, 0.1% formic acid) to afford 2-(6-(diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-4-carboxamide (26-mg) as an off-white solid. LC-MS (ES) m/z = 418 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 9.79 (br. s., 1H), 8.93 (d, J = 1.5 Hz, 1H), 8.34 (dd, J = 1.8, 9.4 Hz, 1H), 8.18 (d, J = 7.4 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.36 - 7.50 (m, 2H), 6.89 (d, J = 9.4 Hz, 1H), 6.68 (br. s., 1H), 6.17 (d, J = 2.3 Hz, 1H), 5.48 (s, 2H), 4.17 (q, J = 7.4 Hz, 2H), 3.73 (q, J = 7.1 Hz, 4H), 1.48 (t, J = 7.4 Hz, 3H), 1.36 (t, J = 7.1 Hz, 6H).

Intermediate 63N-((1-Ethyl-1H-pyrazol-3-yl)methyl)-4-methyl-2-nitroaniline

A solution of 1-fluoro-4-methyl-2-nitrobenzene (158 mg, 1.019 mmol), (1-ethyl-1H-pyrazol-3-yl)methanamine (140 mg, 1.120 mmol), and N,N-diisopropylethylamine (213 μ l, 1.222 mmol) in DMF was stirred at room temperature for 16 hours. The reaction was concentrated, and the resulting residue was purified via silica gel chromatography (0% to 30% EtOAc/hexanes) to afford N-((1-ethyl-1H-pyrazol-3-yl)methyl)-4-methyl-2-nitroaniline (77 mg) as a yellow/orange oil. LC-MS (ES) m/z = 261 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (br. s., 1H), 8.00 (d, J = 1.0 Hz, 1H), 7.37 (d, J = 2.3 Hz, 1H), 7.22 - 7.31 (m, 1H), 6.90 (d, J = 8.6 Hz, 1H), 6.21 (d, J = 2.3 Hz, 1H), 4.53 (d, J = 5.1 Hz, 2H), 4.18 (q, J = 7.2 Hz, 2H), 2.28 (s, 3H), 1.51 (t, J = 7.2 Hz, 3H).

Intermediate 64N1-((1-Ethyl-1H-pyrazol-3-yl)methyl)-4-methylbenzene-1,2-diamine

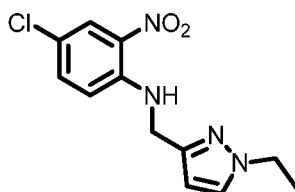
A mixture of N-((1-ethyl-1H-pyrazol-3-yl)methyl)-4-methyl-2-nitroaniline (77 mg, 0.296 mmol) and $NiCl_2 \cdot 6H_2O$ (176 mg, 0.740 mmol) in CH_3OH (20 mL) was cooled in a ice water bath. Sodium borohydride (56.0 mg, 1.479 mmol) was added, and the reaction mixture was stirred in ice water bath for 10 minutes. The reaction was concentrated, NH_4OH (28%) was added, and the resulting mixture was extracted with CH_2Cl_2 . The combined organic extract was dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified via silica gel chromatography (0% to 100% EtOAc/hexanes) to afford N1-((1-ethyl-1H-pyrazol-3-yl)methyl)-4-methylbenzene-1,2-diamine (53 mg). LC-MS (ES) m/z = 231 $[M+H]^+$. This material was used immediately into the next step.

Example 34**N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-methyl-1H-benzo[d]imidazol-2-yl)pyridin-2-amine**

- 5 A mixture of N1-((1-ethyl-1H-pyrazol-3-yl)methyl)-4-methylbenzene-1,2-diamine (54 mg, 0.234 mmol), 6-(diethylamino)nicotinaldehyde (41.8mg, 0.234mmol), and oxone (94 mg, 0.152 mmol) in water (10 mL) and DMF (10 mL) was stirred at room temperature for 30 minutes. Saturated aqueous NaHCO₃ was added, and the resulting mixture was extracted with EtOAc. The combined EtOAc extract was washed sequentially with water and brine,
- 10 dried over MgSO₄, filtered, and concentrated. The resulting residue was purified via silica gel chromatography (0% to 100% EtOAc/hexanes) followed by reverse phase HPLC (10% CH₃CN/H₂O, 0.1% formic acid to 40% CH₃CN/H₂O, 0.1% formic acid) to afford N,N-diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-methyl-1H-benzo[d]imidazol-2-yl)pyridin-2-amine (18 mg) as a white solid. LC-MS (ES) m/z = 389 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.60 (s, 1H), 8.01 (br. s., 1H), 7.66 (br. s., 1H), 7.10 (d, J = 8.1 Hz, 1H), 6.62 (d, J = 8.9 Hz, 1H), 5.99 (s, 1H), 5.38 - 5.54 (m, 2H), 4.20 (q, J = 7.2 Hz, 2H), 3.61 (q, J = 7.0 Hz, 4H), 2.52 (s, 3H), 1.54 (t, J = 7.4 Hz, 3H), 1.15 - 1.36 (m, 6H).
- 15

Intermediate 65

- 20 **4-Chloro-N-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline**

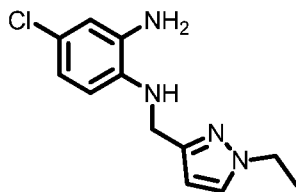


- A solution of 4-chloro-1-fluoro-2-nitrobenzene (225 mg, 1.282 mmol), (1-ethyl-1H-pyrazol-3-yl)methanamine (176 mg, 1.410 mmol), and N,N-diisopropylethylamine (269 μl, 1.538 mmol) in DMF was stirred at room temperature for 16 hours. The reaction was
- 25 concentrated, and the resulting residue was purified via silica gel chromatography (0% to 27% EtOAc/hexanes) to afford 4-chloro-N-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline (289 mg) as a yellow/orange oil. LC-MS (ES) m/z = 281, 283 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.47 (br. s., 1H), 8.21 (d, J = 2.5 Hz, 1H), 7.40 (dt, J = 2.7, 4.37 Hz, 2H), 6.98 (d,

$J = 9.4$ Hz, 1H), 6.23 (d, $J = 2.0$ Hz, 1H), 4.55 (d, $J = 5.3$ Hz, 2H), 4.20 (q, $J = 7.4$ Hz, 2H), 1.53 (t, $J = 7.4$ Hz, 3H).

Intermediate 66

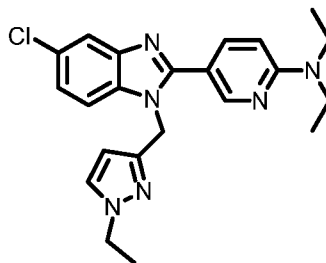
5 4-Chloro-N1-((1-ethyl-1H-pyrazol-3-yl)methyl)benzene-1,2-diamine



A mixture of 4-chloro-N-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline (100 mg, 0.356 mmol) and $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (212 mg, 0.891 mmol) in CH_3OH (20 mL) was cooled in a ice water bath. Sodium borohydride (67.4 mg, 1.781 mmol) was added, and the reaction mixture was stirred in ice water bath for 10 minutes. The reaction was concentrated, NH_4OH (28%) was added, and the resulting mixture was extracted with CH_2Cl_2 . The combined EtOAc extracts was dried over MgSO_4 , filtered, and concentrated to afford 4-chloro-N1-((1-ethyl-1H-pyrazol-3-yl)methyl)benzene-1,2-diamine (79 mg). LC-MS (ES) $m/z = 251, 253$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 7.38 (d, $J = 2.0$ Hz, 1H), 6.63 - 6.87 (m, 3H), 6.25 (d, $J = 2.3$ Hz, 1H), 4.34 (s, 2H), 4.19 (q, $J = 7.4$ Hz, 2H), 1.52 (t, $J = 7.4$ Hz, 3H).

Example 35

5-(5-Chloro-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine

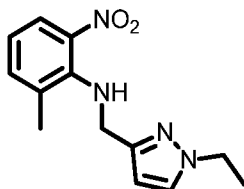


A mixture of 4-chloro-N1-((1-ethyl-1H-pyrazol-3-yl)methyl)benzene-1,2-diamine (79 mg, 0.252 mmol), 6-(diethylamino)nicotinaldehyde (44.9 mg, 0.252 mmol), and oxone (101 mg, 0.164 mmol) in DMF (10 mL) and water (4 mL) was stirred at room temperature for 30 minutes. Saturated aqueous NaHCO_3 was added, and the resulting mixture was extracted with EtOAc. The combined organic extract was washed sequentially with water and brine, dried over MgSO_4 , filtered, and concentrated. The resulting residue was purified via silica gel chromatography (0% to 80% EtOAc/hexanes) to afford 5-(5-chloro-1-((1-ethyl-1H-

pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (47 mg) as a glass. LC-MS (ES) m/z = 409/411 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, J = 2.3 Hz, 1H), 7.97 (dd, J = 2.3, 9.1 Hz, 1H), 7.80 (d, J = 1.5 Hz, 1H), 7.35 (d, J = 2.3 Hz, 1H), 7.29-7.33 (m, 1H), 7.21 (dd, J = 1.9, 8.5 Hz, 1H), 6.62 (d, J = 8.6 Hz, 1H), 5.99 (d, J = 2.3 Hz, 1H),
 5 5.44 (s, 2H), 4.20 (q, J = 7.4 Hz, 2H), 3.62 (q, J = 7.1 Hz, 4H), 1.53 (t, J = 7.4 Hz, 3H), 1.26 (t, J = 7.1 Hz, 6H).

Intermediate 67

N-((1-Ethyl-1H-pyrazol-3-yl)methyl)-2-methyl-6-nitroaniline



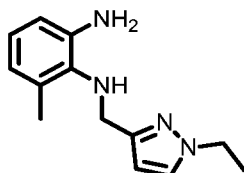
10

A solution of 2-fluoro-1-methyl-3-nitrobenzene (172 mg, 1.109 mmol), (1-ethyl-1H-pyrazol-3-yl)methanamine (153 mg, 1.220 mmol), and N,N-diisopropylethylamine (0.232 mL, 1.331 mmol) in DMF (20 mL) was heated at 60 °C for 16 hours. The reaction was concentrated, and the resulting residue was purified via silica gel chromatography (0% to 27%
 15 EtOAc/hexanes) to afford N-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-methyl-6-nitroaniline (99 mg) as a yellow/orange oil. LC-MS (ES) m/z = 261 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 7.89 (dd, J = 1.0, 8.4 Hz, 1H), 7.26 - 7.45 (m, 2H), 6.91 - 7.25 (m, 1H), 6.82 (dd, J = 7.4, 8.4 Hz, 1H), 6.09 (d, J = 2.4 Hz, 1H), 4.43 (s, 2H), 4.13 (q, J = 7.4 Hz, 2H), 2.51 (s, 3H), 1.47 (t, J = 7.4 Hz, 3H).

20

Intermediate 68

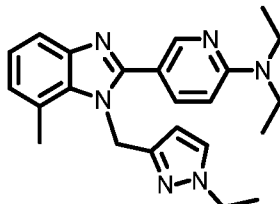
N1-((1-Ethyl-1H-pyrazol-3-yl)methyl)-6-methylbenzene-1,2-diamine



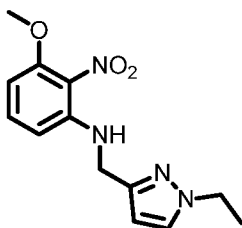
A mixture of N-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-methyl-6-nitroaniline (99 mg, 0.380
 25 mmol) and $NiCl_2 \cdot 6H_2O$ (226 mg, 0.951 mmol) in CH_3OH (20 mL) was cooled in a ice water bath. Sodium borohydride (71.9 mg, 1.902 mmol) was added, and the reaction mixture was stirred in ice water bath for 10 minutes. The reaction was concentrated, NH_4OH (28%) was added, and the resulting mixture was extracted with CH_2Cl_2 . The combined organic extract was dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified via

silica gel chromatography (0% to 100% EtOAc/hexanes) to afford N1-((1-ethyl-1H-pyrazol-3-yl)methyl)-6-methylbenzene-1,2-diamine (57 mg). LC-MS (ES) m/z = 231 $[M+H]^+$. This material was taken immediately into the next step without further purification.

5

Example 36**N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-7-methyl-1H-benzo[d]imidazol-2-yl)pyridin-2-amine**

A mixture of N1-((1-ethyl-1H-pyrazol-3-yl)methyl)-6-methylbenzene-1,2-diamine (54 mg, 0.188 mmol), 6-(diethylamino)nicotinaldehyde (33.4 mg, 0.188 mmol), and oxone (75.0 mg, 0.122 mmol) in DMF (10 mL) and water (4 mL) was stirred at room temperature for 30 minutes. Saturated aqueous NaHCO_3 was added, and the resulting mixture was extracted with EtOAc. The combined organic extract was washed sequentially with water and brine, dried over MgSO_4 , filtered, and concentrated. The resulting residue was purified via silica gel chromatography (0% to 100% EtOAc/hexanes) to afford N,N-diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-7-methyl-1H-benzo[d]imidazol-2-yl)pyridin-2-amine (18 mg) as a glass. LC-MS (ES) m/z = 389 $[M+H]^+$. ^1H NMR (400 MHz, CDCl_3): δ 8.49 (d, J = 1.8 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.33 (d, J = 2.0 Hz, 1H), 7.19 (t, J = 7.7 Hz, 1H), 6.99 (d, J = 7.1 Hz, 1H), 6.57 (d, J = 9.1 Hz, 1H), 5.81 (d, J = 2.0 Hz, 1H), 5.64 (s, 2H), 4.19 (q, J = 7.4 Hz, 2H), 3.59 (q, J = 7.1 Hz, 4H), 2.57 (s, 3H), 1.52 (t, J = 7.4 Hz, 3H), 1.24 (t, J = 7.1 Hz, 6H).

Intermediate 69**N-((1-Ethyl-1H-pyrazol-3-yl)methyl)-3-methoxy-2-nitroaniline**

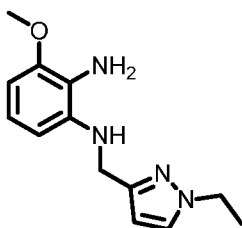
25

A solution of 1-fluoro-3-methoxy-2-nitrobenzene (154 mg, 0.900 mmol), (1-ethyl-1H-pyrazol-3-yl)methanamine (124 mg, 0.990 mmol), and N,N-diisopropylethylamine (0.189 mL, 1.080 mmol) in DMF (15 mL) was stirred at room temperature for 16 hours. The

reaction was concentrated, and the resulting residue was purified via silica gel chromatography (0% to 50% EtOAc/hexanes) to afford N-((1-ethyl-1H-pyrazol-3-yl)methyl)-3-methoxy-2-nitroaniline (60 mg) as a yellow oil. LC-MS (ES) m/z = 277 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, J = 2.3 Hz, 1H), 7.19 - 7.32 (m, 1H), 6.58 (br. s., 1H), 6.51 (dd, J = 0.8, 8.6 Hz, 1H), 6.32 (dd, J = 0.9, 8.2 Hz, 1H), 6.21 (d, J = 2.0 Hz, 1H), 4.43 (d, J = 2.0 Hz, 2H), 4.18 (q, J = 7.4 Hz, 2H), 3.91 (s, 3H), 1.52 (t, J = 7.2 Hz, 3H).

Intermediate 70

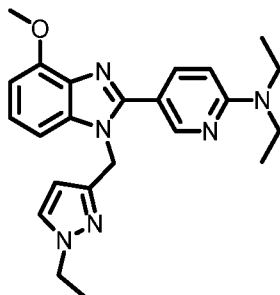
N1-((1-Ethyl-1H-pyrazol-3-yl)methyl)-3-methoxybenzene-1,2-diamine



10

A mixture of N-((1-ethyl-1H-pyrazol-3-yl)methyl)-3-methoxy-2-nitroaniline (60mg, 0.217 mmol) and $NiCl_2 \cdot 6H_2O$ (129 mg, 0.543 mmol) in CH_3OH (20 mL) was cooled in an ice water bath. Sodium borohydride (41.1 mg, 1.086 mmol) was added, and the reaction mixture was stirred in ice water bath for 10 minutes. The reaction was concentrated, NH_4OH (28%) was added, and the resulting mixture was extracted with CH_2Cl_2 . The combined organic extract was dried over $MgSO_4$, filtered, and concentrated to afford N1-((1-ethyl-1H-pyrazol-3-yl)methyl)-3-methoxybenzene-1,2-diamine (61 mg) as a tan solid. LC-MS (ES) m/z = 247 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, J = 2.0 Hz, 1H), 6.81 (t, J = 8.1 Hz, 1H), 6.50 (dd, J = 8.0, 19.0 Hz, 2H), 6.25 (d, J = 2.0 Hz, 1H), 4.38 (s, 2H), 4.20 (q, J = 7.4 Hz, 2H), 3.89 (s, 3H), 3.68 (br. s., 2H), 1.53 (t, J = 7.2 Hz, 3H).

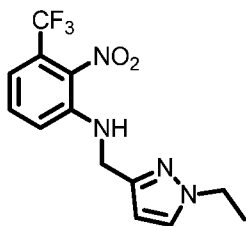
20

Example 37**N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-4-methoxy-1H-benzo[d]imidazol-2-yl)pyridin-2-amine**

- 5 A mixture of N1-((1-ethyl-1H-pyrazol-3-yl)methyl)-3-methoxybenzene-1,2-diamine (61 mg, 0.198 mmol), 6-(diethylamino)nicotinaldehyde (35.3 mg, 0.198 mmol), and oxone (79 mg, 0.129 mmol) in DMF (10 mL) and water (4 mL) was stirred at room temperature for 16 hours. Saturated aqueous NaHCO₃ was added, and the resulting mixture was extracted with EtOAc. The combined organic extract was washed sequentially with water and brine,
- 10 dried over MgSO₄, filtered, and concentrated. The resulting residue was purified via silica gel chromatography (0% to 100% EtOAc/hexanes) and freeze dried to afford N,N-diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-4-methoxy-1H-benzo[d]imidazol-2-yl)pyridin-2-amine (25 mg) as a white solid. LC-MS (ES) m/z = 405 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃):
- 15 δ 8.52 - 8.67 (m, 1H), 8.03 (dd, *J* = 2.4, 9.0 Hz, 1H), 7.28 - 7.38 (m, 1H), 7.09 - 7.24 (m, 1H), 6.99 (dd, *J* = 0.8, 8.1 Hz, 1H), 6.74 (d, *J* = 7.4 Hz, 1H), 6.51 - 6.61 (m, 1H), 5.94 (d, *J* = 2.0 Hz, 1H), 5.45 (s, 2H), 4.20 (q, *J* = 7.4 Hz, 2H), 4.08 (s, 3H), 3.60 (q, *J* = 7.1 Hz, 4H), 1.53 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 6H).

Intermediate 71

- 20 **N-((1-Ethyl-1H-pyrazol-4-yl)methyl)-2-nitro-3-(trifluoromethyl)aniline**



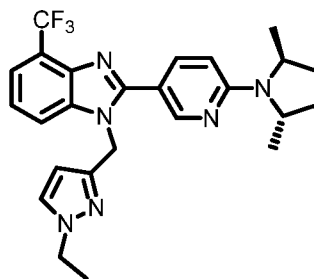
- A solution of 1-fluoro-2-nitro-3-(trifluoromethyl)benzene (150 mg, 0.717 mmol), (1-ethyl-1H-pyrazol-3-yl)methanamine (99 mg, 0.789 mmol), and N,N-diisopropylethylamine (0.150 mL, 0.861 mmol) in DMF (15 mL) was stirred for 16 hours. The reaction was concentrated,
- 25 and the resulting residue was purified via silica gel chromatography (0% to 35% EtOAc/hexanes) to afford N-((1-ethyl-1H-pyrazol-4-yl)methyl)-2-nitro-3-

(trifluoromethyl)aniline (204 mg) as an orange oil. LC-MS (ES) m/z = 315 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 7.41 - 7.48 (m, 1H), 7.39 (d, J = 2.0 Hz, 1H), 7.19 (d, J = 8.6 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H), 6.40 (br. s., 1H), 6.20 (d, J = 2.3 Hz, 1H), 4.47 (d, J = 5.1 Hz, 2H), 4.19 (q, J = 7.4 Hz, 2H), 1.52 (t, J = 7.4 Hz, 3H).

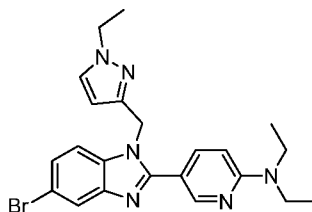
5

Example 38

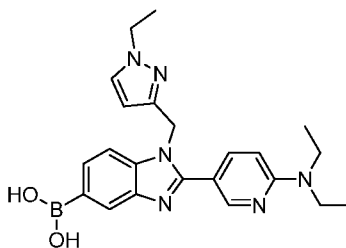
2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-4-(trifluoromethyl)-1H-benzo[d]imidazole



- 10 A mixture of N-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-nitro-3-(trifluoromethyl)aniline (100 mg, 0.318 mmol), sodium hydrosulfite (166 mg, 85%, 0.812 mmol), and 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (68.2 mg, 0.334 mmol) in EtOH (4 mL) and water (2 mL) was heated at 130 °C under microwave conditions for 40 minutes. The reaction was filtered, and the filtrate was concentrated to dryness. CH_2Cl_2 was then added, and the
- 15 resulting mixture was filtered again. The filtrate was purified via silica gel chromatography (0% to 80% EtOAc/hexanes) to afford 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-4-(trifluoromethyl)-1H-benzo[d]imidazole (28 mg) as a white solid. LC-MS (ES) m/z = 469 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, J = 1.8 Hz, 1H), 7.95 (dd, J = 2.0, 8.9 Hz, 1H), 7.51 - 7.60 (m, 2H), 7.33 (d, J = 2.3 Hz, 1H), 7.20 - 7.30 (m, 1H), 6.49 (d, J = 8.9 Hz, 1H), 5.97 (d, J = 2.0 Hz, 1H), 5.46 (s, 2H), 4.23 - 4.37 (m, 2H), 4.08 - 4.22 (m, 2H), 2.22 - 2.38 (m, 2H), 1.71 (d, J = 5.6 Hz, 2H), 1.47 - 1.55 (m, 3H),
- 20 1.21 (d, J = 6.1 Hz, 6H).

Intermediate 725-(5-Bromo-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine

5 Into a microwave vial were added 4-bromo-N-((1-ethyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline (261 mg, 0.803 mmol), 6-(diethylamino)nicotinaldehyde (157 mg, 0.883 mmol), ethanol (2 mL), water (1 mL), and sodium hydrosulfite (419 mg, 85%, 2.047 mmol), and the reaction mixture was heated under microwave conditions for 30 minutes at 130 °C. The reaction was diluted with water (10 mL) and extracted with EtOAc (4 x 5 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ (gradient of 0 to 70% EtOAc/hexanes) afforded 5-(5-bromo-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (246 mg) as a light brown oil. LC-MS (ES) m/z = 454 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 1.24 (t, J = 7.0 Hz, 6H), 1.51 (t, J = 7.4 Hz, 3H), 3.59 (q, J = 7.1 Hz, 4H), 4.14 - 4.22 (m, 2H), 5.42 (s, 2H), 5.95 (d, J = 2.3 Hz, 1H), 6.58 (s, 1H), 7.22 - 7.26 (m, 1H), 7.29 - 7.34 (m, 2H), 7.90 - 7.97 (m, 2H), 8.58 (d, J = 2.3 Hz, 1H).

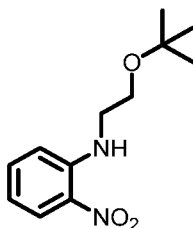
Example 39(2-(6-(Diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-5-yl)boronic acid

25 Into a 20 mL microwave vial were added sequentially hypodiboric acid (73.0 mg, 0.814 mmol), triphenylphosphine (14.23 mg, 0.054 mmol), 1,3-bis(diphenylphosphino)propane-nickel(II) chloride (29.4 mg, 0.054 mmol), 5-(5-bromo-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (246 mg, 0.543 mmol), and EtOH (5 mL), and the resulting mixture was de-gassed with argon for 10 minutes. N,N-

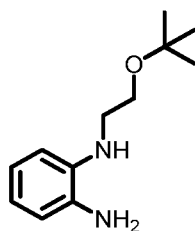
diisopropylethylamine (0.284 mL, 1.628 mmol) was then added, and the reaction mixture was heated under microwave conditions at 80 °C for 1 hour. The reaction was filtered through celite and washed with EtOH. The filtrate was concentrated, and the resulting residue was purified by chromatography on SiO₂ (gradient of 0 to 50% (80:20:2
5 CH₂Cl₂:CH₃OH:NH₄OH)/CH₂Cl₂) to afford (2-(6-(diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-5-yl)boronic acid (107 mg) as a white solid after freeze-drying. LC-MS (ES) m/z = 419 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.24 (t, J = 7.0 Hz, 6H), 1.43 (t, J = 7.4 Hz, 3H), 3.63 (q, J = 7.0 Hz, 4H), 4.16 (q, J = 7.4 Hz, 2H), 5.49 (s, 2H), 6.09 (d, J = 2.3 Hz, 1H), 6.78 (d, J = 8.9 Hz, 1H), 7.48 - 7.60 (m, 3H), 7.95 (dd, J =
10 8.9, 2.5 Hz, 1H), 7.99 (s, 1H), 8.53 (d, J = 2.3 Hz, 1H).

Intermediate 73

N-(2-(Tert-butoxy)ethyl)-2-nitroaniline



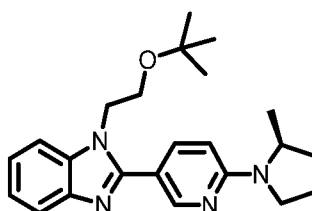
To 2-(tert-butoxy)ethan-1-amine (3.00 g, 25.6 mmol) in DMF (100 mL) were added 1-fluoro-2-nitrobenzene (3.61 g, 25.6 mmol) and K₂CO₃ (3.54 g, 25.6 mmol), and the reaction mixture was stirred overnight at room temperature. The solids were filtered and washed with Et₂O. The filtrate was diluted with water (600 mL), and the resulting mixture was extracted with Et₂O (200 mL, 3x). The combined organic layers were washed with brine (20
20 mL), dried over Na₂SO₄, filtered, and concentrated. The resulting residue was purified by flash chromatography on SiO₂ (0-60% EtOAc/hexanes) to give N-(2-(tert-butoxy)ethyl)-2-nitroaniline (4.85 g) as a yellow oil. LC-MS (ES) m/z = 239 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.31 (br. s., 1H), 8.22 (dd, J = 1.5, 8.6 Hz, 1H), 7.47 (ddd, J = 1.7, 7.0, 8.6 Hz, 1H), 6.90 (dd, J = 1.0, 8.6 Hz, 1H), 6.68 (ddd, J = 1.3, 7.0, 8.5 Hz, 1H), 3.71 (t, J = 5.5 Hz,
25 2H), 3.48 (t, J = 5.5 Hz, 2H), 1.30 (s, 9H).

Intermediate 74N1-(2-(Tert-butoxy)ethyl)benzene-1,2-diamine

- 5 A solution of N-(2-(tert-butoxy)ethyl)-2-nitroaniline (4.85 g, 20.35 mmol) and $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (12.09 g, 50.9 mmol) was purged with N_2 , then cooled in an ice-bath. To the chilled solution was added sodium borohydride (3.85 g, 102 mmol) in 4 portions, and the reaction mixture was stirred at room temperature for 2 hours. The reaction was concentrated, and the remaining residue was partitioned between concentrated NH_4OH (200 mL) and CH_2Cl_2 (300 mL). [Caution: effervescence/some of the solution was lost.] The aqueous phase was
- 10 extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , filtered, and concentrated. The remaining residue was purified by flash chromatography on SiO_2 (0-60% EtOAc/hexanes) to afford N1-(2-(tert-butoxy)ethyl)benzene-1,2-diamine (4.52 g) as a green waxy solid. LC-MS (ES) m/z = 209
- 15 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 6.61 - 6.95 (m, 4H), 3.77 - 4.27 (m, 2H), 3.67 (br. s., 2H), 3.10 - 3.44 (m, 2H), 1.27 (s, 9H).

Example 40

20 (S)-1-(2-(Tert-butoxy)ethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole

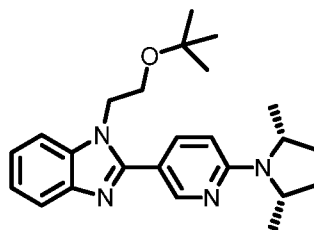


- To N1-(2-(tert-butoxy)ethyl)benzene-1,2-diamine (108 mg, 0.518 mmol) and (S)-6-(2-methylpyrrolidin-1-yl)nicotinaldehyde (109 mg, 0.570 mmol) in DMF (4 mL) and water (3 mL) was added oxone (207 mg, 0.337 mmol), and the reaction mixture was stirred at room
- 25 temperature for 45 minutes. The reaction was quenched with saturated aqueous NH_4Cl (8 mL), and the resulting mixture was extracted with EtOAc (6 x 25 mL) followed by 3% $\text{CH}_3\text{OH}/\text{EtOAc}$ (3 x 25 mL). The pH of the aqueous layer was adjusted to ~9 with

NH₄OH, and the resulting aqueous mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (6 mL), dried over Na₂SO₄, filtered, and concentrated. The resulting residue was purified by flash chromatography on SiO₂ (0-100% EtOAc/hexanes) to afford (S)-1-(2-(tert-butoxy)ethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole (96 mg) as a gold-brown solid. LC-MS (ES) m/z = 379 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.62 - 8.80 (m, 1H), 8.06 - 8.28 (m, 1H), 7.79 - 8.03 (m, 1H), 7.51 - 7.65 (m, 1H), 7.38 (br. s., 2H), 6.43 - 6.70 (m, 1H), 4.46 (br. s., 2H), 4.19 - 4.38 (m, 1H), 3.78 - 3.91 (m, 2H), 3.60 - 3.76 (m, 1H), 3.39 - 3.57 (m, 1H), 2.18 (br. s., 3H), 1.75 - 1.90 (m, 1H), 1.25 - 1.32 (m, 3H), 1.04 - 1.11 (m, 9H).

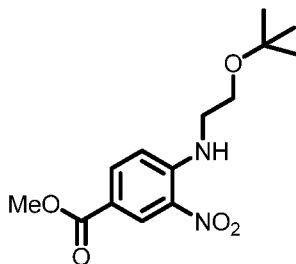
Example 41

1-(2-(Tert-butoxy)ethyl)-2-(6-((2S,5R)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole

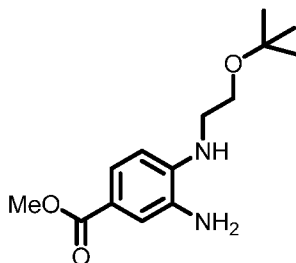


To N1-(2-(tert-butoxy)ethyl)benzene-1,2-diamine (104 mg, 0.499 mmol) and 6-((2S,5R)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (112 mg, 0.549 mmol) in DMF (3 mL) and water (3 mL) was added oxone (199 mg, 0.325 mmol), and the reaction mixture was stirred at room temperature for 45 minutes. The reaction was quenched with saturated aqueous NH₄Cl (8 mL), and the pH was adjusted to ~ 10 with NH₄OH (10 mL). The resulting mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (3 mL), dried over Na₂SO₄, filtered, and concentrated. The remaining residue was purified by flash chromatography on SiO₂ (0-100% EtOAc/hexanes) to afford 1-(2-(tert-butoxy)ethyl)-2-(6-((2S,5R)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole (117 mg) as a red-brown solid. LC-MS (ES) m/z = 393 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.63 (d, J = 2.0 Hz, 1H), 7.97 - 8.10 (m, 1H), 7.76 - 7.93 (m, 1H), 7.53 (d, J = 4.1 Hz, 1H), 7.32 (d, J = 4.1 Hz, 2H), 6.55 (d, J = 9.1 Hz, 1H), 4.41 (t, J = 5.7 Hz, 2H), 4.19 (d, J = 5.3 Hz, 2H), 3.82 (t, J = 5.8 Hz, 2H), 2.07 - 2.25 (m, 2H), 1.74 - 1.92 (m, 2H), 1.40 (d, J = 6.1 Hz, 6H), 0.99 - 1.18 (m, 9H).

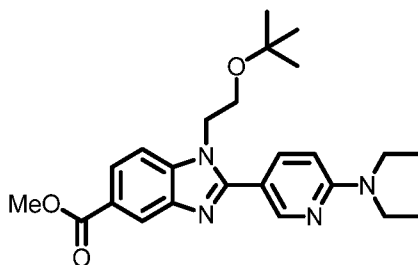
Intermediate 75

Methyl 4-((2-(tert-butoxy)ethyl)amino)-3-nitrobenzoate

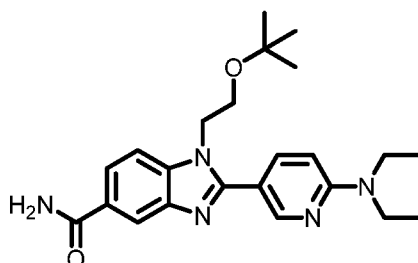
To a solution of methyl 4-fluoro-3-nitrobenzoate (600 mg, 3.01 mmol) in DMF (20 mL) were added 2-(tert-butoxy)ethanamine (353 mg, 3.01 mmol) and K₂CO₃ (416 mg, 3.01 mmol), and the mixture was stirred at room temperature for 18 hours. The mixture was quenched with water (30 mL) and extracted with EtOAc (3x). The extract was dried (Na₂SO₄) and concentrated. The residue was purified using column chromatography (silica gel, 0 to 60% EtOAc/hexanes) to give the desired product (590 mg) as a white solid. LC-MS (ES) m/z = 297 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 1.30 (s, 9H), 3.53 (d, J = 4.8 Hz, 2H), 3.69 - 3.75 (m, 2H), 3.94 (s, 3H), 6.92 (d, J = 9.1 Hz, 1H), 8.09 (dd, J = 8.9, 2.0 Hz, 1H), 8.93 (d, J = 2.0 Hz, 1H).

Intermediate 76Methyl 3-amino-4-((2-(tert-butoxy)ethyl)amino)benzoate

To a solution of methyl 4-((2-(tert-butoxy)ethyl)amino)-3-nitrobenzoate (540 mg, 1.822 mmol) in CH₃OH (13 mL) were added NiCl₂•6H₂O (1084 mg, 4.56 mmol) and sodium borohydride (345 mg, 9.11 mmol) at 0 °C, and the mixture was stirred at 0 °C for 20 minutes. The reaction mixture was concentrated, and the residue was treated with saturated NH₄OH aqueous solution and extracted with EtOAc (3x). The extract was dried (Na₂SO₄) and concentrated to give the desired product (430 mg) as a pale brown oil. LC-MS (ES) m/z = 267 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 1.26 (s, 9H), 3.34 (t, J = 5.3 Hz, 2H), 3.67 (t, J = 5.3 Hz, 2H), 3.89 (s, 3H), 6.65 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 2.0 Hz, 1H), 7.61 (dd, J = 8.2, 1.9 Hz, 1H).

Example 42**Methyl 1-(2-(tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylate**

- 5 To a solution of methyl 3-amino-4-((2-(tert-butoxy)ethyl)amino)benzoate (250 mg, 0.939 mmol) in DMF (5 mL) and water (1 mL) was added 6-(diethylamino)nicotinaldehyde (167 mg, 0.939 mmol) and oxone (577 mg, 0.939 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was quenched with 10% K₂CO₃ aqueous solution (5 mL) and extracted with EtOAc (3x). The extract was dried (Na₂SO₄)
- 10 and concentrated. The residue was purified using column chromatography (silica gel, 0 to 60% EtOAc/hexanes) to give the desired product (280 mg) as a white solid. LC-MS (ES) m/z = 425 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 0.98 (s, 9H), 1.25 (t, J = 7.1 Hz, 6H), 3.65 (q, J = 7.1 Hz, 4H), 3.82 (t, J = 5.1 Hz, 2H), 3.97 (s, 3H), 4.49 (t, J = 5.1 Hz, 2H), 6.78 (d, J = 9.1 Hz, 1H), 7.72 (d, J = 8.6 Hz, 1H), 7.98 - 8.12 (m, 2H), 8.36 (d, J = 1.3 Hz, 1H),
- 15 8.60 (d, J = 2.0 Hz, 1H).

Example 43**1-(2-(Tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide**

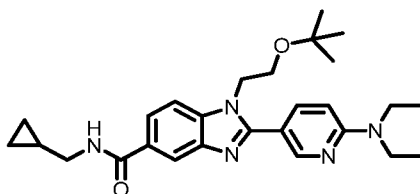
- 20 To a solution of methyl 1-(2-(tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylate (80 mg, 0.188 mmol) in CH₃OH (1 mL) was added 8N NaOH (0.2 mL, 1.60 mmol), and the mixture was stirred at 40 °C for 18 hours. The reaction mixture was neutralized by adding aqueous 6N HCl (0.267 mL, 1.602 mmol) and
- 25 concentrated. The residue was dried under vacuum and treated with dimethyl sulfoxide (DMSO) (1 mL). To this mixture were added NH₄Cl (18.14 mg, 0.339 mmol), N-

methymorpholine (0.124 mL, 1.131 mmol), EDC (72.2 mg, 0.377 mmol), and 1-hydroxy-7-azabenzotriazole (51.3 mg, 0.377 mmol), and the mixture was stirred at room temperature for 18 hours. The reaction was quenched with water (5 mL). The precipitate was collected by filtration and dried under vacuum to give the desired product (69 mg) as an off-white solid. LC-MS (ES) m/z = 410 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 0.99 (s, 9H), 1.25 (t, J = 7.1 Hz, 6 H), 3.65 (q, J = 7.1 Hz, 4H), 3.82 (t, J = 5.1 Hz, 2H), 4.48 (t, J = 5.1 Hz, 2H), 6.78 (d, J = 9.1 Hz, 1H), 7.71 (d, J = 8.6 Hz, 1H), 7.89 (dd, J = 8.5, 1.7 Hz, 1H), 8.05 (dd, J = 9.0, 2.4 Hz, 1H), 8.24 (d, J = 1.3 Hz, 1H), 8.60 (d, J = 2.3 Hz, 1H).

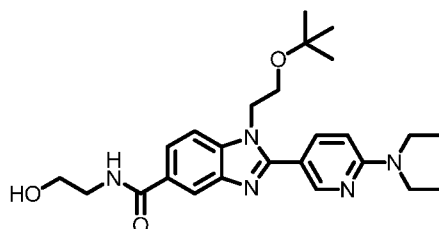
10

Example 44

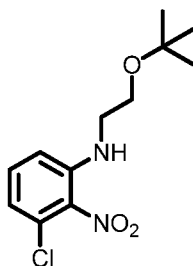
1-(2-(Tert-butoxy)ethyl)-N-(cyclopropylmethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide



To a solution of methyl 1-(2-(tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylate (80 mg, 0.188 mmol) in CH_3OH (1.5 mL) was added 8N NaOH (0.2 mL, 1.600 mmol), and the mixture was stirred at 40 °C for 18 hours. The reaction mixture was neutralized by adding aqueous 6N HCl (0.267 mL, 26.8 mg, 1.602 mmol) and concentrated. The residue was dried under vacuum and treated with DMSO (1.5 mL). To this mixture were added cyclopropylmethanamine (32.7 μ l, 0.377 mmol), *N*-methymorpholine (124 μ l, 1.131 mmol), EDC (72.2 mg, 0.377 mmol), and 1-hydroxy-7-azabenzotriazole (51.3 mg, 0.377 mmol), and the mixture was stirred at room temperature for 18 hours. The reaction was quenched with water (5 mL). The precipitate was collected by filtration and dried under vacuum to give the desired product (72 mg) as an off-white solid. LC-MS (ES) m/z = 464 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 0.27 - 0.37 (m, 2H), 0.50 - 0.62 (m, 2H), 0.98 (s, 9H), 1.12 - 1.19 (m, 1H), 1.19 - 1.31 (m, 6H), 3.30 (m, 2H), 3.64 (q, J = 7.1 Hz, 4H), 3.82 (t, J = 5.1 Hz, 2H), 4.48 (t, J = 4.9 Hz, 2H), 6.78 (d, J = 9.1 Hz, 1H), 7.71 (d, J = 8.6 Hz, 1 H), 7.81 - 7.89 (m, 1H), 8.05 (dd, J = 9.1, 2.3 Hz, 1H), 8.18 (d, J = 1.0 Hz, 1H), 8.60 (d, J = 2.0 Hz, 1H).

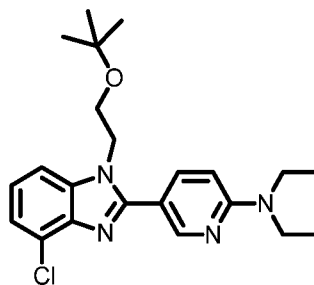
Example 45**1-(2-(Tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-N-(2-hydroxyethyl)-1H-benzo[d]imidazole-5-carboxamide**

To a solution of methyl 1-(2-(tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylate (85 mg, 0.200 mmol) in CH₃OH (1.5 mL) was added NaOH (0.200 mL, 1.602 mmol), and the mixture was stirred at room temperature for 18 hours. The reaction mixture was neutralized by adding aqueous 6N HCl (0.267 mL, 1.602 mmol) and concentrated to give crude 1-(2-(tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylic acid. The residue was dried under vacuum and treated with DMSO (1.5 mL). To this mixture were added 2-aminoethan-1-ol (0.024 mL, 0.400 mmol), N-methylmorpholine (0.132 mL, 1.201 mmol), EDC (77 mg, 0.400 mmol), and 1-hydroxy-7-azabenzotriazole (54.5 mg, 0.400 mmol), and the mixture was stirred at room temperature for 18 hours. The reaction was quenched with water (5 mL). The precipitate was collected by filtration and dried under vacuum to give the desired product (81 mg) as an off-white solid. LC-MS (ES) m/z = 454 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 0.92 - 1.03 (m, 9H), 1.25 (t, J = 7.0 Hz, 6H), 2.68 (s, 2H), 3.54 - 3.63 (m, 3H), 3.63 - 3.71 (m, 3H), 3.72 - 3.86 (m, 4H), 4.48 (t, J = 5.1 Hz, 2H), 6.78 (d, J = 8.9 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.82 - 7.91 (m, 1H), 8.05 (dd, J = 9.0, 2.1 Hz, 1H), 8.20 (d, J = 1.0 Hz, 1H), 8.60 (d, J = 2.3 Hz, 1H).

Intermediate 77**N-(2-(Tert-butoxy)ethyl)-3-chloro-2-nitroaniline**

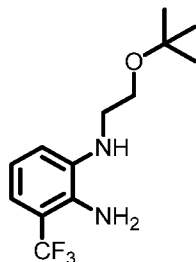
To a solution of 1-chloro-3-fluoro-2-nitrobenzene (300 mg, 1.709 mmol) in DMF (8 mL) were added 2-(tert-butoxy)ethanamine (200 mg, 1.709 mmol) and K_2CO_3 (236 mg, 1.709 mmol), and the mixture was stirred at room temperature for 18 hours. The reaction mixture was quenched with water (15 mL) and extracted with EtOAc (3x). The extract was dried (Na₂SO₄) and concentrated. The residue was purified using column chromatography (silica gel, 0 to 50% EtOAc/hexanes) to give the desired product (230 mg) as a pale brown oil. LC-MS (ES) m/z = 273, 275 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 1.24 - 1.30 (m, 9H), 3.34 (t, J = 5.3 Hz, 2H), 3.63 (t, J = 5.3 Hz, 2H), 6.72 - 6.82 (m, 1H), 6.77 (dd, J = 6.0, 1.14 Hz, 1H), 7.20 - 7.29 (m, 1H).

10

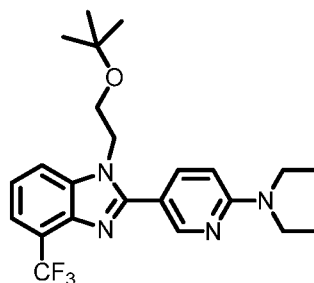
Example 46**5-(1-(2-(Tert-butoxy)ethyl)-4-chloro-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine**

To a 30-mL microwave tube were added N-(2-(tert-butoxy)ethyl)-3-chloro-2-nitroaniline (130 mg, 0.477 mmol), 6-(diethylamino)nicotinaldehyde (85 mg, 0.477 mmol), sodium hydrosulfite (295 mg, 85%, 1.216 mmol), EtOH (3 mL), and water (2 mL), the tube was sealed, and the reaction mixture was heated at 135 °C for 20 minutes under microwave conditions. The reaction mixture was cooled, quenched with water (10 mL) and extracted with EtOAc (3x). The extract was dried (Na₂SO₄) and concentrated, and the resulting residue was purified by silica gel chromatography (0 to 90% EtOAc/hexanes) to give the desired product (27 mg) as a white solid. LC-MS (ES) m/z = 401, 403 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 0.99 (s, 9H), 1.22 - 1.32 (m, 6H), 3.65 (q, J = 7.1 Hz, 4H), 3.80 (t, J = 5.1 Hz, 2H), 4.44 (t, J = 5.2 Hz, 2H), 6.78 (d, J = 9.1 Hz, 1H), 7.23 - 7.37 (m, 2H), 7.59 (dd, J = 7.9, 1.3 Hz, 1H), 8.04 (dd, J = 8.9, 2.5 Hz, 1H), 8.59 (d, J = 2.5 Hz, 1H).

25

Intermediate 78N1-(2-(Tert-butoxy)ethyl)-3-(trifluoromethyl)benzene-1,2-diamine

To a stirring solution of N-(2-(tert-butoxy)ethyl)-2-nitro-3-(trifluoromethyl)aniline (130 mg, 0.424 mmol) and sodium borohydride (80 mg, 2.122 mmol) in CH₃OH (3 mL) was added NiCl₂•6H₂O (253 mg, 1.061 mmol) in portions at 0 °C, and the reaction mixture was stirred at room temperature for 30 minutes. The mixture was concentrated, and the resulting residue was dissolved into concentrated NH₄OH and extracted with CH₂Cl₂ (3x). The extract was dried (Na₂SO₄) and concentrated to give the desired product (110 mg) as a pale brown oil. LC-MS (ES) m/z = 277 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 1.20 - 1.29 (m, 9H), 3.26 (t, J = 5.1 Hz, 2H), 3.68 (t, J = 5.2 Hz, 2H), 6.77 - 6.93 (m, 2H), 7.02 - 7.08 (m, 1H).

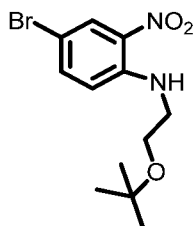
Example 475-(1-(2-(Tert-butoxy)ethyl)-4-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine

To a solution of N1-(2-(tert-butoxy)ethyl)-3-(trifluoromethyl)benzene-1,2-diamine (110 mg, 0.398 mmol) in DMF (2.5 mL) and water (0.500 mL) were added oxone (245 mg, 0.398 mmol) and 6-(diethylamino)nicotinaldehyde (71.0 mg, 0.398 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was basified using 10% K₂CO₃ and extracted with EtOAc (3x). The extract was dried (Na₂SO₄) and concentrated, and the resulting residue was purified using column chromatography (silica gel, 0 to 60% EtOAc/hexanes) to give the desired product (136 mg) as an off-white solid. LC-MS (ES) m/z = 435 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 0.99 (s, 9H), 1.25 (t, J = 7.1 Hz, 6H), 3.65 (q, J = 7.1 Hz, 4H), 3.80 (t, J = 5.1 Hz, 2H), 4.48 (t, J = 5.1 Hz, 2H), 6.78 (d, J = 9.1 Hz, 1H),

7.43 (t, $J = 8.0$ Hz, 1H), 7.59 (d, $J = 7.6$ Hz, 1H), 7.91 (d, $J = 8.1$ Hz, 1H), 8.03 (dd, $J = 9.1$, 2.5 Hz, 1H), 8.58 (d, $J = 2.0$ Hz, 1H).

Intermediate 79

5 4-Bromo-N-(2-(tert-butoxy)ethyl)-2-nitroaniline

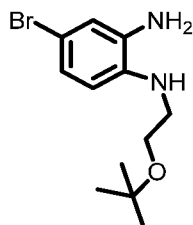


A solution of 4-bromo-1-fluoro-2-nitrobenzene (625 mg, 2.84 mmol), 2-(tert-butoxy)ethan-1-amine (366 mg, 3.13 mmol), and N,N-diisopropylethylamine (595 μ l, 3.41 mmol) in DMF was stirred at room temperature for 16 hours. The reaction was concentrated, and the residue was purified via silica gel chromatography (0% to 30% EtOAc/hexanes) to give 4-bromo-N-(2-(tert-butoxy)ethyl)-2-nitroaniline (860 mg) as an oil. LC-MS (ES) $m/z = 261$, 263 $[M-C_4H_8+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.25 - 8.49 (m, 1H), 7.51 (dd, $J = 2.3$, 9.12 Hz, 1H), 6.82 (d, $J = 9.1$ Hz, 1H), 3.70 (t, $J = 5.3$ Hz, 2H), 3.45 (q, $J = 5.1$ Hz, 2H), 1.29 (s, 9H).

15

Intermediate 80

4-Bromo-N1-(2-(tert-butoxy)ethyl)benzene-1,2-diamine

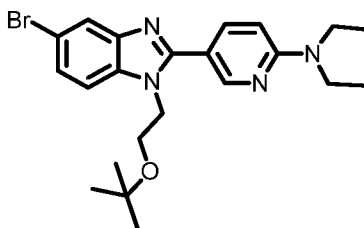


A mixture of 4-bromo-N-(2-(tert-butoxy)ethyl)-2-nitroaniline (600 mg, 1.892 mmol) and $NiCl_2 \cdot 6H_2O$ (1.126 g, 4.73 mmol) in CH_3OH (20 mL) was cooled in an ice water bath. Sodium borohydride (358 mg, 9.46 mmol) was added, and the reaction mixture was stirred in ice water bath for 10 minutes. The reaction was concentrated. NH_4OH (28% in water) was added, and the resulting mixture was extracted with CH_2Cl_2 . The combined CH_2Cl_2 extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified via silica gel chromatography (0% to 35% EtOAc/hexanes) to yield 4-bromo-N1-(2-(tert-butoxy)ethyl)benzene-1,2-diamine (375 mg) as a white solid. LC-MS (ES) $m/z = 287$, 289 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 6.90 (dd, $J = 2.3$, 8.4 Hz, 1H), 6.85 (d, J

= 2.3 Hz, 1H), 6.54 (d, J = 8.4 Hz, 1H), 3.62 (t, J = 5.2 Hz, 2H), 3.21 (t, J = 5.2 Hz, 2H), 1.24 (s, 9H).

Example 48

5 5-(5-Bromo-1-(2-(tert-butoxy)ethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine

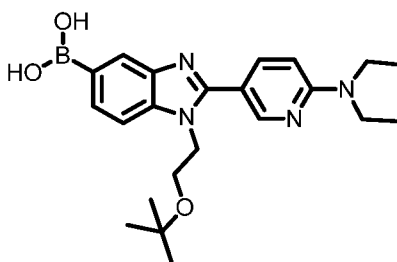


A mixture of 4-bromo-N1-(2-(tert-butoxy)ethyl)benzene-1,2-diamine (375 mg, 1.306 mmol) and 6-(diethylamino)nicotinaldehydeoxone (522 mg, 0.849 mmol) in water (10 mL) and DMF (10 mL) was stirred at room temperature for 16 hours. Saturated aqueous NaHCO_3 was added, and the resulting mixture was extracted with EtOAc. The organic extract was washed sequentially with water and brine, dried over MgSO_4 , filtered and concentrated. The resulting residue was purified via silica gel chromatography (0% to 50% EtOAc/hexanes) to give 5-(5-bromo-1-(2-(tert-butoxy)ethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (527 mg) as a tan solid. LC-MS (ES) m/z = 445, 447 $[M+H]^+$. ^1H NMR (400 MHz, CDCl_3): δ 8.56 (d, J = 2.0 Hz, 1H), 7.97 (dd, J = 2.4, 9.0 Hz, 1H), 7.92 (d, J = 1.3 Hz, 1H), 7.35 - 7.43 (m, 2H), 6.59 (d, J = 9.1 Hz, 1H), 4.36 (t, J = 5.3 Hz, 2H), 3.77 (t, J = 5.5 Hz, 2H), 3.61 (q, J = 6.9 Hz, 4H), 1.25 (t, J = 7.0 Hz, 6H), 1.06 (s, 9H).

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Example 49

1-(2-(Tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazol-5-yl)boronic acid

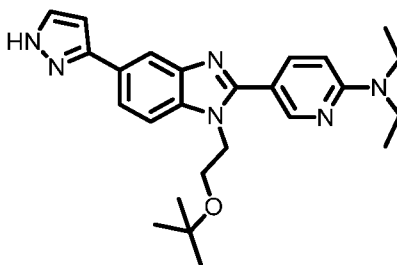


Through a mixture of hypodiboric acid (31.4 mg, 0.350 mmol), 1,3-bis(diphenylphosphino)propane-nickel(II) chloride (6.33 mg, 0.012 mmol), 5-(5-bromo-1-(2-(tert-butoxy)ethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (104 mg, 0.233

mmol), triphenylphosphine (6.12 mg, 0.023 mmol), and N,N-diisopropylethylamine (0.122 mL, 0.700 mmol) in EtOH (10 mL) was bubbled argon gas for 10 minutes, and the reaction mixture was heated at 80 °C for 16 hours. The reaction was concentrated, and the resulting material was purified by reverse phase HPLC (20% CH₃CN/(H₂O, 0.1% formic acid) to 60% CH₃CN/(H₂O, 0.1% formic acid)) to afford (1-(2-(tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazol-5-yl)boronic acid (16 mg) as a solid. LC-MS (ES) m/z = 411 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 8.60 (d, J = 2.0 Hz, 1H), 8.05 (dd, J = 2.4, 9.0 Hz, 1H), 7.92 - 8.02 (m, 1H), 7.64 (br. s., 2H), 6.78 (d, J = 8.9 Hz, 1H), 4.46 (t, J = 5.1 Hz, 2H), 3.83 (t, J = 5.2 Hz, 2H), 3.65 (q, J = 6.9 Hz, 4H), 1.25 (t, J = 7.1 Hz, 6H), 0.99 (s, 9H).

Example 50

5-(1-(2-(Tert-butoxy)ethyl)-5-(1H-pyrazol-3-yl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine

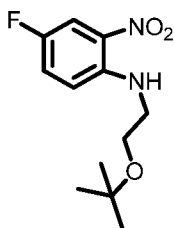


Through a mixture of 5-(5-bromo-1-(2-(tert-butoxy)ethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (80 mg, 0.180 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (41.8 mg, 0.216 mmol), tetrakis(triphenylphosphine)palladium(0) (10.38 mg, 8.98 μmol), and Na₂CO₃ (47.6 mg, 0.449 mmol) in 1,4-dioxane (3 mL) and water (1 mL) was bubbled argon gas for 10 minutes, and the reaction mixture was heated into a capped vessel at 75 °C for 6 hours. Additional tetrakis(triphenylphosphine)palladium(0) (10.38 mg, 8.98 μmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (84 mg), and Na₂CO₃ (47.6 mg, 0.449 mmol) were added, and the reaction mixture was heated at 80 °C for 6 hours. Water was added, and the resulting mixture was extracted with CH₂Cl₂. The combined organic extract was washed with water, dried over MgSO₄, filtered and concentrated. Purification by reverse phase HPLC (10% CH₃CN/(H₂O, 0.1% formic acid) to 80% CH₃CN/(H₂O, 0.1% formic acid)) afforded 5-(1-(2-(tert-butoxy)ethyl)-5-(1H-pyrazol-3-yl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (16 mg) as a white solid. LC-MS (ES) m/z = 433 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.64 (d, J = 2.0 Hz, 1H), 8.15 (s, 1H), 8.05 (dd, J = 2.3, 8.9 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.69 (d, J = 2.3 Hz, 1H), 7.58

(d, $J = 8.4$ Hz, 1H), 6.71 (d, $J = 2.0$ Hz, 1H), 6.63 (d, $J = 8.9$ Hz, 1H), 4.43 (t, $J = 5.5$ Hz, 2H), 3.83 (t, $J = 5.6$ Hz, 2H), 3.64 (q, $J = 7.1$ Hz, 4H), 1.21 - 1.41 (m, 6H), 1.09 (s, 9H).

Intermediate 81

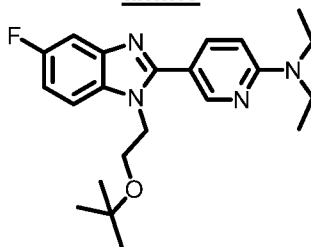
5 N-(2-(Tert-butoxy)ethyl)-4-fluoro-2-nitroaniline



A solution of 1,4-difluoro-2-nitrobenzene (150 mg, 0.943 mmol), 2-(tert-butoxy)ethan-1-amine (110 mg, 0.943 mmol) and N,N-diisopropylethylamine (0.198 mL, 1.131 mmol) in DMF (15 mL) was stirred at room temperature for 16 hours. The reaction mixture was concentrated, and the resulting residue was purified via silica gel chromatography (0% to 12% EtOAc/hexanes) to afford N-(2-(tert-butoxy)ethyl)-4-fluoro-2-nitroaniline (126 mg) as an orange oil. LC-MS (ES) $m/z = 201$ $[M-C_4H_8+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.20 (br. s., 1H), 7.90 (dd, $J = 3.0, 9.1$ Hz, 1H), 7.21 - 7.37 (m, 1H), 6.88 (dd, $J = 4.6, 9.4$ Hz, 1H), 3.70 (t, $J = 5.3$ Hz, 2H), 3.45 (t, $J = 5.2$ Hz, 2H), 1.28 (s, 9H).

Example 51

5-(1-(2-(tert-butoxy)ethyl)-5-fluoro-1H-benzof[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine

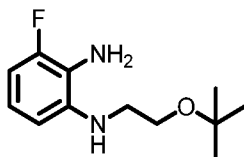


A mixture of N-(2-(tert-butoxy)ethyl)-4-fluoro-2-nitroaniline (120 mg, 0.468 mmol), sodium hydrosulfite (245 mg, 85%, 1.194 mmol), and 6-(diethylamino)nicotinaldehyde (88 mg, 0.492 mmol) in EtOH (4 mL) and water (32 mL) was heated at 130 °C under microwave conditions for 30 minutes. NH_4OH (28% in water) was then added, and the resulting mixture was extracted with EtOAc. The combined EtOAc extract was washed sequentially with water and brine, dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified via silica gel chromatography (0% to 50% EtOAc/hexanes) to afford 5-(1-(2-(tert-

butoxy)ethyl)-5-fluoro-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (37 mg) as a white solid. LC-MS (ES) m/z = 385 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.58 (d, J = 2.0 Hz, 1H), 7.99 (dd, J = 2.4, 9.0 Hz, 1H), 7.42 - 7.53 (m, 2H), 7.05 (dt, J = 2.4, 9.2 Hz, 1H), 6.61 (d, J = 8.9 Hz, 1H), 4.38 (t, J = 5.6 Hz, 2H), 3.80 (t, J = 5.5 Hz, 2H), 3.63 (q, J = 7.1 Hz, 4H), 1.27 (t, J = 7.1 Hz, 6H), 1.09 (s, 9H).

Intermediate 82

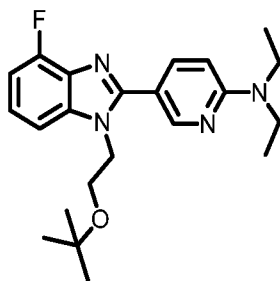
N-(2-(Tert-butoxy)ethyl)-3-fluoro-2-nitroaniline



10 A solution of 1,3-difluoro-2-nitrobenzene (150 mg, 0.943 mmol), 2-(tert-butoxy)ethan-1-amine (110 mg, 0.943 mmol), and N,N-diisopropylethylamine (0.198 mL, 1.131 mmol) in DMF (20 mL) was stirred for 16 hours. The reaction was concentrated and the residue was purified via silica gel chromatography (0% to 22% EtOAc/hexanes) to afford N-(2-(tert-butoxy)ethyl)-3-fluoro-2-nitroaniline (179 mg) as an orange oil. ^1H NMR (400 MHz, $CDCl_3$):
 15 δ 7.51 (br. s., 1H), 7.18 - 7.37 (m, 1H), 6.62 (d, J = 8.9 Hz, 1H), 6.45 (ddd, J = 1.0, 8.1, 11.4 Hz, 1H), 3.67 (t, J = 5.3 Hz, 2H), 3.40 (t, J = 5.3 Hz, 2H), 1.16 - 1.33 (m, 9H).

Example 52

5-(1-(2-(Tert-butoxy)ethyl)-4-fluoro-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine

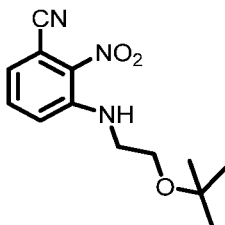


A mixture of N-(2-(tert-butoxy)ethyl)-3-fluoro-2-nitroaniline (179 mg, 0.698 mmol), sodium hydrosulfite (365 mg, 85%, 1.781 mmol), and 6-(diethylamino)nicotinaldehyde (143 mg, 0.803 mmol) in EtOH (4 mL) and water (2 mL) was heated at 125 °C under microwave
 25 conditions for 30 minutes. NH_4OH (28% in water) was added, and the resulting mixture was extracted with EtOAc. The combined EtOAc extract was washed sequentially with water and brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified

via silica gel chromatography (0% to 60% EtOAc/hexanes) to afford 5-(1-(2-(tert-butoxy)ethyl)-4-fluoro-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (75 mg) as a white solid. LC-MS (ES) $m/z = 385$ $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.59 (d, $J = 2.0$ Hz, 1H), 8.04 (dd, $J = 9.1, 2.5$ Hz, 1H), 7.45 (d, $J = 8.1$ Hz, 1H), 7.28 (td, $J = 8.1, 4.6$ Hz, 1H), 7.03 (dd, $J = 10.8, 8.0$ Hz, 1H), 6.77 (d, $J = 8.9$ Hz, 1H), 4.45 (t, $J = 5.2$ Hz, 2H), 3.81 (t, $J = 5.1$ Hz, 2H), 3.64 (q, $J = 7.1$ Hz, 4H), 1.25 (t, $J = 7.1$ Hz, 6H), 0.99 (s, 9H).

Intermediate 83

3-((2-(Tert-butoxy)ethyl)amino)-2-nitrobenzonitrile

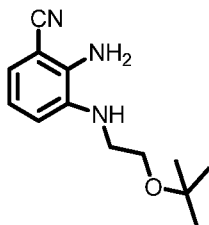


10

A solution of 3-fluoro-2-nitrobenzonitrile (300 mg, 1.806 mmol), 2-(tert-butoxy)ethan-1-amine (233 mg, 1.987 mmol), and N,N-diisopropylethylamine (0.379 mL, 2.167 mmol) in DMF (20mL) was stirred for 16 hours. The reaction was concentrated, and the resulting residue was purified via silica gel chromatography (0% to 40% EtOAc/hexanes) to afford 3-((2-(tert-butoxy)ethyl)amino)-2-nitrobenzonitrile (450 mg) as a orange solid. LC-MS (ES) $m/z = 264$ $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.39 (br. s., 1H), 7.49 (dd, $J = 7.1, 8.9$ Hz, 1H), 7.19 (dd, $J = 1.0, 8.9$ Hz, 1H), 7.14 (dd, $J = 1.1, 7.2$ Hz, 1H), 3.63 - 3.82 (m, 2H), 3.48 (q, $J = 5.1$ Hz, 2H), 1.29 (s, 9H).

20 Intermediate 84

2-Amino-3-((2-(tert-butoxy)ethyl)amino)benzonitrile



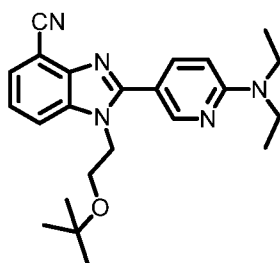
To a solution of 3-((2-(tert-butoxy)ethyl)amino)-2-nitrobenzonitrile (450 mg, 1.709 mmol) in EtOH (25 mL) was added tin(II) chloride (1296 mg, 6.84 mmol), and the reaction mixture was refluxed for 16 hours. The reaction was concentrated and ice water was then added followed by saturated aqueous $NaHCO_3$ until pH~9. EtOAc was added, and the resulting mixture was filtered through celite. The organic layer was separated, and the aqueous

25

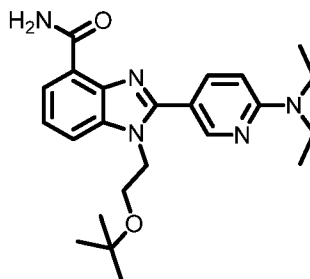
phase was back extracted with EtOAc (3x). The combined organic extract was washed with brine, dried over MgSO_4 , filtered, and concentrated. The resulting residue was purified via silica gel chromatography (0% to 100% EtOAc/hexanes) to afford 2-amino-3-((2-(tert-butoxy)ethyl)amino)benzonitrile (129 mg) as a solid. LC-MS (ES) m/z = 177.96 [$\text{M}-\text{C}_4\text{H}_8+\text{H}$] $^+$. ^1H NMR (400 MHz, CDCl_3): δ 6.98 (dd, J = 1.5, 7.9 Hz, 1H), 6.83 - 6.89 (m, 1H), 6.74 - 6.82 (m, 1H), 3.60 - 3.71 (m, 2H), 3.25 (t, J = 5.1 Hz, 2H), 1.27 (s, 9H).

Example 53

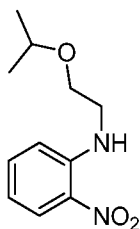
1-(2-(Tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazole-4-carbonitrile



A mixture of 2-amino-3-((2-(tert-butoxy)ethyl)amino)benzonitrile (129 mg, 0.442 mmol), 6-(diethylamino)nicotinaldehyde (87 mg, 0.487 mmol), and oxone (177 mg, 0.288 mmol) in DMF (10 mL) and water (4 mL) was stirred for 16 hours. Saturated aqueous NaHCO_3 was added, and the resulting mixture was extracted with EtOAc. The combined organic extract was washed sequentially with water and brine, dried over MgSO_4 , filtered, and concentrated. The resulting residue was purified via silica gel chromatography (0% to 50% EtOAc/hexanes) to afford 1-(2-(tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazole-4-carbonitrile (98 mg) as a oil. LC-MS (ES) m/z = 392 [$\text{M}+\text{H}$] $^+$. ^1H NMR (400 MHz, CDCl_3): δ 8.60 (d, J = 2.3 Hz, 1H), 8.05 (dd, J = 2.5, 8.9 Hz, 1H), 7.78 (dd, J = 0.8, 8.4 Hz, 1H), 7.60 (dd, J = 0.8, 7.4 Hz, 1H), 7.30 (t, J = 7.9 Hz, 1H), 6.61 (d, J = 8.9 Hz, 1H), 4.43 (t, J = 5.3 Hz, 2H), 3.80 (t, J = 5.2 Hz, 2H), 3.62 (q, J = 7.1 Hz, 4H), 1.19 - 1.34 (m, 6H), 1.06 (s, 9H).

Example 54**1-(2-(Tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazole-4-carboxamide**

- 5 A solution of 1-(2-(tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazole-4-carbonitrile (75 mg, 0.192 mmol) and sodium hydroxide (0.958 mL, 0.958 mmol) in water (2 mL) and EtOH (2mL) was heated at 128 °C under microwave conditions for 90 minutes. The reaction was concentrated, water was then added, and the resulting mixture was extracted with CH₂Cl₂. The combined CH₂Cl₂ extract was washed sequentially with 1N
- 10 NaOH, water, and brine. The organic extract was then dried over MgSO₄, filtered, and concentrated to afford 1-(2-(tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazole-4-carboxamide (41 mg) as a off white solid. LC-MS (ES) m/z = 410 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 9.86 (br. s., 1H), 8.69 (br. s., 1H), 8.19 (dd, J = 0.9, 7.7 Hz, 1H), 8.07 (d, J = 7.6 Hz, 1H), 7.68 (dd, J = 1.0, 7.9 Hz, 1H), 7.40 (t, J = 7.9 Hz, 1H),
- 15 6.63 (d, J = 8.9 Hz, 1H), 5.92 (d, J = 3.6 Hz, 1H), 4.45 (t, J = 5.5 Hz, 2H), 3.84 (t, J = 5.5 Hz, 2H), 3.65 (q, J = 6.9 Hz, 4H), 1.29 (t, J = 7.1 Hz, 6H), 1.09 (s, 9H).

Intermediate 85**N-(2-Isopropoxyethyl)-2-nitroaniline**

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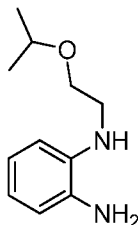
- To 2-isopropoxyethan-1-amine (324 mg, 3.14 mmol) in DMF (15 mL) were added 1-fluoro-2-nitrobenzene (0.302 mL, 2.86 mmol) and K₂CO₃ (434 mg, 3.14 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with water (40 mL) and then extracted with EtOAc (4 x 30 mL). The organic extracts were combined
- 25 and washed with brine, dried (MgSO₄), filtered, and concentrated. Purification by flash chromatography on SiO₂ (gradient from 0 to 25% EtOAc/hexanes) afforded N-(2-

isopropoxyethyl)-2-nitroaniline (545 mg) as a orange/amber color oil. LC-MS (ES) m/z = 225 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 1.12 (d, J = 6.1 Hz, 6H), 3.47 (m, 2H), 3.58 - 3.67 (m, 3H), 6.70 (m, 1H), 7.08 (dd, J = 8.7, 0.9 Hz, 1H), 7.51 - 7.62 (m, 1H), 8.07 (dd, J = 8.6, 1.5 Hz, 1H), 8.22 (br. s., 1H).

5

Intermediate 86

N1-(2-Isopropoxyethyl)benzene-1,2-diamine

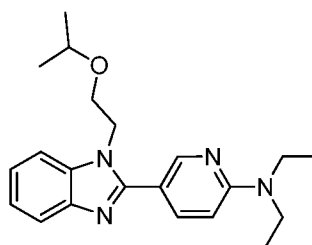


To a solution of N-(2-isopropoxyethyl)-2-nitroaniline (545 mg, 2.430 mmol) in CH₃OH (15 mL) cooled in an ice bath was added NiCl₂·6H₂O (1.45 g, 6.08 mmol) followed by sodium borohydride (460 mg, 12.15 mmol) in small portion over 10 minutes, and the reaction mixture was stirred at room temperature for 30 minutes. The reaction was then diluted with concentrated NH₄OH (20 mL) and extracted with CH₂Cl₂ (3 x 30 mL). The organic extracts were combined and washed with brine, dried (MgSO₄), filtered and concentrated to afford N1-(2-isopropoxyethyl)benzene-1,2-diamine (458 mg) as a light amber color oil. LC-MS (ES) m/z = 195 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 1.11 (d, J = 6.1 Hz, 6H), 3.15 (m, 2H), 3.54 - 3.63 (m, 3H), 4.34 (t, J = 5.7 Hz, 1H), 4.44 (s, 2H), 6.39 - 6.58 (m, 4H).

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Example 55

N,N-Diethyl-5-(1-(2-isopropoxyethyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine

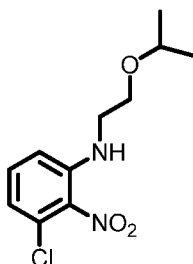


To N1-(2-isopropoxyethyl)benzene-1,2-diamine (80 mg, 0.412 mmol) in DMF (2 mL) and water (2 mL) was added 6-(diethylamino)nicotinaldehyde (81 mg, 0.453 mmol) followed by oxone (165 mg, 0.268 mmol), and the reaction mixture was stirred at room temperature for 30 minutes. The reaction was quenched with saturated aqueous NH₄Cl followed by saturated aqueous NaHCO₃ (5 mL), and the resulting mixture was extracted with EtOAc (3 x 20 mL). The organic extracts were combined and washed with brine, dried (MgSO₄),

filtered and concentrated. Purification by flash chromatography on SiO₂ (gradient from 0 to 45% EtOAc/hexanes) afforded N,N-diethyl-5-(1-(2-isopropoxyethyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine (97 mg) as a yellow oil. LC-MS (ES) m/z = 353 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆): δ 0.93 (d, J = 6.1 Hz, 6H), 1.13 - 1.18 (m, 6H), 3.42 (m, 1H), 3.58 (q, J = 6.9 Hz, 4H), 3.76 (t, J = 5.3 Hz, 2H), 4.39 (t, J = 5.3 Hz, 2H), 6.73 (d, J = 9.1 Hz, 1H), 7.18 - 7.27 (m, 2H), 7.61 - 7.65 (m, 2H), 7.99 (dd, J = 8.9, 2.5 Hz, 1H), 8.55 (d, J = 1.8 Hz, 1H).

Intermediate 87

3-Chloro-N-(2-isopropoxyethyl)-2-nitroaniline



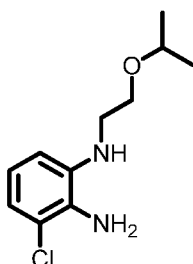
10

To a solution of 1-chloro-3-fluoro-2-nitrobenzene (800 mg, 4.56 mmol) in DMF (20 mL) were added 2-isopropoxyethan-1-amine (470 mg, 4.56 mmol) and potassium carbonate (630 mg, 4.56 mmol), and the mixture was stirred at room temperature for 18 hours. The mixture was quenched with water (15 mL) and extracted with EtOAc (3x). The extract was dried and concentrated, and the resulting residue was purified using column chromatography (silica gel, 0 to 60% EtOAc/hexanes) to give the desired product (900 mg) as a pale brown oil. LC-MS (ES) m/z = 259, 261 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 1.23 (d, J = 6.1 Hz, 6H), 3.36 (t, J = 5.3 Hz, 2H), 3.63 - 3.73 (m, 3H), 6.73 - 6.83 (m, 2H) 7.20 - 7.30 (m, 1H).

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20 Intermediate 88

3-Chloro-N1-(2-isopropoxyethyl)benzene-1,2-diamine



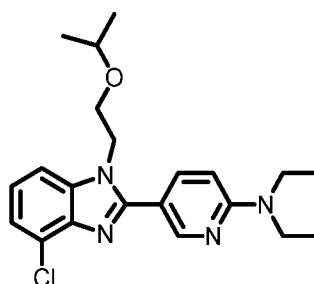
To a stirring solution of 3-chloro-N-(2-isopropoxyethyl)-2-nitroaniline (350 mg, 1.353 mmol) and NiCl₂·6H₂O (805 mg, 3.38 mmol) in CH₃OH (8 mL) was added sodium borohydride (256 mg, 6.76 mmol) in portions at 0 °C, and the reaction mixture was stirred at room

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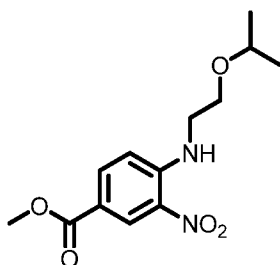
temperature for 30 minutes. The mixture was concentrated, and the resulting residue was dissolved into concentrated NH_4OH and extracted with EtOAc (3x). The extract was dried (Na_2SO_4) and concentrated to give the desired product (300 mg) as a pale brown oil. LC-MS (ES) m/z = 229, 231 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 1.19 - 1.27 (m, 6H), 3.25 - 3.34 (m, 2H), 3.64 - 3.76 (m, 3H), 3.84 (br. s., 2H), 6.59 - 6.65 (m, 1H), 6.70 - 6.79 (m, 1H), 6.81 - 6.89 (m, 1H).

Example 56

5-(4-Chloro-1-(2-isopropoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine

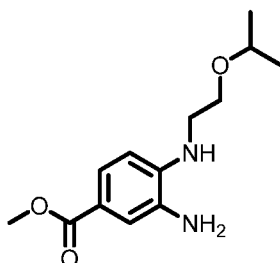


To a solution of 3-chloro-N1-(2-isopropoxyethyl)benzene-1,2-diamine (280 mg, 1.224 mmol) in DMF (8 mL) and water (1 mL) were added 6-(diethylamino)nicotinaldehyde (218 mg, 1.224 mmol) and oxone (753 mg, 1.224 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was basified using 10% K_2CO_3 aqueous solution and extracted with EtOAc (3x). The extract was dried (Na_2SO_4) and concentrated. The residue was purified using column chromatography (silica gel, 0 to 70% EtOAc/hexanes) to give the desired product (178 mg) as a pale brown oil. LC-MS (ES) m/z = 387, 389 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.00 (d, J = 6.1 Hz, 6H), 1.25 (t, J = 7.1 Hz, 6H), 3.45 (dt, J = 12.2, 6.1 Hz, 1H), 3.64 (q, J = 7.1 Hz, 4H), 3.85 (t, J = 5.2 Hz, 2H), 4.46 (t, J = 5.2 Hz, 2H), 6.77 (d, J = 9.1 Hz, 1H), 7.23 - 7.36 (m, 2H), 7.58 (dd, J = 7.9, 1.3 Hz, 1H), 8.02 (dd, J = 9.0, 2.4 Hz, 1H), 8.57 (dd, J = 2.5, 0.8 Hz, 1H).

Intermediate 89Methyl 4-((2-isopropoxyethyl)amino)-3-nitrobenzoate

To a solution of 2-isopropoxyethan-1-amine (2.0 g, 19.39 mmol) in DMF (100 mL) were
5 added methyl 4-fluoro-3-nitrobenzoate (3.86 g, 19.39 mmol) and K_2CO_3 (2.68 g, 19.39
mmol), and the reaction mixture was stirred at room temperature overnight. The reaction
was diluted with water (200 mL), and the resulting mixture was extracted with EtOAc (3 x
100 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 ,
filtered, and concentrated. The resulting residue was purified by flash chromatography on
10 SiO_2 (0-60% EtOAc/hexanes) to afford methyl 4-((2-isopropoxyethyl)amino)-3-
nitrobenzoate (5.43 g) as a bright yellow solid. LC-MS (ES) m/z = 283 $[M+H]^+$. ^1H NMR (400
MHz, $CDCl_3$): δ 8.91 (d, J = 2.0 Hz, 1H), 8.63 (br. s., 1H), 8.07 (dd, J = 2.2, 9.0 Hz, 1H),
6.90 (d, J = 9.1 Hz, 1H), 3.92 (s, 3H), 3.74 - 3.79 (m, 2H), 3.70 (td, J = 6.1, 12.2 Hz, 1H),
3.54 (q, J = 5.1 Hz, 2H), 1.24 (d, J = 6.1 Hz, 6H).

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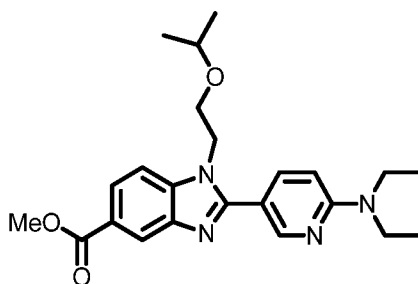
Intermediate 90Methyl 3-amino-4-((2-isopropoxyethyl)amino)benzoate

A solution of methyl 4-((2-isopropoxyethyl)amino)-3-nitrobenzoate (5.43 g, 19.24 mmol)
20 and $NiCl_2 \cdot 6H_2O$ (11.43 g, 48.1 mmol) in CH_3OH (200 mL) was purged with N_2 , then cooled
in an ice-bath for 20 minutes. To the chilled solution was added sodium borohydride (3.64
g, 96 mmol) in 4 portions, the ice-bath was then removed, and the reaction mixture was
stirred at room temperature for 2 hours. The reaction was concentrated in-vacuo, and the
remaining residue taken up into concentrated NH_4OH (150 mL) and EtOAc (200 mL). The
25 resulting mixture was filtered through celite rinsing with EtOAc (2 x 100 mL). The organic
layer was separated, and the aqueous phase was further extracted with EtOAc (2 x 100

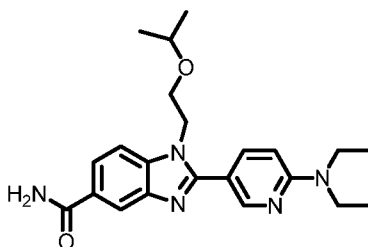
mL). The organic extract was washed with brine (6 mL), dried over Na₂SO₄, filtered, concentrated, and dried under high vacuum overnight to afford methyl 3-amino-4-((2-isopropoxyethyl)amino)benzoate (4.88 g) as a light tan solid. LC-MS (ES) *m/z* = 253 [M+H]⁺.
¹H NMR (400 MHz, CDCl₃): δ 7.59 (d, *J* = 7.9 Hz, 1H), 7.44 (s, 1H), 6.64 (d, *J* = 8.4 Hz, 1H),
 5 3.87 (s, 3H), 3.72 (t, *J* = 5.2 Hz, 2H), 3.69 - 3.62 (m, 1H), 3.36 (br. s., 2H), 1.21 (d, *J* = 6.1 Hz, 6H).

Intermediate 91

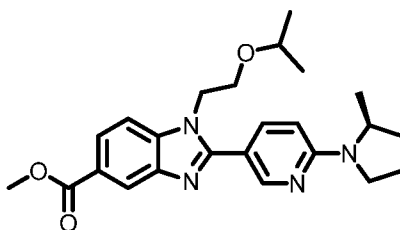
Methyl 2-(6-(diethylamino)pyridin-3-yl)-1-(2-isopropoxyethyl)-1H-benzo[d]imidazole-5-
 10 carboxylate



To a solution of methyl 3-amino-4-((2-isopropoxyethyl)amino)benzoate (350 mg, 1.387 mmol) in DMF (8 mL) and water (1.6 mL) were added 6-(diethylamino)nicotinaldehyde (247 mg, 1.387 mmol) and oxone (853 mg, 1.387 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was basified using 10% K₂CO₃ aqueous solution and extracted with EtOAc (3x). The extract was dried (Na₂SO₄) and concentrated, and the resulting residue was purified using column chromatography (silica gel, 0 to 70%
 20 EtOAc/hexanes) to give the desired product (380 mg) as a pale brown solid. LC-MS (ES) *m/z* = 411 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 0.99 (d, *J* = 6.1 Hz, 6H), 1.21 - 1.30 (m, 6H), 3.46 (quin, *J* = 6.1 Hz, 1H), 3.64 (q, *J* = 7.0 Hz, 4H), 3.87 (t, *J* = 5.2 Hz, 2H), 3.96 (s, 3H), 4.50 (t, *J* = 5.2 Hz, 2H), 6.78 (d, *J* = 9.1 Hz, 1H), 7.71 (d, *J* = 8.6 Hz, 1H), 8.02 (dt, *J* = 8.7, 2.2 Hz, 2H), 8.36 (d, *J* = 1.5 Hz, 1H), 8.53 - 8.63 (m, 1H).

Example 57**2-(6-(Diethylamino)pyridin-3-yl)-1-(2-isopropoxyethyl)-1H-benzo[d]imidazole-5-carboxamide**

- 5 To a solution of methyl 2-(6-(diethylamino)pyridin-3-yl)-1-(2-isopropoxyethyl)-1H-benzo[d]imidazole-5-carboxylate (80 mg, 0.195 mmol) in CH₃OH (2 mL) was added 8N NaOH (0.200 mL, 1.600 mmol), and the mixture was stirred at room temperature for 18 hours. The reaction mixture was neutralized by adding 6N aqueous HCl (0.267 mL, 1.600 mmol), and then concentrated to give crude 2-(6-(diethylamino)pyridin-3-yl)-1-(2-isopropoxyethyl)-1H-benzo[d]imidazole-5-carboxylic acid. The residue was dried under vacuum and treated with DMSO (2 mL). To this mixture were added NH₄Cl (20.85 mg, 0.390 mmol), N-methylmorpholine (0.129 mL, 1.169 mmol), EDC (74.7 mg, 0.390 mmol), and 1-hydroxy-7-azabenzotriazole (53.1 mg, 0.390 mmol), and the mixture was stirred at room temperature for 18 hours. The reaction was quenched with water (5 mL), and the resulting precipitate was collected by filtration and dried under vacuum to give the desired product (37 mg) as an off-white solid. LC-MS (ES) m/z = 396 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD):
- 10 δ 1.00 (d, J = 6.1 Hz, 6H), 1.25 (t, J = 7.0 Hz, 6H), 3.46 (dt, J = 12.2, 5.9 Hz, 1H), 3.65 (q, J = 7.1 Hz, 4 H), 3.88 (t, J = 5.1 Hz, 2H), 4.50 (t, J = 5.1 Hz, 2H), 6.78 (d, J = 9.12 Hz, 1H), 7.71 (d, J = 8.36 Hz, 1H), 7.89 (dd, J = 8.6, 1.5 Hz, 1H), 8.02 (dd, J = 9.0, 2.4 Hz, 1H), 8.24
- 15 (d, J = 1.0 Hz, 1H), 8.58 (d, J = 2.0 Hz, 1H).
- 20

Intermediate 92**(S)-Methyl 1-(2-isopropoxyethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylate**

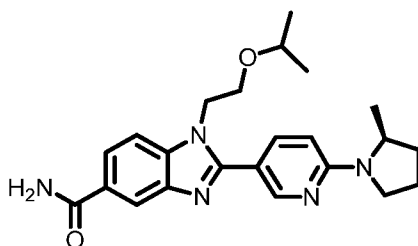
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To a mixture of methyl 3-amino-4-((2-isopropoxyethyl)amino)benzoate (120 mg, 0.476 mmol) and (S)-6-(2-methylpyrrolidin-1-yl)nicotinaldehyde (100 mg, 0.523 mmol) in DMF (4

mL) and water (3 mL) was added oxone (190 mg, 0.309 mmol), and the reaction mixture was stirred at room temperature for 45 minutes. The reaction was diluted with saturated aqueous Na₂CO₃ (7 mL) and EtOAc (15 mL). The aqueous was washed with EtOAc (2 x 15 mL). The combined organic layers were washed with brine (6 mL), dried over Na₂SO₄,
 5 filtered, and concentrated. The resulting residue was purified on silica (0-100% EtOAc/hexanes) to afford methyl (S)-1-(2-isopropoxyethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylate (183 mg) as a gold-brown solid. LC-MS (ES) m/z = 423 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.57 (d, *J* = 2.0 Hz, 1H), 8.23 (d, *J* = 1.0 Hz, 1H), 8.01 (dd, *J* = 2.3, 8.9 Hz, 1H), 7.88 (dd, *J* = 1.7, 8.5 Hz, 1H), 7.76 (d, *J* = 8.6 Hz, 1H), 6.61 (d, *J* = 8.9 Hz, 1H), 4.44 (t, *J* = 5.2 Hz, 2H), 4.24 (t, *J* = 5.6 Hz, 1H), 3.88
 10 (s, 3H), 3.76 (t, *J* = 5.3 Hz, 2H), 3.53 - 3.61 (m, 1H), 3.34 - 3.37 (m, 3H), 2.01 - 2.12 (m, 2H), 1.68 - 1.75 (m, 1H), 1.21 (d, *J* = 6.3 Hz, 3H), 0.91 (dd, *J* = 0.8, 6.1 Hz, 6H).

Example 58

15 (S)-1-(2-Isopropoxyethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide

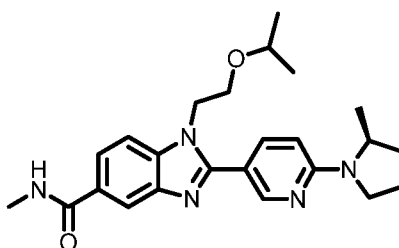


To methyl (S)-1-(2-isopropoxyethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylate (180 mg, 0.426 mmol) in CH₃OH (4 mL) was added 10N
 20 NaOH (0.043 mL, 0.426 mmol) and THF (1 mL; to aid solubility), and the reaction mixture was stirred at 40 °C overnight. Additional 10N NaOH (0.298 mL, 2.98 mmol) was then added, and the reaction was stirred at 40 °C for 2 additional hours. The heat was removed and the pH was adjusted to near neutral with 6N HCl (0.575 mL, 3.45 mmol). The solvents were removed in-vacuo and the remaining solid was taken up in DMSO (3 mL). The DMSO
 25 solution was decanted and transferred to a 20 mL vial. To the DMSO solution were added EDC (163 mg, 0.852 mmol), HOAT (131 mg, 0.852 mmol), ammonium chloride (45.6 mg, 0.852 mmol), and N-methyl morpholine (0.281 mL, 2.56 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with water (6 mL), and the resulting aqueous solution was extracted with Et₂O (3 x 9 mL) followed by EtOAc
 30 (3 x 6 mL). The combined organic layers were washed with 0.5N HCl (6 mL). The acidic aqueous extract was made basic with 1N Na₂CO₃ (3 mL), and the aqueous mixture was

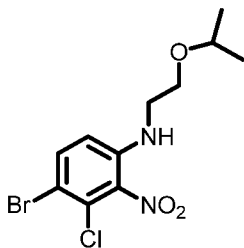
extracted with EtOAc (2 x 6 mL). The combined organic extract was washed with brine (2 mL), dried over Na₂SO₄, filtered, concentrated, and dried under high vacuum. The resulting residue was freeze dried to afford (S)-1-(2-isopropoxyethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide (15 mg) as a tan solid. LC-MS (ES) m/z = 408 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.69 (s, 1H), 8.27 (s, 1H), 8.18 - 8.06 (m, J = 6.6 Hz, 1H), 7.96 (dd, J = 1.5, 8.6 Hz, 1H), 7.61 (d, J = 8.6 Hz, 1H), 6.59 (d, J = 8.9 Hz, 1H), 4.47 (t, J = 5.3 Hz, 2H), 3.88 (t, J = 5.4 Hz, 3H), 3.51 (td, J = 6.1, 12.2 Hz, 2H), 2.25 - 2.08 (m, 5H), 1.31 (d, J = 6.3 Hz, 4H), 1.07 (d, J = 6.1 Hz, 8H).

Example 59

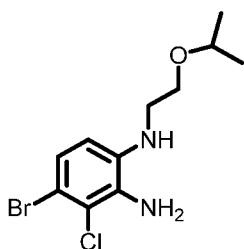
(S)-1-(2-Isopropoxyethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide



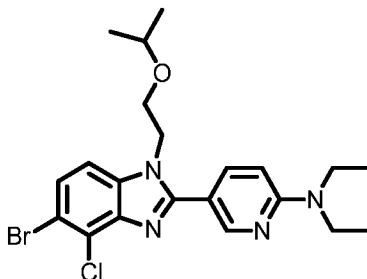
A DMSO (1 mL) solution of (S)-1-(2-isopropoxyethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylic acid (58.0 mg, 0.142 mmol) was treated with EDC (54.4 mg, 0.284 mmol), HOAT (43.8 mg, 0.284 mmol), NMM (0.094 mL, 0.852 mmol), and methanamine hydrochloride (19.17 mg, 0.284 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with water (6 mL), and the resulting aqueous mixture was washed with EtOAc (3 x 9 mL). The combined organic layers were washed sequentially with 1N Na₂CO₃ (3 mL), brine (2 mL), dried over Na₂SO₄, filtered, concentrated, and dried under high vacuum. The remaining residue was purified by silica gel chromatography (0-100%, EtOAc/hexanes) and freeze dried to afford (S)-1-(2-isopropoxyethyl)-N-methyl-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide (20 mg) as a tan solid. LC-MS (ES) m/z = 422 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.60 (d, J = 2.0 Hz, 1H), 8.13 (d, J = 1.3 Hz, 1H), 7.99 (dd, J = 2.4, 9.0 Hz, 1H), 7.85 (dd, J = 1.7, 8.5 Hz, 1H), 7.55 (d, J = 8.6 Hz, 1H), 6.52 (d, J = 1.8 Hz, 1H), 6.25 - 6.35 (m, J = 4.6 Hz, 1H), 4.42 (t, J = 5.6 Hz, 2H), 4.27 (t, J = 5.8 Hz, 1H), 3.84 (t, J = 5.6 Hz, 2H), 3.74 (q, J = 7.0 Hz, 1H), 3.62 - 3.70 (m, 1H), 3.48 (m, 2H), 3.07 (d, J = 4.8 Hz, 3H), 2.10 - 2.21 (m, 2H), 1.27 - 1.31 (m, 4H), 1.06 (dd, J = 1.0, 6.1 Hz, 6H).

Intermediate 934-Bromo-3-chloro-N-(2-isopropoxyethyl)-2-nitroaniline

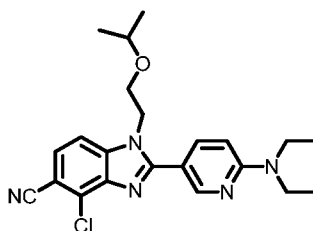
To a solution of 3-chloro-N-(2-isopropoxyethyl)-2-nitroaniline (700 mg, 2.71 mmol) in acetic acid (15 mL) was added NBS (482 mg, 2.71 mmol), and the mixture was stirred at 100 °C for 3 hours. The reaction mixture was concentrated, and the resulting residue was purified using column chromatography (silica gel, 0 to 60% EtOAc/hexanes) to give the desired product (790 mg) as a pale brown solid. LC-MS (ES) m/z = 337, 339 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 (d, J = 6.1 Hz, 6H), 3.32 (t, J = 5.3 Hz, 2H), 3.60 - 3.69 (m, 3H), 6.67 (d, J = 9.4 Hz, 1H), 7.53 (d, J = 9.1 Hz, 1H).

Intermediate 944-Bromo-3-chloro-N1-(2-isopropoxyethyl)benzene-1,2-diamine

To a solution of 4-bromo-3-chloro-N-(2-isopropoxyethyl)-2-nitroaniline (540 mg, 1.600 mmol) in CH_3OH (10 mL) were added $NiCl_2 \cdot 6H_2O$ (952 mg, 4.00 mmol) and sodium borohydride (303 mg, 8.00 mmol) at 0 °C, and the mixture was stirred at 0 °C for 20 minutes. The reaction mixture was concentrated, and the resulting residue was treated with NH_4OH and extracted with EtOAc (3x). The extract was dried (Na_2SO_4) and concentrated to give the desired product (470 mg) as a pale brown oil. LC-MS (ES) m/z = 307, 309 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 - 1.26 (m, 6H), 3.22 - 3.30 (m, 2H), 3.95 (m, 3H), 3.63 - 3.76 (m, 3H), 6.51 (d, J = 8.6 Hz, 1H), 7.02 - 7.09 (m, 1H).

Intermediate 955-(5-Bromo-4-chloro-1-(2-isopropoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine

- 5 To a solution of 4-bromo-3-chloro-N1-(2-isopropoxyethyl)benzene-1,2-diamine (470 mg, 1.528 mmol) in DMF (10 mL) and water (2 mL) were added 6-(diethylamino)nicotinaldehyde (272 mg, 1.528 mmol) and oxone (751 mg, 1.222 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was basified using 10% K₂CO₃ aqueous solution and extracted with EtOAc (3x). The organic extract was dried (Na₂SO₄)
- 10 and concentrated, and the resulting residue was purified using column chromatography (silica gel, 0 to 70% EtOAc/hexanes) to give the desired product (430 mg) as a pale brown solid. LC-MS (ES) m/z = 465, 467 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 1.05 - 1.13 (m, 6H), 1.22 - 1.31 (m, 6H), 3.51 (dt, J = 12.2, 6.2 Hz, 1H), 3.62 (q, J = 7.1 Hz, 4H), 3.80 - 3.88 (m, 2H), 4.34 - 4.44 (m, 2H), 6.60 (d, J = 8.9 Hz, 1H), 7.30 - 7.38 (m, 1H), 7.50 (d, J = 8.6 Hz,
- 15 1H), 7.94 - 8.02 (m, 1H), 8.54 - 8.58 (m, 1H).

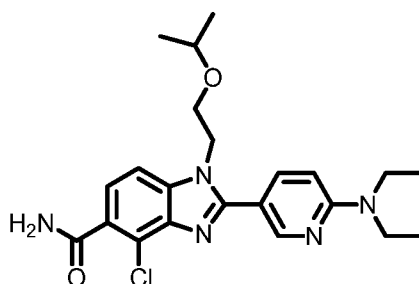
Intermediate 964-Chloro-2-(6-(diethylamino)pyridin-3-yl)-1-(2-isopropoxyethyl)-1H-benzo[d]imidazole-5-carbonitrile

- 20 To a solution of 5-(5-bromo-4-chloro-1-(2-isopropoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (100 mg, 0.215 mmol) in N-methyl-2-pyrrolidone (NMP) (2 mL) was added Zn(CN)₂ (55.5 mg, 0.472 mmol), and the mixture was degassed for 5 minutes by bubbling N₂. Pd(PPh₃)₄ (37.2 mg, 0.032 mmol) was then added and the mixture was stirred
- 25 at 120 °C for 18 hours. The mixture was cooled to room temperature, quenched with water (5 mL), and extracted with EtOAc (3x). The extract was dried (Na₂SO₄) and concentrated.

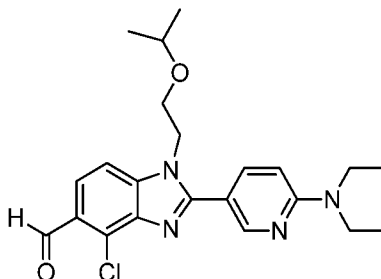
The resulting residue was purified using column chromatography (silica gel, 0 to 70% EtOAc/hexanes) to give the desired product (31 mg) as a brown solid. LC-MS (ES) m/z = 412, 414 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 1.02 - 1.10 (m, 6H), 1.26 (t, J = 7.1 Hz, 6H), 3.44 - 3.54 (m, 1H), 3.62 (q, J = 6.9 Hz, 4H), 3.83 (t, J = 5.3 Hz, 2H), 4.42 (t, J = 5.2 Hz, 2H), 6.61 (d, J = 9.1 Hz, 1H), 7.50 - 7.54 (m, 2H), 7.99 (dd, J = 9.0, 1.9 Hz, 1H), 8.56 (d, J = 2.0 Hz, 1H).

Example 60

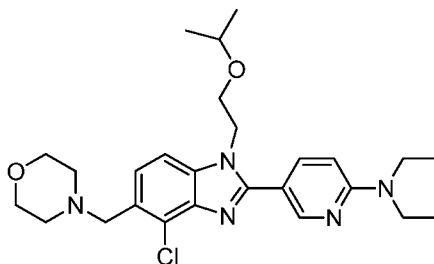
4-Chloro-2-(6-(diethylamino)pyridin-3-yl)-1-(2-isopropoxyethyl)-1H-benzo[d]imidazole-5-carboxamide



To a solution of 4-chloro-2-(6-(diethylamino)pyridin-3-yl)-1-(2-isopropoxyethyl)-1H-benzo[d]imidazole-5-carbonitrile (30 mg, 0.073 mmol) in EtOH (2 mL) was added aqueous 1N NaOH (0.728 mL, 0.728 mmol), and the mixture was stirred at 85 °C for 10 hours. The mixture was concentrated, and the resulting residue was treated with 1N NaOH (3 mL) and extracted with EtOAc (3x). The extract was dried (Na_2SO_4) and concentrated, and the resulting residue was purified by silica gel chromatography (0 to 100% (3:1 EtOAc:EtOH)/hexanes) to give the desired product (20 mg) as an off-white solid. LC-MS (ES) m/z = 430, 432 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 0.99 (d, J = 6.3 Hz, 6H), 1.25 (t, J = 7.0 Hz, 6H), 3.46 (dt, J = 12.2, 6.1 Hz, 1H), 3.61 - 3.72 (m, 4H), 3.85 (t, J = 5.2 Hz, 2H), 4.48 (t, J = 5.1 Hz, 2H), 6.78 (d, J = 9.6 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 8.02 (dd, J = 9.1, 2.5 Hz, 1H), 8.58 (d, J = 1.8 Hz, 1H).

Intermediate 974-Chloro-2-(6-(diethylamino)pyridin-3-yl)-1-(2-isopropoxyethyl)-1H-benzo[d]imidazole-5-carbaldehyde

- 5 To a solution of 5-(5-bromo-4-chloro-1-(2-isopropoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (180 mg, 0.386 mmol) in THF (3 mL) was added n-butyllithium in hexanes (2M, 0.213 mL, 0.425 mmol), and the mixture was stirred at -78 °C for 30 minutes. DMF (0.045 mL, 0.580 mmol) was added, and the mixture was slowly warmed to -10 °C and stirred for 1 hour. The reaction was quenched with aqueous NH₄Cl solution and
- 10 extracted with EtOAc (3x). The extract was dried (Na₂SO₄) and concentrated. The resulting residue was purified using column chromatography (silica gel, 0 to 100% EtOAc/hexanes) to give the desired product (33 mg) as a white solid. LC-MS (ES) m/z =415, 417 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.02 - 1.12 (m, 6H), 1.23 - 1.32 (m, 6H), 3.50 (dt, J = 12.2, 6.1 Hz, 1H), 3.63 (q, J = 7.1 Hz, 4H), 3.84 (t, J = 5.3 Hz, 2H), 4.44 (t, J = 5.3 Hz, 2H), 6.61 (d, J = 9.1 Hz, 1H), 7.47 - 7.56 (m, 1H), 7.91 (d, J = 8.4 Hz, 1H), 8.00 (dd, J = 9.0, 2.4 Hz, 1H),
- 15 8.59 (d, J = 2.0 Hz, 1H), 10.66 (s, 1H).

Example 615-(4-Chloro-1-(2-isopropoxyethyl)-5-(morpholinomethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine

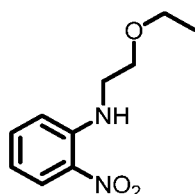
- To a solution of 4-chloro-2-(6-(diethylamino)pyridin-3-yl)-1-(2-isopropoxyethyl)-1H-benzo[d]imidazole-5-carbaldehyde (32 mg, 0.077 mmol) in 1,2-dichloroethane (1 mL) were added morpholine (8.06 µl, 0.093 mmol) and sodium triacetoxyborohydride (32.7 mg, 0.154
- 25 mmol), and the reaction mixture was stirred overnight at room temperature. The mixture

was quenched with saturated NaHCO_3 and extracted with CH_2Cl_2 (3x). The organic extract was dried over Na_2SO_4 , filtered, and concentrated. The resulting residue was purified using column chromatography (silica gel, 0 to 100% EtOAc/heptane) to give the desired product (27 mg) as a colorless oil. LC-MS (ES) m/z = 486, 488 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CD_3OD):

5 δ 1.00 (d, J = 6.1 Hz, 6H), 1.21 - 1.31 (m, 6H), 2.54 - 2.63 (m, 4H), 3.46 (dt, J = 12.2, 6.1 Hz, 1H), 3.64 (q, J = 7.1 Hz, 4H), 3.69 - 3.76 (m, 4H), 3.81 - 3.88 (m, 4H), 4.45 (t, J = 5.2 Hz, 2H), 6.78 (d, J = 8.9 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 8.01 (dd, J = 9.1, 2.5 Hz, 1H), 8.57 (d, J = 2.0 Hz, 1H).

10 Intermediate 98

N-(2-Ethoxyethyl)-2-nitroaniline



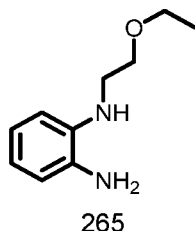
To 2-ethoxyethan-1-amine (5.00 g, 56.1 mmol) in DMF (100 mL) were added 1-fluoro-2-nitrobenzene (7.91 g, 56.1 mmol) and K_2CO_3 (7.75 g, 56.1 mmol), and the reaction mixture was stirred overnight at room temperature. The mixture was filtered, rinsing with EtOAc (20 mL). The filtrate was diluted with water (250 mL), and the resulting mixture was extracted with EtOAc (5 x 120 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , filtered, and concentrated in-vacuo. The remaining residue was purified

15 by silica gel chromatography (0-60%, EtOAc/hexanes) to afford the desired product (11.18 g) as an orange oil. LC-MS (ES) m/z = 211 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.17 - 8.28 (m, 1H), 8.07 (dd, J = 1.5, 8.6 Hz, 1H), 7.55 (ddd, J = 1.1, 7.1, 8.5 Hz, 1H), 7.09 (dd, J = 1.0, 8.6 Hz, 1H), 6.70 (ddd, J = 1.1, 7.1, 8.5 Hz, 1H), 3.59 - 3.69 (m, 2H), 3.45 - 3.55 (m, 4H), 1.14 (t, J = 7.0 Hz, 3H).

25

Intermediate 99

N1-(2-Ethoxyethyl)benzene-1,2-diamine

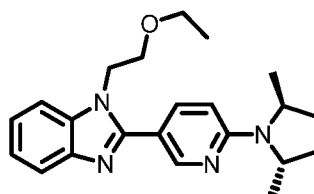


265

A solution of N-(2-ethoxyethyl)-2-nitroaniline (11.18 g, 53.2 mmol) and $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (31.6 g, 133 mmol) in CH_3OH (400 mL) was purged with N_2 , and then cooled to 0 °C. To this solution was added sodium borohydride (10.06 g, 266 mmol) in portions to maintain the reaction's temperature around 0 °C. After the addition was completed, the reaction mixture was allowed to warm up to 20 °C. The reaction was filtered through celite, and the filtrate was then concentrated in-vacuo. The remaining residue was taken up into concentrated NH_4OH (150 mL) and EtOAc (200 mL), and the resulting mixture was filtered through celite, washing with EtOAc (2 x 100 mL). The organic phase was separated, and the aqueous phase was further extracted with EtOAc (2 x 100 mL). The organic extract was filtered through a pad of celite on top of silica, and the filtrate was concentrated. The remaining residue was taken up in CH_2Cl_2 and NH_4OH . The organic layer was separated and filtered through a pad of celite on silica. The organic filtrate was washed with brine (6 mL), dried over Na_2SO_4 , filtered, concentrated in-vacuo, and dried under high vacuum overnight to afford the desired product (3.15 g) as a black oil. LC-MS (ES) m/z = 181 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 6.39 - 6.59 (m, 4H), 4.47 (s, 2H), 4.38 (t, J = 5.7 Hz, 1H), 3.57 (t, J = 5.8 Hz, 2H), 3.48 (q, J = 6.9 Hz, 2H), 3.18 (q, J = 5.8 Hz, 2H), 1.10 - 1.19 (m, 3H).

Example 62

2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole

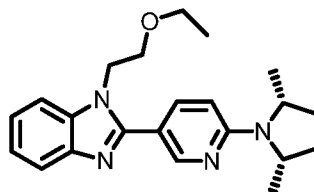


To N1-(2-ethoxyethyl)benzene-1,2-diamine (155 mg, 0.860 mmol) and 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (193 mg, 0.946 mmol) in DMF (3 mL) and water (3 mL) was added oxone (344 mg, 0.559 mmol), and the reaction mixture was stirred at room temperature for 45 minutes. The reaction was quenched with saturated aqueous NH_4Cl (8 mL), and the pH was adjusted to ~10 with NH_4OH (10 mL). The product was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (3 mL), dried over Na_2SO_4 , filtered, and concentrated. The remaining residue was purified by silica gel chromatography (0-100%, EtOAc/hexanes) and freeze dried to afford the desired product (228 mg) as a red-brown sticky solid. LC-MS (ES) m/z = 365 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.54 (d, J = 1.8 Hz, 1H), 7.93 - 7.98 (m, 1H), 7.58 - 7.66 (m, 2H), 7.16 - 7.28 (m, 2H), 6.62 (d, J = 8.9 Hz, 1H), 4.42 (t, J = 5.3 Hz, 2H), 4.25 (br. s., 2H), 3.76 (t, J = 5.5

Hz, 2H), 3.26 - 3.34 (m, 2H), 2.24 (br. s., 2H), 1.66 (d, $J = 5.6$ Hz, 2H), 1.15 (d, $J = 6.1$ Hz, 6H), 0.97 (t, $J = 7.0$ Hz, 3H).

Example 63

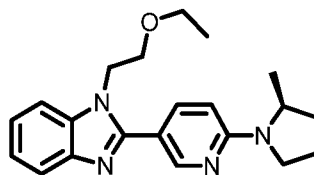
5 2-(6-((2S,5R)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole



To a mixture of N1-(2-ethoxyethyl)benzene-1,2-diamine (220 mg, 1.221 mmol) and 6-((2S,5R)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (274 mg, 1.343 mmol) in DMF (3 mL) and water (3 mL) was added oxone (488 mg, 0.793 mmol), and the reaction mixture was stirred at room temperature for 45 minutes. The reaction was quenched with saturated aqueous NH_4Cl (8 mL), and the pH was adjusted to ~ 10 with concentrated NH_4OH (10 mL). The product was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (3 mL), dried over Na_2SO_4 , filtered, and concentrated. The resulting residue was purified by silica gel chromatography (0-60%, EtOAc/hexanes) to afford the desired product (390 mg) as a red-brown sticky solid. LC-MS (ES) $m/z = 365$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.55 (d, $J = 2.3$ Hz, 1H), 7.98 (dd, $J = 2.5, 8.9$ Hz, 1H), 7.57 - 7.69 (m, 2H), 7.15 - 7.29 (m, 2H), 6.63 (d, $J = 8.9$ Hz, 1H), 4.42 (t, $J = 5.3$ Hz, 2H), 4.06 - 4.20 (m, 2H), 3.77 (t, $J = 5.3$ Hz, 2H), 3.28 - 3.34 (m, 2H), 2.08 (d, $J = 2.0$ Hz, 2H), 1.75 (d, $J = 7.4$ Hz, 2H), 1.31 (d, $J = 6.3$ Hz, 6H), 0.98 (t, $J = 7.0$ Hz, 3H).

Example 64

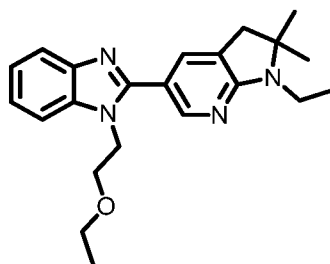
25 (S)-1-(2-Ethoxyethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole



To a mixture of N1-(2-ethoxyethyl)benzene-1,2-diamine (45.0 mg, 0.250 mmol) and (S)-6-(2-methylpyrrolidin-1-yl)nicotinaldehyde (52.2 mg, 0.275 mmol) in DMF (1.5 mL) and water (1.5 mL) was added oxone (100 mg, 0.162 mmol), and the reaction mixture was stirred at room temperature for 45 minutes. The reaction was quenched with saturated aqueous NH_4Cl

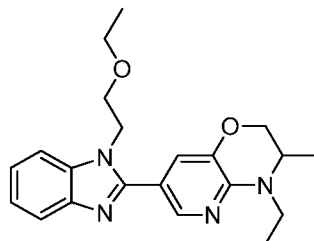
(8 mL), and the pH was adjusted to ~ 10 (paper) with NH₄OH (10 mL). The product was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (3 mL), dried over Na₂SO₄, filtered, and concentrated. The remaining residue was purified by reverse phase HPLC (0-25% CH₃CN/0.1%TFA in water) to afford (19 mg) as a pale-yellow sticky solid. LC-MS (ES) m/z = 351 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.73 (d, *J* = 1.8 Hz, 1H), 8.21 (dd, *J* = 2.5, 9.1 Hz, 1H), 7.93 - 8.02 (m, 1H), 7.79 - 7.87 (m, 1H), 7.60 - 7.69 (m, 2H), 6.83 - 7.03 (m, 1H), 4.65 - 4.74 (m, 2H), 4.28 - 4.49 (m, 1H), 4.00 (t, *J* = 5.1 Hz, 2H), 3.70 - 3.80 (m, 1H), 3.52 - 3.62 (m, 1H), 3.48 (q, *J* = 7.1 Hz, 2H), 2.09 - 2.38 (m, 3H), 1.84 - 1.95 (m, 1H), 1.33 (d, *J* = 6.3 Hz, 3H), 1.10 (t, *J* = 7.0 Hz, 3H).

10

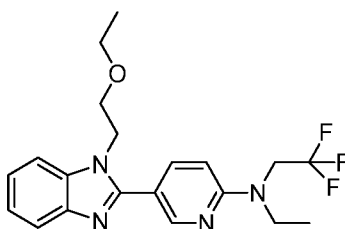
Example 65**1-(2-Ethoxyethyl)-2-(1-ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-benzo[d]imidazole**

A mixture of N1-(2-ethoxyethyl)benzene-1,2-diamine (37.9 mg, 0.211 mmol), 1-ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-5-carbaldehyde (43 mg, 0.211 mmol), and oxone (129 mg, 0.211 mmol) in water (10 mL) and DMF (10 mL) was stirred at room temperature over weekend. Saturated aqueous NaHCO₃ was then added, and the resulting aqueous mixture was extracted with EtOAc. The combined organic extracts were washed with water followed by brine, dried over MgSO₄, filtered, and concentrated. The resulting residue was purified via SiO₂ chromatography (0% to 100% (3:1 EtOAc:EtOH)/heptane) to afford a purple solid. Additional purification by reverse phase HPLC (5% to 95% CH₃CN/(0.1%NH₄OH in H₂O)) afforded 1-(2-ethoxyethyl)-2-(1-ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-benzo[d]imidazole (40 mg) as a tan solid. LC-MS (ES) m/z = 365 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.20 - 8.36 (m, 1H), 7.76 - 7.88 (m, 1H), 7.66 (d, *J* = 1.8 Hz, 1H), 7.45 - 7.56 (m, 1H), 7.19 - 7.35 (m, 2H), 4.44 (t, *J* = 6.0 Hz, 2H), 3.86 (t, *J* = 6.0 Hz, 2H), 3.43 (m, 4H), 2.90 (s, 2H), 1.35 (s, 6H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.0 Hz, 3H).

25

Example 66**7-(1-(2-Ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-4-ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine**

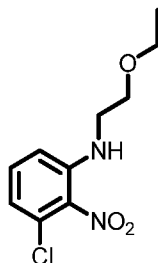
- 5 A mixture of 4-ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-7-carbaldehyde (280 mg, 1.358 mmol), N1-(2-ethoxyethyl)benzene-1,2-diamine (245 mg, 1.358 mmol), and sodium metabisulfite (336 mg, 1.765 mmol) in DMF (15 mL) was stirred at 90 °C for 12 hours. The reaction mixture was poured onto water (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and
- 10 concentrated. The resulting residue was purified by silica gel chromatography (eluting with 0 to 20% EtOAc/hexanes) to give the desired product (160 mg) as a brown solid. LC-MS (ES) m/z = 367 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.20 (d, J = 1.5 Hz, 1H), 7.86 – 7.77 (m, 1H), 7.53 – 7.44 (m, 2H), 7.34 – 7.27 (m, 2H), 4.42 (t, J = 5.8 Hz, 2H), 4.13 – 4.01 (m, 3H), 3.84 (t, J = 5.8 Hz, 2H), 3.76 – 3.67 (m, 1H), 3.49 – 3.32 (m, 3H), 1.32 (d, J = 6.6 Hz,
- 15 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.14 (t, J = 7.0 Hz, 3H).

Example 67**5-(1-(2-Ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N-ethyl-N-(2,2,2-trifluoroethyl)pyridin-2-amine**

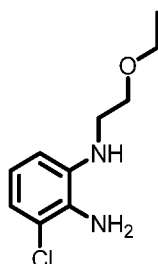
- 20 To a solution of 6-(ethyl(2,2,2-trifluoroethyl)amino)nicotinaldehyde (200 mg, 0.861 mmol) and sodium metabisulfite (213 mg, 1.120 mmol) in DMF (10 mL) was added N1-(2-methoxyethyl)benzene-1,2-diamine (143 mg, 0.861 mmol), and the mixture was stirred at 90 °C for 12 hours. The mixture was poured onto the water (150 ml) and extracted with
- 25 EtOAc (2 x 100 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 0 to 20% EtOAc/hexanes) to give the desired product (260 mg) as pale-yellow solid. LC-

MS (ES) m/z = 393 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.64 (s, 1H), 8.07 (d, J = 8.9 Hz, 1H), 7.85 – 7.78 (m, 1H), 7.51 – 7.44 (m, 1H), 7.34 – 7.28 (m, 2H), 6.74 (d, J = 8.9 Hz, 1H), 4.44 – 4.31 (m, 4H), 3.85 (t, J = 5.6 Hz, 2H), 3.65 (q, J = 7.1 Hz, 2H), 3.43 (q, J = 7.0 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H), 1.13 (t, J = 7.0 Hz, 3H).

5

Intermediate 1003-Chloro-N-(2-ethoxyethyl)-2-nitroaniline

To a solution of 1-chloro-3-fluoro-2-nitrobenzene (400 mg, 2.279 mmol) in DMF (10 mL) were added 2-ethoxyethan-1-amine (203 mg, 2.279 mmol) and K_2CO_3 (315 mg, 2.279 mmol), and the mixture was stirred at room temperature for 18 hours. The mixture was quenched with water (20 mL) and extracted with EtOAc (3x). The extract was dried and concentrated, and the resulting residue was purified using column chromatography (silica gel, 0 to 60% EtOAc/hexanes) to give the desired product (400 mg) as a pale brown oil. LC-MS (ES) m/z = 245, 247 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 1.17 - 1.44 (m, 3H), 3.34 - 3.44 (m, 2H), 3.49 - 3.65 (m, 2H), 3.65 - 3.76 (m, 2H), 6.66 - 6.89 (m, 2H), 7.17 - 7.38 (m, 1H).

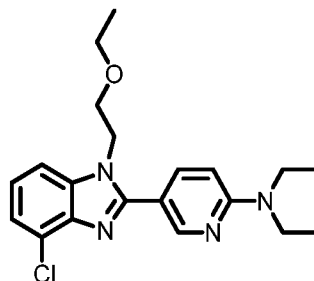
Intermediate 1013-Chloro-N1-(2-ethoxyethyl)benzene-1,2-diamine

To a solution of 3-chloro-N-(2-ethoxyethyl)-2-nitroaniline (240mg, 0.981 mmol) in CH_3OH (6 mL) were added $NiCl_2 \cdot 6H_2O$ (584 mg, 2.452 mmol) and sodium borohydride (186 mg, 4.90 mmol) at 0 °C, and the mixture was stirred at 0 °C for 20 minutes. The reaction mixture

was concentrated, and the resulting residue was treated with NH_4OH and extracted with EtOAc (3x). The extract was dried (Na_2SO_4) and concentrated to give the desired product (203 mg) as a pale brown oil. LC-MS (ES) m/z = 215, 217 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 1.25 - 1.30 (m, 3H), 3.31 (t, J = 4.9 Hz, 2H), 3.59 (q, J = 7.0 Hz, 2H), 3.69 - 3.78 (m, 2H), 6.56 - 6.66 (m, 1H), 6.75 (t, J = 8.0 Hz, 1H), 6.81 - 6.89 (m, 1H).

Example 68

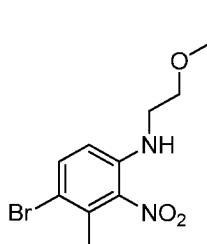
5-(4-Chloro-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine



- 10 To a solution of 3-chloro-N1-(2-ethoxyethyl)benzene-1,2-diamine (210 mg, 0.978 mmol) in DMF (5 mL) and water (1 mL) were added 6-(diethylamino)nicotinaldehyde (174 mg, 0.978 mmol) and oxone (601 mg, 0.978 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was basified using 10% K_2CO_3 aqueous solution and extracted with EtOAc (3x). The extract was dried (Na_2SO_4) and concentrated.
- 15 The resulting residue was purified using column chromatography (silica gel, 0 to 70% EtOAc/hexanes) to give the desired product (195 mg) as a pale brown oil. LC-MS (ES) m/z = 373, 375 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.07 (t, J = 7.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 6H), 3.35 - 3.48 (m, 2H), 3.67 (q, J = 7.1 Hz, 4H), 3.88 (t, J = 5.1 Hz, 2H), 4.52 (t, J = 5.1 Hz, 2H), 6.91 (d, J = 9.1 Hz, 1H), 7.31 - 7.42 (m, 2H), 7.64 (dd, J = 8.0, 1.14 Hz, 1H),
- 20 8.04 - 8.13 (m, 1H), 8.59 (d, J = 1.8 Hz, 1H).

Intermediate 102

4-Bromo-N-(2-ethoxyethyl)-3-methyl-2-nitroaniline

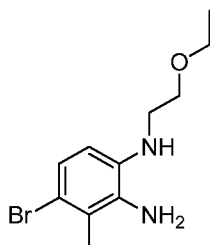


- 25 To a solution of 1-bromo-4-fluoro-2-methyl-3-nitrobenzene (1 g, 4.27 mmol) in DMF (20 mL) were added 2-ethoxyethan-1-amine (0.381 g, 4.27 mmol) and K_2CO_3 (0.591 g, 4.27 mmol),

and the mixture was stirred at room temperature for 18 hours. The reaction mixture was filtered, and the filtrate was concentrated. The resulting residue was purified using column chromatography (silica gel, 0 to 60% EtOAc/hexanes) to give the desired product (760 mg) as a pale brown oil. LC-MS (ES) m/z = 303, 305 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (t, J = 7.1 Hz, 3H), 2.47 (s, 3H), 3.36 (t, J = 5.3 Hz, 2H), 3.58 (q, J = 7.1 Hz, 2H), 3.65 - 3.72 (m, 2H), 6.61 (d, J = 9.1 Hz, 1H), 7.51 (d, J = 9.1 Hz, 1H).

Intermediate 103

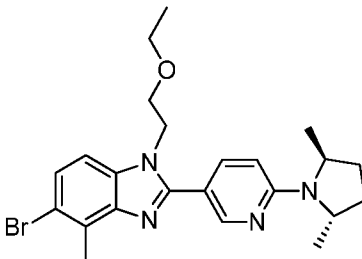
4-Bromo-N1-(2-ethoxyethyl)-3-methylbenzene-1,2-diamine



To a solution of 4-bromo-N-(2-ethoxyethyl)-3-methyl-2-nitroaniline (400 mg, 1.319 mmol) in CH_3OH (7 mL) were added $NiCl_2 \cdot 6H_2O$ (785 mg, 3.30 mmol) and sodium borohydride (250 mg, 6.60 mmol) at 0 °C, and the mixture was stirred at 0 °C for 20 minutes. The reaction mixture was concentrated, and the residue was treated with concentrated NH_4OH aqueous solution and extracted with EtOAc (3x). The extract was dried (Na_2SO_4) and concentrated to give the desired product (352 mg) as a pale brown solid. LC-MS (ES) m/z = 273, 275 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.19 - 1.30 (m, 3H), 2.29 (s, 3H), 3.22 - 3.28 (m, 2H), 3.53 - 3.63 (m, 2H), 3.66 - 3.73 (m, 2H), 6.47 (d, J = 8.6 Hz, 1H), 6.89 (d, J = 8.6 Hz, 1H).

Intermediate 104

5-Bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-4-methyl-1H-benzo[d]imidazole

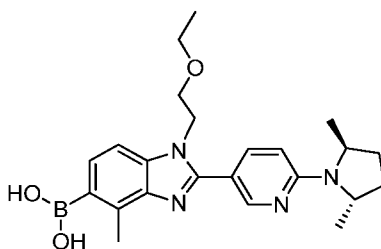


To a solution of 4-bromo-N1-(2-ethoxyethyl)-3-methylbenzene-1,2-diamine (350 mg, 1.281 mmol) in DMF (6 mL) and water (1.2 mL) were added 6-((2S,5S)-2,5-dimethylpyrrolidin-1-

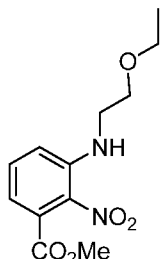
yl)nicotinaldehyde (262 mg, 1.281 mmol) and oxone (591 mg, 0.961 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was basified using 10% K₂CO₃ aqueous solution and extracted with EtOAc (3x). The extract was dried (Na₂SO₄) and concentrated. The resulting residue was purified using column chromatography (silica gel, 0 to 100% EtOAc/hexanes) to give the desired product (320 mg) as a pale brown solid. LC-MS (ES) m/z = 457, 459 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 1.11 - 1.20 (m, 3H), 1.24 (d, J = 6.3 Hz, 6H), 1.65 - 1.82 (m, 2H), 2.27 - 2.40 (m, 2H), 2.79 (s, 3H), 3.45 (q, J = 6.9 Hz, 2H), 3.77 - 3.91 (m, 2H), 4.25 - 4.43 (m, 4H), 6.52 (d, J = 8.9 Hz, 1 H), 7.23 (d, J = 8.6 Hz, 1H), 7.46 (d, J = 8.6 Hz, 1H), 7.92 (d, J = 7.9 Hz, 1H), 8.57 (s, 1H).

Example 69

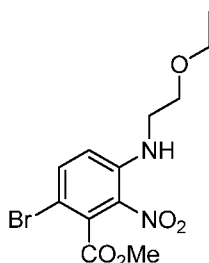
(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-4-methyl-1H-benzo[d]imidazol-5-yl)boronic acid



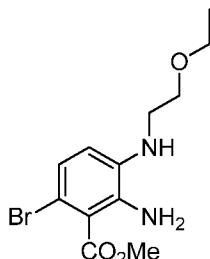
To a microwave tube were added 5-bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-4-methyl-1H-benzo[d]imidazole (300 mg, 0.656 mmol), ethanol (4 mL), hypodiboric acid (88 mg, 0.984 mmol), 1,3-bis(diphenylphosphino)propane-nickel(II) chloride (10.67 mg, 0.020 mmol), and triphenylphosphine (10.32 mg, 0.039 mmol), and the mixture was degassed for 10 minutes by bubbling argon. N,N-diisopropylethylamine (0.344 mL, 1.968 mmol) was added, the tube was sealed, and the mixture was stirred at 80 °C for 3 hours. The mixture was concentrated, and the resulting residue was purified using column chromatography (silica gel, 0 to 60% (3:1 EtOAc:EtOH)/heptane) to give the desired product (150 mg) as a pale brown solid. LC-MS (ES) m/z = 423 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.07 (t, J = 7.1 Hz, 3H), 1.18 - 1.29 (m, 6H), 1.76 (d, J = 5.8 Hz, 2H), 2.31 - 2.43 (m, 2H), 2.64 (s, 3H), 3.35 - 3.44 (m, 4H), 3.85 (t, J = 5.2 Hz, 2H), 4.33 (br. s., 2H), 4.44 (t, J = 5.2 Hz, 2H), 6.70 (d, J = 8.9 Hz, 1 H), 7.23 (d, J = 8.1 Hz, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.98 (dd, J = 9.0, 2.4 Hz, 1H), 8.54 (d, J = 2.3 Hz, 1H).

Intermediate 105Methyl 3-((2-ethoxyethyl)amino)-2-nitrobenzoate

To a solution of methyl 3-fluoro-2-nitrobenzoate (1 g, 5.02 mmol) in DMF (20 mL) were
 5 added 2-ethoxyethan-1-amine (0.448 g, 5.02 mmol) and K_2CO_3 (0.694 g, 5.02 mmol), and
 the mixture was stirred at room temperature for 18 hours. The reaction mixture was filtered,
 and the filtrate was concentrated. The resulting residue was purified using column
 chromatography (silica gel, 0 to 60% EtOAc/hexanes) to give the desired product (980 mg)
 as a pale brown oil. LC-MS (ES) m/z = 268 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 1.23 -
 10 1.34 (m, 3H), 3.50 (t, J = 5.4 Hz, 2 H), 3.61 (q, J = 7.0 Hz, 2H), 3.71 - 3.78 (m, 2H), 3.93 (s,
 3H), 6.82 (dd, J = 7.1, 1.3 Hz, 1H), 6.99 (dd, J = 8.7, 1.1Hz, 1H), 7.44 (dd, J = 8.7, 7.2 Hz,
 1H).

Intermediate 10615 Methyl 6-bromo-3-((2-ethoxyethyl)amino)-2-nitrobenzoate

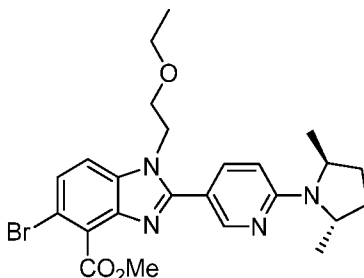
To a solution of methyl 3-((2-ethoxyethyl)amino)-2-nitrobenzoate (725mg, 2.70 mmol) in
 acetic acid (15 mL) was added NBS (481 mg, 2.70 mmol), and the mixture was stirred at
 100 °C for 2 hours. The reaction mixture was concentrated, and the residue was purified
 20 using column chromatography (silica gel, 0 to 60% EtOAc/hexanes) to give the desired
 product (715 mg) as a pale brown solid. LC-MS (ES) m/z = 347, 349 $[M+H]^+$. ^1H NMR (400
 MHz, $CDCl_3$): δ 1.23 - 1.33 (m, 3H), 3.48 - 3.56 (m, 2H), 3.61 (q, J = 7.1 Hz, 2H), 3.73 - 3.81
 (m, 2H), 6.90 (d, J = 9.1 Hz, 1H), 7.59 (d, J = 9.4 Hz, 1H).

Intermediate 107Methyl 2-amino-6-bromo-3-((2-ethoxyethyl)amino)benzoate

To a solution of methyl 6-bromo-3-((2-ethoxyethyl)amino)-2-nitrobenzoate (375 mg, 1.080 mmol) in ethanol (10 mL) was added tin(II) chloride dihydrate (2437 mg, 10.80 mmol), and the mixture was stirred at 70 °C for 3 hours. The mixture was cooled, quenched with water (10 mL), neutralized with 1N NaOH, treated with EtOAc (30 mL), and filtered. The organic layer was collected, and the aqueous layer was further extracted with EtOAc (3x). The combined organic layers were dried (Na₂SO₄) and concentrated to give the desired product (196 mg) as a pale brown oil. LC-MS (ES) *m/z* = 317, 319 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 1.27 (t, *J* = 7.1 Hz, 3H), 3.18 - 3.32 (m, 2H), 3.58 (q, *J* = 6.9 Hz, 2H), 3.69 - 3.77 (m, 2H), 3.98 (s, 3H), 6.61 (d, *J* = 8.6 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H).

Intermediate 108

Methyl 5-bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzod[*d*]imidazole-4-carboxylate

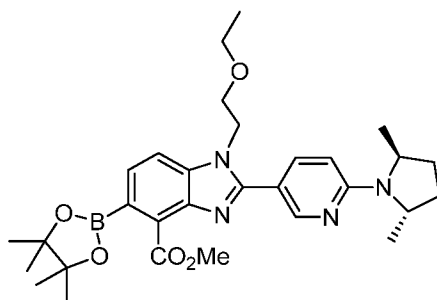


To a solution of methyl 2-amino-6-bromo-3-((2-ethoxyethyl)amino)benzoate (250 mg, 0.788 mmol) in DMF (3 mL) and water (0.600 mL) were added 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (161 mg, 0.788 mmol) and oxone (363 mg, 0.591 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was basified using 10% K₂CO₃ aqueous solution and extracted with EtOAc (3x). The extract was dried (Na₂SO₄) and concentrated. The residue was purified using column chromatography (silica gel, 0 to 100% EtOAc/hexanes) to give the desired product (273 mg) as a pale brown solid. LC-MS (ES) *m/z* = 501, 503 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 1.10 - 1.20 (m, 3H), 1.21

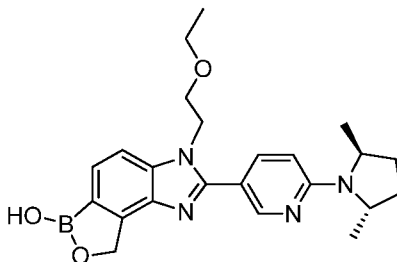
- 1.29 (m, 6H), 1.64 (br. s., 2H), 1.74 (br. s., 2H), 2.33 (br. s., 2H), 3.46 (q, $J = 6.8$ Hz, 2H), 3.83 (t, $J = 5.3$ Hz, 2H), 4.11 (s, 3H), 4.37 - 4.47 (m, 2H), 7.42 - 7.48 (m, 2H).

Intermediate 109

- 5 Methyl 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazole-4-carboxylate



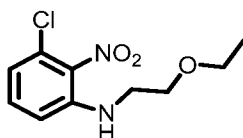
- To a solution of methyl 5-bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole-4-carboxylate (270 mg, 0.538 mmol) in 1,4-dioxane (4 mL) were added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (191 mg, 0.754 mmol) and potassium acetate (238 mg, 2.423 mmol), and the mixture was degassed for 10 minutes by bubbling N_2 . $PdCl_2(dppf)$ (19.70 mg, 0.027 mmol) was added, and the mixture was stirred at 90 °C for 14 hours. The mixture was cooled to room temperature, diluted with EtOAc, and filtered through a short pad of Celite. The filtrate was concentrated, and the resulting residue was purified using column chromatography (silica gel, 0 to 90% EtOAc/hexanes) to give the desired product (195 mg) as a pale brown solid. LC-MS (ES) $m/z = 549 [M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.06 (t, $J = 7.1$ Hz, 3H), 1.23 (d, $J = 6.1$ Hz, 6H), 1.35 - 1.44 (m, 12H), 1.76 (d, $J = 5.8$ Hz, 2H), 2.30 - 2.41 (m, 2H), 3.35 - 3.44 (m, 2H), 3.85 (t, $J = 5.2$ Hz, 2H), 3.97 - 4.05 (m, 3H), 4.33 (br. s., 2H), 4.50 (t, $J = 5.2$ Hz, 2H), 6.70 (d, $J = 8.9$ Hz, 1H), 7.57 (d, $J = 8.1$ Hz, 1H), 7.78 (d, $J = 8.1$ Hz, 1H), 7.99 (dd, $J = 9.0$, 2.4 Hz, 1H), 8.54 - 8.59 (m, 1H).

Example 70**2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-3H-[1,2]oxaborolo[4',3':3,4]benzo[1,2-d]imidazol-6(8H)-ol**

- 5 To a solution of methyl 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazole-4-carboxylate (90 mg, 0.164 mmol) in ethanol (3 mL) was added sodium borohydride (41.0 mg, 1.083 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 hours. The mixture was quenched with 2N HCl, stirred for 10 minutes, and then concentrated. The
- 10 resulting residue was treated with 10% NaHCO₃ and extracted with EtOAc (3x). The extract was dried (Na₂SO₄) and concentrated, and the resulting residue was purified using column chromatography (silica gel, 0 to 80% (3:1 EtOAc:EtOH)/heptane) to give the desired product (39 mg) as a white solid. LC-MS (ES) m/z = 421 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.02 - 1.11 (m, 3H), 1.19 - 1.29 (m, 6H), 1.76 (d, J = 5.8 Hz, 2H), 2.30 - 2.45 (m, 2H), 3.35
- 15 - 3.44 (m, 4H), 3.88 (t, J = 5.2 Hz, 2H), 4.33 (br. s., 1H), 4.52 (t, J = 5.3 Hz, 2H), 5.40 (s, 2H), 6.70 (d, J = 8.6 Hz, 1H), 7.53 - 7.68 (m, 2H), 8.00 (dd, J = 8.9, 2.5 Hz, 1H), 8.50 - 8.63 (m, 1H).

Intermediate 110

- 20 **3-Chloro-N-(2-ethoxyethyl)-2-nitroaniline**

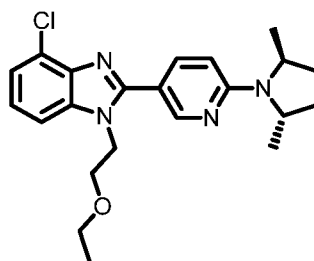


- A solution of 1-chloro-3-fluoro-2-nitrobenzene (158 mg, 0.900 mmol), 2-ethoxyethan-1-amine (88 mg, 0.990 mmol), and N,N-diisopropylethylamine (0.189 mL, 1.080 mmol) in DMF (15 mL) was stirred at room temperature for 16 hours. The reaction was concentrated
- 25 to dryness and the residue was purified via silica gel column (0% to 30% EtOAc/hexanes) to afford 3-chloro-N-(2-ethoxyethyl)-2-nitroaniline (98 mg) as an oil. LC-MS (ES) m/z = 245, 247 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.25 (dd, J = 7.9, 8.6 Hz, 1H), 6.77 (ddd, J =

1.0, 8.2, 16.1 Hz, 2H), 3.69 (t, $J = 5.3$ Hz, 2H), 3.58 (q, $J = 7.0$ Hz, 2H), 3.38 (t, $J = 5.3$ Hz, 2H), 1.27 (t, $J = 7.0$ Hz, 3H).

Example 71

5 4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole

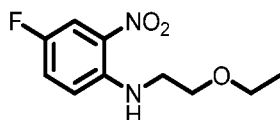


A mixture of 3-chloro-N-(2-ethoxyethyl)-2-nitroaniline (98 mg, 0.401 mmol), sodium hydrosulfite (209 mg, 85%, 1.022 mmol), and 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (86 mg, 0.421 mmol) in EtOH (4 mL) and water (2 mL) was heated under microwave conditions to 130 °C for 20 minutes. The reaction was filtered, and the filtrate was concentrated to dryness. To the resulting residue was added CH₂Cl₂ and the mixture was filtered again. The filtrate was purified via silica gel column (0% to 100% EtOAc/hexanes) to afford 4-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H benzo[d]imidazole (38 mg) as a solid. LC-MS (ES) $m/z = 399, 401$ [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.54 - 8.78 (m, 1H), 7.40 (dd, $J = 0.9, 8.0$ Hz, 1H), 7.27 - 7.34 (m, 2H), 7.12 - 7.25 (m, 1H), 6.53 (d, $J = 6.6$ Hz, 1H), 4.42 (dt, $J = 2.0, 5.7$ Hz, 2H), 4.31 (br. s, 2H), 3.84 (t, $J = 5.7$ Hz, 2H), 3.44 (q, $J = 7.1$ Hz, 2H), 2.23 - 2.40 (m, 2H), 1.74 (d, $J = 5.6$ Hz, 2H), 1.24 (d, $J = 6.1$ Hz, 6H), 1.14 (t, $J = 7.0$ Hz, 3H).

20

Intermediate 111

N-(2-Ethoxyethyl)-4-fluoro-2-nitroaniline

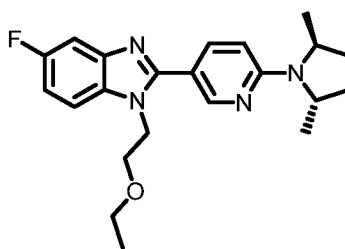


A solution of 1,4-difluoro-2-nitrobenzene (400 mg, 2.51 mmol), 2-ethoxyethan-1-amine (247 mg, 2.77 mmol), and N,N-diisopropylethylamine (0.527 mL, 3.02 mmol) in DMF (15 mL) was stirred for 16 hours. The reaction was concentrated, and the resulting residue was purified via silica gel chromatography (0% to 30% EtOAc/hexanes) to afford N-(2-ethoxyethyl)-4-fluoro-2-nitroaniline (452 mg) as an orange oil. LC-MS (ES) $m/z = 229$ [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.17 (br. s., 1H), 7.91 (dd, $J = 3.0, 9.12$ Hz, 1H), 7.22

- 7.36 (m, 1H), 6.89 (dd, $J = 4.6, 9.4$ Hz, 1H), 3.72 - 3.88 (m, 2H), 3.61 (q, $J = 7.0$ Hz, 2H), 3.50 (t, $J = 4.7$ Hz, 2H), 1.28 (t, $J = 7.0$ Hz, 3H).

Example 72

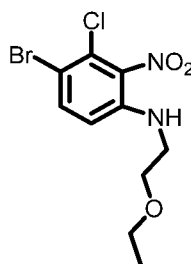
5 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-5-fluoro-1H-benzo[d]imidazole



A mixture of N-(2-ethoxyethyl)-4-fluoro-2-nitroaniline (131 mg, 0.574 mmol), sodium hydrosulfite (300 mg, 85%, 1.464 mmol), and 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (123 mg, 0.603 mmol) in EtOH (4 mL) and water (2 mL) was heated at 130 °C under microwave conditions for 20 minutes. NH₄OH (28% in water) was added, and the resulting mixture was extracted with EtOAc. The combined EtOAc extract was washed sequentially with water and brine, dried over MgSO₄, filtered and concentrated. The resulting residue was purified via silica gel chromatography (0% to 100% EtOAc/hexanes) to afford 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-5-fluoro-1H-benzo[d]imidazole (152 mg) as a viscous oil. LC-MS (ES) $m/z = 383$ [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.58 (d, $J = 2.0$ Hz, 1H), 7.95 (dd, $J = 2.3, 8.9$ Hz, 1H), 7.48 (dd, $J = 2.3, 9.4$ Hz, 1H), 7.44 (dd, $J = 4.6, 8.9$ Hz, 1H), 7.05 (dt, $J = 2.5, 9.1$ Hz, 1H), 6.53 (d, $J = 8.9$ Hz, 1H), 4.40 - 4.46 (m, 2H), 4.20 - 4.39 (m, 2H), 3.87 (t, $J = 5.7$ Hz, 2H), 3.47 (q, $J = 7.0$ Hz, 2H), 2.27 - 2.42 (m, 2H), 1.74 (d, $J = 5.8$ Hz, 2H), 1.25 (d, $J = 6.3$ Hz, 6H), 1.17 (t, $J = 7.0$ Hz, 3H).

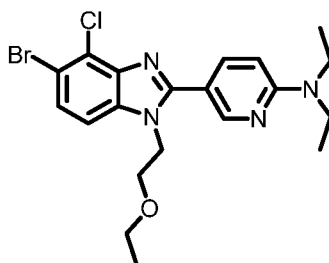
Intermediate 112

4-Bromo-3-chloro-N-(2-ethoxyethyl)-2-nitroaniline



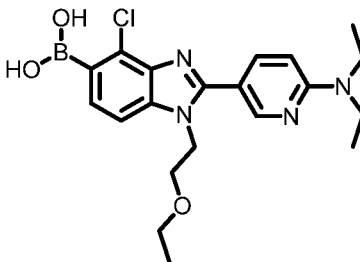
A solution of 3-chloro-N-(2-ethoxyethyl)-2-nitroaniline (2.11 g, 8.62 mmol) and N-bromosuccinimide (1.535 g, 8.62 mmol) in acetic acid was heated at 100 °C for 4 hours. The reaction mixture was concentrated, and the resulting residue was purified via silica gel chromatography (0% to 35% EtOAc/hexanes) to afford 4-bromo-3-chloro-N-(2-ethoxyethyl)-2-nitroaniline (2.15 g) as an orange solid. LC-MS (ES) m/z = 322, 324[M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.55 (d, J = 9.1 Hz, 1H), 6.69 (d, J = 9.1 Hz, 1H), 5.71 (br. s., 1H), 3.64 - 3.73 (m, 2H), 3.57 (q, J = 7.1 Hz, 2H), 3.36 (t, J = 5.2 Hz, 2H), 1.27 (t, J = 7.0 Hz, 3H).

10

Example 73**5-(5-Bromo-4-chloro-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine**

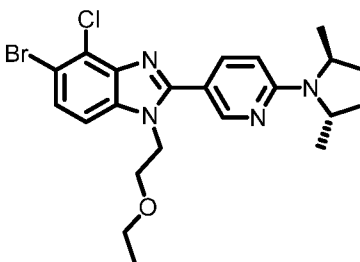
A mixture of 4-bromo-3-chloro-N-(2-ethoxyethyl)-2-nitroaniline (200mg, 0.618 mmol), sodium hydrosulfite (323 mg, 85%, 1.576 mmol), and 6-(diethylamino)nicotinaldehyde (116 mg, 0.649 mmol) in EtOH (4 mL) and water (2mL) was heated under microwave conditions at 130 °C for 20 minutes. The reaction was then filtered and concentrated to dryness. CH₂Cl₂ was added, and the resulting mixture was filtered again. The filtrate was purified via silica gel chromatography (0% to 100% EtOAc/hexanes) to afford 5-(5-bromo-4-chloro-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (134 mg) as an oil. LC-MS (ES) m/z = 451, 453 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.57 (br. s., 1H), 7.99 (d, J = 8.1 Hz, 1H), 7.51 (d, J = 8.6 Hz, 1H), 7.33 (d, J = 8.6 Hz, 1H), 6.61 (d, J = 8.9 Hz, 1H), 4.42 (t, J = 5.5 Hz, 2H), 3.84 (t, J = 5.6 Hz, 2H), 3.63 (q, J = 7.0 Hz, 4H), 3.45 (q, J = 6.9 Hz, 2H), 1.27 (t, J = 7.1 Hz, 6H), 1.16 (t, J = 7.0 Hz, 3H).

25

Example 74**(4-Chloro-2-(6-(diethylamino)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)boronic acid**

- 5 To a solution of 5-(5-bromo-4-chloro-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (124 mg, 0.274 mmol) and triisopropyl borate (0.076 mL, 0.329 mmol) in THF (4 mL) and toluene (16 mL) cooled in a dry ice acetone bath was added n-butyllithium (0.132 mL, 0.329 mmol, 1.6 M in hexanes) dropwise, and the reaction mixture was stirred for 30 minutes. The reaction was then allowed to warm to -20 °C. 1N HCl (10
- 10 mL) was added dropwise, and the resulting mixture was allowed to warm to room temperature. The aqueous layer was separated, and the organic layer was further extracted with water. The combined aqueous extract was concentrated by freeze drying, and the resulting residue was purified by reverse phase HPLC (5% to 35% CH₃CN/(0.1% formic acid in H₂O) to afford (4-chloro-2-(6-(diethylamino)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)boronic acid (40 mg) as a white solid. LC-MS (ES) m/z = 417 [M+H]⁺.
- 15 ¹H NMR (400 MHz, CD₃OD): δ 8.57 (d, J = 2.0 Hz, 1H), 8.00 (dd, J = 2.5, 9.1 Hz, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.25 (d, J = 8.1 Hz, 1H), 6.78 (d, J = 8.9 Hz, 1H), 4.48 (t, J = 5.1 Hz, 2H), 3.85 (t, J = 5.2 Hz, 2H), 3.65 (q, J = 7.1 Hz, 4H), 3.36 - 3.44 (m, 2H), 1.25 (t, J = 7.0 Hz, 6H), 1.07 (t, J = 7.0 Hz, 3H).

20

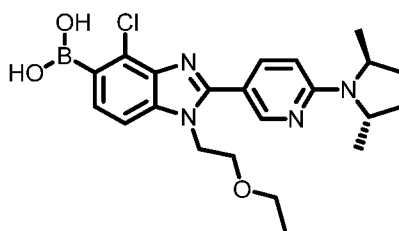
Example 75**5-Bromo-4-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole**

- 25 A mixture of 4-bromo-3-chloro-N-(2-ethoxyethyl)-2-nitroaniline (1.53 g, 4.73 mmol), sodium hydrosulfite (2.470 g, 85%, 12.062 mmol), and 6-((2S,5S)-2,5-dimethylpyrrolidin-1-

yl)nicotinaldehyde (1.111 g, 5.44 mmol) in ethanol (30 mL) and water (8mL) was split into 2 microwave vials and each heated at 130 °C for 80 minutes under microwave conditions. Reactions were combined, filtered, and concentrated. Water was added, and the resulting mixture was extracted with CH₂Cl₂. The combined organic extract was washed with water followed by brine, dried over MgSO₄, filtered, and concentrated. The resulting residue was purified via silica gel chromatography (0% to 100% EtOAc/hexanes) to afford 5-bromo-4-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole (1.55 g) as a foam. LC-MS (ES) m/z = 476, 478 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.57 (br. s., 1H), 7.96 (d, *J* = 7.9 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.34 (d, *J* = 8.6 Hz, 1H), 6.52 (d, *J* = 8.9 Hz, 1H), 4.42 (dt, *J* = 1.9, 5.5 Hz, 2H), 4.3 – 4.0 (br.s, 2H), 3.84 (t, *J* = 5.6 Hz, 2H), 3.46 (q, *J* = 7.1 Hz, 2H), 2.20-2.43 (m, 2H), 1.75 (d, *J* = 5.6 Hz, 2H), 1.25 (d, *J* = 6.3 Hz, 6H), 1.16 (t, *J* = 7.0 Hz, 3H).

Example 76

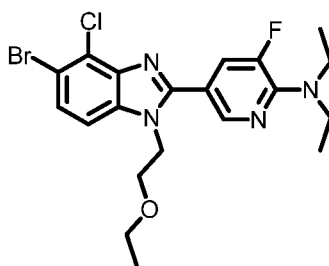
(4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)boronic acid



To a solution of 5-bromo-4-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole (9.90 g, 20.72 mmol) and triisopropyl borate (5.74 mL, 24.86 mmol) in THF (8 mL) and toluene (32 mL) at -78 °C was added n-butyllithium in hexanes (2.5M, 9.94 mL, 24.86 mmol) dropwise over 5 minutes, and the reaction mixture was stirred for 30 minutes. The reaction was allowed to warm to -25 °C and quenched by dropwise addition of 2N aqueous HCl (40 mL) keeping the reaction temperature below -20 °C. The resulting mixture was warmed to room temperature and then washed with EtOAc. Saturated aqueous NaHCO₃ was added to the aqueous phase until pH~7-8. The resulting basic aqueous mixture was extracted with EtOAc. The organic extracts were combined and washed sequentially with water and brine, dried over MgSO₄, filtered, and concentrated. The resulting residue was purified via silica gel chromatography (0% to 60% (3:1 EtOAc:EtOH)/hexanes (1.5% NH₄OH)) to afford after freeze drying 4-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl boronic acid (1.88 g) as a white solid. LC-MS (ES) m/z = 443 [M+H]⁺. ¹H NMR (400

MHz, CD₃OD): δ 8.58 (d, J = 1.8 Hz, 1H), 8.00 (dd, J = 2.4, 9.0 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.25 (d, J = 8.1 Hz, 1H), 6.70 (d, J = 8.6 Hz, 1H), 4.48 (t, J = 5.2 Hz, 2H), 4.33 (br. s., 2H), 3.86 (t, J = 5.2 Hz, 2H), 3.40 (q, J = 7.1 Hz, 2H), 2.28 - 2.42 (m, 2H), 1.76 (d, J = 5.6 Hz, 2H), 1.23 (d, J = 6.1 Hz, 6H), 1.07 (t, J = 7.1 Hz, 3H).

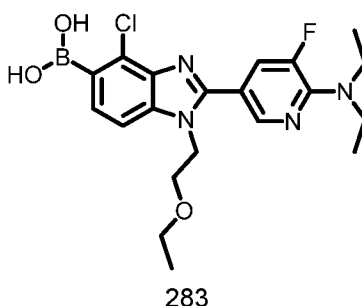
5

Example 77**5-(5-Bromo-4-chloro-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethyl-3-fluoropyridin-2-amine**

- 10 A mixture of 4-bromo-3-chloro-N-(2-ethoxyethyl)-2-nitroaniline (160 mg, 0.494 mmol), sodium hydrosulfite (258 mg, 85%, 1.260 mmol), and 6-(diethylamino)-5-fluoronicotinaldehyde (97 mg, 0.494 mmol) in EtOH (4 mL) and water (2mL) was heated under microwave conditions at 130 °C for 50 minutes. The reaction was filtered, and the filtrate was concentrated to dryness. CH₂Cl₂ was then added, and the resulting mixture
- 15 was filtered again. The filtrate was purified via silica gel chromatography (0% to 100% EtOAc/hexanes) to afford 5-(5-bromo-4-chloro-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethyl-3-fluoropyridin-2-amine (89 mg) as a white solid. LC-MS (ES) m/z = 468, 471 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.40 (t, J = 1.8 Hz, 1H), 7.85 (dd, J = 1.8, 15.0 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 2.0 Hz, 1H), 4.42 (t, J = 5.3 Hz, 2H), 3.86 (t, J = 5.3 Hz, 2H), 3.66 (dq, J = 1.5, 7.0 Hz, 4H), 3.46 (q, J = 6.9 Hz, 2H), 1.29 (t, J = 7.0 Hz, 6H), 1.17 (t, J = 7.0 Hz, 3H).
- 20

Example 78**(4-Chloro-2-(6-(diethylamino)-5-fluoropyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)boronic acid**

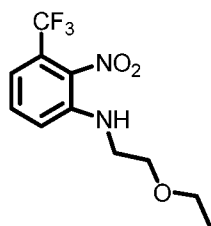
25



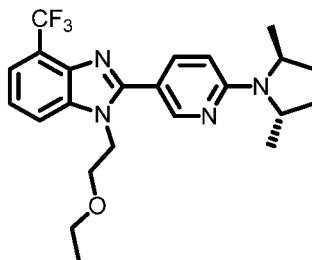
To a solution of 5-(5-bromo-4-chloro-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethyl-3-fluoropyridin-2-amine (61 mg, 0.130 mmol) and triisopropyl borate (0.036 mL, 0.156 mmol) in THF (4 mL) and toluene (16 mL) cooled in a dry ice acetone bath was added n-butyllithium (0.062 mL, 0.156 mmol, 1.6 M in hexanes) dropwise over 5 minutes, and the reaction mixture was stirred for 30 minutes. The reaction was then allowed to warm to -20 °C. 1N HCl (10 mL) was added dropwise, and the resulting mixture was allowed to warm to room temperature. The aqueous phase was separated, and the organic phase was further extracted with water. The combined aqueous extract was concentrated by freeze drying. The resulting residue was purified via reverse phase HPLC (5% to 90% CH₃CN/(0.1% NH₄OH in H₂O) to afford (4-chloro-2-(6-(diethylamino)-5-fluoropyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)boronic acid (17 mg) as a white solid. LC-MS (ES) m/z = 435, 437 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 8.43 (t, J = 1.8 Hz, 1H), 7.94 (dd, J = 1.9, 15.3 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.27 (d, J = 8.1 Hz, 1H), 4.49 (t, J = 5.1 Hz, 2H), 3.87 (t, J = 5.1 Hz, 2H), 3.68 (dq, J = 1.7, 7.0 Hz, 4H), 3.42 (q, J = 7.0 Hz, 2H), 1.28 (t, J = 7.0 Hz, 6H), 1.09 (t, J = 7.0 Hz, 3H).

Intermediate 113

N-(2-Ethoxyethyl)-2-nitro-3-(trifluoromethyl)aniline



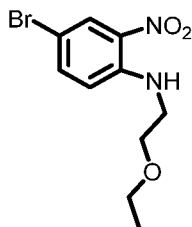
A solution of 1-fluoro-2-nitro-3-(trifluoromethyl)benzene (150 mg, 0.717 mmol), 2-ethoxyethan-1-amine (77 mg, 0.861 mmol), and N,N-diisopropylethylamine (0.163 mL, 0.933 mmol) in DMF (15 mL) was stirred at room temperature for 16 hours. The reaction was concentrated, and the resulting residue was purified via silica gel chromatography (0% to 35% EtOAc/hexanes) to afford N-(2-ethoxyethyl)-2-nitro-3-(trifluoromethyl)aniline (190 mg) as an orange oil. LC-MS (ES) m/z = 279 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.46 (dt, J = 0.8, 8.1 Hz, 1H), 7.00 - 7.16 (m, 2H), 6.17 (br. s., 1H), 3.66 - 3.75 (m, 2H), 3.59 (q, J = 7.0 Hz, 2H), 3.42 (t, J = 5.3 Hz, 2H), 1.27 (t, J = 7.0 Hz, 3H).

Example 79**2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-4-(trifluoromethyl)-1H-benzo[d]imidazole**

- 5 A mixture of N-(2-ethoxyethyl)-2-nitro-3-(trifluoromethyl)aniline (95 mg, 0.341 mmol), sodium hydrosulfite (178 mg, 85%, 0.87 mmol), and 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (73.2 mg, 0.359 mmol) in EtOH (4 mL) and water (2 mL) was heated at 130 °C under microwave conditions for 20 minutes. The reaction was filtered, and the filtrate was concentrated to dryness. CH₂Cl₂ was then added, and the resulting mixture was
- 10 filtered again. The filtrate was purified via silica gel chromatography (0% to 70% EtOAc/hexanes) to afford 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-4-(trifluoromethyl)-1H-benzo[d]imidazole (54 mg) as a viscous oil. LC-MS (ES) m/z = 433 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.59 (d, J = 1.8 Hz, 1H), 7.96 (dd, J = 2.3, 8.9 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.58 (d, J = 7.4 Hz, 1H), 7.27 - 7.42 (m, 1H), 6.51 (d, J = 8.9 Hz, 1H), 4.46 (dt, J = 2.4, 5.6 Hz, 2H), 4.31 (br. s., 2H), 3.86 (t, J = 5.6 Hz, 2H), 3.47
- 15 (q, J = 6.8 Hz, 2H), 2.19 - 2.37 (m, 2H), 1.73 (d, J = 5.6 Hz, 2H), 1.24 (d, J = 6.1 Hz, 6H), 1.16 (t, J = 7.0 Hz, 3H).

Intermediate 114

- 20 **4-bromo-N-(2-ethoxyethyl)-2-nitroaniline**



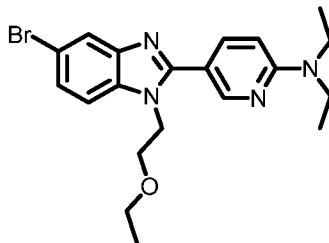
- To a solution of 4-bromo-1-fluoro-2-nitrobenzene (2.0g, 9.09 mmol) and N,N-diisopropylethylamine (1.905 mL, 10.91 mmol) in DMF (20 mL) was added 2-ethoxyethan-1-amine (972 mg, 10.91 mmol), and the reaction mixture was stirred at room temperature
- 25 for 16 hours. The reaction was concentrated, and the resulting residue was purified via silica gel chromatography (0% to 30% EtOAc/hexanes) to afford 4-bromo-N-(2-

ethoxyethyl)-2-nitroaniline (2.49 g) as a orange oil. LC-MS (ES) m/z = 288, 290 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, J = 2.5 Hz, 1H), 8.28 (br. s., 1H), 7.52 (dd, J = 2.5, 9.1 Hz, 1H), 6.82 (d, J = 9.1 Hz, 1H), 3.72 - 3.80 (m, 2H), 3.61 (q, J = 6.9 Hz, 2H), 3.50 (m, 2H), 1.28 (t, J = 7.0 Hz, 3H).

5

Example 80

5-(5-Bromo-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine

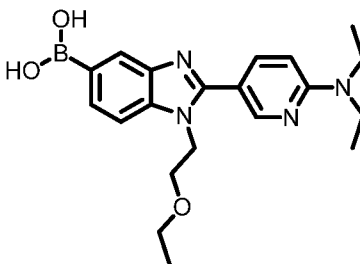


A mixture of 4-bromo-N-(2-ethoxyethyl)-2-nitroaniline (230mg, 0.795 mmol), sodium hydrosulfite (416 mg, 85%, 2.028 mmol), and 6-(diethylamino)nicotinaldehyde (149 mg, 0.835 mmol) in EtOH (4 mL) and water (2 mL) was heated under microwave conditions at 130 °C for 20 minutes. The reaction was filtered and concentrated to dryness. CH_2Cl_2 was then added, and the resulting mixture was filtered again. The resulting residue was purified via silica gel chromatography (0% to 100% EtOAc/hexanes) to afford 5-(5-bromo-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (213 mg) as a white solid. LC-MS (ES) m/z = 417, 418 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.58 (d, J = 2.0 Hz, 1H), 7.91 - 8.05 (m, 2H), 7.41 (d, J = 1.0 Hz, 2H), 6.62 (d, J = 8.9 Hz, 1H), 4.42 (t, J = 5.7 Hz, 2H), 3.86 (t, J = 5.6 Hz, 2H), 3.63 (q, J = 7.1 Hz, 4H), 3.47 (q, J = 7.1 Hz, 2H), 1.23 - 1.34 (m, 6H), 1.17 (t, J = 7.0 Hz, 3H).

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Example 81

(2-(6-(Diethylamino)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)boronic acid

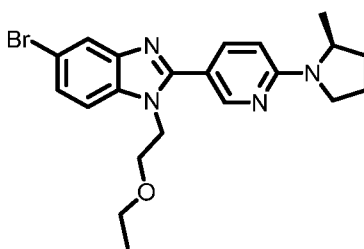


Through a mixture of hypodiboric acid (53.2 mg, 0.593 mmol), 1,3-bis(diphenylphosphino)propane-nickel(II) chloride (10.71 mg, 0.020 mmol), 5-(5-bromo-1-

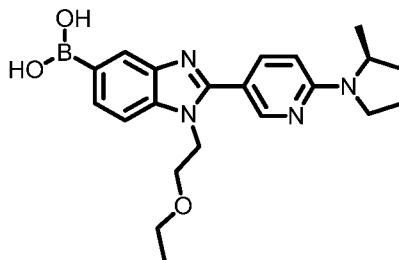
(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (165 mg, 0.395 mmol), triphenylphosphine (10.37 mg, 0.040 mmol), and N,N-diisopropylethylamine (0.207 mL, 1.186 mmol) in EtOH (10 mL) was bubbled argon for 15 minutes, and the reaction mixture was heated at 80 °C for 16 hours. The reaction was concentrated, and the resulting residue was purified via silica gel chromatography (0% to 100% (3:1 EtOAc:EtOH)/hexanes) to afford (2-(6-(diethylamino)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)boronic acid (55 mg) as a white solid. LC-MS (ES) m/z = 383 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.57 (d, J = 2.0 Hz, 1H), 7.94 - 8.04 (m, 2H), 7.62 (s, 2H), 6.78 (d, J = 8.6 Hz, 1H), 4.49 (t, J = 5.2 Hz, 2H), 3.88 (t, J = 5.2 Hz, 2H), 3.64 (q, J = 7.1 Hz, 4H), 3.36 - 3.45 (m, 2H), 1.25 (t, J = 7.0 Hz, 6H), 1.07 (t, J = 7.0 Hz, 3H).

Intermediate 115

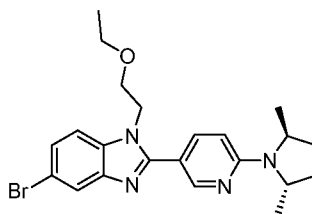
(S)-5-Bromo-1-(2-ethoxyethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole



A mixture of 4-bromo-N-(2-ethoxyethyl)-2-nitroaniline (142 mg, 0.491 mmol), sodium hydrosulfite (257 mg, 85%, 1.252 mmol), and (S)-6-(2-methylpyrrolidin-1-yl)nicotinaldehyde (98 mg, 0.516 mmol) in EtOH (4 mL) and water (2mL) was heated at 130 °C under microwave conditions for 20 minutes. The reaction was filtered, and the filtrate was concentrated to dryness. CH_2Cl_2 was then added, and the resulting mixture was filtered again. The filtrate was concentrated, and the resulting residue was purified via silica gel chromatography (0% to 90% EtOAc/hexanes) to afford (S)-5-bromo-1-(2-ethoxyethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole (105 mg) as a viscous oil. LC-MS (ES) m/z = 429, 431 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, J = 1.8 Hz, 1H), 7.91 - 8.07 (m, 2H), 7.41 (d, J = 1.0 Hz, 2H), 6.53 (d, J = 8.9 Hz, 1H), 4.42 (t, J = 5.7 Hz, 2H), 4.29 (br. s., 1H), 3.86 (t, J = 5.7 Hz, 2H), 3.68 (t, J = 7.7 Hz, 1H), 3.46 (q, J = 7.1 Hz, 3H), 2.03 - 2.33 (m, 3H), 1.77 - 1.87 (m, 1H), 1.28 - 1.42 (m, 3H), 1.17 (t, J = 7.0 Hz, 3H).

Example 82**(S)-(1-(2-Ethoxyethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-5-yl)boronic acid**

- 5 Through a mixture of hypodiboric acid (106 mg, 1.181 mmol), 1,3-bis(diphenylphosphino)propane-nickel(II) chloride (21.34 mg, 0.039 mmol), (S)-5-bromo-1-(2-ethoxyethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole (338 mg, 0.787 mmol), triphenylphosphine (20.65 mg, 0.079 mmol), and N,N-diisopropylethylamine (0.412 mL, 2.362 mmol) in EtOH (10 mL) was bubbled argon gas for 15 minutes, and the
- 10 reaction mixture was heated at 80 °C for 16 hours. The reaction was concentrated, and the resulting residue was purified via silica gel chromatography (0% to 100% (3:1 EtOAc:EtOH)/hexanes) to afford (S)-(1-(2-ethoxyethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-5-yl)boronic acid (159 mg) as a white solid. LC-MS (ES) m/z = 395 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.56 (d, J = 2.0 Hz, 1H), 8.00 (dd, J = 2.3, 8.9 Hz, 2H), 7.61 (br. s., 2H), 6.66 (d, J = 8.9 Hz, 1H), 4.46 (t, J = 5.1 Hz, 2H), 4.27 (quin, J = 5.9 Hz, 1H), 3.86 (t, J = 5.2 Hz, 2H), 3.60 - 3.69 (m, 1H), 3.35 - 3.52 (m, 3H), 2.01 - 2.29 (m, 3H), 1.77 - 1.93 (m, 1H), 1.27 (d, J = 6.3 Hz, 3H), 1.07 (t, J = 7.0 Hz, 3H).
- 15

Example 83**5-Bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole**

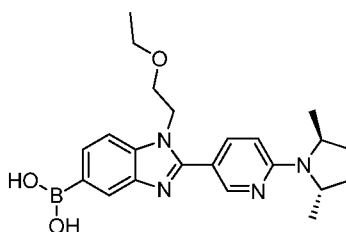
- Into a microwave vial were added 4-bromo-N-(2-ethoxyethyl)-2-nitroaniline (833 mg, 2.88 mmol), 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (647 mg, 3.17 mmol),
- 25 ethanol (4 mL), water (2 mL), and sodium hydrosulfite (1505 mg, 85%, 7.344 mmol), and the reaction mixture was heated under microwave conditions for 120 minutes at 130 °C. The reaction was diluted with water (20 mL) and extracted with EtOAc (4 x 20 mL). The

organic extracts were combined, washed with brine, dried over MgSO_4 , filtered, and concentrated. Purification by chromatography on SiO_2 (gradient of 0 to 60% EtOAc/Hexane) afforded 5-bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole (1.02 g) as a clear oil. LC-MS (ES) $m/z = 444$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 0.95 (t, $J = 7.0$ Hz, 3H), 1.12 - 1.17 (m, 6H), 1.66 (d, $J = 5.1$ Hz, 2H), 2.24 (br. s., 2H), 3.27 - 3.32 (m, 2H), 3.74 (t, $J = 5.2$ Hz, 2H), 4.26 (br. s., 2H), 4.43 (t, $J = 5.2$ Hz, 2H), 6.62 (d, $J = 8.9$ Hz, 1H), 7.37 (dd, $J = 8.5, 1.9$ Hz, 1H), 7.64 (d, $J = 8.6$ Hz, 1H), 7.82 (d, $J = 2.0$ Hz, 1H), 7.96 (dd, $J = 8.9, 2.5$ Hz, 1H), 8.54 (d, $J = 2.3$ Hz, 1H).

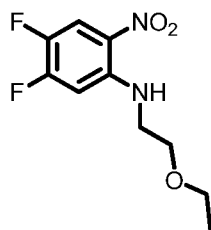
10

Example 84

(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)boronic acid



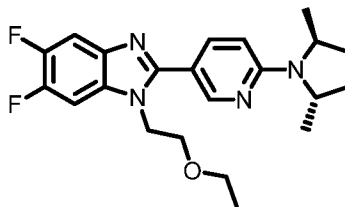
Into a 20 mL microwave vial were added sequentially hypodiboric acid (160 mg, 1.783 mmol), triphenylphosphine (31.2 mg, 0.119 mmol), 1,3-bis(diphenylphosphino)propane-nickel(II) chloride (64.4 mg, 0.119 mmol), 5-bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole (527 mg, 1.189 mmol), and EtOH (5 mL), and the mixture was de-gassed with argon gas for 10 minutes. N,N-diisopropylethylamine (0.623 mL, 3.57 mmol) was then added, and the reaction mixture was heated under microwave conditions at 80 °C for 1 hour. The reaction was filtered through celite washing with EtOH, and the filtrate was concentrated. Purification by chromatography on SiO_2 (gradient of 0 to 50% (80:20:2 CH_2Cl_2 : CH_3OH : NH_4OH)/ CH_2Cl_2) followed by freeze-drying afforded (2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)boronic acid (312 mg) as a white solid. LC-MS (ES) $m/z = 409$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 0.94 - 1.01 (m, 3H), 1.12 - 1.18 (m, 6H), 1.61 - 1.72 (m, 2H), 2.25 (br. s., 2H), 3.28 - 3.32 (m, 2H), 3.71 - 3.81 (m, 2H), 4.27 (br. s., 2H), 4.41 (t, $J = 5.5$ Hz, 2H), 6.59 - 6.65 (m, 1H), 7.57 (d, $J = 8.1$ Hz, 1H), 7.62 - 7.70 (m, 1H), 7.93 - 7.99 (m, 3H), 8.11 (s, 1H), 8.53 - 8.58 (m, 1H).

Intermediate 116N-(2-Ethoxyethyl)-4,5-difluoro-2-nitroaniline

A solution of 1,2,4-trifluoro-5-nitrobenzene (1.0 g, 5.65 mmol), 2-ethoxyethan-1-amine (554 mg, 6.21 mmol), and N,N-diisopropylethylamine (1.184 mL, 6.78 mmol) in DMF (15 mL) was stirred at room temperature for 16 hours. The reaction was concentrated, and the resulting residue was purified via silica gel chromatography (0% to 20% (3:1 EtOAc:EtOH)/hexanes) to afford N-(2-ethoxyethyl)-4,5-difluoro-2-nitroaniline (230 mg) as a yellow/orange solid. LC-MS (ES) m/z = 247 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.33 (br. s., 1H), 8.09 (dd, J = 8.5, 10.8 Hz, 1H), 6.70 (dd, J = 6.8, 12.7 Hz, 1H), 3.76 (t, J = 5.3 Hz, 2H), 3.62 (q, J = 6.8 Hz, 2H), 3.47 (q, J = 5.1 Hz, 2H), 1.29 (t, J = 7.0 Hz, 3H).

Example 85

2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-5,6-difluoro-1H-benzo[d]imidazole

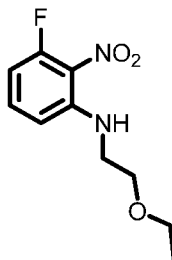


A mixture of N-(2-ethoxyethyl)-4,5-difluoro-2-nitroaniline (125 mg, 0.508 mmol), sodium hydrosulfite (265 mg, 85%, 1.294 mmol), and 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (109 mg, 0.533 mmol) in EtOH (4 mL) and water (2 mL) was heated at 130 °C under microwave conditions for 20 minutes. The reaction was filtered, and the filtrate was concentrated. CH_2Cl_2 was then added, and the resulting mixture was filtered again. The filtrate was purified via silica gel chromatography (0% to 100% EtOAc/hexanes) to afford 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-5,6-difluoro-1H-benzo[d]imidazole (105 mg) as a white/yellow solid. LC-MS (ES) m/z = 401 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.49 - 8.55 (m, 1H), 7.88 (dd, J = 2.5, 8.9 Hz, 1H), 7.54 (dd, J = 7.4, 10.7 Hz, 1H), 7.36 (dd, J = 7.1, 10.4 Hz, 1H), 6.50 (d, J = 8.9 Hz, 1H), 4.33 - 4.39 (m,

4H), 3.84 (t, $J = 5.5$ Hz, 2H), 3.47 (q, $J = 7.1$ Hz, 2H), 2.26 - 2.36 (m, 2H), 1.72 (d, $J = 5.6$ Hz, 2H), 1.23 (d, $J = 6.7$ Hz, 6H), 1.17 (t, $J = 7.0$ Hz, 3H).

Intermediate 117

5 N-(2-Ethoxyethyl)-3-fluoro-2-nitroaniline

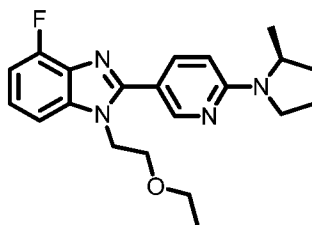


A solution of 1,3-difluoro-2-nitrobenzene (400 mg, 2.51 mmol), 2-ethoxyethan-1-amine (247 mg, 2.77 mmol), and N,N-diisopropylethylamine (0.527 mL, 3.02 mmol) in DMF (15 mL) was stirred at room temperature for 16 hours. The reaction was concentrated, and the resulting residue was purified via silica gel chromatography (0% to 30% EtOAc/hexanes) to afford N-(2-ethoxyethyl)-3-fluoro-2-nitroaniline (421 mg) as a orange oil. LC-MS (ES) $m/z = 229$ $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 7.44 (br. s., 1H), 7.26 - 7.37 (m, 1H), 6.59 - 6.70 (m, 1H), 6.47 (ddd, $J = 1.3, 8.1, 11.4$ Hz, 1H), 3.70 - 3.77 (m, 2H), 3.60 (q, $J = 7.1$ Hz, 2H), 3.45 (t, $J = 5.5$ Hz, 2H), 1.28 (t, $J = 7.0$ Hz, 3H).

15

Example 86

(S)-1-(2-Ethoxyethyl)-4-fluoro-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole



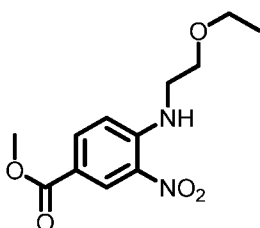
20 A mixture of N-(2-ethoxyethyl)-3-fluoro-2-nitroaniline (125 mg, 0.548 mmol), sodium hydrosulfite (286 mg, 85%, 1.40 mmol), and (S)-6-(2-methylpyrrolidin-1-yl)nicotinaldehyde (109 mg, 0.575 mmol) in EtOH (4 mL) and water (2 mL) was heated at 130 °C under microwave conditions for 20 minutes. NH_4OH (28%) was then added, and the resulting mixture was extracted with EtOAc. The combined organic extract was washed sequentially with water and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified via silica gel chromatography (0% to 100% EtOAc/hexanes) to afford (S)-1-(2-ethoxyethyl)-

25

4-fluoro-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole (100 mg) as a viscous oil. LC-MS (ES) m/z = 369 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.63 (br. s., 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.29 (d, J = 1.0 Hz, 1H), 7.22 (dt, J = 4.6, 8.0 Hz, 1H), 7.02 (ddd, J = 0.9, 7.98, 10.4 Hz, 1H), 6.53 (d, J = 8.9 Hz, 1H), 4.44 (t, J = 5.7 Hz, 3H), 4.29 (br. s., 1H), 3.87 (t, J = 5.8 Hz, 2H), 3.69 (br. s., 1H), 3.39 - 3.55 (m, 2H), 2.04 - 2.30 (m, 4H), 11.23 - 1.39 (m, 3H), 1.17 (t, J = 7.1 Hz, 3H).

Intermediate 118

Methyl 4-((2-ethoxyethyl)amino)-3-nitrobenzoate



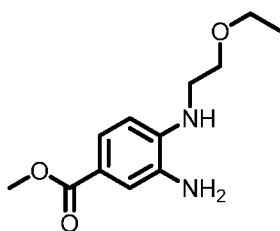
10

To 2-ethoxyethan-1-amine (1.500 g, 16.82 mmol) in DMF (100 mL) were added methyl 4-fluoro-3-nitrobenzoate (3.35 g, 16.82 mmol) and K_2CO_3 (2.325 g, 16.82 mmol), and the reaction mixture was stirred overnight at room temperature. The mixture was filtered, washing with Et_2O . The filtrate was diluted with water (250 mL), and the resulting mixture was extracted with $EtOAc$ (3 x 100 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , filtered, and concentrated in-vacuo. The remaining residue was purified by silica gel chromatography (0-60%, $EtOAc$ /hexanes). The fractions containing the desired product were combined and concentrated until almost dry. Crystallization from the remaining solvent afforded the desired product (4.2 g) as a yellow hexagonal crystals. LC-MS (ES) m/z = 269 $[M+H]^+$. ^1H NMR (400 MHz, $DMSO-d_6$): δ 8.64 (d, J = 2.0 Hz, 1H), 8.61 (t, J = 4.9 Hz, 1H), 7.99 (dd, J = 2.0, 9.1 Hz, 1H), 7.21 (d, J = 9.1 Hz, 1H), 3.84 (s, 3H), 3.56 - 3.67 (m, 4H), 3.51 (q, J = 7.0 Hz, 2H), 1.13 (t, J = 7.0 Hz, 3H).

20

Intermediate 119

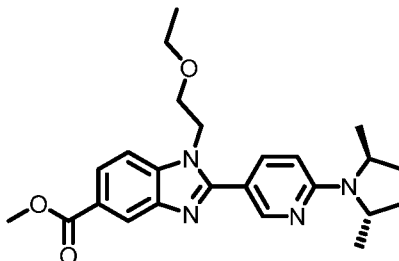
25 Methyl 3-amino-4-((2-ethoxyethyl)amino)benzoate



A mixture of methyl 4-((2-ethoxyethyl)amino)-3-nitrobenzoate (4.20 g, 15.66 mmol) and $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (9.30 g, 39.1 mmol) in CH_3OH (150 mL) was stirred at 70 °C under inert atmosphere until all methyl 4-((2-ethoxyethyl)amino)-3-nitrobenzoate dissolved. The reaction was cooled to 0 °C (ice bath) and charged with sodium borohydride (2.96 g, 78 mmol) in 3 equal portions. The reaction gradually warmed to room temperature and was filtered through celite, then concentrated in-vacuo. The remaining residue taken up in concentrated NH_4OH (150 mL) and CH_2Cl_2 (200 mL) and filtered. The filter cake was washed with CH_2Cl_2 (2 x 100 mL). The aqueous was washed with CH_2Cl_2 (2 x 100 mL). The combined organic layers were filtered through a pad of celite layered on a pad of silica. The organic layer was washed with brine (6 mL), dried over Na_2SO_4 , filtered, concentrated, and dried under high vacuum overnight to afford the desired product (3.58 g) as a tan solid. LC-MS (ES) m/z = 239 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.15 - 7.25 (m, 2H), 6.47 (d, J = 8.4 Hz, 1H), 5.25 (t, J = 5.5 Hz, 1H), 4.78 (s, 2H), 3.73 (s, 3H), 3.57 (t, J = 5.8 Hz, 2H), 3.48 (q, J = 7.1 Hz, 2H), 3.29 (q, J = 5.6 Hz, 2H), 1.13 (t, J = 7.0 Hz, 3H).

Example 87

Methyl 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole-5-carboxylate

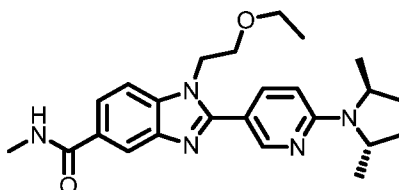


To a mixture of methyl 3-amino-4-((2-ethoxyethyl)amino)benzoate (200 mg, 0.839 mmol) and 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (189 mg, 0.923 mmol) in DMF (4 mL) and water (4 mL) was added oxone (335 mg, 0.546 mmol), and the reaction mixture was stirred overnight at room temperature. The reaction was diluted with water (7 mL), saturated aqueous Na_2CO_3 (7 mL) and EtOAc (15 mL). The organic layer was separated, and the aqueous layer was further extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with brine (6 mL), dried over Na_2SO_4 , filtered, and concentrated. The resulting residue was purified by silica gel chromatography (0-100%, EtOAc/hexanes) to afford the desired product (153 mg) as a gold-oil. LC-MS (ES) m/z = 423 $[\text{M}+\text{H}]^+$. ^1H NMR (400MHz, $\text{MeOD}-d_4$): δ 8.62 - 8.55 (m, 1H), 8.37 (d, J = 1.0 Hz, 1H), 8.02 (ddd, J = 2.0, 6.9, 8.8 Hz, 2H), 7.72 (d, J = 8.6 Hz, 1H), 6.72 (s, 1H), 4.53 (d, J = 5.3 Hz, 2H), 4.42 - 4.24

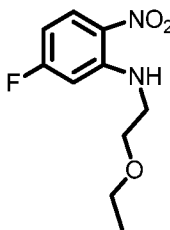
(m, 2H), 3.97 (s, 3H), 3.88 (t, $J = 5.2$ Hz, 2H), 3.45 - 3.37 (m, 2H), 2.43 - 2.28 (m, 2H), 1.76 (d, $J = 5.8$ Hz, 2H), 1.24 (d, $J = 6.3$ Hz, 6H), 1.07 (t, $J = 7.0$ Hz, 3H).

Example 88

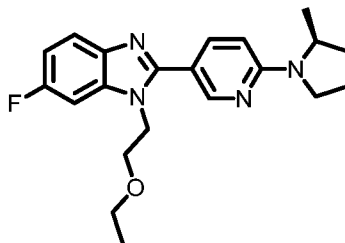
5 **2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide**



Step 1: To methyl 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole-5-carboxylate (225 mg, 0.533 mmol) in CH₃OH (4 mL, 0.533 mmol) and THF (4 mL, 0.533 mmol) was added 10N NaOH (0.426 mL, 4.26 mmol), and the reaction mixture was stirred at 40 °C for 3 hours. The heat was removed and the pH brought to neutral with 6N HCl (0.719 mL, 4.31 mmol). The mixture was concentrated, and the remaining solid was taken up in DMSO (3 mL). The DMSO solution was decanted, diluted with DMSO to 6 mL and split into 3 equal (2 mL) portions. Step 2: To a DMSO solution (2 mL from the previous Step 1)) of 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole-5-carboxylic acid were added EtOAc (4 mL), triethylamine (0.256 mL, 1.836 mmol), T3P propylphosphonic anhydride in EtOAc (0.328 mL, 0.551 mmol), and methylamine hydrochloride (49.6 mg, 0.734 mmol), and the reaction mixture was stirred overnight at room temperature. The reaction was diluted with DMF (4.00 mL), charged with fresh T3P propylphosphonic anhydride in EtOAc (0.328 mL, 0.551 mmol) and methylamine hydrochloride (49.6 mg, 0.734 mmol), and the reaction mixture was stirred for 4 additional hours. The reaction was quenched with water (9 mL) and extracted with EtOAc (3 x 9 mL). The combined organics were washed with brine (3 mL), dried over Na₂SO₄, filtered and concentrated. The remaining residue was purified by reverse phase HPLC (15-55% CH₃CN/0.1% formic acid in water) to afford the desired product (14.8 mg) as a white solid. LC-MS (ES) $m/z = 422$ $[M+H]^+$. ¹H NMR (400 MHz, CD₃OD): δ 8.58 (d, $J = 2.3$ Hz, 1H), 8.17 (d, $J = 1.3$ Hz, 1H), 8.01 (dd, $J = 2.3, 8.9$ Hz, 1H), 7.84 (dd, $J = 1.7, 8.5$ Hz, 1H), 7.71 (d, $J = 8.4$ Hz, 1H), 6.71 (d, $J = 9.1$ Hz, 1H), 4.52 (t, $J = 4.9$ Hz, 2H), 3.88 (t, $J = 5.1$ Hz, 2H), 3.41 (q, $J = 7.0$ Hz, 2H), 3.37 (s, 1H), 2.95 - 3.02 (m, 3H), 2.68 (s, 1H), 2.36 (t, $J = 7.6$ Hz, 2H), 1.76 (d, $J = 5.8$ Hz, 2H), 1.23 (d, $J = 6.1$ Hz, 6H), 1.02 - 1.10 (m, 3H).

Intermediate 120N-(2-Ethoxyethyl)-5-fluoro-2-nitroaniline

A solution of 2,4-difluoro-1-nitrobenzene (400mg, 2.51 mmol), 2-ethoxyethan-1-amine (247 mg, 2.77 mmol), and N,N-diisopropylethylamine (0.527 mL, 3.02 mmol) in DMF (15 mL) was stirred at room temperature for 16 hours. The reaction was concentrated, and the resulting residue was purified via silica gel column (0% to 30% EtOAc/hexanes) to afford N-(2-ethoxyethyl)-5-fluoro-2-nitroaniline (499 mg) as a orange oil. LC-MS (ES) m/z = 229 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.41 (br. s., 1H), 8.25 (dd, J = 6.2, 9.5 Hz, 1H), 6.54 (dd, J = 2.5, 11.4 Hz, 1H), 6.40 (ddd, J = 2.5, 7.2, 9.6 Hz, 1H), 3.71 - 3.79 (m, 2H), 3.62 (q, J = 6.8 Hz, 2H), 3.47 (q, J = 5.2 Hz, 2H), 1.24 - 1.33 (m, 3H).

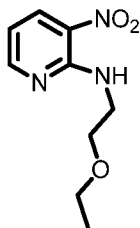
Example 89(S)-1-(2-Ethoxyethyl)-6-fluoro-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole

A mixture of N-(2-ethoxyethyl)-5-fluoro-2-nitroaniline (125mg, 0.548 mmol), sodium hydrosulfite (286 mg, 85%, 1.40 mmol), and (S)-6-(2-methylpyrrolidin-1-yl)nicotinaldehyde (109 mg, 0.575 mmol) in EtOH (4 mL) and water (2mL) was heated under microwave conditions at 130 °C for 20 minutes. 28% NH_4OH was then added, and the resulting mixture was extracted with EtOAc. The combined organic extract was washed with water followed by brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified via silica gel chromatography (0% to 100% EtOAc/hexanes) to afford (S)-1-(2-ethoxyethyl)-6-fluoro-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole (67 mg) as a viscous oil. LC-MS (ES) m/z = 369 $[M+H]^+$. ^1H NMR (400 MHz $CDCl_3$): δ 8.57 (d, J = 1.8 Hz, 1H), 7.95 (dd, J = 2.5, 8.9 Hz, 1H), 7.73 (dd, J = 4.8, 8.9 Hz, 1H), 7.24 (dd, J = 2.4, 9.0 Hz, 1H), 7.06 (ddd, J = 2.5, 8.8, 9.7 Hz, 1H), 6.52 (d, J = 8.9 Hz, 1H), 4.38 (t, J = 5.7 Hz,

2H), 4.28 (m, 1H), 3.85 (t, $J = 5.7$ Hz, 2H), 3.67 (m, 1H), 3.42 - 3.53 (m, 3H), 2.02 - 2.23 (m, 3H), 1.77 - 1.89 (m, 1H), 1.25 - 1.38 (m, 3H), 1.18 (t, $J = 7.0$ Hz, 3H).

Intermediate 121

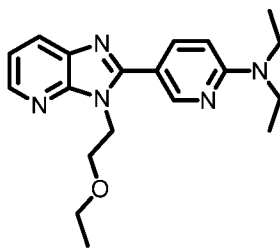
5 N-(2-Ethoxyethyl)-3-nitropyridin-2-amine



A solution of 2-chloro-3-nitropyridine (490 mg, 3.09 mmol), 2-ethoxyethan-1-amine (303 mg, 3.40 mmol), and N,N-diisopropylethylamine (0.648 mL, 3.71 mmol) in DMSO (20 mL) was heated to 80 °C for 45 minutes. Water was added, and the resulting mixture was extracted with EtOAc. The combined organic extract was washed with water followed by brine, dried over MgSO₄, filtered, and concentrated. The resulting residue was purified via silica gel chromatography (0% to 30% EtOAc/hexanes) to afford N-(2-ethoxyethyl)-3-nitropyridin-2-amine (567 mg) as a yellow oil. LC-MS (ES) $m/z = 212$ $[M+H]^+$. ¹H NMR (400 MHz, CDCl₃): δ 8.44 - 8.57 (m, 1H), 8.40 - 8.44 (m, 2H), 6.67 (dd, $J = 4.7, 8.2$ Hz, 1H), 3.86 (q, $J = 5.3$ Hz, 2H), 3.67 - 3.75 (m, 2H), 3.59 (q, $J = 6.9$ Hz, 2H), 1.27 (t, $J = 7.1$ Hz, 3H).

Example 90

5-(3-(2-Ethoxyethyl)-3H-imidazo[4,5-b]pyridin-2-yl)-N,N-diethylpyridin-2-amine



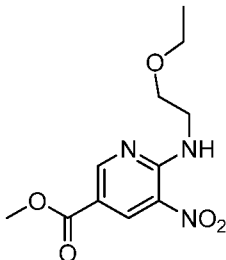
A mixture of N-(2-ethoxyethyl)-3-nitropyridin-2-amine (125 mg, 0.592 mmol), sodium hydrosulfite (309 mg, 85%, 1.509 mmol), and 6-(diethylamino)nicotinaldehyde (127 mg, 0.710 mmol) in EtOH (4 mL) and water (2mL) was heated under microwave conditions at 130 °C for 20 minutes. The reaction was then filtered, and the filtrate was concentrated to dryness. CH₂Cl₂ was added, and the resulting mixture was filtered again. The filtrate was purified via silica gel chromatography (0% to 100% EtOAc/hexanes) to afford 5-(3-(2-ethoxyethyl)-3H-imidazo[4,5-b]pyridin-2-yl)-N,N-diethylpyridin-2-amine (814 mg) as a yellow oil. LC-MS (ES) $m/z = 340$ $[M+H]^+$. ¹H NMR (400 MHz, CDCl₃): δ 8.71 - 8.77 (m,

1H), 8.36 (dd, $J = 1.5, 4.8$ Hz, 1H), 8.08 (dd, $J = 2.5, 9.1$ Hz, 1H), 8.04 (dd, $J = 1.4, 8.0$ Hz, 1H), 7.25 (dd, $J = 4.8, 7.9$ Hz, 1H), 6.60 (d, $J = 9.1$ Hz, 1H), 4.57 (t, $J = 5.8$ Hz, 2H), 3.98 (t, $J = 5.7$ Hz, 2H), 3.62 (q, $J = 6.9$ Hz, 4H), 3.44 (q, $J = 7.1$ Hz, 2H), 1.26 (t, $J = 7.1$ Hz, 6H), 1.11 (t, $J = 7.0$ Hz, 3H).

5

Intermediate 122

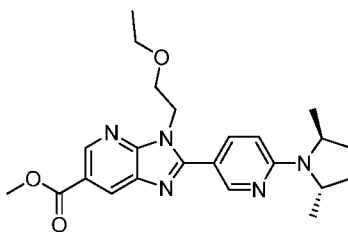
Methyl 6-((2-ethoxyethyl)amino)-5-nitronicotinate



To 1-bromo-2-ethoxyethane (342 mg, 2.232 mmol) in DMF (3 mL) were added methyl 6-amino-5-nitronicotinate (400 mg, 2.029 mmol) and K_2CO_3 (421 mg, 3.04 mmol), and the reaction mixture was stirred overnight at room temperature. The reaction was diluted with water (5 mL) and extracted with EtOAc (4 x 5 mL). The organic extracts were combined and washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography on SiO_2 (gradient of 0 to 25% EtOAc/hexanes) afforded methyl 6-((2-ethoxyethyl)amino)-5-nitronicotinate (398 mg) as a yellow color oil. LC-MS (ES) $m/z = 270$ $[M+H]^+$. ^1H NMR (400 MHz, $DMSO-d_6$): δ 1.12 (t, $J = 7.0$ Hz, 3H), 3.49 (q, $J = 7.0$ Hz, 2H), 3.60 (t, $J = 5.8$ Hz, 2H), 3.80 (q, $J = 5.9$ Hz, 2H), 3.86 (s, 3H), 8.75 (d, $J = 2.3$ Hz, 1H), 8.92 (m, 2H).

Intermediate 123

Methyl 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-3H-imidazo[4,5-b]pyridine-6-carboxylate

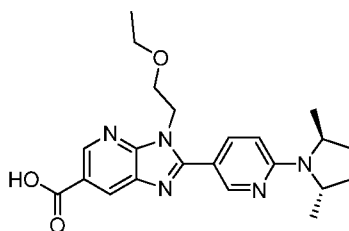


Into a microwave vial were added methyl 6-((2-ethoxyethyl)amino)-5-nitronicotinate (250 mg, 0.928 mmol), 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (209 mg, 1.021

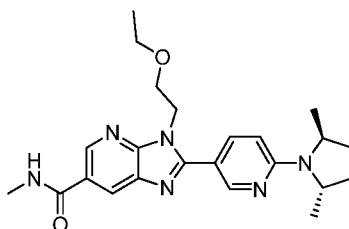
mmol), EtOH (4 mL), water (2 mL), and sodium hydrosulfite (485 mg, 85%, 2.372 mmol), and the reaction mixture was heated under microwave conditions for 30 minutes at 130 °C. The reaction was diluted with water (10 mL) then extracted with EtOAc (4 x 5 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ (gradient of 0 to 60% EtOAc/hexanes) afforded methyl 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-3H-imidazo[4,5-b]pyridine-6-carboxylate (176 mg) as a white solid. LC-MS (ES) *m/z* = 424 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 0.92 (t, *J* = 7.0 Hz, 3H), 1.16 (d, *J* = 7.0 Hz, 6H), 1.66 (d, *J* = 5.6 Hz, 2H), 2.25 (br. s., 2H), 3.27 - 3.33 (m, 2H), 3.82 (t, *J* = 5.5 Hz, 2H), 3.92 (s, 3H), 4.27 (br. s., 2H), 4.57 (t, *J* = 5.5 Hz, 2H), 6.66 (d, *J* = 9.1 Hz, 1H), 8.07 (dd, *J* = 9.0, 2.4 Hz, 1H), 8.49 (d, *J* = 2.0 Hz, 1H), 8.68 (d, *J* = 2.3 Hz, 1H), 8.92 (d, *J* = 1.8 Hz, 1H).

Intermediate 124

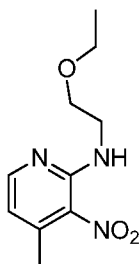
2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid



To methyl 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-3H-imidazo[4,5-b]pyridine-6-carboxylate (170 mg, 0.401 mmol) in CH₃OH (3 mL) was added 10 N NaOH (0.803 mL, 8.03 mmol), and the reaction mixture was stirred overnight at room temperature. The reaction was concentrated under vacuum, water (5 mL) was added, and the pH was adjusted with 6N HCl (1.4 mL, 8.0 mmol). The resulting solid was then isolated by filtration and dried under vacuum oven to afford 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid (112 mg) as a white solid. LC-MS (ES) *m/z* = 424 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 0.92 (t, *J* = 7.0 Hz, 3H), 1.16 (d, *J* = 6.3 Hz, 6H), 1.66 (d, *J* = 5.3 Hz, 2H), 2.25 (br. s., 2H), 3.28 - 3.32 (m, 2H), 3.83 (t, *J* = 5.5 Hz, 2H), 4.27 (br. s., 2H), 4.56 (t, *J* = 5.5 Hz, 2H), 6.66 (d, *J* = 8.9 Hz, 1H), 8.07 (dd, *J* = 9.0, 2.4 Hz, 1H), 8.46 (d, *J* = 2.0 Hz, 1H), 8.67 (d, *J* = 2.3 Hz, 1H), 8.90 (d, *J* = 1.8 Hz, 1H), 13.18 (s, 1H).

Example 91**2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-N-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide**

- 5 To 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid (52 mg, 0.127 mmol) in DMSO (2 mL) were added EDC (48.7 mg, 0.254 mmol), HOBt (38.9 mg, 0.254 mmol), methylamine hydrochloride (15.43 mg, 0.229 mmol), and N-methylmorpholine (0.112 mL, 1.016 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with water (5 mL)
- 10 and extracted with EtOAc (4 x 5 mL). The organic extracts were combined and washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ (gradient of 0 to 10% CH₃OH/CH₂Cl₂) afforded 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-N-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide (47 mg) as a white solid after freeze-drying. LC-MS (ES) m/z = 423 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 0.92 (t, *J* = 7.0 Hz, 3H) 1.11 - 1.19 (m, 6H), 1.59 - 1.72 (m, 2H), 2.19 - 2.29 (m, 2H), 2.84 (d, *J* = 4.6 Hz, 3H), 3.28 - 3.32 (m, 2H), 3.82 (t, *J* = 5.6 Hz, 2H), 4.28 (br. s., 2H), 4.54 (t, *J* = 5.3 Hz, 2H), 6.65 (d, *J* = 9.1 Hz, 1H), 8.06 (dd, *J* = 9.0, 2.4 Hz, 1H), 8.43 (d, *J* = 1.8 Hz, 1H), 8.57 - 8.63 (m, 1H), 8.66 (d, *J* = 2.5 Hz, 1H), 8.81 (d, *J* = 1.8 Hz, 1H).
- 15

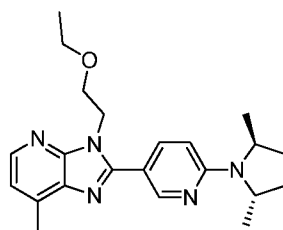
20 Intermediate 125**N-(2-Ethoxyethyl)-4-methyl-3-nitropyridin-2-amine**

- To 2-ethoxyethan-1-amine (0.659 g, 7.40 mmol) in DMF (10 mL) were added 2-fluoro-4-methyl-3-nitropyridine (1.05g, 6.73 mmol) and K₂CO₃ (1.022 g, 7.40 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction was diluted with water (30 mL) and extracted with EtOAc (4 x 20 mL). The organic extracts were combined and
- 25

washed with brine, dried over MgSO_4 , filtered, and concentrated. Purification by chromatography on silica gel (0 to 30% EtOAc/hexanes) afforded N-(2-ethoxyethyl)-4-methyl-3-nitropyridin-2-amine (1.52 g) as an orange color oil. LC-MS (ES) m/z = 226 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 1.11 (t, J = 7.0 Hz, 3H), 2.39 (s, 3H), 3.46 (q, J = 6.8 Hz, 2H), 3.50 - 3.55 (m, 2H), 3.56 - 3.63 (m, 2H), 6.64 (d, J = 4.8 Hz, 1H), 7.54 (t, J = 5.1 Hz, 1H), 8.16 (d, J = 4.8 Hz, 1H).

Example 92

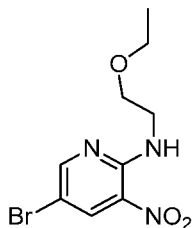
2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-7-methyl-3H-imidazo[4,5-b]pyridine



Into a microwave vial were added N-(2-ethoxyethyl)-4-methyl-3-nitropyridin-2-amine (55 mg, 0.244 mmol), 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (54.9 mg, 0.269 mmol), EtOH (1.5 mL), water (0.75 mL), and sodium hydrosulfite (128 mg, 85%, 0.623 mmol), and the reaction mixture was heated under microwave conditions for 30 minutes at 130 °C. The reaction was then diluted with water (10 mL) and extracted with EtOAc (4 x 5 mL). The organic extracts were combined, washed with brine, dried over MgSO_4 , filtered, and concentrated. Purification by chromatography on SiO_2 (gradient of 0 to 70% EtOAc/hexanes) afforded 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-7-methyl-3H-imidazo[4,5-b]pyridine (30 mg) as a light clear oil. LC-MS (ES) m/z = 380 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 0.94 (t, J = 7.0 Hz, 3H), 1.15 (d, J = 6.1 Hz, 6H), 1.66 (d, J = 5.8 Hz, 2H), 2.20 - 2.29 (m, 2H), 2.59 (s, 3H), 3.30 (q, J = 1.0 Hz, 2H), 3.81 (t, J = 5.7 Hz, 2H), 4.27 (br. s., 2H), 4.47 (t, J = 5.6 Hz, 2H), 6.64 (d, J = 8.9 Hz, 1H), 7.12 (d, J = 5.1 Hz, 1H), 8.02 (dd, J = 8.9, 2.5 Hz, 1H), 8.18 (d, J = 5.1 Hz, 1H), 8.61 (d, J = 2.3 Hz, 1H).

Intermediate 126

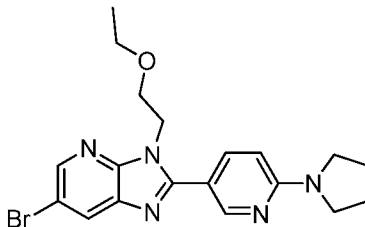
5-Bromo-N-(2-ethoxyethyl)-3-nitropyridin-2-amine



To ethoxymethanamine (0.510 g, 6.79 mmol) in DMF (10 mL) were added 5-bromo-2-fluoro-3-nitropyridine (1.5 g, 6.79 mmol) and K₂CO₃ (0.938 g, 6.79 mmol), and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with water (30 mL) and extracted with EtOAc (4 x 20 mL). The organic extracts were combined and washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ (gradient of 0 to 25% EtOAc/hexanes) afforded 5-bromo-N-(2-ethoxyethyl)-3-nitropyridin-2-amine (1.81 g) as an orange color oil. LC-MS (ES) m/z = 291 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆): δ 1.12 (t, J = 7.0 Hz, 3H), 3.48 (q, J = 6.8 Hz, 2H), 3.55 - 3.60 (m, 2H), 3.71 (m, 2H), 8.53 (t, J = 5.3 Hz, 1H), 8.56 - 8.62 (m, 2H).

Intermediate 127

5-(6-Bromo-3-(2-ethoxyethyl)-3H-imidazo[4,5-b]pyridin-2-yl)-N,N-diethylpyridin-2-amine

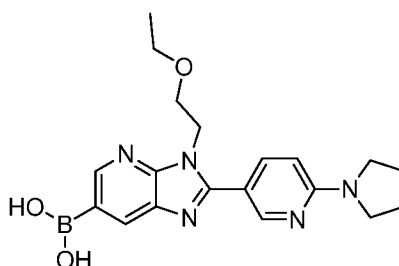


Into a microwave vial were added 5-bromo-N-(2-ethoxyethyl)-3-nitropyridin-2-amine (292 mg, 1.006 mmol), 6-(diethylamino)nicotinaldehyde (215 mg, 1.208 mmol), EtOH (3 mL), water (1.5 mL), and sodium hydrosulfite (526 mg, 85%, 2.566 mmol), and the reaction mixture was heated under microwave conditions for 90 minutes at 130 °C. The reaction was then diluted with water (10 mL) and extracted with EtOAc (4 x 5 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ (gradient of 0 to 30% EtOAc/hexanes) afforded 5-(6-bromo-3-(2-ethoxyethyl)-3H-imidazo[4,5-b]pyridin-2-yl)-N,N-diethylpyridin-2-amine (240 mg) as a clear solid. LC-MS (ES) m/z = 419 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆): δ 0.94 (t, J = 7.0 Hz, 3H), 1.12 - 1.18 (m, 6H), 3.28 - 3.34 (m, 2H), 3.58 (q, J = 7.1 Hz, 4H), 3.82

(t, J = 5.5 Hz, 2H), 4.50 (t, J = 5.3 Hz, 2H), 6.77 (d, J = 8.9 Hz, 1H), 8.07 (dd, J = 9.0, 2.4 Hz, 1H), 8.33 (d, J = 2.0 Hz, 1H), 8.42 (d, J = 2.0 Hz, 1H), 8.66 (d, J = 2.3 Hz, 1H).

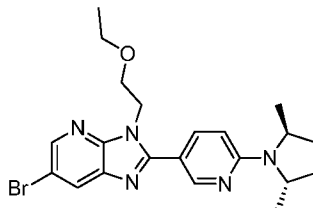
Example 93

5 (2-(6-(Diethylamino)pyridin-3-yl)-3-(2-ethoxyethyl)-3H-imidazo[4,5-b]pyridin-6-yl)boronic acid



Into a 20 mL microwave vial were added hypodiboric acid (51.4 mg, 0.574 mmol), triphenylphosphine (10.03 mg, 0.038 mmol), 1,3-bis(diphenylphosphino)propane-nickel(II) chloride (20.73 mg, 0.038 mmol), 5-(6-bromo-3-(2-ethoxyethyl)-3H-imidazo[4,5-b]pyridin-2-yl)-N,N-diethylpyridin-2-amine (160 mg, 0.382 mmol), and EtOH (5 mL), and the resulting mixture was purged with argon gas for 10 minutes. N,N-diisopropylethylamine (0.20 mL, 1.147 mmol) was then added, and the reaction mixture was heated under microwave conditions at 80 °C for 1 hour. The reaction was filtered, and the filtrate was concentrated.

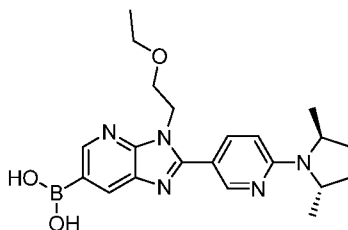
15 Water (10 mL) was then added, and the resulting aqueous mixture was extracted with EtOAc (4 x 10 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ (gradient of 0 to 100% (80:20:2 CH₂Cl₂:CH₃OH:formic acid)/CH₂Cl₂) afforded (2-(6-(diethylamino)pyridin-3-yl)-3-(2-ethoxyethyl)-3H-imidazo[4,5-b]pyridin-6-yl)boronic acid (67 mg) as an off-white solid. LC-MS (ES) m/z = 384 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 0.95 (t, J = 1.0 Hz, 3H), 1.16 (t, J = 1.0 Hz, 6H), 3.32 (q, J = 6.9 Hz, 2H), 3.58 (q, J = 6.8 Hz, 4H), 3.83 (t, J = 5.6 Hz, 2H), 4.49 (t, J = 5.5 Hz, 2H), 6.76 (d, J = 9.1 Hz, 1H), 8.05 (dd, J = 9.1, 2.5 Hz, 1H), 8.32 (d, J = 1.5 Hz, 1H), 8.63 (d, J = 2.0 Hz, 1H), 8.66 (d, J = 1.3 Hz, 1H).

Intermediate 1286-Bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-3H-imidazo[4,5-b]pyridine

- 5 Into a microwave vial were added 5-bromo-N-(2-ethoxyethyl)-3-nitropyridin-2-amine (200 mg, 0.689 mmol), 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (155 mg, 0.758 mmol), EtOH (2 mL), water (1 mL), and sodium hydrosulfite (360 mg, 85%, 1.758 mmol), and the reaction mixture was heated under microwave conditions for 30 minutes at 130 °C. The reaction was diluted with water (10 mL) and extracted with EtOAc (4 x 5 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ (gradient of 0 to 70% EtOAc/hexanes) afforded 6-bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-3H-imidazo[4,5-b]pyridine (156 mg) as a light brown oil. LC-MS (ES) m/z = 445 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 0.93 (t, *J* = 7.0 Hz, 3H), 1.12 - 1.18 (m, 6H), 1.66 (d, *J* = 5.3 Hz, 2H), 2.25 (br. s., 2H), 3.28 - 3.32 (m, 2H), 3.81 (t, *J* = 5.5 Hz, 2H), 4.26 (br. s., 2H), 4.51 (t, *J* = 5.5 Hz, 2H), 6.65 (d, *J* = 8.9 Hz, 1H), 8.05 (dd, *J* = 9.0, 2.4 Hz, 1H), 8.32 (d, *J* = 2.0 Hz, 1H), 8.42 (d, *J* = 2.0 Hz, 1H), 8.66 (d, *J* = 2.3 Hz, 1H).

Example 94

20 (2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-3H-imidazo[4,5-b]pyridin-6-yl)boronic acid

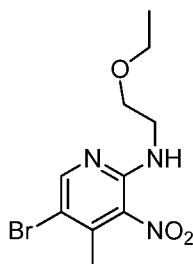


- Into a microwave vial were added hypodiboric acid (30.3 mg, 0.338 mmol), triphenylphosphine (5.90 mg, 0.023 mmol), 1,3-bis(diphenylphosphino)propane-nickel(II) chloride (12.20 mg, 0.023 mmol), 6-bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-3H-imidazo[4,5-b]pyridine (100 mg, 0.225 mmol), and EtOH (5 mL), and the resulting mixture was purged with argon gas for 10 minutes. N,N-Diisopropylethylamine (0.118 mL, 0.675 mmol) was then added, and the reaction mixture

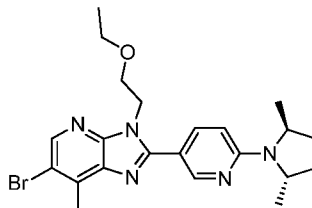
was heated under microwave conditions at 80 °C for 1 hour. The reaction was filtered, washing with EtOH, and the filtrate was concentrated. Purification by chromatography on SiO₂ (gradient of 0 to 50% (80:20:2) CH₂Cl₂:CH₃OH:NH₄OH/CH₂Cl₂) afforded (2-(6-
 5 b]pyridin-6-yl)boronic acid (28 mg) as an off-white solid. The solid was dissolved in CH₃OH (2 mL) and treated with 7N NH₃ in CH₃OH (200 μ L), and the resulting mixture was stirred for 0.5 hour. The solution was concentrated, and the resulting residue was freeze-dried to afford the desired product. LC-MS (ES) m/z = 445 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 0.90 - 0.96 (m, 3H), 1.15 (br. s., 6H), 1.66 (d, J = 5.1 Hz, 2H), 2.25 (br. s., 2H), 3.28 - 3.32
 10 (m, 2H), 3.82 (t, J = 5.6 Hz, 2H), 4.26 (br. s., 2H), 4.47 - 4.57 (m, 2H), 6.64 (d, J = 8.9 Hz, 1H), 8.02 - 8.09 (m, 1H), 8.26 (s, 2H), 8.37 (d, J = 1.5 Hz, 1H), 8.63 (d, J = 2.5 Hz, 1H), 8.68 (d, J = 1.3 Hz, 1H).

Intermediate 129

15 5-Bromo-N-(2-ethoxyethyl)-4-methyl-3-nitropyridin-2-amine



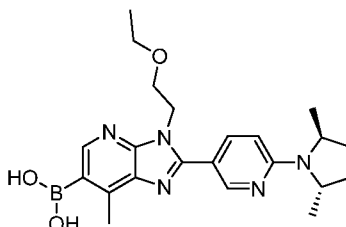
To N-(2-ethoxyethyl)-4-methyl-3-nitropyridin-2-amine (250 mg, 1.110 mmol) in DMF (3 mL) cooled in ice bath was added N-bromosuccinimide (217 mg, 1.221 mmol), and the reaction mixture was allowed to slowly warm to room temperature and stirred overnight at room
 20 temperature. The reaction was quenched with water (5 mL) and extracted with EtOAc (4 x 5 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ (gradient of 0 to 20% EtOAc/hexanes) afforded 5-bromo-N-(2-ethoxyethyl)-4-methyl-3-nitropyridin-2-amine (240 mg, 0.789 mmol) as a yellow oil. LC-MS (ES) m/z = 305 [M+H]⁺. ¹H NMR (400 MHz, DMSO-
 25 *d*₆): δ 1.06 - 1.13 (m, 3H), 2.34 (s, 3H), 3.44 (q, J = 7.1 Hz, 2H), 3.47 - 3.58 (m, 4H), 7.32 (t, J = 5.1 Hz, 1H), 8.39 (s, 1H).

Intermediate 1306-Bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-7-methyl-3H-imidazo[4,5-b]pyridine

- 5 Into a microwave vial were added 5-bromo-N-(2-ethoxyethyl)-4-methyl-3-nitropyridin-2-amine (240 mg, 0.789 mmol), 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (177 mg, 0.868 mmol), EtOH (3 mL), water (1.5 mL), and sodium hydrosulfite (412 mg, 85%, 2.012 mmol), and the reaction mixture was heated under microwave conditions for 30 minutes at 130 °C. The reaction was diluted with water (10 mL) and extracted with EtOAc
- 10 (4 x 5 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ (gradient of 0 to 30% EtOAc/hexanes) afforded 6-bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-7-methyl-3H-imidazo[4,5-b]pyridine (270 mg) as a yellow oil. LC-MS (ES) m/z = 459 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 0.93 (t, *J* = 7.0 Hz, 3H), 1.13 - 1.18 (m, 6H), 1.66 (d, *J* = 5.6 Hz, 2H), 2.25 (br. s., 2H), 2.63 (s, 3H), 3.30 (q, *J* = 7.0 Hz, 2H), 3.79 (t, *J* = 5.6 Hz, 2H), 4.27 (br. s., 2H), 4.48 (t, *J* = 5.5 Hz, 2H), 6.64 (d, *J* = 8.9 Hz, 1H), 8.03 (dd, *J* = 8.9, 2.28 Hz, 1H), 8.40 (s, 1H), 8.63 (s, 1H).
- 15

Example 95

- 20 (2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-7-methyl-3H-imidazo[4,5-b]pyridin-6-yl)boronic acid

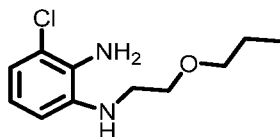


- Into a 20 mL microwave vial were added hypodiboric acid (79 mg, 0.884 mmol), triphenylphosphine (15.45 mg, 0.059 mmol), 1,3-bis(diphenylphosphino)propane-nickel(II) chloride (31.9 mg, 0.059 mmol), 6-bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-7-methyl-3H-imidazo[4,5-b]pyridine (270 mg, 0.589 mmol), and EtOH (5 mL), and the resulting mixture was purged with argon for 10 minutes. N,N-diisopropylethylamine (0.309 mL, 1.767 mmol) was then added, and the reaction mixture
- 25

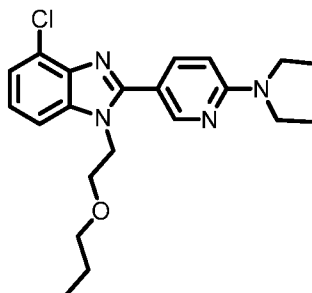
was heated under microwave conditions at 80 °C for 1 hour. The reaction filtered, washing with EtOH, and the filtrate was concentrated. The resulting material was diluted with water (10 mL) then extracted with EtOAc (4 x 10 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ (gradient of 0 to 100% (80:20:2) CH₂Cl₂:CH₃OH:NH₄OH/CH₂Cl₂) afforded (2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-7-methyl-3H-imidazo[4,5-b]pyridin-6-yl)boronic acid (77 mg) as an off-white solid. LC-MS (ES) m/z = 424 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 0.91 - 0.97 (m, 3H), 1.15 (d, *J* = 6.1 Hz, 6H), 1.66 (d, *J* = 5.1 Hz, 2H), 2.25 (br. s., 2H), 2.71 (s, 3H), 3.26 - 3.32 (m, 2H), 3.76 - 3.85 (m, 2H), 4.27 (br. s., 2H), 4.43 - 4.52 (m, 2H), 6.64 (d, *J* = 8.9 Hz, 1H), 8.02 (dd, *J* = 8.9, 2.53 Hz, 1H), 8.15 (s, 2H), 8.39 (s, 1H), 8.60 - 8.65 (m, 1H).

Intermediate 131

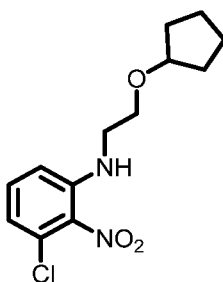
3-Chloro-N1-(2-propoxyethyl)benzene-1,2-diamine



A mixture of 3-chloro-2-nitro-N-(2-propoxyethyl)aniline (190 mg, 0.734 mmol) and NiCl₂•6H₂O (437 mg, 1.836 mmol) in CH₃OH (20 mL) was cooled in a ice water bath. Sodium borohydride (139 mg, 3.67 mmol) was added, and the reaction mixture was stirred in ice water bath for 10 minutes. The reaction was concentrated to dryness. NH₄OH (28% in water) was added, and the resulting mixture was extracted with CH₂Cl₂. The combined CH₂Cl₂ extract was dried over MgSO₄, filtered, and concentrated. The residue was purified via flash chromatography on SiO₂ (0% to 50% EtOAc/hexanes) to give the desired product (99 mg) as a solid. LC-MS (ES) m/z = 229, 231 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 6.81 - 6.91 (m, 1H), 6.76 (t, *J* = 8.0 Hz, 1H), 6.61 (dd, *J* = 1.3, 7.9 Hz, 1H), 3.67 - 3.77 (m, 2H), 3.49 (t, *J* = 6.7 Hz, 2H), 3.31 (t, *J* = 5.2 Hz, 2H), 1.67 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H).

Example 96**5-(4-Chloro-1-(2-propoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine**

- 5 A mixture of 3-chloro-N1-(2-propoxyethyl)benzene-1,2-diamine (99 mg, 0.346 mmol), 6-(diethylamino)nicotinaldehyde (61.7 mg, 0.346 mmol), and oxone (138 mg, 0.225 mmol) in DMF (10 mL) and water (4 mL) was stirred at room temperature for 16 hours. Saturated aqueous NaHCO₃ was added, and the resulting mixture was extracted with EtOAc. The combined EtOAc extract was washed with water, brine, dried over MgSO₄, filtered and
- 10 concentrated. The resulting residue was purified via silica gel chromatography (0% to 50% EtOAc/hexanes) to give 5-(4-chloro-1-(2-propoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (65 mg) as an oil. LC-MS (ES) m/z = 387, 389 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.55 - 8.61 (m, 1H), 7.99 (dd, J = 2.4, 9.0 Hz, 1H), 7.41 (dd, J = 0.9, 8.0 Hz, 1H), 7.28 - 7.35 (m, 1H), 7.16 - 7.24 (m, 1H), 6.59 (d, J = 8.9 Hz, 1H), 4.42 (t, J =
- 15 5.7 Hz, 2H), 3.84 (t, J = 5.6 Hz, 2H), 3.61 (q, J = 7.1 Hz, 4H), 3.34 (t, J = 6.6 Hz, 2H), 1.46 - 1.62 (m, 2H), 1.26 (t, J = 7.1 Hz, 6H), 0.85 (t, J = 7.4 Hz, 3H).

Intermediate 132**3-Chloro-N-(2-(cyclopentyloxy)ethyl)-2-nitroaniline**

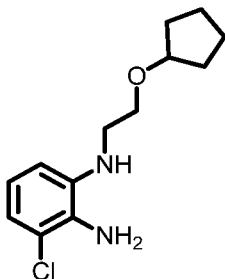
20

To a solution of 1-chloro-3-fluoro-2-nitrobenzene (300 mg, 1.709 mmol) in DMF (8 mL) were added 2-(cyclopentyloxy)ethanamine (221 mg, 1.709 mmol) and K₂CO₃ (236 mg, 1.709 mmol), and the mixture was stirred at room temperature for 18 hours. The mixture was quenched with water (15 mL) and extracted with EtOAc (3x). The extract was dried and

concentrated, and the resulting residue was purified using column chromatography (silica gel, 0 to 60% EtOAc/hexanes) to give the desired product (360 mg) as a pale brown oil. LC-MS (ES) m/z = 285, 287 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 1.52 - 1.82 (m, 9H), 3.36 (t, J = 5.3 Hz, 2H), 3.62 - 3.69 (m, 2H), 3.93 - 4.02 (m, 1H), 6.69 - 6.84 (m, 2H), 7.25 (t, J = 8.2 Hz, 1H).

Intermediate 133

3-Chloro-N1-(2-(cyclopentyloxy)ethyl)benzene-1,2-diamine

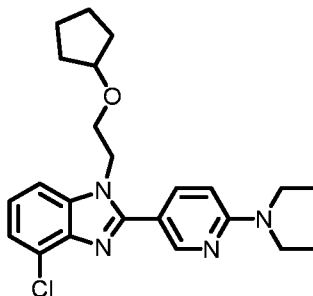


To a stirring solution of N-(2-(cyclopentyloxy)ethyl)-2-nitroaniline (290 mg, 1.159 mmol) and $NiCl_2 \cdot 6H_2O$ (689 mg, 2.90 mmol) in CH_3OH (8 mL) was added sodium borohydride (219 mg, 5.79 mmol) in portions at 0 °C, and the reaction mixture was stirred at room temperature for 30 minutes. The mixture was concentrated, and the residue was dissolved into concentrated NH_4OH and extracted with CH_2Cl_2 (3x). The extract was dried (Na_2SO_4) and concentrated to give the desired product (220 mg) as a pale brown oil. LC-MS (ES) m/z = 255, 257 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 1.54 - 1.84 (m, 8H), 3.24 - 3.34 (m, 2H), 3.65 - 3.72 (m, 2H), 3.95 - 4.06 (m, 1H), 6.61 (dd, J = 7.9, 1.3 Hz, 1H), 6.71 - 6.78 (m, 1H), 6.81 - 6.86 (m, 1H).

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Example 97

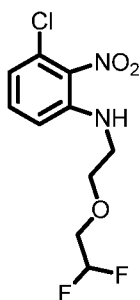
5-(4-Chloro-1-(2-(cyclopentyloxy)ethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine



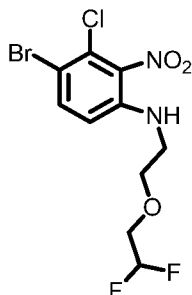
To a solution of 3-chloro-N1-(2-(cyclopentyloxy)ethyl)benzene-1,2-diamine (210 mg, 0.824 mmol) in DMF (5 mL) and water (1 mL) were added oxone (507 mg, 0.824 mmol) and 6-(diethylamino)nicotinaldehyde (147 mg, 0.824 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was basified using 10% K₂CO₃ aqueous solution and extracted with EtOAc (3x). The extract was dried (Na₂SO₄) and concentrated, and the resulting residue was purified using column chromatography (silica gel, 0 to 70% EtOAc/hexanes) to give the desired product (180 mg) as a pale brown oil. LC-MS (ES) m/z = 413, 415 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.19 - 1.31 (m, 6H), 1.37 - 1.61 (m, 8H), 3.64 (q, J = 7.1 Hz, 4H), 3.74 - 3.84 (m, 3H), 4.46 (t, J = 5.2 Hz, 2H), 6.77 (d, J = 8.9 Hz, 1H), 7.24 - 7.36 (m, 2H), 7.58 (dd, J = 7.9, 1.3 Hz, 1H), 8.00 (dd, J = 9.0, 2.4 Hz, 1H), 8.53 - 8.61 (m, 1H).

Intermediate 134

3-Chloro-N-(2-(2,2-difluoroethoxy)ethyl)-2-nitroaniline



A solution of 1-chloro-3-fluoro-2-nitrobenzene (272 mg, 1.547 mmol), 2-(2,2-difluoroethoxy)ethan-1-amine hydrochloride (250 mg, 1.547 mmol), and N,N-diisopropylethylamine (0.324 mL, 1.857 mmol) in DMF (20 mL) was stirred at room temperature for 16 hours. The reaction was then heated at 80 °C for 16 hours. The reaction was concentrated, and the resulting residue was purified via SiO₂ chromatography (0% to 30% EtOAc/hexanes) to afford 3-chloro-N-(2-(2,2-difluoroethoxy)ethyl)-2-nitroaniline (251 mg) as an orange oil. LC-MS (ES) m/z = 281 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.24 (dd, J = 7.9, 8.6 Hz, 1H), 6.66 - 6.88 (m, 2H), 5.75 - 6.08 (m, 2H), 3.68 - 3.83 (m, 4H), 3.41 (t, J = 5.2 Hz, 2H).

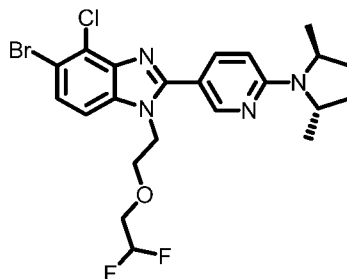
Intermediate 1354-Bromo-3-chloro-N-(2-(2,2-difluoroethoxy)ethyl)-2-nitroaniline

A solution of 3-chloro-N-(2-(2,2-difluoroethoxy)ethyl)-2-nitroaniline (251 mg, 0.894 mmol) and N-bromosuccinimide (159 mg, 0.894 mmol) in acetic acid (25 mL) was heated at 80 °C for 2 hours. The reaction was concentrated, and the resulting residue was purified by SiO₂ chromatography (0% to 25% EtOAc/hexanes) to afford 4-bromo-3-chloro-N-(2-(2,2-difluoroethoxy)ethyl)-2-nitroaniline (267 mg) as a orange oil. LC-MS (ES) m/z = 258, 260 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.54 (d, J = 9.1 Hz, 1H), 6.67 (d, J = 9.1 Hz, 1H), 5.73 - 6.08 (m, 1H), 5.46 - 5.72 (m, 1H), 3.68 - 3.82 (m, 4H), 3.39 (t, J = 5.2 Hz, 2H).

Example 98

5-Bromo-4-chloro-1-(2-(2,2-difluoroethoxy)ethyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole

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A mixture of 4-bromo-3-chloro-N-(2-(2,2-difluoroethoxy)ethyl)-2-nitroaniline (267mg, 0.743 mmol), sodium hydrosulfite (388 mg, 85%, 1.894 mmol), and 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (174 mg, 0.854 mmol) in EtOH (4 mL) and water (1 mL) was heated under microwave conditions at 130 °C for 75 minutes. The reaction was filtered, and the filtrate was concentrated to dryness. Water was then added, and the resulting aqueous mixture was extracted with CH₂Cl₂. The combined organic extracts were washed with water followed by brine, dried over MgSO₄, filtered, and concentrated. The resulting residue was purified via SiO₂ chromatography (0% to 100% EtOAc/hexanes) to

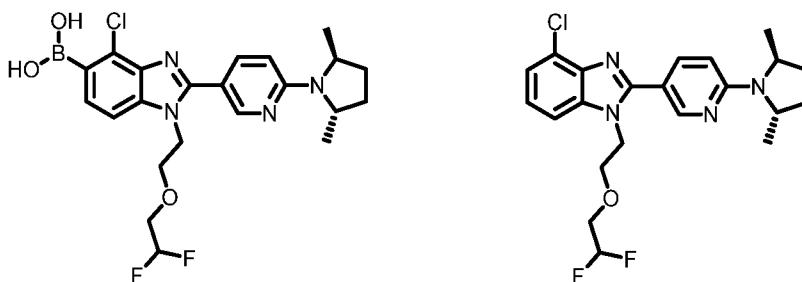
afford 5-bromo-4-chloro-1-(2-(2,2-difluoroethoxy)ethyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole (209 mg). LC-MS (ES) m/z = 515, 517 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.51 (br. s., 1H), 7.90 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 8.6 Hz, 1H), 7.28 (s, 1H), 6.51 (d, J = 8.9 Hz, 1H), 5.54 - 6.08 (m, 1H), 4.2 - 4.37 (br. s., 2H), 4.37 - 4.60 (m, 2H), 3.96 (t, J = 5.5 Hz, 2H), 3.61 (dt, J = 4.1, 13.8 Hz, 2H), 2.31 (t, J = 7.4 Hz, 2H), 1.60 - 1.89 (m, 2H), 1.22 (d, J = 6.3 Hz, 6H).

Example 99

(4-Chloro-1-(2-(2,2-difluoroethoxy)ethyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-5-yl)boronic acid

Example 100

4-Chloro-1-(2-(2,2-difluoroethoxy)ethyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1Hbenzo[d]imidazole

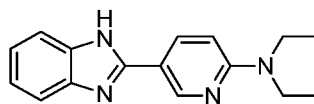


To a solution of 5-bromo-4-chloro-1-(2-(2,2-difluoroethoxy)ethyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole (193 mg, 0.376 mmol) and triisopropyl borate (0.113 mL, 0.488 mmol) in THF (4 mL) and toluene (12 mL) cooled in a dry ice acetone bath was added *n*-butyllithium (0.180 mL, 0.451 mmol, 2.5 M in hexanes) dropwise over 5 minutes, and the reaction mixture was stirred for 30 minutes. 2N HCl (6 mL) was added dropwise, and the resulting mixture was allowed to warm to room temperature. The mixture was washed with EtOAc, and the aqueous phase was treated with saturated aqueous $NaHCO_3$ until pH~7-8. The resulting aqueous mixture was extracted with EtOAc, and the combined organic extract was washed with water followed by brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by SiO_2 chromatography (0% to 100% (3:1 EtOAc:EtOH)/hexanes) followed by reverse phase HPLC purification (20% to 60% CH_3CN /(0.1% NH_4OH in H_2O) to afford after freeze drying (4-chloro-1-(2-(2,2-difluoroethoxy)ethyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-5-yl)boronic acid (31 mg). LC-MS (ES) m/z = 479, 481 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.55 (br. s., 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz,

1H), 6.53 (d, $J = 8.1$ Hz, 1H), 5.60 - 6.06 (m, 1H), 4.23 - 4.60 (m, 4H), 3.99 (t, $J = 5.3$ Hz, 2H), 3.62 (dt, $J = 3.8, 13.8$ Hz, 2H), 2.33 (br. s., 2H), 1.75 (d, $J = 5.3$ Hz, 2H), 1.25 (d, $J = 6.1$ Hz, 6H). Also was obtained 4-chloro-1-(2-(2,2-difluoroethoxy)ethyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole (46 mg). LC-MS (ES) $m/z = 435, 437$ $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.54 (br. s., 1H), 7.94 (d, $J = 5.6$ Hz, 1H), 7.33 - 7.42 (m, 2H), 7.21 - 7.27 (m, 1H), 6.53 (d, $J = 8.1$ Hz, 1H), 5.54 - 6.11 (m, 1H), 4.42 - 4.60 (m, 2H), 4.21 - 4.30 (br. s., 2H), 3.99 (t, $J = 5.5$ Hz, 2H), 3.63 (dt, $J = 4.1, 13.8$ Hz, 2H), 2.25 - 2.39 (m, 2H), 1.75 (d, $J = 5.6$ Hz, 2H), 1.25 (d, $J = 6.3$ Hz, 6H).

10 Intermediate 136

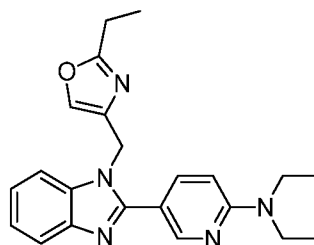
5-(1H-Benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine



A mixture of 6-(diethylamino)nicotinaldehyde (8.6 g, 48.3 mmol), sodium metabisulfite (11.92 g, 62.7 mmol) and benzene-1,2-diamine (5.22 g, 48.3 mmol) in DMF (150 mL) was stirred at 100 °C for 12 hours. The reaction mixture was cooled to room temperature and poured into water (450 mL), and the resulting solid was collected by filtration to give the desired product (9.0 g) as a yellow solid. LC-MS (ES) $m/z = 267$ $[M+H]^+$.

Example 101

20 N,N-Diethyl-5-(1-(2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine



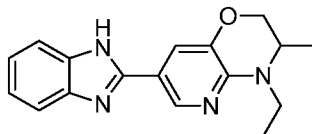
A mixture of 5-(1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (400 mg, 1.502 mmol), 4-(chloromethyl)-2-ethyloxazole (328 mg, 2.253 mmol), and NaH (60%, 240 mg, 6.01 mmol) in THF (20 mL) was stirred at 95 °C into a sealed tube for 18 hours. Water (5 mL) was then added, and the mixture was concentrated under vacuum. The resulting residue was poured onto water (100 mL), and extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 20:1 CH_2Cl_2/CH_3OH) to give

the desired product (150 mg) as a pale gum. LC-MS (ES) m/z = 376 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, J = 2.0 Hz, 1H), 7.97 (dd, J = 8.9, 2.2 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.36 – 7.24 (m, 3H), 7.23 (s, 1H), 6.58 (d, J = 9.0 Hz, 1H), 5.31 (s, 2H), 3.58 (q, J = 7.0 Hz, 4H), 2.80 (q, J = 7.6 Hz, 2H), 1.35 (t, J = 7.6 Hz, 3H), 1.22 (t, J = 7.0 Hz, 6H).

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Intermediate 137

7-(1H-Benzo[d]imidazol-2-yl)-4-ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine



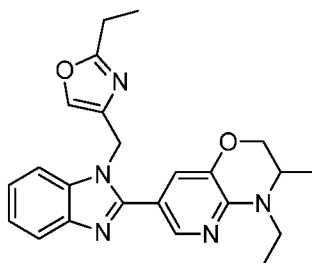
To a solution of 4-ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-7-carbaldehyde (500 mg, 2.424 mmol) and sodium metabisulfite (599 mg, 3.15 mmol) in DMF (10 mL) was added benzene-1,2-diamine (262 mg, 2.424 mmol), and the reaction mixture was stirred at 90 °C for 12 hours. The mixture was poured onto the water (150 ml) and extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 0 to 20% EtOAc/hexanes) to give the desired product (300 mg) as a yellow solid. LC-MS (ES) m/z = 295 $[M+H]^+$.

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Example 102

4-Ethyl-7-(1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine

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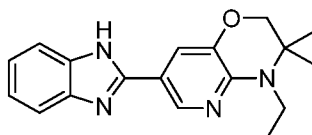
To a solution of 7-(1H-benzo[d]imidazol-2-yl)-4-ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine (300 mg, 1.019 mmol) in DMF (5 mL) was added NaH (60%, 82 mg, 2.038 mmol), and the mixture was stirred for 10 minutes. 4-(Chloromethyl)-2-ethyloxazole (223 mg, 1.529 mmol) was then added, and the reaction mixture was stirred at 75 °C for 12 hours. The reaction mixture was poured onto water (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified by silica gel chromatography (eluting with

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1:1 EtOAc/hexanes) to give the desired product (100 mg) as a white solid). LC-MS (ES) $m/z = 404 [M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.82 (d, $J = 7.6$ Hz, 1H), 7.49 (s, 1H), 7.37 – 7.29 (m, 2H), 7.29 – 7.27 (m, 1H), 7.23 (s, 1H), 5.32 (s, 2H), 4.03 (dd, $J = 7.3$ Hz, 3H), 3.74 – 3.68 (m, 1H), 3.41 – 3.34 (m, 1H), 2.80 (q, $J = 7.6$ Hz, 2H), 1.35 (t, $J = 7.6$ Hz, 3H), 1.32 (d, $J = 6.6$ Hz, 3H), 1.23 (t, $J = 7.1$ Hz, 3H).

Intermediate 138

7-(1H-Benzo[d]imidazol-2-yl)-4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine



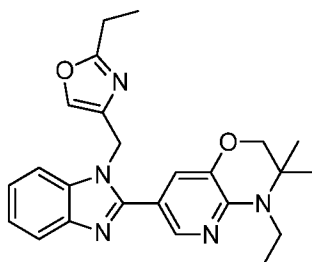
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To a solution of 4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-7-carbaldehyde (340 mg, 1.544 mmol) in DMF (10 mL) was added sodium metabisulfite (381 mg, 2.007 mmol) and benzene-1,2-diamine (167 mg, 1.544 mmol), and the reaction mixture was stirred at 90 °C for 12 hours. The mixture was poured onto the water (150 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 0 to 20% EtOAc/hexanes) to give the desired product (237 mg) as yellow solid. LC-MS (ES) $m/z = 309 [M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, $J = 1.8$ Hz, 1H), 7.65 (d, $J = 1.7$ Hz, 1H), 7.58 (s, 2H), 7.21 (dd, $J = 5.9, 3.1$ Hz, 2H), 3.85 (s, 2H), 3.60 (q, $J = 6.9$ Hz, 2H), 2.05 (s, 1H), 1.31 (s, 6H), 1.24 (t, $J = 7.3$ Hz, 3H).

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Example 103

4-Ethyl-7-(1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine



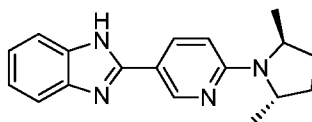
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To a solution of 7-(1H-benzo[d]imidazol-2-yl)-4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine (237 mg, 0.769 mmol) in DMF (10 mL) was added NaH (36.9 mg, 1.537 mmol), and the mixture was stirred for 10 minutes. 4-(Chloromethyl)-2-ethyloxazole

(224 mg, 1.537 mmol) was then added, and the reaction mixture was stirred at 75 °C for 12 hours. The reaction mixture was poured onto water (100 mL), and extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 20:1 CH₂Cl₂/CH₃OH) to give the desired product (70 mg) as a white solid. LC-MS (ES) m/z = 418 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.32 (d, *J* = 1.3 Hz, 1H), 8.11 (s, 1H), 7.69 - 7.61 (m, 2H), 7.58 - 7.52 (m, 1H), 7.25 - 7.16 (m, 2H), 5.31 (s, 2H), 3.93 (s, 2H), 3.61 (q, *J* = 6.5 Hz, 2H), 2.72 (q, *J* = 7.5 Hz, 2H), 1.29 (s, 6H), 1.23 - 1.16 (m, 6H).

10 Intermediate 139

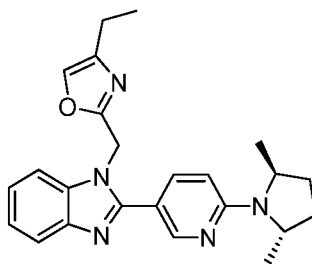
2-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole



To a solution of benzene-1,2-diamine (260 mg, 2.400 mmol) in DMF (10 mL) were added sodium metabisulfite (494 mg, 2.60 mmol) and 6-((2R,5R)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (409 mg, 2 mmol), and the reaction mixture was stirred at 80 °C for 12 hours. The reaction mixture was quenched with water (80 mL), and the resulting precipitate was collected by filtration and dried under vacuum to give the desired product (530 mg) as a brown solid. LC-MS (ES) m/z = 293 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.50 - 12.98 (m, 10H), 8.85 (s, 1H), 8.16 (d, *J* = 9.0 Hz, 1H), 7.57 (dd, *J* = 5.8, 3.1 Hz, 2H), 7.22 (dd, *J* = 5.8, 3.2 Hz, 2H), 6.67 (d, *J* = 9.0 Hz, 1H), 4.27 (s, 1H), 2.24 (s, 2H), 1.66 (d, *J* = 5.5 Hz, 2H), 1.15 (d, *J* = 6.1 Hz, 6H).

Example 104

2-((2-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)-4-ethyloxazole



A mixture of 2-(chloromethyl)-5-ethyloxazole (106 mg, 0.728 mmol), 2-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole (213 mg, 0.728 mmol), and NaH (60%, 35 mg, 0.88 mmol) in DMF (15 mL) was stirred at 80 °C for 12 hours. The mixture

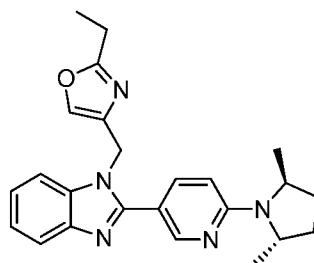
was concentrated under vacuum, and the residue was treated with water (20 mL) and extracted with EtOAc (2 x 40 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 0 to 3.5% CH₃OH/CH₂Cl₂) to give the desired product (200 mg) as a gray solid.

- 5 LC-MS (ES) m/z = 402 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.56 (d, J = 1.9 Hz, 1H), 7.94 (dd, J = 8.9, 2.1 Hz, 1H), 7.69 – 7.61 (m, 1H), 7.59 – 7.51 (m, 1H), 7.28 – 7.20 (m, 2H), 6.84 (s, 1H), 6.63 (d, J = 8.9 Hz, 1H), 5.59 (s, 2H), 4.40 – 4.08 (m, 2H), 2.61 (q, J = 7.6 Hz, 2H), 2.30 – 2.16 (m, 2H), 1.70 – 1.59 (m, 2H), 1.19 – 1.08 (m, 9H).

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Example 105

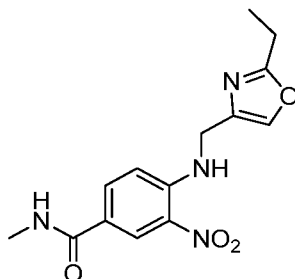
4-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)-2-ethyloxazole



- To a solution of 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole (180 mg, 0.616 mmol) in DMF (6 mL) was added NaH (60%, 49 mg, 1.23 mmol), and the reaction mixture was stirred at 60 °C for 30 minutes. 4-(Chloromethyl)-2-ethyloxazole (179 mg, 1.231 mmol) was then added, and the reaction mixture was stirred overnight at 80 °C. The reaction mixture was quenched with water (2 mL), concentrated, poured into water (50 mL), and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 0 to 5% CH₃OH/CH₂Cl₂) to give the desired product (60 mg) as a white solid. LC-MS (ES) m/z = 402 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.53 (s, 1H), 7.95 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.36 – 7.27 (m, 2H), 7.26 – 7.18 (m, 3H), 6.49 (d, J = 8.9 Hz, 1H), 5.31 (s, 2H), 4.45 – 4.00 (m, 2H), 2.81 (q, J = 7.6 Hz, 2H), 2.35 – 2.20 (m, 2H), 1.76 – 1.61 (m, 2H), 1.36 (t, J = 7.6 Hz, 3H), 1.20 (d, J = 6.2 Hz, 6H).

Intermediate 140

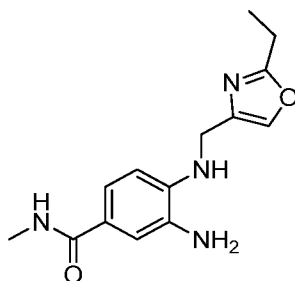
4-(((2-Ethyloxazol-4-yl)methyl)amino)-N-methyl-3-nitrobenzamide



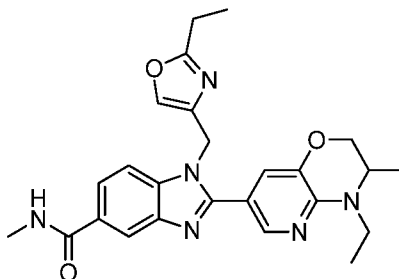
A mixture of 4-fluoro-N-methyl-3-nitrobenzamide (400 mg, 2.019 mmol), triethylamine (817 mg, 8.07 mmol), and (2-ethyloxazol-4-yl)methanamine (255 mg, 2.019 mmol) in DMF (20 mL) was stirred at 70 °C for 12 hours. The mixture was concentrated under vacuum, and the resulting residue was poured onto water (150 mL) and extracted with EtOAc (2 x 150 mL). The combined organic layer was dried with anhydrous Na₂SO₄ and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 0 to 5% CH₃OH/CH₂Cl₂) to give the desired product (600 mg, 94% yield) as a yellow solid. LC-MS (ES) m/z = 305 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.55 (d, J = 2.0 Hz, 2H), 7.98 (dd, J = 9.0, 2.0 Hz, 1H), 7.50 (s, 1H), 6.98 (d, J = 9.0 Hz, 1H), 4.48 (d, J = 4.7 Hz, 2H), 3.02 (d, J = 4.6 Hz, 3H), 2.81 (q, J = 7.6 Hz, 2H), 1.35 (t, J = 7.6 Hz, 3H).

Intermediate 141

3-Amino-4-(((2-ethyloxazol-4-yl)methyl)amino)-N-methylbenzamide

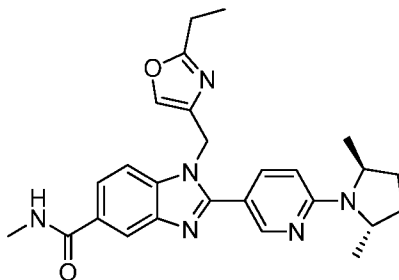


A mixture of 4-(((2-ethyloxazol-4-yl)methyl)amino)-N-methyl-3-nitrobenzamide (250 mg, 0.822 mmol) and palladium on carbon (8.74 mg, 0.082 mmol) in CH₃OH (15 mL) was stirred at 25 °C for 4 hours under a hydrogen atmosphere. The reaction mixture was filtered, and the filtrate was concentrated under vacuum to afford the desired product (213 mg) as a brown solid. LC-MS (ES) m/z = 275 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.45 (s, 1H), 7.25 (d, J = 1.8 Hz, 1H), 7.19 - 7.15 (1H), 6.63 (d, J = 8.2 Hz, 1H), 6.05 (s, 1H), 4.25 (s, 2H), 3.49 (s, 1H), 2.97 (d, J = 4.8 Hz, 3H), 2.78 (q, J = 7.6 Hz, 2H), 1.34 (t, J = 7.6 Hz, 3H).

Example 106**2-(4-Ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-1-((2-ethyloxazol-4-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide**

- 5 To a solution of 4-ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-7-carbaldehyde (244 mg, 1.181 mmol) in DMF (15 mL) were added sodium metabisulfite (292 mg, 1.535 mmol) and 3-amino-4-(((2-ethyloxazol-4-yl)methyl)amino)-N-methylbenzamide (324 mg, 1.181 mmol), and the reaction mixture was stirred at 90 °C for 12 hours. The mixture was concentrated under vacuum, and the resulting residue was treated with water (20 mL) and
- 10 aqueous NaHCO₃ (4 mL). The aqueous mixture was extracted with CH₂Cl₂ (2 x 40 mL), and the combined organic layer was dried over anhydrous Na₂SO₄ and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 0 to 3.5% CH₃OH/CH₂Cl₂) to give the desired product (290 mg) as a white solid. LC-MS (ES) m/z = 461 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.44 – 8.38 (m, 1H), 8.31 (d, *J* = 1.9 Hz, 1H), 8.15 (s, 1H), 8.12 (s, 1H), 7.74 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.64 (d, *J* = 1.9 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 1H), 5.34 (s, 2H), 4.12 (dd, *J* = 10.8, 2.4 Hz, 1H), 4.04 – 3.90 (m, 2H), 3.86 – 3.78 (m, 1H), 3.43 – 3.35 (m, 1H), 2.81 (d, *J* = 4.4 Hz, 3H), 2.71 (q, *J* = 7.6 Hz, 2H), 1.24 (d, *J* = 6.5 Hz, 3H), 1.20 – 1.10 (m, 6H).

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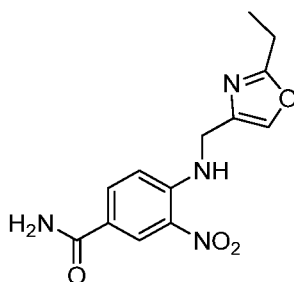
Example 107**2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide**

- To a solution of 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (159 mg, 0.776 mmol) and sodium metabisulfite (192 mg, 1.009 mmol) in DMF (10mL) was added 3-amino-
- 25

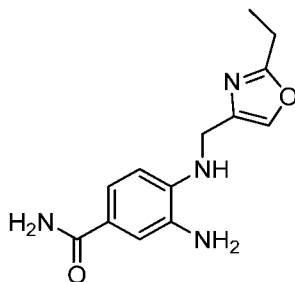
4-(((2-ethyloxazol-4-yl)methyl)amino)-N-methylbenzamide (213 mg, 0.776 mmol), and the reaction mixture was stirred at 90 °C for 12 hours. The mixture was concentrated under vacuum, and the resulting residue was treated with water (20 mL) and saturated aqueous NaHCO₃ (4 mL). The resulting aqueous mixture was extracted with CH₂Cl₂ (2 x 40 mL), and the combined organic layer was dried with anhydrous Na₂SO₄ and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 0 to 3.5% CH₃OH/CH₂Cl₂) to give the desired product (145 mg) as a white solid. LC-MS (ES) m/z = 459 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.67 (s, 1H), 8.43 – 8.37 (m, 1H), 8.17 – 8.08 (m, 3H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 1H), 6.65 (d, *J* = 9.0 Hz, 1H), 5.34 (s, 2H), 4.34 – 4.17 (m, 2H), 2.80 (d, *J* = 4.3 Hz, 3H), 2.71 (dd, *J* = 15.1, 7.6 Hz, 2H), 2.29 – 2.18 (m, 2H), 1.71 – 1.60 (m, 2H), 1.21 – 1.12 (m, 9H).

Intermediate 142

4-(((2-Ethyloxazol-4-yl)methyl)amino)-3-nitrobenzamide



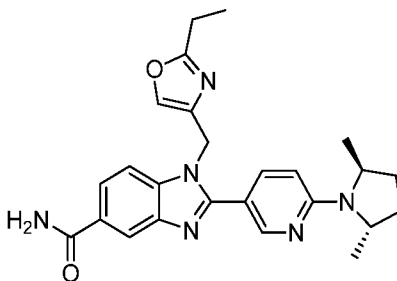
A mixture of 4-fluoro-3-nitrobenzamide (400 mg, 2.172 mmol), (2-ethyloxazol-4-yl)methanamine (274 mg, 2.172 mmol), and triethylamine (879 mg, 8.69 mmol) in DMF (20 mL) was stirred at 70 °C for 12 hours. The mixture was concentrated under vacuum, and the resulting residue was poured onto water (150 mL) and extracted with EtOAc (2 x 150 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 0 to 5% CH₃OH/CH₂Cl₂) to give the desired product (510 mg) as a yellow solid. LC-MS (ES) m/z = 291 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.77 – 8.62 (m, 2H), 8.00 (d, *J* = 8.2 Hz, 2H), 7.31 (s, 1H), 7.14 (d, *J* = 9.1 Hz, 1H), 4.53 (d, *J* = 5.7 Hz, 2H), 2.74 (q, *J* = 7.6 Hz, 2H), 1.26 – 1.15 (m, 3H).

Intermediate 1433-Amino-4-(((2-ethyloxazol-4-yl)methyl)amino)benzamide

A mixture of 4-(((2-ethyloxazol-4-yl)methyl)amino)-3-nitrobenzamide (260 mg, 0.896 mmol)
 5 and palladium on carbon (9.53 mg, 0.090 mmol) in CH₃OH (15 mL) was stirred at 25 °C for
 4 hour under a hydrogen atmosphere. The reaction mixture was filtered, the filtrate was
 concentrated under vacuum to afford the desired product (233 mg) as a yellow solid. LC-
 MS (ES) m/z = 261 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.46 (s, 1H), 7.29 (s, 1H), 7.23 (s,
 1H), 6.65 (d, J = 8.4 Hz, 1H), 4.27 (s, 2H), 3.49 (s, 1H), 2.79 (q, J = 7.6 Hz, 2H), 1.34 (t, J
 10 = 7.6 Hz, 3H).

Example 108

2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-
1H-benzo[d]imidazole-5-carboxamide

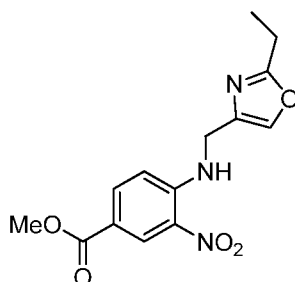


15 To a solution of 6-((2S,5S)-2,3,5-trimethylpyrrolidin-1-yl)nicotinaldehyde (195 mg, 0.895
 mmol) in DMF (10mL) were added sodium metabisulfite (221 mg, 1.164 mmol) and 3-
 amino-4-(((2-ethyloxazol-4-yl)methyl)amino)benzamide (233 mg, 0.895 mmol), and the
 mixture was stirred at 90 °C for 12 hours. The mixture was concentrated under vacuum,
 20 and the resulting residue was treated with water (20 mL) and saturated NaHCO₃ (2 mL).
 The resulting aqueous mixture was extracted with CH₂Cl₂ (2 x 40 mL), and the combined
 organic layer was dried over anhydrous Na₂SO₄ and concentrated. The resulting residue
 was purified by silica gel chromatography (eluting with 0 to 3.5% CH₃OH/CH₂Cl₂) to give
 the desired product (149 mg) as a white solid. LC-MS (ES) m/z = 445 [M+H]⁺. ¹H NMR (400
 25 MHz, DMSO-*d*₆): δ 8.67 (d, J = 2.3 Hz, 1H), 8.20 (s, 1H), 8.15 – 8.06 (m, 2H), 7.95 (br s,

1H), 7.77 (dd, $J = 8.4, 1.4$ Hz, 1H), 7.59 (d, $J = 8.5$ Hz, 1H), 7.26 (br s, 1H), 6.65 (d, $J = 9.0$ Hz, 1H), 5.34 (s, 2H), 4.33 – 4.17 (m, 2H), 2.71 (q, $J = 7.6$ Hz, 2H), 2.28 – 2.19 (m, 2H), 1.71 – 1.60 (m, 2H), 1.21 – 1.12 (m, 9H).

5 Intermediate 144

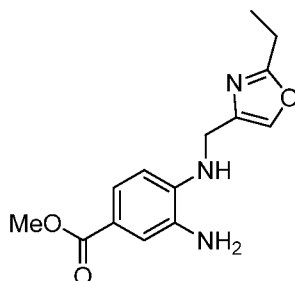
Methyl 4-(((2-ethyloxazol-4-yl)methyl)amino)-3-nitrobenzoate



To a solution of methyl 4-fluoro-3-nitrobenzoate (800 mg, 4.02 mmol) in DMF (20 mL) were added (2-ethyloxazol-4-yl)methanamine (507 mg, 4.02 mmol) and K_2CO_3 (555 mg, 4.02 mmol), and the mixture was stirred at room temperature for 18 hours. The mixture was filtered, and the filtrate was concentrated. The resulting residue was washed with water and dried under vacuum to give the desired product (1.05 g) as a pale brown solid. LC-MS (ES) $m/z = 306$ $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 1.31 - 1.41 (m, 3H), 2.77 - 2.87 (m, 2H), 3.92 (s, 3H), 4.49 (dd, $J = 5.4, 0.9$ Hz, 2H), 6.96 (d, $J = 8.9$ Hz, 1H), 7.48 - 7.57 (m, 1H), 8.09 (dd, $J = 9.4, 1.8$ Hz, 1H), 8.65 (br. s., 1H), 8.91 (d, $J = 2.0$ Hz, 1H).

Intermediate 145

Methyl 3-amino-4-(((2-ethyloxazol-4-yl)methyl)amino)benzoate

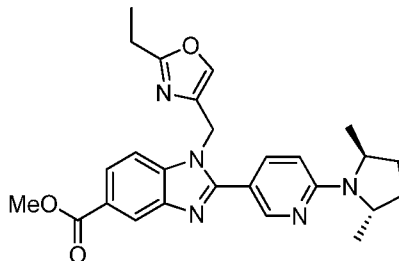


To a solution of methyl 4-(((2-ethyloxazol-4-yl)methyl)amino)-3-nitrobenzoate (1 g, 3.28 mmol) in CH_3OH (20 mL) were added $NiCl_2 \cdot 6H_2O$ (1.949 g, 8.19 mmol) and sodium borohydride (0.620 g, 16.38 mmol) at 0 °C, and the mixture was stirred at 0 °C for 20 minutes. The reaction mixture was concentrated, and the residue was treated with concentrated NH_4OH aqueous solution and extracted with EtOAc (3x). The extract was dried (Na_2SO_4) and concentrated to give the desired product (860 mg) as a pale brown

solid. LC-MS (ES) m/z = 276 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.33 (t, J = 7.6 Hz, 3H), 1.95 (s, 2H), 2.81 (q, J = 7.6 Hz, 2H), 3.82 (s, 3H), 4.31 - 4.37 (m, 2H), 6.60 (d, J = 8.4 Hz, 1H), 7.36 - 7.45 (m, 2H), 7.68 (s, 1H).

5 Intermediate 146

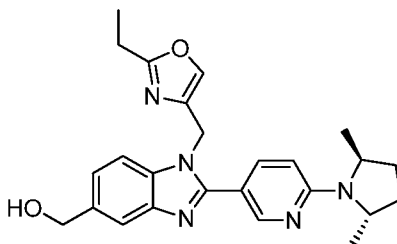
Methyl 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carboxylate



To a solution of methyl 3-amino-4-(((2-ethyloxazol-4-yl)methyl)amino)benzoate (600 mg, 2.179 mmol) in DMF (9mL) and water (1.8 mL) were added 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (445 mg, 2.179 mmol) and oxone (1005 mg, 1.635 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was basified using 10% K_2CO_3 aqueous solution and extracted with EtOAc (3x). The extract was dried (Na_2SO_4) and concentrated. The resulting residue was purified using column chromatography (silica gel, 0 to 100% EtOAc/hexanes) to give the desired product (690 mg) as a pale brown solid. LC-MS (ES) m/z = 460 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.18 - 1.34 (m, 9H), 1.76 (d, J = 5.8 Hz, 2H), 2.30 - 2.41 (m, 2H), 2.77 (q, J = 7.6 Hz, 2H), 3.95 (s, 3H), 4.33 (br. s., 2H), 5.39 - 5.43 (m, 2H), 6.72 (d, J = 9.1 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.84 (s, 1H), 7.99 (dd, J = 8.6, 1.5 Hz, 1H), 8.08 (dd, J = 9.1, 2.5 Hz, 1H), 8.36 (d, J = 1.3 Hz, 1H), 8.65 (d, J = 2.0 Hz, 1H).

Example 109

(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-5-yl)methanol

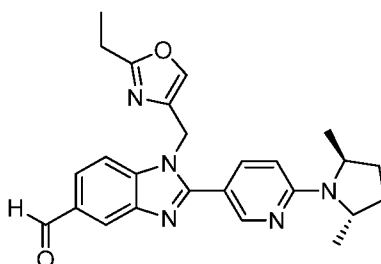


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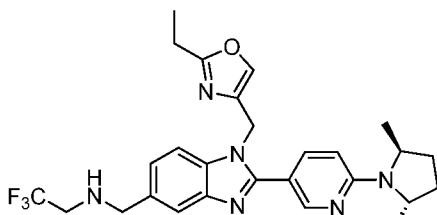
To a solution of methyl 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carboxylate (680 mg, 1.480 mmol) in THF (8 mL) was added LiAlH₄ in THF (2M, 1.480 mL, 2.96 mmol) at 0 °C, and the mixture was stirred at 0 °C for 2 hours. The mixture was quenched by adding water dropwise until no H₂ was generated, then diluted with EtOAc (30 mL) and filtered. The filtrate was dried (Na₂SO₄) and concentrated. The resulting residue was purified using column chromatography (silica gel, 0 to 100% (3:1 EtOAc:EtOH)/heptane) to give the desired product (420 mg) as a white solid. LC-MS (ES) m/z = 432 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.17 - 1.33 (m, 9H), 1.70 - 1.79 (m, 2H), 2.29 - 2.40 (m, 2H), 2.77 (q, J = 7.6 Hz, 2H), 4.32 (br. s., 2H), 4.74 (s, 2H), 5.36 (s, 2H), 6.71 (d, J = 8.9 Hz, 1H), 7.31 (dd, J = 8.4, 1.5 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.69 (s, 1H), 7.78 (s, 1H), 8.05 (dd, J = 9.0, 2.4 Hz, 1H), 8.61 (d, J = 2.3 Hz, 1H).

Intermediate 147

2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carbaldehyde



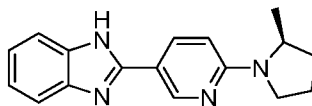
To a solution of 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-yl)methanol (390 mg, 0.904 mmol) in CH₂Cl₂ (5 mL) was added Dess-Martin periodinane (575 mg, 1.356 mmol), and the mixture was stirred at room temperature for 4 hours. The mixture was concentrated, and the resulting residue was purified using column chromatography (silica gel, 0 to 60% EtOAc/hexanes) to give the desired product (310 mg) as a pale brown solid. LC-MS (ES) m/z = 430 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.20 - 1.34 (m, 9H), 1.72 - 1.82 (m, 2H), 2.28 - 2.43 (m, 2H), 2.77 (q, J = 7.6 Hz, 2H), 4.33 (m, 2H), 5.44 (s, 2H), 6.73 (d, J = 8.9 Hz, 1H), 7.72 (d, J = 8.6 Hz, 1H), 7.85 - 7.91 (m, 2H), 8.10 (dd, J = 8.9, 2.5 Hz, 1H), 8.24 (d, J = 1.0 Hz, 1H), 8.67 (d, J = 2.3 Hz, 1H), 10.07 (s, 1H).

Example 110**N-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-5-yl)methyl)-2,2,2-trifluoroethanamine**

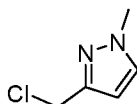
- 5 To 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carbaldehyde (100 mg, 0.233 mmol) in 1,2-dichloroethane (2 mL) were added 2,2,2-trifluoroethan-1-amine (34.6 mg, 0.349 mmol) and sodium triacetoxyborohydride (99 mg, 0.466 mmol), and the reaction mixture was stirred overnight at room temperature. The mixture was quenched with saturated NaHCO₃ and extracted
- 10 with CH₂Cl₂ (3x). The extract was dried over Na₂SO₄, filtered, and concentrated. The residue was purified using column chromatography (silica gel, 0 to 100% EtOAc/heptane) to give the desired product (83 mg) as a white solid. LC-MS (ES) m/z = 513 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.22 (d, J = 6.3 Hz, 6H), 1.29 (t, J = 7.6 Hz, 3H), 1.75 (d, J = 5.6 Hz, 2H), 2.30 - 2.43 (m, 2H), 2.77 (q, J = 7.6 Hz, 2H), 3.19 (q, J = 9.9 Hz, 2H), 3.99 (s, 2H), 4.32 (br. s., 2H), 5.32 - 5.40 (m, 2H), 6.71 (d, J = 8.9 Hz, 1H), 7.31 (dd, J = 8.4, 1.5 Hz, 1H), 7.51 (d, J = 8.1 Hz, 1H), 7.66 - 7.71 (m, 1H), 7.78 (s, 1H), 8.05 (dd, J = 9.0, 2.4 Hz, 1H), 8.62 (d, J = 2.3 Hz, 1H).

Intermediate 148

- 20 **(S)-2-(6-(2-Methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole**



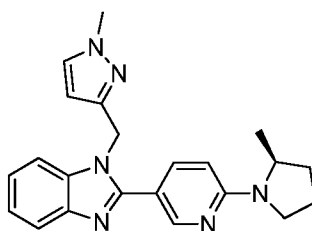
- A solution of benzene-1,2-diamine (0.433 g, 4 mmol), (S)-6-(2-methylpyrrolidin-1-yl)nicotinaldehyde (0.761 g, 4.00 mmol), and sodium metabisulfite (0.989 g, 5.20 mmol) in DMF (40 mL) was stirred at 80 °C for 12 hours. The reaction mixture was quenched with water (50 mL), and the precipitate was collected by filtration and dried to give the desired product (1 g) as an off-white solid. LC-MS (ES) m/z = 279 [M+H]⁺.

Intermediate 1493-(Chloromethyl)-1-methyl-1H-pyrazole

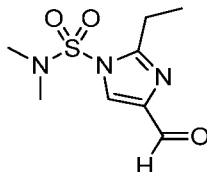
To (1-methyl-1H-pyrazol-3-yl)methanol (315 mg, 2.81 mmol) cooled in ice bath was added
 5 thionyl chloride (3075 μ L, 42.1 mmol) dropwise followed by DMF (20 μ L), and the reaction
 mixture was stirred at room temperature for 2 hours. The reaction was slowly added to ice,
 and the resulting mixture was treated with saturated aqueous NaHCO_3 solution and solid
 NaHCO_3 until pH was slightly basic. The aqueous mixture was extracted with EtOAc (3 x
 20 mL), and the organic extracts were then combined, washed with brine, dried over
 10 MgSO_4 , filtered, and concentrated to afford 3-(chloromethyl)-1-methyl-1H-pyrazole (289
 mg) as a clear oil. LC-MS (ES) m/z = 131 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 3.81 (s,
 3H), 4.67 (s, 2H), 6.28 (s, 1H), 7.65 (d, J = 2.0 Hz, 1H).

Example 111

15 (S)-1-((1-Methyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-
1H-benzo[d]imidazole

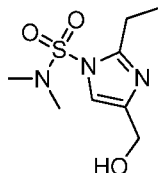


To a solution of (S)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole (418
 mg, 1.5 mmol) in THF (20 mL) was added NaH (120 mg, 3.00 mmol, 60%), and the reaction
 20 mixture was stirred at 60 $^{\circ}\text{C}$ for 30 minutes. 3-(Chloromethyl)-1-methyl-1H-pyrazole (294
 mg, 2.250 mmol) was then added, and the reaction mixture was stirred at 90 $^{\circ}\text{C}$ for 12
 hours. The reaction mixture was poured onto water (50 mL) and extracted with CH_2Cl_2 (2 x
 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated.
 The resulting residue was purified by silica gel chromatography (eluting with 1:20
 25 $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$) to give the desired product (120 mg) as an off-white solid. LC-MS (ES) m/z
 = 373 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 8.58 (d, J = 2.1 Hz, 1H), 7.96 (dd, J = 8.8, 2.1
 Hz, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.26 – 7.17
 (m, 2H), 6.48 (d, J = 8.9 Hz, 1H), 5.95 (d, J = 1.9 Hz, 1H), 5.41 (s, 2H), 4.27 – 4.17 (m, 1H),
 3.88 (s, 3H), 3.66 – 3.57 (m, 1H), 3.47 – 3.38 (m, 1H), 2.15 – 1.99 (m, 3H), 1.80 – 1.71 (m,
 30 1H), 1.25 (d, J = 6.3 Hz, 3H).

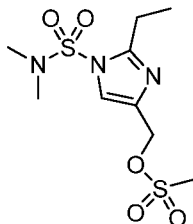
Intermediate 1502-Ethyl-4-formyl-N,N-dimethyl-1H-imidazole-1-sulfonamide

- 5 To a solution of 2-ethyl-N,N-dimethyl-1H-imidazole-1-sulfonamide (3.2 g, 15.74 mmol) in THF (100 mL) at -78 °C was added n-butyllithium in hexanes (7.87 mL, 18.89 mmol), and the mixture was stirred at -78 °C for 1 hour. DMF (7.31 mL, 94 mmol) was then added, and the reaction mixture was warmed to room temperature and stirred several hours. Water (5 mL) was added, and the mixture was concentrated under vacuum. The resulting residue
- 10 was poured onto water (150 mL), and extracted with EtOAc (2 x 150 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 1:4 hexanes/EtOAc) to give the desired product (2.5 g) as a white solid. LC-MS (ES) m/z = 232 [M+H]⁺.

15 Intermediate 151

2-Ethyl-4-(hydroxymethyl)-N,N-dimethyl-1H-imidazole-1-sulfonamide

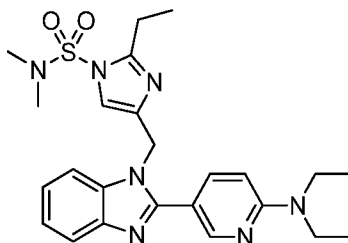
- A mixture of 2-ethyl-4-formyl-N,N-dimethyl-1H-imidazole-1-sulfonamide (2.5 g, 10.81 mmol) and NaBH₄ (0.818 g, 21.62 mmol) in CH₃OH (25 mL) was stirred at room temperature
- 20 for 12 hours. Water (5 mL) was then added, and the mixture was concentrated under vacuum. The resulting residue was poured onto water (100 mL), and extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 10:1 CH₂Cl₂/CH₃OH) to give the desired product (1.8 g, 7.10 mmol) as a white solid. LC-
- 25 MS (ES) m/z = 234 [M+H]⁺.

Intermediate 152(1-(N,N-Dimethylsulfamoyl)-2-ethyl-1H-imidazol-4-yl)methyl methanesulfonate

- 5 To a solution of 2-ethyl-4-(hydroxymethyl)-N,N-dimethyl-1H-imidazole-1-sulfonamide (1.8 g, 7.72 mmol) and triethylamine (1.291 mL, 9.26 mmol) in CH₂Cl₂ (40 mL) was added methanesulfonyl chloride (1.061 g, 9.26 mmol), and the resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was poured onto water (150 mL), basified to pH 9 by addition of aqueous NaHCO₃, and extracted with CH₂Cl₂ (2 x 150 mL).
- 10 The combined organic layer was dried with anhydrous Na₂SO₄ and concentrated to afford the crude product (1.2 g) as a brown oil, which was used in next step without further purification. LC-MS (ES) m/z = 234 [M+H-Ms]⁺

Intermediate 153

- 15 4-((2-(6-(Diethylamino)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)-2-ethyl-N,N-dimethyl-1H-imidazole-1-sulfonamide

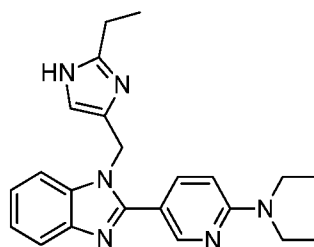


- 20 A mixture of 5-(1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (700 mg, 2.63 mmol), (1-(N,N-dimethylsulfamoyl)-2-ethyl-1H-imidazol-4-yl)methyl methanesulfonate (1228 mg, 3.94 mmol), and NaH (60%, 105 mg, 2.63 mmol) in DMF (20 mL) was stirred at 90 °C in sealed tube for 12 hours. Water (5 mL) was then added, and the mixture was concentrated under vacuum. The resulting residue was poured onto water (100 mL), and extracted with
- 25 EtOAc (2 x 100 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated. The resulting residue was purified by silica gel chromatography (eluting with

10:1 CH₂Cl₂/CH₃OH) to give the desired product (420 mg) as a white solid. LC-MS (ES) m/z = 482 [M+H]⁺.

Example 112

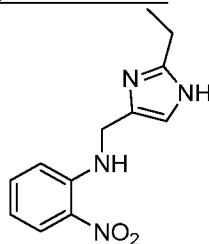
5 N,N-Diethyl-5-(1-((2-ethyl-1H-imidazol-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine



To a solution of 4-((2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)-2-ethyl-N,N-dimethyl-1H-imidazole-1-sulfonamide (450 mg, 0.934 mmol) in CH₂Cl₂ (20 mL) was added HCl in EtOH (2 mL, 33% w/w), and the reaction mixture was stirred at room temperature for 12 hours. The mixture was concentrated under vacuum, and the resulting residue was poured into water (50 mL). The resulting aqueous mixture was basified to pH 9 using aqueous NaHCO₃ and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 20:1 CH₂Cl₂/CH₃OH) to give the desired product (200 mg) as a white solid. LC-MS (ES) m/z = 375 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 9.95 (br s, 1H), 8.50 (d, J = 2.2 Hz, 1H), 7.89 (dd, J = 8.9, 2.0 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 7.7 Hz, 1H), 7.25 – 7.15 (m, 2H), 6.51 (d, J = 9.0 Hz, 1H), 6.41 (s, 1H), 5.35 (s, 2H), 3.53 (q, J = 7.0 Hz, 4H), 2.72 (q, J = 7.6 Hz, 2H), 1.29 (t, J = 7.6 Hz, 3H), 1.18 (t, J = 7.0 Hz, 6H).

Intermediate 154

N-((2-Ethyl-1H-imidazol-4-yl)methyl)-2-nitroaniline

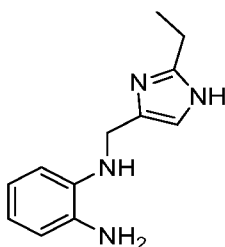


To a solution of (2-ethyl-1H-imidazol-4-yl)methanamine hydrochloride (122 mg, 0.755 mmol) and 1-fluoro-2-nitrobenzene (107 mg, 0.755 mmol) in DMF (8 mL) was added triethylamine (0.526 mL, 3.77 mmol), and the reaction mixture was stirred at 70 °C for 15

hours. The mixture was concentrated, and the resulting residue was purified by silica gel chromatography (eluting with 0 to 8% CH₃OH/CH₂Cl₂) to afford the desired product (180 mg) as a yellow solid. LC-MS (ES) m/z = 247 [M+H]⁺.

5 Intermediate 155

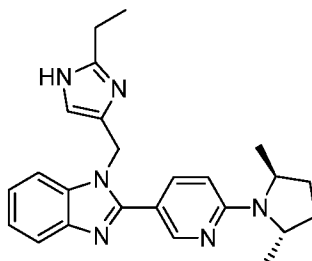
N1-((2-Ethyl-1H-imidazol-4-yl)methyl)benzene-1,2-diamine



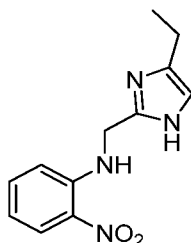
A mixture of N-((2-ethyl-1H-imidazol-4-yl)methyl)-2-nitroaniline (180 mg, 0.731 mmol) and Pd-C (78 mg, 0.731 mmol) in CH₃OH (20 mL) was stirred under a hydrogen atmosphere for 3 hours. The mixture was filtered, and the filtrate was concentrated to get the desired product (150 mg). LC-MS (ES) m/z = 217 [M+H]⁺.

Example 113

2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyl-1H-imidazol-4-yl)methyl)-1H-benzo[d]imidazole



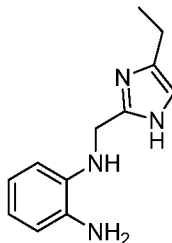
To a solution of N1-((2-ethyl-1H-imidazol-4-yl)methyl)benzene-1,2-diamine (90 mg, 0.416 mmol) in DMF (8 mL) were added 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (85 mg, 0.416 mmol) and sodium metabisulfite (95 mg, 0.499 mmol), and the reaction mixture was stirred at 70 °C for 12 hours. The reaction mixture was concentrated, and the resulting residue was purified by silica gel chromatography (eluting with 0 to 10% CH₃OH/CH₂Cl₂) to give the desired product (145 mg) as a yellow solid. LC-MS (ES) m/z = 401 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.71 (br s, 1H), 8.77 (s, 1H), 8.27 (d, *J* = 8.2 Hz, 1H), 7.70 – 7.49 (m, 2H), 7.22 – 7.13 (m, 2H), 7.02 (s, 1H), 6.63 (d, *J* = 8.9 Hz, 1H), 5.24 (s, 2H), 4.44 – 4.10 (m, 2H), 2.58 (q, *J* = 7.6 Hz, 2H), 2.31 – 2.16 (m, 2H), 1.72 – 1.57 (m, 2H), 1.21 – 1.09 (m, 9H).

Intermediate 156N-((4-Ethyl-1H-imidazol-2-yl)methyl)-2-nitroaniline

5

To a solution of (4-ethyl-1H-imidazol-2-yl)methanamine (115 mg, 0.919 mmol) in DMF (8 mL) were added 1-fluoro-2-nitrobenzene (130 mg, 0.919 mmol) and triethylamine (0.640 mL, 4.59 mmol), and the reaction mixture was stirred at 60 °C for 12 hours. The reaction mixture was concentrated, and the resulting residue was purified by silica gel chromatography (eluting with 0 to 4% CH₃OH/CH₂Cl₂) to give the desired product as a yellow oil. LC-MS (ES) m/z = 247 [M+H]⁺.

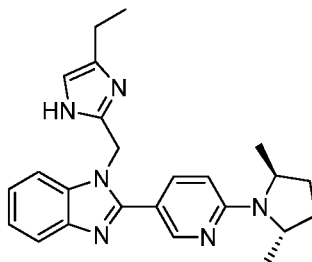
10

Intermediate 157N1-((4-ethyl-1H-imidazol-2-yl)methyl)benzene-1,2-diamine

15

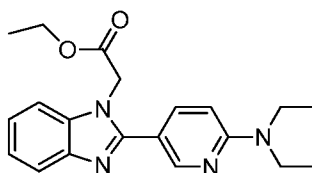
A mixture of N-((4-ethyl-1H-imidazol-2-yl)methyl)-2-nitroaniline (220 mg, 0.893 mmol) and Pd-C (95 mg, 0.893 mmol) in CH₃OH (20 mL) was stirred at room temperature for 3 hours. The mixture was then filtered, and the filtrate was concentrated. The resulting residue was purified by silica gel chromatography (eluting with 0 to 4% CH₃OH/CH₂Cl₂) to give the desired product (160 mg) as a yellow oil. LC-MS (ES) m/z = 217 [M+H]⁺.

20

Example 114**2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((4-ethyl-1H-imidazol-2-yl)methyl)-1H-benzo[d]imidazole**

- 5 To a solution of N1-((4-ethyl-1H-imidazol-2-yl)methyl)benzene-1,2-diamine (160 mg, 0.740 mmol) in DMF (8 mL) were added 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (151 mg, 0.740 mmol) and sodium metabisulfite (169 mg, 0.888 mmol), and reaction mixture was stirred at 70 °C for 15 hours. The reaction mixture was concentrated, and the resulting residue was purified by silica gel chromatography (eluting with 0 to 8% CH₃OH/CH₂Cl₂) to give the desired product (65 mg) as a yellow solid. LC-MS (ES) m/z = 401 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 12.66 (br s, 1H), 8.32 (d, J = 2.1 Hz, 1H), 7.24 – 7.16 (m, 1H), 7.11 (d, J = 8.0 Hz, 1H), 7.06 – 6.98 (m, 1H), 6.92 (s, 1H), 6.85 – 6.75 (m, 2H), 5.99 (d, J = 8.9 Hz, 1H), 5.42 (s, 2H), 4.61 – 3.69 (m, 2H), 2.77 (q, J = 7.4 Hz, 2H), 2.33 – 2.16 (m, 2H), 1.79 – 1.64 (m, 2H), 1.34 (t, J = 7.5 Hz, 3H), 1.17 (s, 6H).

15

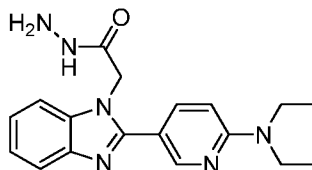
Intermediate 158**Ethyl 2-(2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)acetate**

- To a solution of 5-(1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (1.065 g, 4 mmol) in THF (25 mL) was added NaH (0.144 g, 6.00 mmol), and the reaction mixture was stirred at 60 °C for 30 minutes. A solution of ethyl 2-bromoacetate (0.802 g, 4.80 mmol) in THF (5 mL) was then added, and the reaction mixture was stirred at 80 °C for 12 hours. The reaction mixture was poured onto water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 1:17 EtOAc/CH₂Cl₂) to give the desired product (1 g) as a yellow oil. LC-MS (ES) m/z = 353 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.44 (d, J = 2.4 Hz, 1H), 7.92 – 7.77 (m, 2H), 7.30 (dt, J = 11.3, 3.8 Hz, 2H), 7.26

(s, 1H), 6.59 (d, $J = 9.0$ Hz, 1H), 4.92 (s, 2H), 4.27 (q, $J = 7.1$ Hz, 2H), 3.58 (q, $J = 7.1$ Hz, 4H), 2.07 (d, $J = 16.9$ Hz, 3H), 1.30 – 1.24 (m, 6H).

Intermediate 159

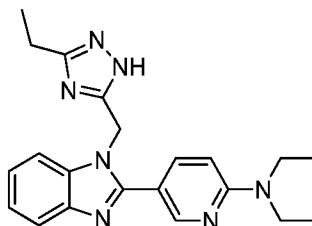
5 2-(2-(6-(Diethylamino)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)acetohydrazide



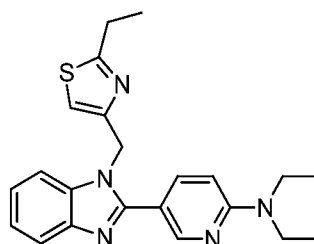
A solution of ethyl 2-(2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)acetate (987 mg, 2.8 mmol) and hydrazine (1.758 mL, 56.0 mmol) in CH₃CN (20 mL) was stirred at 50 °C for 4 hours. The reaction mixture was concentrated to give the desired product (700 mg) as a pink solid. LC-MS (ES) $m/z = 339$ [M+H]⁺.

Example 115

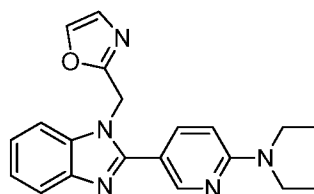
N,N-Diethyl-5-(1-((3-ethyl-1H-1,2,4-triazol-5-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine



To a solution of 2-(2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)acetohydrazide (711 mg, 2.1 mmol) and sodium ethoxide (2858 mg, 42.0 mmol) in ethanol (30 mL) was added ethyl propionimidate hydrochloride (5780 mg, 42.0 mmol), and the reaction mixture was heated to reflux for 36 hours. The reaction was concentrated, poured into ice water, and extracted with EtOAc (2 x 40 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 0 to 10% DCM/EtOAc) to afford the crude product (150 mg). This material was washed with Et₂O/hexanes (1:1) to give the desired product (98 mg) as a white solid. LC-MS (ES) $m/z = 376$ [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 12.50 (s, 1H), 8.69 (s, 1H), 8.04 (d, $J = 8.3$ Hz, 1H), 7.65 (s, 1H), 7.46 (d, $J = 4.9$ Hz, 1H), 7.22 – 7.14 (m, 2H), 6.48 (d, $J = 9.0$ Hz, 1H), 5.40 (s, 2H), 3.53 (q, $J = 7.0$ Hz, 4H), 2.72 (q, $J = 7.6$ Hz, 2H), 1.26 (t, $J = 7.6$ Hz, 3H), 1.19 (t, $J = 7.1$ Hz, 6H).

Example 116**N,N-Diethyl-5-(1-(2-ethylthiazol-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine**

- 5 A mixture of 5-(1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (400 mg, 1.502 mmol), 4-(chloromethyl)-2-ethylthiazole (364 mg, 2.253 mmol), and NaH (60%, 180 mg, 4.51 mmol) in THF (15 mL) was stirred at 95 °C into a sealed tube for 18 hours. Water (5 mL) was then added, and the mixture was concentrated under vacuum. The resulting residue was poured onto water (100 mL), and extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 20:1 CH₂Cl₂/CH₃OH) to give the desired product (100 mg) as a white solid. LC-MS (ES) m/z = 392 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.52 (d, J = 1.9 Hz, 1H), 7.98 (dd, J = 8.8, 1.8 Hz, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.34 – 7.22 (m, 3H), 6.70 (s, 1H), 6.58 (d, J = 9.0 Hz, 1H), 5.53 (s, 2H), 3.57 (q, J = 7.0 Hz, 4H), 3.06 (q, J = 7.6 Hz, 2H), 1.42 (t, J = 7.6 Hz, 3H), 1.21 (t, J = 7.0 Hz, 6H).

Example 117**N,N-Diethyl-5-(1-(oxazol-2-ylmethyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine**

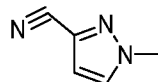
- 20 To a solution of 5-(1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (400 mg, 1.502 mmol) in THF (20 mL) was added NaH (60%, 240 mg, 6.01 mmol), and the resulting mixture was stirred at room temperature for 30 minutes. 2-(Chloromethyl)oxazole (265 mg, 2.253 mmol) was then added, and the reaction mixture was stirred into a sealed vessel at 95 °C for 12 hours. Water (5 mL) was added, and the mixture was concentrated under vacuum.
- 25 The resulting residue was poured onto water (100 mL), and extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 20:1 CH₂Cl₂/CH₃OH) to give the desired product (150 mg) as a white solid. LC-MS (ES) m/z =

348 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.68 (d, *J* = 2.2 Hz, 1H), 7.99 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.83 – 7.75 (m, 1H), 7.65 (s, 1H), 7.52 – 7.42 (m, 1H), 7.32 – 7.26 (m, 2H), 7.15 (s, 1H), 6.61 (d, *J* = 9.0 Hz, 1H), 5.48 (s, 2H), 3.59 (q, *J* = 7.0 Hz, 4H), 1.23 (t, *J* = 7.1 Hz, 6H).

5

Intermediate 159

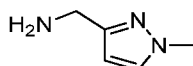
1-Methyl-1H-pyrazole-3-carbonitrile



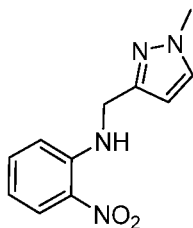
To a mixture of NaH (2.80 g, 70.1 mmol, 60%) in THF (50 mL) cooled in ice bath was added
 10 a solution of 1H-pyrazole-3-carbonitrile (5.02 g, 53.9 mmol) in THF (25 mL) dropwise, and
 the resulting mixture was stirred at room temperature for 1 hour. Iodomethane (3.71 mL,
 59.3 mmol) was then added, and the reaction mixture was stirred overnight at room
 temperature. The reaction was quenched with water (30 mL) and extracted with EtOAc (3
 X 30 mL). The organic extracts were combined, washed with brine, dried (MgSO₄), filtered,
 15 and concentrated. Purification by chromatography on SiO₂ (0 to 50% EtOAc/hexanes)
 afforded 1-methyl-1H-pyrazole-3-carbonitrile (2.7 g) as a white solid upon. LC-MS (ES) *m/z*
 = 108 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 3.95 (s, 3H), 6.96 (d, *J* = 2.3 Hz, 1H), 7.99
 (s, 1H).

20 Intermediate 160

(1-Methyl-1H-pyrazol-3-yl)methanamine

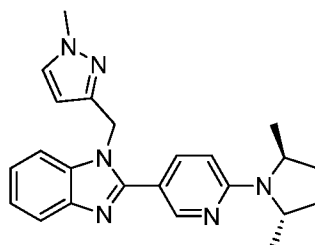


To 1-methyl-1H-pyrazole-3-carbonitrile (2.7 g, 25.2 mmol) in Et₂O (150 mL) cooled in ice
 bath was added LiAlH₄ (27.7 mL, 55.5 mmol, 2M in THF) slowly, and the reaction mixture
 25 was allowed to warm to room temperature and stirred overnight. The reaction was then
 cooled in ice bath and quenched by sequential addition of water (4 mL), 15%NaOH solution
 (4 mL), and water (12 mL). The mixture was then stirred for 15 minutes, and the resulting
 solid was filtered. The filtrate was dried over MgSO₄ and concentrated to afford (1-methyl-
 1H-pyrazol-3-yl)methanamine (1.28 g) as a clear oil. LC-MS (ES) *m/z* = 112 [M+H]⁺. ¹H
 30 NMR (400 MHz, DMSO-*d*₆): δ 1.69 (br. s, *J* = 1.5 Hz, 2H), 3.60 (s, 2H), 3.75 (s, 3H), 6.12
 (d, *J* = 2.0 Hz, 1H), 7.53 (d, *J* = 2.0 Hz, 1H).

Intermediate 161N-((1-Methyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline

To 1-fluoro-2-nitrobenzene (300 mg, 2.126 mmol) in DMF (3 mL) were added (1-methyl-1H-pyrazol-3-yl)methanamine (248 mg, 2.232 mmol) and K₂CO₃ (382 mg, 2.76 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction was then quenched with water (10 mL) and extracted with EtOAc (4 x 8 mL). The organic extracts were combined and washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ (0 to 60% EtOAc/hexanes) afforded N-((1-methyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline (405 mg) as a dark amber color oil. LC-MS (ES) m/z = 233 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 3.81 (s, 3H), 4.51 (d, *J* = 5.3 Hz, 2H), 6.19 (d, *J* = 2.3 Hz, 1H), 6.70 (ddd, *J* = 8.5, 7.0, 1.3 Hz, 1H), 7.07 - 7.12 (m, 1H), 7.49 - 7.57 (m, 1H), 7.64 (d, *J* = 2.3 Hz, 1H), 8.08 (dd, *J* = 8.6, 1.5 Hz, 1H), 8.53 (t, *J* = 5.5 Hz, 1H).

15

Example 1182-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole

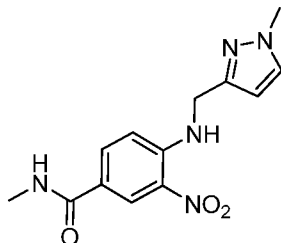
Into a 20 mL microwave vial were added N-((1-methyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline (113 mg, 0.487 mmol), 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (109 mg, 0.535 mmol), ethanol (1.5 mL), water (0.750 mL), and sodium hydrosulfite (254 mg, 85%, 1.241 mmol), and the reaction mixture was heated at 130 °C for 1.5 hour under microwave conditions. The reaction was then diluted with water (10 mL) and extracted with EtOAc (4 x 5 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ (0 to 10% CH₃OH/CH₂Cl₂) afforded 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole (127 mg) as a white solid after freeze

drying. LC-MS (ES) $m/z = 387$ $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 1.14 (d, $J = 6.3$ Hz, 6H), 1.65 (m, 2H), 2.19 - 2.28 (m, 2H), 3.79 (s, 3H), 4.25 (br. s., 2H), 5.40 (s, 2H), 6.12 (d, $J = 2.3$ Hz, 1H), 6.63 (d, $J = 8.9$ Hz, 1H), 7.16 - 7.23 (m, 2H), 7.45 - 7.52 (m, 1H), 7.61 - 7.66 (m, 2H), 8.00 (dd, $J = 8.9, 2.5$ Hz, 1H), 8.59 (d, $J = 1.8$ Hz, 1H).

5

Intermediate 162

N-Methyl-4-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)-3-nitrobenzamide

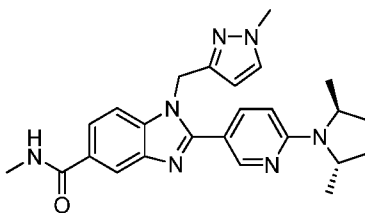


To 4-fluoro-N-methyl-3-nitrobenzamide (350 mg, 1.766 mmol) in DMF (5 mL) were added
 10 (1-methyl-1H-pyrazol-3-yl)methanamine (206 mg, 1.855 mmol) and K_2CO_3 (317 mg, 2.296 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction was then quenched with water (10 mL), and the resulting solid was isolated by filtration, washed with water, and dried in vacuum oven for 4 hours to afford N-methyl-4-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)-3-nitrobenzamide (390 mg) as an orange color solid. LC-MS
 15 (ES) $m/z = 290$ $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 2.76 (d, $J = 4.3$ Hz, 3H), 3.81 (s, 3), 4.57 (d, $J = 5.3$ Hz, 2H), 6.19 (d, $J = 2.0$ Hz, 1H), 7.15 (d, $J = 9.1$ Hz, 1H), 7.64 (d, $J = 2.3$ Hz, 1H), 7.96 (dd, $J = 9.0, 2.2$ Hz, 1H), 8.46 (d, $J = 4.8$ Hz, 1H), 8.63 (d, $J = 2.3$ Hz, 1H), 8.77 (t, $J = 5.6$ Hz, 1H).

20

Example 119

2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzod[*d*]imidazole-5-carboxamide

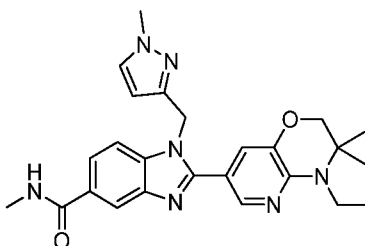


Into a 20 mL microwave vial were added N-methyl-4-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)-3-nitrobenzamide (109 mg, 0.377 mmol), 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (85 mg, 0.414 mmol), ethanol (1.5 mL), water (0.750 mL), and sodium hydrosulfite (197 mg, 85%, 0.961 mmol), and the reaction mixture was

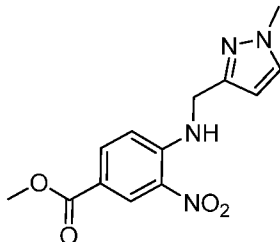
heated at 130 °C for 1.5 hours under microwave conditions. The reaction was then diluted with water (10 mL) and extracted with EtOAc (4 x 5 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ (0 to 10% CH₃OH/CH₂Cl₂) afforded 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide (101 mg, 0.228 mmol) as a white solid after freeze drying. LC-MS (ES) m/z = 444 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.15 (d, *J* = 6.1 Hz, 6H), 1.65 (d, *J* = 5.6 Hz, 2H), 2.24 (br. s., 2H), 2.81 (d, *J* = 4.3 Hz, 3H), 4.25 (br. s., 2H), 5.43 (s, 2H), 6.13 (d, *J* = 2.0 Hz, 1H), 6.64 (d, *J* = 8.6 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 2.0 Hz, 1H), 7.73 (dd, *J* = 8.5, 1.65 Hz, 1H), 8.01 (dd, *J* = 8.9, 2.28 Hz, 1H), 8.14 (d, *J* = 1.0 Hz, 1H), 8.41 (q, *J* = 4.2 Hz, 1H), 8.60 (d, *J* = 2.5 Hz, 1H).

Example 120

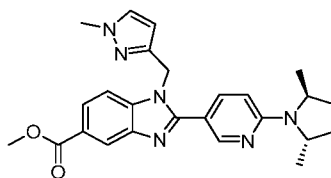
2-(4-Ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide



Into a microwave vial were added N-methyl-4-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)-3-nitrobenzamide (60 mg, 0.207 mmol), 4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-7-carbaldehyde (50.3 mg, 0.228 mmol), ethanol (1.5 mL), water (0.750 mL), and sodium hydrosulfite (108 mg, 85%, 0.529 mmol), and the reaction mixture was heated at 130 °C for 1.5 hours under microwave conditions. The reaction was then diluted with water (10 mL) and extracted with EtOAc (4 x 5 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ (0 to 10% CH₃OH/CH₂Cl₂) afforded 2-(4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide (54 mg) as a white solid after freeze drying. LC-MS (ES) m/z = 460 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.20 (t, *J* = 6.8 Hz, 3H), 1.30 (s, 6H), 2.81 (d, *J* = 4.6 Hz, 3H), 3.61 (d, *J* = 6.8 Hz, 2H), 3.78 (s, 3H), 3.93 (s, 2H), 5.43 (s, 2H), 6.15 (d, *J* = 2.0 Hz, 1H), 7.51 (d, *J* = 2.0 Hz, 1H), 7.53 (d, *J* = 8.6 Hz, 1H), 7.65 (d, *J* = 2.3 Hz, 1H), 7.73 (dd, *J* = 8.5, 1.7 Hz, 1H), 8.15 (d, *J* = 1.3 Hz, 1H), 8.24 (d, *J* = 2.0 Hz, 1H), 8.41 (d, *J* = 4.6 Hz, 1H).

Intermediate 163Methyl 4-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)-3-nitrobenzoate

- 5 To methyl 4-fluoro-3-nitrobenzoate (350 mg, 1.758 mmol) in DMF (5 mL) were added (1-methyl-1H-pyrazol-3-yl)methanamine (205 mg, 1.845 mmol) and K₂CO₃ (316 mg, 2.285 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction was then quenched with water (10 mL), and the resulting solid was isolated by filtration, washed with water, and dried in vacuum oven for 4 hours to afford methyl 4-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)-3-nitrobenzoate (395 mg) as a yellow solid. LC-MS (ES) m/z = 291 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 3.81 (s, 3H), 3.83 (s, 3H), 4.59 (d, *J* = 5.8 Hz, 2H), 6.20 (d, *J* = 2.3 Hz, 1H), 7.19 (d, *J* = 9.4 Hz, 1H), 7.64 (d, *J* = 2.0 Hz, 1H), 7.97 (dd, *J* = 9.0, 1.9 Hz, 1H), 8.64 (d, *J* = 2.0 Hz, 1H), 8.96 (t, *J* = 5.6 Hz, 1H).

15 Intermediate 164Methyl 2-(6-(((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylate

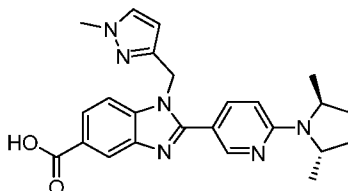
- Into a microwave 20 mL vial were added methyl 4-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)-3-nitrobenzoate (75 mg, 0.258 mmol), 6-(((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)nicotinaldehyde (58.1 mg, 0.284 mmol), sodium hydrosulfite (135 mg, 85%, 0.642 mmol), ethanol (1.5 mL), and water (0.750 mL), and the reaction mixture was heated at 130 °C for 1.5 hours under microwave conditions. The reaction was then diluted with water (10 mL) and extracted with EtOAc (4 x 5 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ (0 to 10% CH₃OH/CH₂Cl₂) afforded methyl 2-(6-(((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylate (84 mg) as a light brown solid. LC-MS (ES) m/z = 445 [M+H]⁺. ¹H NMR (400 MHz, DMSO-

d_6): δ 1.12 - 1.16 (m, 6H), 1.65 (d, J = 5.3 Hz, 2H), 2.24 (br. s., 2H), 3.78 (s, 3H), 3.87 (s, 3H), 4.26 (br. s., 2H), 5.46 (s, 2H), 6.14 (d, J = 2.03 Hz, 1H), 6.64 (d, J = 8.9 Hz, 1H), 7.61 (d, J = 8.6 Hz, 1H), 7.65 (d, J = 2.3 Hz, 1H), 7.85 (dd, J = 8.5, 1.65 Hz, 1H), 8.01 (dd, J = 9.0, 2.4 Hz, 1H), 8.23 (d, J = 1.3 Hz, 1H), 8.61 (d, J = 2.5 Hz, 1H).

5

Intermediate 165

2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid

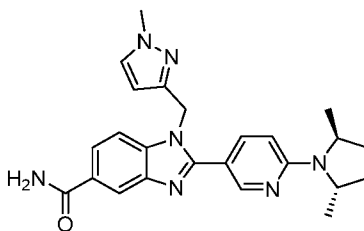


- 10 To methyl 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylate (87 mg, 0.196 mmol) in CH₃OH (3 mL) was added NaOH (0.391 mL, 3.91 mmol), and the reaction mixture was stirred overnight at 45 °C. The pH was adjusted with 1N HCl (3.91 mL, 3.91 mmol), and the resulting precipitate was isolated by filtration and dried in vacuum oven for 3 hours to afford 2-(6-((2S,5S)-2,5-
- 15 dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid (57 mg) as a white solid. LC-MS (ES) m/z = 431 $[M+H]^+$. ¹H NMR (400 MHz, DMSO- d_6): δ 1.15 (d, J = 6.1 Hz, 6H), 1.66 (d, J = 5.6 Hz, 2H), 2.24 (br. s., 2H), 3.78 (s, 3H), 4.25 (br. s., 2H), 5.45 (s, 2H), 6.15 (d, J = 2.0 Hz, 1H), 6.65 (d, J = 9.4 Hz, 1H), 7.58 (d, J = 8.6 Hz, 1H), 7.65 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 8.4, 1.5
- 20 Hz, 1H), 8.02 (dd, J = 8.7, 2.4 Hz, 1H) 8.21 (d, J = 1.3 Hz, 1H) 8.61 (d, J = 2.3 Hz, 1H) 12.73 (s, 1H).

Example 121

2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide

25



To 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid (57 mg, 0.132 mmol) in DMSO (2 mL)

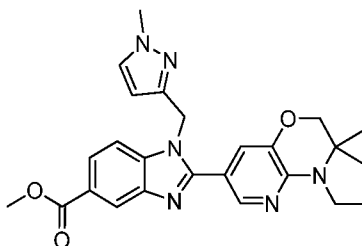
were added NH_4Cl (12.75 mg, 0.238 mmol), EDC (50.8 mg, 0.265 mmol), HOBT (40.6 mg, 0.265 mmol), and N-methylmorpholine (0.087 mL, 0.794 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction was then quenched with water (5 mL) and extracted with EtOAc (3 x 10 mL). The organic extracts were combined, dried over

5 MgSO_4 , filtered, and concentrated. Purification by chromatography on SiO_2 (0 to 10% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$) afforded 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide (37 mg) as a white solid after freeze drying. LC-MS (ES) m/z = 430 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 1.14 (d, J = 6.3 Hz, 6H), 1.65 (d, J = 5.3 Hz, 2H) 2.18 - 2.28 (m, 2H), 3.78 (s, 3 H) 4.25 (br.

10 s., 2H), 5.43 (s, 2H), 6.13 (d, J = 2.3 Hz, 1H), 6.64 (d, J = 9.1 Hz, 1H), 7.27 (br. s., 1H), 7.53 (d, J = 8.6 Hz, 1H), 7.65 (d, J = 2.3 Hz, 1H), 7.77 (dd, J = 8.6, 1.5 Hz, 1H), 7.97 (br. s., 1H), 8.01 (dd, J = 8.9, 2.3 Hz, 1H), 8.20 (d, J = 1.3 Hz, 1H), 8.60 (d, J = 2.5 Hz, 1H).

Intermediate 166

15 2-(4-Ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylate



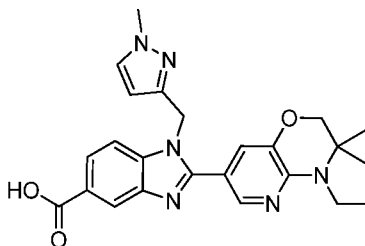
Into a microwave vial were added methyl 4-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)-3-nitrobenzoate (75 mg, 0.258 mmol), 4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-7-carbaldehyde (62.6 mg, 0.284 mmol), ethanol (1.5 mL), water (0.750 mL), and sodium hydrosulfite (135 mg, 85%, 0.659 mmol), and the reaction mixture was heated at 130 °C for 1.5 hours under microwave conditions. The reaction was then diluted with water (10 mL) and extracted with EtOAc (4 x 5 mL). The organic extracts then combined, washed with brine, dried over MgSO_4 , filtered, and concentrated. Purification by

25 chromatography on SiO_2 (0 to 10% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$) afforded methyl 2-(4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylate (80 mg) as a light brown solid. LC-MS (ES) m/z = 461 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 1.20 (t, J = 7.0 Hz, 3H), 1.30 (s, 6H), 3.61 (q, J = 6.8 Hz, 2H), 3.78 (s, 3H), 3.87 (s, 3H), 3.93 (s, 2H), 5.45 (s, 2H), 6.16 (d, J =

30 2.3 Hz, 1H), 7.51 (d, J = 2.0 Hz, 1H), 7.60 (d, J = 8.6 Hz, 1H), 7.66 (d, J = 2.3 Hz, 1H), 7.85 (dd, J = 8.6, 1.5 Hz, 1H), 8.23 (d, J = 1.3 Hz, 1H), 8.25 (d, J = 2.0 Hz, 1H).

Intermediate 167

2-(4-Ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid



5

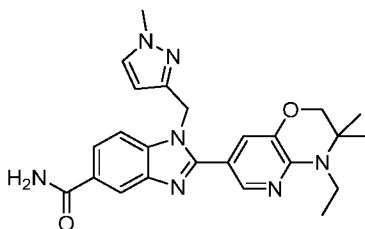
To methyl 2-(4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylate (80 mg, 0.174 mmol) in CH₃OH (3 mL) was added 10N NaOH (0.347 mL, 3.47 mmol), and the reaction mixture was stirred overnight at 45 °C. The pH was adjusted with 1N HCl (3.47 mL, 3.47 mmol), and the resulting precipitate was isolated by filtration and dried in vacuum oven for 3 hours to afford 2-(4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid (63 mg) as a white solid. LC-MS (ES) m/z = 447 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.20 (t, *J* = 6.8 Hz, 3H), 1.30 (s, 6H), 3.61 (q, *J* = 6.8 Hz, 2H), 3.78 (s, 3H), 3.93 (s, 2H), 5.45 (s, 2H), 6.16 (d, *J* = 2.0 Hz, 1H), 7.51 (d, *J* = 2.0 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 2.0 Hz, 1H), 7.83 (dd, *J* = 8.4, 1.5 Hz, 1H), 8.21 (d, *J* = 1.3 Hz, 1H), 8.25 (d, *J* = 2.0 Hz, 1H), 12.73 (s, 1H).

15

Example 122

2-(4-Ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide

20



To 2-(4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid (80 mg, 0.179 mmol) in DMSO (2 mL) were added NH₄Cl (17.25 mg, 0.323 mmol), EDC (68.7 mg, 0.358 mmol), HOBt (54.9 mg, 0.358 mmol), and N-methylmorpholine (0.118 mL, 1.075 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with water (5 mL) and extracted with EtOAc (3 x 10 mL). The organic extracts were

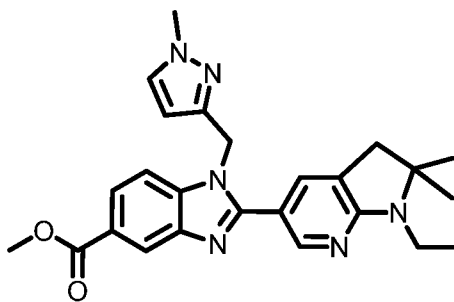
25

combined, dried over MgSO_4 , filtered, and concentrated. Purification by chromatography on SiO_2 (0 to 10% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$) afforded 2-(4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide (57 mg) as a white solid after freeze drying. LC-MS (ES) $m/z = 446$ $[\text{M}+\text{H}]^+$.

- 5 ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 1.20 (t, $J = 6.8$ Hz, 3H), 1.30 (s, 6H), 3.61 (q, $J = 6.8$ Hz, 2H), 3.78 (s, 3H), 3.93 (s, 2H), 5.43 (s, 2H), 6.15 (d, $J = 2.3$ Hz, 1H), 7.27 (br. s., 1H), 7.49 - 7.54 (m, 2H), 7.65 (d, $J = 2.3$ Hz, 1H), 7.77 (dd, $J = 8.5, 1.4$ Hz, 1H), 7.97 (br. s., 1H), 8.22 (d, $J = 1.3$ Hz, 1H), 8.24 (d, $J = 2.0$ Hz, 1H).

10 Intermediate 168

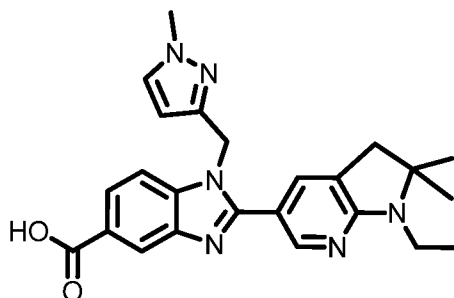
Methyl 2-(1-ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylate



- Methyl 4-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)-3-nitrobenzoate (0.250 g, 0.861 mmol), 1-ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-5-carbaldehyde (0.194 g, 0.947 mmol), ethanol (3 mL), water (1.5 mL), and sodium hydrosulfite (0.450 g, 85%, 2.193 mmol) were added to a 20 mL microwave vial. The vial was capped, and the reaction mixture was heated at 130°C for 90 minutes under microwave conditions. The reaction was diluted with water (10 mL), then extracted with EtOAc (4 x 10 mL). The combined organic layers were washed with brine, then dried over MgSO_4 , filtered, and concentrated. The crude material was purified by silica gel chromatography eluting with a gradient of 0 to 100% EtOAc in CH_2Cl_2 to provide methyl 2-(1-ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylate (259 mg) as a light yellow solid. LC-MS (ES) $m/z = 445$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 8.38 (d, $J = 1.3$ Hz, 1H), 8.20 (d, $J = 2.0$ Hz, 1H), 7.84 (dd, $J = 1.5, 8.6$ Hz, 1H), 7.56 (d, $J = 1.8$ Hz, 1H), 7.27 (d, $J = 8.6$ Hz, 1H), 7.17 (d, $J = 2.3$ Hz, 1H), 5.86 (d, $J = 2.3$ Hz, 1H), 5.34 (s, 2H), 3.83 (s, 3H), 3.76 (s, 3H), 3.28 (q, $J = 7.1$ Hz, 2H), 2.79 (s, 2H), 1.22 (s, 6H), 1.17 (t, $J = 7.1$ Hz, 3H).

Intermediate 169

2-(1-Ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid

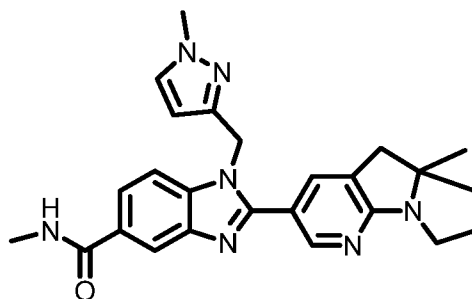


- 5 To a solution of methyl 2-(1-ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylate (0.255 g, 0.574 mmol) in CH₃OH (4 mL) was added 10N aqueous sodium hydroxide solution (1.147 mL, 11.47 mmol), and the reaction mixture was stirred at 45 °C for 2 hours. The reaction was partially concentrated, and then 1N aqueous HCl solution (12.47 mL, 12.47 mmol) was added.
- 10 The resulting white solid was isolated by filtration and then dried in vacuum oven overnight to provide 2-(1-ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid (136 mg, 0.316 mmol) as a white solid. LC-MS (ES) m/z = 431 [M+H]⁺.

15

Example 123

2-(1-Ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide

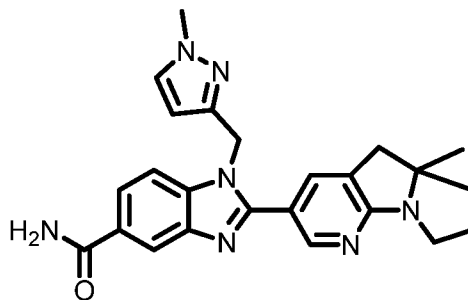


- To a solution of 2-(1-ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid (120 mg, 0.279 mmol) in DMSO (2 mL) were added methylamine hydrochloride (33.9 mg, 0.502 mmol), EDC (107 mg, 0.557 mmol), HOBT hydrate (85 mg, 0.557 mmol), and N-methylmorpholine (0.184 mL, 1.672 mmol), and the reaction mixture was sealed and allowed to stir at room temperature overnight. The reaction was then quenched with saturated aqueous NaHCO₃
- 20

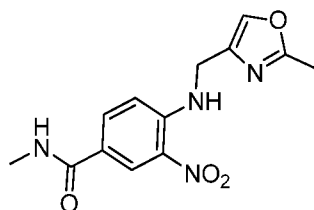
solution (5 mL) and extracted with EtOAc containing 10% CH₃OH (3 x 10 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated. Purification by silica gel chromatography eluting with a gradient of 0 to 15% CH₃OH in CH₂Cl₂ provided 2-(1-ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide (28.6 mg) as a light yellow oil that crystallized upon standing to provide a light yellow solid. LC-MS (ES) m/z = 444 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.26 (s, 1H), 8.12 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.64 (s, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.31 - 7.24 (m, 1H), 6.44 (d, J = 4.3 Hz, 1H), 5.95 (d, J = 1.8 Hz, 1H), 5.44 (s, 2H), 3.89 (s, 3H), 3.39 (q, J = 7.0 Hz, 2H), 3.02 (d, J = 4.8 Hz, 3H), 2.89 (s, 2H), 1.34 (s, 6H), 1.28 (t, J = 7.1 Hz, 3H).

Example 124

2-(1-Ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide



To a solution of 2-(1-ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid (120 mg, 0.279 mmol) in DMSO (2 mL) were added NH₄Cl (26.8 mg, 0.502 mmol), EDC (107 mg, 0.557 mmol), HOBt hydrate (85 mg, 0.557 mmol), and N-methylmorpholine (0.184 mL, 1.672 mmol), and the reaction mixture was sealed and allowed to stir at room temperature overnight. The reaction was quenched with saturated aqueous NaHCO₃ solution (5 mL), then extracted with EtOAc containing 10% CH₃OH (3 x 10 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated. Purification by silica gel chromatography eluting with a gradient of 0 to 15% CH₃OH in CH₂Cl₂ provided 2-(1-ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide (84 mg) as a light yellow oil that crystallized upon standing to provide a light yellow solid. LC-MS (ES) m/z = 430 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 8.26 - 8.21 (m, 2H), 7.84 (dd, J = 1.5, 8.6 Hz, 1H), 7.66 - 7.63 (m, 1H), 7.58 - 7.53 (m, 2H), 6.13 (d, J = 2.3 Hz, 1H), 5.49 (s, 2H), 3.86 (s, 3H), 3.43 (q, J = 7.1 Hz, 2H), 2.98 (s, 2H), 1.38 (s, 6H), 1.27 (t, J = 7.1 Hz, 3H).

Intermediate 170N-Methyl-4-(((2-methyloxazol-4-yl)methyl)amino)-3-nitrobenzamide

5

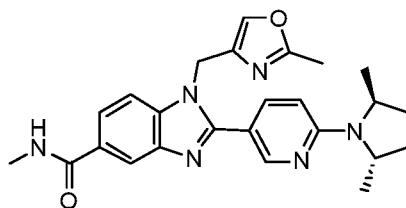
To a solution of 4-fluoro-N-methyl-3-nitrobenzamide (460 mg, 2.321 mmol) and triethylamine (0.356 mL, 2.55 mmol) in DMF (8 mL) at 70 °C was added a solution of (2-methyloxazol-4-yl)methanamine (273 mg, 2.438 mmol) in DMF (2 mL) dropwise, and the reaction mixture was stirred at the same temperature for 15 minutes. The heat was removed, and the reaction was quenched with water (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated. The remaining residue was purified on silica (0-100%, EtOAc/Hexanes) to afford the desired product (535 mg) as a bright yellow-gold solid. LC-MS (ES) m/z = 291 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.68 (t, *J* = 5.7 Hz, 1H), 8.64 (d, *J* = 2.3 Hz, 1H), 8.47 (q, *J* = 4.2 Hz, 1H), 7.96 (dd, *J* = 2.0, 9.1 Hz, 1H), 7.90 (s, 1H), 7.16 (d, *J* = 9.1 Hz, 1H), 4.51 (d, *J* = 5.8 Hz, 2H), 2.76 (d, *J* = 4.3 Hz, 3H), 2.39 (s, 3H).

15

Example 125

2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-methyl-1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide

20



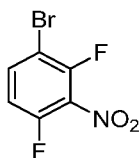
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A solution of N-methyl-4-(((2-methyloxazol-4-yl)methyl)amino)-3-nitrobenzamide (160 mg, 0.551 mmol), 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (118 mg, 0.579 mmol), and sodium hydrosulfite (288 mg, 85%, 1.406 mmol) in ethanol (3 mL) and water (0.75 mL) was heated at 110 °C for 1 hour under microwave conditions. The solids were filtered out, and the reaction was partitioned between CH₂Cl₂ (10 mL) and water (4 mL). The aqueous layer was extracted with CH₂Cl₂ (4 x 8 mL). The combined organic layers were washed with

brine (2 mL), dried over Na₂SO₄, filtered, and concentrated. The remaining residue was taken up in DMSO (1 mL) and precipitated with CH₃OH (6 mL). The solid was collected and dried under high vacuum overnight to afford the title compound (60 mg) as a white solid. LC-MS (ES) *m/z* = 445 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.70 (d, *J* = 2.3 Hz, 1H), 8.42 (q, *J* = 4.5 Hz, 1H), 8.14 (d, *J* = 1.3 Hz, 1H), 8.13 (s, 1H), 8.10 (dd, *J* = 2.4, 9.0 Hz, 1H), 7.73 (dd, *J* = 1.5, 8.6 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 6.66 (d, *J* = 8.9 Hz, 1H), 5.34 (s, 2H), 4.27 (br. s., 2H), 2.81 (d, *J* = 4.3 Hz, 3H), 2.36 (s, 3H), 2.25 (t, *J* = 7.0 Hz, 2H), 1.66 (d, *J* = 5.8 Hz, 2H), 1.15 (d, *J* = 6.3 Hz, 6H).

10 Intermediate 171

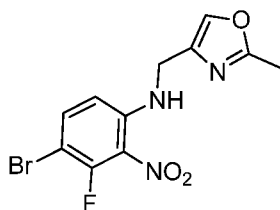
1-Bromo-2,4-difluoro-3-nitrobenzene



A solution of 1,3-difluoro-2-nitrobenzene (6.77 g, 42.6 mmol) and N-bromosuccinimide (7.57 g, 42.6 mmol) in trifluoroacetic acid (TFA) (24 mL) and concentrated sulfuric acid (12.00 mL) was stirred at 70 °C for 1 hour. The reaction was quenched on ice and extracted with EtOAc (3 x 80 mL). The combined organic layers were washed with water (20 mL), saturated aqueous NaHCO₃, dried over Na₂SO₄, filtered, and concentrated. The remaining oil was purified on silica (0-10%, CH₂Cl₂/hexanes) to afford the desired product (6.7 g) as a clear colorless oil. GC-MS (ES) *m/z* = 238, 240 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.18 (ddd, *J* = 5.4, 7.6, 9.3 Hz, 1H), 7.55 (dt, *J* = 1.9, 9.6 Hz, 1H).

Intermediate 172

4-Bromo-3-fluoro-N-((2-methyloxazol-4-yl)methyl)-2-nitroaniline

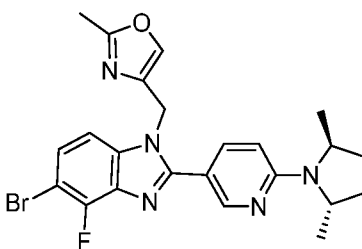


A solution of (2-methyloxazol-4-yl)methanamine (396 mg, 3.53 mmol) in DMF (4 mL) was added dropwise to a solution of 1-bromo-2,4-difluoro-3-nitrobenzene (800 mg, 3.36 mmol) and triethylamine (0.515 mL, 3.70 mmol) in DMF (16 mL) at 70 °C, and the reaction mixture

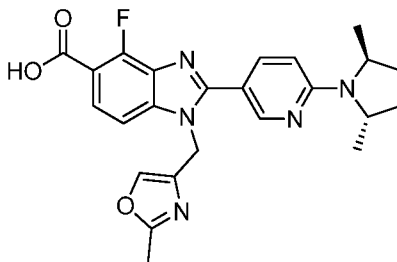
was stirred for 15 minutes at the same temperature. The heat was removed, and the reaction quenched with water (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The remaining residue was purified on silica (0-80%, EtOAc/hexanes) to afford the desired product (337 mg) as a white solid. LC-MS (ES) *m/z* = 230, 232 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.85 (s, 1H), 7.71 (t, *J* = 5.8 Hz, 1H), 7.66 (dd, *J* = 7.6, 9.4 Hz, 1H), 6.84 (d, *J* = 9.4 Hz, 1H), 4.36 (d, *J* = 5.6 Hz, 2H), 2.38 (s, 3H).

Intermediate 173

4-((5-Bromo-2-(6-((2*S*,5*S*)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-1*H*-benzo[d]imidazol-1-yl)methyl)-2-methyloxazole

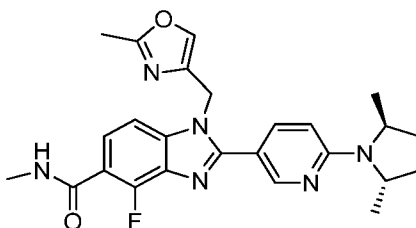


A solution of 4-bromo-3-fluoro-N-((2-methyloxazol-4-yl)methyl)-2-nitroaniline (330 mg, 1.00 mmol), 6-((2*S*,5*S*)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (214 mg, 1.050 mmol), and sodium hydrosulfite (522 mg, 85%, 2.55 mmol) in ethanol (6 mL) and water (1.500 mL) was heated at 110 °C for 1 hour under microwave conditions. The solids were filtered out and the organic solvent removed in-vacuo. The remaining residue was partitioned between CH₂Cl₂ (10 mL) and water (4 mL). The aqueous layer was extracted with CH₂Cl₂ (2X), and the combined organic layers were washed with brine (3 mL), dried over Na₂SO₄, filtered, and concentrated. The remaining residue was purified on silica (0-100%, EtOAc/hexanes) to afford the desired product (322 mg) as a tan foam. LC-MS (ES) *m/z* = 484, 486 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.69 (d, *J* = 2.3 Hz, 1H), 8.11 (s, 2H), 7.41 (s, 2H), 6.66 (d, *J* = 9.1 Hz, 1H), 5.35 (s, 2H), 4.15 - 3.99 (m, *J* = 5.6 Hz, 1H), 2.36 (s, 3H), 2.25 (t, *J* = 7.7 Hz, 2H), 1.66 (d, *J* = 5.6 Hz, 2H), 1.15 (d, *J* = 6.3 Hz, 6H).

Intermediate 1742-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid

- 5 N-Methyl-2-pyrrolidone (NMP) (10 mL) was degassed by bubbling N₂, then charged with 4-((5-bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-1H-benzo[d]imidazol-1-yl)methyl)-2-methyloxazole (322 mg, 0.665 mmol), potassium 2-ethoxy-2-oxoacetate (156 mg, 0.997 mmol), 1,3-bis(diphenylphosphino)propane (82 mg, 0.199 mmol), and palladium(II) trifluoroacetate (44.2 mg, 0.133 mmol), and the reaction mixture
- 10 was stirred at 150 °C for 6 hours. After cooling to room temperature, the reaction was filtered through celite and rinsed with EtOAc (2 x 10 mL). The filtrate was concentrated in-vacuo, and the remaining oil was partitioned between EtOAc (30 mL) and 1N Na₂CO₃. The aqueous layer was extracted with EtOAc (3 x 15 mL), and the combined organic extracts were concentrated in-vacuo. The resulting residue was dissolved in CH₃OH (2 mL), then
- 15 purified by reverse phase HPLC (50-99% CH₃CN/0.1% NH₄OH in water) to afford the desired product (63 mg) as a tan foam. LC-MS (ES) m/z = 450 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 10.02 (br. s., 1H), 8.74 (br. s., 1H), 8.09 (br. s., 1H), 7.86 (br. s., 1H), 7.47 (br. s., 1H), 7.21 (d, J = 7.1 Hz, 1H), 6.62 (br. s., 1H), 5.45 - 5.24 (m, 2H), 3.50 (br. s., 2H), 2.45 (br. s., 3H), 2.31 (br. s., 2H), 1.74 (br. s., 2H), 1.23 (br. s., 6H).

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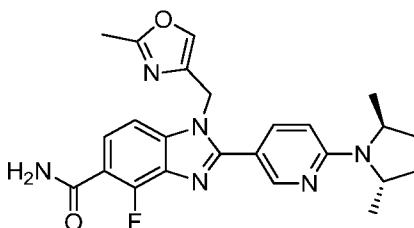
Example 1262-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-N-methyl-1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide

- 25 To a solution of 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid (62 mg, 0.138 mmol) in

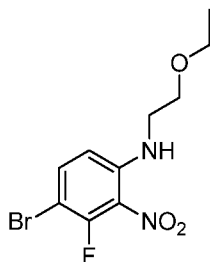
DMSO (2 mL) were added EDC (52.9 mg, 0.276 mmol), HOAT (42.5 mg, 0.276 mmol), and N-methylmorpholine (0.091 mL, 0.828 mmol) followed by methanamine hydrochloride (9.31 mg, 0.138 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction was purified by reverse phase HPLC (15-55% CH₃CN/0.1% formic acid in water) to afford the desired product (37 mg) as a white solid. LC-MS (ES) m/z = 463 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.61 (d, J = 2.3 Hz, 1H), 8.07 - 7.92 (m, 2H), 7.33 (s, 1H), 7.22 (d, J = 8.6 Hz, 1H), 6.89 (dd, J = 4.7, 12.5 Hz, 1H), 6.52 (d, J = 8.9 Hz, 1H), 5.31 (s, 2H), 4.30 (br. s., 2H), 3.10 (d, J = 4.3 Hz, 3H), 2.48 (s, 3H), 2.38 - 2.22 (m, 2H), 1.72 (d, J = 5.8 Hz, 2H), 1.22 (d, J = 6.1 Hz, 6H).

Example 127

2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide

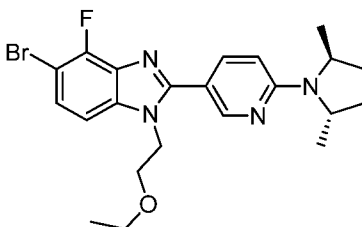


To a solution of 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid (55 mg, 0.122 mmol) in DMSO (2 mL) were added EDC (46.9 mg, 0.245 mmol), HOAT (37.7 mg, 0.245 mmol), and N-methylmorpholine (0.081 mL, 0.734 mmol) followed by NH₄Cl (11.78 mg, 0.220 mmol), and the reaction mixture was stirred at room temperature overnight. The solids were filtered out and the reaction solution was purified by reverse phase HPLC (15-55% CH₃CN/0.1% formic acid in water) to afford the desired product (24 mg) as a solid. LC-MS (ES) m/z = 449 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.66 (br. s., 1H), 8.05 (dd, J = 6.8, 8.6 Hz, 2H), 7.38 (br. s., 1H), 7.27 (d, J = 8.6 Hz, 1H), 6.87 (d, J = 11.2 Hz, 1H), 6.56 (d, J = 8.9 Hz, 1H), 5.95 (br. s., 1H), 5.34 (s, 2H), 4.31 (br. s., 2H), 2.50 (s, 3H), 2.39 - 2.26 (m, 2H), 1.76 (d, J = 5.6 Hz, 2H), 1.25 (d, J = 6.3 Hz, 6H).

Intermediate 1754-Bromo-N-(2-ethoxyethyl)-3-fluoro-2-nitroaniline

To a solution of N-(2-ethoxyethyl)-3-fluoro-2-nitroaniline (3.25 g, 14.24 mmol) in DMF (100 mL) at 0 °C under an inert atmosphere was added 1-bromopyrrolidine-2,5-dione (2.53 g, 14.24 mmol), and the reaction mixture was stirred at room temperature for 30 minutes. The reaction was poured into stirring water (300 mL), and the resulting precipitate was extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (15 mL), dried over Na₂SO₄, filtered, and concentrated. The remaining oil was purified on silica (0-30% EtOAc/hexanes) to afford the desired product (3.57 g) as a yellow solid. LC-MS (ES) m/z = 309 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.68 (dd, *J* = 7.6, 9.3 Hz, 1H), 7.39 (t, *J* = 5.3 Hz, 1H), 6.87 (dd, *J* = 1.7, 9.6 Hz, 1H), 3.53 -3.61 (m, 2H), 3.40 - 3.51 (m, 4H), 1.08 - 1.16 (m, 3H).

15

Example 1285-Bromo-2-(6-((2*S*,5*S*)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-4-fluoro-1*H*-benzo[d]imidazole

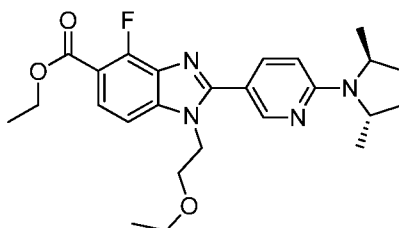
A solution of 4-bromo-N-(2-ethoxyethyl)-3-fluoro-2-nitroaniline (450 mg, 1.465 mmol) in ethanol (8 mL) and water (2 mL) was charged with sodium hydrosulfite (765 mg, 85%, 3.74 mmol), and the reaction mixture was stirred at 110 °C under microwave conditions for 60 minutes. The solids were filtered out and the remaining residue was partitioned between CH₂Cl₂ (60 mL) and water (10 mL). The aqueous layer was extracted with CH₂Cl₂ (2 x 15 mL), and the combined organic extracts were washed with brine (3 mL), dried over Na₂SO₄, filtered, and concentrated onto silica. The silica adsorbed residue was purified by flash chromatography (0-100% EtOAc/hexanes) to afford the desired product (1.04 g) as a pale

yellow solid. LC-MS (ES) m/z = 461, 463 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 8.56 (d, J = 2.2 Hz, 1H), 7.97 (dd, J = 2.5, 8.87 Hz, 1H), 7.32 - 7.63 (m, 2H), 6.63 (d, J = 8.8 Hz, 1H), 4.46 (t, J = 5.2 Hz, 2H), 3.74 (t, J = 5.2 Hz, 2H), 3.27 - 3.34 (m, 4H), 2.25 (t, J = 6.8 Hz, 2H), 1.66 (d, J = 5.5 Hz, 2H), 1.15 (d, J = 6.0 Hz, 6H), 0.95 (t, J = 6.9 Hz, 3H).

5

Intermediate 176

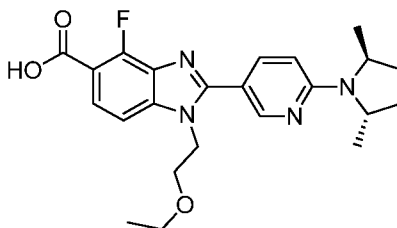
Ethyl 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-4-fluoro-1H-benzo[d]imidazole-5-carboxylate



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A solution of 5-bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-4-fluoro-1H-benzo[d]imidazole (584mg, 0.886 mmol) in N-methyl-2-pyrrolidone (NMP) (2 mL) was charged with potassium 2-ethoxy-2-oxoacetate (208 mg, 1.329 mmol), 1,3-bis(diphenylphosphino)propane (54.8 mg, 0.133 mmol), and palladium(II) trifluoroacetate (29.5 mg, 0.089 mmol) under an inert atmosphere, and the reaction mixture was stirred at 150 °C for 18 hours. The reaction was cooled to room temperature and filtered through celite. The filtrate was washed with EtOAc (2 x 10 mL). The solvent was concentrated in-vacuo and the remaining oil was partitioned between EtOAc (30 mL) and 1N Na₂CO₃. The aqueous layer was extracted with EtOAc (3 x 15 mL), and combined organic extracts were concentrated in-vacuo. The resulting residue purified by reverse phase HPLC (50-99% CH₃CN/0.1% NH₄OH in water) to afford the desired product (100 mg) as a tan foam. LC-MS (ES) m/z = 455 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 8.57 (d, J = 2.3 Hz, 1H), 7.98 (dd, J = 2.4, 9.0 Hz, 1H), 7.74 (dd, J = 6.3, 8.4 Hz, 1H), 7.59 (d, J = 8.6 Hz, 1H), 6.64 (d, J = 8.9 Hz, 1H), 4.48 (t, J = 5.2 Hz, 2H), 4.35 (q, J = 7.1 Hz, 2H), 3.75 (t, J = 5.2 Hz, 2H), 3.30 (d, J = 7.1 Hz, 2H), 2.29 - 2.19 (m, 2H), 1.66 (d, J = 6.3 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H), 1.15 (d, J = 6.3 Hz, 6H), 0.94 (t, J = 7.0 Hz, 3H).

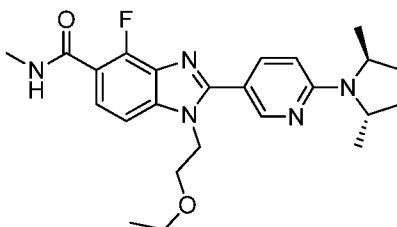
25

Intermediate 1772-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-4-fluoro-1H-benzo[d]imidazole-5-carboxylic acid

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To a solution of ethyl 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-4-fluoro-1H-benzo[d]imidazole-5-carboxylate (95 mg, 0.209 mmol) in ethanol (2 mL) and water (0.667 mL) was added 5N NaOH (0.627 mL, 3.13 mmol), and the reaction mixture was stirred at 98 °C for 1 hour. The organic solvent was removed in-vacuo and the pH of the aqueous was adjusted to ~2 with 6N HCl (0.488 mL, 2.93 mmol) at 0 °C. The solid was collected, washed with water (2 mL), and dried under vacuum to afford the desired product (91 mg) as a white solid. LC-MS (ES) m/z = 427 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 8.57 (d, J = 2.0 Hz, 1H), 8.24 (br. s., 1H), 7.79 (dd, J = 6.5, 8.5 Hz, 1H), 7.62 (d, J = 8.6 Hz, 1H), 7.09 (br. s., 1H), 4.51 (t, J = 5.1 Hz, 2H), 4.47 - 4.33 (m, 2H), 3.76 (t, J = 5.1 Hz, 2H), 3.33 (dq, J = 1.4, 7.0 Hz, 2H), 2.34 - 2.28 (m, 2H), 1.74 (d, J = 5.8 Hz, 2H), 1.19 (d, J = 6.3 Hz, 6H), 0.96 (t, J = 7.1 Hz, 3H).

20

Example 1292-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-4-fluoro-N-methyl-1H-benzo[d]imidazole-5-carboxamide

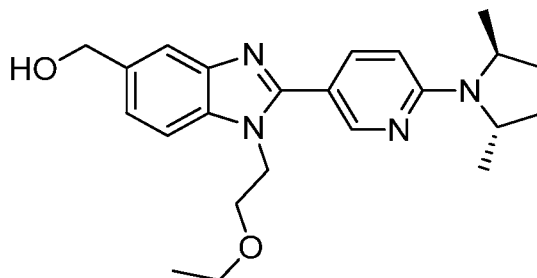
To a solution of 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-4-fluoro-1H-benzo[d]imidazole-5-carboxylic acid (61 mg, 0.143 mmol) in DMF (2 mL) were added HATU (65.3 mg, 0.172 mmol) and triethylamine (0.080 mL, 0.572 mmol), and the resulting mixture was stirred at room temperature for 20 minutes. Methanamine hydrochloride (14.49 mg, 0.215 mmol) was then added, and the reaction mixture was stirred

overnight. After reaction completion the solids were collected and washed with CH₂Cl₂ (3 mL). The combined organic solvents were removed in-vacuo, and the remaining residue was purified via reverse phase HPLC (30-85% CH₃CN/0.1%NH₄OH in water) to afford the desired product (18 mg) as a glassy solid. LC-MS (ES) m/z = 440 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.56 (d, *J* = 2.3 Hz, 1H), 8.24 - 8.15 (m, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.58 - 7.46 (m, 2H), 6.65 (d, *J* = 8.6 Hz, 1H), 4.47 (t, *J* = 5.1 Hz, 2H), 4.28 (br. s., 2H), 3.74 (t, *J* = 5.1 Hz, 2H), 3.30 (q, *J* = 6.8 Hz, 2H), 2.82 (d, *J* = 4.3 Hz, 3H), 2.25 (t, *J* = 7.9 Hz, 2H), 1.66 (d, *J* = 5.6 Hz, 2H), 1.15 (d, *J* = 6.1 Hz, 6H), 0.95 (t, *J* = 7.1 Hz, 3H).

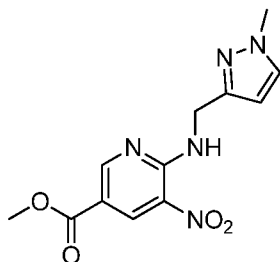
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Example 130

(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)methanol



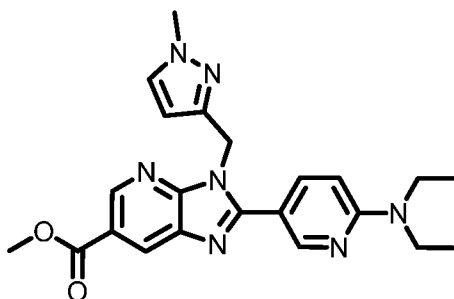
To a solution of 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-4-fluoro-1H-benzo[d]imidazole-5-carboxylic acid (61 mg, 0.143 mmol) in THF (0.5 mL) at 0 °C was added LiAlH₄ (0.143 mL, 0.286 mmol), and the reaction mixture was stirred for 2 hours. Saturated aqueous Na₂SO₄ (0.05 mL) was then added, and the resulting mixture was stirred for 20 minutes followed with filtration. The precipitate was washed with EtOAc (2 x 8 mL). The combined organic solvents were removed in-vacuo, and the remaining residue was purified via reverse phase HPLC (30-85% CH₃CN/ 0.1%NH₄OH in water) to afford the desired product (12 mg) as a thin film on glass. LC-MS (ES) m/z = 395 [M+H]⁺. ¹H NMR (400MHz, CDCl₃): δ 8.57 (d, *J* = 2.0 Hz, 1H), 7.94 (dd, *J* = 2.5, 8.9 Hz, 1H), 7.78 (s, 1H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.34 (dd, *J* = 1.5, 8.4 Hz, 1H), 6.51 (d, *J* = 8.9 Hz, 1H), 4.83 (s, 2H), 4.43 (t, *J* = 5.7 Hz, 2H), 4.30 (br. s., 2H), 3.85 (t, *J* = 5.8 Hz, 2H), 3.45 (q, *J* = 7.1 Hz, 2H), 2.36 - 2.22 (m, 2H), 1.77 - 1.68 (m, 2H), 1.23 (d, *J* = 6.3 Hz, 6H), 1.15 (t, *J* = 7.0 Hz, 3H).

Intermediate 178Methyl 6-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)-5-nitronicotinate

To a solution of methyl 6-chloro-5-nitronicotinate (900 mg, 4.16 mmol) in CH₂Cl₂ (20 mL)
 5 were added (1-methyl-1H-pyrazol-3-yl)methanamine (462 mg, 4.16 mmol) and N,N-diisopropylethylamine (0.944 mL, 5.40 mmol), and the mixture was stirred at room temperature for 20 hours. The mixture was concentrated and the residue was washed with water and dried under vacuum to give the desired product (1.10 g) as a pale yellow solid. LC-MS (ES) m/z = 292 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 3.94 - 3.99 (m, 6H), 4.89 -
 10 4.98 (m, 2H), 6.28 (d, J = 2.3 Hz, 1H), 7.38 (d, J = 2.3 Hz, 1H), 8.95 (br. s., 1H), 9.05 - 9.09 (m, 2H).

Intermediate 179Methyl 2-(6-(diethylamino)pyridin-3-yl)-3-(((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxylate

15

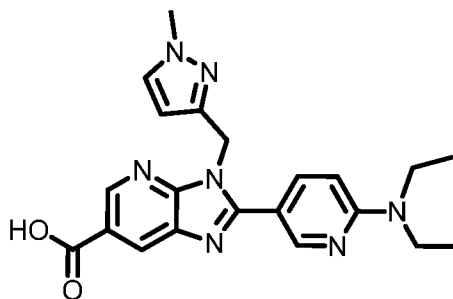


Methyl 6-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)-5-nitronicotinate (0.150 g, 0.515 mmol), 6-(diethylamino)nicotinaldehyde (0.101 g, 0.566 mmol), ethanol (3 mL), water (1.5 mL), and sodium hydrosulfite (0.269 g, 85%, 1.313 mmol) were combined in a microwave
 20 vial. The vial was sealed, and the reaction mixture was heated at 130 °C for 90 minutes under microwave conditions. The reaction was diluted with water (10 mL), then extracted with EtOAc (4 x 5 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, then concentrated. The crude material was purified by silica gel chromatography using a gradient of 0 to 10% CH₃OH in CH₂Cl₂ to provide methyl 2-(6-(diethylamino)pyridin-3-yl)-3-(((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-
 25

b]pyridine-6-carboxylate (0.200 g) as a light yellow solid. LC-MS (ES) m/z = 420 $[M+H]^+$.
 ^1H NMR (400 MHz, DMSO- d_6): δ 8.90 (d, J = 2.0 Hz, 1H), 8.66 (d, J = 2.3 Hz, 1H), 8.48 (d, J = 2.0 Hz, 1H), 8.08 (dd, J = 2.5, 9.1 Hz, 1H), 7.61 (d, J = 2.3 Hz, 1H), 6.75 (d, J = 9.1 Hz, 1H), 6.09 (d, J = 2.3 Hz, 1H), 5.55 (s, 2H), 3.91 (s, 3H), 3.75 (s, 3H), 3.57 (q, J = 6.9 Hz, 4H), 1.14 (t, J = 7.0 Hz, 6H).

Intermediate 180

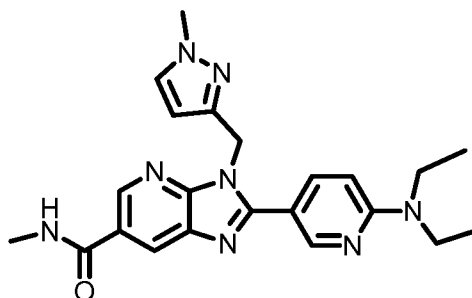
2-(6-(Diethylamino)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid



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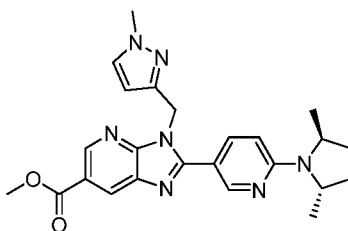
To a solution of methyl 2-(6-(diethylamino)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxylate (0.200 g, 0.477 mmol) in CH_3OH (4 mL) was added 10N aqueous sodium hydroxide solution (0.954 mL, 9.54 mmol), and the reaction mixture was stirred at 45 °C for 2 hours. The reaction was partially concentrated, then 1N aqueous HCl solution (10.54 mL, 10.54 mmol) was added. The resulting mixture was filtered, the white solid was discarded, and the filtrate was concentrated. Purification by silica gel chromatography eluting with a gradient from 0 to 15% CH_3OH in CH_2Cl_2 provided 2-(6-(diethylamino)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid (149 mg, 0.367 mmol) as a white solid. LC-MS (ES) m/z = 406 $[M+H]^+$.

20

Example 131**2-(6-(Diethylamino)pyridin-3-yl)-N-methyl-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide**

- 5 To a solution of 2-(6-(diethylamino)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid (120 mg, 0.296 mmol) in DMSO (2 mL) were added methylamine hydrochloride (36.0 mg, 0.533 mmol), EDC (113 mg, 0.592 mmol), HOBt hydrate (91 mg, 0.592 mmol), and N-methylmorpholine (0.195 mL, 1.776 mmol), and the reaction mixture was sealed and allowed to stir at room temperature overnight. The reaction
- 10 was quenched with saturated aqueous NaHCO₃ solution (5 mL), then extracted with EtOAc containing 10% CH₃OH (3 x 10 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated. Purification by silica gel chromatography eluting with 0 to 15% CH₃OH in CH₂Cl₂ provided 2-(6-(diethylamino)pyridin-3-yl)-N-methyl-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide (105.9 mg, 0.253 mmol)
- 15 as a colorless oil that crystallized upon standing to provide a white solid. LC-MS (ES) m/z = 419 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.79 (d, *J* = 1.8 Hz, 1H), 8.65 (d, *J* = 2.3 Hz, 1H), 8.60 (d, *J* = 4.6 Hz, 1H), 8.43 (d, *J* = 1.8 Hz, 1H), 8.07 (dd, *J* = 2.4, 9.0 Hz, 1H), 7.61 (d, *J* = 2.0 Hz, 1H), 6.75 (d, *J* = 9.1 Hz, 1H), 6.07 (d, *J* = 2.3 Hz, 1H), 5.53 (s, 2H), 3.76 (s, 3H), 3.57 (q, *J* = 6.9 Hz, 4H), 2.84 (d, *J* = 4.6 Hz, 3H), 1.15 (t, *J* = 7.0 Hz, 6H).

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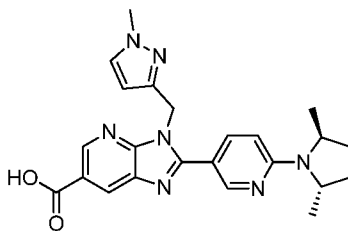
Intermediate 181**Methyl 2-(6-(((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxylate**

- 25 Into microwave vial were added methyl 6-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)-5-nitronicotinate (157 mg, 0.539 mmol), 6-((2S,5S)-2,5-dimethylpyrrolidin-1-

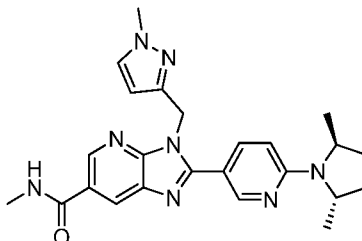
yl)nicotinaldehyde (121 mg, 0.593 mmol), ethanol (3 mL), water (1.5 mL), and sodium hydrosulfite (282 mg, 85%, 1.374 mmol), and the reaction mixture was heated at 130 °C for 1.5 hours under microwave conditions. The reaction was then diluted with water (10 mL) and extracted with EtOAc (4 x 20 mL). The organic extracts were combined, washed with
 5 brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ (0 to 70% EtOAc/hexanes) afforded methyl 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxylate (130 mg) as a yellow oil. LC-MS (ES) m/z = 446 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.14 (d, *J* = 6.3 Hz, 6H), 1.65 (d, *J* = 5.1 Hz, 2H), 2.24 (br. s., 2H), 3.75 (s, 3H), 3.92 (s, 3H), 4.26 (br. s., 2H), 5.56 (s, 2H), 6.08 (d, *J* = 2.3 Hz, 1H), 6.64 (d, *J* = 9.1 Hz, 1H), 7.61 (d, *J* = 2.3 Hz, 1H), 8.07 (dd, *J* = 9.0, 2.4 Hz, 1H), 8.49 (d, *J* = 1.8 Hz, 1H), 8.67 (d, *J* = 2.3 Hz, 1H), 8.90 (d, *J* = 1.8 Hz, 1H).

Intermediate 182

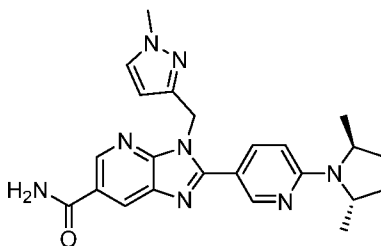
15 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid



To methyl 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxylate (130 mg, 0.292 mmol) in CH₃OH (5 mL)
 20 was added 10N NaOH (0.584 mL, 5.84 mmol), and the reaction mixture was stirred overnight at room temperature. The reaction was concentrated and diluted with water (10 mL) followed by 6N HCl (0.973 mL, 5.84 mmol). The resulting mixture was extracted with EtOAc (4 x 10 mL), and the organic extracts were then combined, washed with brine, dried over MgSO₄, filtered, and concentrated to afford 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid (115 mg) as a light yellow solid. LC-MS (ES) m/z = 432 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.14 (d, *J* = 6.3 Hz, 6H), 1.66 (d, *J* = 5.3 Hz, 2H), 2.24 (br. s., 2H), 3.75 (s, 3H), 4.26 (br. s., 2H), 5.56 (s, 2H), 6.07 (d, *J* = 2.0 Hz, 1H), 6.65 (d, *J* = 9.1 Hz, 1H), 7.61 (d, *J* = 2.3 Hz, 1H), 8.04 - 8.09 (m, 1H), 8.46 (d, *J* = 1.8 Hz, 1H), 8.67 (d, *J* = 2.3 Hz,
 25 1H), 8.89 (d, *J* = 1.8 Hz, 1H), 13.17 (br. s., 1H).

Example 132**2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-methyl-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide**

- 5 To 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid (66 mg, 0.153 mmol) in DMSO (2 mL) were added methylamine hydrochloride (15.49 mg, 0.229 mmol), EDC (58.6 mg, 0.306 mmol), HOBt (46.8 mg, 0.306 mmol), and N-methylmorpholine (0.118 mL, 1.071 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction was then
- 10 dilute with water (5 mL) and extracted with EtOAc (3 x 10 mL). The organic extracts were combined, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ (0 to 10% CH₃OH/CH₂Cl₂) afforded 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-methyl-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide (54 mg) as a white solid after freeze drying. LC-MS (ES) m/z = 445 [M+H]⁺.
- 15 ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.14 (d, *J* = 6.1 Hz, 6H), 1.65 (d, *J* = 5.3 Hz, 2H), 2.23 (br. s., 2H), 2.84 (d, *J* = 4.6 Hz, 3H), 3.75 (s, 3H), 4.25 (br. s., 2H), 5.54 (s, 2H), 6.06 (d, *J* = 2.3 Hz, 1H), 6.63 (d, *J* = 8.9 Hz, 1H), 7.61 (d, *J* = 2.0 Hz, 1H), 8.06 (dd, *J* = 9.0, 2.4 Hz, 1H), 8.43 (d, *J* = 2.0 Hz, 1H), 8.60 (d, *J* = 4.6 Hz, 1H), 8.66 (d, *J* = 2.3 Hz, 1H), 8.79 (d, *J* = 1.8 Hz, 1H).
- 20

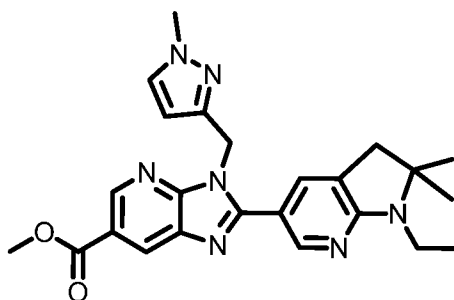
Example 133**2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide**

- 25 To 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid (51 mg, 0.118 mmol) in DMSO (2

mL) were added NH_4Cl (11.38 mg, 0.213 mmol), EDC (45.3 mg, 0.236 mmol), HOBt (36.2 mg, 0.236 mmol), and N-methylmorpholine (0.078 mL, 0.709 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with water (5 mL) and extracted with EtOAc (3 x 10 mL). The organic extracts were combined, washed with brine, dried over MgSO_4 , filtered, and concentrated. Purification by chromatography on SiO_2 (0 to 10% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$) afforded 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide (38 mg) as a white solid after freeze drying. LC-MS (ES) $m/z = 431$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 1.14 (d, $J = 6.01$ Hz, 6H), 1.65 (m, $J = 5.6$ Hz, 2H), 2.17 - 2.28 (m, 2H), 3.75 (s, 3H), 4.25 (br. s., 2H), 5.54 (s, 2H), 6.06 (d, $J = 2.3$ Hz, 1H), 6.63 (d, $J = 9.1$ Hz, 1H), 7.51 (s, 1H), 7.61 (d, $J = 2.3$ Hz, 1H), 8.06 (dd, $J = 9.0, 2.41$ Hz, 1H), 8.14 (s, 1H), 8.48 (d, $J = 1.8$ Hz, 1H), 8.66 (d, $J = 2.5$ Hz, 1H), 8.83 (d, $J = 1.8$ Hz, 1H).

Intermediate 183

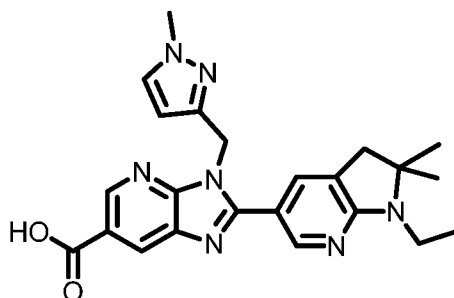
Methyl 2-(1-ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-5-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxylate



Methyl 6-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)-5-nitronicotinate (0.150 g, 0.515 mmol), 1-ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-5-carbaldehyde (0.116 g, 0.566 mmol), ethanol (3 mL), water (1.500 mL), and sodium hydrosulfite (0.269 g, 85%, 1.313 mmol) were combined in a 20 mL microwave vial. The mixture was then capped and heated at 130 °C for 90 minutes under microwave conditions. The reaction was diluted with water (10 mL), then extracted with EtOAc (4 x 10 mL). The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated. The crude material was purified by silica gel chromatography eluting with a gradient of 0 to 100% EtOAc in CH_2Cl_2 to provide methyl 2-(1-ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-5-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxylate (0.151 g) as a slightly impure light yellow solid. LC-MS (ES) $m/z = 446$ $[\text{M}+\text{H}]^+$.

Intermediate 184

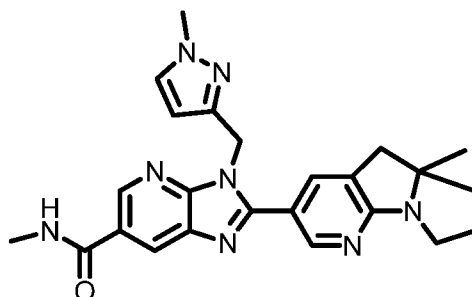
2-(1-Ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid



- 5 To a solution of methyl 2-(1-ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxylate (0.151 g, 0.339 mmol) in CH₃OH (4 mL) was added 10N aqueous NaOH solution (0.678 mL, 6.78 mmol), and the reaction mixture was stirred at 45 °C for 2 hours. The reaction was partially concentrated, 1N aqueous HCl solution (7.78 mL, 7.78 mmol) was then added, and the
- 10 resulting mixture was filtered. The filtrate was concentrated, and the resulting residue was purified by silica gel chromatography eluting with a gradient of 0 to 15% CH₃OH in CH₂Cl₂ to provide 2-(1-ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid (121 mg) as a white solid. LC-MS (ES) m/z = 432 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 9.15 (d, J = 1.8 Hz, 1H), 8.70 (s, 1H), 8.69 (d, J = 1.8 Hz, 1H), 8.06 (s, 1H), 7.63 (d, J = 2.3 Hz, 1H), 6.48 (d, J = 2.3 Hz, 1H), 5.76 (s, 2H), 3.90 (s, 3H), 3.75 (q, J = 7.3 Hz, 2H), 3.31 (s, 2H), 1.59 (s, 6H), 1.42 (t, J = 7.2 Hz, 3H).
- 15

Example 134

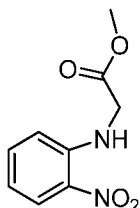
- 20 2-(1-Ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-methyl-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide



To a solution of 2-(1-ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid (115 mg,

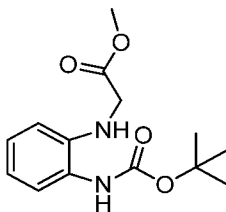
0.267 mmol) in DMSO (2 mL) were added NH_4Cl (25.7 mg, 0.480 mmol), EDC (102 mg, 0.533 mmol), HOBt (82 mg, 0.533 mmol), and N-methylmorpholine (0.176 mL, 1.599 mmol), and the reaction mixture was stirred at room temperature overnight in a sealed vessel. The reaction was quenched with saturated aqueous NaHCO_3 solution (5 mL) and then extracted with 10% CH_3OH in EtOAc (3 x 10 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated. Purification by silica gel chromatography eluting with a gradient of 0 to 25% CH_3OH in CH_2Cl_2 provided 2-(1-ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-methyl-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide (93.7 mg) as a colorless oil that crystallized upon standing to provide a white solid. LC-MS (ES) $m/z = 445$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.78 (d, $J = 2.0$ Hz, 1H), 8.59 (d, $J = 4.3$ Hz, 1H), 8.40 (d, $J = 1.8$ Hz, 1H), 8.36 (d, $J = 1.8$ Hz, 1H), 7.77 (d, $J = 1.8$ Hz, 1H), 7.61 (d, $J = 2.3$ Hz, 1H), 6.06 (d, $J = 2.3$ Hz, 1H), 5.51 (s, 2H), 3.76 (s, 3H), 3.38 - 3.30 (m, 2H), 2.90 (s, 2H), 2.84 (d, $J = 4.6$ Hz, 3H), 1.30 (s, 6H), 1.19 (t, $J = 7.1$ Hz, 3H).

15

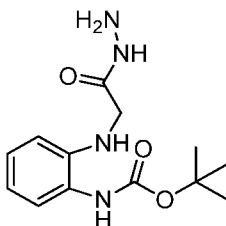
Intermediate 185Methyl 2-((2-nitrophenyl)amino)acetate

A mixture of 1-fluoro-2-nitrobenzene (2.82 g, 19.99 mmol) and methyl 2-aminoacetate (2.137 g, 23.98 mmol) in DMF (60 mL) was stirred at 60 °C for 12 hours. The mixture was concentrated under vacuum, and the resulting residue was treated with water (30 mL) and extracted by EtOAc (2x). The combined organic layers were concentrated, and the resulting residue was purified by silica gel chromatography (0 to 40% EtOAc/hexanes) to give the desired product (3.4 g) as a yellow solid. LC-MS (ES) $m/z = 211$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 8.40 (s, 1H), 8.22 (d, $J = 8.5$ Hz, 1H), 7.47 (t, $J = 7.8$ Hz, 1H), 6.77 – 6.66 (m, 2H), 4.12 (s, 2H), 3.83 (s, 3H).

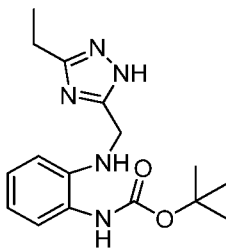
25

Intermediate 186Methyl 2-((2-((tert-butoxycarbonyl)amino)phenyl)amino)acetate

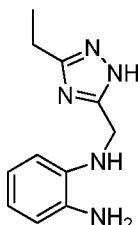
A mixture of methyl 2-((2-nitrophenyl)amino)acetate (1.05 g, 5.00 mmol), di-*tert*-butyl
 5 dicarbonate (2.181 g, 9.99 mmol), and palladium on carbon (10%, 0.106 g) in CH₃OH (30 mL) was stirred at 25 °C for 12 hours under a hydrogen atmosphere. The reaction mixture was filtered to remove the catalyst, and the filtrate was concentrated. The resulting residue was purified by silica gel chromatography (0 to 3.5% CH₃OH/CH₂Cl₂) to give the desired product (798 mg) as a white solid. LC-MS (ES) *m/z* = 281 [M+H]⁺. ¹H NMR (400 MHz,
 10 CDCl₃): δ 7.36 (d, *J* = 7.0 Hz, 1H), 7.12 – 7.03 (m, 1H), 6.82 (t, *J* = 7.4 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 3.92 (s, 2H), 3.79 (s, 3H), 1.54 – 1.50 (m, 9H).

Intermediate 187*tert*-Butyl (2-((2-hydrazinyl-2-oxoethyl)amino)phenyl)carbamate (N60912-66-A1)

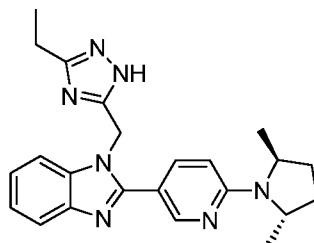
15 A mixture of methyl 2-((2-((tert-butoxycarbonyl)amino)phenyl)amino)acetate (798 mg, 2.85 mmol) and hydrazine (0.279 mL, 5.69 mmol) in ethanol (25 mL) was stirred at 80 °C for 12 hours. The reaction mixture was concentrated, and the resulting residue was purified by silica gel chromatography (0 to 8.5% CH₃OH/CH₂Cl₂) to give the desired product (500 mg)
 20 as a white solid. LC-MS (ES) *m/z* = 281 [M+H]⁺.

Intermediate 188tert-Butyl (2-(((3-ethyl-1H-1,2,4-triazol-5-yl)methyl)amino)phenyl)carbamate

A mixture of tert-butyl (2-((2-hydrazinyl-2-oxoethyl)amino)phenyl)carbamate (500 mg, 1.784 mmol), sodium ethanolate (364 mg, 5.35 mmol), and ethyl propionimidate-hydrochloride (491 mg, 3.57 mmol) in ethanol (25 mL) was stirred at 90 °C for 12 hours. The mixture was concentrated, and the resulting residue was treated with water (20 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The resulting residue was purified by silica gel chromatography (0 to 4% CH₃OH/CH₂Cl₂) to give the desired product (468 mg) as a yellow solid. LC-MS (ES) m/z = 318 [M+H]⁺.

Intermediate 189N1-((3-Ethyl-1H-1,2,4-triazol-5-yl)methyl)benzene-1,2-diamine

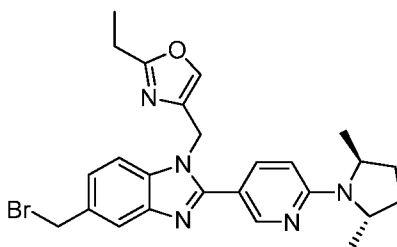
A mixture of HCl (33% in ethanol, 3.81 mL, 18.27 mmol) and tert-butyl (2-(((3-ethyl-1H-1,2,4-triazol-5-yl)methyl)amino)phenyl)carbamate (580 mg, 1.827 mmol) in CH₂Cl₂ (25 mL) was stirred at 25 °C for 4 hours. The mixture was concentrated under vacuum, and the resulting residue was treated with EtOAc (20 mL) and washed with saturated aqueous NaHCO₃ (20 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated to afford the desired product (270 mg) as a yellow oil. LC-MS (ES) m/z = 218 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 6.83 – 6.76 (m, 1H), 6.70 (d, J = 3.6 Hz, 2H), 6.66 (d, J = 7.8 Hz, 1H), 5.35 – 5.0 (m, 3H), 4.42 (s, 2H), 2.76 (q, J = 7.6 Hz, 2H), 1.31 (t, J = 7.6 Hz, 3H).

Example 135**2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((3-ethyl-1H-1,2,4-triazol-5-yl)methyl)-1H-benzo[d]imidazole**

5

A mixture of N1-((3-ethyl-1H-1,2,4-triazol-5-yl)methyl)benzene-1,2-diamine (270 mg, 1.243 mmol), 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (305 mg, 1.491 mmol), and sodium metabisulfite (307 mg, 1.615 mmol) in DMF (15 mL) was stirred at 80 °C for 12 hours. The mixture was concentrated under vacuum, and the resulting residue was purified by silica gel chromatography (0 to 3.5% CH₃OH/CH₂Cl₂) to give the desired product (170 mg) as a white solid. LC-MS (ES) m/z = 402 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.65 (br s, 1H), 8.71 (d, *J* = 1.9 Hz, 1H), 8.13 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.65 – 7.59 (m 1H), 7.59 – 7.49 (m, 1H), 7.23 – 7.17 (m, 2H), 6.63 (d, *J* = 8.9 Hz, 1H), 5.39 (s, 2H), 4.37 – 4.05 (m, 2H), 2.70 (q, *J* = 7.6 Hz, 2H), 2.30 – 2.18 (m, 2H), 1.71 – 1.60 (m, 2H), 1.20 (t, *J* = 7.6 Hz, 3H), 1.14 (d, *J* = 6.1 Hz, 6H).

15

Intermediate 190**4-((5-(Bromomethyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)-2-ethyloxazole**

20

To a solution of (3-chloro-4-iodophenyl)methanol (250 mg, 0.931 mmol) and triphenylphosphine (293 mg, 1.117 mmol) in THF (5 mL) was added NBS (199 mg, 1.117 mmol) in portions at 0 °C, and the mixture was stirred at room temperature for 40 minutes. The reaction was quenched with water and extracted with EtOAc (3x). The extract was dried (Na₂SO₄) and concentrated. The resulting residue was purified by silica gel chromatography (0 to 50% EtOAc/hexanes) to give the desired product (140 mg) as a white solid. LC-MS

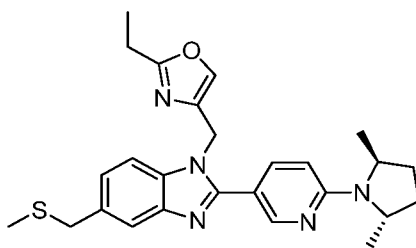
25

(ES) m/z = 494, 496 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.25 - 1.33 (m, 9H), 1.74 - 1.91 (m, 2H), 2.40 (br. s., 2H), 2.78 (q, J = 7.6 Hz, 2H), 4.65 (s, 2H), 5.56 (s, 2H), 6.93 (d, J = 8.9 Hz, 1H), 7.49 - 7.57 (m, 1H), 7.74 - 7.86 (m, 2H), 8.11 (s, 1H), 8.28 (dd, J = 9.1, 2.3 Hz, 1H), 8.82 (d, J = 2.0 Hz, 1H).

5

Intermediate 191

4-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-5-((methylthio)methyl)-1H-benzo[d]imidazol-1-yl)methyl)-2-ethyloxazole

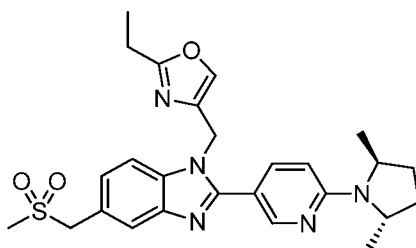


- 10 To a solution of 4-((5-(bromomethyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)-2-ethyloxazole (130 mg, 0.263 mmol) in ethanol (2 mL) was added sodium methanethiolate (18.43 mg, 0.263 mmol), and the mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated, and the resulting residue was washed with water and dried under vacuum to give the desired product (110
- 15 mg) as a white solid. LC-MS (ES) m/z = 462 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.14 - 1.25 (m, 6H), 1.26 - 1.36 (m, 3H), 1.67 - 1.82 (m, 2H), 1.89 (s, 3H), 2.32 - 2.42 (m, 2H), 2.78 (q, J = 7.6 Hz, 2H), 3.83 (s, 2H), 4.32 (br. s., 2H), 5.35 (s, 2H), 6.71 (d, J = 8.9 Hz, 1H), 7.29 (dd, J = 8.4, 1.5 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.59 - 7.63 (m, 1H), 7.79 (s, 1H), 8.05 (dd, J = 8.9, 2.5 Hz, 1H), 8.62 (d, J = 2.0 Hz, 1H).

20

Example 136

4-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-5-((methylsulfonyl)methyl)-1H-benzo[d]imidazol-1-yl)methyl)-2-ethyloxazole

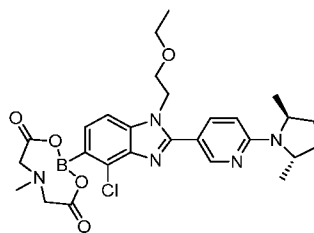


- 25 To a solution of 4-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-5-((methylthio)methyl)-1H-benzo[d]imidazol-1-yl)methyl)-2-ethyloxazole (110 mg, 0.238

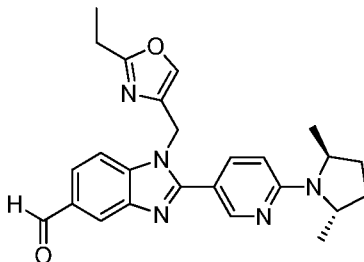
mmol) in CH₃OH (4 mL) was added a solution of oxone (322 mg, 0.524 mmol) in water (1.60 mL), and the mixture was stirred at room temperature for 3 hours. The mixture was concentrated, and the residue was treated with water (3 mL) and extracted with CH₂Cl₂ (3x). The extract was dried (Na₂SO₄) and concentrated. The resulting residue was purified by silica gel chromatography (0 to 100% EtOAc/heptane) to give the desired product (58 mg) as a white solid. LC-MS (ES) m/z = 494 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.23 (d, J = 6.3 Hz, 6H), 1.25 - 1.35 (m, 3H), 1.76 (d, J = 5.8 Hz, 2H), 2.29 - 2.42 (m, 2H), 2.78 (q, J = 7.7 Hz, 2H), 2.89 (s, 3H), 4.32 (br. s., 2H), 4.57 (s, 2H), 5.39 (s, 2H), 6.72 (d, J = 8.6 Hz, 1H), 7.39 (dd, J = 8.5, 1.6 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 1.0 Hz, 1H), 7.83 (s, 1H), 8.07 (dd, J = 8.9, 2.5 Hz, 1H), 8.62 - 8.68 (m, 1H)

Example 137

2-(4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione

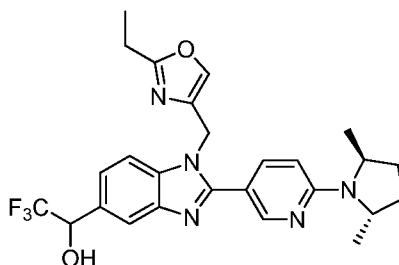


To a solution of (4-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)boronic acid (150 mg, 0.339 mmol) in toluene (6 mL) and DMSO (0.667 mL) were added 2,2'-(methylazanediyl)diacetic acid (74.8 mg, 0.508 mmol) and magnesium sulfate (408 mg, 3.39 mmol), and the mixture was stirred at reflux for 1 hour. The mixture was cooled to room temperature and concentrated. The resulting residue was purified by silica gel chromatography (0 to 100% (3:1 EtOAc:EtOH)/heptane) to give the desired product (160 mg) as a white solid. LC-MS (ES) m/z = 554 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.07 (t, J = 7.0 Hz, 3H), 1.18 - 1.26 (m, 6H), 1.72 - 1.81 (m, 2H), 2.27 - 2.42 (m, 2H), 2.77 (s, 3H), 3.40 (q, J = 7.1 Hz, 2H), 3.86 (t, J = 5.2 Hz, 2H), 4.19 - 4.43 (m, 6H), 4.48 (t, J = 5.1 Hz, 2H), 6.70 (d, J = 8.9 Hz, 1 H), 7.56 - 7.68 (m, 2H), 8.00 (dd, J = 9.0, 2.4 Hz, 1H), 8.57 (d, J = 2.0 Hz, 1H)

Intermediate 1922-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carbaldehyde

- 5 To a solution of 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-5-yl)methanol (390 mg, 0.904 mmol) in CH₂Cl₂ (5 mL) was added Dess-Martin periodinane (575 mg, 1.356 mmol), and the mixture was stirred at room temperature for 4 hours. The mixture was concentrated, and the resulting residue was purified by silica gel chromatography (0 to 60% EtOAc/hexanes) to give the desired product
- 10 (310 mg) as a pale brown solid. LC-MS (ES) *m/z* = 430 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.18 - 1.25 (m, 6H), 1.25 - 1.33 (m, 3H), 1.71 - 1.82 (m, 2H), 2.31 - 2.43 (m, 2H), 2.77 (q, *J* = 7.6 Hz, 2H), 4.33 (d, *J* = 6.8 Hz, 2H), 5.44 (s, 2H), 6.73 (d, *J* = 8.9 Hz, 1H), 7.72 (d, *J* = 8.7 Hz, 1H), 7.84 - 7.93 (m, 2H), 8.10 (dd, *J* = 8.9, 2.5 Hz, 1H), 8.24 (d, *J* = 1.0 Hz, 1H), 8.67 (d, *J* = 2.3 Hz, 1H), 10.07 (s, 1H).

15

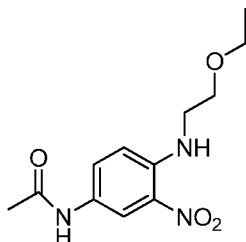
Example 1381-(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-yl)-2,2,2-trifluoroethanol

- 20 To a solution of 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carbaldehyde (56 mg, 0.130 mmol) in DMF (1 mL) were added trimethyl(trifluoromethyl)silane (185 mg, 1.304 mmol) and K₂CO₃ (36.0 mg, 0.261 mmol), and the reaction mixture was stirred at room temperature for 48 hours. The mixture was quenched with water (5 mL) and extracted with EtOAc (3x). The extract was dried
- 25 (Na₂SO₄) and concentrated. The residue was dissolved into THF (2.00 mL), treated with 6N aqueous HCl slowly, and the mixture stirred for 3 hours at room temperature. Water (10

mL) was then added, and the resulting mixture was extracted with EtOAc (3 x 10 mL). The extract was dried over Na₂SO₄, filtered, and concentrated. The resulting residue was purified by silica gel chromatography (0 to 100% EtOAc/heptane) to give the desired product (41 mg) as a white solid. LC-MS (ES) m/z = 500 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.17 - 1.25 (m, 6H), 1.30 (t, J = 7.6 Hz, 3H), 1.69 - 1.81 (m, 2H), 2.31 - 2.40 (m, 2H), 2.72 - 2.81 (m, 2H), 4.32 (br. s., 2H), 5.17 (q, J = 7.1 Hz, 1H), 5.33 - 5.43 (m, 2H), 6.72 (d, J = 8.6 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.6 Hz, 1H), 7.79 - 7.87 (m, 2H), 8.06 (dd, J = 8.9, 2.5 Hz, 1H), 8.63 (d, J = 1.8 Hz, 1H).

10 Intermediate 193

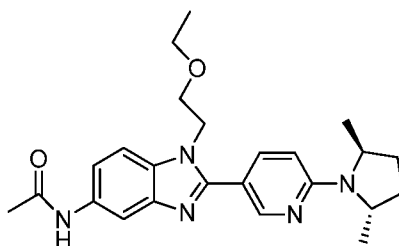
N-(4-((2-Ethoxyethyl)amino)-3-nitrophenyl)acetamide



To a solution of N-(4-fluoro-3-nitrophenyl)acetamide (800mg, 4.04 mmol) in ethanol (20 mL) were added 2-ethoxyethan-1-amine (396 mg, 4.44 mmol) and Na₂CO₃ (941 mg, 8.88 mmol), and the reaction mixture was stirred at 60 °C for 20 hours. The mixture was filtered, and the filtrate was concentrated. The resulting residue was treated with EtOAc (30 mL) and filtered. The filtrate was concentrated to give the desired product (1.02 g) as a brown solid. LC-MS (ES) m/z = 268 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.19 - 1.28 (m, 3H), 2.12 (m, 3H), 3.48 - 3.65 (m, 4H), 3.68 - 3.78 (m, 2H), 7.03 (d, J = 9.4 Hz, 1H), 7.66 (dd, J = 9.1, 2.5 Hz, 1H), 8.18 (br. s., 1H), 8.42 (d, J = 2.8 Hz, 1H).

Example 139

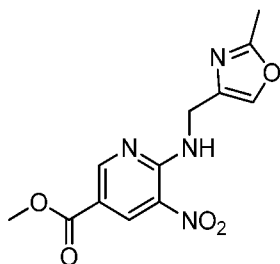
N-(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)acetamide



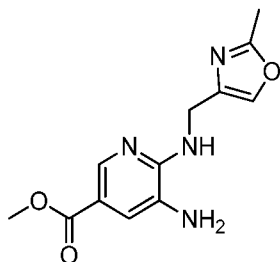
To a 20-mL microwave tube were added N-(4-((2-ethoxyethyl)amino)-3-nitrophenyl)acetamide (250 mg, 0.935 mmol), 4-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)benzaldehyde (228 mg, 1.122 mmol), sodium hydrosulfite (574 mg, 85%, 2.81 mmol), ethanol (4 mL) and water (1 mL), and the mixture was stirred at 130 °C under microwave conditions for 80 minutes. The mixture was then cooled to room temperature, filtered and concentrated. The residue was treated with water and extracted with CH₂Cl₂ (3x). The extract was dried (Na₂SO₄) and concentrated. The resulting residue was purified by silica gel chromatography (0% to 100% (3:1 EtOAc:EtOH)/heptane) to give the desired product (240 mg) as an off-white solid. LC-MS (ES) m/z = 422 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.08 (t, J = 7.0 Hz, 3H), 1.18 - 1.29 (m, 6H), 1.72 - 1.80 (m, 2H), 2.18 (s, 3H), 2.30 - 2.41 (m, 2H), 3.36 - 3.46 (m, 2H), 3.87 (t, J = 5.3 Hz, 2H), 4.33 (br. s., 2H), 4.47 (t, J = 5.2 Hz, 2H), 6.69 (d, J = 8.9 Hz, 1H), 7.44 - 7.50 (m, 1H), 7.56 (d, J = 8.9 Hz, 1H), 7.93 - 8.00 (m, 2H), 8.55 (d, J = 2.5 Hz, 1H).

15 Intermediate 194

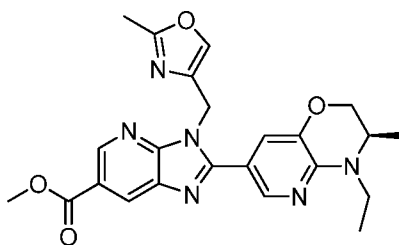
Methyl 6-(((2-methyloxazol-4-yl)methyl)amino)-5-nitronicotinate



To a solution of methyl 6-chloro-5-nitronicotinate (700 mg, 3.23 mmol) in CH₂Cl₂ (20 mL) were added (2-methyloxazol-4-yl)methanamine (362 mg, 3.23 mmol) and N,N-diisopropylethylamine (0.734 mL, 4.20 mmol), and the reaction mixture was stirred at room temperature for 20 hours. The mixture was concentrated, and the resulting residue was washed with water and dried under vacuum to give the desired product (920 mg) as a pale yellow solid. LC-MS (ES) m/z = 293 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 2.45 (s, 3H), 3.93 (s, 3H), 4.79 (d, J = 1.0 Hz, 2H), 7.74 (t, J = 1.0 Hz, 1H), 8.93 - 8.96 (m, 1H), 8.96 - 8.99 (m, 1H).

Intermediate 195Methyl 5-amino-6-(((2-methyloxazol-4-yl)methyl)amino)nicotinate

To a solution of methyl 6-(((2-methyloxazol-4-yl)methyl)amino)-5-nitronicotinate (920 mg, 3.15 mmol) in CH₃OH (18 mL) were added NiCl₂•6H₂O (1873 mg, 7.87 mmol) and sodium borohydride (595 mg, 15.74 mmol) at 0 °C, and the mixture was stirred at 0 °C for 20 minutes. The reaction mixture was quenched with water (10 mL) and saturated aqueous NH₄OH solution (8 mL), and the resulting mixture was filtered through Celite. The blue solid was washed with EtOAc. The organic layer was collected, and the aqueous layer was further extracted with EtOAc (3x). The combined organic layers were dried (Na₂SO₄) and concentrated to give the desired product (710 mg) as an off-white solid. LC-MS (ES) m/z = 263 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 2.45 (s, 3H), 3.85 (s, 3H), 4.56 (d, J = 1.0 Hz, 2H), 7.36 (d, J = 2.0 Hz, 1H), 7.67 (t, J = 1.1 Hz, 1H), 8.19 (d, J = 2.0 Hz, 1H).

15 Intermediate 196
(R)-Methyl 2-(4-ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-3-((2-methyloxazol-4-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxylate


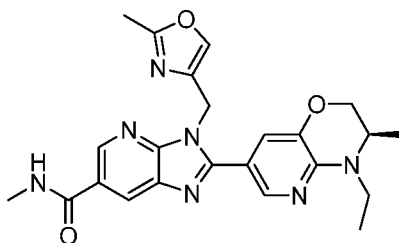
To a solution of methyl 5-amino-6-(((2-methyloxazol-4-yl)methyl)amino)nicotinate (200 mg, 0.763 mmol) in DMF (5 mL) and water (1 mL) were added (R)-4-ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-7-carbaldehyde (157 mg, 0.763 mmol) and oxone (352 mg, 0.572 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was basified using 10% K₂CO₃ aqueous solution and extracted with EtOAc (3x). The organic extract was dried (Na₂SO₄) and concentrated. The resulting residue was purified by silica gel chromatography (0 to 100% EtOAc/hexanes) to give the desired product (110 mg) as a pale yellow solid. LC-MS (ES) m/z = 449 [M+H]⁺. ¹H NMR (400 MHz,

CD₃OD): δ 1.27 (t, J = 7.1 Hz, 3H), 1.32 - 1.37 (m, 3H), 2.40 (s, 3H), 3.47 (dd, J = 13.9, 7.1 Hz, 1H), 3.79 - 3.91 (m, 1H), 3.95 - 4.08 (m, 5H), 4.12 - 4.20 (m, 1H), 5.53 (s, 2H), 7.58 (d, J = 2.0 Hz, 1H), 7.75 (s, 1H), 8.32 (d, J = 2.0 Hz, 1H), 8.58 (d, J = 1.8 Hz, 1H), 9.01 (d, J = 1.8 Hz, 1H).

5

Example 140

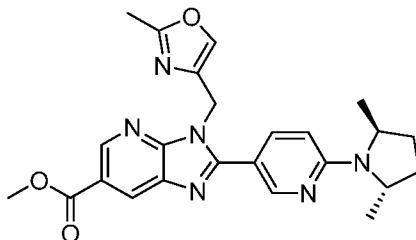
(R)-2-(4-ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-N-methyl-3-((2-methyloxazol-4-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide



- 10 To a solution of methyl (R)-2-(4-ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-3-((2-methyloxazol-4-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxylate (46 mg, 0.103 mmol) in CH₃OH (1 mL) was added aqueous NaOH (5N, 0.2 mL, 1.000 mmol), and the reaction mixture was stirred at 40 °C for 18 hours. The reaction mixture was neutralized by adding HCl (6N, 0.167 mL, 1.000 mmol) and concentrated. The resulting residue was dried
- 15 under vacuum and treated with DMSO (1.000 mL). To this mixture were added methylamine hydrochloride (11.08 mg, 0.164 mmol), N-methylmorpholine (0.079 mL, 0.718 mmol), EDC (39.3 mg, 0.205 mmol), and 1-hydroxy-7-azabenzotriazole (27.9 mg, 0.205 mmol), and the reaction mixture was stirred at room temperature for 18 hours. The reaction was quenched with water (5 mL) and extracted with EtOAc (3x). The extract was dried (Na₂SO₄) and
- 20 concentrated. The resulting residue was purified by silica gel chromatography (0 to 100% (3:1 EtOAc:EtOH)/heptane) to give the desired product (28 mg) as a pale yellow solid. LC-MS (ES) m/z = 448 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.21 - 1.31 (m, 3H), 1.35 (d, J = 6.6 Hz, 3H), 2.40 (s, 3H), 2.99 (s, 3H), 3.39 - 3.55 (m, 1H), 3.81 - 3.88 (m, 1H), 3.97 - 4.09 (m, 2H), 4.11 - 4.19 (m, 1H), 5.52 (s, 2H), 7.57 (d, J = 2.0 Hz, 1H), 7.74 (s, 1H), 8.31 (d, J = 2.0 Hz, 1H), 8.45 (d, J = 2.0 Hz, 1H), 8.85 (d, J = 2.0 Hz, 1H).
- 25

Intermediate 197

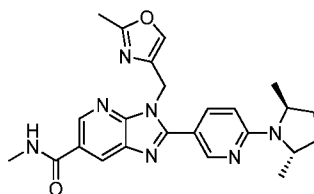
Methyl 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((2-methyloxazol-4-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxylate



- 5 To a 20-mL microwave tube were added methyl 6-(((2-methyloxazol-4-yl)methyl)amino)-5-nitronicotinate (150 mg, 0.513 mmol), 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (126 mg, 0.616 mmol), sodium hydrosulfite (268 mg, 85%, 1.308 mmol), ethanol (4 mL), and water (1 mL), and the reaction mixture was stirred at 130 °C under microwave conditions for 80 minutes. The mixture was then cooled to room temperature,
- 10 filtered, and concentrated. The residue was treated with water and extracted with CH₂Cl₂ (3x). The organic extract was dried (Na₂SO₄) and concentrated. The resulting residue was purified by silica gel chromatography (0% to 100% EtOAc/heptane) to give the desired product (148 mg) as an off-white solid. LC-MS (ES) m/z = 447 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.16 - 1.27 (m, 6H), 1.76 (d, J = 5.6 Hz, 2H), 2.33 - 2.42 (m, 5H), 4.00 (s, 3H),
- 15 4.33 (m, 2H), 5.33 (s, 2H), 6.72 (d, J = 8.9 Hz, 1H), 7.72 - 7.81 (m, 1H), 8.11 (dd, J = 8.9, 2.5 Hz, 1H), 8.58 (d, J = 2.0 Hz, 1H), 8.69 (d, J = 2.0 Hz, 1H), 9.01 (d, J = 1.8 Hz, 1H).

Example 141

20 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-methyl-3-((2-methyloxazol-4-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

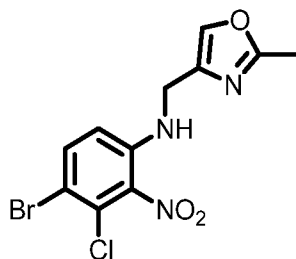


- To a solution of methyl 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((2-methyloxazol-4-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxylate (70 mg, 0.157 mmol) in CH₃OH (1.5 mL) was added aqueous NaOH (5N, 0.26 mL, 1.30 mmol), and the reaction
- 25 mixture was stirred at 40 °C for 18 hours. The reaction mixture was neutralized by adding HCl (6N, 0.217 mL, 1.30 mmol) and concentrated. The resulting residue was dried under vacuum and treated with DMSO (1.50 mL). To this mixture were added methylamine

hydrochloride (16.94 mg, 0.251 mmol), EDC (60.1 mg, 0.314 mmol), 1-hydroxy-7-azabenzotriazole (42.7 mg, 0.314 mmol), and N-methylmorpholine (0.103 mL, 0.941 mmol), and the reaction mixture was stirred at room temperature for 18 hours. The reaction was quenched with water (5 mL) and extracted with EtOAc (3x). The extract was dried (Na₂SO₄) and concentrated. The resulting residue was purified by silica gel chromatography (0 to 100% (3:1 EtOAc:EtOH)/heptane) to give the desired product (49 mg) as an off-white solid. LC-MS (ES) *m/z* = 446 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.17 - 1.28 (m, 6H), 1.76 (d, *J* = 5.6 Hz, 2H), 2.29 - 2.43 (m, 5H), 2.99 (s, 3H), 4.32 (br. s., 2H), 5.52 (m, 2H), 6.71 (d, *J* = 8.9 Hz, 1H), 7.75 (s, 1H), 8.09 (dd, *J* = 8.9, 2.5 Hz, 1H), 8.44 (d, *J* = 2.0 Hz, 1H), 8.68 (d, *J* = 2.0 Hz, 1H), 8.85 (d, *J* = 2.0 Hz, 1H).

Intermediate 198

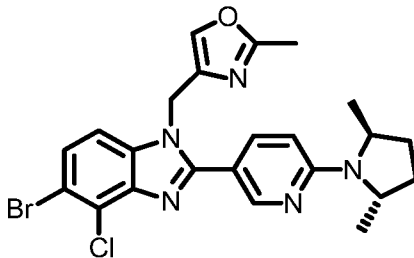
4-Bromo-3-chloro-N-((2-methyloxazol-4-yl)methyl)-2-nitroaniline



To a solution of 1-bromo-2-chloro-4-fluoro-3-nitrobenzene (920 mg, 3.62 mmol) in CHCl₃ (10 mL) were added (2-methyloxazol-4-yl)methanamine (405 mg, 3.62 mmol) and K₂CO₃ (500 mg, 3.62 mmol), and the reaction mixture was stirred at room temperature for 16 hours. The mixture was quenched with 1M aqueous HCl solution (10 mL) and then extracted with EtOAc (3x). The combined organic extracts were dried, filtered, and concentrated. The resulting residue was purified using silica gel chromatography eluting with a gradient of 0 to 60% EtOAc in hexanes to provide 4-bromo-3-chloro-N-((2-methyloxazol-4-yl)methyl)-2-nitroaniline (852 mg, 2.458 mmol) as a yellowish orange oil. LC-MS (ES) *m/z* = 346, 348, 350 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.53 (d, *J* = 9.1 Hz, 1H), 7.45 (s, 1H), 6.71 (d, *J* = 9.1 Hz, 1H), 5.75 (br. s., 1H), 4.28 (d, *J* = 4.6 Hz, 2H), 2.46 (s, 3H).

Intermediate 199

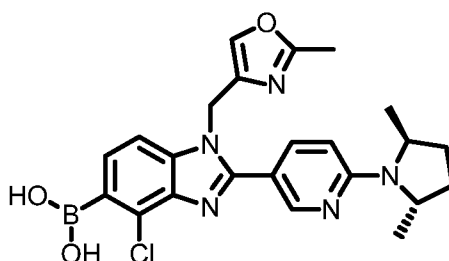
4-((5-Bromo-4-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)-2-methyloxazole



- 5 4-Bromo-3-chloro-N-((2-methyloxazol-4-yl)methyl)-2-nitroaniline (250mg, 0.721 mmol), 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (177 mg, 0.866 mmol), sodium hydrosulfite (443 mg, 85%, 2.164 mmol), ethanol (8 mL), and water (2mL) were combined in a microwave vial. The vial was sealed, and the mixture was stirred at 130 °C under microwave conditions for 80 minutes. The mixture was then cooled to room temperature,
- 10 filtered, and concentrated. The resulting residue was treated with water and extracted with CH₂Cl₂ (3x). The combined organic extracts were dried over Na₂SO₄, then concentrated. The resulting residue was purified using silica gel chromatography eluting with a gradient from 0% to 100% EtOAc in heptane to provide 4-((5-bromo-4-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)-2-methyloxazole
- 15 (0.340 g) as a foam. LC-MS (ES) m/z = 500, 502, 504 [M+H]⁺.

Example 142

(4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-5-yl)boronic acid

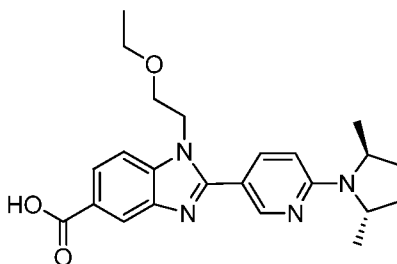


- 20 A solution of 4-((5-bromo-4-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)-2-methyloxazole (340 mg, 0.679 mmol) and triisopropyl borate (0.188 mL, 0.815 mmol) in a mixture of THF (0.5 mL) and toluene (2 mL) was cooled to -78 °C in a dry ice acetone bath. n-Butyllithium (2.5 M in hexane, 0.726 mL, 1.815 mmol)
- 25 was added dropwise over 5 minutes in 3 portions, and the reaction mixture was stirred for a total of 90 minutes at -78 °C. The reaction mixture was warmed to -25 °C, and then 2N

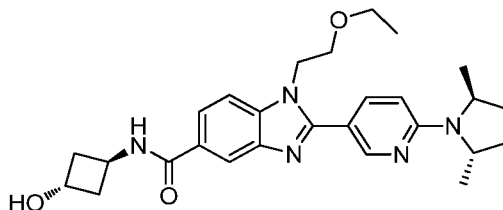
aqueous HCl solution (5 mL) was added dropwise while maintaining the reaction temperature below -20 °C. The mixture was then allowed to warm to room temperature and washed with EtOAc. Saturated aqueous NaHCO₃ solution was added to the aqueous phase until the pH was between 7 and 8. The aqueous phase was extracted with EtOAc, and the combined organic extracts were washed with water, brine, dried over MgSO₄, filtered, and concentrated. The resulting residue was purified by silica gel chromatography eluting with a gradient from 0% to 60% of [3:1 EtOAc/EtOH containing 1.5% ammonium hydroxide] in hexanes to provide (4-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-5-yl)boronic acid (21.1 mg) as a solid with a yellow tint. LC-MS (ES) m/z = 466 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 8.65 (d, J = 2.3 Hz, 1H), 8.06 (dd, J = 2.4, 9.0 Hz, 1H), 7.81 (s, 1H), 7.48 (d, J = 7.9 Hz, 1H), 7.20 (d, J = 7.9 Hz, 1H), 6.69 (d, J = 9.1 Hz, 1H), 5.33 (s, 2H), 4.31 (br. s., 2H), 2.40 (s, 3H), 2.37 - 2.29 (m, 2H), 1.74 (d, J = 5.6 Hz, 2H), 1.21 (d, J = 6.1 Hz, 6H).

Intermediate 200

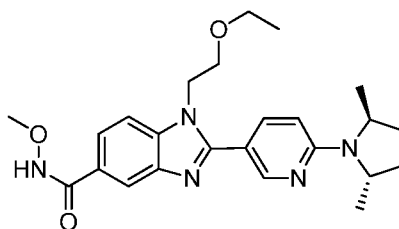
2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole-5-carboxylic acid



A solution of methyl 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole-5-carboxylate (800 mg, 1.893 mmol) in CH₃OH (8 mL) and THF (8.00 mL) was treated with 10N sodium hydroxide (0.947 mL, 9.47 mmol) at 55 °C overnight. The heat was removed and the solvents evaporated in-vacuo. The remaining white solid was taken up in water (7 mL) and the pH adjusted to ~4 with 6N HCl (1.325 mL, 7.95 mmol). The pH was brought back up to ~6-7 (paper) with 1N NaOH (0.568 mL, 0.568 mmol). The white solid was collected via filtration and dried at 50 °C under vacuum to afford the desired product (416 mg) as a white powder. LC-MS (ES) m/z = 409 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.01 (br. s., 1H), 8.61 (d, J = 1.7 Hz, 1H), 8.25 (s, 1H), 8.08 (br. s., 1H), 7.87 - 8.00 (m, 2H), 6.81 (br. s., 1H), 4.56 (t, J = 4.6 Hz, 2H), 3.80 (d, J = 10.1 Hz, 3H), 3.33 (d, J = 6.8 Hz, 3H), 1.67 - 1.72 (m, 2H), 1.17 (d, J = 6.0 Hz, 8H), 0.96 (t, J = 6.9 Hz, 3H).

Example 143**2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-N-((1r,3S)-3-hydroxycyclobutyl)-1H-benzo[d]imidazole-5-carboxamide**

- 5 A solution of 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole-5-carboxylic acid (50.0 mg, 0.122 mmol), N-methylmorpholine (0.047 mL, 0.428 mmol), and HATU (55.8 mg, 0.147 mmol) in DMF (1.5 mL) was stirred at room temperature 15 minutes. (1r,3r)-3-aminocyclobutan-1-ol hydrochloride (18.15 mg, 0.147 mmol) was then added, and the reaction mixture was stirred at room temperature overnight.
- 10 The reaction was filtered and then purified by reverse HPLC (15 to 55% CH₃CN/(water(0.1%-formic acid))) to afford the desired product (20 mg) as a white solid. LC-MS (ES) m/z = 478 [M+H]⁺. ¹H NMR (400 MHz, CD₃CN): δ 8.56 (d, J = 2.0 Hz, 1H), 8.15 (s, 1H), 8.13 (s, 1H), 7.94 (dd, J = 2.4, 9.0 Hz, 1H), 7.79 (dd, J = 1.0, 8.4 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.37 (d, J = 5.6 Hz, 1H), 6.60 (d, J = 8.9 Hz, 1H), 4.62 - 4.50 (m, 3H), 4.44 (t, J = 5.1 Hz, 2H), 4.29 (br. s., 2H), 3.82 (t, J = 5.3 Hz, 2H), 3.37 (q, J = 6.9 Hz, 2H), 2.45 - 2.21 (m, 6H), 1.77 - 1.62 (m, 2H), 1.20 (d, J = 6.1 Hz, 6H), 1.02 (t, J = 7.0 Hz, 3H).
- 15

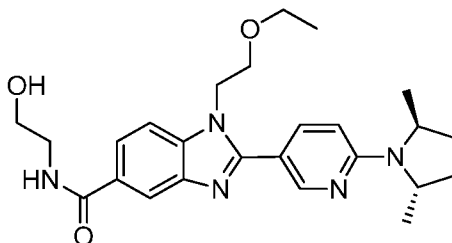
Example 144**2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-N-methoxy-1H-benzo[d]imidazole-5-carboxamide**

- A solution of 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole-5-carboxylic acid (50.0 mg, 0.122 mmol), N-methylmorpholine (0.047 mL, 0.428 mmol), and HATU (55.8 mg, 0.147 mmol) in DMF (1.5 mL) was stirred at room temperature for 15 minutes. O-methylhydroxylamine hydrochloride (10.22 mg, 0.122 mmol) was then added, and the reaction mixture was stirred at room temperature for 45 minutes. The reaction was purified by reverse phase HPLC (15 to 55% CH₃CN/0.1% TFA in H₂O) to
- 20
- 25

afford the desired product (36.8 mg) as a white solid. LC-MS (ES) m/z = 438 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 11.72 (s, 1H), 8.56 (d, J = 2.0 Hz, 1H), 8.05 (s, 1H), 7.97 (dd, J = 2.5, 8.8 Hz, 1H), 7.65 - 7.75 (m, 2H), 6.63 (d, J = 8.6 Hz, 1H), 4.46 (t, J = 5.2 Hz, 2H), 3.69 - 3.79 (m, 5H), 3.26 - 3.34 (m, 4H), 2.25 (m, 2H), 1.66 (m, 2H), 1.15 (d, J = 6.3 Hz, 6H), 0.95 (t, J = 6.9 Hz, 3H).

Example 145

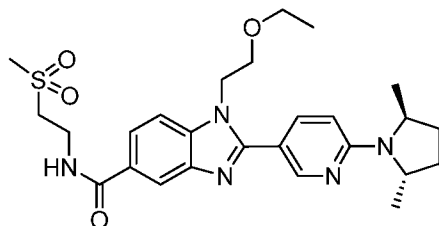
2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-N-(2-hydroxyethyl)-1H-benzo[d]imidazole-5-carboxamide



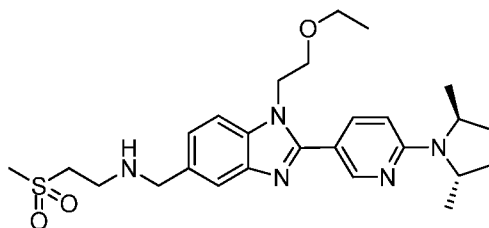
10

A solution of 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole-5-carboxylic acid (50.0 mg, 0.122 mmol) in DMF (1.5 mL) was treated with N-methylmorpholine (0.047 mL, 0.428 mmol) and HATU (55.8 mg, 0.147 mmol), and the resulting mixture stirred at room temperature for 15 minutes. 2-Aminoethan-1-ol (5.16 μ l, 0.122 mmol) was then added, and the reaction mixture was stirred at room temperature for 45 minutes. Purification by reverse phase HPLC (15 to 55% CH_3CN /0.1% formic acid in water) afforded the desired product (48.2 mg) as a white powder after freeze-drying. LC-MS (ES) m/z = 452 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 8.56 (d, J = 2.2 Hz, 1H), 8.39 - 8.47 (m, 1H), 8.18 (s, 1H), 7.97 (dd, J = 2.2, 8.8 Hz, 1H), 7.76 - 7.82 (m, J = 1.5 Hz, 1H), 7.63 - 7.73 (m, 1H), 6.63 (d, J = 8.6 Hz, 1H), 4.75 (t, J = 5.8 Hz, 1H), 4.46 (t, J = 5.5 Hz, 2H), 3.76 (t, J = 5.3 Hz, 2H), 3.54 (q, J = 6.0 Hz, 2H), 3.35 - 3.43 (m, J = 6.0 Hz, 2H), 3.32 (s, 5H), 2.21 - 2.28 (m, 2H), 1.66 (d, J = 5.3 Hz, 2H), 1.15 (d, J = 6.0 Hz, 6H), 0.95 (t, J = 6.9 Hz, 3H).

20

Example 146**2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-N-(2-(methylsulfonyl)ethyl)-1H-benzo[d]imidazole-5-carboxamide**

- 5 A solution of 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole-5-carboxylic acid (85 mg, 0.208 mmol), N-methylmorpholine (0.080 mL, 0.728 mmol), and HATU (95 mg, 0.250 mmol) in DMF (1.5 mL) was stirred at room temperature for 15 minutes. 2-(Methylsulfonyl)ethan-1-amine hydrochloride (33.2 mg, 0.208 mmol) was then added, and the reaction mixture was stirred at room temperature for
- 10 45 minutes. Additional portions of HATU, N-methylmorpholine, and 2-(methylsulfonyl)ethan-1-amine hydrochloride were added and the reaction continued to stir at room temperature for 3 days. The solvent was removed in-vacuo and the remaining residue purified via reverse phase HPLC (15-55% CH₃CN/0.1% formic acid in water). The desired fractions were concentrated and dried under high vacuum, then freeze dried to
- 15 afford the desired product (45.5 mg) as a white powder. LC-MS (ES) m/z = 514 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆): δ 8.72 (s, 1H), 8.56 (d, J = 2.2 Hz, 1H), 8.16 (d, J = 1.2 Hz, 1H), 7.97 (dd, J = 2.5, 8.8 Hz, 1H), 7.76 (d, J = 1.7 Hz, 1H), 7.66-7.74 (m, 1H), 6.56-6.68 (m, 1H), 4.46 (t, J = 5.2 Hz, 2H), 3.67-3.81 (m, 4H), 3.42 (t, J = 6.8 Hz, 2H), 3.26-3.33 (m, 4H), 3.06 (s, 3H), 2.25 (t, J = 7.8 Hz, 2H), 1.66 (d, J = 5.5 Hz, 2H), 1.15 (d, J = 6.3 Hz, 6H),
- 20 0.95 (t, J = 6.9 Hz, 3H).

Example 147**N-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)methyl)-2-(methylsulfonyl)ethanamine**

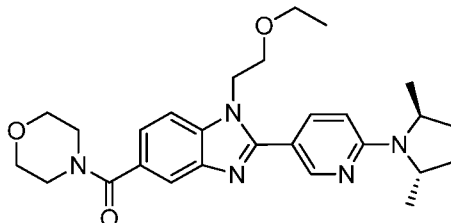
25

To a solution of 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-N-(2-(methylsulfonyl)ethyl)-1H-benzo[d]imidazole-5-carboxamide (32.9 mg, 0.064 mmol) in

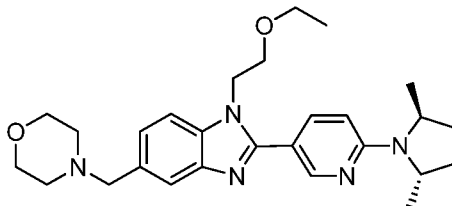
THF (1.5 mL) was added $\text{BH}_3 \cdot \text{THF}$ (0.192 mL, 0.192 mmol) dropwise, and the reaction mixture was stirred at room temperature for 2 hours. The reaction was cooled to 8 °C, quenched with 2.5N NaOH (0.102 mL, 0.256 mmol), and then stirred at 50 °C for 1 hour. The reaction was concentrated, and the remaining residue was partitioned between water (1 mL) and EtOAc (3 mL). The aqueous layer was extracted with EtOAc (2 x 2 mL), and the combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The remaining residue was purified by reverse phase HPLC (5 to 70% $\text{CH}_3\text{CN}/0.1\%\text{NH}_4\text{OH}$ in water) to afford the desired product (3 mg) as a thin film on glass after freeze drying. LC-MS (ES) $m/z = 500 [\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.56 (d, $J = 2.2$ Hz, 1H), 7.99 (dd, $J = 2.5$, 8.8 Hz, 1H), 7.6 (s, 1H), 7.60 (d, $J = 8.3$ Hz, 1H), 7.35 (dd, $J = 1.52$, 8.36 Hz, 1H), 6.70 (d, $J = 9.1$ Hz, 1H), 4.48 (t, $J = 5.2$ Hz, 2H), 4.25 - 4.40 (m, 2H), 3.95 (s, 2H), 3.87 (t, $J = 5.2$ Hz, 2H), 3.40 (q, $J = 7.1$ Hz, 2H), 3.09 - 3.16 (m, 2H), 3.03 (s, 3H), 2.31 - 2.40 (m, 2H), 1.76 (d, $J = 5.5$ Hz, 2H), 1.23 (d, $J = 6.0$ Hz, 6H), 1.07 (t, $J = 6.9$ Hz, 3H).

15 Intermediate 201

(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)(morpholino)methanone



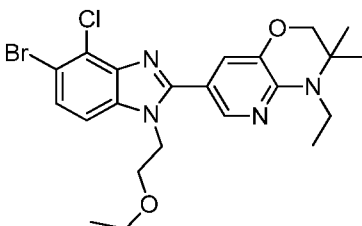
A solution of 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole-5-carboxylic acid (85 mg, 0.208 mmol), N-methylmorpholine (0.080 mL, 0.728 mmol), and HATU (95 mg, 0.250 mmol) in DMF (1.5 mL) was stirred at room temperature for 15 minutes. Morpholine (0.020 mL, 0.229 mmol) was then added, and the reaction mixture was stirred at room temperature for 1 hour. The DMF was removed in vacuo, and the remaining residue was purified by reverse phase HPLC (15 to 55% $\text{CH}_3\text{CN}/0.1\%\text{formic acid}$ in water) to afford the desired product (65 mg) as a white powder after freeze-drying. LC-MS (ES) $m/z = 478 [\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.56 (d, $J = 2.2$ Hz, 1H), 7.94 - 8.01 (m, $J = 11.1$ Hz, 1H), 7.70 (d, $J = 8.3$ Hz, 2H), 7.30 (d, $J = 9.6$ Hz, 1H), 6.63 (d, $J = 8.8$ Hz, 1H), 4.45 (t, $J = 5.3$ Hz, 2H), 3.77 (d, $J = 10.3$ Hz, 2H), 3.43 - 3.68 (m, 8H), 3.28 - 3.33 (m, 3H), 2.25 (t, $J = 8.1$ Hz, 3H), 1.66 (d, $J = 5.5$ Hz, 2H), 1.15 (d, $J = 6.3$ Hz, 6H), 0.97 (t, $J = 6.9$ Hz, 3H).

Example 148**4-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)methyl)morpholine**

- 5 To a solution of (2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)(morpholino)methanone (46.0 mg, 0.096 mmol) in THF (1.5 mL) was added $\text{BH}_3 \cdot \text{THF}$ (0.289 mL, 0.289 mmol) dropwise, and the reaction mixture was stirred at room temperature overnight. The reaction was then cooled to 8 °C (jacket) and quenched with 2.5N NaOH (0.154 mL, 0.385 mmol). The reaction was warmed to 50 °C and stirred
- 10 for 1 hour. The solvent was concentrated in-vacuo, and the remaining residue was partitioned between water (1 mL) and EtOAc (3 mL). The aqueous layer was extracted with EtOAc (2 x 2 mL), and the combined organic extracts were washed with brine. Product remained in the aqueous. All solvent was removed in-vacuo and the remaining residue was taken up in CH_3OH (3 mL) and the solids filtered out. The solution was purified via reverse
- 15 phase HPLC (5 to 35% $\text{CH}_3\text{CN}/0.1\%\text{NH}_4\text{OH}$ in water) to afford the desired product (4 mg) as a thin film on glass. LC-MS (ES) $m/z = 464$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.56 (d, $J = 2.2$ Hz, 1H), 7.99 (dd, $J = 2.4, 9.0$ Hz, 1H), 7.66 (s, 1H), 7.59 (d, $J = 8.3$ Hz, 1H), 7.35 (dd, $J = 1.3, 8.2$ Hz, 1H), 6.70 (d, $J = 9.1$ Hz, 1H), 4.48 (t, $J = 5.2$ Hz, 2H), 4.33 (br. s., 2H), 3.87 (t, $J = 5.2$ Hz, 2H), 3.71 - 3.74 (m, 4H), 3.70 (s, 2H), 3.40 (q, $J = 6.8$ Hz, 2H), 2.54
- 20 (br. s., 4H), 2.32 - 2.40 (m, 2H), 1.76 (d, $J = 5.83$ Hz, 2H), 1.23 (d, $J = 6.3$ Hz, 6H), 1.07 (t, $J = 6.9$ Hz, 3H)

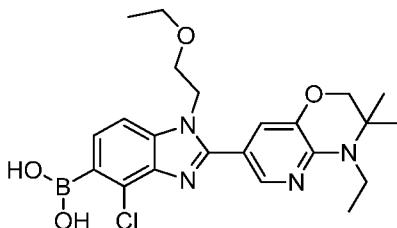
Intermediate 202

- 7-(5-Bromo-4-chloro-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine
- 25



To 4-bromo-3-chloro-N-(2-ethoxyethyl)-2-nitroaniline (145 mg, 0.448 mmol) and 4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-7-carbaldehyde in ethanol (4 mL), water (1 mL), and CH₂Cl₂ (1 mL) was added sodium hydrosulfite (234 mg, 85%, 1.142 mmol), and the reaction mixture was heated at 130 °C under microwave conditions for 80 minutes, then again for 60 minutes. The solids were filtered, and the filtrate was concentrated in-vacuo. The remaining residue was partitioned between CH₂Cl₂ (2 x 10 mL) and water (3 mL). The combined organic extracts were washed with brine (3 mL), dried over Na₂SO₄, filtered, and concentrated. The resulting residue was purified by silica gel chromatography (0 to 100 % EtOAc/hexanes) to afford the desired product (153 mg) as a pale yellow solid. LC-MS (ES) m/z = 493, 495 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.19 (d, *J* = 2.0 Hz, 1H), 7.61 - 7.68 (m, 1H), 7.53 - 7.60 (m, 1H), 7.48 (d, *J* = 2.0 Hz, 1H), 4.46 (t, *J* = 4.9 Hz, 2H), 3.94 (s, 2H), 3.74 (t, *J* = 5.1 Hz, 2H), 3.62 (q, *J* = 6.8 Hz, 2H), 3.27 - 3.32 (m, *J* = 7.1 Hz, 2H), 1.30 (s, 6H), 1.21 (t, *J* = 7.0 Hz, 3H), 0.95 (t, *J* = 7.0 Hz, 3H).

15

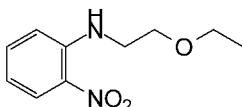
Example 149**(4-Chloro-1-(2-ethoxyethyl)-2-(4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-1H-benzo[d]imidazol-5-yl)boronic acid**

To a solution of 7-(5-bromo-4-chloro-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine (150 mg, 0.304 mmol) and triisopropyl borate (0.084 mL, 0.364 mmol) in toluene (8 mL) and THF (2.000 mL) cooled to -69 °C (internal) was added *n*-butyllithium (0.146 mL, 0.364 mmol) dropwise, and the reaction mixture was stirred for 40 minutes. The reaction was then warmed to -25 °C (internal), quenched with 2N HCl (0.456 mL, 0.911 mmol), and then warmed to room temperature. The mixture was partitioned between EtOAc (20 mL) and water (2 mL), and the pH of the aqueous layer was adjusted to 7 (paper) with saturated NaHCO₃ (1.5 mL). Water (2 mL) was then added, and the aqueous layer was extracted with EtOAc (20 mL). The combined organic extract was washed with brine (2 mL), dried over Na₂SO₄, filtered, and concentrated. The resulting residue was dried under high vacuum and purified by silica gel chromatography (30 to 100% (3:1 EtOAc:EtOH)/hexanes) to afford the desired product (25.5 mg) as a white solid after freeze-drying. LC-MS (ES) m/z = 459 [M+H]⁺. ¹H NMR (400

MHz, DMSO- d_6): δ 8.14 - 8.22 (m, 2H), 7.57 (d, J = 8.1 Hz, 1H), 7.48 (d, J = 1.7 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 4.44 (t, J = 4.8 Hz, 2H), 3.94 (s, 2H), 3.74 (t, J = 5.0 Hz, 2H), 3.62 (q, J = 6.9 Hz, 2H), 3.25 - 3.33 (m, 3H), 1.30 (s, 6H), 1.17-1.25 (m, 3H), 0.92 - 1.00 (m, 3H)

5 Intermediate 203

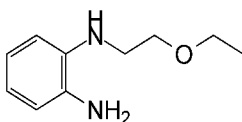
N-(2-Ethoxyethyl)-2-nitroaniline



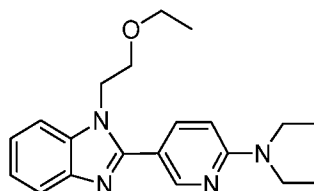
To a 25 mL screw cap vial was added 1-fluoro-2-nitrobenzene (1 g, 7.09 mmol), 2-ethoxyethan-1-amine (0.735 mL, 7.09 mmol), K_2CO_3 (0.979 g, 7.09 mmol), and $CHCl_3$ (10 mL), and the reaction mixture was stirred overnight at 50 °C. The solution was diluted with EtOAc and 1N HCl, and the layers were separated. The aqueous layer was further extracted with EtOAc, and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to provide an orange oil. The resulting residue was adsorbed on silica and purified by silica gel chromatography (0 to 50% EtOAc/hexanes) to afford N-(2-ethoxyethyl)-2-nitroaniline (837 mg) as an orange oil. LC-MS (ES) m/z = 211 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (t, J = 7.0 Hz, 3H), 3.50 (q, J = 5.3 Hz, 2H), 3.60 (q, J = 6.8 Hz, 2H), 3.69 - 3.80 (m, 2H), 6.66 (m, 1H), 6.88 (dd, J = 8.9, 1.0 Hz, 1H), 7.45 (m, 1H), 8.19 (dd, J = 8.6, 1.5 Hz, 1H).

20 Intermediate 204

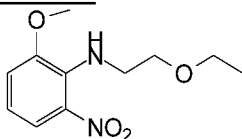
N1-(2-Ethoxyethyl)benzene-1,2-diamine



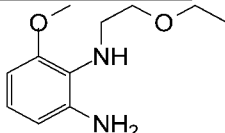
N-(2-Ethoxyethyl)-2-nitroaniline (837 mg, 3.98 mmol) was dissolved in CH_3OH (100 mL) and hydrogenated by continuous flow through a 10% Pd/C cartridge at 1 bar. The final solution was evaporated to yield N1-(2-ethoxyethyl)benzene-1,2-diamine (698 mg) as a dark brown oil. LC-MS (ES) m/z = 181 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.19 - 1.25 (m, 3H), 3.24 - 3.29 (m, 2H), 3.56 (q, J = 7.0 Hz, 2H), 3.64 - 3.70 (m, 2H), 6.59 - 6.68 (m, 2H), 6.70 - 6.76 (m, 2H).

Example 150**5-(1-(2-Ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine**

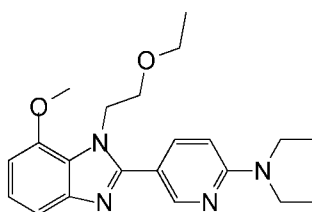
To N1-(2-ethoxyethyl)benzene-1,2-diamine (200 mg, 1.110 mmol) and 6-
 5 (diethylamino)nicotinaldehyde (218 mg, 1.221 mmol) dissolved in DMF (3 mL) and water (3 mL) was added oxone (443 mg, 0.721 mmol), and the reaction mixture was stirred at room temperature for 1 hour. The reaction was quenched with saturated aqueous NH₄Cl (5 mL), and the pH was adjusted to ~ 10 with NH₄OH (~8mL). The resulting aqueous mixture was extracted with EtOAc (3 x 20 mL), and the combined organic extracts were washed with
 10 water (2 x 10 mL), brine (10 mL), dried (MgSO₄), filtered, and concentrated. The resulting residue was adsorbed on silica and purified by silica gel chromatography (0 to 50% (3:1 EtOAc:ethanol)/hexanes) to afford 5-(1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (202 mg) as an oily white solid after lyophilization. LC-MS (ES) m/z = 339 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.06 (t, J = 7.0 Hz, 3H), 1.24 (t, J = 7.1 Hz,
 15 6H), 3.35 - 3.45 (m, 2H), 3.63 (q, J = 7.1 Hz, 4H) 3.86 (t, J = 5.3 Hz, 2H), 4.46 (t, J = 5.2 Hz, 2H), 6.71 - 6.82 (m, 1H), 7.24 - 7.35 (m, 2H), 7.54 - 7.77 (m, 2H), 7.98 (dd, J = 9.1, 2.5 Hz, 1H), 8.51 - 8.61 (m, 1H).

Intermediate 205**N-(2-Ethoxyethyl)-2-methoxy-6-nitroaniline****Reference: patent WO2012172043**

To a 40 mL screw cap vial were added 2-bromo-1-methoxy-3-nitrobenzene (1 g, 4.31 mmol), 2-ethoxyethan-1-amine (2.233 mL, 21.55 mmol), and 1,4-dioxane (15 mL), and the
 25 resulting solution was stirred at 100 °C over the weekend. The reaction mixture was evaporated, and the resulting residue was adsorbed on silica and purified by silica gel chromatography (0 to 50% EtOAc/hexanes) to afford N-(2-ethoxyethyl)-2-methoxy-6-nitroaniline (825 mg) as an orange oil. LC-MS (ES) m/z = 241 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 1.25 (t, J = 7.1 Hz, 3H), 3.55 (q, J = 6.9 Hz, 2H), 3.58 - 3.63 (m, 2H), 3.74 - 3.80
 30 (m, 2H), 3.88 (s, 3H), 6.69 (dd, J = 8.6, 7.9 Hz, 1H), 6.96 (dd, J = 7.9, 1.3 Hz, 1H), 7.74 (dd, J = 8.7, 1.4 Hz, 1H).

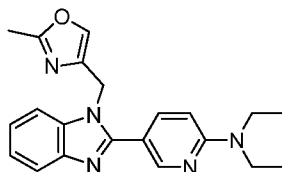
Intermediate 206N1-(2-Ethoxyethyl)-6-methoxybenzene-1,2-diamine

- 5 N-(2-Ethoxyethyl)-2-methoxy-6-nitroaniline (825 mg, 3.43 mmol) was dissolved in CH₃OH (100 mL)-0.034 mol/L and hydrogenated by continuous flow through a 10% Pd/C cartridge at 1 bar. The solution was evaporated to afford N1-(2-ethoxyethyl)-6-methoxybenzene-1,2-diamine (807 mg) as a dark amber oil. LC-MS (ES) m/z = 211 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.16 - 1.31 (m, 3H), 3.14 (t, J = 5.1 Hz, 2H), 3.45 - 3.60 (m, 4H), 3.82 (s, 3H),
10 6.36 - 6.49 (m, 2H), 6.86 (t, J = 8.1 Hz, 1H).

Example 1515-(1-(2-Ethoxyethyl)-7-methoxy-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine

- 15 To a mixture of N1-(2-ethoxyethyl)-6-methoxybenzene-1,2-diamine (100 mg, 0.476 mmol) and 6-(diethylamino)nicotinaldehyde (93 mg, 0.523 mmol) in DMF (2 mL) and water (2 mL) was added oxone (190 mg, 0.309 mmol), and the reaction mixture was stirred for 1 hour. The reaction was quenched with saturated aqueous NH₄Cl (10 mL) and the pH adjusted to
20 ~10 by addition of NH₄OH (~20 mL). The resulting aqueous mixture was extracted with EtOAc (3 x 20 mL), and the combined extracts were washed with water (2 x 10 mL) followed by brine (10 mL), dried (MgSO₄), and concentrated. The resulting residue was adsorbed on silica and purified by silica gel chromatography (0 to 50% (3:1 EtOAc:ethanol)/hexanes) to afford after lyophilization 5-(1-(2-ethoxyethyl)-7-methoxy-1H-benzo[d]imidazol-2-yl)-N,N-
25 diethylpyridin-2-amine (67.9 mg) as a grey solid. LC-MS (ES) m/z = 369 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.01 (t, J = 7.0 Hz, 3H), 1.14 - 1.27 (m, 6H), 3.21 - 3.34 (m, 2H), 3.52 - 3.67 (m, 4H), 3.78 (t, J = 5.3 Hz, 2H), 3.90 - 4.00 (m, 3H), 4.52 (t, J = 5.3 Hz, 2H), 6.71 (dd, J = 9.1, 0.8 Hz, 1H), 6.81 (dd, J = 8.1, 0.8 Hz, 1H), 7.12 - 7.23 (m, 1H), 7.24 - 7.31 (m, 1H), 7.82 - 7.98 (m, 1H), 8.43 - 8.55 (m, 1H).

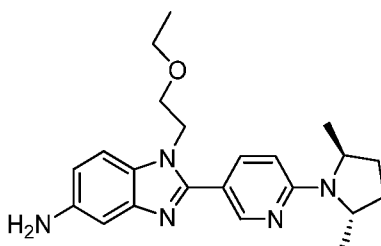
30

Example 152**N,N-Diethyl-5-(1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine**

- 5 To a solution of 5-(1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (50 mg, 0.19 mmol) in DMF (1.9 mL) cooled to 0 °C was added NaH (60% dispersion in oil, 9.8 mg, 0.24 mmol). After 5 minutes, 4-(bromomethyl)-2-methyloxazole (36 mg, 0.21 mmol) was added, and the mixture was warmed to room temperature. After 15 minutes, the reaction was heated at 60 °C and stirred for 4 hours. The reaction was quenched with saturated aqueous
- 10 NH₄Cl (2 mL) and diluted with EtOAc (20 mL) and water (20 mL). The phases were separated, and the aqueous layer was further extracted with EtOAc (2 x 10 mL). The combined organic extract was washed with water (10 mL) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 10 to 70% EtOAc/hexanes) to afford the desired product
- 15 (28 mg) as a clear film. LC-MS (ES) m/z = 362 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.57 (d, J = 1.8 Hz, 1H), 7.99 (dd, J = 9.0, 2.4 Hz, 1H), 7.85 (s, 1H), 7.38 - 7.26 (m, 4H), 6.62 (d, J = 8.9 Hz, 1H), 5.33 (s, 2H), 3.61 (q, J = 7.1 Hz, 4H), 2.51 (s, 3H), 1.26 (t, J = 7.1 Hz, 6H).

Example 153

20 **2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-amine**

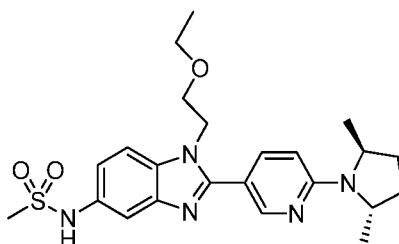


- A mixture of N-(2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)acetamide (230 mg, 0.546 mmol) and aqueous HCl (1N, 3 mL, 3.0
- 25 mmol) was stirred at 100 °C for 2 hours. The mixture was concentrated, and the residue was dried under vacuum to give the desired product (210 mg) product as a pale brown solid (HCl salt). LC-MS (ES) m/z = 380 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.09 - 1.17 (m, 3H), 1.26 - 1.41 (m, 6H), 1.85 - 1.98 (m, 2H), 2.50 (br. s., 2H), 3.46 - 3.58 (m, 2H), 4.00 (br.

s., 2H), 4.53 (br. s., 2H), 4.75 (br. s., 2H), 7.45 (d, $J = 8.1$ Hz, 1H), 7.61 (d, $J = 7.6$ Hz, 1H), 7.81 - 7.91 (m, 1H), 8.17 (m, 1H), 8.34 - 8.47 (m, 1H), 8.77 - 8.90 (m, 1H).

Example 154

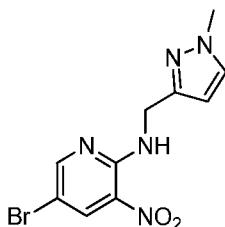
5 N-(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)methanesulfonamide



To a solution of 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-amine (80 mg, 0.211 mmol) in CH_2Cl_2 (2 mL) were added
 10 methanesulfonyl chloride (0.020 mL, 0.253 mmol) and N,N-diisopropylethylamine (0.074 mL, 0.422 mmol), and the reaction mixture was stirred at reflux for 2 hours. The mixture was concentrated, and the resulting residue was purified by silica gel chromatography (0 to 100 % (3:1 EtOAc:EtOH)/heptane) to give the desired product (36 mg) as an off-white solid. LC-MS (ES) $m/z = 458$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.03 - 1.18 (m, 3H), 1.24 -
 15 1.33 (m, 6H), 1.85 (d, $J = 5.6$ Hz, 2H), 2.42 (br. s., 2H), 3.05 (s, 3H), 3.45 - 3.52 (m, 2H), 3.99 (t, $J = 4.9$ Hz, 2H), 4.34 (br. s., 1H), 4.51 (br. s., 1H), 4.62 - 4.73 (m, 2H), 7.04 (d, $J = 9.1$ Hz, 1H), 7.46 (dd, $J = 8.9, 2.0$ Hz, 1H), 7.76 (d, $J = 1.8$ Hz, 1H), 7.89 - 7.96 (m, 1H), 8.22 (dd, $J = 9.4, 2.5$ Hz, 1H), 8.74 (d, $J = 2.0$ Hz, 1H).

20 Intermediate 207

5-Bromo-N-((1-methyl-1H-pyrazol-3-yl)methyl)-3-nitropyridin-2-amine

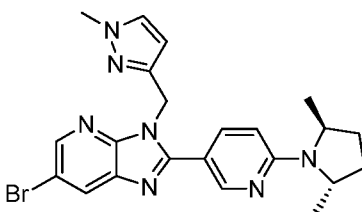


To a solution of 5-bromo-2-chloro-3-nitropyridine (600 mg, 2.53 mmol) in CH_3CN (12 mL) were added (1-methyl-1H-pyrazol-3-yl)methanamine (281 mg, 2.53 mmol) and N,N-diisopropylethylamine (0.530 mL, 3.03 mmol), and the reaction mixture was stirred at room
 25 temperature for 20 hours. The mixture was concentrated, and the resulting residue was washed with water and dried under vacuum to give the desired product (750 mg) as a pale

yellow solid. LC-MS (ES) m/z = 312, 314 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 3.87 (s, 3H), 4.80 (d, J = 5.6 Hz, 2H), 6.25 (d, J = 2.3 Hz, 1H), 7.52 (d, J = 2.3 Hz, 1H), 8.51 (d, J = 2.3 Hz, 1H), 8.63 (d, J = 2.3 Hz, 1H).

5 Intermediate 208

6-Bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine



10

To a 20-mL microwave tube were added 5-bromo-N-((1-methyl-1H-pyrazol-3-yl)methyl)-3-nitropyridin-2-amine (400 mg, 1.282 mmol), 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (314 mg, 1.538 mmol), sodium hydrosulfite (85%, 787 mg, 3.84 mmol), ethanol (6 mL), and water (1.5 mL). The tube was sealed, and the reaction mixture was stirred at 130 °C under microwave conditions for 80 minutes. The mixture was then cooled to room temperature, diluted with EtOAc, filtered, and concentrated. The resulting residue was washed with water and dried to give the desired product (380 mg) as an off-white solid. LC-MS (ES) m/z = 466, 468 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.17 - 1.24 (m, 6H), 1.75 (d, J = 5.6 Hz, 2H), 2.34 (br. s., 2H), 3.81 - 3.88 (m, 3H), 4.31 (br. s., 2H), 5.58 (s, 2H), 6.15 (d, J = 2.3 Hz, 1H), 6.68 (d, J = 8.6 Hz, 1H), 7.53 (d, J = 2.3 Hz, 1H), 7.99 (dd, J = 9.0, 2.4 Hz, 1H), 8.20 (d, J = 2.0 Hz, 1H), 8.43 (d, J = 2.0 Hz, 1H), 8.54 - 8.62 (m, 1H).

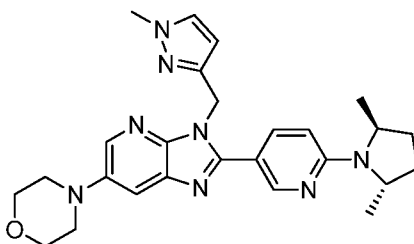
15

20

Example 155

4-(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridin-6-yl)morpholine

25

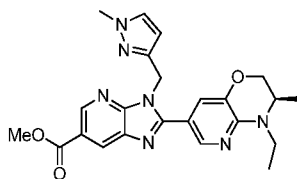


To a solution of 6-bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine (150 mg, 0.322 mmol) in 2-

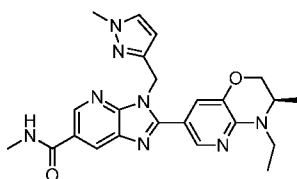
methyl tetrahydrofuran (3 mL) were added morpholine (0.056 mL, 0.643 mmol), 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl (6.33 mg, 0.016 mmol), Pd₂(dba)₃ (5.89 mg, 6.43 μmol), and sodium *tert*-butoxide (93 mg, 0.965 mmol), and the resulting mixture was degassed for 10 minutes by bubbling argon. The reaction mixture was then stirred at 80 °C for 2 hours. The reaction was cooled to room temperature, quenched with brine (10 mL), and extracted with EtOAc (2x). The combined organic extract was dried and concentrated. The resulting residue was purified by silica gel column chromatography (0 to 100% (3:1 EtOAc:EtOH)/heptane) to give the desired product (93 mg) as a white solid. LC-MS (ES) *m/z* = 473 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.17 - 1.24 (m, 6H), 1.75 (d, *J* = 5.8 Hz, 2H), 2.28 - 2.39 (m, 2H), 3.19 - 3.26 (m, 4H), 3.85 (s, 3H), 3.89 - 3.95 (m, 4H), 4.30 (br. s., 2H), 5.54 (s, 2H), 6.10 (d, *J* = 2.3 Hz, 1H), 6.67 (d, *J* = 8.9 Hz, 1H), 7.52 (d, *J* = 2.3 Hz, 1H), 7.63 (d, *J* = 2.5 Hz, 1H), 7.94 (dd, *J* = 8.9, 2.5 Hz, 1H), 8.20 (d, *J* = 2.5 Hz, 1H), 8.46 - 8.59 (m, 1H).

15 Intermediate 209

(R)-Methyl 2-(4-ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxylate

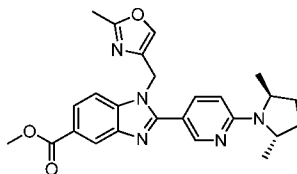


To a 20-mL microwave tube were added methyl 6-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)-5-nitronicotinate (110 mg, 0.378 mmol), (R)-4-ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-7-carbaldehyde (86 mg, 0.415 mmol), sodium hydrosulfite (85%, 232 mg, 1.133 mmol), ethanol (2mL), and water (0.5 mL). The tube was sealed, and the reaction mixture was stirred at 130 °C under microwave conditions for 80 minutes. The mixture was then cooled to room temperature, filtered, and concentrated. The resulting residue was treated with water and extracted with CH₂Cl₂ (3x). The combined organic extract was dried (Na₂SO₄) and concentrated. The resulting residue was purified by silica gel chromatography (0% to 100% EtOAc/heptane) to give the desired product (140 mg) as a pale yellow solid. LC-MS (ES) *m/z* = 448 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.20 - 1.29 (m, 3H), 1.30 - 1.37 (m, 3H), 3.45 (dq, *J* = 14.1, 7.0 Hz, 1H), 3.80 - 3.88 (m, 4H), 3.96 - 4.06 (m, 5H), 4.10 - 4.17 (m, 1H), 5.62 (s, 2H) 6.16 (d, *J* = 2.3 Hz, 1H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.54 (d, *J* = 2.3 Hz, 1H), 8.22 (d, *J* = 2.0 Hz, 1H), 8.58 (d, *J* = 1.8 Hz, 1H), 9.01 (d, *J* = 1.8 Hz, 1H).

Example 156**(R)-2-(4-Ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-N-methyl-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide**

5

To a solution of methyl (R)-2-(4-ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxylate (98 mg, 0.219 mmol) in CH₃OH (1.5 mL) was added aqueous NaOH (5N, 0.36 mL, 1.800 mmol), and the reaction mixture was stirred 40 °C for 18 hours. The reaction was neutralized by adding HCl (6 N, 0.3 mL, 1.8 mmol) and concentrated. To the resulting residue in DMSO (1.5 mL) were added methylamine hydrochloride (23.66 mg, 0.350 mmol), EDC (84 mg, 0.438 mmol), 1-hydroxy-7-azabenzotriazole (59.6 mg, 0.438 mmol), and N-methylmorpholine (0.144 mL, 1.314 mmol), and the reaction mixture was stirred at room temperature for 18 hours. The reaction was quenched with water (5 mL) and extracted with EtOAc (3x). The combined organic extract was dried (Na₂SO₄) and concentrated. The resulting residue was purified by silica gel chromatography (0 to 100 % (3:1 EtOAc:EtOH)/heptane) to give the desired product (72 mg) as a pale yellow solid. LC-MS (ES) m/z = 447 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.20 - 1.28 (m, 3H), 1.33 (d, J = 6.6 Hz, 3H), 2.99 (s, 3H), 3.45 (dq, J = 14.2, 7.0 Hz, 1H), 3.79 - 3.89 (m, 4H), 3.95 - 4.05 (m, 2H), 4.09 - 4.18 (m, 1H), 5.62 (s, 2H), 6.15 (d, J = 2.3 Hz, 1H), 7.46 (d, J = 2.3 Hz, 1H), 7.53 (d, J = 2.3 Hz, 1H), 8.21 (d, J = 2.0 Hz, 1H), 8.45 (d, J = 2.0 Hz, 1H), 8.86 (d, J = 1.8 Hz, 1H).

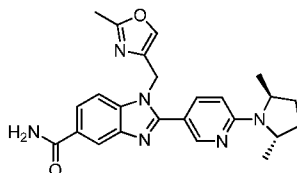
Intermediate 210**Methyl 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carboxylate**

To a 20-mL microwave tube were added methyl 4-(((2-methyloxazol-4-yl)methyl)amino)-3-nitrobenzoate (300 mg, 1.030 mmol), 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde

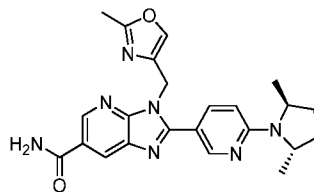
(231 mg, 1.133 mmol), sodium hydrosulfite (85%, 633 mg, 3.09 mmol), ethanol (4 mL), and water (1 mL), and the reaction mixture was stirred at 130 °C under microwave conditions for 80 minutes. The mixture was then cooled to room temperature, diluted with EtOAc, and concentrated. The resulting residue was washed with water and dried under vacuum to give the desired product (350 mg) as an off-white solid. LC-MS (ES) m/z = 446 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.23 (d, J = 6.1 Hz, 6H), 1.69 - 1.79 (m, 2H), 2.30 - 2.38 (m, 2H), 2.41 (s, 3H), 3.95 (s, 3H), 4.32 (br. s., 1H), 5.40 (s, 2H), 6.72 (d, J = 8.9 Hz, 1H), 7.61 (d, J = 8.6 Hz, 1H), 7.85 (s, 1H), 7.99 (dd, J = 8.6, 1.5 Hz, 1H), 8.07 (dd, J = 8.9, 2.5 Hz, 1H), 8.36 (d, J = 1.0 Hz, 1H), 8.66 (d, J = 2.0 Hz, 1H).

Example 157

2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide

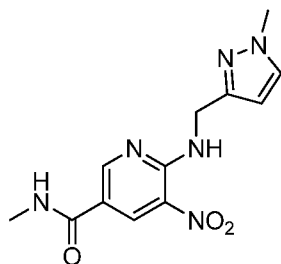


To a solution of methyl 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carboxylate (100 mg, 0.224 mmol) in CH_3OH (2 mL) was added aqueous NaOH (5N, 400 μ L, 2.000 mmol), and the reaction mixture was stirred 40 °C for 18 hours. The reaction was neutralized by adding aqueous HCl (6N, 333 μ L, 2.000 mmol) and concentrated. To the resulting residue in DMSO (2 mL) were added NH_4Cl (20.41 mg, 0.382 mmol), EDC (86 mg, 0.449 mmol), 1-hydroxy-7-azabenzotriazole (61.1 mg, 0.449 mmol), and N-methylmorpholine (148 μ L, 1.347 mmol), and the reaction mixture was stirred at room temperature for 18 hours. The reaction was quenched with water (5 mL) and extracted with EtOAc (3x). The combined organic extract was dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel chromatography (0 to 100 % (3:1 EtOAc:EtOH)/heptane) to give the desired product (51 mg) as a pale brown solid. LC-MS (ES) m/z = 431 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.18 - 1.29 (m, 6H), 1.72 - 1.81 (m, 2H), 2.29 - 2.39 (m, 2H), 2.42 (s, 3H), 2.68 (s, 3H), 4.33 (br. s., 2 H), 5.36 - 5.43 (m, 2H), 6.73 (d, J = 8.9 Hz, 1H), 7.61 (d, J = 8.6 Hz, 1H), 7.83 - 7.92 (m, 2H), 8.07 (dd, J = 9.0, 2.4 Hz, 1H), 8.21 - 8.27 (m, 1H), 8.66 (d, J = 2.3 Hz, 1H).

Example 158**2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((2-methyloxazol-4-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide**

- 5 To a solution of methyl 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((2-methyloxazol-4-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxylate (69 mg, 0.155 mmol) in CH₃OH (2 mL) was added NaOH (5N, 260 μ l, 1.30 mmol), and the reaction mixture was stirred 40 °C for 18 hours. The reaction was neutralized by adding aqueous HCl (6N, 217 μ l, 1.300 mmol) and then concentrated. To the resulting residue in DMSO (2 mL) were
- 10 added NH₄Cl (14.88 mg, 0.278 mmol), EDC (59.2 mg, 0.309 mmol), 1-hydroxy-7-azabenzotriazole (42.1 mg, 0.309 mmol), and N-methylmorpholine (102 μ l, 0.927 mmol), and the reaction mixture was stirred at room temperature for 18 hours. The reaction was quenched with water (5 mL) and extracted with EtOAc (3x). The combined organic extract was dried (Na₂SO₄) and concentrated. The resulting resulting residue was purified by silica
- 15 gel chromatography (0 to 100 % (3:1 EtOAc:EtOH)/heptane) to give the desired product (48 mg) as a pale yellow solid. LC-MS (ES) m/z = 432 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.23 (d, J = 6.1 Hz, 6H), 1.76 (d, J = 5.8 Hz, 2 H), 2.29 - 2.44 (m, 5H), 2.68 (s, 2H), 4.25 - 4.45 (m, 2H), 5.49 - 5.57 (m, 2H), 6.72 (d, J = 9.1 Hz, 1H), 7.75 (s, 1H), 8.10 (dd, J = 9.1, 2.5 Hz, 1H), 8.52 (d, J = 2.0 Hz, 1H), 8.69 (d, J = 1.8 Hz, 1H), 8.91 (d, J = 2.0 Hz, 1H).

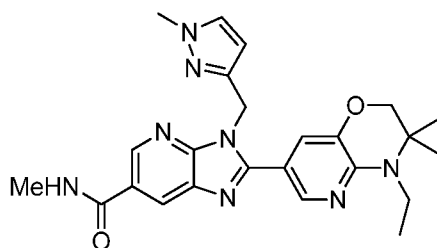
20

Intermediate 211**N-Methyl-6-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)-5-nitronicotinamide**

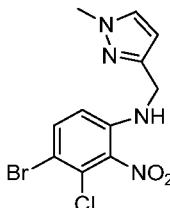
- To a solution of methyl 6-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)-5-nitronicotinate (7.1 g, 24.38 mmol) in CH₃OH (350 mL) was added aqueous NaOH (10N, 48.8 mL, 488 mmol), and the reaction mixture was stirred at room temperature overnight. The mixture was then concentrated to remove most of CH₃OH, diluted with water (100 mL), and treated with
- 25

aqueous HCl (6N, 81 mL). The resulting precipitate was collected by filtration and dried under vacuum overnight to afford 6-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)-5-nitronicotinic acid (6.71 g) as a light yellow solid. LC-MS (ES) m/z = 278 $[M+H]^+$. To a solution of 6-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)-5-nitronicotinic acid (6.7 g, 24.17 mmol) in DMSO (150 mL) were added HOBT (4.81 g, 31.4 mmol), EDC (6.02 g, 31.4 mmol), methylamine hydrochloride (1.958 g, 29.0 mmol), and N-methylmorpholine (21.26 mL, 193 mmol), and the mixture was stirred at room temperature overnight. The reaction was quenched with water (200 mL). The resulting precipitate was collected by filtration and dried under vacuum to give N-methyl-6-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)-5-nitronicotinamide (5.64 g) as a bright yellow solid. LC-MS (ES) m/z = 291 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 2.79 (d, J = 4.3 Hz, 3H), 3.80 (s, 3H), 4.76 (d, J = 5.6 Hz, 2H), 6.17 (d, J = 2.0 Hz, 1H), 7.61 (d, J = 2.0 Hz, 1H), 8.60 (d, J = 4.6 Hz, 1H), 8.88 (d, J = 2.3 Hz, 1H), 8.91 (d, J = 2.0 Hz, 1H), 9.03 (t, J = 5.3 Hz, 1H).

15

Example 159**2-(4-Ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-N-methyl-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide**

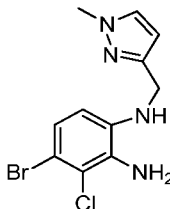
To a 10-mL microwave tube were added N-methyl-6-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)-5-nitronicotinamide (80 mg, 0.276 mmol), 4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-7-carbaldehyde (60.7 mg, 0.276 mmol), sodium hydrosulfite (85%, 169 mg, 0.827 mmol), ethanol (2 mL), and water (0.5 mL), and the reaction mixture was stirred at 130 °C under microwave conditions for 80 minutes. The mixture was then cooled to room temperature, diluted with EtOAc, filtered, and concentrated. The resulting residue was washed with water and dried under vacuum to give the desired product (98 mg) as a pale brown solid. LC-MS (ES) m/z = 461 $[M+H]^+$. ^1H NMR (400 MHz, CD $_3$ OD): δ 1.25 - 1.31 (m, 3H), 1.33 - 1.40 (m, 6H), 3.00 (s, 3H), 3.62 - 3.76 (m, 2H), 3.84 (s, 3H), 3.90 - 3.96 (m, 2H), 5.63 (s, 2H), 6.14 (d, J = 2.3 Hz, 1H), 7.45 (d, J = 2.0 Hz, 1H), 7.54 (d, J = 2.3 Hz, 1H), 8.23 (d, J = 2.0 Hz, 1H), 8.45 (d, J = 1.8 Hz, 1H), 8.86 (d, J = 2.3 Hz, 1H).

Intermediate 2124-Bromo-3-chloro-N-((1-methyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline

- 5 A solution of 1-bromo-2-chloro-4-fluoro-3-nitrobenzene (2621 mg, 10.30 mmol), (1-methyl-1H-pyrazol-3-yl)methanamine (954 mg, 8.58 mmol), and K₂CO₃ (3559 mg, 25.8 mmol) in CH₃CN (20 mL) was stirred at 70 °C for 30 hours. The reaction mixture was filtered, and the filtrate was concentrated. The resulting residue was purified by silica gel chromatography (0 to 20 % EtOAc/CH₂Cl₂) to give the desired product (891 mg) as a pale yellow solid. LC-MS (ES) m/z = 345, 347 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 1.80 (s, 1H), 3.92 (s, 3H), 4.41 (s, 2H), 5.87 (s, 1H), 6.19 (d, J = 2.0 Hz, 1H), 6.77 (d, J = 9.2 Hz, 1H), 7.34 (d, J = 2.0 Hz, 1H), 7.53 (d, J = 9.2 Hz, 1H).
- 10

Intermediate 213

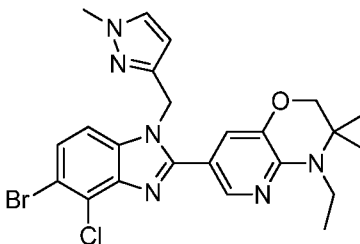
- 15 4-Bromo-3-chloro-N1-((1-methyl-1H-pyrazol-3-yl)methyl)benzene-1,2-diamine



- A solution of 4-bromo-3-chloro-N-((1-methyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline (891 mg, 2.58 mmol) and tin(II) chloride dihydrate (1164 mg, 5.16 mmol) in ethanol (20 mL) was stirred at 80 °C for 2 hours. The mixture was concentrated under vacuum, and the resulting residue was treated with saturated NaHCO₃ solution (20 mL) and extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated. The resulting residue was purified by silica gel chromatography (0 to 20 % EtOAc/CH₂Cl₂) to give the desired product (640 mg) as a pale yellow solid. LC-MS (ES) m/z = 315, 317 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 3.41 (m, 3H), 3.88 (s, 3H), 4.30 (s, 2H), 6.20 (s, 1H), 6.55 (d, J = 8.6 Hz, 1H), 7.01 (d, J = 8.6 Hz, 1H), 7.31 (s, 1H).
- 20
- 25

Intermediate 214

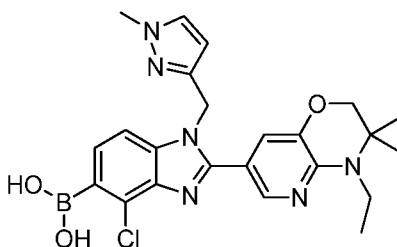
7-(5-Bromo-4-chloro-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine



- 5 A mixture of 4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-7-carbaldehyde (370 mg, 1.679 mmol) and 4-bromo-3-chloro-N1-((1-methyl-1H-pyrazol-3-yl)methyl)benzene-1,2-diamine (530 mg, 1.679 mmol) in acetic acid (20 mL) was stirred at 80 °C for 16 hours. The mixture was concentrated under vacuum, and the residue was poured into water (50 mL), basified using aqueous NaHCO₃ solution to pH 9, and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated. The resulting residue was purified by silica gel chromatography (0 to 5 % EtOAc/CH₂Cl₂) to give the desired product (452 mg) as a white solid. LC-MS (ES) m/z = 515, 517 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 1.26 (d, J = 6.9 Hz, 3H), 1.33 (s, 6H), 3.63 (d, J = 6.7 Hz, 2H), 3.86 (s, 2H), 3.89 (s, 3H), 5.41 (d, J = 6.8 Hz, 2H), 5.93 (s, 1H), 7.14 (d, J = 8.5 Hz, 1H), 7.27 (s, 1H), 7.41 (d, J = 8.6 Hz, 1H), 7.45 (s, 1H), 8.20 (s, 1H).

Example 160

(4-Chloro-2-(4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-5-yl)boronic acid

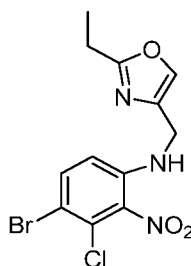


- 20 To a solution of 7-(5-bromo-4-chloro-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine (252 mg, 0.489 mmol) and triisopropyl borate (276 mg, 1.466 mmol) in THF (5 mL) and toluene (1.25 mL) was added n-butyllithium (0.244 mL, 0.586 mmol) at -78 °C under N₂, and the resulting mixture was stirred at -78 °C for 1 hour. The reaction was then warmed up to room temperature and stirred overnight. The reaction was quenched with aqueous NH₄Cl (4 mL)

and the mixture was concentrated under vacuum. The resulting residue was poured onto water (30 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (0 to 5 % $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$) to give the desired product (55 mg) as a yellow solid. LC-MS (ES) $m/z = 481$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 1.26 (s, 3H), 1.32 (s, 6H), 3.63 (dd, $J = 13.9, 6.9$ Hz, 2H), 3.86 (s, 2H), 3.88 (s, 3H), 5.41 (s, 2H), 5.90 (d, $J = 2.0$ Hz, 1H), 7.25 (s, 1H), 7.29 (d, $J = 12.2$ Hz, 1H), 7.44 (d, $J = 1.8$ Hz, 1H), 7.71 (d, $J = 8.2$ Hz, 1H), 8.19 (d, $J = 1.7$ Hz, 1H).

10 Intermediate 215

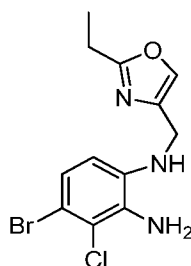
4-Bromo-3-chloro-N-((2-ethyloxazol-4-yl)methyl)-2-nitroaniline



A mixture of 1-bromo-2-chloro-4-fluoro-3-nitrobenzene (1.5 g, 5.90 mmol), (2-ethyloxazol-4-yl)methanamine hydrochloride (0.959 g, 5.90 mmol) and K_2CO_3 (2.444 g, 17.69 mmol) in CH_3CN (30 mL) was stirred at 70 °C for 5 hours. The reaction mixture was filtered, and the filtrate was concentrated. The resulting residue was purified by silica gel chromatography (0 to 3% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$) to give the desired product (1.0 g) as a yellow solid. LC-MS (ES) $m/z = 360, 362$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 1.34 (t, $J = 7.6$ Hz, 3H), 2.78 (q, $J = 7.6$ Hz, 2H), 4.29 (d, $J = 4.5$ Hz, 2H), 5.71 (s, 1H), 6.70 (d, $J = 9.2$ Hz, 1H), 7.44 (s, 1H), 7.52 (d, $J = 9.2$ Hz, 1H).

Intermediate 216

4-Bromo-3-chloro-N1-((2-ethyloxazol-4-yl)methyl)benzene-1,2-diamine



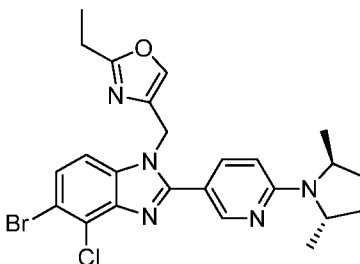
25 To a stirred solution of 4-bromo-3-chloro-N-((2-ethyloxazol-4-yl)methyl)-2-nitroaniline (500 mg, 1.387 mmol) and ammonium chloride (742 mg, 13.87 mmol) in THF (10 mL) and water

(5 mL) was added zinc (453 mg, 6.93 mmol), and the resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was filtered, and the filtrate was concentrated under vacuum. The residue was poured onto water (100 mL), basified using aqueous NaHCO₃ to pH 9, and extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated. The resulting residue was purified by silica gel chromatography (0-5% CH₃OH/CH₂Cl₂) to give the desired product (360 mg) as a brown oil. LC-MS (ES) m/z = 330, 332 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 1.34 (t, J = 7.6 Hz, 3H), 2.78 (m, 2H), 4.18 (s, 2H), 6.50 (d, J = 8.6 Hz, 1H), 7.01 (d, J = 8.5 Hz, 1H), 7.45 (d, J = 5.5 Hz, 1H).

10

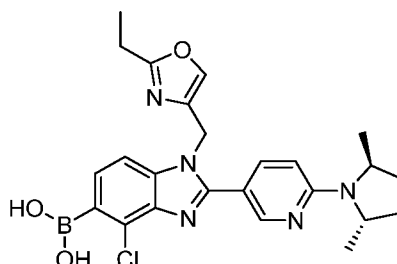
Intermediate 217

4-((5-Bromo-4-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)-2-ethyloxazole

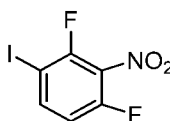


15 A mixture of 4-bromo-3-chloro-N1-((2-ethyloxazol-4-yl)methyl)benzene-1,2-diamine (360 mg, 1.089 mmol) and 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (222 mg, 1.089 mmol) in ethanol (15 mL) and acetic acid (0.5 mL) was stirred at 80 °C for 12 hours. The mixture was concentrated under vacuum, and the resulting residue was poured into water (50 mL), basified using aqueous NaHCO₃ to pH 9, and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated. The resulting residue was purified by silica gel chromatography (0-5% CH₃OH/CH₂Cl₂) to give the desired product (390 mg) as a brown oil. LC-MS (ES) m/z = 514, 516 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 1.26 – 1.12 (m, 6H), 1.34 (t, J = 7.6 Hz, 3H), 1.71 (d, J = 5.3 Hz, 2H), 2.29 (s, 2H), 2.79 (q, J = 7.6 Hz, 2H), 4.14 (d, J = 7.1 Hz, 2H), 5.27 (s, 1H), 6.51 (s, 1H), 7.18 (s, 1H), 7.45 (d, J = 8.6 Hz, 1H), 7.97 (s, 1H), 8.55 (s, 1H).

25

Example 161**(4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-5-yl)boronic acid**

To a stirred solution of 4-((5-bromo-4-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)-2-ethyloxazole (390 mg, 0.758 mmol) and triisopropyl borate (0.528 mL, 2.273 mmol) in toluene (8 mL) and THF (2 mL) was added n-butyllithium (0.379 mL, 0.909 mmol) at -78 °C under Ar, and the reaction mixture was stirred at -78 °C for 1 hour. Triisopropyl borate (0.528 mL, 2.273 mmol) and THF (4 mL) were added followed by n-butyllithium (0.379 mL, 0.909 mmol), and the resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with aqueous NH₄Cl (2 mL) and the mixture was concentrated under vacuum. The residue was poured onto water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated. The resulting residue was purified by silica gel chromatography (0-5% CH₃OH/CH₂Cl₂) to give the desired product (65 mg) as a white solid. LC-MS (ES) m/z = 480, 481, 482 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.23 (d, J = 6.2 Hz, 6H), 1.29 (t, J = 7.6 Hz, 3H), 1.80 – 1.70 (m, 2H), 2.42 – 2.29 (m, 2H), 2.77 (q, J = 7.6 Hz, 2H), 4.33 (s, 2H), 5.36 (s, 2H), 6.72 (d, J = 9.0 Hz, 1H), 7.22 (d, J = 8.1 Hz, 1H), 7.51 (d, J = 8.1 Hz, 1H), 7.81 (s, 1H), 8.07 (dd, J = 8.9, 2.3 Hz, 1H), 8.64 (d, J = 2.2 Hz, 1H).

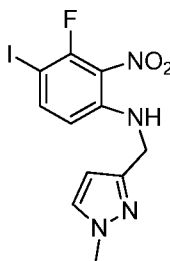
Intermediate 218**1,3-Difluoro-4-iodo-2-nitrobenzene**

To a solution of 1,3-difluoro-2-nitrobenzene (5.0 g, 31.4 mmol) in trifluoroacetic acid (TFA) (20.0 mL) and concentrated sulfuric acid (10 mL) was added N-iodosuccinimide (7.07 g, 31.4 mmol), and the reaction mixture was heated at 60 °C for 45 minutes. The reaction

was cooled to room temperature and poured onto ice. The resulting mixture was extracted with EtOAc, and the combined organic extract was washed with water followed by saturated aqueous NaHCO₃, dried over MgSO₄, filtered, and concentrated to afford 1,3-difluoro-2-nitrobenzene (5.0 g) as a white solid. GC-MS(Cl) m/z = 286 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.97 (ddd, J = 5.7, 6.6, 9.0 Hz, 1H), 6.90 - 7.08 (m, J = 1.8, 9.0, 9.0 Hz, 1H).

Intermediate 219

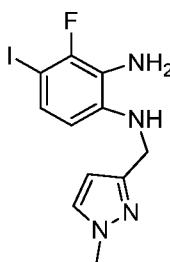
3-Fluoro-4-iodo-N-((1-methyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline



A solution of 1,3-difluoro-4-iodo-2-nitrobenzene (1.0 g, 3.51 mmol) and triethylamine (0.538 mL, 3.86 mmol) in DMF (25 mL) was heated at 75 °C. A solution of 1-methyl-1H-pyrazol-3-yl)methanamine (410 mg, 3.68 mmol) in DMF (3 mL) was then added dropwise, and the reaction mixture was stirred at 75 °C for 2 hours. The reaction was cooled, then concentrated, and treated with CH₂Cl₂. The resulting organic mixture was washed with water followed by brine, dried over MgSO₄, filtered, and concentrated. Purification by flash chromatography on SiO₂ (0% to 60% EtOAc/hexanes) afforded 3-fluoro-4-iodo-N-((1-methyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline (697 mg) as a orange solid. LC-MS (ES) m/z = 377 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.61 (dd, J = 6.3, 9.4 Hz, 1H), 7.54 (br. s., 1H), 7.35 (d, J = 2.3 Hz, 1H), 6.60 (dd, J = 1.5, 9.4 Hz, 1H), 6.21 (d, J = 2.3 Hz, 1H), 4.47 (d, J = 5.1 Hz, 2H), 3.93 (s, 3H).

Intermediate 220

3-Fluoro-4-iodo-N1-((1-methyl-1H-pyrazol-3-yl)methyl)benzene-1,2-diamine

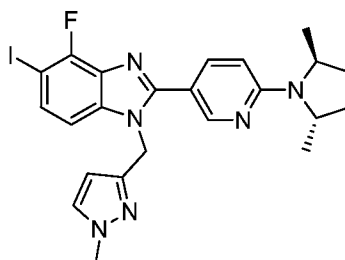


A mixture of 3-fluoro-4-iodo-N-((1-methyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline (200 mg, 0.532 mmol) and sodium hydrosulfite (278 mg, 85%, 1.356 mmol) in ethanol (4 mL) and

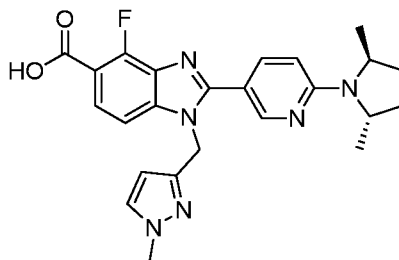
water (2mL) was heated under microwave conditions at 130 °C for 10 minutes. The reaction was then filtered and concentrated to dryness. Water was added, and the resulting aqueous mixture was extracted with CH₂Cl₂. The combined organic extract was washed with water, dried over MgSO₄, filtered, and concentrated. Purification by flash chromatography on SiO₂ (0% to 100% EtOAc/hexanes) afforded 3-fluoro-4-iodo-N1-((1-methyl-1H-pyrazol-3-yl)methyl)benzene-1,2-diamine (98 mg). LC-MS (ES) m/z = 347 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.35 (d, *J* = 2.3 Hz, 1H), 7.12 (dd, *J* = 6.8, 8.6 Hz, 1H), 6.40 (dd, *J* = 1.1, 8.5 Hz, 1H), 6.24 (d, *J* = 2.3 Hz, 1H), 4.35 (s, 2H), 3.93 (s, 3H).

10 Intermediate 221

2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-5-iodo-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole



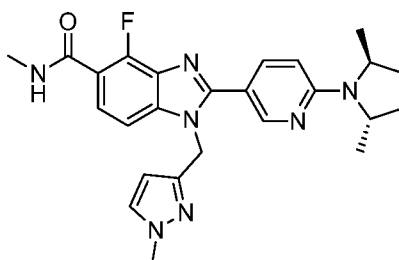
A mixture of 3-fluoro-4-iodo-N1-((1-methyl-1H-pyrazol-3-yl)methyl)benzene-1,2-diamine (98 mg, 0.226 mmol), 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (46.3 mg, 0.226 mmol), and oxone (91 mg, 0.147 mmol) in DMF (10 mL) and water (4 mL) was stirred at room temperature for 16 hours. Saturated aqueous NaHCO₃ was then added, and the resulting mixture was extracted with CH₂Cl₂. The combined organic extract was washed with water followed by brine, dried over MgSO₄, filtered, and concentrated. Purification by flash chromatography on SiO₂ (0% to 70% (3:1 EtOAc:EtOH):heptane) afforded 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-5-iodo-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole (108 mg) as a tan solid. LC-MS (ES) m/z = 531 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.59 (br. s., 1H), 7.95 (d, *J* = 7.9 Hz, 1H), 7.48 (dd, *J* = 5.6, 8.4 Hz, 1H), 7.30 (d, *J* = 2.3 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.50 (d, *J* = 7.9 Hz, 1H), 5.96 (br. s., 1H), 5.41 (s, 2H), 4.3 (br. s, 2H), 3.91 (s, 3H), 2.30 (br. s., 2H), 1.72 (d, *J* = 5.6 Hz, 2H), 1.22 (d, *J* = 6.3 Hz, 6H).

Intermediate 2222-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid

- 5 A mixture of 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-5-iodo-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole (110 mg, 0.207 mmol), potassium 2-ethoxy-2-oxoacetate (48.6 mg, 0.311 mmol), 1,3-bis(diphenylphosphino)propane (25.7 mg, 0.062 mmol), and palladium(II) trifluoroacetate (13.79 mg, 0.041 mmol) in N-Methyl-2-pyrrolidone (NMP) (4 mL) was degassed with argon for 10 minutes. The reaction vial was
- 10 then capped, and the reaction mixture was stirred at 150 °C for 60 minutes. The reaction was filtered and purified via reverse phase HPLC (10 to 100% CH₃CN/0.1%NH₄OH in H₂O) to afford 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid (24 mg) as an off-white solid. LC-MS (ES) m/z = 449 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.65 (d, J = 2.3 Hz, 1H), 8.01
- 15 (dd, J = 2.3, 9.1 Hz, 1H), 7.90 (dd, J = 6.3, 8.4 Hz, 1H), 7.33 (d, J = 2.0 Hz, 1H), 7.21 (d, J = 8.9 Hz, 1H), 6.54 (d, J = 8.9 Hz, 1H), 6.02 (d, J = 2.3 Hz, 1H), 5.48 (s, 2H), 4.3 (br. s., 2H), 3.93 (s, 3H), 2.31 (br. s., 2H), 1.73 (d, J = 5.6 Hz, 2H), 1.24 (d, J=6.34 Hz, 6H).

Example 162

- 20 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide

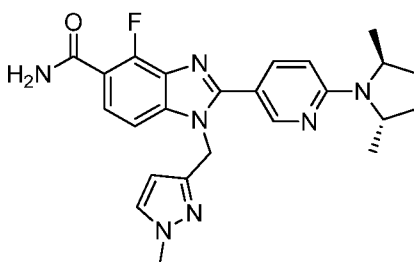


- A solution of 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid (46 mg, 0.103 mmol),
- 25 EDC (39.3 mg, 0.205 mmol), 1-hydroxy-7-azabenzotriazole (27.9 mg, 0.205 mmol), methanamine hydrochloride (7.96 mg, 0.118 mmol) and N-methylmorpholine (67.7 µl, 0.615

mmol) in DMSO (20 mL) was stirred at room temperature for 16 hours. Water was added, and the resulting mixture was extracted with EtOAc. The combined organic extract was washed with water followed by brine, dried over MgSO_4 , filtered, and concentrated. Purification by flash chromatography on SiO_2 (0% to 15% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$) afforded 2-(6-
 5 ((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide (43 mg) as a tan solid. LC-MS (ES) m/z = 462 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 8.61 (br. s., 1H), 7.90 - 8.13 (m, 2H), 7.30 (d, J = 2.0 Hz, 1H), 7.21 (d, J = 8.6 Hz, 1H), 6.88 (dd, J = 4.7, 12.8 Hz, 1H), 6.50 (d, J = 8.9 Hz, 1H), 5.98 (d, J = 1.8 Hz, 1H), 5.42 (s, 2H), 4.27 (br. s., 2H), 3.91 (s, 3H), 3.09 (d,
 10 J = 4.1 Hz, 3H), 2.19 - 2.39 (m, 2H), 1.71 (d, J = 5.6 Hz, 2H), 1.21 (d, J = 6.3 Hz, 6H).

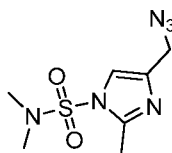
Example 163

2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide

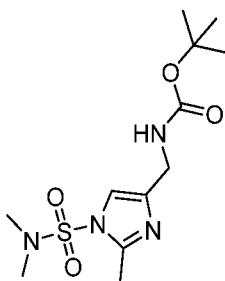


15 A solution of 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid (30 mg, 0.067 mmol), EDC (25.6 mg, 0.134 mmol), 1-hydroxy-7-azabenzotriazole (18.21 mg, 0.134 mmol), N-methylmorpholine (44.1 μL , 0.401 mmol), and NH_4Cl (3.58 mg, 0.067 mmol) in DMSO (20
 20 mL) was stirred at room temperature for 16 hours. Water was then added, and the resulting mixture was extracted with EtOAc. The combined organic extract was washed with water followed by brine, dried over MgSO_4 , filtered, and concentrated. Purification by flash chromatography on SiO_2 (0% to 15% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$) afforded 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-
 25 benzo[d]imidazole-5-carboxamide (19 mg) as a white solid after freeze drying. LC-MS (ES) m/z = 448 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.56 (d, J = 2.0 Hz, 1H), 7.97 (dd, J = 2.4, 9.0 Hz, 1H), 7.74 (dd, J = 6.5, 8.6 Hz, 1H), 7.56 (d, J = 2.3 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 6.69 (d, J = 9.1 Hz, 1H), 6.16 (d, J = 2.3 Hz, 1H), 5.49 (s, 2H), 4.3 (br. s, 2H), 3.86 (s, 3H), 2.27 - 2.45 (m, 2H), 1.75 (d, J = 5.8 Hz, 2H), 1.22 (d, J = 6.1 Hz, 6H).

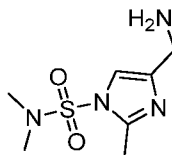
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Intermediate 2234-(Azidomethyl)-N,N,2-trimethyl-1H-imidazole-1-sulfonamide

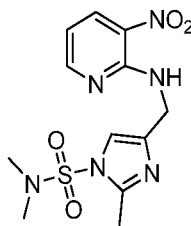
- To a solution of 4-(hydroxymethyl)-N,N,2-trimethyl-1H-imidazole-1-sulfonamide (3.24g, 14.78 mmol) and diphenyl phosphoryl azide (4.88 g, 17.73 mmol) in THF cooled in an ice water bath was added DBU (2.67 ml, 17.73 mmol) dropwise, and the reaction mixture was stirred at room temperature for 16 hours. Water was then added, and the mixture was acidified to pH~6 and then extracted with EtOAc. The combined organic extract was washed with water followed by brine, dried over MgSO₄, filtered, and concentrated.
- Purification by flash chromatography on SiO₂ (0% to 60% (3:1 EtOAc:EtOH)/heptane) afforded 4-(azidomethyl)-N,N,2-trimethyl-1H-imidazole-1-sulfonamide (2.79 g) as a clear oil. LC-MS (ES) m/z = 245 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 6.96 (s, 1H), 4.53 (s, 2H), 2.99 (s, 6H), 2.64 (s, 3H).

15 Intermediate 224tert-Butyl ((1-(N,N-dimethylsulfamoyl)-2-methyl-1H-imidazol-4-yl)methyl)carbamate

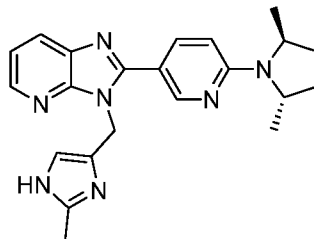
- A mixture of 4-(azidomethyl)-N,N,2-trimethyl-1H-imidazole-1-sulfonamide (3.24 g, 13.26 mmol), di-tert-butyl dicarbonate (6.16 mL, 26.5 mmol), and 10% palladium on carbon (30 mg, 0.282 mmol) in CH₃OH was exposed to hydrogen atmosphere via balloon hydrogenation for 16 hours. The reaction was filtered and concentrated. Purification by flash chromatography on SiO₂ (0% to 100% (3:1 EtOAc:EtOH)/heptane) afforded tert-butyl ((1-(N,N-dimethylsulfamoyl)-2-methyl-1H-imidazol-4-yl)methyl)carbamate (2.95 g) as a white solid. LC-MS (ES) m/z = 319 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 6.89 (s, 1H), 5.23 (br. s., 1H), 4.41 (d, J = 6.1 Hz, 2H), 2.96 (s, 6H), 2.63 (s, 3H), 1.46 (s, 9H).

Intermediate 2254-(Aminomethyl)-N,N,2-trimethyl-1H-imidazole-1-sulfonamide

A solution of tert-butyl ((1-(N,N-dimethylsulfamoyl)-2-methyl-1H-imidazol-4-yl)methyl)carbamate (1.5 g, 4.71 mmol) in 1,1,1,3,3,3-hexafluoro-2-propanol (15 mL) was heated at 120 °C under microwave conditions for 150 minutes. The reaction was concentrated to dryness to afford crude 4-(aminomethyl)-N,N,2-trimethyl-1H-imidazole-1-sulfonamide (1.64 g) as a oil which was used as is into the next step. LC-MS (ES) m/z = 219 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 6.80 (s, 1H), 3.91 (s, 2H), 2.95 (s, 6H), 2.62 (s, 3H).

Intermediate 226N,N,2-Trimethyl-4-(((3-nitropyridin-2-yl)amino)methyl)-1H-imidazole-1-sulfonamide

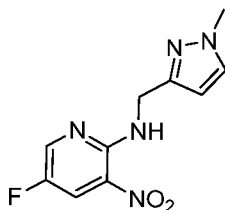
A solution of 2-chloro-3-nitropyridine (100 mg, 0.631 mmol), 4-(aminomethyl)-N,N,2-trimethyl-1H-imidazole-1-sulfonamide (236 mg, 0.757 mmol) and N,N-diisopropylethylamine (0.165 mL, 0.946 mmol) in DMSO (30 mL) was heated at 85 °C for 16 hours. The reaction was poured onto water and extracted with EtOAc. The organic extract was washed with water followed by brine, dried over MgSO₄, filtered, and concentrated. Purification by flash chromatography on SiO₂ (0% to 70% (3:1 EtOAc:EtOH)/heptane) afforded N,N,2-trimethyl-4-(((3-nitropyridin-2-yl)amino)methyl)-1H-imidazole-1-sulfonamide (188 mg) as a yellow oil. LC-MS (ES) m/z = 341 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.65 (t, J = 5.5 Hz, 1H), 8.34 - 8.48 (m, 2H), 6.88 (s, 1H), 6.60 - 6.73 (m, 1H), 4.96 (d, J = 6.1 Hz, 2H), 2.95 (s, 6H), 2.56 (s, 3H).

Example 164**2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((2-methyl-1H-imidazol-4-yl)methyl)-3H-imidazo[4,5-b]pyridine**

5 A mixture of N,N,2-trimethyl-4-(((3-nitropyridin-2-yl)amino)methyl)-1H-imidazole-1-sulfonamide (188 mg, 0.552 mmol), 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (124 mg, 0.608 mmol), and sodium hydrosulfite (289 mg, 85%, 1.41 mmol) in ethanol (4 mL) and water (2mL) was heated at 130 °C under microwave conditions for 4 hours. The reaction was concentrated. CH₂Cl₂ was then added, and the resulting organic mixture was

10 washed with water, dried over MgSO₄, filtered, and concentrated. Purification by flash chromatography on SiO₂ (0% to 100% (3:1 EtOAc:EtOH)/heptane) afforded impure 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((2-methyl-1H-imidazol-4-yl)methyl)-3H-imidazo[4,5-b]pyridine. Further purification by reverse phase HPLC (5 to 70% CH₃CN/0.1%NH₄OH in H₂O) afforded 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((2-methyl-1H-imidazol-4-yl)methyl)-3H-imidazo[4,5-b]pyridine (33 mg) as a white solid after freeze drying. LC-MS (ES) m/z = 388 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 8.53 (d, J = 2.0 Hz, 1H), 8.35 (dd, J = 1.4, 4.9 Hz, 1H), 8.06 (dd, J = 1.3, 7.9 Hz, 1H), 7.95 (dd, J = 2.4, 9.0 Hz, 1H), 7.36 (dd, J = 4.9, 8.0 Hz, 1H), 6.62 - 6.69 (m, 2H), 5.52 (s, 2H), 4.29 (br. s., 2H), 2.32 (s, 5H), 1.73 (d, J = 5.6 Hz, 2H), 1.20 (d, J = 6.3 Hz, 6H).

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Intermediate 227**5-Fluoro-N-((1-methyl-1H-pyrazol-3-yl)methyl)-3-nitropyridin-2-amine**

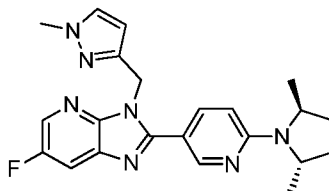
To 2-chloro-5-fluoro-3-nitropyridine (305 mg, 1.728 mmol) in DMSO (5 mL) were added (1-methyl-1H-pyrazol-3-yl)methanamine (211 mg, 1.901 mmol) and K₂CO₃ (310 mg, 2.246 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction was then quenched with water (10 mL), and the resulting precipitate was isolated by

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filtration, washed with water, and then dried in vacuum oven for 4 hours to afford 5-fluoro-N-((1-methyl-1H-pyrazol-3-yl)methyl)-3-nitropyridin-2-amine (210 mg) as a yellow color solid. LC-MS (ES) m/z = 252 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 3.80 (s, 3H), 4.69 (d, J = 5.3 Hz, 2H), 6.16 (d, J = 2.3 Hz, 1H), 7.60 (d, J = 2.3 Hz, 1H), 8.44 (dd, J = 8.5, 2.9 Hz, 1H), 8.66 (d, J = 2.8 Hz, 1H), 8.69 (t, J = 5.3 Hz, 1H).

Example 165

2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-6-fluoro-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine



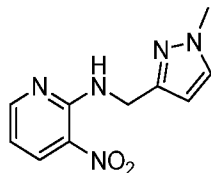
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Into a microwave vial were added 5-fluoro-N-((1-methyl-1H-pyrazol-3-yl)methyl)-3-nitropyridin-2-amine (75 mg, 0.299 mmol), 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (67.1 mg, 0.328 mmol), sodium hydrosulfite (156 mg, 85%, 0.762 mmol), ethanol (1.5 mL), and water (0.75 mL), and the reaction mixture was heated under microwave conditions for 90 minutes at 130 °C. The reaction was then diluted with water (10 mL) and extracted with EtOAc (4 x 5 mL). The organic extracts were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography on SiO_2 (0 to 10% CH_3OH/CH_2Cl_2) afforded 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-6-fluoro-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine (45 mg) as a light brown solid. LC-MS (ES) m/z = 406 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 1.14 (d, J = 6.1 Hz, 6H), 1.65 (d, J = 5.3 Hz, 2H), 2.23 (br. s., 2H), 3.76 (s, 3H), 4.26 (br. s., 2H), 5.50 (s, 2H), 6.06 (d, J = 2.3 Hz, 1H), 6.63 (d, J = 8.9 Hz, 1H), 7.61 (d, J = 2.3 Hz, 1H), 8.02 (dd, J = 9.4, 2.5 Hz, 1H), 8.06 (dd, J = 9.0, 2.4 Hz, 1H), 8.32 (t, J = 2.2 Hz, 1H), 8.66 (d, J = 2.5 Hz, 1H).

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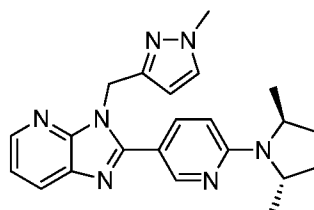
Intermediate 228

N-((1-Methyl-1H-pyrazol-3-yl)methyl)-3-nitropyridin-2-amine



To 2-fluoro-3-nitropyridine (124 mg, 0.873 mmol) in DMSO (3 mL) were added (1-methyl-1H-pyrazol-3-yl)methanamine (97 mg, 0.873 mmol) and K₂CO₃ (157 mg, 1.134 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction was then quenched with water (20 mL), and the resulting precipitate was isolated by filtration and dried under vacuum oven overnight to afford N-((1-methyl-1H-pyrazol-3-yl)methyl)-3-nitropyridin-2-amine (160 mg) as a yellow solid. LC-MS (ES) m/z = 234 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 3.80 (s, 3H), 4.71 (d, *J* = 5.3 Hz, 2H), 6.16 (d, *J* = 2.3 Hz, 1H), 6.81 (dd, *J* = 8.4, 4.6 Hz, 1H), 7.61 (d, *J* = 2.3 Hz, 1H), 8.46 (dd, *J* = 8.4, 1.8 Hz, 1H), 8.51 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.73 (t, *J* = 4.9 Hz, 1H).

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Example 166**2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine**

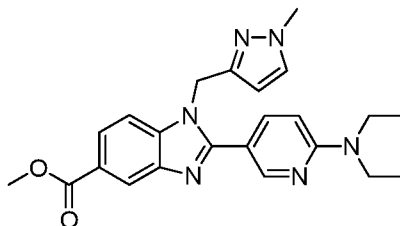
15 Into a microwave vial were added N-((1-methyl-1H-pyrazol-3-yl)methyl)-3-nitropyridin-2-amine (160 mg, 0.686 mmol), 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (154 mg, 0.755 mmol), ethanol (2 mL), water (1 mL), and sodium hydrosulfite (358 mg, 85%, 1.749 mmol), and the reaction mixture was heated under microwave conditions for 90 minutes at 130 °C. The reaction was then diluted with water (10 mL) and extracted with EtOAc (4 x 5 mL). The organic extracts were then combined, washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ (0 to 10% CH₃OH/CH₂Cl₂) afforded 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine (160 mg) as a yellow solid after freeze drying. LC-MS (ES) m/z = 388 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.14 (d, *J* = 6.1 Hz, 6H), 1.65 (d, *J* = 5.6 Hz, 2H), 2.23 (br. s., 2H), 3.76 (s, 3H), 4.25 (br. s., 2H), 5.51 (s, 2H), 6.04 (d, *J* = 2.3 Hz, 1H), 6.63 (d, *J* = 8.9 Hz, 1H), 7.29 (dd, *J* = 8.0, 4.7 Hz, 1H), 7.60 (s, 1H), 8.02 - 8.08 (m, 2H), 8.30 (dd, *J* = 4.7, 1.4 Hz, 1H), 8.65 (d, *J* = 2.3 Hz, 1H).

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Intermediate 229

Methyl 2-(6-(Diethylamino)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylate

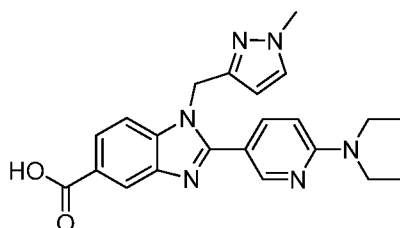


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Into a microwave vial were added methyl 4-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)-3-nitrobenzoate (75 mg, 0.258 mmol), 6-(diethylamino)nicotinaldehyde (50.7 mg, 0.284 mmol), ethanol (1.5 mL), water (0.750 mL), and sodium hydrosulfite (135 mg, 85%, 0.659 mmol), and the reaction mixture was heated under microwave conditions for 90 minutes at 130 °C. The reaction was then diluted with water (10 mL) and extracted with EtOAc (4 x 5 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ (0 to 10% CH₃OH/CH₂Cl₂) afforded methyl 2-(6-(diethylamino)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylate (71 mg) as a light yellow solid. LC-MS (ES) m/z = 419 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.12 - 1.18 (m, 6H), 3.57 (q, *J* = 7.0 Hz, 4H), 3.78 (s, 3H), 3.88 (s, 3H), 5.45 (s, 2H), 6.15 (d, *J* = 2.3 Hz, 1H), 6.76 (d, *J* = 8.9 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 2.3 Hz, 1H), 7.85 (dd, *J* = 8.5, 1.7 Hz, 1H), 8.03 (dd, *J* = 9.0, 2.4 Hz, 1H), 8.23 (d, *J* = 1.3 Hz, 1H), 8.61 (d, *J* = 2.0 Hz, 1H).

20 Intermediate 230

2-(6-(Diethylamino)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid

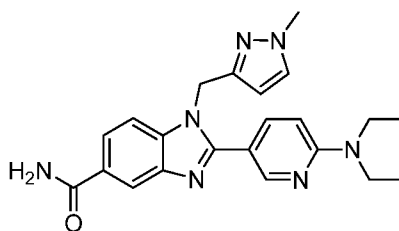


To methyl 2-(6-(diethylamino)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylate (70 mg, 0.167 mmol) in CH₃OH (3 mL) was added NaOH (0.335 mL, 3.35 mmol, 10N), and the reaction mixture was stirred at room temperature overnight. The reaction was concentrated, HCl (3.35 mL, 3.35 mmol, 1N) was added, and

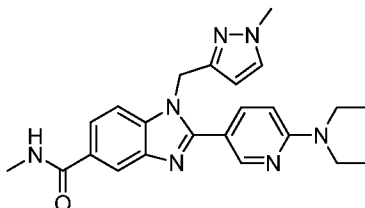
the resulting precipitate was isolated by filtration to give the desired product (28 mg) as a white solid. The filtrate was extracted with EtOAc (4 x 5 mL), and the organic extracts were combined, dried over MgSO₄, filtered, and concentrated to afford additional desired product (18 mg) as a white solid. The solids isolated were then combined to give 2-(6-(diethylamino)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid (46 mg) as a white solid. LC-MS (ES) m/z = 405 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.17 (t, J = 7.0 Hz, 6H), 3.61 (q, J = 6.8 Hz, 4H), 3.78 (s, 3H), 5.53 (s, 2H), 6.26 (d, J = 1.8 Hz, 1H), 6.88 (d, J = 8.9 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 8.9 Hz, 1H), 8.10 (d, J = 7.6 Hz, 1H), 8.24 (s, 1H), 8.65 (d, J = 2.3 Hz, 1H), 12.87 - 13.05 (m, 1H).

Example 167

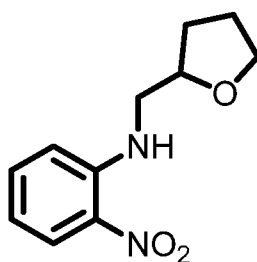
2-(6-(Diethylamino)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide



To 2-(6-(diethylamino)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid (48 mg, 0.119 mmol) in DMSO (2 mL) were added NH₄Cl (11.43 mg, 0.214 mmol), EDC (45.5 mg, 0.237 mmol), HOBt (36.3 mg, 0.237 mmol), and N-methylmorpholine (0.078 mL, 0.712 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with water (5 mL) and extracted with EtOAc (3 x 10 mL). The organic extracts were combined, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ (0 to 10% CH₃OH/CH₂Cl₂) afforded 2-(6-(diethylamino)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide (32 mg) as a white solid after freeze drying. LC-MS (ES) m/z = 405 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.15 (t, J = 7.0 Hz, 6H), 3.57 (q, J = 7.1 Hz, 4H), 3.78 (s, 3H), 5.43 (s, 2H), 6.14 (d, J = 2.0 Hz, 1H), 6.76 (d, J = 8.9 Hz, 1H), 7.27 (br. s., 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 2.3 Hz, 1H), 7.77 (dd, J = 8.4, 1.52 Hz, 1H), 7.96 (br. s., 1H), 8.03 (dd, J = 9.1, 2.5 Hz, 1H), 8.21 (d, J = 1.3 Hz, 1H), 8.60 (d, J = 2.3 Hz, 1H).

Example 168**2-(6-(Diethylamino)pyridin-3-yl)-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide**

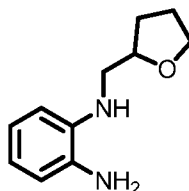
- 5 Into a microwave vial were added N-methyl-4-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)-3-nitrobenzamide (78.4 mg, 0.271 mmol), 6-(diethylamino)nicotinaldehyde (53.1 mg, 0.298 mmol), ethanol (1.5 mL), water (0.75 mL), and sodium hydrosulfite (142 mg, 85%, 0.693 mmol), and the reaction mixture was heated under microwave conditions for 90 minutes at 130 °C. The reaction was then diluted with water (10 mL) and extracted with EtOAc (4 x
- 10 5mL). The organic extracts were combined, washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ (0 to 10% CH₃OH/CH₂Cl₂) afforded 2-(6-(diethylamino)pyridin-3-yl)-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide (65 mg) as a white solid after freeze drying. LC-MS (ES) m/z = 418 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.15 (t, *J* = 7.1 Hz, 6H), 2.81 (d, *J* = 4.6 Hz, 3H), 3.57 (q, *J* = 7.1 Hz, 4H), 3.78 (s, 3H), 5.43 (s, 2H), 6.14 (d, *J* = 2.3 Hz, 1H), 6.76 (d, *J* = 9.1 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 2.3 Hz, 1H), 7.73 (dd, *J* = 8.5, 1.7 Hz, 1H), 8.03 (dd, *J* = 9.1, 2.5 Hz, 1H), 8.15 (d, *J* = 1.3 Hz, 1H), 8.41 (d, *J* = 4.6 Hz, 1H), 8.60 (d, *J* = 2.3 Hz, 1H).

20 **Intermediate 231****2-Nitro-N-((tetrahydrofuran-2-yl)methyl)aniline**

- 25 To a solution of 1-fluoro-2-nitrobenzene (419 mg, 2.967 mmol) in DMF (5 mL) were added (tetrahydrofuran-2-yl)methanamine (300 mg, 2.97 mmol) and K₂CO₃ (410 mg, 2.97 mmol), and the mixture was stirred at room temperature for 6 hours. The mixture was then

quenched with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined extracts were dried over sodium sulfate, then concentrated. The residue was then purified using column chromatography (silica gel, gradient from 0 to 60% EtOAc/hexanes) to provide 2-nitro-N-((tetrahydrofuran-2-yl)methyl)aniline (0.64 g) as a reddish-brown oil. LC-MS (ES) $m/z = 223 [M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.25 (br. s., 1H), 8.18 (dd, $J = 1.5, 8.6$ Hz, 1H), 7.44 (ddd, $J = 1.6, 7.0, 8.6$ Hz, 1H), 6.90 (dd, $J = 0.9, 8.7$ Hz, 1H), 6.66 (ddd, $J = 1.3, 7.2, 8.6$ Hz, 1H), 4.22 (dq, $J = 4.4, 6.8$ Hz, 1H), 3.97 (td, $J = 6.5, 8.5$ Hz, 1H), 3.84 (td, $J = 6.9, 8.3$ Hz, 1H), 3.51 - 3.44 (m, 1H), 3.41 - 3.34 (m, 1H), 2.15 - 2.07 (m, 1H), 2.03 - 1.92 (m, 2H), 1.73 (tdd, $J = 7.2, 8.6, 12.0$ Hz, 1H).

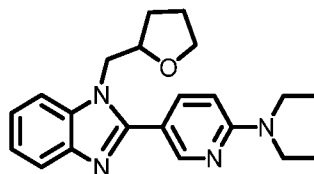
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Intermediate 232N1-((Tetrahydrofuran-2-yl)methyl)benzene-1,2-diamine

To a stirring solution of 2-nitro-N-((tetrahydrofuran-2-yl)methyl)aniline (0.64 g, 2.88 mmol) and $NiCl_2 \cdot 6H_2O$ (1.706 g, 7.20 mmol) cooled to 0 °C in CH_3OH (5 mL) was added sodium borohydride (0.545 g, 14.40 mmol) in portions. The reaction mixture was allowed to warm to room temperature, and then stirred at room temperature for 30 minutes [the reaction turned black after ~30 seconds]. The mixture was concentrated, and the resulting residue was dissolved into concentrated aqueous NH_4OH and extracted with CH_2Cl_2 (3 x 10 mL).

The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel eluted with a gradient from 0 to 70% EtOAc/hexanes to afford N1-((tetrahydrofuran-2-yl)methyl)benzene-1,2-diamine (0.341 g) as a light yellow oil. LC-MS (ES) $m/z = 193 [M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 6.92 - 6.85 (m, 1H), 6.80 - 6.70 (m, 3H), 4.29 - 4.19 (m, 1H), 3.96 (td, $J = 6.7, 8.1$ Hz, 1H), 3.90 - 3.83 (m, 1H), 3.65 (br. s., 3H), 3.27 (dd, $J = 3.5, 12.2$ Hz, 1H), 3.14 (dd, $J = 8.0, 12.0$ Hz, 1H), 2.15 - 2.05 (m, 1H), 2.04 - 1.92 (m, 2H), 1.78 - 1.67 (m, 1H).

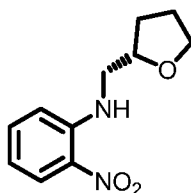
25

Example 169**N,N-Diethyl-5-(1-((tetrahydrofuran-2-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine**

- 5 To a solution of N1-((tetrahydrofuran-2-yl)methyl)benzene-1,2-diamine (0.227 g, 1.181 mmol) in DMF (2 mL) at 0 °C was added 6-(diethylamino)nicotinaldehyde (0.210 g, 1.181 mmol) followed by a solution of oxone (0.726 g, 1.181 mmol) in water (2 mL), and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was basified using 10% NaHCO₃, then extracted with EtOAc (3 x 15 mL). The combined extracts
- 10 were dried (Na₂SO₄), then concentrated. The residue was then purified by silica gel chromatography (gradient: 0 to 70% EtOAc/hexanes) to provide N,N-diethyl-5-(1-((tetrahydrofuran-2-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine (0.166 g, 0.474 mmol) as a yellow oil. LC-MS (ES) m/z = 351 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.51 (d, J = 2.5 Hz, 1H), 7.86 (dd, J = 2.5, 8.9 Hz, 1H), 7.78 - 7.73 (m, 1H), 7.46 (td, J = 2.3, 4.6
- 15 Hz, 1H), 7.26 - 7.20 (m, 2H), 6.53 (d, J = 8.9 Hz, 1H), 4.31 - 4.22 (m, 3H), 3.78 (td, J = 6.9, 8.3 Hz, 1H), 3.67 (td, J = 6.8, 8.4 Hz, 1H), 3.54 (q, J = 7.1 Hz, 4H), 1.93 (td, J = 6.2, 12.4 Hz, 1H), 1.84 - 1.74 (m, 2H), 1.53 - 1.43 (m, 1H), 1.19 (t, J = 7.1 Hz, 6H).

Intermediate 233

- 20 **(S)-2-Nitro-N-((tetrahydrofuran-2-yl)methyl)aniline**



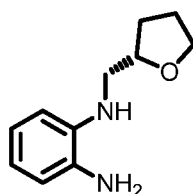
- To a solution of 1-fluoro-2-nitrobenzene (419 mg, 2.967 mmol) in CHCl₃ (5 mL) was added (S)-((tetrahydrofuran-2-yl)methanamine (300 mg, 2.97 mmol) and K₂CO₃ (410 mg, 2.97 mmol), and the reaction mixture was stirred at room temperature for 18 hours. The mixture
- 25 was quenched with 1M aqueous HCl solution (10 mL) and extracted with EtOAc (3x). The combined extracts were dried, then concentrated. The resulting residue was purified using column chromatography on silica gel eluting with a gradient from 0 to 60% EtOAc/hexanes to provide (S)-2-nitro-N-((tetrahydrofuran-2-yl)methyl)aniline (384 mg) as a orangish-yellow oil. LC-MS (ES) m/z = 223 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.22 (br. s., 1H), 8.13

(dd, $J = 1.3, 8.6$ Hz, 1H), 7.40 (ddd, $J = 1.5, 6.9, 8.6$ Hz, 1H), 6.86 (d, $J = 8.6$ Hz, 1H), 6.61 (ddd, $J = 1.0, 7.0, 8.4$ Hz, 1H), 4.18 (dq, $J = 4.3, 6.8$ Hz, 1H), 3.94 (td, $J = 6.8, 8.2$ Hz, 1H), 3.84 - 3.75 (m, 1H), 3.48 - 3.39 (m, 1H), 3.37 - 3.28 (m, 1H), 2.13 - 2.01 (m, 1H), 2.01 - 1.87 (m, 2H), 1.75 - 1.63 (m, 1H).

5

Intermediate 234

(S)-N1-((Tetrahydrofuran-2-yl)methyl)benzene-1,2-diamine



10

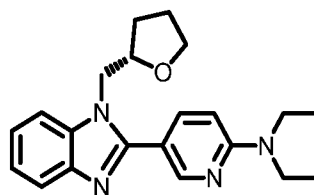
To a solution of (S)-2-nitro-N-((tetrahydrofuran-2-yl)methyl)aniline (384 mg, 1.728 mmol) in CH₃OH (5 mL) that was cooled to 0 °C was added NiCl₂•6H₂O (821 mg, 3.46 mmol) followed by sodium borohydride (261 mg, 6.91 mmol), and the reaction mixture was stirred at room temperature for 30 minutes [reaction turned black after ~20 sec]. The reaction mixture was basified using NH₄OH, then extracted with CH₂Cl₂ (3 x 10 mL). The combined extracts were dried (Na₂SO₄), then concentrated to provide (S)-N1-((tetrahydrofuran-2-yl)methyl)benzene-1,2-diamine (156 mg) as an amber oil. LC-MS (ES) $m/z = 193$ [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 6.91 - 6.83 (m, 1H), 6.80 - 6.70 (m, 3H), 4.24 (dq, $J = 3.8, 7.3$ Hz, 1H), 3.95 (td, $J = 6.7, 8.4$ Hz, 1H), 3.90 - 3.82 (m, 1H), 3.64 (br. s., 3H), 3.27 (dd, $J = 3.8, 12.2$ Hz, 1H), 3.13 (dd, $J = 7.9, 12.2$ Hz, 1H), 2.15 - 2.04 (m, 1H), 2.03 - 1.90 (m, 2H), 1.78 - 1.66 (m, 1H).

20

Example 170

(S)-N,N-Diethyl-5-(1-((tetrahydrofuran-2-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine

25

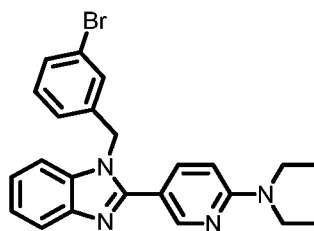


To a solution of (S)-N1-((tetrahydrofuran-2-yl)methyl)benzene-1,2-diamine (156 mg, 0.811 mmol) in DMF (3 mL) at 0 °C was added 6-(diethylamino)nicotinaldehyde (145 mg, 0.811

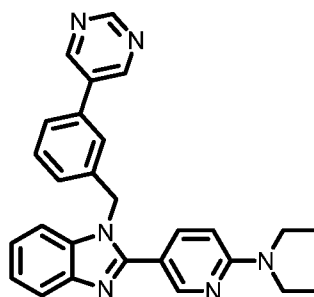
mmol) followed by a solution of oxone (349 mg, 0.568 mmol) in water (3 mL), and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was basified using saturated aqueous NaHCO_3 and extracted with EtOAc (3 x 10 mL). The combined extracts were dried (Na_2SO_4), then concentrated. The resulting residue was purified using column chromatography on silica gel eluting with a gradient from 0 to 70% EtOAc/hexanes to provide (S)-N,N-diethyl-5-(1-((tetrahydrofuran-2-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine (240 mg) as a red-brown oil. LC-MS (ES) m/z = 351 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 8.49 (d, J = 1.8 Hz, 1H), 7.80 (dd, J = 2.4, 9.0 Hz, 1H), 7.74 - 7.68 (m, 1H), 7.42 - 7.36 (m, 1H), 7.21 - 7.14 (m, 2H), 6.47 (d, J = 9.1 Hz, 1H), 4.24 - 4.14 (m, 3H), 3.71 (td, J = 6.9, 8.3 Hz, 1H), 3.59 (td, J = 6.8, 8.4 Hz, 1H), 3.48 (q, J = 7.1 Hz, 4H), 1.87 (dd, J = 6.2, 12.5 Hz, 1H), 1.76 - 1.67 (m, 2H), 1.41 (dd, J = 7.4, 12.4 Hz, 1H), 1.13 (t, J = 7.1 Hz, 6H).

Intermediate 235

5-(1-(3-Bromobenzyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine

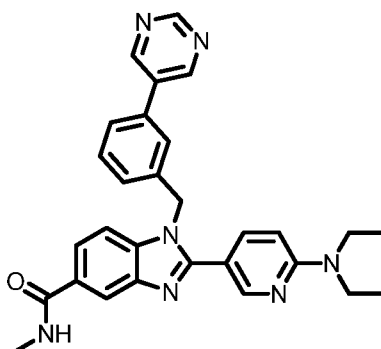


To a solution of 5-(1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (150 mg, 0.563 mmol) in DMF (5.6 L) at 0 °C was added NaH (29.3 mg, 0.732 mmol, 60% in oil). After 5 minutes, 1-bromo-3-(bromomethyl)-benzene (155 mg, 0.619 mmol) was added, and the reaction mixture was allowed to warm to room temperature. After 30 minutes, the reaction was quenched with saturated aqueous NH_4Cl (2 mL), diluted with water (20 mL), and then extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4 , filtered, and concentrated. The resulting residue was purified via silica gel chromatography (10 to 100% EtOAc/hexanes) to afford the desired product (195 mg) as a beige solid. LC-MS (ES) m/z = 437 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 8.39 (d, J = 2.5 Hz, 1H), 7.93 - 7.77 (m, 2H), 7.46 (d, J = 7.9 Hz, 1H), 7.39 - 7.29 (m, 2H), 7.26 - 7.12 (m, 3H), 7.03 (d, J = 7.9 Hz, 1H), 6.57 (d, J = 9.1 Hz, 1H), 5.46 (s, 2H), 3.58 (q, J = 7.1 Hz, 4H), 1.23 (t, J = 7.0 Hz, 6H).

Example 171**N,N-Diethyl-5-(1-(3-(pyrimidin-5-yl)benzyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine**

To a suspension of 5-(1-(3-bromobenzyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (50 mg, 0.12 mmol), pyrimidin-5-ylboronic acid (17 mg, 0.14 mmol), and Cs₂CO₃ (112 mg, 0.345 mmol) in 10:1 THF:water (2.5 mL) under a nitrogen atmosphere was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (4.2 mg, 0.0057 mmol), and the reaction mixture was stirred in a sealed vessel at 100 °C for 4 hours, at which point the solvent had evaporated. The residue was redissolved in THF (2.5 mL), and additional pyrimidin-5-ylboronic acid (17 mg, 0.14 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (4.2 mg, 0.0057 mmol) were added. The mixture was flushed with nitrogen, capped, heated at 80 °C for 19 hours, then cooled to room temperature and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 0 to 100% EtOAc/hexanes) to afford the desired product (30 mg) as a clear film. LC-MS (ES) m/z = 435 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 9.21 (s, 1H), 8.87 (s, 2H), 8.41 (d, J = 2.3 Hz, 1H), 7.99 - 7.77 (m, 2H), 7.59-7.44 (m, 2H), 7.38 - 7.11 (m, 5H), 6.58 (d, J = 8.9 Hz, 1H), 5.59 (s, 2H), 3.57 (q, J = 7.1 Hz, 4H), 1.22 (t, J = 7.1 Hz, 6H).

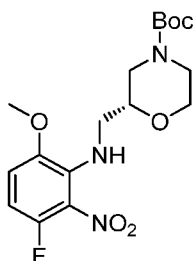
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Example 172**2-(6-(Diethylamino)pyridin-3-yl)-N-methyl-1-(3-(pyrimidin-5-yl)benzyl)-1H-benzo[d]imidazole-5-carboxamide**

To (3-(pyrimidin-5-yl)phenyl)methanamine (62.0 mg, 0.333 mmol) in ethanol (0.7 mL) were added 4-fluoro-N-methyl-3-nitrobenzamide (60 mg, 0.303 mmol) and N,N-diisopropylethylamine (0.058 mL, 0.333 mmol), and the reaction mixture was heated under nitrogen at 150 °C for 20 minutes under microwave conditions. The resulting mixture was transferred to a scintillation vial (25 mL) with a minimum of ethanol (~4 mLs). Sodium dithionite (0.75 g, 4.31 mmol) in water (3 mL) was then added, and the reaction mixture was heated at 70 °C for about 1 hour. 6-(Diethylamino)nicotinaldehyde (54 mg, 0.30 mmol) was then added, and the reaction mixture was heated at 60 °C for 48 hours. The reaction was partitioned between 2N NH₄OH and EtOAc (40 mL). The aqueous layer was further extracted with EtOAc (2 x 20 mL). The organic combined organic extractes were washed with brine (2 x 20 mL), dried over Na₂SO₄, and evaporated in vacuo to give the crude product as a colourless oil. Purification by reverse phase HPLC (12 to 42% CH₃CN/0.1%TFA in water) afforded a TFA salt of the desired product (90 mg) as a white solid after freeze-drying. LC-MS (ES) m/z = 492 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 1.24 (t, J = 7.2 Hz, 6H), 3.03 (d, J = 4.4 Hz, 3H), 3.60 (m, 4H), 5.74 (s, 2H), 6.72 (d, J = 9.2 Hz, 1H), 7.08 (m, 1H), 7.16 (d, J = 7.2 Hz, 1H), 7.38 (m, 2H), 7.55 – 7.62 (m, 2H), 8.05 (m, 2H), 8.40 (s, 1H), 8.47 (s, 1H), 8.92 (bs, 1H), 9.25 (bs, 1H).

20 Intermediate 236

tert-Butyl (R)-2-(((3-fluoro-6-methoxy-2-nitrophenyl)amino)methyl)morpholine-4-carboxylate

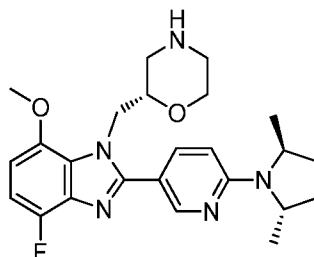


To a solution of 1,3-difluoro-4-methoxy-2-nitrobenzene (2.5 g, 13.22 mmol) in DMF (45 mL) were added tert-butyl (R)-2-(aminomethyl)morpholine-4-carboxylate, acetic acid salt (4.02 g, 14.54 mmol) and K₂CO₃ (4.57 g, 33.0 mmol), and the reaction mixture was stirred at 55 °C for 30 hours. The mixture was filtered, and the filtrate was concentrated. The resulting residue was purified by column chromatography on silica gel (gradient: 0 to 100% EtOAc/heptane) to give the desired product (4.60 g) as a brown oil. LC-MS (ES) m/z = 386 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 1.45 - 1.52 (m, 9H), 2.70 (m, 1H), 2.91 - 3.03 (m,

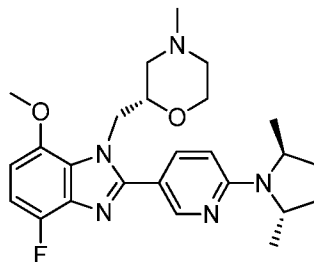
1H), 3.17 (dd, $J = 13.2, 8.1$ Hz, 1H), 3.40 (m, 1H), 3.47 - 3.59 (m, 2H), 3.82 - 3.97 (m, 6H), 6.57 (t, $J = 9.5$ Hz, 1H), 6.82 (dd, $J = 9.0, 4.7$ Hz, 1H).

Example 173

5 **(S)-2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine**



To a solution of tert-butyl (R)-2-(((3-fluoro-6-methoxy-2-nitrophenyl)amino)methyl)morpholine-4-carboxylate (250 mg, 0.649 mmol) and 6-((2S,5S)-
 10 2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (139 mg, 0.681 mmol) in a 2:1 mixture of CH₃OH:water (3 mL) was added sodium hydrosulfite (339 mg, 85%, 1.658 mmol), and the reaction mixture was stirred in a sealed vessel at 100 °C for 18 hours. The reaction was then cooled to room temperature and diluted with saturated aqueous NaHCO₃ (10 mL). The aqueous solution was extracted with EtOAc (4 x 10 mL), and the combined organic layers
 15 were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. To a solution of the crude residue in CH₂Cl₂ (2 mL) was added trifluoroacetic acid (0.50 mL, 6.5 mmol), and the reaction mixture was stirred at room temperature for 20 hours. The reaction was then diluted with additional CH₂Cl₂ (30 mL), and the resulting organic solution was washed with saturated aqueous NaHCO₃ (2 x 15 mL) followed by brine (15 mL), dried
 20 over anhydrous Na₂SO₄, filtered, and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 0 to 10% CH₃OH/CH₂Cl₂) to afford the desired product (170 mg) as a white solid. LC-MS (ES) $m/z = 440$ [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.60 (d, $J = 2.0$ Hz, 1H), 7.89 (dd, $J = 8.9, 2.3$ Hz, 1H), 6.87 (dd, $J = 9.8, 8.7$ Hz, 1H), 6.58 (dd, $J = 8.9, 3.3$ Hz, 1H), 6.49 (d, $J = 8.9$ Hz, 1H), 4.52 - 4.33 (m, 2H), 4.29 (br s, 1H), 3.95 (s, 3H), 3.94 - 3.87 (m, 2H), 3.81 (dd, $J = 11.5, 1.9$ Hz, 1H), 3.46 - 3.37 (m, 1H), 2.92 - 2.81 (m, 1H), 2.76 (d, $J = 11.7$ Hz, 2H), 2.52 (dd, $J = 11.9, 10.4$ Hz, 1H), 2.40 - 2.22 (m, 2H), 1.71 (d, $J = 5.6$ Hz, 2H), 1.26 - 1.14 (m, 6H).

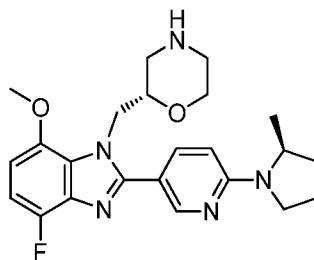
Example 174**(S)-2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine**

5 To a solution of (S)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine (40 mg, 0.091 mmol) in 1,2-dichloroethane (2 mL) were added formaldehyde (36.5% solution, 0.034 mL, 0.46 mmol) and sodium triacetoxyborohydride (58 mg, 0.27 mmol), and the reaction mixture was stirred at room temperature for 30 minutes. The reaction was then concentrated in vacuo, and the

10 resulting residue was purified by reverse phase HPLC (0.1% 10 mM NH_4HCO_3 with NH_4OH modifier, eluting with 50 to 99% CH_3CN /water). The fractions containing product were concentrated and lyophilized to afford the desired product (32 mg) as a white solid. LC-MS (ES) $m/z = 454$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 8.60 (d, $J = 2.3$ Hz, 1H), 7.88 (dd, $J = 8.9, 2.5$ Hz, 1H), 6.86 (dd, $J = 9.6, 8.9$ Hz, 1H), 6.56 (dd, $J = 8.7, 3.2$ Hz, 1H), 6.48 (d, $J = 8.9$ Hz, 1H), 4.83 (br s, 5H), 4.59 - 4.15 (m, 4H), 4.06 - 3.95 (m, 1H), 3.94 (s, 3H), 3.81

15 (dd, $J = 11.5, 1.6$ Hz, 1H), 3.59 - 3.41 (m, 1H), 2.59 (d, $J = 11.4$ Hz, 2H), 2.35 - 2.27 (m, 1H), 2.11 (td, $J = 11.5, 3.3$ Hz, 1H), 1.79 (t, $J = 10.6$ Hz, 1H), 1.71 (d, $J = 5.8$ Hz, 1H), 1.22 (d, $J = 6.3$ Hz, 6H).

20

Example 175**(S)-2-((4-Fluoro-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine**

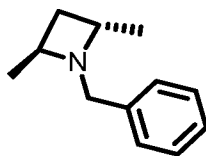
To a solution of tert-butyl(R)-2-(((3-fluoro-6-methoxy-2-nitrophenyl)amino)methyl)morpholine-4-carboxylate (80 mg, 0.21 mmol) and (S)-6-(2-methylpyrrolidin-1-yl)nicotinaldehyde (42 mg, 0.22 mmol) in a 2:1 mixture of CH_3OH :water

25

(3 mL) was added sodium hydrosulfite (108 mg, 85%, 0.529 mmol), and the reaction mixture was stirred in a sealed vessel at 100 °C for 3 days. The reaction was then cooled to room temperature and diluted with saturated aqueous NaHCO₃ (10 mL). The aqueous solution was extracted with EtOAc (4 x 10 mL), and the combined organic layers were washed with
5 brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. To a solution of the crude residue in CH₂Cl₂ (5 mL) was added TFA (0.16 mL, 2.1 mmol), and the reaction mixture was stirred at room temperature for 21 hours. The reaction was concentrated in vacuo, and the resulting residue was purified by reverse phase HPLC (0.1% 10 mM NH₄HCO₃ with NH₄OH modifier, eluting with 30 to 85% CH₃CN/water). The fractions
10 containing product were concentrated and lyophilized to afford the desired product (49 mg) as an off-white solid. LC-MS (ES) m/z = 426 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.62 (d, J = 2.0 Hz, 1H), 7.93 (dd, J = 8.9, 2.3 Hz, 1H), 6.88 (dd, J = 9.8, 8.7 Hz, 1H), 6.59 (dd, J = 8.9, 3.3 Hz, 1H), 6.52 - 6.41 (m, 1H), 4.54 - 4.35 (m, 2H), 4.34-4.17 (m, 1H), 4.05 - 3.87 (m, 1H), 3.97 (s, 3H), 3.81 (dd, J = 11.5, 2.2 Hz, 1H), 3.74-3.58 (m, 1H), 3.56 - 3.39 (m,
15 1H), 3.36 - 3.17 (m, 1H), 2.92 - 2.80 (m, 1H), 2.75 (d, J = 11.9 Hz, 2H), 2.51 (dd, J = 11.8, 10.5 Hz, 1H), 2.30 - 2.08 (m, 2H), 1.80 (dt, J = 4.9, 2.3 Hz, 1H), 1.64 (dt, J = 7.9, 4.2 Hz, 1H), 1.50 - 1.36 (m, 1H), 1.33 - 1.21 (m, 3H).

Intermediate 237

20 (2S,4S)-1-Benzyl-2,4-dimethylazetidene



Ref: J. Org. Chem. **1989**, 54, 1755.

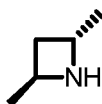
To a solution of (2R,4R)-pentane-2,4-diol (4 g, 38.4 mmol) in CH₂Cl₂ (70 mL) was added triethylamine (13.38 mL, 96 mmol). The solution was cooled to -20 °C, and methanesulfonyl chloride (6.67 mL, 86 mmol) was added dropwise with vigorous stirring over 40 minutes while the temperature was maintained between -20 °C and -15 °C. After the addition was completed, the mixture was allowed to warm to 0 °C, stirred at 0 °C for 2 hours, and then poured into cold 1N aqueous HCl solution (50 mL). The organic layer was separated, and
25 the aqueous layer was extracted with CH₂Cl₂ (3 x 30 mL). The combined organic extracts were washed with saturated aqueous NaHCO₃ solution, dried over Na₂SO₄, filtered, and concentrated to afford crude (2R,4R)-pentane-2,4-diyl dimethanesulfonate (10.0 g) as an
30

oil. ^1H NMR (400 MHz, CDCl_3): δ 4.97 - 4.86 (m, 2H), 3.07 (s, 6H), 1.91 (dd, J = 5.6, 7.1 Hz, 2H), 1.47 (d, J = 6.1 Hz, 6H).

This material was dissolved in benzylamine (29.4 mL, 269 mmol), and the resulting mixture was stirred at room temperature for 40 hours. The mixture was then transferred to an ice-cooled 2N aqueous NaOH solution (50 mL), and the resulting solution was extracted with hexane (4 x 70 mL). The combined organic extracts were concentrated, and the crude product was purified in 3 portions by silica gel chromatography eluting with a gradient from 0 - 10% (2M NH_3 in CH_3OH) in CH_2Cl_2 to afford (2S,4S)-1-benzyl-2,4-dimethylazetidine (5.2 g) as a light yellow oil. LC-MS (ES) m/z = 176 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 7.40 - 7.28 (m, 5H), 7.25 (d, J = 7.1 Hz, 1H), 3.80 - 3.74 (m, 1H), 3.73 - 3.64 (m, 2H), 3.63 - 3.58 (m, 1H), 1.92 (t, J = 6.3 Hz, 2H), 1.15 (d, J = 6.6 Hz, 6H).

Intermediate 238

(2S,4S)-2,4-Dimethylazetidine, acetic acid salt

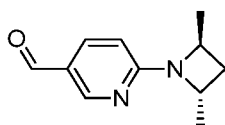


Ref: J. Org. Chem. **1989**, 54, 1755.

(2S,4S)-1-Benzyl-2,4-dimethylazetidine (5.1 g, 29.1 mmol) was dissolved in acetic acid (20 mL), washing the remnants into the Parr flask with CH_3OH (20 mL). Palladium hydroxide on carbon (20%) (6.19 g, 44.1 mmol) was added followed by palladium on carbon (10%) (5.8 g, 54.5 mmol) as a slurry in EtOAc (10 mL), and the resulting mixture was attached to a Parr shaker and shaken under 55psi of hydrogen pressure for 3 days. The reaction was filtered, washing the catalyst with EtOAc. The filtrate was acidified further to prevent the free base from being lost during concentration. The amine was collected to provide (2S,4S)-2,4-dimethylazetidine, acetic acid salt (2.04 g). LC-MS (ES) m/z = 86 $[\text{M}+\text{H}]^+$.

Intermediate 239

6-((2S,4S)-2,4-Dimethylazetidin-1-yl)nicotinaldehyde

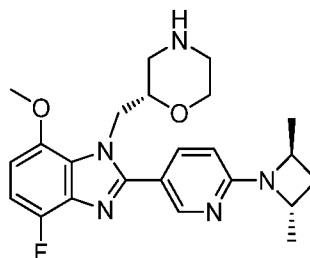


A solution of 6-fluoronicotinaldehyde (2.96 g, 23.64 mmol), (2S,4S)-2,4-dimethylazetidine, acetic acid salt (2.5 g, 20.56 mmol), and N,N-diisopropylethylamine (12.57 mL, 72.0 mmol) in DMSO (30 mL) was stirred at 80 °C for 16 hours. The reaction was quenched with water,

and the resulting mixture was extracted with EtOAc. The organic extract was washed with water followed by brine, dried over Na₂SO₄, filtered, and concentrated. The resulting residue was purified via silica gel chromatography (0 - 30% EtOAc/hexanes) to provide 6-((2S,4S)-2,4-dimethylazetidin-1-yl)nicotinaldehyde (1.75 g) as a light yellow solid. LC-MS (ES) m/z = 191 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 9.73 (s, 1H), 8.50 (d, J = 2.0 Hz, 1H), 7.85 (dd, J = 2.2, 8.7 Hz, 1H), 6.24 (d, J = 8.9 Hz, 1H), 4.81 - 4.38 (m, 2H), 2.18 (t, J = 6.6 Hz, 2H), 1.50 (br. s., 6H).

Example 176

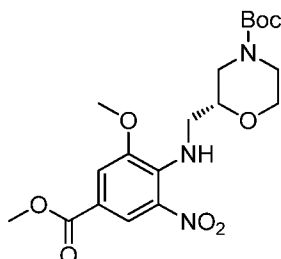
(S)-2-((2-(6-((2S,4S)-2,4-Dimethylazetidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine



To a solution of tert-butyl(R)-2-(((3-fluoro-6-methoxy-2-nitrophenyl)amino)methyl)morpholine-4-carboxylate (80 mg, 0.222 mmol) and 6-((2S,4S)-2,4-dimethylazetidin-1-yl)nicotinaldehyde (42 mg, 0.22 mmol) in a 2:1 mixture of CH₃OH:water (3 mL) was added sodium hydrosulfite (108 mg, 85%, 0.529 mmol), and the reaction mixture was stirred in a sealed vessel at 100 °C for 3 days. The reaction was then cooled to room temperature and diluted with saturated aqueous NaHCO₃ (10 mL). The aqueous solution was extracted with EtOAc (4 x 10 mL), and the combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. To a solution of the crude residue in CH₂Cl₂ (2 mL) was added trifluoroacetic acid (0.16 mL, 2.1 mmol), and the reaction mixture was stirred at room temperature for 21 hours. The reaction was concentrated in vacuo, and the resulting residue was purified by reverse phase HPLC (0.1% 10 mM NH₄HCO₃ with NH₄OH modifier, eluting with 30 to 85% CH₃CN/water). The fractions containing product were concentrated and lyophilized to afford the desired product (36 mg) as a white solid. LC-MS (ES) m/z = 426 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.59 (d, J = 1.8 Hz, 1H), 7.88 (dd, J = 8.6, 2.3 Hz, 1H), 6.87 (dd, J = 9.8, 8.7 Hz, 1H), 6.58 (dd, J = 8.6, 3.3 Hz, 1H), 6.34 (d, J = 8.6 Hz, 1H), 4.72 - 4.49 (m, 2H), 4.47 - 4.28 (m, 2H), 3.96 (s, 3H), 3.96 - 3.86 (m, 1H), 3.79 (dd, J = 11.5, 2.2 Hz, 1H), 3.50 - 3.34 (m, 1H), 2.96 - 2.71 (m, 3H), 2.52 (dd, J = 11.9, 10.4 Hz, 1H), 2.17 (t, J = 6.46 Hz, 2H), 1.49 (d, J = 6.1 Hz, 6H).

Intermediate 240

tert-Butyl(R)-2-(((2-methoxy-4-(methoxycarbonyl)-6-nitrophenyl)amino)methyl)morpholine-4-carboxylate



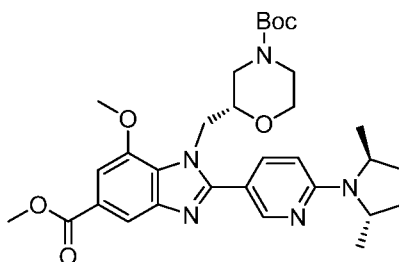
5

To a solution of tert-butyl(R)-2-(aminomethyl)morpholin-4-carboxylate (291 mg, 1.34 mmol) and methyl 4-chloro-3-methoxy-5-nitrobenzoate (330 mg, 1.34 mmol) in DMF (3 mL) was added K_2CO_3 (223 mg, 1.61 mmol), and the reaction mixture was stirred in a sealed vessel at 60 °C for 19 hours. The reaction was then cooled to room temperature and diluted with EtOAc (20 mL). The organic solution was washed with water (2 x 15 mL), and the combined aqueous fractions were back-extracted with EtOAc (15 mL). The combined organic fractions were washed with brine (15 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 0 to 40% EtOAc/hexanes) to afford the desired product (572 mg) as an orange oil. LC-MS (ES) m/z = 426 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.67 - 8.39 (m, 1H), 7.54 (d, J = 1.8 Hz, 1H), 4.04 - 3.83 (m, 10H), 3.78 - 3.48 (m, 3H), 3.01 (br s, 1H), 2.76 (br s, 1H), 1.59 - 1.41 (m, 9H).

15

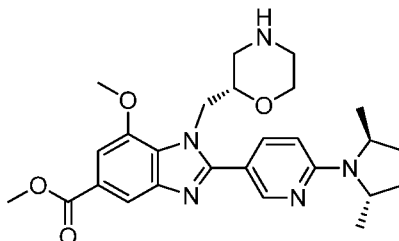
Intermediate 241

20 tert-Butyl(R)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-5-(methoxycarbonyl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate



Intermediate 242

Methyl 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1-(((S)-morpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxylate



5

To a solution of tert-butyl(R)-2-(((2-methoxy-4-(methoxycarbonyl)-6-nitrophenyl)amino)methyl)morpholine-4-carboxylate (570 mg, 1.34 mmol) and 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (287 mg, 1.41 mmol) in a 2:1 mixture of CH₃OH:water (4.5 mL) was added sodium hydrosulfite (700 mg, 85%, 3.417 mmol), and the reaction mixture was stirred in a sealed vessel at 100 °C for 3 days. The reaction was then cooled to room temperature and diluted with saturated aqueous NaHCO₃ (10 mL). The aqueous solution was extracted with EtOAc (4 x 10 mL), and the combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 0 to 5% CH₃OH/CH₂Cl₂) to afford the desired products as clear films.

15

Intermediate 241:

Clear film (263 mg). LC-MS (ES) m/z = 590 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.65 (d, J = 2.0 Hz, 1H), 8.16 (d, J = 1.0 Hz, 1H), 7.89 (dd, J = 8.9, 2.3 Hz, 1H), 7.46 (d, J = 0.8 Hz, 1H), 6.50 (d, J = 8.9 Hz, 1H), 4.63 - 4.16 (m, 5H), 4.07 (s, 3H), 3.96 (s, 3H), 3.93 - 3.64 (m, 2H), 3.36 (br s, 1H), 3.10 - 2.81 (m, 1H), 2.63 (t, J = 11.7 Hz, 1H), 2.42 - 2.23 (m, 2H), 2.06 (d, J = 10.4 Hz, 1H), 1.72 (d, J = 5.6 Hz, 2H), 1.55 - 1.36 (m, 9H), 1.26 - 1.14 (m, 6H).

20

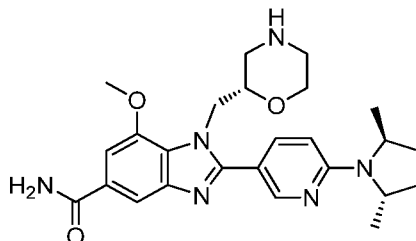
Intermediate 242:

Clear film (169 mg). LC-MS (ES) m/z = 480 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.61 (d, J = 2.0 Hz, 1H), 8.14 (d, J = 1.3 Hz, 1H), 7.88 (dd, J = 8.9, 2.5 Hz, 1H), 7.44 (d, J = 1.0 Hz, 1H), 6.49 (d, J = 8.9 Hz, 1H), 4.63 - 4.10 (m, 4H), 4.03 (s, 3H), 3.96 (s, 3H), 3.96 - 3.91 (m, 1H), 3.89 - 3.73 (m, 2H), 2.97 - 2.70 (m, 3H), 2.68 - 2.40 (m, 2H), 2.37 - 2.17 (m, 2H), 1.72 (d, J = 5.6 Hz, 2H), 1.32 - 1.11 (m, 6H).

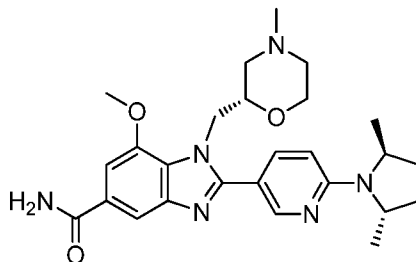
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Intermediate 243

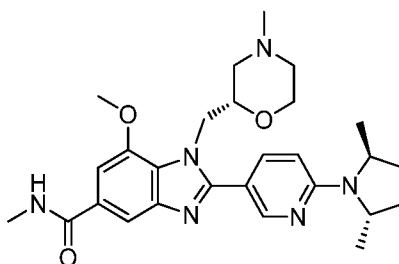
2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1-(((S)-morpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide



- 5 To a solution of tert-butyl(R)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-5-(methoxycarbonyl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (80 mg, 0.14 mmol) in CH₃OH (2 mL) was added NaOH (5M aqueous solution, 0.055 mL, 0.28 mmol), and the reaction mixture was stirred at 60 °C for 17 hours. The reaction was then cooled to room temperature and concentrated in vacuo. To a solution of the resulting
- 10 residue in DMSO (1.4 mL) was added NH₄Cl (22 mg, 0.41 mmol), EDC (53 mg, 0.28 mmol), 1-hydroxy-7-azabenzotriazole (38 mg, 0.28 mmol), and N,N-diisopropylethylamine (0.14 mL, 0.83 mmol), and the reaction mixture was stirred at room temperature for 3.5 hours. Additional EDC (53 mg, 0.28 mmol), 1-hydroxy-7-azabenzotriazole (38 mg, 0.28 mmol), and diisopropylethylamine (0.14 mL, 0.83 mmol) were added, and the reaction mixture was
- 15 stirred for an additional 17 hours. The reaction was quenched with water (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. To a solution of the resulting residue in CH₂Cl₂ (3 mL) was added trifluoroacetic acid (0.053 mL, 0.69 mmol), and the reaction mixture was stirred at room temperature for 1 hour. Additional
- 20 trifluoroacetic acid (0.053 mL, 0.69 mmol) was added and, after 18 hours, the mixture was concentrated in vacuo. The resulting residue was purified by reverse phase HPLC (0.1% 10 mM NH₄HCO₃ with NH₄OH modifier, eluting with 30 to 85% CH₃CN/water). The fractions containing product were concentrated and lyophilized to afford the desired product (38 mg) as a white solid. LC-MS (ES) m/z = 465 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.71 - 8.52
- 25 (m, 1H), 7.99 - 7.75 (m, 2H), 7.44 (s, 1H), 6.92 (br s, 1H), 6.51 (d, J = 8.9 Hz, 1H), 5.62 (br s, 1H), 4.62 - 4.18 (m, 4H), 4.05 (s, 3H), 4.00 - 3.87 (m, 1H), 3.82 (dd, J = 11.4, 2.0 Hz, 1H), 3.57 - 3.33 (m, 1H), 3.00 - 2.72 (m, 3H), 2.55 (dd, J = 11.8, 10.5 Hz, 1H), 2.43 - 2.19 (m, 2H), 1.81 - 1.59 (m, 2H), 1.29 - 1.16 (m, 6H).

Example 177**2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1-(((S)-4-methylmorpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide**

- 5 To a solution of 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1-(((S)-morpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide (19 mg, 0.041 mmol) in 1,2-dichloroethane (2 mL) were added formaldehyde (36.5% solution, 0.015 mL, 0.20 mmol) and sodium triacetoxyborohydride (26 mg, 0.12 mmol), and the reaction mixture was stirred at room temperature for 1 hour. The reaction was then concentrated in vacuo, and the
- 10 resulting residue was purified by reverse phase HPLC (0.1% 10 mM NH_4HCO_3 with NH_4OH modifier, eluting with 30 to 85% CH_3CN /water). The fractions containing product were concentrated and lyophilized to afford the desired product (13 mg) as a white solid. LC-MS (ES) m/z = 479 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 8.74 - 8.40 (m, 1H), 7.92 (d, J = 1.3 Hz, 1H), 7.90 - 7.81 (m, 1H), 7.43 (d, J = 1.3 Hz, 1H), 7.11 - 6.87 (m, 1H), 6.50 (d, J = 8.9
- 15 Hz, 1H), 5.64 (br s, 1H), 4.67 - 4.13 (m, 3H), 4.04 (s, 3H) 4.04 - 3.94 (m, 1H), 3.90 - 3.79 (m, 1H), 3.78 - 3.72 (m, 2H), 3.60 - 3.35 (m, 2H), 2.63 (dd, J = 16.9, 11.3 Hz, 2H), 2.40 - 2.24 (m, 4H), 1.89 - 1.77 (m, 1H), 1.75 - 1.60 (m, 2H), 1.32 - 1.14 (m, 6H).

Example 178**2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-N-methyl-1-(((S)-4-methylmorpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide**

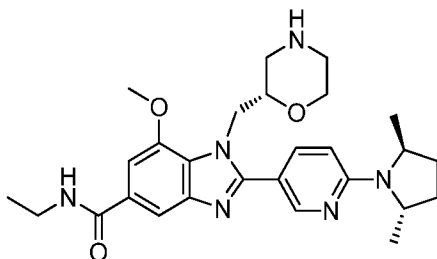
- To a solution of methyl 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1-(((S)-morpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxylate (75 mg, 0.16 mmol) in
- 25 1,2-dichloroethane (2 mL) were added formaldehyde (36.5% solution, 0.059 mL, 0.78 mmol) and sodium triacetoxyborohydride (99 mg, 0.47 mmol), and the reaction mixture was

stirred at room temperature for 30 minutes. The reaction was then diluted with CH₂Cl₂ (20 mL), and the resulting organic solution was washed with saturated aqueous NaHCO₃ (15 mL) followed by brine (15 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. To a solution of the resulting residue in CH₃OH (2 mL) was added NaOH (5M aqueous, 0.065 mL, 0.32 mmol), and the reaction mixture was stirred at 60 °C for 1 hour, then at 80 °C for 20 hours. The reaction was cooled to room temperature and concentrated in vacuo. To a solution of the resulting residue in DMSO (1.6 mL) was added methanamine hydrochloride (33 mg, 0.49 mmol), EDC (62 mg, 0.32 mmol), 1-hydroxy-7-azabenzotriazole (44 mg, 0.32 mmol), and N,N-diisopropylethylamine (0.17 mL, 0.97 mmol), and the reaction mixture was stirred at room temperature for 2.5 hours. Additional methanamine hydrochloride (33 mg, 0.49 mmol) was added, and the reaction mixture was stirred for an additional 2 hours. The mixture was filtered and purified by reverse phase HPLC (0.1% 10 mM NH₄HCO₃ with NH₄OH modifier, eluting with 30 to 85% CH₃CN/water). The fractions containing product were concentrated and lyophilized to afford the desired product (32 mg) as a white solid.

LC-MS (ES) m/z = 493 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.62 (d, J = 2.0 Hz, 1H), 7.88 (dd, J = 8.9, 2.3 Hz, 1H), 7.71 (d, J = 1.0 Hz, 1H), 7.39 (d, J = 1.3 Hz, 1H), 6.61 - 6.40 (m, 2H), 4.57 - 4.37 (m, 2H), 4.35 - 4.17 (m, 1H), 4.05 (s, 3H), 4.05 - 3.94 (m, 1H), 3.82 (dd, J = 11.5, 1.6 Hz, 1H), 3.52 (s, 3H), 3.52-3.43 (m, 2H), 3.04 (d, J = 4.8 Hz, 3H), 2.73 - 2.53 (m, 2H), 2.39 - 2.24 (m, 2H), 2.19 - 2.09 (m, 1H), 1.77 - 1.62 (m, 3H), 1.24 (d, J = 6.3 Hz, 6H).

Example 179

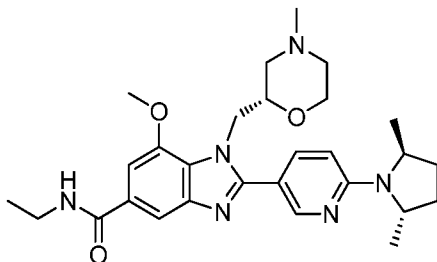
2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-ethyl-7-methoxy-1-((S)-morpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide



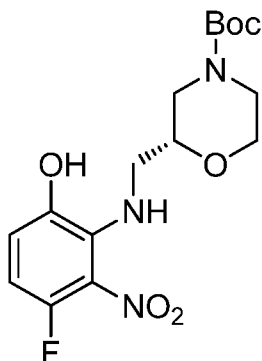
To a solution of tert-butyl(R)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-5-(methoxycarbonyl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (80 mg, 0.14 mmol) in CH₃OH (2 mL) was added NaOH (5M aqueous solution, 0.055 mL, 0.28 mmol), and the reaction mixture was stirred at 60 °C for 17 hours. The reaction was then cooled to room temperature and concentrated in vacuo. To a solution of the resulting residue in DMSO (1.4 mL) was added ethanamine (2M in THF, 0.21 mL, 0.41 mmol), EDC (53 mg, 0.28 mmol), 1-hydroxy-7-azabenzotriazole (38 mg, 0.28 mmol), and N,N-

diisopropylethylamine (0.14 mL, 0.83 mmol), and the reaction was stirred at room temperature for 2 hours. Additional ethanamine (2M in THF, 0.21 mL, 0.41 mmol) was then added. After 1.5 hours, additional EDC (53 mg, 0.28 mmol), 1-hydroxy-7-azabenzotriazole (38 mg, 0.28 mmol), and ethanamine (2M in THF, 0.21 mL, 0.41 mmol) were added. After 5 21 hours, ethylamine hydrochloride (56 mg, 0.69 mmol) was added. After 2 hours, additional ethylamine hydrochloride (56 mg, 0.69 mmol) was added. After 19 hours, ethylamine hydrochloride (56 mg, 0.69 mmol), EDC (53 mg, 0.28 mmol), N,N-diisopropylethylamine (0.14 mL, 0.83 mmol), and 1-hydroxy-7-azabenzotriazole (38 mg, 0.28 mmol) were added. After 5 hours, the reaction was diluted with EtOAc (20 mL), 10 followed by 1N HCl to pH = 4. The aqueous layer was back-extracted with EtOAc (3 x 20 mL), and the combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. To a solution of the resulting residue in DMSO (1.4 mL) was added ethylamine hydrochloride (56 mg, 0.69 mmol), EDC (53 mg, 0.28 mmol), 1-hydroxy-7-azabenzotriazole (38 mg, 0.28 mmol), and N,N-diisopropylethylamine (0.14 mL, 0.83 15 mmol). The reaction was stirred at room temperature for 3 days, then quenched with water (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. To a solution of the resulting residue in CH₂Cl₂ (1.4 mL) was added trifluoroacetic acid (0.053 mL, 0.69 mmol). The reaction was stirred at room temperature for 1 hour, and then additional 20 trifluoroacetic acid (0.053 mL, 0.69 mmol) was added. After 20 hours, the mixture was concentrated in vacuo, and the resulting residue was purified by reverse phase HPLC (0.1% 10 mM NH₄HCO₃ with NH₄OH modifier, eluting with 30 to 85% CH₃CN/water). The fractions containing product were concentrated and lyophilized to afford the desired product (39 mg) as a white solid. LC-MS (ES) m/z = 493 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.62 (d, J = 1.8 Hz, 1H), 7.89 (dd, J = 8.9, 2.5 Hz, 1H), 7.68 (s, 1H), 7.39 (d, J = 1.3 Hz, 1H), 6.65 - 6.29 (m, 2H), 4.63 - 4.36 (m, 4H), 4.35 - 4.15 (m, 3H), 3.99 - 3.86 (m, 1H), 3.81 (dd, J = 11.4, 2.0 Hz, 1H), 3.64 - 3.49 (m, 2H), 3.44 (td, J = 11.3, 2.8 Hz, 1H), 2.98 - 2.69 (m, 3H), 2.55 (dd, J = 11.9, 10.4 Hz, 1H), 2.38 - 2.23 (m, 2H), 1.84 - 1.61 (m, 2H), 1.30 (t, J = 7.2 Hz, 3H), 1.25 - 1.22 (m, 6H).

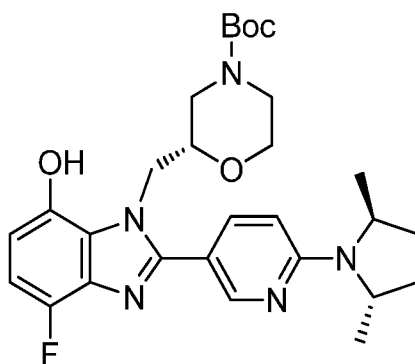
30

Example 180**2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-ethyl-7-methoxy-1-(((S)-4-methylmorpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide**

- 5 To a solution of 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-ethyl-7-methoxy-1-(((S)-morpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide (22 mg, 0.045 mmol) in 1,2-dichloroethane (2 mL) were added formaldehyde (36.5% solution, 0.017 mL, 0.22 mmol) and sodium triacetoxymethylborohydride (28 mg, 0.13 mmol), and the reaction mixture was stirred at room temperature for 1 hour, then concentrated in vacuo. The resulting residue
- 10 was purified by reverse phase HPLC (0.1% 10 mM NH_4HCO_3 with NH_4OH modifier, eluting with 30 to 85% CH_3CN /water). The fractions containing product were concentrated and lyophilized to afford the desired product (22 mg) as a white solid. LC-MS (ES) m/z = 507 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 8.62 (d, J = 2.0 Hz, 1H), 7.89 (dd, J = 8.9, 2.3 Hz, 1H), 7.68 (d, J = 1.3 Hz, 1H), 7.38 (d, J = 1.3 Hz, 1H), 6.50 (d, J = 8.9 Hz, 1H), 6.35 (t, J = 5.2 Hz, 1H), 4.60 - 4.39 (m, 2H), 4.38 - 4.18 (m, 1H), 4.20 - 4.11 (m, 1H), 4.04 (s, 3H), 4.09 - 3.96 (m, 1H), 3.82 (dd, J = 11.4, 1.8 Hz, 1H), 3.51 (s, 3H), 3.65-3.37 (m, 2H), 2.63 (t, J = 10.8 Hz, 2H), 2.39 - 2.24 (m, 3H), 2.20 - 2.09 (m, 1H), 1.92 - 1.76 (m, 1H), 1.76 - 1.65 (m, 2H), 1.34 - 1.26 (m, 3H), 1.24 (d, J = 6.1 Hz, 6H).

Intermediate 244tert-Butyl(R)-2-(((3-fluoro-6-hydroxy-2-nitrophenyl)amino)methyl)morpholine-4-carboxylate

To a solution of tert-butyl(R)-2-(aminomethyl)morpholin-4-carboxylate (124 mg, 0.571 mmol) and 2,4-difluoro-3-nitrophenol (100 mg, 0.571 mmol) in 1,4 dioxane (6 mL) was added N,N-diisopropylethylamine (0.100 mL, 0.571 mmol), and the reaction mixture was stirred at room temperature for 2 hours, then at 50 °C for 18 hours. The reaction was then heated to 70 °C for 1 hour and at 80 °C for 22 hours. The mixture was concentrated in vacuo, and the resulting residue was purified by silica gel chromatography (eluting with 0 to 60% EtOAc/hexanes) to afford the desired product (98 mg) as an orange oil. LC-MS (ES) m/z = 386 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.65 (br s, 1H), 6.99 (dd, J = 9.0 Hz, 1H), 6.76 (t, J = 9.5 Hz, 1H), 4.99 (br s, 1H), 4.10-3.79 (m, 3H), 3.73 - 3.51 (m, 2H), 3.35 (d, J = 14.4 Hz, 1H), 3.20 - 2.57 (m, 3H), 1.54 - 1.40 (m, 9H).

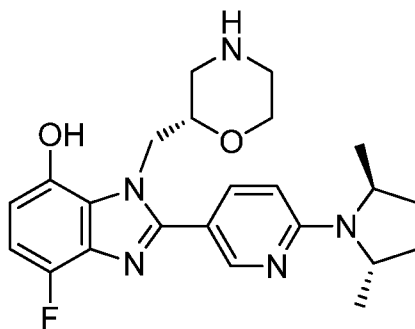
15 Intermediate 245tert-Butyl(R)-2-((2-6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-hydroxy-1H-benzo[d]imidazol-7-yl)methyl)morpholine-4-carboxylate

To a solution of tert-butyl(R)-2-(((3-fluoro-6-hydroxy-2-nitrophenyl)amino)methyl)morpholine-4-carboxylate (90 mg, 0.24 mmol) and 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (52 mg, 0.25 mmol) in a 2:1 mixture of

CH₃OH:water (5 mL) was added sodium hydrosulfite (127 mg, 85%, 0.618 mmol), and the reaction mixture was heated in a microwave reactor at 120 °C for 90 minutes. The reaction was then cooled to room temperature and diluted with saturated aqueous NaHCO₃ (10 mL). The aqueous solution was extracted with EtOAc (4 x 10 mL), and the combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 0 to 60% EtOAc/hexanes) to afford the desired product (526 mg) as a pale yellow solid. LC-MS (ES) m/z = 526 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.47 (br s, 1H), 7.80 (dd, J = 8.9, 2.5 Hz, 1H), 6.93 - 6.79 (m, 1H), 6.69 (dd, J = 8.5, 3.7 Hz, 1H), 6.51 (d, J = 8.9 Hz, 1H), 4.65 - 4.51 (m, 1H), 4.44 (d, J = 14.7 Hz, 1H), 4.37 - 4.21 (m, 2H), 4.06 - 3.84 (m, 3H), 3.66 - 3.47 (m, 1H), 2.99 (br s, 1H), 2.67 (br s, 1H), 2.41 - 2.11 (m, 3H), 1.74 (d, J = 5.8 Hz, 2H), 1.56 - 1.42 (m, 9H), 1.26 - 1.18 (m, 6H).

Example 181

2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-1-(((S)-morpholin-2-yl)methyl)-1H-benzo[d]imidazol-7-ol

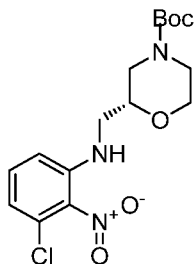


To a solution of tert-butyl(R)-2-((2-6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-hydroxy-1H-benzo[d]imidazol-7-ol-1-yl)methyl)morpholine-4-carboxylate (96 mg, 0.18 mmol) in CH₂Cl₂ (5 mL) was added trifluoroacetic acid (0.93 mL, 1.2 mmol), and the reaction mixture was stirred at room temperature for 3 hours. The reaction was then concentrated in vacuo, and the resulting residue was purified by reverse phase HPLC (0.1% 10 mM NH₄HCO₃ with NH₄OH modifier, eluting with 30 to 85% CH₃CN/water). The fractions containing product were concentrated and lyophilized to afford the desired product (27 mg) as an off-white solid. LC-MS (ES) m/z = 426 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 8.54 (d, J = 2.0 Hz, 1H), 7.94 (dd, J = 8.9, 2.3 Hz, 1H), 6.80 (dd, J = 10.1, 8.6 Hz, 1H), 6.68 (d, J = 8.9 Hz, 1H), 6.58 (dd, J = 8.5, 3.4 Hz, 1H), 4.57 (dd, J = 14.4, 3.0 Hz, 1H), 4.29 (dd, J = 14.4, 8.6 Hz, 3H), 4.14 - 4.01 (m, 1H), 3.81 (dd, J = 11.8, 1.9 Hz, 1H), 3.50 - 3.38 (m, 1H),

2.91 (dd, $J = 12.2, 1.8$ Hz, 1H), 2.85 - 2.66 (m, 2H), 2.52 (dd, $J = 12.3, 10.5$ Hz, 1H), 2.40 - 2.25 (m, 2H), 1.85 - 1.57 (m, 2H), 1.26 - 1.15 (m, 6H).

Intermediate 246

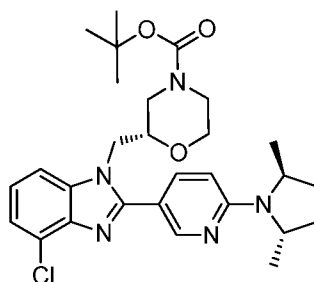
5 tert-Butyl (R)-2-(((3-chloro-2-nitrophenyl)amino)methyl)morpholine-4-carboxylate



To a mixture 1-chloro-3-fluoro-2-nitrobenzene (144 mg, 0.820 mmol) and K_2CO_3 (136 mg, 0.984 mmol) was added a solution of tert-butyl (R)-2-(aminomethyl)morpholine-4-carboxylate (183 mg, 0.845 mmol) in DMF (5 mL), and the reaction mixture was stirred overnight at room temperature. The reaction was then stirred at 35 °C for 3 hours, and at 40 °C for 3 additional hours. The reaction was then allowed to stir for 2 days at 30 °C. The reaction was diluted into saturated aqueous NH_4Cl with stirring and treated with CH_2Cl_2 . The resulting mixture was stirred for 10 minutes. The organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2 . The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford crude (tert-butyl (R)-2-(((3-chloro-2-nitrophenyl)amino)methyl)morpholine-4-carboxylate (330 mg) as an orange residue. LC-MS (ES) $m/z = 316$ $[M+H-tbutyl]^+$.

Intermediate 247

20 tert-Butyl (R)-2-((4-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate

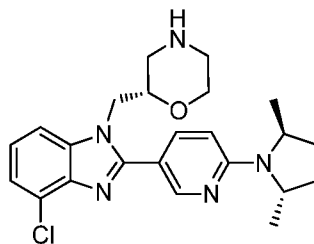


To a mixture of 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (176 mg, 0.863 mmol) and sodium hydrosulfite (481 mg, 85%, 2.346 mmol) was added a solution of tert-butyl (R)-2-(((3-chloro-2-nitrophenyl)amino)methyl)morpholine-4-carboxylate (321 mg, 0.863 mmol)

in hot ethanol (6 mL) followed by water (1.2 mL), and the resulting mixture was stirred for 5 minutes. The vessel was then sealed, and the reaction mixture was stirred at 130 °C for 60 minutes under microwave conditions. The reaction was then poured onto saturated aqueous NH₄Cl with stirring and extracted with EtOAc (2X). The combined organic extracts were dried over MgSO₄, filtered and, concentrated *in vacuo*. The resulting residue was purified by flash chromatography on SiO₂ (0 to 75% (3:1 EtOAc:EtOH with 2% NH₄OH)/heptane) to afford tert-butyl (R)-2-((4-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (190mg) as a solid. LC-MS (ES) m/z = 526 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.55 (d, *J* = 2.0 Hz, 1H), 7.94 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.30 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.23 (t, *J* = 7.9 Hz, 1H), 6.63 (d, *J* = 8.9 Hz, 1H), 4.42 - 4.50 (m, 1H), 4.34 (dd, *J* = 15.2, 8.6 Hz, 2H), 4.26 (br. s., 1H), 3.72 (d, *J* = 11.7 Hz, 2H), 3.64 (d, *J* = 12.9 Hz, 1H), 3.22 (td, *J* = 11.7, 2.7 Hz, 1H), 2.83 (br. s., 1H), 2.57 - 2.71 (m, 1H), 2.24 (br. s., 2H), 1.66 (d, *J* = 5.6 Hz, 2H), 1.38 (s, 9H), 1.33 (br. s., 1H), 1.07 - 1.19 (m, 6H).

Example 182

(S)-2-((4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine

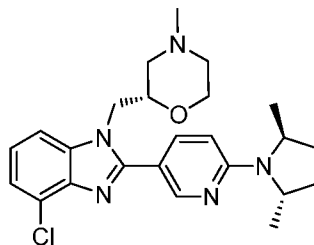


To tert-butyl (R)-2-((4-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (188 mg, 0.357 mmol) in CH₂Cl₂ (8 mL) was added TFA (0.551 mL, 7.15 mmol), and the reaction mixture was stirred at room temperature for 2 hours. The mixture was concentrated, and the resulting residue was purified by flash chromatography on SiO₂ (25 - 100% (3:1 EtOAc:EtOH with 2% NH₄OH)/heptane). Fraction containing the desired product were combined and concentrated. The resulting residue was dissolved in CH₂Cl₂ and concentrated again. The resulting white solid was then stirred in a mixture of water, EtOAc and saturated aqueous NaHCO₃ (1 mL) for 15 minutes. The organic layer was separated, and the aqueous layer was further extracted with EtOAc. The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The resulting residue was dissolved in CH₂Cl₂ and heptane, and the mixture was concentrated and dried in vacuum oven at 40°C overnight to

afford (S)-2-((4-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine (115 mg) as a white solid/foam. LC-MS (ES) m/z = 426 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 8.57 (d, J = 2.0 Hz, 1H), 7.95 (dd, J = 8.9, 2.3 Hz, 1H), 7.62 (dd, J = 7.9, 1.0 Hz, 1H), 7.30 (dd, J = 7.9, 1.0 Hz, 1H), 7.23 (t, J = 7.9 Hz, 1H), 6.63 (d, J = 8.9 Hz, 1H), 4.10 - 4.40 (m, 4H), 3.74 - 3.82 (m, 1H), 3.65 (d, J = 10.9 Hz, 1H), 3.21 - 3.29 (m, 1H), 2.82 (dd, J = 12.2, 2.0 Hz, 1H), 2.56 - 2.67 (m, 2H), 2.41 (dd, J = 12.0, 10.3 Hz, 1H), 2.25 (br. s., 2H), 1.66 (d, J = 5.6 Hz, 2H), 1.09 - 1.19 (m, 6H).

Example 183

10 (S)-2-((4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)-4-methylmorpholine

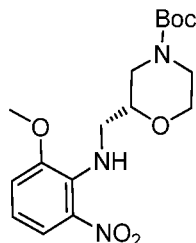


To (S)-2-((4-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine (65 mg, 0.153 mmol) in 1,2-dichloroethane (4.0 mL) was added acetic acid (0.026 mL, 0.458 mmol) followed by formaldehyde (0.057 mL, 0.763 mmol), and the resulting mixture was stirred for 5 minutes. Sodium triacetoxyborohydride (113 mg, 0.534 mmol) was then added, the vessel capped, and the reaction mixture was stirred at room temperature for 90 minutes. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ dropwise followed by saturated aqueous Na_2CO_3 until the pH = 10. CH_2Cl_2 was then added, and the resulting mixture was stirred for 10 minutes. The organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2 . The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (silica gel, gradient: 10-100% (90:10:1 CH_2Cl_2 : CH_3OH : NH_4OH)/ CH_2Cl_2) to afford (S)-2-((4-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)-4-methylmorpholine (53 mg) as a pale yellow glassy solid. LC-MS (ES) m/z = 440 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 8.56 (d, J = 2.5 Hz, 1H), 7.95 (dd, J = 9.0, 2.4 Hz, 1H), 7.63 (dd, J = 8.0, 0.9 Hz, 1H), 7.30 (dd, J = 7.9, 1.0 Hz, 1H), 7.23 (t, J = 7.9 Hz, 1H), 6.63 (d, J = 8.9 Hz, 1H), 4.11 - 4.41 (m, 4H), 3.84 (dt, J = 5.0, 2.4 Hz, 1H), 3.69 (d, J = 11.4 Hz, 1H), 3.26 - 3.32 (m, 1H), 2.73 (d, J = 10.9 Hz, 1H), 2.54 (d, J = 12.7 Hz, 1H), 2.24 (br. s.,

2H), 2.15 (s, 3H), 1.91 - 2.02 (m, 1H), 1.75 (t, $J = 10.6$ Hz, 1H), 1.66 (d, $J = 5.6$ Hz, 2H), 1.15 (d, $J = 6.1$ Hz, 6H).

Intermediate 248

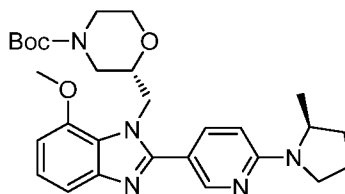
5 (R)-tert-Butyl 2-(((2-methoxy-6-nitrophenyl)amino)methyl)morpholine-4-carboxylate



A solution of 2-fluoro-1-methoxy-3-nitrobenzene (100 mg, 0.584 mmol), tert-butyl (R)-2-(aminomethyl)morpholine-4-carboxylate (126 mg, 0.584 mmol), and triethylamine (0.090 mL, 0.643 mmol) in DMF (10 mL) was stirred at room temperature overnight. The reaction was quenched with water (12 mL) and extracted with CH_2Cl_2 (20 mL). The organic layer was concentrated, and the resulting residue was purified on silica (0 - 100% EtOAc/hexanes) to afford tert-butyl (R)-2-(((2-methoxy-6-nitrophenyl)amino)methyl)morpholine-4-carboxylate (144 mg) as a orange oil. LC-MS (ES) $m/z = 368$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 7.74 (dd, $J = 1.3, 8.6$ Hz, 1H), 6.97 (dd, $J = 1.3, 7.9$ Hz, 1H), 6.72 (t, $J = 8.2$ Hz, 1H), 4.09 - 3.68 (m, 8H), 3.52 (s, 3H), 2.97 (t, $J = 12.2$ Hz, 1H), 2.73 (br. s., 1H), 1.48 (s, 9H).

Intermediate 249

20 (R)-tert-Butyl 2-(((7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate

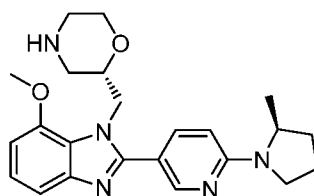


To a 10-mL microwave tube were added tert-butyl (R)-2-(((2-methoxy-6-nitrophenyl)amino)methyl)morpholine-4-carboxylate (200 mg, 0.544 mmol), (S)-6-(2-methylpyrrolidin-1-yl)nicotinaldehyde (104 mg, 0.544 mmol), sodium hydrosulfite (334 mg, 85%, 1.633 mmol), ethanol (3 mL), and water (0.75 mL). The tube was sealed, and the reaction mixture was stirred at 130 °C under microwave conditions for 80 minutes. The mixture was then cooled to room temperature, diluted with EtOAc, and filtered. The filtrate was concentrated, and the resulting residue was purified using column chromatography (silica gel, 0 to 100%

EtOA/heptane) to give the desired product (91 mg) as a white solid. LC-MS (ES) m/z = 508 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.25 - 1.30 (m, 3H), 1.48 (s, 9H), 1.80 - 1.88 (m, 1H), 2.05 - 2.28 (m, 3H), 2.68 (m, 1H), 2.93 (m, 1H), 3.40 - 3.52 (m, 1H), 3.60 - 3.69 (m, 1H), 3.82 (m, 4H), 4.04 (s, 3H), 4.22 - 4.44 (m, 2H), 4.57 (dd, J = 14.7, 2.8 Hz, 1H), 6.67 (d, J = 8.9 Hz, 1H), 6.89 (d, J = 7.4 Hz, 1H), 7.18 - 7.32 (m, 2H), 7.95 (dd, J = 8.9, 2.5 Hz, 1H), 8.53 (d, J = 2.0 Hz, 1H).

Example 184

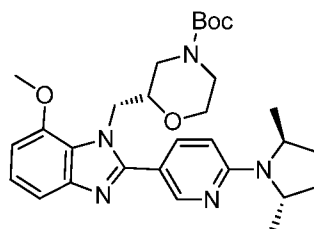
(S)-2-((7-Methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)



To a solution of tert-butyl (R)-2-((7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (50 mg, 0.098 mmol) in CH_2Cl_2 (2 mL) was added TFA (800 μ l, 10.38 mmol), and the reaction mixture was stirred at room temperature for 4 hours. The mixture was treated with 6N HCl (1 mL) and concentrated. The resulting residue was dried under vacuum, treated with saturated Na_2CO_3 aqueous solution (3 mL), and extracted with CH_2Cl_2 (3X). The organic extract was dried (Na_2SO_4) and concentrated, and the resulting residue was dried under vacuum to give the desired product (34 mg) as an off-white solid. LC-MS (ES) m/z = 408 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.28 (d, J = 6.3 Hz, 3H), 1.79 - 1.88 (m, 1H), 2.05 - 2.27 (m, 3H), 2.82 (dd, J = 12.4, 11.2 Hz, 1H), 3.00 - 3.08 (m, 2H), 3.17 - 3.25 (m, 1H), 3.37 - 3.59 (m, 2H), 3.61 - 3.70 (m, 1H), 3.90 - 3.99 (m, 1H), 4.04 (s, 3H), 4.10 - 4.19 (m, 1H), 4.27 (t, J = 5.7 Hz, 1H), 4.38 (dd, J = 14.7, 8.4 Hz, 1H), 4.62 (dd, J = 14.7, 2.8 Hz, 1H), 6.67 (d, J = 8.9 Hz, 1H), 6.90 (dd, J = 7.6, 1.0 Hz, 1H), 7.21 - 7.33 (m, 2H), 7.91 (dd, J = 9.0, 2.4 Hz, 1H), 8.50 (d, J = 2.0 Hz, 1H).

Intermediate 250

(R)-tert-Butyl 2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate



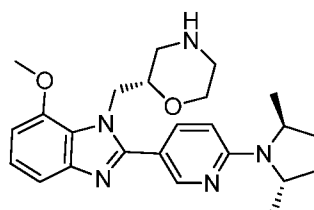
5

A mixture of tert-butyl (R)-2-(((2-methoxy-6-nitrophenyl)amino)methyl)morpholine-4-carboxylate (144 mg, 0.392 mmol), 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (84 mg, 0.412 mmol), and sodium hydrosulfite (205 mg, 85%, 1.00 mmol) in ethanol (5 mL) and water (0.750 mL) was heated at 110 °C under microwave conditions for 1 hour. The solids were filtered out, and the filtrate was concentrated. The resulting residue was purified on silica (0-100% EtOAc/hexanes) to afford tert-butyl (R)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (100 mg) as a white solid. LCMS (ES) m/z = 522 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.51 (d, *J* = 2.3 Hz, 1H), 7.91 (dd, *J* = 2.5, 8.9 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 6.60 (d, *J* = 8.9 Hz, 1H), 4.46 (s, 1H), 4.31 (s, 3H), 3.95 (s, 3H), 3.71 (s, 4H), 3.32 (s, 1H), 3.27 - 3.17 (m, 1H), 2.47 - 2.43 (m, 1H), 2.24 (t, *J* = 7.6 Hz, 2H), 1.65 (d, *J* = 5.3 Hz, 2H), 1.39 (s, 9H), 1.14 (d, *J* = 6.1 Hz, 6H).

20

Example 185

(S)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine

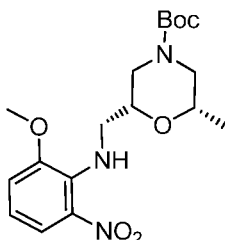


To tert-butyl (R)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (90 mg, 0.173 mmol) was added in 4N HCl in 1,4-dioxane (5090 μl, 20.36 mmol), and the reaction mixture was stirred at room temperature overnight. The resulting precipitate was collected, washed with Et₂O, and dried under high vacuum to afford a HCl salt of (S)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-

yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine (45 mg) as a white solid. LCMS (ES) m/z = 422 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 9.81 (br. s., 1H), 9.52 (br. s., 1H), 8.69 (br. s., 1H), 8.09 (d, J = 9.1 Hz, 1H), 7.55 - 7.46 (m, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.17 (d, J = 7.6 Hz, 1H), 6.91 (br. s., 1H), 4.64 (d, J = 12.4 Hz, 3H), 4.57 - 4.14 (m, 3H), 4.06 (s, 3H), 3.94 (d, J = 11.9 Hz, 1H), 3.64 (t, J = 11.8 Hz, 1H), 3.39 (d, J = 12.4 Hz, 1H), 3.21 - 3.13 (m, 1H), 3.03 (s, 2H), 2.29 (br. s., 2H), 1.72 (br. s., 2H), 1.18 (br. s., 6H).

Intermediate 251

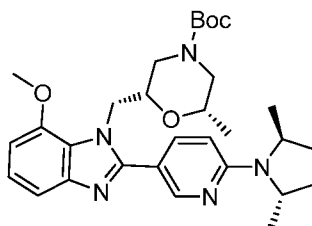
10 tert-Butyl (2R,6S)-2-(((2-methoxy-6-nitrophenyl)amino)methyl)-6-methylmorpholine-4-carboxylate



To a solution of tert-butyl (2R,6S)-2-(aminomethyl)-6-methylmorpholine-4-carboxylate (prepared generally according to Compound 73 of US Patent publication: 20150105370, 16 Apr 2015) (60 mg, 0.261 mmol) and 2-fluoro-1-methoxy-3-nitrobenzene (44.6 mg, 0.261 mmol) in DMF (2 mL) was added K_2CO_3 (36.0 mg, 0.261 mmol), and the reaction mixture was stirred at 23 °C for 18 hours. The reaction was concentrated under vacuum, and the resulting residue was resuspended in EtOAc (10 mL), the solid filtered out, and the filtrate concentrated under vacuum. The resulting residue was purified by silica gel column (0-60% EtOAc/Heptane) to give the desired product tert-butyl (2R,6S)-2-(((2-methoxy-6-nitrophenyl)amino)methyl)-6-methylmorpholine-4-carboxylate (68 mg) as a bright orange oil. LC-MS (ES) m/z = 382 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 7.87 (br. s., 1H), 7.76 (dd, J = 1.3, 8.6 Hz, 1H), 6.98 (d, J = 7.1 Hz, 1H), 6.73 (dd, J = 7.9, 8.6 Hz, 1H), 3.94 - 4.10 (m, 2H), 3.90 (s, 3H), 3.73 - 3.87 (m, 1H), 3.54 - 3.66 (m, 2H), 3.42 - 3.53 (m, 1H), 2.42 - 2.75 (m, 2H), 1.53 (s, 9H), 1.23 (d, J = 6.1 Hz, 3H).

Intermediate 252

(2R,6S)-tert-Butyl 2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-6-methylmorpholine-4-carboxylate



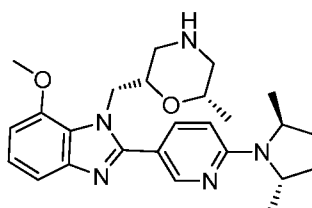
5

To a solution of 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (83 mg, 0.406 mmol), tert-butyl (2R,6S)-2-(((2-methoxy-6-nitrophenyl)amino)methyl)-6-methylmorpholine-4-carboxylate (155 mg, 0.406 mmol) in ethanol (2 mL) and water (0.400 mL) was added sodium hydrosulfite (226 mg, 85%, 1.105 mmol), and the mixture was heated in a 5 mL microwave vial at 130 °C for 60 minutes under the microwave conditions. The mixture was then concentrated under vacuum, and the resulting residue was resuspended in EtOAc. The solid was filtered out and the crude material was purified by silica gel chromatography (0-100% EtOAc/Heptane) to give the desired product tert-butyl (2R,6S)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-6-methylmorpholine-4-carboxylate (160 mg) as a white solid. LC-MS (ES) m/z = 450 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.51 (d, J = 2.0 Hz, 1H), 7.94 (dd, J = 2.3, 9.1 Hz, 1H), 7.19 - 7.30 (m, 2H), 6.88 (d, J = 7.6 Hz, 1H), 6.66 (d, J = 8.9 Hz, 1H), 4.59 (dd, J = 2.7, 14.6 Hz, 1H), 4.23 - 4.42 (m, 3H), 3.99 - 4.07 (m, 3H), 3.78 - 3.96 (m, 3H), 2.54 (br. s., 2H), 2.28 - 2.39 (m, 2H), 1.75 (d, J = 5.8 Hz, 2H), 1.46 (s, 9H), 1.22 (d, J = 6.3 Hz, 6H), 1.09 (d, J = 6.1 Hz, 3H).

20

Example 186

(2S,6S)-2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-6-methylmorpholine



25

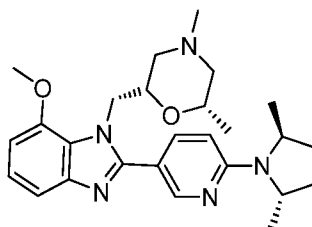
To t-butyl (2R,6S)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-6-methylmorpholine-4-carboxylate (160 mg, 0.299 mmol) was added 6N HCl (1 mL), and the reaction mixture was stirred at room temperature for 1

hour. The reaction mixture was concentrated under vacuum to give a HCl salt of the desired product (2S,6S)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-6-methylmorpholine (178 mg) as a white solid. LC-MS (ES) $m/z = 436 [M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.51 (d, $J = 1.8$ Hz, 1H), 7.95 (dd, $J = 2.3, 8.9$ Hz, 1H), 7.19 - 7.30 (m, 2H), 6.87 (dd, $J = 0.8, 7.9$ Hz, 1H), 6.66 (d, $J = 8.9$ Hz, 1H), 4.56 (dd, $J = 3.2, 14.3$ Hz, 1H), 4.23 - 4.38 (m, $J = 8.4, 14.4$ Hz, 3H), 3.99 (br. s, 3H), 3.90 - 4.00 (m, 1H), 3.43 (ddd, $J = 2.3, 6.1, 10.4$ Hz, 1H), 2.75 - 2.90 (m, 2H), 2.26 - 2.45 (m, 4H), 1.68 - 1.83 (m, $J = 5.8$ Hz, 2H), 1.22 (d, $J = 6.1$ Hz, 6H), 1.04 (d, $J = 6.3$ Hz, 3H).

10

Example 187

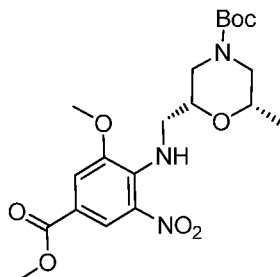
(2S,6S)-2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-4,6-dimethylmorpholine



To a solution of (2S,6S)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-6-methylmorpholine hydrochloride (120 mg, 0.220 mmol) in CH_3OH (5mL) were added formaldehyde (0.051 mL, 0.661 mmol) and $NaBH_3CN$ (41.5 mg, 0.661 mmol), and the reaction mixture was stirred at room temperature for 30 minutes. The reaction was concentrated under vacuum and purified by reverse phase HPLC (30-60% $CH_3CN/0.1\%NH_4OH$) to give the desired product (2S,6S)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-4,6-dimethylmorpholine (24 mg) as a white solid. LC-MS (ES) $m/z = 450 [M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.49 - 8.53 (m, 1H), 7.94 (dd, $J = 2.4, 9.0$ Hz, 1H), 7.19 - 7.30 (m, 2H), 6.87 (dd, $J = 0.9, 7.7$ Hz, 1H), 6.66 (d, $J = 8.9$ Hz, 1H), 4.58 (dd, $J = 2.9, 14.3$ Hz, 1H), 4.22 - 4.41 (m, 3H), 4.05 - 4.13 (m, 1H), 4.01 (s, 3H), 3.42 - 3.55 (m, 1H), 2.80 (d, $J = 11.2$ Hz, 1H), 2.71 (d, $J = 11.2$ Hz, 1H), 2.32 - 2.42 (m, 2H), 2.29 (s, 3H), 1.69 - 1.84 (m, 4H), 1.22 (d, $J = 6.1$ Hz, 6H), 1.08 (d, $J = 6.3$ Hz, 3H).

Intermediate 253

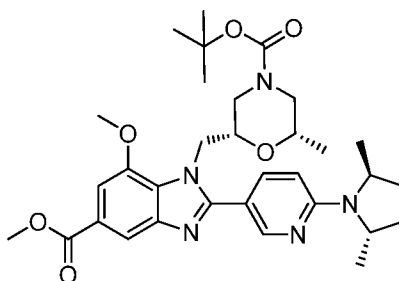
t-Butyl (2R,6S)-2-(((2-methoxy-4-(methoxycarbonyl)-6-nitrophenyl)amino)methyl)-6-methylmorpholine-4-carboxylate



- 5 To a solution of tert-butyl (2R,6S)-2-(aminomethyl)-6-methylmorpholine-4-carboxylate (94 mg, 0.407 mmol) and methyl 4-chloro-3-methoxy-5-nitrobenzoate (100 mg, 0.407 mmol) in DMF (2 mL) was added K_2CO_3 (67.5 mg, 0.489 mmol), and the reaction mixture was stirred at 50 °C for 18 hours. The reaction mixture was concentrated under vacuum, and the resulting material was then resuspended in EtOAc (10 mL) and filtered. The filtrate was
- 10 concentrated, and the resulting residue was purified by silica gel chromatography (0-60% EtOAc/heptane) to give the desired product tert-butyl (2R,6S)-2-(((2-methoxy-4-(methoxycarbonyl)-6-nitrophenyl)amino)methyl)-6-methylmorpholine-4-carboxylate (110 mg) as an orange oil. LC-MS (ES) m/z = 440 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.39 (d, J = 1.8 Hz, 1H), 7.6 (d, J = 1.8 Hz, 1H), 3.86 - 4.00 (m, 9H), 3.50 - 3.68 (m, 3H), 2.37 -
- 15 2.76 (m, 2H), 1.49 (s, 9H), 1.20 (s, 3H).

Intermediate 254

t-Butyl (2R,6S)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-5-(methoxycarbonyl)-1H-benzo[d]imidazol-1-yl)methyl)-6-methylmorpholine-4-carboxylate

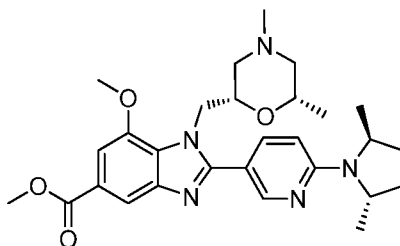


- 20 To a solution of 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (51.1 mg, 0.250 mmol) and tert-butyl (2R,6S)-2-(((2-methoxy-4-(methoxycarbonyl)-6-nitrophenyl)amino)methyl)-6-methylmorpholine-4-carboxylate (110 mg, 0.250 mmol) in ethanol (2 mL) and water (0.400 mL) was added sodium hydrosulfite (139 mg, 85%, 0.681
- 25 mmol), and the reaction mixture was heated in a microwave reactor at 130 °C for 60

minutes. The mixture was concentrated under vacuum, and the resulting residue was dissolved in EtOAc and filtered to remove the solids. The filtrate was concentrated under vacuum, and the resulting residue was purified by silica gel chromatography (0-100% EtOAc/heptane) to give the desired compound tert-butyl (2R,6S)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-5-(methoxycarbonyl)-1H-benzo[d]imidazol-1-yl)methyl)-6-methylmorpholine-4-carboxylate (85 mg) as an amorphous solid. LC-MS (ES) m/z = 594 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.54 (d, J = 2.3 Hz, 1H), 8.01 (d, J = 1.3 Hz, 1H), 7.97 (dd, J = 2.4, 9.0 Hz, 1H), 7.52 (d, J = 0.8 Hz, 1H), 6.64 - 6.72 (m, 1H), 4.64 (dd, J = 2.7, 14.6 Hz, 1H), 4.25 - 4.47 (m, 3H), 4.07 - 4.13 (m, 3H), 3.93 - 3.99 (m, 4H), 3.79 - 3.93 (m, 2H), 3.36 - 3.43 (m, 1H), 2.43 - 2.67 (m, 2H), 2.28 - 2.41 (m, 2H), 1.69 - 1.82 (m, 2H), 1.47 (s, 9H), 1.23 (d, J = 6.3 Hz, 6H), 1.09 (d, J = 6.1 Hz, 3H).

Intermediate 255

Methyl 1-(((2S,6S)-4,6-dimethylmorpholin-2-yl)methyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazole-5-carboxylate

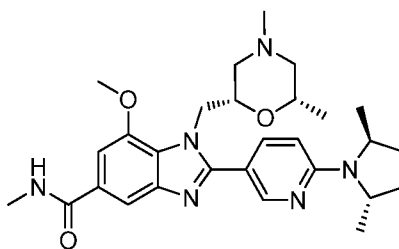


To a solution of tert-butyl (2R,6S)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-5-(methoxycarbonyl)-1H-benzo[d]imidazol-1-yl)methyl)-6-methylmorpholine-4-carboxylate (85 mg, 0.143 mmol) in CH_3OH (2 mL) was added 6N HCl (2.386 mL, 14.32 mmol), and the reaction mixture was stirred at room temperature for 1 hour. The reaction was then concentrated under vacuum, and the resulting crude mixture was dissolved in CH_3OH (2 mL). Formaldehyde (0.020 mL, 0.716 mmol) and sodium cyanoborohydride (27.0 mg, 0.429 mmol) were then added, and the reaction mixture was stirred at 23 °C for 30 minutes. The mixture was concentrated under vacuum and purified by reverse phase HPLC (30-60% $CH_3CN/(0.1\%NH_4OH)$) to give the desired product methyl 1-(((2S,6S)-4,6-dimethylmorpholin-2-yl)methyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazole-5-carboxylate (53 mg) as a white solid. LC-MS (ES) m/z = 508 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.47 - 8.56 (m, 1H), 7.88 - 8.04 (m, 2H), 7.46 - 7.57 (m, 1H), 6.63 - 6.70 (m, 1H), 4.61 (dd, J = 2.8, 14.5 Hz, 1H), 4.23-4.43 (m, 3H), 4.00 - 4.15 (m, 4H), 3.90 - 3.97 (m, 3H), 3.43 - 3.55 (m, 1H), 2.79 - 2.86 (m, 1H), 2.72 (d, J = 11.4

Hz, 1H), 2.33 - 2.41 (m, 2H), 2.30 (s, 3H), 1.67 - 1.83 (m, 4H), 1.17 - 1.28 (m, 6H), 0.99 - 1.13 (m, 3H).

Example 188

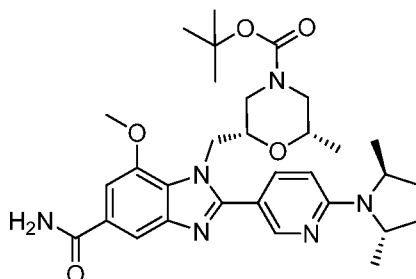
5 **1-(((2S,6S)-4,6-Dimethylmorpholin-2-yl)methyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-N-methyl-1H-benzo[d]imidazole-5-carboxamide**



To methyl 1-(((2S,6S)-4,6-dimethylmorpholin-2-yl)methyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazole-5-carboxylate (65
 10 mg, 0.128 mmol) in CH₃OH (2 mL) was added 5N NaOH (1 mL, 5 mmol), and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated under vacuum, resuspended in 6N HCl (1 mL), and concentrated. To the resulting crude mixture in DMSO (2 mL) were added 3-(((ethylimino)methylene)amino)-N,N-dimethylpropan-1-amine hydrochloride (49.1 mg, 0.256 mmol), 3H-[1,2,3]triazolo[4,5-
 15 b]pyridin-3-ol (34.9 mg, 0.256 mmol), 4-methylmorpholine (0.099 mL, 0.896 mmol), and methanamine hydrochloride (17.29 mg, 0.256 mmol), and the reaction mixture was stirred at room temperature for 18 hours. The reaction was then diluted with water (2 mL) and purified by reverse phase HPLC (30-60% CH₃CN/(0.1%NH₄OH)) to afford 1-(((2S,6S)-4,6-dimethylmorpholin-2-yl)methyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-
 20 methoxy-N-methyl-1H-benzo[d]imidazole-5-carboxamide (22 mg) as a white solid. LC-MS (ES) m/z = 507 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 8.52 (d, J = 1.8 Hz, 1H), 7.96 (dd, J = 2.4, 9.0 Hz, 1H), 7.78 (s, 1H), 7.37 (d, J = 1.3 Hz, 1H), 6.67 (d, J = 8.9 Hz, 1H), 4.61 (dd, J = 2.8, 14.5 Hz, 1H), 4.25 - 4.42 (m, J = 8.6, 14.4 Hz, 3H), 4.02 - 4.12 (m, 4H), 3.42 - 3.52 (m, J = 2.3, 6.4, 10.3 Hz, 1H), 2.97 (s, 3H), 2.82 (d, J = 11.2 Hz, 1H), 2.72 (d, J = 11.2
 25 Hz, 1H), 2.33 - 2.41 (m, 2H), 2.28 (s, 3H), 1.69 - 1.84 (m, 4H), 1.21 (d, J = 6.3 Hz, 6H), 1.08 (d, J = 6.1 Hz, 3H).

Intermediate 256

(2R,6S)-tert-Butyl 2-((5-carbamoyl-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-6-methylmorpholine-4-carboxylate



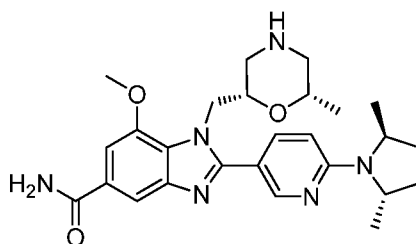
5

- To a solution of tert-butyl (2R,6S)-2-((5-carbamoyl-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-5-(methoxycarbonyl)-1H-benzo[d]imidazol-1-yl)methyl)-6-methylmorpholine-4-carboxylate (800 mg, 1.347 mmol) in CH₃OH (10 mL) was added 5N NaOH (2.69 mL, 13.47 mmol), and the reaction mixture was stirred overnight at room temperature. The reaction
- 10 was acidified using 1N HCl (13.4 mL), and the resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under vacuum to afford the crude 1-(((2R,6S)-4-(tert-butoxycarbonyl)-6-methylmorpholin-2-yl)methyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazole-5-carboxylic acid. LC-MS (ES) m/z = 580 [M+H]⁺.
- 15 To a solution of 1-(((2R,6S)-4-(tert-butoxycarbonyl)-6-methylmorpholin-2-yl)methyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazole-5-carboxylic acid (400 mg, 0.690 mmol) in DMSO (5 mL) were added 3-(((ethylimino)methylene)amino)-N,N-dimethylpropan-1-amine hydrochloride (265 mg, 1.380 mmol), 3H-[1,2,3]triazolo[4,5-b]pyridin-3-ol (188 mg, 1.380 mmol), NH₄Cl (185 mg,
- 20 3.45 mmol), and 4-methylmorpholine (0.759 mL, 6.90 mmol), and the reaction mixture was stirred at room temperature over one weekend. The reaction mixture was diluted with water (25 mL) and extracted with EtOAc (3x). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under vacuum. The resulting residue was purified by silica gel chromatography (0-100% (3:1 EtOAc:EtOH)/CH₂Cl₂) to give the desired product
- 25 tert-butyl (2R,6S)-2-((5-carbamoyl-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-6-methylmorpholine-4-carboxylate (395 mg) as a white solid. LC-MS (ES) m/z = 579 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 8.53 (d, J = 2.0 Hz, 1H), 7.96 (dd, J = 2.4, 9.0 Hz, 1H), 7.87 (d, J = 1.3 Hz, 1H), 7.43 (d, J = 1.0 Hz, 1H), 6.66 (d, J = 8.9 Hz, 1H), 4.62 (dd, J = 2.7, 14.6 Hz, 1H), 4.22 - 4.45 (m, 3H), 4.10 (s, 3H),

3.80 - 4.04 (m, 3H), 3.36 - 3.42 (m, 1H), 2.43 - 2.65 (m, 2H), 2.25 - 2.41 (m, 2H), 1.66 - 1.81 (m, 2H), 1.47 (s, 9H), 1.21 (d, $J = 6.3$ Hz, 6H), 1.09 (d, $J = 6.1$ Hz, 3H).

Intermediate 257

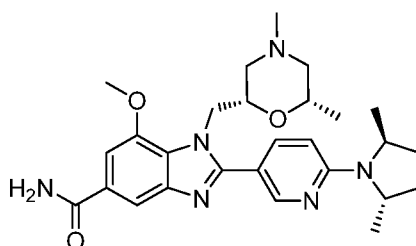
- 5 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1-(((2S,6S)-6-methylmorpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide



- To a solution of tert-butyl (2R,6S)-2-((5-carbamoyl-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-6-methylmorpholine-4-carboxylate (395 mg, 0.683 mmol) in THF (2 mL) was added 6N aqueous HCl (2 mL, 12.00 mmol), and the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under vacuum, and the resulting residue was triturated with Et₂O (3X) to give a HCl salt of the desired product 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1-(((2S,6S)-6-methylmorpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide (404 mg) as a white solid. LC-MS (ES) $m/z = 479$ $[M+H]^+$.

Example 189

1-(((2S,6S)-4,6-Dimethylmorpholin-2-yl)methyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazole-5-carboxamide

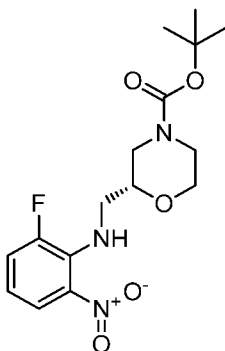


- To a solution of 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1-(((2S,6S)-6-methylmorpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide, hydrochloride (65 mg, 0.104 mmol) and formaldehyde (8.60 μ L, 0.312 mmol) was added NaBH₄CN (19.62 mg, 0.312 mmol), and the reaction mixture was stirred at room temperature for 30 minutes. The reaction was diluted with NH₄OH (1 mL) and purified by reverse phase HPLC (30-70% CH₃CN/0.1%NH₄OH) to afford the desired product 1-

(((2S,6S)-4,6-dimethylmorpholin-2-yl)methyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazole-5-carboxamide (36 mg) as a white solid. LC-MS (ES) m/z = 493 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.53 (d, J = 2.0 Hz, 1H), 7.96 (dd, J = 2.5, 8.9 Hz, 1H), 7.87 (d, J = 1.5 Hz, 1H), 7.43 (d, J = 1.3 Hz, 1H), 6.67 (d, J = 8.9 Hz, 1H), 4.61 (dd, J = 2.8, 14.5 Hz, 1H), 4.34 (dd, J = 8.9, 14.5 Hz, 3H), 4.01 - 4.13 (m, 4H), 3.40 - 3.53 (m, 1H), 2.83 (d, J = 11.2 Hz, 1H), 2.72 (d, J = 11.2 Hz, 1H), 2.33 - 2.43 (m, 2H), 2.31 (s, 3H), 1.68 - 1.83 (m, 4H), 1.23 (d, J = 6.3 Hz, 6H), 1.07 (d, J = 6.1 Hz, 3H).

Intermediate 258

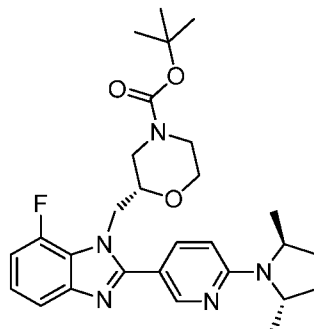
10 t-Butyl (R)-2-(((2-fluoro-6-nitrophenyl)amino)methyl)morpholine-4-carboxylate



To a solution of tert-butyl (R)-2-(aminomethyl)morpholine-4-carboxylate (300 mg, 1.387 mmol) and 1,2-difluoro-3-nitrobenzene (221 mg, 1.387 mmol) in DMF (5 mL) was added K_2CO_3 (192 mg, 1.387 mmol), and the reaction mixture was stirred overnight at room temperature. The reaction mixture was then diluted with water and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under vacuum to afford crude tert-butyl (R)-2-(((2-fluoro-6-nitrophenyl)amino)methyl)morpholine-4-carboxylate (493 mg) as an orange oil. LC-MS (ES) m/z = 300 $[M-tBu+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 7.93 - 7.99 (m, 1H), 7.86 (br. s., 1H), 7.35 (dd, J = 8.0, 14.1 Hz, 1H), 6.66 - 6.77 (m, 1H), 3.90 - 4.01 (m, 2H), 3.85 (tdd, J = 1.4, 2.8, 13.4 Hz, 1H), 3.67 - 3.80 (m, 1H), 3.44 - 3.67 (m, 3H), 2.91 - 3.07 (m, 1H), 2.59 - 2.84 (m, 1H), 1.48 (s, 9H).

Intermediate 259

t-Butyl (R)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-fluoro-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate

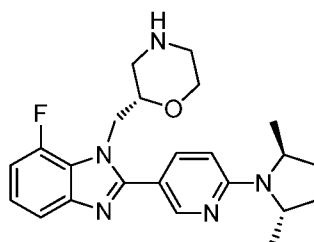


- 5 To a solution of tert-butyl (R)-2-(((2-fluoro-6-nitrophenyl)amino)methyl)morpholine-4-carboxylate (480 mg, 1.351 mmol) and 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (276 mg, 1.351 mmol) in ethanol (8 mL) and water (2 mL) was added sodium hydrosulfite (776 mg, 85%, 3.791 mmol), and the reaction vessel was sealed and heated at 130 °C under microwave conditions for 80 minutes. After cooling, the reaction
- 10 was concentrated under vacuum, and the resulting the residue was resuspended in EtOAc. The mixture was filtered, and the filtrate was concentrated under vacuum and purified by silica gel chromatography (0-100% EtOAc/Heptane) to give the desired product tert-butyl (R)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-fluoro-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (302 mg) as a white solid. LC-MS
- 15 (ES) m/z = 510 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.56 - 8.62 (m, 1H), 7.94 - 8.00 (m, 1H), 7.47 - 7.53 (m, 1H), 7.27 (dt, J = 4.8, 8.1 Hz, 1H), 7.09 (dd, J = 7.7, 11.8 Hz, 1H), 6.70 (d, J = 8.9 Hz, 1H), 4.39 - 4.54 (m, 2H), 4.18 - 4.38 (m, 2H), 3.97 (br. s., 1H), 3.75 - 3.91 (m, 3H), 2.87 - 3.11 (m, 1H), 2.58 - 2.84 (m, 1H), 2.26 - 2.44 (m, 2H), 1.68 - 1.82 (m, 2H), 1.49 (s, 9H), 1.24 (d, J = 6.3 Hz, 6H).

20

Example 190

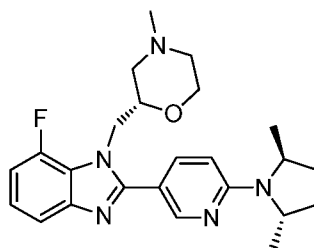
(S)-2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-fluoro-1H-benzo[d]imidazol-1-yl)methyl)morpholine, 3Hydrochloride



To a solution of tert-butyl (R)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-fluoro-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (302 mg, 0.593 mmol) in THF (5 mL) was added 6N aqueous HCl (2 mL, 12.00 mmol), and the reaction mixture was stirred at room temperature for 1 hour. The reaction was concentrated under vacuum, and the resulting material was triturated with Et₂O (2x) to give a HCl salt of the desired product (S)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-fluoro-1H-benzo[d]imidazol-1-yl)methyl)morpholine (307 mg) as a white solid. LC-MS (ES) m/z = 410 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 8.94 (d, J = 1.8 Hz, 1H), 8.30 - 8.39 (m, 1H), 7.67 - 7.82 (m, 2H), 7.46 - 7.61 (m, 2H), 4.78 - 4.92 (m, 2H), 4.67 - 4.76 (m, 1H), 4.43 - 4.65 (m, 3H), 4.22 (dd, J = 2.7, 13.1 Hz, 1H), 3.82 (ddd, J = 3.3, 11.5, 13.1 Hz, 1H), 3.64 (d, J = 11.7 Hz, 1H), 3.39 - 3.46 (m, 1H), 3.22 - 3.30 (m, 1H), 2.52 (t, J = 6.2 Hz, 2H), 1.96 (t, J = 6.7 Hz, 2H), 1.30 - 1.43 (m, 6H).

Example 191

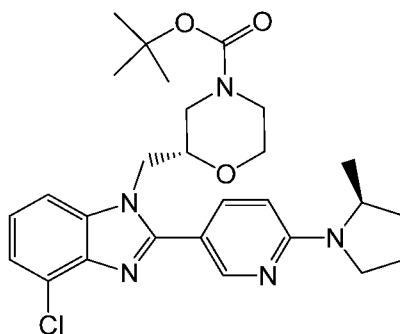
(S)-2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-fluoro-1H-benzo[d]imidazol-1-yl)methyl)-4-methylmorpholine



To a solution of (S)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-fluoro-1H-benzo[d]imidazol-1-yl)methyl)morpholine, 3 hydrochloride (50 mg, 0.096 mmol) in CH₃OH (5 mL) was added formaldehyde (0.015 mL, 0.193 mmol) followed by NaBH₃CN (22 mg, 0.350 mmol), and the reaction mixture was stirred at room temperature for 30 minutes. The reaction was diluted with 0.1% NH₄OH (1 mL) and purified by reverse phase HPLC (30-70% CH₃CN/0.1%NH₄OH) to give the desired product (S)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-fluoro-1H-benzo[d]imidazol-1-yl)methyl)-4-methylmorpholine (23 mg) as a white solid. LC-MS (ES) m/z = 424 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 8.55 - 8.61 (m, 1H), 7.97 (dd, J = 2.5, 8.9 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.27 (dt, J = 4.8, 8.1 Hz, 1H), 7.08 (ddd, J = 0.8, 8.1, 11.9 Hz, 1H), 6.70 (d, J = 8.6 Hz, 1H), 4.38 - 4.50 (m, 2H), 4.33 (br. s., 2H), 4.04 (ddt, J = 1.9, 4.1, 8.2 Hz, 1H), 3.78 - 3.90 (m, 1H), 3.47 (dt, J = 2.4, 11.6 Hz, 1H), 2.85 (d, J = 11.4 Hz, 1H), 2.64 - 2.73 (m, 1H), 2.34 - 2.41 (m, 2H), 2.31 (s, 3H), 2.18 (dt, J = 3.3, 11.7 Hz, 1H), 1.90 - 1.99 (m, 1H), 1.68 - 1.82 (m, 2H), 1.23 (d, J = 6.1 Hz, 6H).

Intermediate 260

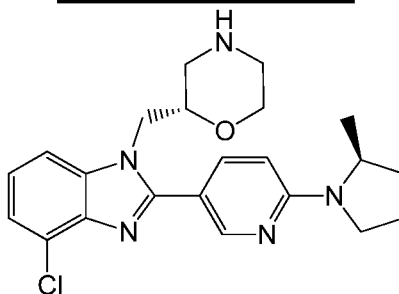
(R)-tert-Butyl 2-(((4-chloro-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate



5

To (S)-6-(2-methylpyrrolidin-1-yl)nicotinaldehyde (61.4 mg, 0.323 mmol) and sodium hydrosulfite (180 mg, 85%, 0.878 mmol) was added tert-butyl (R)-2-(((3-chloro-2-nitrophenyl)amino)methyl)morpholine-4-carboxylate (120 mg, 0.323 mmol) in ethanol (2 mL) followed by water (0.4 mL), and the reaction mixture was heated under microwave conditions at 130 °C for 60 minutes. Saturated aqueous NH₄Cl was then added, and the resulting mixture was extracted with EtOAc (2x). The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on SiO₂ (5 - 70% (3:1 EtOAc/EtOH with 2% NH₄OH)/heptane) to afford the desired product (75 mg) as a white solid. LC-MS (ES) *m/z* = 512 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.55 (d, *J* = 2.0 Hz, 1H), 7.94 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.30 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.23 (t, *J* = 7.9 Hz, 1H), 6.63 (d, *J* = 8.9 Hz, 1H), 4.42 - 4.50 (m, 1H), 4.34 (dd, *J* = 15.2, 8.6 Hz, 2H), 4.26 (br. s., 1H), 3.72 (d, *J* = 11.7 Hz, 2H), 3.64 (d, *J* = 12.9 Hz, 1H), 3.22 (td, *J* = 11.7, 2.7 Hz, 1H), 2.83 (br. s., 1H), 2.57 - 2.71 (m, 1H), 2.24 (br. s., 2H), 1.66 (d, *J* = 5.6 Hz, 2H), 1.38 (s, 9H), 1.33 (br. s., 1H), 1.07 - 1.19 (m, 6H).

20

Example 192**(S)-2-((4-Chloro-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine**

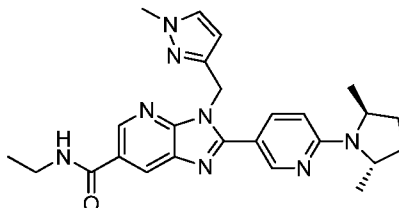
5 To tert-butyl (R)-2-((4-chloro-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (70 mg, 0.137 mmol) in CH₂Cl₂ (4 mL) was added TFA (0.316 mL, 4.10 mmol), and the reaction mixture was stirred at room temperature for 2 hours. The mixture was concentrated, and the resulting residue was purified by flash chromatography on SiO₂ (25 – 100% (3:1 EtOAc/EtOH with

10 2%NH₄OH)/heptane). Fractions containing the desired product were combined and concentrated. The resulting residue was dissolved in CH₂Cl₂, treated with heptane, and the mixture concentrated. The resulting residue was then stirred in a mixture of water, CH₂Cl₂, and saturated aqueous NaHCO₃ (0.5 mL) for 15 minutes. The organic layer was separated, and the aqueous layer was further extracted with CH₂Cl₂. The combined organic extracts

15 were and dried over MgSO₄, filtered, and concentrated *in vacuo*. The resulting residue was dissolved in CH₂Cl₂ and treated with heptane. The mixture was then concentrated and dried in vacuum oven at 40 °C overnight to afford (S)-2-((4-chloro-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine (40 mg) as a white solid foam. LC-MS (ES) *m/z* = 412 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.57 (d, *J* = 2.0 Hz, 1H),

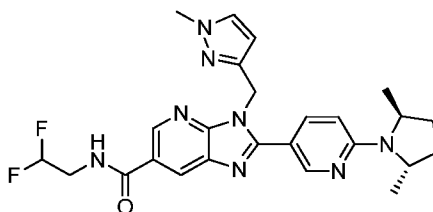
20 7.98 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.62 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.30 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 6.61 (d, *J* = 8.9 Hz, 1H), 4.17 - 4.39 (m, 3H), 3.70 - 3.80 (m, 1H), 3.52 - 3.66 (m, 2H), 3.19 - 3.27 (m, 1H), 2.78 (dd, *J* = 12.0, 2.2 Hz, 1H), 2.56 - 2.63 (m, 2H), 2.37 (dd, *J* = 12.0, 10.3 Hz, 3H), 1.93 - 2.14 (m, 3H), 1.66 - 1.77 (m, 1H), 1.21 (d, *J* = 6.3 Hz, 3H).

25

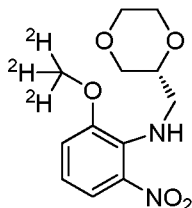
Example 193**2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-ethyl-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide**

- 5 The title compound was prepared from 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid (74 mg, 0.171 mmol) and ethanamine in THF (2M, 0.171 mL, 0.342 mmol) following a similar procedure to the one described for Example 132 to afford the desired product (76 mg) as an off-white solid. LC-MS (ES) $m/z = 459$ $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.17 - 1.26 (m, 6H), 1.26 - 1.34 (m, 3H), 1.67 - 1.85 (m, 2H), 2.34 (m, 2H), 3.43 - 3.54 (m, 2H), 3.84 (s, 3H), 4.32 (m, 2H), 5.63 (s, 2H), 6.16 (d, $J = 2.3$ Hz, 1H), 6.69 (d, $J = 8.9$ Hz, 1H), 7.53 (d, $J = 2.3$ Hz, 1H), 8.00 (dd, $J = 9.1, 2.5$ Hz, 1H), 8.46 (d, $J = 2.0$ Hz, 1H), 8.59 (d, $J = 2.5$ Hz, 1H), 8.86 (d, $J = 2.0$ Hz, 1H).

15

Example 194**N-(2,2-Difluoroethyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide**

- The title compound was prepared from 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid (80 mg, 0.185 mmol) and 2,2-difluoroethan-1-amine (27.1 mg, 0.334 mmol) following a similar procedure to the one described for Example 132 to afford the desired product (32 mg) as an off-white solid. LC-MS (ES) $m/z = 495$ $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.21 (d, $J = 5.8$ Hz, 6H), 1.63 - 1.86 (m, 2H), 2.33 (m, 2H), 3.78 - 3.84 (m, 5H), 4.31 (m, 2H), 5.62 (s, 2H), 6.08 (br. s., 1H), 5.94 - 6.16 (m, 2H), 6.67 (d, $J = 8.9$ Hz, 1H), 7.53 (br. s., 1H), 8.00 (d, $J = 8.1$ Hz, 1H), 8.48 (br. s., 1H), 8.59 (br. s., 1H), 8.88 (br. s., 1H).

Intermediate 261(R)-N-((1,4-Dioxan-2-yl)methyl)-2-(methoxy-d3)-6-nitroaniline

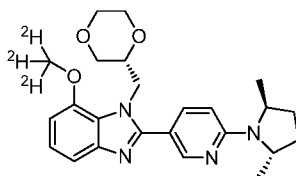
5

To a solution of 2-fluoro-1-(methoxy-d3)-3-nitrobenzene (200 mg, 1.148 mmol) in DMSO (5 mL) were added (R)-(1,4-dioxan-2-yl)methanamine (161 mg, 1.378 mmol) and DIEA (0.261 mL, 1.493 mmol), and the reaction mixture was stirred at 60 °C for 20 hours. The mixture was cooled to room temperature, quenched with water (10 mL), and extracted using EtOAc (3x). The organic extract was dried (Na₂SO₄) and concentrated. The resulting residue was purified using column chromatography (silica gel, 0 to 100% EtOAc/heptane) to give the desired product (210 mg) as a brown solid. LC-MS (ES) m/z = 272 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 3.41 - 3.54 (m, 2H), 3.61 - 3.91 (m, 8H), 6.74 (dd, J = 8.6, 7.9 Hz, 1H), 6.98 (dd, J = 8.0, 1.4 Hz, 1H), 7.76 (dd, J = 8.7, 1.4 Hz, 1H).

15

Example 195

1-(((R)-1,4-Dioxan-2-yl)methyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-(methoxy-d3)-1H-benzo[d]imidazole

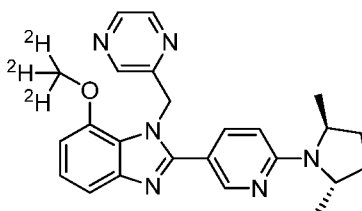


To a microwave vessel were added (R)-N-((1,4-dioxan-2-yl)methyl)-2-(methoxy-d3)-6-nitroaniline (110 mg, 0.405 mmol), 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (87 mg, 0.426 mmol), sodium hydrosulfite (85%, 249 mg, 1.216 mmol), ethanol (2 mL), and water (0.50 mL). The vessel was sealed, and the reaction mixture was stirred at 130 °C conditions for 80 minutes under the microwave. The mixture was then cooled to room temperature, diluted with EtOAc, and filtered. The filtrate was concentrated, and the resulting residue was purified using column chromatography (silica gel, 0 to 100% (3:1 EtOAc:EtOH)/heptane) to give the desired product (31 mg) as an off-white solid. LC-MS (ES) m/z = 426 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.23 (d, J = 6.3 Hz, 6H), 1.76 (d, J = 5.6 Hz, 2H), 2.36 (d, J = 2.3 Hz, 1H), 3.48 - 3.85 (m, 6H), 4.08 (m, 1H), 4.28 (m, 3H), 4.50

(dd, $J = 14.6, 2.9$ Hz, 1H), 6.69 (d, $J = 8.6$ Hz, 1H), 6.88 (dd, $J = 7.7, 1.1$ Hz, 1H), 7.19 - 7.32 (m, 2H), 7.93 (dd, $J = 9.0, 2.4$ Hz, 1H), 8.47 - 8.58 (m, 1H).

Example 196

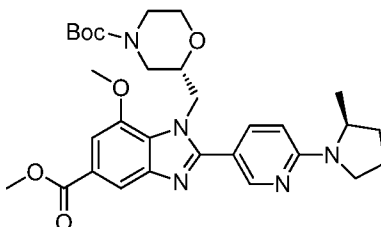
5 **2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-(methoxy-d3)-1-(pyrazin-2-ylmethyl)-1H-benzo[d]imidazole**



2-(Methoxy-d3)-6-nitro-N-(pyrazin-2-ylmethyl)aniline was prepared following a similar procedure to the preparation of Intermediate 261. The title compound was prepared from
 10 2-(methoxy-d3)-6-nitro-N-(pyrazin-2-ylmethyl)aniline (100 mg, 0.380 mmol) and 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (81 mg, 0.399 mmol) following a similar procedure to the one described for the preparation of Example 195 to afford the desired product (42 mg) as a pale brown solid. LC-MS (ES) $m/z = 418$ $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.18 - 1.30 (m, 6H), 1.78 - 1.89 (m, 2H), 2.39 (m, 2H), 4.29 (br. s., 1H), 4.47 (br.
 15 s., 1H), 5.98 (s, 2H), 6.98 (d, $J = 9.4$ Hz, 1H), 7.05 (d, $J = 8.1$ Hz, 1H), 7.36 - 7.43 (m, 1H), 7.46 - 7.58 (m, 1H), 8.12 (dd, $J = 9.2, 2.4$ Hz, 1H), 8.54 (dd, $J = 2.5, 1.5$ Hz, 1H), 8.60 (d, $J = 2.5$ Hz, 1H).

Intermediate 262

20 **(R)-tert-Butyl 2-(((7-methoxy-5-(methoxycarbonyl)-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate**

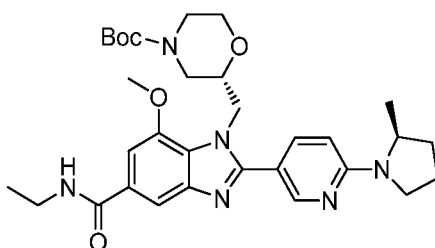


To a sealable vessel were added tert-butyl (R)-2-(((2-methoxy-4-(methoxycarbonyl)-6-nitrophenyl)amino)methyl)morpholine-4-carboxylate (380 mg, 0.893 mmol), (S)-6-(2-methylpyrrolidin-1-yl)nicotinaldehyde (170 mg, 0.893 mmol), sodium hydrosulfite (85%, 549 mg, 2.68 mmol), ethanol (5 mL), and water (1 mL). The vessel was sealed, and the reaction mixture was stirred at 110 °C for 18 hours. The mixture was then cooled to room temperature, diluted with EtOAc, and filtered. The filtrate was concentrated, and the
 25

resulting residue was purified using column chromatography (silica gel, 0 to 100% EtOAc/heptane) to give the desired product (339 mg) as a pale brown solid. LC-MS (ES) m/z = 566 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.23 - 1.31 (m, 3H), 1.43 - 1.50 (m, 9H), 1.80 - 1.88 (m, 1H), 2.04 - 2.27 (m, 3H), 2.69 (br. s., 1H), 2.96 (br. s., 1H), 3.42 - 3.52 (m, 1H),
 5 3.61 - 3.70 (m, 1H), 3.76 - 3.92 (m, 3H), 3.96 (s, 3H), 4.09 (s, 3H), 4.24 - 4.42 (m, 2H) 4.59 (dd, J = 14.7, 2.8 Hz, 1H), 6.67 (d, J = 8.6 Hz, 1H), 7.46 - 7.55 (m, 1H), 7.91 - 8.04 (m, 2H), 8.56 (d, J = 2.0 Hz, 1H).

Intermediate 263

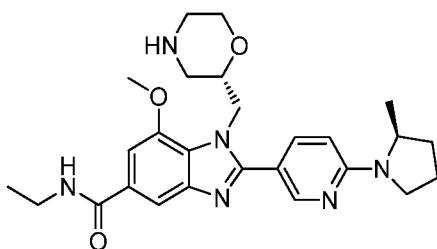
10 (R)-tert-Butyl 2-((5-(ethylcarbamoyl)-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate



To a solution of tert-butyl (R)-2-((7-methoxy-5-(methoxycarbonyl)-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-
 15 carboxylate (130 mg, 0.230 mmol) in CH_3OH (2 mL) was added sodium hydroxide (5N, 800 μ L, 4.00 mmol), and the mixture was stirred at 40 $^{\circ}C$ for 18 hours. The reaction mixture was neutralized by adding HCl (6N, 667 μ L, 4.00 mmol) and concentrated. The resulting residue was dried under vacuum and treated with DMSO (2.0 mL). To this mixture were added
 20 ethanamine in THF (2N, 195 μ L, 0.391 mmol), EDC (88 mg, 0.460 mmol), 1-hydroxy-7-azabenzotriazole (62.6 mg, 0.460 mmol), and N-methylmorpholine (202 μ L, 1.839 mmol), and the mixture was stirred at room temperature for 18 hours. The reaction was quenched with water (5 mL) and extracted with EtOAc (3x). The organic extract was dried (Na_2SO_4) and concentrated. The resulting residue was purified using column chromatography (silica
 25 gel, 0 to 100 % 3:1 EtOAc:EtOH/heptane) to give the desired product (81 mg) as an off-white solid. LC-MS (ES) m/z = 579.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.24 - 1.33 (m, 6H), 1.44 - 1.51 (m, 9H), 1.79 - 1.86 (m, 1H), 2.02 - 2.26 (m, 3H), 2.94 (br. s., 1H), 3.39 - 3.53 (m, 3H), 3.59 - 3.71 (m, 1H), 3.77 - 4.06 (m, 5H), 4.10 (s, 3H), 4.27 (m, 1H), 4.37 (m, 1H), 4.53 - 4.65 (m, 1H), 6.66 (d, J = 8.9 Hz, 1H), 7.36 - 7.42 (m, 1H), 7.79 (d, J = 1.5 Hz,
 30 1H), 7.96 (dd, J = 9.0, 2.4 Hz, 1H), 8.55 (d, J = 2.0 Hz, 1H).

Intermediate 264

N-Ethyl-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1-((S)-morpholin-2-ylmethyl)-1H-benzo[d]imidazole-5-carboxamide



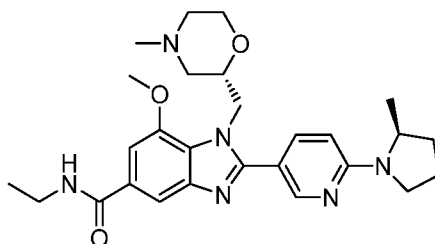
5

To a solution of tert-butyl (R)-2-((5-(ethylcarbamoyl)-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (76 mg, 0.131 mmol) in CH₂Cl₂ (2 mL) was added TFA (500 µl, 6.49 mmol), and the mixture was stirred at room temperature for 4 hours. The mixture was treated with 6N HCl (1 mL) and concentrated. The residue was dried under vacuum and basified with saturated Na₂CO₃ (1 mL) and concentrated. The residue was dried under vacuum and treated with CH₂Cl₂ (5 mL) and filtered. The filtrate was concentrated to give the desired product (48 mg) as an off-white solid. LC-MS (ES) m/z = 479 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.25 - 1.31 (m, 6H), 1.83 (m, 1 H), 2.03 - 2.25 (m, 3H) 2.51 (m, 1H), 2.69 - 2.83 (m, 2H), 2.85 - 2.94 (m, 1H), 3.36 - 3.55 (m, 4H), 3.61 - 3.71 (m, 1H) 3.78 (dd, J = 11.7, 2.0 Hz, 1H), 3.93 - 4.03 (m, 1H), 4.08 (s, 3H), 4.23 - 4.35 (m, 2H), 4.53 (dd, J = 14.6, 2.9 Hz, 1H), 6.59 - 6.73 (m, 1H), 7.35 - 7.42 (m, 1H), 7.79 (d, J = 1.27 Hz, 1H), 7.96 (dd, J = 8.8, 2.5 Hz, 1H), 8.54 (d, J = 1.8 Hz, 1H).

20

Example 197

N-Ethyl-7-methoxy-1-(((S)-4-methylmorpholin-2-yl)methyl)-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide

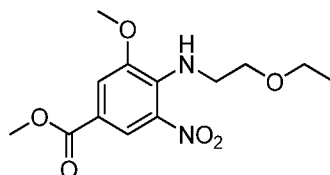


To a solution of N-ethyl-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1-((S)-morpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide (48 mg, 0.100 mmol) in 1,2-

dichloroethane (2 mL) were added formaldehyde (36.5% in water, 0.038 mL, 0.501 mmol) and acetic acid (0.017 mL, 0.301 mmol), and the mixture was stirred at room temperature for 10 minutes. Sodium triacetoxymethylborohydride (74.4 mg, 0.351 mmol) was then added, and the reaction mixture was stirred at room temperature for 2 hours. The reaction was
5 quenched with saturated aqueous NaHCO₃ (2 mL) followed by saturated aqueous Na₂CO₃ to adjust the solution to pH = 10. The resulting mixture was extracted with CH₂Cl₂ (3x), and the organic extract was dried over Na₂SO₄, filtered, and concentrated. The resulting residue was purified by column chromatography (silica gel, 0-100% (90:10:1 CH₂Cl₂:CH₃OH:NH₄OH)/heptane) to give the desired product (30 mg) as an off-white solid.
10 LC-MS (ES) m/z = 493 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.23 - 1.32 (m, 6H), 1.79 - 1.96 (m, 2H), 2.00 - 2.27 (m, 4H), 2.32 (s, 3H), 2.67 (d, J = 11.7 Hz, 1H), 2.84 (d, J = 11.1 Hz, 1H), 3.39 - 3.54 (m, 4H), 3.61 - 3.70 (m, 1H), 3.82 (dd, J = 11.8, 1.9 Hz, 1H), 3.99 - 4.13 (m, 4H), 4.22 - 4.41 (m, 2H), 4.58 (dd, J = 14.4, 2.8 Hz, 1H), 6.67 (d, J = 8.9 Hz, 1H), 7.37 (d, J = 1.3 Hz, 1H), 7.79 (d, J = 1.5 Hz, 1H), 7.96 (dd, J = 9.0, 2.4 Hz, 1H), 8.54 (d, J = 2.5
15 Hz, 1H).

Intermediate 265

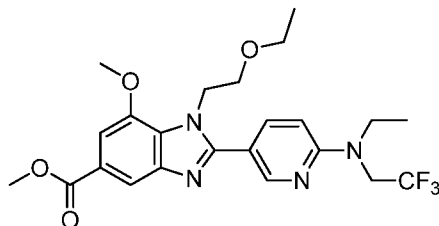
Methyl 4-((2-ethoxyethyl)amino)-3-methoxy-5-nitrobenzoate



20 To a solution of methyl 4-chloro-3-methoxy-5-nitrobenzoate (3.00 g, 12.2 mmol) in 1,4 dioxane (12 mL) was added 2-ethoxyethan-1-amine (1.63 g, 18.3 mmol), and the reaction mixture was stirred in a sealed vessel at 80 °C for 54 hours. The reaction was then cooled to room temperature and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 0 to 100% CH₂Cl₂/hexanes) to afford the desired product
25 (2.90 g) as an orange solid. LC-MS (ES) m/z = 299 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.51 (d, J = 2.0 Hz, 2H), 7.50 (d, J = 1.5 Hz, 1H), 4.07 - 3.82 (m, 8H), 3.64 (t, J = 5.2 Hz, 2H), 3.57 (q, J = 6.8 Hz, 2H), 1.26 (t, J = 7.0 Hz, 3H).

Intermediate 266

Methyl 1-(2-ethoxyethyl)-2-(6-(ethyl(2,2,2-trifluoroethyl)amino)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazole-5-carboxylate

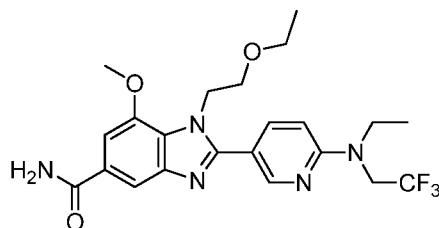


- 5 To a solution of 6-(ethyl(2,2,2-trifluoroethyl)amino)nicotinaldehyde (101 mg, 0.436 mmol) and methyl 4-((2-ethoxyethyl)amino)-3-methoxy-5-nitrobenzoate (130 mg, 0.436 mol) in 2:1 ethanol:water (4.5 mL) was added sodium hydrosulfite (228 mg, 1.11 mmol), and the reaction mixture was heated for 1 hour at 120 °C under microwave conditions. The reaction was cooled to room temperature and then diluted with EtOAc (10 mL) and water (10 mL).
- 10 The phases were separated and the aqueous layer was back-extracted with EtOAc (3 x 10 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 0 to 50% EtOAc/hexanes) to afford the desired product (210 mg) as a yellow solid. LC-MS (ES) *m/z* = 481 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.63 (d, *J* = 2.3 Hz, 1H), 8.16 (s, 1H), 8.03 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.46 (s, 1H), 6.74 (d, *J* = 8.9 Hz, 1H), 4.58 (t, *J* = 5.6 Hz, 2H), 4.37 (q, *J* = 9.1 Hz, 2H), 4.04 (2, 3H), 3.97 (s, 3H), 3.82 (t, *J* = 5.6 Hz, 2H), 3.67 (q, *J* = 7.1 Hz, 2H), 3.36 (q, *J* = 6.8 Hz, 2H), 1.36 - 1.21 (m, 3H), 1.16 - 1.04 (m, 3H).

20

Example 198

1-(2-Ethoxyethyl)-2-(6-(ethyl(2,2,2-trifluoroethyl)amino)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazole-5-carboxamide

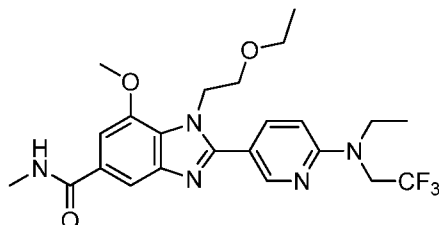


- To a solution of methyl 1-(2-ethoxyethyl)-2-(6-(ethyl(2,2,2-trifluoroethyl)amino)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazole-5-carboxylate (100 mg, 0.208 mmol) in CH₃OH (2 mL) was added sodium hydroxide (5M aqueous solution, 0.083 mL, 0.42 mmol), and the reaction mixture was heated on a sealed vessel at 60 °C for 18 hours. The reaction was

then cooled to room temperature, concentrated, and dried under vacuum. The resulting residue was dissolved in DMSO (2 mL). To this mixture were added NH₄Cl (56 mg, 1.0 mmol), EDC (80 mg, 0.42 mmol), 1-hydroxy-7-azabenzotriazole (57 mg, 0.42 mmol), and N,N-diisopropylethylamine (0.22 mL, 1.2 mmol). After 1 hour, additional NH₄Cl (56 mg, 1.0 mmol) was added, and the mixture was heated at 40 °C for 1 hour. The reaction was diluted with water (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The resulting residue was purified by reverse phase HPLC (eluting with 30 to 85% CH₃CN/water containing 0.1% 10 mM ammonium bicarbonate with ammonium hydroxide modifier). The fractions containing desired product were combined, concentrated, and lyophilized to afford the desired product (65 mg) as a white solid. LC-MS (ES) m/z = 466 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.64 (d, J = 2.3 Hz, 1H), 8.04 (dd, J = 8.9, 2.3 Hz, 1H), 7.74 (d, J = 1.3 Hz, 1H), 7.43 (d, J = 1.3 Hz, 1H), 6.75 (d, J = 8.9 Hz, 1H), 4.58 (t, J = 5.6 Hz, 2H), 4.38 (q, J = 9.1 Hz, 2H), 4.06 (s, 3H), 3.83 (t, J = 5.6 Hz, 2H), 3.68 (q, J = 7.0 Hz, 2H), 3.37 (q, J = 6.8 Hz, 2H), 1.28 (t, J = 7.0 Hz, 3H), 1.09 (t, J = 7.0 Hz, 3H).

Example 199

1-(2-Ethoxyethyl)-2-(6-(ethyl(2,2,2-trifluoroethyl)amino)pyridin-3-yl)-7-methoxy-N-methyl-1H-benzo[d]imidazole-5-carboxamide

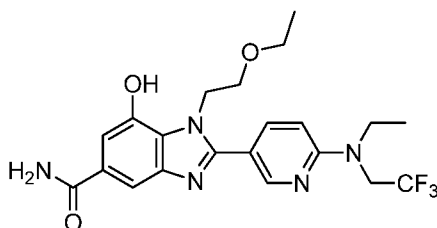


To a solution of methyl 1-(2-ethoxyethyl)-2-(6-(ethyl(2,2,2-trifluoroethyl)amino)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazole-5-carboxylate (100 mg, 0.208 mmol) in CH₃OH (2 mL) was added sodium hydroxide (5M aqueous solution, 0.083 mL, 0.42 mmol), and the reaction mixture was heated on a sealed vessel at 60 °C for 18 hours. The reaction was then cooled to room temperature, concentrated, and dried under vacuum. The resulting residue was dissolved in DMSO (2 mL). To this mixture were added methanamine hydrochloride (70 mg, 1.0 mmol), EDC (80 mg, 0.42 mmol), 1-hydroxy-7-azabenzotriazole (57 mg, 0.42 mmol), and N,N-diisopropylethylamine (0.22 mL, 1.2 mmol). After 4 hour, the reaction was diluted with water (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The resulting residue was purified by reverse phase HPLC (eluting with

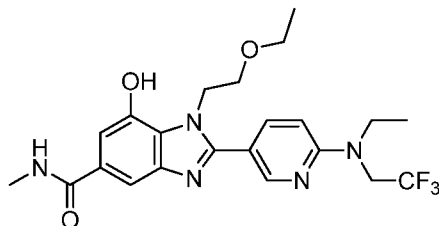
50 to 99% CH₃CN/water containing 0.1% 10 mM ammonium bicarbonate with ammonium hydroxide modifier). The fractions containing desired product were combined, concentrated, and lyophilized to afford the desired product (49 mg) as a white solid. LC-MS (ES) m/z = 480 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.62 (d, J = 2.3 Hz, 1H), 8.20 - 7.92 (m, 1H), 7.65 (d, J = 1.0 Hz, 1H), 7.40 (s, 1H), 6.74 (d, J = 8.9 Hz, 1H), 6.47 - 5.93 (m, 1H), 4.57 (t, J = 5.6 Hz, 2H), 4.37 (d, J = 9.1 Hz, 2H), 4.05 (s, 3H), 3.82 (t, J = 5.6 Hz, 2H), 3.67 (d, J = 7.1 Hz, 2H), 3.36 (d, J = 6.8 Hz, 2H), 3.08 (d, J = 4.8 Hz, 3H), 1.28 (t, J = 7.0 Hz, 3H), 1.09 (t, J = 7.0 Hz, 3H).

Example 200

1-(2-Ethoxyethyl)-2-(6-(ethyl(2,2,2-trifluoroethyl)amino)pyridin-3-yl)-7-hydroxy-1H-benzo[d]imidazole-5-carboxamide

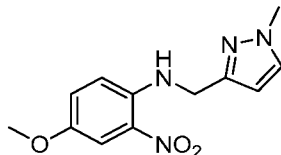


Methyl 1-(2-ethoxyethyl)-2-(6-(ethyl(2,2,2-trifluoroethyl)amino)pyridin-3-yl)-7-hydroxy-1H-benzo[d]imidazole-5-carboxylate was prepared following a similar procedure to the preparation of Intermediate 266. The title compound was prepared from methyl 1-(2-ethoxyethyl)-2-(6-(ethyl(2,2,2-trifluoroethyl)amino)pyridin-3-yl)-7-hydroxy-1H-benzo[d]imidazole-5-carboxylate (65 mg, 0.14 mmol) following a similar procedure to the preparation of Example 198 to afford the desired product (38 mg) as an off-white solid. LC-MS (ES) m/z = 452 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.72 (br s, 1H), 8.48 (d, J = 2.0 Hz, 1H), 7.96 (dd, J = 8.9, 2.3 Hz, 1H), 7.85 (d, J = 1.3 Hz, 1H), 7.28 - 7.19 (m, 1H), 6.80 (d, J = 8.9 Hz, 1H), 6.28 (br s, 1H), 5.56 (br s, 1H), 4.61 (t, J = 4.6 Hz, 2H), 4.38 (q, J = 8.9 Hz, 2H), 3.81 - 3.60 (m, 4H), 3.54 (d, J = 5.1 Hz, 2H), 1.30 (q, J = 7.1 Hz, 6H).

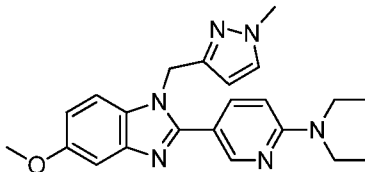
Example 201**1-(2-Ethoxyethyl)-2-(6-(ethyl(2,2,2-trifluoroethyl)amino)pyridin-3-yl)-7-hydroxy-N-methyl-1H-benzo[d]imidazole-5-carboxamide**

- 5 Methyl 1-(2-ethoxyethyl)-2-(6-(ethyl(2,2,2-trifluoroethyl)amino)pyridin-3-yl)-7-hydroxy-1H-benzo[d]imidazole-5-carboxylate was prepared following a similar procedure to the preparation of Intermediate 266. The title compound was prepared from methyl 1-(2-ethoxyethyl)-2-(6-(ethyl(2,2,2-trifluoroethyl)amino)pyridin-3-yl)-7-hydroxy-1H-benzo[d]imidazole-5-carboxylate (65 mg, 0.14 mmol) following a similar procedure to the
- 10 preparation of Example 199 to afford the desired product (3.5 mg) as a tan solid. LC-MS (ES) $m/z = 466$ $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.59 - 8.44 (m, 1H), 8.13 - 7.87 (m, 1H), 7.77 (s, 1H), 7.50 (s, 1H), 6.87 - 6.71 (m, 1H), 6.62 (br s, 1H), 4.68 - 4.47 (m, 2H), 4.38 (q, $J = 8.9$ Hz, 2H), 3.97 (t, $J = 4.6$ Hz, 2H), 3.69 (q, $J = 7.1$ Hz, 2H), 3.57 - 3.48 (m, 2H), 3.12 - 2.99 (m, 3H), 1.32 - 1.10 (m, 6H).

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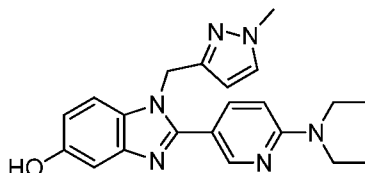
Intermediate 267**4-Methoxy-N-((1-methyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline**

- To a solution of 1-fluoro-4-methoxy-2-nitrobenzene (200 mg, 1.17 mmol) in 1,4 dioxane (4
- 20 mL) was added (1-methyl-1H-pyrazol-3-yl)methanamine (156 mg, 1.40 mmol), and the reaction mixture was stirred in a sealed vessel at room temperature for 18 hours. The reaction was concentrated, and the resulting residue was purified by silica gel chromatography (eluting with 0 to 70% CH_2Cl_2 /hexanes) to afford the desired product (48 mg) as a yellow-orange oil. LC-MS (ES) $m/z = 263$ $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ
- 25 8.39 (br s, 1H), 7.67 (d, $J = 3.0$ Hz, 1H), 7.36 (d, $J = 2.0$ Hz, 1H), 7.18 (dd, $J = 9.4, 3.0$ Hz, 1H), 6.98 (d, $J = 9.4$ Hz, 1H), 6.23 (d, $J = 2.0$ Hz, 1H), 4.56 (d, $J = 5.1$ Hz, 2H), 3.97 (s, 3H), 3.83 (s, 3H).

Example 202**N,N-Diethyl-5-(5-methoxy-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine**

- 5 To a solution of 6-(diethylamino)nicotinaldehyde (42 mg, 0.23 mmol) and 4-methoxy-N-((1-methyl-1H-pyrazol-3-yl)methyl)-2-nitroaniline (47 mg, 0.18 mmol) in 2:1 ethanol:water (3.5 mL) was added sodium hydrosulfite (156 mg, 0.762 mmol), and the reaction mixture was heated at 120 °C for 90 minutes under microwave conditions. The reaction was then cooled to room temperature and diluted with EtOAc (10 mL) and water (10 mL). The phases were
- 10 separated and the aqueous layer was back-extracted with EtOAc (3 x 10 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The resulting residue was purified by reverse phase HPLC (eluting with 30 to 85% CH₃CN/water containing 0.1% formic acid modifier). The fractions containing desired product were combined, concentrated, and lyophilized to afford the
- 15 desired product (9 mg) as a clear film. LC-MS (ES) m/z = 391 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.58 (d, J = 2.0 Hz, 1H), 7.95 (dd, J = 9.0, 2.4 Hz, 1H), 7.37 - 7.14 (m, 3H), 6.89 (dd, J = 8.6, 2.3 Hz, 1H), 6.60 (d, J = 8.9 Hz, 1H), 5.98 (d, J = 2.3 Hz, 1H), 5.41 (s, 2H), 3.93 (s, 3H), 3.90 (s, 3H), 3.61 (q, J = 6.9 Hz, 4H), 1.29 - 1.11 (m, 6H).

20

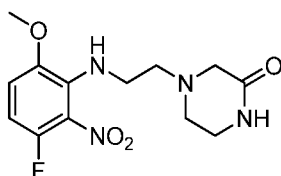
Example 203**2-(6-(Diethylamino)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-5-ol**

- To a solution of N,N-diethyl-5-(5-methoxy-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine (4 mg, 0.01 mmol) in 1,2-dichloroethane (0.2 mL) cooled to 0 °C was added a solution of boron tribromide (1M in CH₂Cl₂, 0.05 mL, 0.05 mmol). After 15 minutes, the reaction was quenched with water (0.3 mL) and concentrated. The resulting residue was purified by reverse phase HPLC (eluting with 30 to 85% CH₃CN/water containing 0.1% formic acid modifier). The fractions containing desired
- 25

product were combined, concentrated, and lyophilized to afford the desired product (3 mg) as an off-white solid. LC-MS (ES) m/z = 377 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.48 (d, J = 2.0 Hz, 1H), 7.91 (dd, J = 9.0, 2.4 Hz, 1H), 7.54 (d, J = 2.3 Hz, 1H), 7.27 (d, J = 8.6 Hz, 1H), 7.06 (d, J = 2.3 Hz, 1H), 6.86 - 6.65 (m, 2H), 6.08 (d, J = 2.3 Hz, 1H), 5.39 (s, 2H), 3.87 (br s, 3H), 3.62 (q, J = 6.9 Hz, 4H), 1.28 - 1.17 (m, 6H).

Intermediate 268

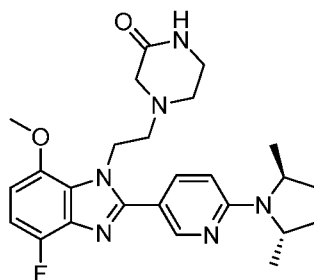
4-(2-((3-Fluoro-6-methoxy-2-nitrophenyl)amino)ethyl)piperazin-2-one



To a solution of 1,3-difluoro-4-methoxy-2-nitrobenzene (90 mg, 0.476 mmol) in DMF (2.5 mL) were added 4-(2-aminoethyl)piperazin-2-one dihydrochloride (103 mg, 0.476 mmol) and K_2CO_3 (197 mg, 1.43 mmol), and the reaction mixture was stirred in a sealed vessel at 50 °C for 3 hours, then at 80 °C for 18 hours, and at 100 °C for 3 nights. The reaction was diluted with EtOAc (30 mL) and washed with saturated aqueous $NaHCO_3$ (3 x 20 mL). The aqueous layer was further extracted with EtOAc (20 mL), and the combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4 , filtered, and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 0 to 5% CH_3OH/CH_2Cl_2) to afford the desired product (31 mg) as an orange oil. LC-MS (ES) m/z = 313 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 6.79 (dd, J = 9.0, 4.7 Hz, 1H), 6.52 (dd, J = 9.9, 8.9 Hz, 1H), 6.16 (br s, 1H), 5.85 (br s, 1H), 3.87 (s, 3H), 3.53 - 3.37 (m, 2H), 3.35 - 3.25 (m, 2H), 3.21 (s, 2H), 2.70 (dt, J = 15.4, 5.5 Hz, 4H).

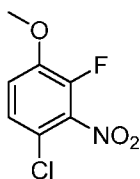
Example 204

4-(2-(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1H-benzo[d]imidazol-1-yl)ethyl)piperazin-2-one



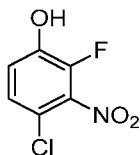
To a solution of 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (46 mg, 0.22 mmol) and 4-(2-((3-fluoro-6-methoxy-2-nitrophenyl)amino)ethyl)piperazin-2-one (70 mg, 0.22 mmol) in 2:1 ethanol:water (4.5 mL) was added sodium hydrosulfite (117 mg, 0.572 mmol), and the reaction mixture was heated at 100 °C for 3 nights. The reaction was cooled to room temperature and diluted with EtOAc (15 mL) and saturated aqueous NaHCO₃ (15 mL). The phases were separated and the aqueous layer was further extracted with EtOAc (3 x 15 mL). The combined organic extract was washed with brine (15 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 0 to 5% CH₃OH/CH₂Cl₂) to afford the desired product (79 mg) as a white solid. LC-MS (ES) m/z = 467 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.50 (d, J = 2.0 Hz, 1H), 7.82 (dd, J = 8.9, 2.3 Hz, 1H), 6.88 (dd, J = 9.8, 8.7 Hz, 1H), 6.59 (dd, J = 8.7, 3.2 Hz, 1H), 6.50 (d, J = 8.9 Hz, 1H), 6.29 (br s, 1H), 4.58 (t, J = 6.8 Hz, 2H), 4.30 (br s, 2H), 3.98 (s, 3H), 3.33 - 3.20 (m, 2H), 3.12 (s, 2H), 2.92 - 2.74 (m, 2H), 2.58 (dd, J = 6.2, 4.7 Hz, 2H), 2.43 - 2.19 (m, 2H), 1.85 - 1.63 (m, 2H), 1.23 (d, J = 6.1 Hz, 6H).

15

Intermediate 2691-Chloro-3-fluoro-4-methoxy-2-nitrobenzene

To a 100 mL round bottom flask attached with an air condensor were added 6-chloro-2-fluoro-3-methoxyaniline (500 mg, 2.85 mmol) and m-chloroperbenzoic acid (1.97 g, 11.4 mmol) in dichloroethane (19 mL). The reaction vessel was covered with aluminum foil and heated at 70 °C for 17 hours. The reaction was diluted with EtOAc (150 mL) and washed with 0.1 N aqueous sodium hydroxide (5 x 50 mL). The organic extract was dried over Na₂SO₄, filtered, and concentrated to afford the desired product (444 mg) as an orange solid. ¹H NMR (400 MHz, CDCl₃): δ 7.72 - 7.59 (m, 1H), 7.59 - 7.49 (m, 1H), 3.95 (s, 3H).

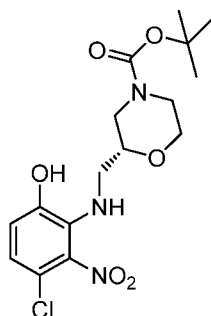
25

Intermediate 2704-Chloro-2-fluoro-3-nitrophenol

To a solution of 1-chloro-3-fluoro-4-methoxy-2-nitrobenzene (98 mg, 0.48 mmol) in 1,2-dichloroethane (5 mL) cooled at 0 °C was added a solution of boron tribromide (1M in CH₂Cl₂, 2.4 mL, 2.4 mmol). The reaction was then warmed to room temperature and stirred for 3 hours. Additional boron tribromide was added (1M in CH₂Cl₂, 1.2 mL, 1.2 mmol), and the reaction was stirred at room temperature for 18 hours. The reaction was quenched with water (2 mL, dropwise), dried over Na₂SO₄, filtered, and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 0 to 5% CH₃OH/CH₂Cl₂) to afford the desired product (75 mg) as an orange solid. ¹H NMR (400 MHz, CDCl₃): δ 7.25 - 7.15 (m, 1H), 7.14 - 6.99 (m, 1H).

Intermediate 271

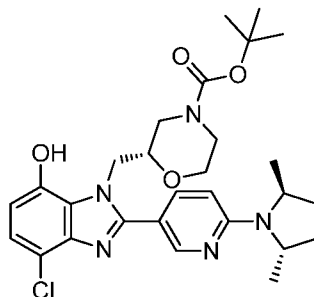
tert-Butyl (R)-2-(((3-chloro-6-hydroxy-2-nitrophenyl)amino)methyl)morpholine-4-carboxylate



To a sealable vessel was added a solution of 4-chloro-2-fluoro-3-nitrophenol (75 mg, 0.39 mmol), tert-butyl (R)-2-(aminomethyl)morpholine-4-carboxylate acetate (141 mg, 0.509 mmol), and N,N-diisopropylethylamine (0.20 mL, 1.2 mmol) in 1,4-dioxane (2.6 mL). The vessel was sealed, and the reaction mixture was heated at 80 °C for 18 hours, then at 100 °C for 24 hours. Additional tert-butyl (R)-2-(aminomethyl)morpholine-4-carboxylate acetate (141 mg, 0.509 mmol) was added, and the mixture was heated at 100 °C for 24 hours. The reaction was diluted with EtOAc (30 mL), and the resulting mixture was washed with water (20 mL) and brine (20 mL), dried over Na₂SO₄, filtered, and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 0 to 5% CH₃OH/CH₂Cl₂) to afford a dark orange oil (50 mg) containing the desired product. LC-MS (ES) m/z = 313 [M+H]⁺. Material is ~3:2 ratio of des-Cl:desired product.

Intermediate 272

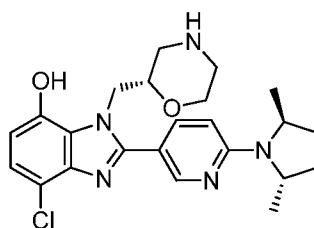
tert-Butyl (R)-2-((4-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-hydroxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate



- 5 To a solution of 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (30 mg, 0.15 mmol) and tert-butyl (R)-2-(((3-chloro-6-hydroxy-2-nitrophenyl)amino)methyl)morpholine-4-carboxylate (50 mg, 0.17 mmol) in 2:1 ethanol:water (3 mL) was added sodium hydrosulfite (76 mg, 0.37 mmol), and the reaction mixture was heated at 100 °C for 18 hours. The reaction was then cooled to room temperature and diluted with EtOAc (10 mL) and water
- 10 (10 mL). The phases were separated and the aqueous layer was further extracted with EtOAc (3 x 10 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 20-100% EtOAc/hexanes) to afford the desired product (9 mg) as a white solid. LC-MS (ES) m/z = 542 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃):
- 15 δ 8.47 (br s, 1H), 7.77 (dd, J = 8.9, 2.5 Hz, 1H), 7.09 (d, J = 8.5 Hz, 1H), 6.69 (d, J = 8.3 Hz, 1H), 6.46 (d, J = 9.0 Hz, 1H), 4.67 - 4.40 (m, 2H), 4.27 (br s, 1H), 4.06 - 3.77 (m, 4H), 3.51 (t, J = 10.8 Hz, 1H), 2.94 (t, J = 11.5 Hz, 1H), 2.63 (t, J = 11.8 Hz, 1H), 2.39 - 2.19 (m, 2H), 1.78 (br s, 2H), 1.75 - 1.60 (m, 2H), 1.56 - 1.39 (m, 9H), 1.21 (d, J = 6.3 Hz, 6H).

20 Intermediate 273

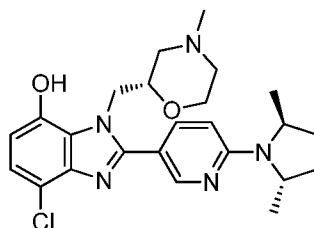
4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(((S)-morpholin-2-yl)methyl)-1H-benzo[d]imidazol-7-ol



- To a solution of tert-butyl (R)-2-((4-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-hydroxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (8.6 mg, 0.016 mmol) in CH₂Cl₂ (0.3 mL) was added trifluoroacetic acid (0.06 mL, 0.8 mmol), and the
- 25

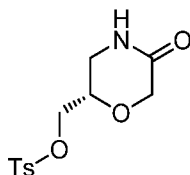
reaction was stirred at room temperature for 16 hours. The reaction was then neutralized with saturated aqueous NaHCO₃ (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with water (5 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated to afford the desired product (7 mg) as a pale yellow solid. LC-MS (ES) m/z = 442 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.55 (d, J = 2.0 Hz, 1H), 8.16 (dd, J = 9.3, 2.0 Hz, 1H), 7.22 (d, J = 8.3 Hz, 1H), 7.07 (d, J = 9.3 Hz, 1H), 6.79 (d, J = 8.3 Hz, 1H), 4.83 - 4.73 (m, 1H), 4.49 - 4.34 (m, 4H), 4.09 (dd, J = 13.0, 3.3 Hz, 1H), 3.70 (td, J = 12.6, 2.3 Hz, 1H), 3.56 - 3.43 (m, 1H), 3.30-3.22 (m, 1H), 3.22 - 3.12 (m, 1H), 3.11 - 2.98 (m, 1H), 2.53 - 2.36 (m, 2H), 1.95 - 1.76 (m, 2H), 1.29 (d, J = 6.3 Hz, 6H).

10

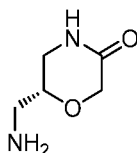
Example 205**4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(((S)-morpholin-2-yl)methyl)-1H-benzo[d]imidazol-7-ol**

To a solution of 4-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(((S)-morpholin-2-yl)methyl)-1H-benzo[d]imidazol-7-ol (5 mg, 0.01 mmol) in 1,2-dichloroethane (1 mL) were added formaldehyde (36.5% in water, 0.004 mL, 0.06 mmol) and sodium triacetoxyborohydride (7 mg, 0.03 mmol), and the reaction mixture was stirred at room temperature for 90 minutes. The reaction was then purified directly by silica gel chromatography (eluting with 0-10% CH₃OH/CH₂Cl₂) to afford the desired product (2.5 mg) as a white solid. LC-MS (ES) m/z = 456 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.54 (d, J = 2.0 Hz, 1H), 7.93 (dd, J = 9.0, 2.4 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.82 - 6.49 (m, 2H), 4.59 (dd, J = 14.4, 3.0 Hz, 1H), 4.32 (dd, J = 14.4, 8.9 Hz, 3H), 4.21 - 4.07 (m, 1H), 3.83 (dd, J = 11.8, 1.9 Hz, 1H), 3.54 - 3.41 (m, 1H), 2.83 (d, J = 11.2 Hz, 1H), 2.65 (d, J = 11.9 Hz, 1H), 2.45 - 2.31 (m, 2H), 2.29 (s, 3H), 2.16 (td, J = 11.6, 3.4 Hz, 1H), 1.96 - 1.84 (m, 1H), 1.82 - 1.67 (m, 2H), 1.23 (d, J = 6.3 Hz, 6H).

25

Intermediate 274(S)-(5-Oxomorpholin-2-yl)methyl 4-methylbenzenesulfonate

To a solution of (S)-6-(hydroxymethyl)morpholin-3-one (1.0 g, 7.63 mmol), 4-methylbenzenesulfonyl chloride (1.890 g, 9.91 mmol) and N,N-dimethylpyridin-4-amine (0.186 g, 1.525 mmol) in CH₂Cl₂ (15 mL) at 23 °C was added triethylamine (1.063 mL, 7.63 mmol), and the reaction mixture was stirred at room temperature for 3 hours. The reaction was quenched with saturated aqueous NH₄Cl (20 mL) and extracted with CH₂Cl₂ (2 x 20 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under vacuum. The resulting residue was purified by silica gel chromatography (0-100% EtOAc/Heptane, then 100% CH₃OH) to afford the desired product (S)-(5-oxomorpholin-2-yl)methyl 4-methylbenzenesulfonate (2.0 g) as a white solid. LC-MS (ES) m/z = 286 [M+H]⁺ ¹H NMR (400 MHz, CD₃OD): δ 7.78 - 7.86 (m, 2H), 7.45 - 7.52 (m, 2H), 4.08 - 4.18 (m, 4H), 3.98 (m, 1H), 3.17 - 3.30 (m, 2H), 2.45 - 2.51 (m, 3H).

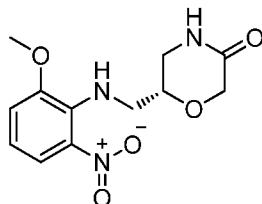
Intermediate 275(R)-6-(Aminomethyl)morpholin-3-one

To a solution of (S)-(5-oxomorpholin-2-yl)methyl 4-methylbenzenesulfonate (2.0 g, 7.01 mmol) in DMF (20 mL) was added NaN₃ (0.684 g, 10.51 mmol), and the reaction mixture was stirred overnight at 80 °C. The reaction mixture was concentrated under vacuum, and the resulting residue was resuspended in CH₂Cl₂ and extracted with saturated aqueous NaHCO₃. The combined organic extracts were dried over MgSO₄, filtered, and concentrated under vacuum. The resulting residue was purified by silica gel chromatography (0-100% ((90:10:1 CH₂Cl₂:CH₃OH:NH₄OH)/CH₂Cl₂) to give (S)-6-(azidomethyl)morpholin-3-one (600 mg). To a mixture of (S)-6-(azidomethyl)morpholin-3-one (600 mg, 3.84 mmol) and palladium on carbon (0.075 g, 0.701 mmol) under nitrogen was added CH₃OH (5 mL; slowly by running down the side of flask), and the reaction mixture was stirred under a H₂ atmosphere for 12 hours at room temperature. The reaction was filtered through a plug of celite, and the filtrate was concentrated under vacuum to give the desired product (500 mg)

as a pale yellow oil. LC-MS (ES) m/z = 131 $[M+H]^+$ ^1H NMR (400 MHz, CH_3OD): δ 4.16 - 4.28 (m, 2H), 3.96 (m, 1H), 3.43 (d, J = 5.1 Hz, 2H), 3.32 - 3.36 (m, 2H).

Intermediate 276

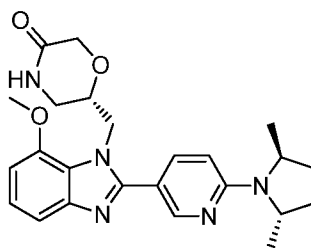
5 (R)-6-(((2-Methoxy-6-nitrophenyl)amino)methyl)morpholin-3-one



To a solution of 2-fluoro-1-methoxy-3-nitrobenzene (263 mg, 1.537 mmol) and (R)-6-(aminomethyl)morpholin-3-one (200 mg, 1.537 mmol) DMF (10 mL) was added triethylamine (0.214 mL, 1.537 mmol), and the reaction mixture was heated at 80 °C for 12 hours. The reaction mixture was concentrated under vacuum, and the resulting residue was resuspended in EtOAc and washed with brine. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum to give the desired product (R)-6-(((2-methoxy-6-nitrophenyl)amino)methyl)morpholin-3-one (350 mg) as a red solid. LC-MS (ES) m/z = 282 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 7.67 (dd, J = 1.4, 8.7 Hz, 1H), 7.16 (dd, J = 1.1, 8.0 Hz, 1H), 6.80 (t, J = 8.2 Hz, 1H), 4.18 - 4.27 (m, 1H), 4.07 - 4.16 (m, 1H), 3.91 (s, 3H), 3.78 - 3.90 (m, 2H), 3.53 (dd, J = 7.4, 13.9 Hz, 1H), 3.24 - 3.31 (m, 2H).

Example 206

20 (R)-6-(((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imi-dazol-1-yl)methyl)morpholin-3-one

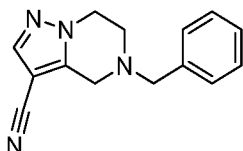


To a solution of (R)-6-(((2-methoxy-6-nitrophenyl)amino)methyl)morpholin-3-one (350 mg, 1.244 mmol) and 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (254 mg, 1.244 mmol) in ethanol (5 mL) and water (1.25 mL) was added sodium hydrosulfite (765 mg, 3.73 mmol), and the reaction mixture was heated into a sealed vessel for 3 hours at 110 °C. The reaction mixture was concentrated under vacuum, resuspended in EtOAc, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by silica gel

chromatography (0-100% (3:1 EtOAc:EtOH)/Heptane) to give the desired product (R)-6-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholin-3-one (388 mg) as a white solid. LC-MS (ES) m/z = 436 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.49 - 8.55 (m, 1H), 7.92 (dd, J = 2.5, 8.9 Hz, 1H), 7.21 - 7.32 (m, 2H), 6.89 (d, J = 7.9 Hz, 1H), 6.68 (d, J = 8.9 Hz, 1H), 4.67 (dd, J = 2.4, 14.6 Hz, 1H), 4.38 - 4.47 (m, 1H), 4.22 - 4.38 (m, 3H), 4.11 - 4.21 (m, 1H), 4.03 (s, 3H), 3.94 - 4.01 (m, 1H), 3.35 - 3.41 (m, 1H), 3.23 - 3.31 (m, 1H), 2.27 - 2.42 (m, 2H), 1.69 - 1.82 (m, 2H), 1.20 (d, J = 6.1 Hz, 6H).

10 Intermediate 277

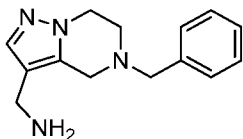
5-Benzyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carbonitrile



To a solution of 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carbonitrile hydrochloride (600 mg, 3.25 mmol) and benzyl bromide (0.387 mL, 3.25 mmol) in DMF (10 mL) was added K_2CO_3 (898 mg, 6.50 mmol), and the reaction mixture was stirred at 23 °C for 12 hours. The reaction mixture was concentrated under vacuum, and the resulting residue was resuspended in CH_2Cl_2 . The mixture was filtered, and the filtrate was concentrated under vacuum. The resulting residue was purified by silica gel chromatography (0-100% (20% CH_3OH/CH_2Cl_2)/ CH_2Cl_2) to give the desired product 5-benzyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carbonitrile (670 mg) as a light yellow oil which solidified upon standing. LC-MS (ES) m/z = 239 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 7.26 - 7.43 (m, 5H), 6.54 (s, 1H), 4.22 (t, J = 5.6 Hz, 2H), 3.78 (s, 2H), 3.71 (s, 2H), 2.96 - 3.08 (m, 2H).

25 Intermediate 278

(5-Benzyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)methanamine

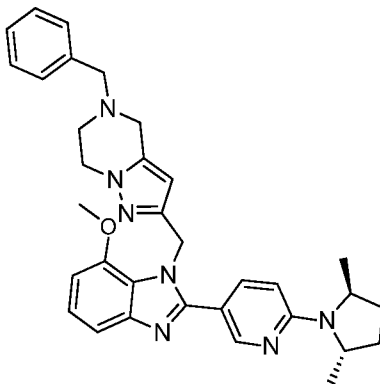


To a solution of 5-benzyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carbonitrile (670 mg, 2.81 mmol) in THF (20 mL) was added $LiAlH_4$ (3.09 mL, 6.19 mmol, 2M in THF), and the reaction mixture was stirred at 23 °C for 2 hours. The reaction was quenched following the

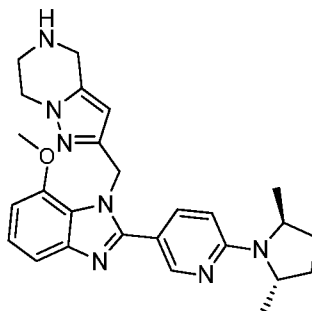
fieser method to obtain the crude product. LC-MS (ES) m/z = 243 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 7.26 - 7.42 (m, 5H), 6.01 (s, 1H), 4.10 (t, J = 5.6 Hz, 2H), 3.75 (s, 2H), 3.73 (s, 2H), 3.66 (s, 2H), 2.93 - 3.01 (m, 2H).

5 Intermediate 279

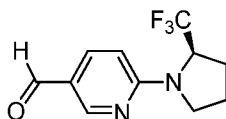
5-Benzyl-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine



- To a solution of (5-benzyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)methanamine (200 mg, 0.825 mmol) and 2-fluoro-1-methoxy-3-nitrobenzene (141 mg, 0.825 mmol) in DMF (5 mL) at 23 °C was added triethylamine (0.138 mL, 0.990 mmol), and the reaction mixture was stirred for 3 days. The reaction was concentrated, and the resulting residue was taken up in 3:1 EtOH/ H_2O and then treated with 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (169 mg, 0.825 mmol) and sodium hydrosulfite (507 mg, 2.476 mmol).
- The resulting mixture was heated into a sealed vessel at 110 °C for 3 hours. Upon completion the mixture was concentrated under vacuum and the residue was taken up in EtOAc. The mixture was filtered, and the filtrate was concentrated under vacuum. The resulting residue was purified by silica gel chromatography (0-100% (3:1 EtOAc:EtOH)/Hep) to give the desired product 5-benzyl-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (280 mg) as a white solid. LC-MS (ES) m/z = 548.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.39 (d, J = 2.3 Hz, 1H), 7.81 (dd, J = 2.5, 8.9 Hz, 1H), 7.25 - 7.39 (m, 6H), 7.13 - 7.23 (m, 1H), 6.81 (d, J = 8.1 Hz, 1H), 6.62 (d, J = 9.1 Hz, 1H), 5.68 (s, 1H), 5.61 (s, 2H), 4.16 - 4.36 (m, 2H), 4.07 (t, J = 5.6 Hz, 2H), 3.86 (s, 3H), 3.67 - 3.71 (m, 2H), 3.59 (s, 2H), 2.90 - 2.96 (m, 2H), 2.24 - 2.37 (m, 2H), 1.67 - 1.80 (m, 2H), 1.18 (d, J = 6.1 Hz, 6H).

Example 207**2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine**

- 5 To a solution of 5-benzyl-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (280 mg, 0.511 mmol) in CH₃OH (10 mL) at 23 °C under an N₂ atmosphere was added palladium on carbon (109 mg, 0.102 mmol), and the reaction mixture was stirred at room temperature under a H₂ atmosphere for 12 hours. The reaction was filtered through a plug of celite, and
- 10 the filtrate was concentrated under vacuum. The resulting residue was purified by silica gel chromatography (0-100% (20%CH₃OH/CH₂Cl₂)/CH₂Cl₂) to give the desired product 2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (115 mg) as a white solid. LC-MS (ES) m/z = 458 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 8.40 (dd, J = 0.78, 2.5 Hz, 1H), 7.82 (dd, J = 2.5, 9.1 Hz, 1H), 7.26 - 7.30 (m, 1H), 7.16 - 7.25 (m, 1H), 6.82 (dd, J = 0.8, 7.9 Hz, 1H), 6.63 (d, J = 8.6 Hz, 1H), 5.71 (s, 1H), 5.64 (s, 2H), 4.28 (br. s., 2H), 4.05 (t, J = 5.7 Hz, 2H), 3.93 (s, 2H), 3.87 (s, 3H), 3.23 (t, J = 5.6 Hz, 2H), 2.26 - 2.41 (m, 2H), 1.67 - 1.80 (m, 2H), 1.20 (d, J = 6.3 Hz, 6H).

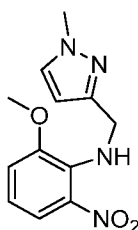
20 Intermediate 280**(R)-6-(2-(Trifluoromethyl)pyrrolidin-1-yl)nicotinaldehyde**

- To 6-fluoronicotinaldehyde (310 mg, 2.478 mmol) were added DMSO (1.5 mL), triethylamine (0.691 mL, 4.96 mmol), and (R)-2-(trifluoromethyl)pyrrolidine (345 mg, 2.478 mmol), and the reaction mixture was then capped and heated at 90 °C over the weekend.
- 25 The reaction was then diluted with water (3 mL), and the resulting mixture was extracted with EtOAc (4 x 5 mL). The organic extracts were combined and then washed with brine,

dried over MgSO_4 , filtered, and concentrated. Purification by chromatography on SiO_2 with a gradient from 0 to 25% EtOAc in Hexanes afforded (R)-6-(2-(trifluoromethyl)pyrrolidin-1-yl)nicotinaldehyde (600 mg) as a light-yellow oil. LC-MS (ES) m/z = 245 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 2.04 - 2.23 (m, 4H) 3.47 - 3.57 (m, 1H) 3.72 (ddd, J = 10.7, 6.5, 4.2 Hz, 1H) 5.18 (t, J = 7.9 Hz, 1H), 6.88 (d, J = 8.9 Hz, 1H) 7.99 (dd, J = 8.9, 2.3 Hz, 1H), 8.67 (d, J = 2.3 Hz, 1H), 9.83 (s, 1H).

Intermediate 281

2-Methoxy-N-((1-methyl-1H-pyrazol-3-yl)methyl)-6-nitroaniline



10

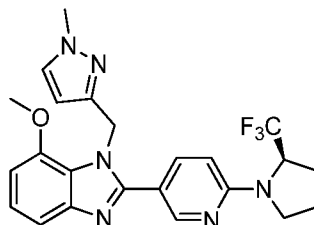
A mixture of (1-methyl-1H-pyrazol-3-yl)methanamine (383 mg, 3.45 mmol) and 2-bromo-1-methoxy-3-nitrobenzene (400mg, 1.724 mmol) in 1,4-dioxane (3.5 mL) was stirred into a sealed vessel at 120 °C overnight. The reaction was then heated at 150 °C for 24 hours followed by 120 °C over the weekend. The reaction was concentrated in vacuo, and the resulting residue was purified by silica gel chromatography (0-50% EtOAc/hexanes) to afford the desired product (288 mg) as an orange oil. LC-MS (ES) m/z = 263 $[\text{M}+\text{H}]^+$.

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Example 208

(R)-7-Methoxy-1-((1-methyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-(trifluoromethyl)pyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole

20



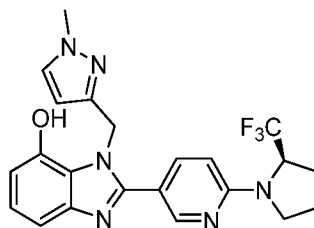
To 2-methoxy-N-((1-methyl-1H-pyrazol-3-yl)methyl)-6-nitroaniline (68 mg, 0.259 mmol) were added (R)-6-(2-(trifluoromethyl)pyrrolidin-1-yl)nicotinaldehyde (63.3 mg, 0.259 mmol), sodium hydrosulfite (135 mg, 0.659 mmol), ethanol (2 mL), and water (1 mL), and the reaction mixture was heated into a sealed vessel under microwave conditions for 1 hour at 130 °C. The reaction was then quenched with water (5 mL), and extracted with EtOAc (3 x

25

10 mL). The organic extracts were then combined and washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ with a gradient from 0 to 8% CH₃OH in CH₂Cl₂ afforded (R)-7-methoxy-1-((1-methyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-(trifluoromethyl)pyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole (48 mg) as a white solid after freeze drying. LC-MS (ES) m/z = 457 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 2.06 - 2.19 (m, 4H), 3.41 - 3.50 (m, 1H), 3.67 - 3.72 (m, 1H), 3.74 (s, 3H), 3.85 (s, 3H), 5.09 (t, *J* = 7.7 Hz, 1H), 5.55 (s, 2H), 5.90 (d, *J* = 2.3 Hz, 1H), 6.79 (d, *J* = 7.9 Hz, 1H), 6.86 (d, *J* = 8.9 Hz, 1H), 7.13 (t, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 7.9 Hz, 1H), 7.56 (d, *J* = 2.3 Hz, 1H), 8.08 (dd, *J* = 8.9, 2.5 Hz, 1H), 8.59 (d, *J* = 2.0 Hz, 1H).

Example 209

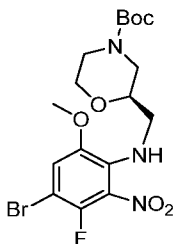
(R)-1-((1-Methyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-(trifluoromethyl)pyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-7-ol



To (R)-7-methoxy-1-((1-methyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-(trifluoromethyl)pyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole (26 mg, 0.057 mmol) in 1,2-dichloroethane (3 mL) was added boron tribromide (0.228 mL, 0.228 mmol), and the reaction mixture was stirred for 2 hours at 45 °C. Additional boron tribromide (0.228 mL, 0.228 mmol) was added, and the reaction mixture was stirred overnight at 45 °C. The reaction was quenched with water followed by slow addition of NaHCO₃ until no more gas evolution was observed. The resulting mixture was extracted with EtOAc (4 x 5 mL), and the organic extracts were then combined and washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ with a gradient from 0 to 10% CH₃OH in CH₂Cl₂ afforded (R)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-(trifluoromethyl)pyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-7-ol (21 mg) as a white solid after freeze-drying. LC-MS (ES) m/z = 443 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 2.12 (d, *J* = 9.1 Hz, 4H), 3.44 (d, *J* = 9.4 Hz, 1H), 3.66 - 3.72 (m, 1H), 3.73 (s, 3H), 5.05 - 5.14 (m, 1H), 5.60 (s, 2H), 5.85 (d, *J* = 2.3 Hz, 1H), 6.59 (d, *J* = 7.9 Hz, 1H), 6.85 (d, *J* = 8.9 Hz, 1H), 6.94 - 7.01 (m, 1H), 7.10 (d, *J* = 7.9 Hz, 1H), 7.55 (d, *J* = 2.3 Hz, 1H), 8.03 (dd, *J* = 8.7, 2.4 Hz, 1H), 8.54 (d, *J* = 2.3 Hz, 1H), 9.92 (s, 1H).

Intermediate 282

tert-Butyl (R)-2-(((4-bromo-3-fluoro-6-methoxy-2-nitrophenyl)amino)methyl)morpholine-4-carboxylate



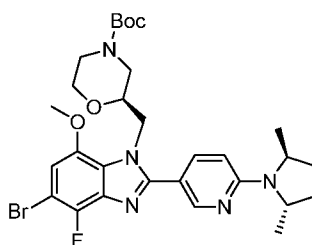
5

To a solution of tert-butyl (R)-2-(((3-fluoro-6-methoxy-2-nitrophenyl)amino)methyl)morpholine-4-carboxylate (4.5 g, 11.68 mmol) in DMF (55 mL) was added NBS (2.182 g, 12.26 mmol), and the reaction mixture was stirred at room temperature for 18 hours. The mixture was quenched with water (100 mL), and extracted with EtOAc (3x). The combined organic extract was dried (Na₂SO₄) and concentrated. The resulting residue was purified by column chromatography on silica gel (gradient: 0 to 80% EtOAc/heptane) to give the desired product (4.85 g) as a brown oil. LC-MS (ES) m/z = 464, 466 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 1.42 - 1.52 (m, 9H), 2.69 (br. s., 1H), 2.89 - 3.04 (m, 1H), 3.14 (dd, J = 13.2, 8.1 Hz, 1H), 3.35 (br. s., 1H), 3.46 - 3.61 (m, 2H), 3.81 - 3.98 (m, 6H), 6.96 (d, J = 5.8 Hz, 1H).

15

Intermediate 283

tert-Butyl (R)-2-((5-bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1H-benzod[imidazol-1-yl)methyl)morpholine-4-carboxylate



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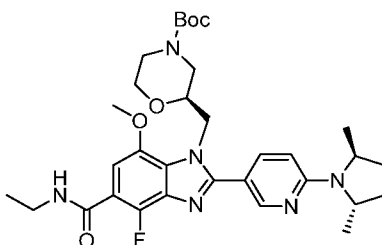
To a solution of tert-butyl (R)-2-(((4-bromo-3-fluoro-6-methoxy-2-nitrophenyl)amino)methyl)morpholine-4-carboxylate (3.7 g, 7.97 mmol) in DMSO (30 mL) were added 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (1.628 g, 7.97 mmol), sodium hydrosulfite (85%, 4.90 g, 23.91 mmol) and water (6.0 mL), and the reaction mixture was stirred at 97 °C for 2 hours. The reaction mixture was cooled, quenched with water (60 mL), and extracted with EtOAc (3x). The combined organic extract was dried (Na₂SO₄) and

25

concentrated. The resulting residue was purified by column chromatography on silica gel (gradient: 0 to 80% (3:1 EtOAc:EtOH)/heptane) to give the desired product (3.40 g) as an off-white solid. LC-MS (ES) m/z = 618, 620 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.18 - 1.25 (m, 6H), 1.44 - 1.51 (m, 9H), 1.71 - 1.83 (m, 2H), 2.29 - 2.44 (m, 2H), 2.68 (m, 1H), 2.96 (br. s., 1H), 3.76 - 3.92 (m, 3H), 3.94 - 4.06 (m, 4H), 4.34 (dd, J = 14.6, 8.5 Hz, 3H), 4.55 (dd, J = 14.7, 2.5 Hz, 1H), 6.70 (d, J = 8.6 Hz, 1H), 7.00 (d, J = 4.8 Hz, 1H), 7.95 (dd, J = 8.9, 2.5 Hz, 1H), 8.56 (d, J = 2.0 Hz, 1H).

Intermediate 284

10 tert-Butyl (R)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-5-(ethylcarbamoyl)-4-fluoro-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate

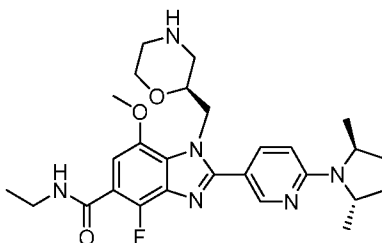


To a solution of tert-butyl (R)-2-((5-bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (166 mg, 0.268 mmol) in THF (3 mL) at -15 °C was added isopropylmagnesium chloride lithium chloride complex (0.826 mL, 1.073 mmol, 1.6 M in THF), and the resulting mixture was stirred at -15 °C for 15 minutes, then warmed to 0 °C and stirred for 1 hour. The reaction was then warmed to 10 °C and stirred for 1 hour. Additional isopropylmagnesium chloride lithium chloride complex (0.826 mL, 1.073 mmol, 1.6 M in THF) was then added, and the resulting mixture was stirred for an additional 1 hour. Carbon dioxide was then gently bubbled through the reaction mixture for 10 minutes. The reaction was then concentrated. Aqueous NaOH (5 mL, 1N) was added followed by 1N HCl until pH was about 4. The resulting mixture was extracted with EtOAc (3 x 10 mL), and the organic extracts were then combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated. To the resulting yellow oil was added DMSO (3 mL), EDC (51.4 mg, 0.268 mmol), HOBt (41.1 mg, 0.268 mmol), ethanamine hydrochloride (43.8 mg, 0.537 mmol), and N-methylmorpholine (0.207 mL, 1.879 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with water (5 mL) and then extracted with EtOAc (4 x 10 mL). The organic extracts were then combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification on HPLC system under NH_4OH condition afforded tert-butyl (R)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-5-(ethylcarbamoyl)-4-fluoro-7-

methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (32 mg) as a white solid after freeze-drying. LC-MS (ES) m/z = 611 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 1.11 - 1.17 (m, 9H), 1.40 (s, 9H), 1.66 (d, J = 5.8 Hz, 2H), 2.24 (br. s., 2H), 3.17 - 3.26 (m, 1H), 3.28 - 3.32 (m, 2H), 3.62 - 3.81 (m, 4H), 3.97 (s, 3H), 4.19 - 4.39 (m, 3H), 4.46 - 4.54 (m, 1H), 6.62 (d, J = 8.9 Hz, 1H), 6.98 (d, J = 4.3 Hz, 1H), 7.93 (dd, J = 9.0, 2.4 Hz, 1H), 8.23 (d, J = 3.0 Hz, 1H), 8.54 (d, J = 2.3 Hz, 1H).

Example 210

10 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-ethyl-4-fluoro-7-methoxy-1-(((S)-morpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide

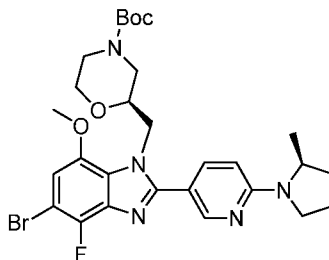


To tert-butyl (R)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-5-(ethylcarbamoyl)-4-fluoro-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (32 mg, 0.052 mmol) was added a pre-mixed solution of CH_2Cl_2 (1.5 mL) and TFA (0.5 mL, 6.49 mmol), and the reaction mixture was stirred at room temperature for 2 hours. The mixture was concentrated under reduced pressure, and the resulting material was diluted with saturated aqueous $NaHCO_3$ (5 mL) and extracted with EtOAc (3 x 1 mL). The organic extracts were combined and washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting material was diluted with MeCN (2 mL) and water (2 mL), and then freeze-dried to give a 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-ethyl-4-fluoro-7-methoxy-1-(((S)-morpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide (23 mg) white solid. LC-MS (ES) m/z = 511 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 1.11 - 1.18 (m, 9H), 1.66 (d, J = 5.3 Hz, 2H), 2.25 (br. s., 2H), 2.30 - 2.39 (m, 2H), 2.55 - 2.72 (m, 3H), 3.22 (m, 1H), 3.28 - 3.33 (m, 2H), 3.62 (d, J = 11.2 Hz, 1H), 3.67 - 3.75 (m, 1H), 3.96 (s, 3H), 4.29 (dd, J = 14.6, 8.2 Hz, 3H), 4.38 - 4.46 (m, 1H), 6.62 (d, J = 8.6 Hz, 1H), 6.97 (d, J = 4.6 Hz, 1H), 7.93 (dd, J = 8.9, 2.3 Hz, 1H), 8.22 (d, J = 3.3 Hz, 1H), 8.53 (d, J = 2.5 Hz, 1H).

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Intermediate 285

tert-Butyl (R)-2-((5-bromo-4-fluoro-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate

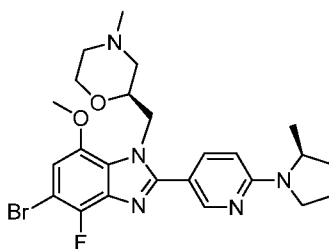


- 5 To tert-butyl (R)-2-(((4-bromo-3-fluoro-6-methoxy-2-nitrophenyl)amino)methyl)morpholine-4-carboxylate (570 mg, 1.228 mmol) were added ethanol (5 mL), water (2.5 mL), (S)-6-(2-methylpyrrolidin-1-yl)nicotinaldehyde (234 mg, 1.228 mmol), and sodium hydrosulfite (754 mg, 3.68 mmol, 85%), and the reaction mixture was heated into a sealed vessel under microwave conditions for 1 hour at 130 °C. The reaction was then quenched with water (5 mL) and extracted with EtOAc (4 x 5 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ with a gradient from 0 to 10% CH₃OH in CH₂Cl₂ afforded tert-butyl (R)-2-((5-bromo-4-fluoro-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (350 mg) as an off-clear oil. LC-MS (ES) m/z = 605
- 10 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆): δ 1.18 - 1.21 (m, 3H), 1.39 (s, 9H), 1.68 - 1.76 (m, 1H), 1.98 (d, J = 2.3 Hz, 1H), 2.02 - 2.12 (m, 2H), 2.57 - 2.69 (m, 1H), 2.82 (br. s., 1H), 2.78 - 2.78 (m, 1H), 3.21 (m, 1H), 3.34 - 3.39 (m, 1H), 3.56 (dd, J = 10.4, 7.6 Hz, 1H), 3.62 - 3.77 (m, 4H), 3.96 (s, 3H), 4.20 - 4.26 (m, 1H), 4.33 (dd, J = 15.0, 8.1 Hz, 1H), 4.43 - 4.51 (m, 1H), 7.02 (d, J = 4.8 Hz, 1H), 7.94 (dd, J = 8.9, 2.5 Hz, 1H), 8.53 (d, J = 2.3 Hz, 1H).

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Intermediate 286

(S)-2-((5-Bromo-4-fluoro-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)-4-methylmorpholine

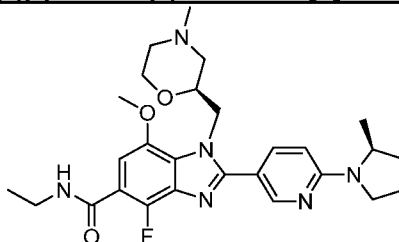


- 25 To tert-butyl (R)-2-((5-bromo-4-fluoro-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (165 mg, 0.273 mmol)

was added a premixed solution of CH₂Cl₂ (1.5 mL) and TFA (0.5 mL, 6.49 mmol), and the reaction mixture was stirred at room temperature for 1 hour. The reaction was concentrated and then quenched with saturated aqueous NaHCO₃ solution (5 mL). The resulting mixture was extracted with EtOAc (4 x 5 mL), and the combined organic extracts were washed with
 5 brine, dried over MgSO₄, filtered, and concentrated. The resulting clear oil was diluted with 1,2-dichloroethane (5 mL) and treated with formaldehyde (0.106 mL, 1.365 mmol, 35.6% in water) and acetic acid (0.055 mL, 0.955 mmol). After stirring the resulting mixture for 10 minutes, sodium triacetoxyborohydride (174 mg, 0.819 mmol) was added, and the reaction mixture was stirred for 1 hour. The reaction was quenched with saturated aqueous NaHCO₃
 10 solution (2 mL) and treated with saturated aqueous Na₂CO₃ solution (1 mL) until pH was 10. The mixture was extracted with CH₂Cl₂ (4 x 5 mL), and the combined organic extracts were washed with brine, dried over MgSO₄, filtered, and concentrated to give (S)-2-((5-bromo-4-fluoro-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)-4-methylmorpholine (134 mg) as a clear oil. LC-MS (ES) m/z
 15 = 519 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.19 - 1.21 (m, 3H), 1.65 - 1.74 (m, 2H), 1.89 - 2.02 (m, 2H), 2.02 - 2.10 (m, 2H), 2.14 (s, 3H), 2.49 (br. s., 1H), 2.60 (d, *J* = 10.7 Hz, 1H), 3.28 (td, *J* = 11.2, 2.3 Hz, 1H), 3.36 - 3.39 (m, 1H), 3.52 - 3.61 (m, 1H), 3.65 (d, *J* = 10.9 Hz, 1H), 3.72 - 3.80 (m, 1H), 3.95 (s, 3H), 4.20 - 4.28 (m, 1H), 4.28 - 4.37 (m, 1H), 4.40 - 4.47 (m, 1H), 6.59 (d, *J* = 9.1 Hz, 1H), 7.00 (d, *J* = 4.6 Hz, 1H), 7.94 (dd, *J* = 8.9, 2.3
 20 Hz, 1H), 8.52 (d, *J* = 2.3 Hz, 1H).

Example 211

N-ethyl-4-fluoro-7-methoxy-1-(((S)-4-methylmorpholin-2-yl)methyl)-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide

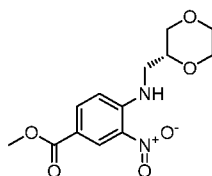


25

To a solution of (S)-2-((5-bromo-4-fluoro-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)-4-methylmorpholine (175 mg, 0.338 mmol) in THF (3 mL) at 0 °C was added isopropylmagnesium chloride lithium chloride
 30 complex (2.60 mL, 3.38 mmol, 1.6M in THF), and the resulting mixture was stirred at 0 °C for 15 minutes. Additional Isopropylmagnesium chloride lithium chloride complex (5.2 mL, 6.76 mmol, 1.6M in THF) was added, and the resulting mixture was stirred for additional 15 minutes. The reaction was cooled in a dry ice/acetone bath and CO₂ was then bubbled

through the reaction mixture for 5 minutes. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was concentrated, and the resulting material was treated with 1N NaOH (5 mL) followed by 1N HCl until pH was about 4. The resulting mixture was extracted with EtOAc (3 x 10 mL). The aqueous layer was freeze-dried over the weekend. To the resulting solid was added DMSO (10 mL), EDC (194 mg, 1.013 mmol), HOBt (155 mg, 1.013 mmol), ethanamine hydrochloride (138 mg, 1.688 mmol), and N-methylmorpholine (0.371 mL, 3.38 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with water (5 mL) and extracted with EtOAc (4 x 10 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, filtered, and concentrated. The crude oil was then diluted with DMSO (1 mL) and purified by reverse phase HPLC (5-35% CH₃CN/(0.075% NH₄OH in water) to give N-ethyl-4-fluoro-7-methoxy-1-(((S)-4-methylmorpholin-2-yl)methyl)-2-(6-(((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide (2.5 mg) as a white solid after freeze drying. LC-MS (ES) m/z = 511 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.26 - 1.31 (m, 6H), 1.80 - 1.87 (m, 1H), 1.90 (t, J = 10.8 Hz, 1H), 2.06 - 2.26 (m, 5H), 2.32 (s, 3H), 2.67 (d, J = 11.4 Hz, 1H), 2.85 (d, J = 11.2 Hz, 1H), 3.40 - 3.54 (m, 4H), 3.62 - 3.70 (m, 1H), 3.82 (d, J = 9.6 Hz, 1H), 3.99 - 4.06 (m, 4H), 4.25 - 4.39 (m, 2H), 4.58 (dd, J = 14.5, 2.5 Hz, 1H), 6.68 (d, J = 9.1 Hz, 1H), 7.17 (d, J = 4.6 Hz, 1H), 7.97 (dd, J = 9.0, 2.2 Hz, 1H), 8.55 (d, J = 2.0 Hz, 1H).

20

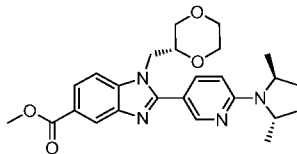
Intermediate 287Methyl (R)-4-(((1,4-dioxan-2-yl)methyl)amino)-3-nitrobenzoate

A mixture of methyl 4-fluoro-3-nitrobenzoate (250 mg, 1.255 mmol), K₂CO₃ (347 mg, 2.51 mmol), and (R)-((1,4-dioxan-2-yl)methanamine hydrochloride (199 mg, 1.293 mmol) in DMF (5 mL) was stirred at room temperature overnight. The reaction was slowly diluted into saturated aqueous NH₄Cl with stirring for 10 minutes. The resulting precipitate was collected by filtration, washed with small amount of water, air-dried for 10 minutes, and dried under vacuum at 40 °C for 3 hours to afford crude methyl (R)-4-(((1,4-dioxan-2-yl)methyl)amino)-3-nitrobenzoate (372 mg). LC-MS (ES) m/z = 297 [M+H]⁺.

30

Intermediate 288

(S)-2-((4-Chloro-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine

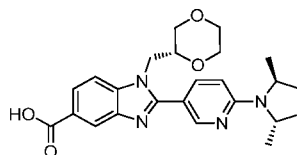


- 5 A mixture of 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (256 mg, 1.256 mmol), sodium hydrosulfite (699 mg, 4.02 mmol), and methyl (R)-4-(((1,4-dioxan-2-yl)methyl)amino)-3-nitrobenzoate (372 mg, 1.256 mmol) in ethanol (8 mL) and water (1.600 mL) was heated into a sealed vessel at 130 °C under microwave conditions for 60 minutes. The reaction was poured onto saturated aqueous NH₄Cl with stirring for 15 minutes. The
- 10 resulting mixture was extracted with EtOAc (2x), and the combined organic extracts were dried over MgSO₄, filtered, and concentrated. The resulting residue was purified by silica gel chromatography using a gradient of 5% to 70% (3:1 EtOAc/EtOH (2%NH₄OH))/Heptane to afford methyl 1-(((R)-1,4-dioxan-2-yl)methyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylate (410 mg) as a white solid. LC-MS
- 15 (ES) m/z = 451 [M+H]⁺. ¹H NMR (DMSO-*d*₆): δ 8.58 (d, *J* = 2.0 Hz, 1H), 8.22 (d, *J* = 1.0 Hz, 1H), 7.97 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.88 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 6.63 (d, *J* = 8.9 Hz, 1H), 4.13 - 4.42 (m, 4H), 3.93 - 4.00 (m, 1H), 3.83 (dd, *J* = 11.4, 2.3 Hz, 1H), 3.59 - 3.69 (m, 2H), 3.37 - 3.52 (m, 2H), 3.26 - 3.33 (m, 2H), 2.24 (br. s., 2H), 1.66 (d, *J* = 5.6 Hz, 2H), 1.06 - 1.18 (m, 7H).

20

Intermediate 289

1-(((R)-1,4-Dioxan-2-yl)methyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylic acid

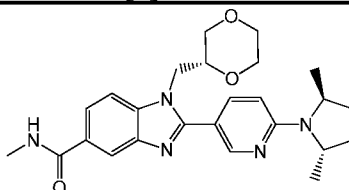


- 25 To methyl 1-(((R)-1,4-dioxan-2-yl)methyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylate (410 mg, 0.910 mmol) in CH₃OH (10 mL) and THF (2 mL) at room temperature was added slowly 5N NaOH (0.910 mL, 4.55 mmol) via syringe, and the reaction mixture was heated at 40-45 °C for 18 hours. The reaction was cooled in an ice bath and 6N HCl (6M) (0.766 mL, 4.60 mmol) was then added via syringe
- 30 very slowly. The resulting mixture was concentrated to afford crude 1-(((R)-1,4-dioxan-2-

yl)methyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylic acid as a solid. LC-MS (ES) $m/z = 437 [M+H]^+$.

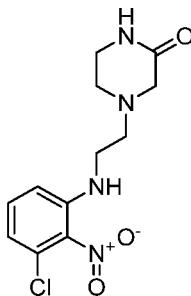
Example 212

5 **1-(((R)-1,4-Dioxan-2-yl)methyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide**

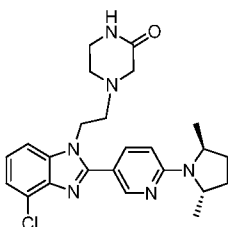


To a mixture of 1-(((R)-1,4-dioxan-2-yl)methyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylic acid (160 mg, 0.220 mmol),
 10 methylamine hydrochloride (148 mg, 2.199 mmol), HOAt (35.9 mg, 0.264 mmol), and EDC (50.6 mg, 0.264 mmol) in DMSO (3 mL) at room temperature was added N-methylmorpholine (0.242 mL, 2.199 mmol), and the reaction mixture was stirred overnight at room temperature. The reaction was diluted with saturated aqueous NH_4Cl , and the resulting precipitate was collected by filtration and washed with small amount of water. The
 15 aqueous layer was extracted with CH_2Cl_2 (2 x 8 mL), and the combined organic extracts were dried over MgSO_4 , filtered, and then added to solid that was collected by filtration. The resulting mixture was concentrated in vacuo, and the resulting residue was purified by silica gel chromatography (gradient: 8 to 80% (3:1 EtOAc/EtOH (2% NH_4OH))/Heptane). Fraction containing the desired product were taken up in CH_2Cl_2 and treated with heptane (0.5 mL).
 20 The resulting mixture was concentrated under vacuum to afford 1-(((R)-1,4-dioxan-2-yl)methyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide (92 mg) as a white solid. LC-MS (ES) $m/z = 450 [M+H]^+$.
 1H NMR ($\text{DMSO}-d_6$): δ 8.57 (d, $J = 2.0$ Hz, 1H), 8.43 (q, $J = 4.2$ Hz, 1H), 8.14 (d, $J = 1.3$ Hz, 1H), 7.96 (dd, $J = 8.9, 2.5$ Hz, 1H), 7.77 (dd, $J = 8.6, 1.5$ Hz, 1H), 7.71 (d, $J = 8.4$ Hz, 1H), 6.63 (d, $J = 8.9$ Hz, 1H), 4.11 - 4.41 (m, 4H), 3.92 - 4.01 (m, 1H), 3.83 (dd, $J = 11.4, 2.3$ Hz, 1H), 3.64 (dd, $J = 19.4, 10.3$ Hz, 2H), 3.37 - 3.52 (m, 2H), 3.29 (dd, $J = 11.4, 10.1$ Hz, 1H), 2.82 (d, $J = 4.6$ Hz, 3H), 2.24 (br. s., 2H), 1.66 (d, $J = 5.3$ Hz, 2H), 1.07 - 1.20 (m, 6H).

30

Intermediate 2904-(2-((3-Chloro-2-nitrophenyl)amino)ethyl)piperazin-2-one

- 5 A mixture of 1-chloro-3-fluoro-2-nitrobenzene (160 mg, .911 mmol), K_2CO_3 (378 mg, 2.73 mmol), and 4-(2-aminoethyl)piperazin-2-one, 2Hydrochloride (203 mg, 0.939 mmol) in DMF (6 mL) was stirred at room temperature for 10 minutes and then at 45°C overnight. Additional amine was added and the reaction mixture was stirred for an additional 12 hours. The reaction was diluted into saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (2x). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to a orange residue that was dried on hivac for 2hrs. The resulting material was purified by silica gel chromatography using a gradient from 20-100% (3:1 EtOAc/EtOH (2% NH_4OH))/Heptane to afford 4-(2-((3-chloro-2-nitrophenyl)amino)ethyl)piperazin-2-one (150 mg) as a yellow solid. LC-MS (ES) m/z = 299 $[M+H]^+$. ^1H NMR ($DMSO-d_6$): δ 7.76 (br. s., 1H), 7.36 (t, J = 8.2 Hz, 1H), 6.91 - 6.96 (m, 1H), 6.82 (dd, J = 7.9, 1.0 Hz, 1H), 6.33 (t, J = 5.1 Hz, 1H), 3.26 - 3.31 (m, 2H), 3.11 - 3.17 (m, 2H), 2.99 (s, 2H), 2.56 - 2.62 (m, 4H).

Example 2134-(2-(4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzof[d]imidazol-1-yl)ethyl)piperazin-2-one

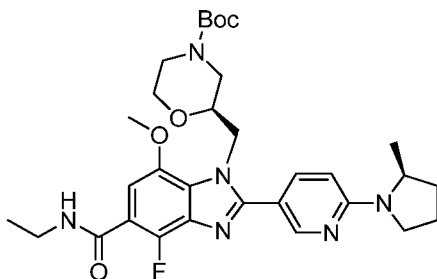
- A mixture of 4-(2-((3-chloro-2-nitrophenyl)amino)ethyl)piperazin-2-one (150 mg, 0.502 mmol), 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (118 mg, 0.577 mmol), and sodium hydrosulfite (329 mg, 1.607 mmol) in ethanol (3 mL) and water (1.0 mL) was stirred into a sealed vessel at 130 °C for 55 minutes under microwave conditions. The reaction was poured onto saturated aqueous $NaHCO_3$ with stirring. After 15 minutes, the mixture

was extracted with EtOAc (2x), and combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue/foam was purified by silica gel chromatography (gradient: 8% to 75% (90:10:1 CH₂Cl₂/CH₃OH/NH₄OH)/CH₂Cl₂) to afford 4-(2-(4-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)ethyl)piperazin-2-one (170 mg) as a solid. LC-MS (ES) m/z = 453 [M+H]⁺. ¹H NMR (DMSO-*d*₆): δ 8.53 (d, *J* = 2.0 Hz, 1H), 7.91 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.60 - 7.72 (m, 2H), 7.18 - 7.33 (m, 2H), 6.63 (d, *J* = 8.6 Hz, 1H), 4.44 (t, *J* = 6.5 Hz, 2H), 4.26 (br. s., 2H), 2.92 - 3.02 (m, 2H), 2.79 - 2.90 (m, 2H), 2.70 (m, 2H), 2.43 - 2.48 (m, 2H), 2.18 - 2.31 (m, 2H), 1.65 (d, *J* = 5.6 Hz, 2H), 1.10 - 1.17 (m, 6H).

10

Intermediate 291

tert-Butyl (R)-2-((5-(ethylcarbamoyl)-4-fluoro-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate

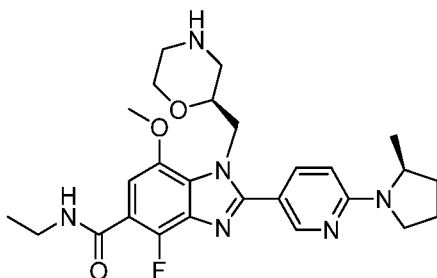


- 15 To tert-butyl (R)-2-((5-bromo-4-fluoro-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (175 mg, 0.289 mmol) in THF (3 mL) at -15 °C was added isopropylmagnesium chloride lithium chloride complex (0.891 mL, 1.158 mmol, 1.6 M in THF), and the reaction mixture was stirred at -15 °C for 15 minutes. The reaction was then stirred at 0 °C for 1 hour, and at 10 °C for 1 hour.
- 20 Additional isopropylmagnesium chloride lithium chloride complex (0.891 mL, 1.158 mmol, 1.6 M in THF) was then added, and the reaction mixture was stirred at 10 °C for 1 hour. Carbon dioxide was then bubbled through the reaction mixture for 15 minutes, and the reaction was stirred for 1 additional hour. The reaction was concentrated and then treated with 1N NaOH (5 mL) followed by 1N HCl until pH was about 4. The resulting mixture was
- 25 extracted with EtOAc (3 x 10 mL), and the combined organic extracts were washed with brine, dried over MgSO₄, filtered, and concentrated. To the resulting yellow oil was added DMSO (3.00 mL), EDC (55.5 mg, 0.289 mmol), HOBt (44.3 mg, 0.289 mmol), ethanamine hydrochloride (47.2 mg, 0.579 mmol), and N-methylmorpholine (0.223 mL, 2.026 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction was
- 30 quenched with water (5 mL) and extracted with EtOAc (4 x 10 mL). The organic extracts

were combined, washed with brine, dried over MgSO_4 , filtered, and concentrated. The resulting material was purified by reverse phase HPLC (gradient: 50-99% CH_3CN in 0.1% NH_4OH) to afford tert-butyl (R)-2-((5-(ethylcarbamoyl)-4-fluoro-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (26 mg) as a white solid after freeze drying. LC-MS (ES) $m/z = 597$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 1.15 (t, $J = 7.2$ Hz, 3H), 1.20 (d, $J = 6.3$ Hz, 3H), 1.39 (s, 9H), 1.72 (br. s., 1H), 1.96 - 2.14 (m, 3H), 2.45 - 2.49 (m, 2H), 3.16 - 3.24 (m, 1H), 3.28 - 3.32 (m, 3H), 3.53 - 3.59 (m, 1H), 3.61 - 3.79 (m, 4H), 3.97 (s, 3H), 4.24 (br. s., 1H), 4.34 (dd, $J = 15.1, 8.2$ Hz, 1H), 4.51 (d, $J = 12.2$ Hz, 1H), 6.60 (d, $J = 8.9$ Hz, 1H), 6.98 (d, $J = 4.6$ Hz, 1H), 7.95 (dd, $J = 8.7, 2.4$ Hz, 1H), 8.23 (d, $J = 2.8$ Hz, 1H), 8.53 (d, $J = 2.3$ Hz, 1H).

Example 214

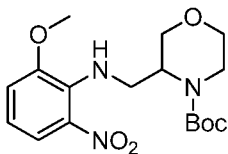
N-Ethyl-4-fluoro-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1-(((S)-morpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide



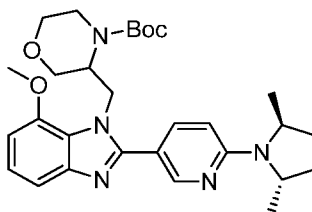
15

To tert-butyl (R)-2-((5-(ethylcarbamoyl)-4-fluoro-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (26 mg, 0.044 mmol) was added a premixed solution of CH_2Cl_2 (1.5 mL) and TFA (0.5 mL, 6.49 mmol), and the reaction mixture was stirred at room temperature for 1 hour. The reaction was concentrated, and the resulting material was diluted with saturated aqueous NaHCO_3 (2mL) and then extracted with EtOAc (4 x 10 mL). The organic extracts were combined, washed with brine, dried over MgSO_4 , filtered, and concentrated to afford N-ethyl-4-fluoro-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1-(((S)-morpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide (20 mg) a white solid after freeze-drying. LC-MS (ES) $m/z = 497$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 1.15 (t, $J = 7.2$ Hz, 3H), 1.20 (d, $J = 6.3$ Hz, 3H), 1.69 - 1.77 (m, 1H), 1.95 - 2.13 (m, 3H), 2.28 - 2.37 (m, 1H), 2.56 - 2.61 (m, 2H), 2.64 - 2.70 (m, 1H), 3.22 (m, 1H), 3.28 - 3.32 (m, 2H), 3.36 - 3.41 (m, 1H), 3.53 - 3.64 (m, 2H), 3.64 - 3.72 (m, 1H), 3.96 (s, 3H), 4.20 - 4.34 (m, 2H), 4.39 - 4.46 (m, 1H), 6.60 (d, $J = 8.9$ Hz, 1H), 6.98 (d, $J = 4.6$ Hz, 1H), 7.95 (dd, $J = 8.9, 2.5$ Hz, 1H), 8.22 (d, $J = 2.8$ Hz, 1H), 8.53 (d, $J = 2.0$ Hz, 1H).

30

Intermediate 292tert-Butyl 3-(((2-methoxy-6-nitrophenyl)amino)methyl)morpholine-4-carboxylate

- 5 To 2-fluoro-1-methoxy-3-nitrobenzene (400 mg, 2.337 mmol) in DMSO (3 mL) were added tert-butyl 3-(aminomethyl)morpholine-4-carboxylate (506 mg, 2.337 mmol), K₂CO₃ (323 mg, 2.337 mmol), and diisopropylethyl amine (0.408 mL, 2.337 mmol), and the reaction mixture was heated in a microwave reactor for 1 hour at 90 °C. The reaction was diluted with water (10 mL) extracted with EtOAc (4 x 5 mL). The organic extracts were combined, washed with
- 10 brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ with a gradient of 0 to 40% EtOAc in hexanes afforded tert-butyl 3-(((2-methoxy-6-nitrophenyl)amino)methyl)morpholine-4-carboxylate (770 mg) as a red oil that solidified upon sitting. LC-MS (ES) m/z = 368 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.20 (br. s., 9H), 3.14 (m, 1H), 3.25 - 3.33 (m, 1H), 3.44 (m, 1H), 3.60 - 3.80 (m, 4H), 3.84 (s, 3H), 3.86
- 15 - 3.93 (m, 1H), 4.05 (d, *J* = 9.9 Hz, 1H), 6.68 - 6.75 (m, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.62 - 7.75 (m, 1H).

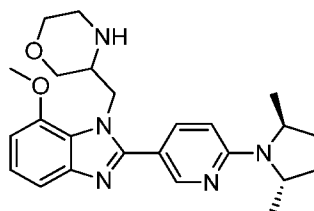
Intermediate 293
tert-Butyl 3-((2-(6-((2*S*,5*S*)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate


- To tert-butyl 3-(((2-methoxy-6-nitrophenyl)amino)methyl)morpholine-4-carboxylate (82 mg, 0.223 mmol) were added 6-((2*S*,5*S*)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (45.6 mg, 0.223 mmol), sodium hydrosulfite (117 mg, 0.571 mmol), ethanol (1.5 mL), and water (0.750
- 25 mL), and the reaction mixture was heated under microwave conditions for 1 hour at 130 °C. The reaction was diluted with water and extracted with EtOAc (4 x 5 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ with a gradient of 0 to 10% CH₃OH in CH₂Cl₂ afforded tert-butyl 3-((2-(6-((2*S*,5*S*)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-

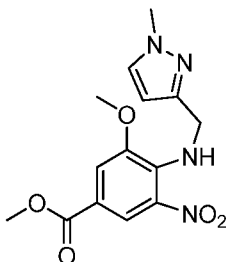
benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (88 mg) as a clear oil. LC-MS (ES) $m/z = 522$ $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 0.72 (br. s., 9H), 1.13 (t, $J = 5.8$ Hz, 6H), 1.60 - 1.71 (m, 2H), 1.85 (d, $J = 11.7$ Hz, 1H), 2.18 - 2.29 (m, 2H), 3.17 (t, $J = 12.0$ Hz, 1H), 3.25 - 3.32 (m, 1H), 3.44 (d, $J = 11.4$ Hz, 1H), 3.49 - 3.60 (m, 1H), 3.80 - 3.87 (m, 1H), 3.93 (s, 3H), 4.16 (d, $J = 10.1$ Hz, 1H), 4.27 (br. s., 2H), 4.54 - 4.82 (m, 2H), 6.63 (d, $J = 8.9$ Hz, 1H), 6.82 (d, $J = 8.1$ Hz, 1H), 7.12 (t, $J = 8.0$ Hz, 1H), 7.24 (dd, $J = 7.6, 3.8$ Hz, 1H), 7.63 (dd, $J = 12.7, 9.4$ Hz, 1H), 8.19 - 8.30 (m, 1H).

Example 215

10 **3-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine**



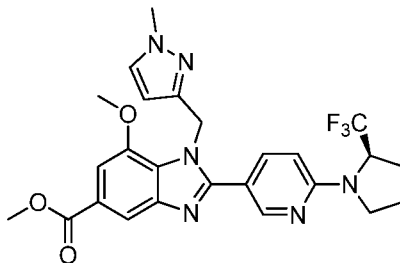
To tert-butyl 3-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (86 mg, 0.165 mmol) was added HCl (2 mL, 65.8 mmol, 1.25 M in CH₃OH), and the reaction mixture was stirred for 2 hour. The mixture was concentrated, and the resulting material was purified by chromatography on SiO₂ with a gradient of 0 to 40% ((80:20:2) CH₂Cl₂:CH₃OH:NH₄OH) in CH₂Cl₂ to afford 3-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine (51 mg) as a white solid after freeze-drying. LC-MS (ES) $m/z = 422$ $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 1.16 (d, $J = 5.6$ Hz, 6H), 1.66 (d, $J = 5.6$ Hz, 2H), 2.16 (br. s., 1H), 2.25 (br. s., 2H), 2.56 - 2.62 (m, 1H), 2.91 - 2.99 (m, 2H), 3.21 - 3.30 (m, 2H), 3.50 (d, $J = 10.7$ Hz, 1H), 3.95 (s, 3H), 4.26 (br. s., 2H), 4.30 - 4.36 (m, 2H), 6.61 (d, $J = 8.9$ Hz, 1H), 6.82 (d, $J = 7.9$ Hz, 1H), 7.10 - 7.15 (m, 1H), 7.20 - 7.25 (m, 1H), 7.86 - 7.91 (m, 1H), 8.47 (dd, $J = 6.1, 2.3$ Hz, 1H).

Intermediate 294Methyl 3-methoxy-4-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)-5-nitrobenzoate

To methyl 4-chloro-3-methoxy-5-nitrobenzoate (1 g, 4.07 mmol) in DMSO (8 mL) were
 5 added (1-methyl-1H-pyrazol-3-yl)methanamine (0.498 g, 4.48 mmol) and K₂CO₃ (0.731 g, 5.29 mmol), and the reaction mixture was stirred at 50 °C for 48 hours. The reaction was quenched with water (25 mL), and the resulting precipitate was collected by filtration and dried in vacuum over to afford crude methyl 3-methoxy-4-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)-5-nitrobenzoate (740 mg) as an orange solid. LC-MS (ES) m/z = 321
 10 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 3.78 (s, 3H), 3.84 (s, 3H), 3.91 (s, 3H), 4.73 (s, 2H), 6.10 (d, *J* = 2.0 Hz, 1H), 7.46 (d, *J* = 1.8 Hz, 1H), 7.61 (d, *J* = 2.0 Hz, 1H), 8.19 (d, *J* = 2.0 Hz, 1H), 8.36 (br. s., 1H).

Intermediate 295

15 Methyl (R)-7-methoxy-1-(((1-methyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-(trifluoromethyl)pyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylate

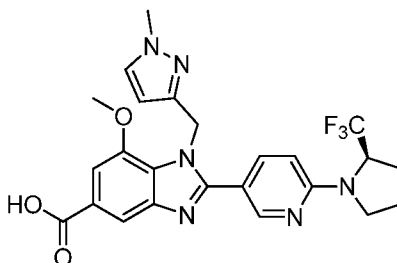


To methyl 3-methoxy-4-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)-5-nitrobenzoate (100 mg, 0.312 mmol) were added (R)-6-(2-(trifluoromethyl)pyrrolidin-1-yl)nicotinaldehyde (76
 20 mg, 0.312 mmol), sodium hydrosulfite (163 mg, 0.796 mmol), ethanol (2 mL), water (1 mL), and the reaction mixture was heated into a sealed vessel under microwave conditions for 1 hour at 130 °C. The reaction was quenched with water (5 mL), and extracted with EtOAc (3 x 10 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ with a gradient of 0 to 35% ((80:20:2) CH₂Cl₂:CH₃OH:NH₄OH) in CH₂Cl₂ afforded methyl (R)-7-methoxy-1-(((1-methyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-(trifluoromethyl)pyrrolidin-1-yl)pyridin-3-yl)-1H-
 25

benzo[d]imidazole-5-carboxylate (92 mg) as an off-white solid. LC-MS (ES) m/z = 515 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 2.05 - 2.21 (m, 4H), 3.41 - 3.50 (m, 1H), 3.67 - 3.72 (m, 1H), 3.73 (s, 3H), 3.88 (s, 3H), 3.92 (s, 3H), 5.10 (t, J = 7.6 Hz, 1H), 5.58 (s, 2H), 5.95 (d, J = 2.3 Hz, 1H), 6.88 (d, J = 8.9 Hz, 1H), 7.34 (d, J = 1.3 Hz, 1H), 7.58 (d, J = 2.3 Hz, 1H), 7.91 (d, J = 1.3 Hz, 1H), 8.10 (dd, J = 8.7, 2.4 Hz, 1H), 8.61 (d, J = 2.3 Hz, 1H).

Intermediate 296

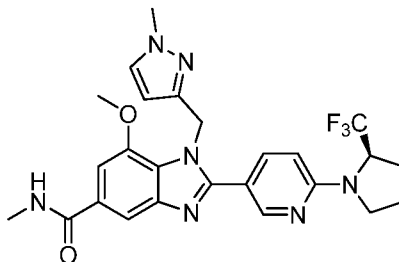
(R)-7-Methoxy-1-((1-methyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-(trifluoromethyl)pyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylic acid



10

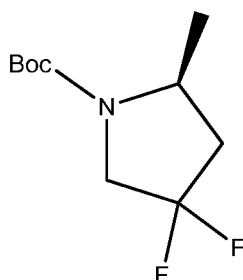
To methyl (R)-7-methoxy-1-((1-methyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-(trifluoromethyl)pyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylate (92 mg, 0.179 mmol) CH_3OH (3 mL) was added 8N NaOH (0.447 mL, 3.58 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction was concentrated, and the mixture was treated with 1N HCl 1M (3.58 mL, 3.58 mmol). The resulting precipitate was collected by filtration and dried in vacuum oven for 4-hours to give crude (R)-7-methoxy-1-((1-methyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-(trifluoromethyl)pyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylic acid (89 mg) as a white solid. LC-MS (ES) m/z = 501 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ 2.06 - 2.19 (m, 4H), 3.40 - 3.51 (m, 1H), 3.70 (d, J = 5.1 Hz, 1H), 3.75 (br. s., 3H), 3.91 (s, 3H), 5.11 (t, J = 6.7 Hz, 1H), 5.58 (s, 2H), 5.96 (d, J = 2.3 Hz, 1H), 6.89 (d, J = 8.9 Hz, 1H), 7.35 (d, J = 1.0 Hz, 1H), 7.58 (d, J = 2.0 Hz, 1H), 7.88 (d, J = 1.3 Hz, 1H), 8.10 (dd, J = 8.7, 2.4 Hz, 1H), 8.61 (d, J = 2.5 Hz, 1H), 12.84 (br. s., 1H).

25

Example 216**(R)-7-Methoxy-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-(trifluoromethyl)pyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide**

- 5 To (R)-7-methoxy-1-((1-methyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-(trifluoromethyl)pyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylic acid (89 mg, 0.178 mmol) in DMSO (1.5 mL) were added methylamine hydrochloride (21.61 mg, 0.320 mmol), EDC (61.4 mg, 0.320 mmol), HOBt (49.0 mg, 0.320 mmol), and N-methylmorpholine (0.117 mL, 1.067 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction
- 10 was quenched with water (5 mL) and extracted with EtOAc (4 x 5 mL). The organic extracts were combined, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ with a gradient of 0 to 40% ((80:20:2) CH₂Cl₂:CH₃OH:NH₄OH) in CH₂Cl₂ afforded (R)-7-methoxy-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-(trifluoromethyl)pyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide (71 mg)
- 15 as a white solid after freeze-drying. LC-MS (ES) m/z = 514 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 2.06 - 2.19 (m, 4H), 2.81 (d, *J* = 4.6 Hz, 3H), 3.40 - 3.50 (m, 1H), 3.67 - 3.72 (m, 1H), 3.73 (s, 3H), 3.90 (s, 3H), 5.06 - 5.15 (m, 1H), 5.56 (s, 2H), 5.93 (d, *J* = 2.3 Hz, 1H), 6.87 (d, *J* = 8.9 Hz, 1H), 7.29 (d, *J* = 1.3 Hz, 1H), 7.57 (d, *J* = 2.0 Hz, 1H), 7.80 (d, *J* = 1.3 Hz, 1H), 8.09 (dd, *J* = 8.9, 2.5 Hz, 1H), 8.43 (d, *J* = 4.6 Hz, 1H), 8.59 (d, *J* = 2.3 Hz, 1H).

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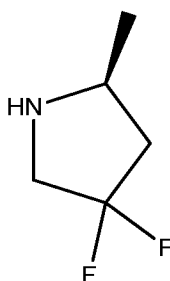
Intermediate 297**(S)-tert-Butyl 4,4-difluoro-2-methylpyrrolidine-1-carboxylate**

- To a solution of (S)-tert-butyl 2-methyl-4-oxopyrrolidine-1-carboxylate (850 mg, 4.27 mmol)
- 25 in 1,2-dichloroethane (20 mL) at 20°C was added DAST (5.64 mL, 42.7 mmol), and the

reaction mixture was stirred in a sealed tube at 60 °C for 3 hours. The reaction mixture was quenched with saturated aqueous NaHCO₃ and washed brine, dried over Na₂SO₄, filtered, and concentrated. The resulting yellow oil was purified by flash chromatography on SiO₂ (2-5% EtOAc/Heptane) to afford the desired product as a light yellow oil. LC-MS (ES) m/z = 166 [M-tert-Butyl+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 4.23 - 4.01 (m, 1H), 3.88 – 3.60 (m, 2H), 2.61 – 2.43 (m, 1H), 2.03 (m, 1H), 1.45 (s, 9H), 1.30 (d, J = 6.4 Hz, 3H).

Intermediate 298

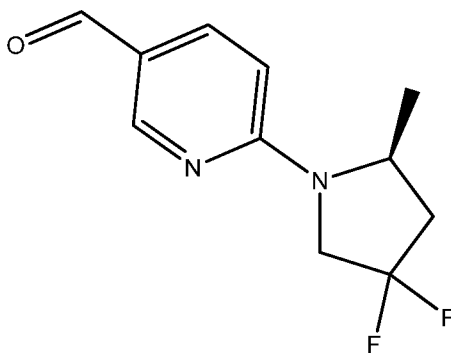
(S)-4,4-Difluoro-2-methylpyrrolidine



To a solution of (S)-tert-butyl 4,4-difluoro-2-methylpyrrolidine-1-carboxylate (500 mg, 2.260 mmol) in CH₂Cl₂ (12 mL) was added HCl (5 mL, 23.99 mmol, 33 wt% in water), and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated to afford the crude product as an HCl salt. LC-MS (ES) m/z = 122 [M+H]⁺.

Intermediate 299

(S)-6-(4,4-Difluoro-2-methylpyrrolidin-1-yl)nicotinaldehyde

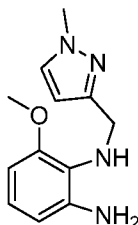


To a solution of (S)-4,4-difluoro-2-methylpyrrolidine hydrochloride (180 mg, 1.142 mmol) and 6-fluoronicotinaldehyde (143 mg, 1.142 mmol) in (DMF) (8 mL) at 20°C was added triethylamine (0.478 mL, 3.43 mmol), and the reaction mixture was stirred at 70 °C for 15

hours. The reaction mixture was concentrated, and the crude product was purified by flash chromatography on SiO₂ (0-15% EtOAc/hexanes) to afford the product (S)-6-(4,4-difluoro-2-methylpyrrolidin-1-yl)nicotinaldehyde (170 mg) as a colorless oil. LC-MS (ES) m/z = 227 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 9.82 (s, 1H), 8.60 (s, 1H), 7.98 (d, J = 8.9 Hz, 1H), 6.44 (d, J = 8.9 Hz, 1H), 4.61 - 4.48 (m, 1H), 4.03 - 3.91 (m, 2H), 2.80 - 2.60 (m, 1H), 2.35 - 2.19 (m, 1H), 1.41 (d, J = 6.4 Hz, 3H).

Intermediate 300

6-Methoxy-N1-((1-methyl-1H-pyrazol-3-yl)methyl)benzene-1,2-diamine



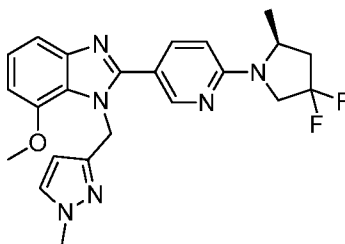
10

To a solution of 2-methoxy-N-((1-methyl-1H-pyrazol-3-yl)methyl)-6-nitroaniline (200 mg, 0.763 mmol) in CH₃OH (20 mL) was added Pd-C (81 mg, 0.076 mmol), and the reaction mixture was stirred under hydrogen atmosphere at room temperature for 2 hours by using a hydrogen balloon. The reaction was filtered, and the filtrate was concentrated. The resulting crude product was purified by flash chromatography on SiO₂ (0-4% CH₃OH in CH₂Cl₂) to afford 6-methoxy-N1-((1-methyl-1H-pyrazol-3-yl)methyl)benzene-1,2-diamine (80 mg) as a light yellow oil. LC-MS (ES) m/z = 233 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.28 (d, J = 1.3 Hz, 1H), 6.85 (t, J = 8.1 Hz, 1H), 6.40 (d, J = 8.0 Hz, 1H), 6.33 (d, J = 8.2 Hz, 1H), 6.18 (d, J = 1.5 Hz, 1H), 4.09 (s, 2H), 3.89 (s, 3H), 3.77 (s, 3H).

20

Example 217

(S)-2-(6-(4,4-Difluoro-2-methylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzod[*h*]imidazole

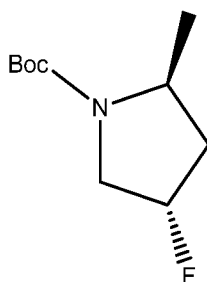


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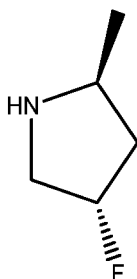
To a solution of 6-methoxy-N1-((1-methyl-1H-pyrazol-3-yl)methyl)benzene-1,2-diamine (80 mg, 0.344 mmol) and (S)-6-(4,4-difluoro-2-methylpyrrolidin-1-yl)nicotinaldehyde (78 mg, 0.344 mmol) in DMF (8 mL) was added sodium metabisulfite (65.5 mg, 0.344 mmol), and the reaction mixture was stirred at 70 °C for 15 hours. The reaction was concentrated, and the resulting crude product was purified by flash chromatography on SiO₂ (0-8% CH₃OH in CH₂Cl₂) to afford (S)-2-(6-(4,4-difluoro-2-methylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole (110 mg) as a light yellow oil. LC-MS (ES) *m/z* = 439 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.57 (d, *J* = 2.1 Hz, 1H), 7.95 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.24 – 7.15 (m, 2H), 6.71 (d, *J* = 7.9 Hz, 1H), 6.44 (d, *J* = 8.8 Hz, 1H), 5.89 (d, *J* = 2.0 Hz, 1H), 5.62 (s, 2H), 4.52 – 4.36 (m, 1H), 3.98 – 3.88 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 2.76 – 2.57 (m, 1H), 2.29 – 2.17 (m, 1H), 1.38 (d, *J* = 6.4 Hz, 3H).

Intermediate 301

(2S,4S)-tert-Butyl 4-fluoro-2-methylpyrrolidine-1-carboxylate

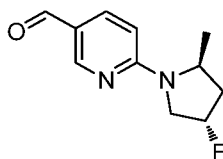


To a solution of tert-butyl (2S,4R)-4-hydroxy-2-methylpyrrolidine-1-carboxylate (1000mg, 4.97 mmol) in CH₂Cl₂ (3 mL) at 0 °C was added DAST (0.788 mL, 5.96 mmol), and the reaction mixture was stirred for 20 minutes at 0 °C followed by 16 hours at room temperature. The reaction was quenched by addition of saturated aqueous NaHCO₃. After stirring for 15 minutes, the aqueous layer was extracted with CH₂Cl₂, and the combined organic extracts were dried over MgSO₄, filtered, and concentrated. Purification by flash chromatography on SiO₂ (0% to 15% EtOAc/hexanes) afforded tert-butyl (2S,4S)-4-fluoro-2-methylpyrrolidine-1-carboxylate (391 mg). ¹H NMR (400 MHz, CDCl₃): δ 4.98 - 5.26 (m, 1H), 3.72 - 4.18 (m, 2H), 3.35 - 3.57 (m, 1H), 2.34 - 2.57 (m, 1H), 1.60 - 1.85 (m, 1H), 1.49 (s, 9H), 1.30 (br. s., 3H).

Intermediate 302(2S,4S)-4-Fluoro-2-methylpyrrolidine

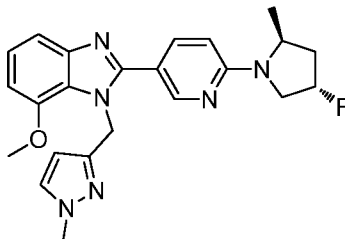
A solution of tert-butyl (2S,4S)-4-fluoro-2-methylpyrrolidine-1-carboxylate (391 mg, 1.924 mmol) and hydrochloric acid (1.443 mL, 5.77 mmol, 4M in dioxane) in CH₂Cl₂ (20 mL) was heated at 40 °C for 2 hours. The reaction was concentrated to afford (2S,4S)-4-fluoro-2-methylpyrrolidine hydrochloride (254 mg) as a tan solid. LC-MS (ES) m/z = 104 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 5.31 - 5.57 (m, 1H), 3.89 - 4.05 (m, 1H), 3.49 - 3.76 (m, 2H), 2.42 - 2.63 (m, 1H), 1.80 - 2.06 (m, 1H), 1.50 (d, J = 6.6 Hz, 3H).

10

Intermediate 3036-((2S,4S)-4-Fluoro-2-methylpyrrolidin-1-yl)nicotinaldehyde

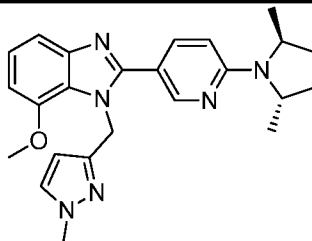
A solution of 6-fluoronicotinaldehyde (228 mg, 1.819 mmol), (2S,4S)-4-fluoro-2-methylpyrrolidine hydrochloride (254 mg, 1.819 mmol), and diisopropylethylamine (1.430 mL, 8.19 mmol) in DMF (20 mL) was heated at 80 °C for 16 hours. The reaction was concentrated, and the resulting material was taken up in EtOAc. The resulting organic mixture was washed with water followed by brine, dried over MgSO₄, filtered, and concentrated. The resulting residue was purified via silica gel chromatography (0% to 25% EtOAc:hexanes) to afford 6-((2S,4S)-4-fluoro-2-methylpyrrolidin-1-yl)nicotinaldehyde (290 mg) as a oil. LC-MS (ES) m/z = 209 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 9.81 (s, 1H), 8.60 (d, J = 2.3 Hz, 1H), 7.96 (dd, J = 2.3, 8.9 Hz, 1H), 6.50 (d, J = 8.9 Hz, 1H), 5.19 - 5.49 (m, 1H), 4.33 - 4.57 (m, 1H), 4.03 - 4.25 (m, 1H), 3.67 - 3.88 (m, 1H), 2.55 - 2.72 (m, 1H), 1.87 - 2.12 (m, 1H), 1.39 (d, J = 6.3 Hz, 3H).

25

Example 218**2-(6-((2S,4S)-4-Fluoro-2-methylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole**

- 5 A mixture of 2-methoxy-N-((1-methyl-1H-pyrazol-3-yl)methyl)-6-nitroaniline (90mg, 0.343 mmol), sodium hydrosulfite (179 mg, 0.874 mmol), and 6-((2S,4S)-4-fluoro-2-methylpyrrolidin-1-yl)nicotinaldehyde (71.5 mg, 0.343 mmol) in ethanol (4 mL) and water (2 mL) was heated under microwave conditions at 130 °C for 1 hour. The reaction was filtered, and the filtrate was concentrated to dryness. Water was then added water, and the resulting
- 10 mixture was extracted with CH₂Cl₂. The combined organic extracts were washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by flash chromatography on SiO₂ (0% to 100% (3:1 (v/v) EtOAc/EtOH):Heptane) afforded 2-(6-((2S,4S)-4-fluoro-2-methylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole (74 mg). LC-MS (ES) m/z = 421 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ
- 15 8.59 (d, J = 2.0 Hz, 1H), 7.95 (d, J = 8.1 Hz, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.15 - 7.26 (m, 2H), 6.73 (d, J = 7.9 Hz, 1H), 6.52 (d, J = 8.9 Hz, 1H), 5.89 (d, J = 2.0 Hz, 1H), 5.66 (d, J = 2.0 Hz, 2H), 5.21 - 5.46 (m, 1H), 4.33 (q, J = 7.1 Hz, 1H), 3.96 - 4.10 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.67 - 3.84 (m, 1H), 2.52 - 2.82 (m, 1H), 1.83 - 2.06 (m, 1H), 1.37 (d, J = 6.1 Hz, 3H).

20

Example 219**2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole**

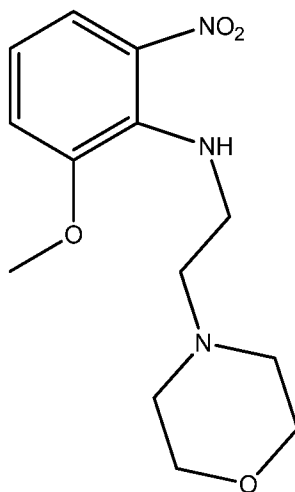
- 25 A mixture of 2-methoxy-N-((1-methyl-1H-pyrazol-3-yl)methyl)-6-nitroaniline (65 mg, 0.248 mmol), 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (55.7 mg, 0.273 mmol), and sodium hydrosulfite (129 mg, 0.744 mmol, 85%) in ethanol (1271 μl) and water (635 μl) was

heated into a sealed vessel at 100 °C over the weekend. The reaction was diluted with water (10 mL) and then extracted with EtOAc (4 x 10 mL). The organic fractions were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated. The resulting material was purified by reverse phase HPLC (15-55% CH₃CN in H₂O (0.1% formic acid)).

- 5 Fractions containing the desired product were taken up in EtOAc, and the resulting mixture was washed with saturated aqueous NaHCO₃ followed by water, dried over Na₂SO₄, filtered, and concentrated to afford the desired product (73 mg) as a clear film. LC-MS (ES) m/z = 417 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 1.21 (d, J = 6.1 Hz, 6H), 1.71 (d, J = 5.6 Hz, 2H), 2.20 - 2.40 (m, 2H), 3.80 - 3.87 (s, 3H), 3.89 (s, 3H), 4.28 (br. s., 2H), 5.68 (d, J = 1.8 Hz, 2H), 5.88 (d, J = 2.3 Hz, 1H), 6.46 (d, J = 8.4 Hz, 1H), 6.66 - 6.78 (m, 1H), 7.13 - 7.28 (m, 2H), 7.44 (dd, J = 8.1, 0.8 Hz, 1H), 7.86 (dd, J = 8.9, 2.5 Hz, 1H), 8.54 (dd, J = 2.5, 0.8 Hz, 1H).
- 10

Intermediate 304

- 15 2-Methoxy-N-(2-morpholinoethyl)-6-nitroaniline

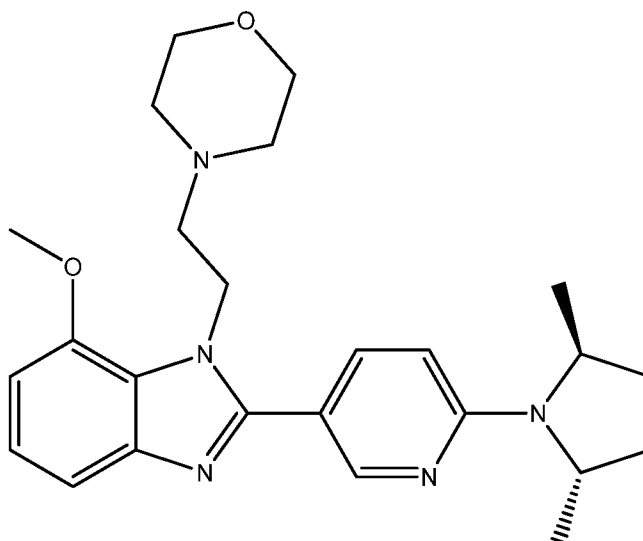


- A solution of 2-fluoro-1-methoxy-3-nitrobenzene (317 mg, 1.852 mmol), 2-morpholinoethan-1-amine (241 mg, 1.852 mmol), and diisopropylethylamine (0.485 mL, 2.78 mmol) in DMF (15 mL) was heated at 60 °C for 16 hours. The mixture was concentrated, and the resulting material was taken up in water and extracted with EtOAc. The combined organic extract was washed with water followed by brine, dried over MgSO₄, filtered, and concentrated. Purification by flash chromatography on SiO₂ (0% to 100% EtOAc:hexanes) afforded 2-methoxy-N-(2-morpholinoethyl)-6-nitroaniline (473 mg) as an orange oil. LC-MS (ES) m/z = 282 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.02 (br. s., 1H),
- 20
- 25

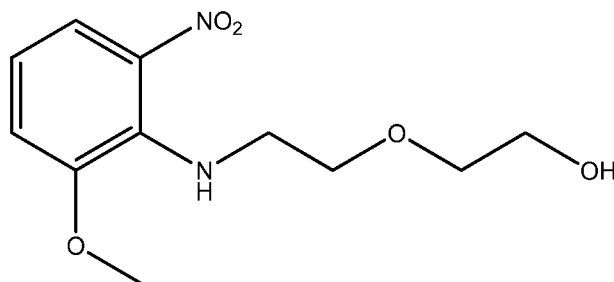
7.75 (dd, $J = 1.4, 8.7$ Hz, 1H), 6.96 (dd, $J = 1.0, 7.9$ Hz, 1H), 6.64 - 6.75 (m, 1H), 3.90 (s, 3H), 3.77 (d, $J = 4.1$ Hz, 4H), 3.68 (d, $J = 5.3$ Hz, 2H), 2.60 (br. s., 2H), 2.51 (br. s., 4H).

Example 220

5 **4-(2-(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)ethyl)morpholine**



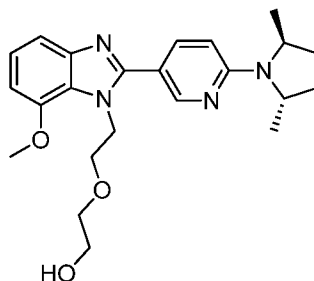
A mixture of 2-methoxy-N-(2-morpholinoethyl)-6-nitroaniline (68 mg, 0.242 mmol), sodium hydrosulfite (126mg, 0.615 mmol), and 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (49.4 mg, 0.242 mmol) in ethanol (4 mL) and water (2 mL) was heated under microwave conditions at 130 °C for 105 minutes. The reaction mixture was concentrated to dryness, and the resulting material was taken up in water and extracted with EtOAc. The combined organic extract was washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by flash chromatography on SiO₂ (0% to 100% (3:1 EtOAc/EtOH):Heptane) afforded 4-(2-(2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)ethyl)morpholine (34.3 mg) as a white solid after freeze drying. LC-MS (ES) $m/z = 436$ [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 8.45 (d, $J = 1.8$ Hz, 1H), 7.85 (dd, $J = 2.5, 8.9$ Hz, 1H), 7.14 - 7.35 (m, 2H), 6.87 (dd, $J = 0.9, 7.7$ Hz, 1H), 6.71 (d, $J = 8.6$ Hz, 1H), 4.61 (t, $J = 6.6$ Hz, 2H), 4.3 (br. s., 2H), 4.02 (s, 3H), 3.47 - 3.58 (m, 4H), 2.72 (m, 2H), 2.29 - 2.43 (m, 5H), 1.76 (d, $J = 5.8$ Hz, 2H), 1.23 (d, $J = 6.1$ Hz, 6H).

Intermediate 3052-(2-((2-Methoxy-6-nitrophenyl)amino)ethoxy)ethan-1-ol

- 5 A solution of 2-(2-aminoethoxy)ethan-1-ol (135 mg, 1.286 mmol), 2-fluoro-1-methoxy-3-nitrobenzene (200 mg, 1.169 mmol), and diisopropylethylamine (0.306 mL, 1.753 mmol) in DMF (10 mL) was heated at 80 °C for 16 hours. The reaction was concentrated, and the resulting material was purified by flash chromatography on SiO₂ (0% to 50% EtOAc/hexanes) to afford 2-(2-((2-methoxy-6-nitrophenyl)amino)ethoxy)ethan-1-ol (281
- 10 mg) as a orange/red oil. LC-MS (ES) m/z = 257 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.76 (dd, J = 1.4, 8.7 Hz, 1H), 6.99 (dd, J = 1.5, 7.9 Hz, 1H), 6.74 (dd, J = 7.9, 8.6 Hz, 1H), 3.91 (s, 3H), 3.76 - 3.81 (m, 4H), 3.66 - 3.72 (m, 2H), 3.58 - 3.64 (m, 2H).

Example 221

- 15 2-(2-(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)ethoxy)ethan-1-ol

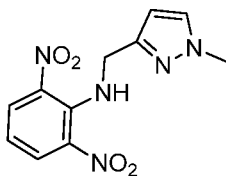


- A mixture of 2-(2-((2-methoxy-6-nitrophenyl)amino)ethoxy)ethan-1-ol (140mg, 0.546 mmol), sodium hydrosulfite (285 mg, 1.391 mmol), and 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (112 mg, 0.546 mmol) in ethanol (4 mL) and water (2mL) was heated under microwave conditions at 130 °C for 1 hour. The reaction mixture was concentrated to dryness, and the resulting material was taken up in water and extracted with CH₂Cl₂. The combined organic extract was washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by flash chromatography on SiO₂ (0% to 100% (3:1
- 25 EtOAc:EtOH)/Heptane) afforded 2-(2-(2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-

yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)ethoxy)ethan-1-ol (80 mg) as a white solid/foam after freeze-drying. LC-MS (ES) $m/z = 411$ $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 8.48 - 8.55 (m, 1H), 7.98 (dd, $J = 2.4, 9.0$ Hz, 1H), 7.17 - 7.30 (m, 2H), 6.87 (dd, $J = 0.9, 7.7$ Hz, 1H), 6.69 (d, $J = 9.1$ Hz, 1H), 4.61 (t, $J = 5.3$ Hz, 2H), 4.32 (br. s., 2H), 4.01 (s, 3H), 3.92 (t, $J = 5.5$ Hz, 2H), 3.53 - 3.60 (m, 2H), 3.36 - 3.42 (m, 2H), 2.31 - 2.40 (m, 2H), 1.75 (d, $J = 5.8$ Hz, 2H), 1.23 (d, $J = 6.3$ Hz, 6H).

Intermediate 306

N-((1-Methyl-1H-pyrazol-3-yl)methyl)-2,6-dinitroaniline



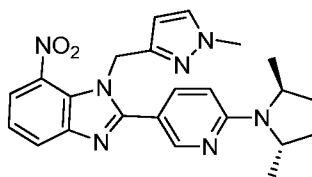
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A solution of 2-chloro-1,3-dinitrobenzene (700 mg, 3.46 mmol), (1-methyl-1H-pyrazol-3-yl)methanamine (403 mg, 3.63 mmol), and triethylamine (0.530 mL, 3.80 mmol) in DMF (10 mL) was stirred at room temperature overnight. The reaction was quenched with water (30 mL), and the resulting mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated. The resulting residue was purified by silica gel chromatography (0% - 50% EtOAc/hexanes) to afford N-((1-methyl-1H-pyrazol-3-yl)methyl)-2,6-dinitroaniline (821 mg) as a yellow solid. LCMS (ES) $m/z = 278$. ^1H NMR (400 MHz, $DMSO-d_6$): δ 8.65 (t, $J = 4.8$ Hz, 1H), 8.30 (d, $J = 8.4$ Hz, 2H), 7.63 (d, $J = 2.0$ Hz, 1H), 6.94 (t, $J = 8.1$ Hz, 1H), 6.15 (d, $J = 2.3$ Hz, 1H), 4.14 (d, $J = 4.8$ Hz, 2H), 3.79 (s, 3H).

20

Intermediate 307

2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-7-nitro-1H-benzo[d]imidazole



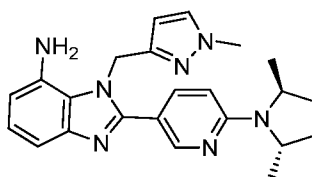
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A solution of N-((1-methyl-1H-pyrazol-3-yl)methyl)-2,6-dinitroaniline (752 mg, 2.71 mmol), 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (593 mg, 2.90 mmol), and sodium hydrosulfite (1417 mg, 8.14 mmol) in ethanol (15 mL) and water (3.75 mL) was heated under microwave conditions at 100 °C for 1 hour. The mixture was filtered, and the filtrate

was concentrated. The resulting residue was partitioned between CH₂Cl₂ (20 mL) and water (14 mL). The layers were separated, and the aqueous layer was further extracted with CH₂Cl₂ (2 x 18 mL). The combined organic extracts were washed with brine (3 mL), dried over Na₂SO₄, filtered, and concentrated. The resulting residue was purified by silica gel chromatography (0% - 100% (0.1% NH₄OH in 3:1 EtOAc:EtOH)/hexanes) to afford 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-7-nitro-1H-benzo[d]imidazole (225 mg) as a light tan solid. LCMS (ES) m/z = 432 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.64 (s, 1H), 8.06 (dd, J = 1.0, 7.9 Hz, 1H), 7.90 (dd, J = 2.5, 8.9 Hz, 1H), 7.82 (dd, J = 1.0, 8.1 Hz, 1H), 7.36 - 7.32 (m, 1H), 7.15 (d, J = 2.3 Hz, 1H), 6.54 (d, J = 8.6 Hz, 1H), 5.75 (d, J = 2.0 Hz, 1H), 5.70 (s, 2H), 3.75 (s, 3H), 2.39 - 2.27 (m, 2H), 1.80 (br. s., 2H), 1.74 (d, J = 5.8 Hz, 2H), 1.28 - 1.20 (m, 6H).

Example 222

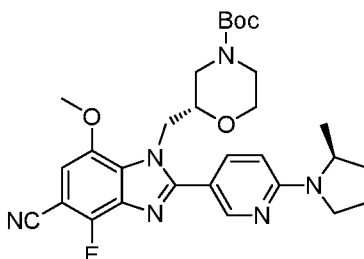
2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-7-amine



To a solution of 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-7-nitro-1H-benzo[d]imidazole (220 mg, 0.510 mmol) in CH₃OH (15 mL) was added Pd-C (54.3 mg, 0.510 mmol), and the reaction mixture was stirred under a hydrogen atmosphere overnight at room temperature. The mixture was filtered to remove the Pd-C, and the filtrate was concentrated. The resulting residue was purified by silica gel chromatography (5% - 100% (0.1% NH₄OH in 3:1 EtOAc:EtOH)/hexanes) to afford 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-7-amine (93 mg) as a white foam. LCMS (ES) m/z = 402 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.38 (d, J = 1.8 Hz, 1H), 7.78 (dd, J = 2.4, 8.7 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 6.96 - 6.86 (m, J = 1.5 Hz, 2H), 6.60 (d, J = 8.9 Hz, 1H), 6.48 (dd, J = 1.1, 7.2 Hz, 1H), 6.01 (d, J = 2.0 Hz, 1H), 5.48 (s, 2H), 4.99 (s, 2H), 4.24 (br. s., 2H), 3.81 (s, 3H), 3.31 (s, 1H), 2.24 (s, 1H), 1.65 (d, J = 5.6 Hz, 2H), 1.14 (d, J = 6.1 Hz, 6H).

Intermediate 308

tert-Butyl (R)-2-((5-cyano-4-fluoro-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate



5

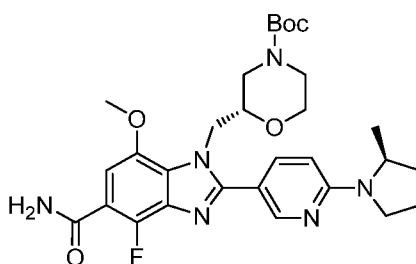
To tert-butyl (R)-2-((5-bromo-4-fluoro-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (411 mg, 0.680 mmol) in DMF (10 mL) was bubbled N₂ for 5 minutes. Pd₂(dba)₃ (187 mg, 0.204 mmol), Davephos (80 mg, 0.204 mmol), and zinc cyanide (159 mg, 1.360 mmol) were then added, and the reaction mixture was then capped and heated at 85 °C overnight. The reaction was filtered over celite, and the filtrate was diluted with water (30 mL) and extracted with EtOAc (3 x 20 mL). The organic extracts were combined and washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ with a gradient of 0 to 60% EtOAc in hexanes afforded tert-butyl (R)-2-((5-cyano-4-fluoro-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (310 mg) as a clear oil. LC-MS (ES) m/z = 551 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.18 - 1.22 (m, 3H), 1.40 (s, 9H), 1.67 - 1.77 (m, 1H), 1.95 - 2.12 (m, 3H), 2.46 - 2.49 (m, 1H), 2.58 - 2.66 (m, 1H), 3.21 (m, 1H), 3.35 - 3.40 (m, 1H), 3.57 (dd, *J* = 10.1, 7.6 Hz, 1H), 3.61 - 3.85 (m, 4H), 4.00 (s, 3H), 4.25 (d, *J* = 5.6 Hz, 1H), 4.37 (dd, *J* = 15.0, 8.1 Hz, 1H), 4.55 (dd, *J* = 14.7, 2.3 Hz, 1H), 6.61 (d, *J* = 8.9 Hz, 1H), 7.22 (d, *J* = 4.1 Hz, 1H), 7.94 - 7.99 (m, 1H), 8.56 (d, *J* = 2.0 Hz, 1H).

20

Intermediate 309

tert-Butyl (R)-2-((5-carbamoyl-4-fluoro-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate

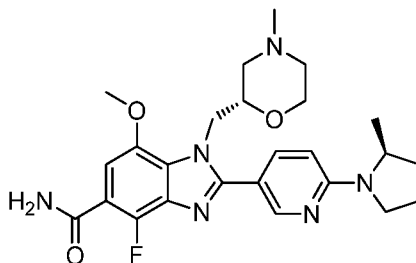
25



To tert-butyl (R)-2-((5-cyano-4-fluoro-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (1.1 g, 1.998 mmol) in DMSO (8 mL) and ethanol (8 mL) was added 1N NaOH (2.4 mL, 2.4 mmol) followed by H₂O₂ (0.37 mL, 3.60 mmol, 30% in water) dropwise, and the reaction mixture was stirred for 10 minutes. Water (50 mL) was then added (gummy solid formed), and the resulting mixture was extracted with EtOAc (4 x 50 mL). The organic extracts were then combined and washed with brine, dried over MgSO₄, filtered, and concentrated to give crude tert-butyl (R)-2-((5-carbamoyl-4-fluoro-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (1.32 g) as a beige color oil. LC-MS (ES) m/z = 569 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.18 - 1.22 (m, 3H), 1.39 (s, 9H), 1.72 (d, *J* = 3.0 Hz, 1H), 1.95 - 2.02 (m, 1H), 2.02 - 2.11 (m, 2H), 2.46 - 2.49 (m, 1H), 3.16 - 3.25 (m, 1H), 3.37 (br. s., 1H), 3.57 (dd, *J* = 9.9, 7.6 Hz, 1H), 3.60 - 3.81 (m, 4H), 3.97 (s, 3H), 4.20 - 4.27 (m, 1H), 4.35 (dd, *J* = 15.0, 7.6 Hz, 1H), 4.47 - 4.54 (m, 1H), 6.60 (d, *J* = 9.1 Hz, 1H), 7.06 (d, *J* = 4.8 Hz, 1H), 7.62 (d, *J* = 14.7 Hz, 2H), 7.95 (dd, *J* = 8.7, 2.4 Hz, 1H), 8.54 (d, *J* = 2.3 Hz, 1H).

Example 223

4-Fluoro-7-methoxy-1-(((S)-4-methylmorpholin-2-yl)methyl)-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide

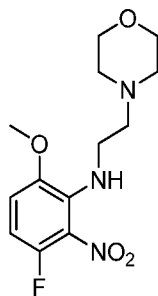


To tert-butyl (R)-2-((5-carbamoyl-4-fluoro-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (1.08 g, 1.9 mmol) in CH₂Cl₂ (10 mL) was added TFA (4 mL, 51.9 mmol), and the reaction mixture was stirred for 1 hour at room temperature. Saturated aqueous NaHCO₃ was then added, and the resulting basic mixture was extracted sequentially with EtOAc (2 x 30 mL), 20% isopropanol in CH₂Cl₂ (2 x 50 mL), and EtOAc (2 x 30 mL). The extracts were combined and washed with brine, dried over MgSO₄, filtered, and concentrated. To the resulting solid was added 1,2-dichloroethane (20 mL), acetic acid (0.326 mL, 5.70 mmol), and formaldehyde (0.717 mL, 9.50 mmol, 36.5% in water), and the resulting mixture was stirred for 10 minutes. Sodium triacetoxyborohydride (1409 mg, 6.65 mmol) was then added, and

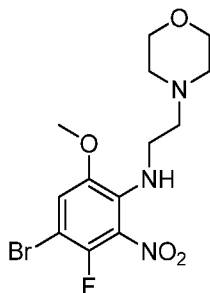
the reaction mixture was stirred for 45 minutes. Saturated aqueous NaHCO_3 was then added, and the resulting basic mixture was extracted with CH_2Cl_2 (2 x 30 mL) followed by EtOAc (2 x 30 mL). The organic extracts were combined and washed with brine, dried over MgSO_4 , filtered, and concentrated. Purification by chromatography on SiO_2 with a gradient of 0 to 50% (80:20:2 CH_2Cl_2 : CH_3OH : NH_4OH) in CH_2Cl_2 afforded 4-fluoro-7-methoxy-1-(((S)-4-methylmorpholin-2-yl)methyl)-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide (520 mg) as a white solid after freeze-drying. LC-MS (ES) m/z = 483 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 1.18 - 1.22 (m, 3H), 1.65 - 1.74 (m, 2H), 1.89 - 2.02 (m, 2H), 2.03 - 2.12 (m, 2H), 2.14 (s, 3H), 2.49 (br. s., 1H), 2.60 (d, J = 10.9 Hz, 1H), 3.27 (m, 1H), 3.35 - 3.40 (m, 1H), 3.53 - 3.60 (m, 1H), 3.65 (d, J = 10.7 Hz, 1H), 3.74 - 3.81 (m, 1H), 3.96 (s, 3H), 4.20 - 4.28 (m, 1H), 4.34 (dd, J = 14.7, 8.6 Hz, 1H), 4.43 - 4.50 (m, 1H), 6.59 (d, J = 8.9 Hz, 1H), 7.05 (d, J = 4.6 Hz, 1H), 7.62 (d, J = 13.9 Hz, 2H), 7.95 (dd, J = 8.9, 2.3 Hz, 1H), 8.52 (d, J = 2.0 Hz, 1H).

15 Intermediate 310

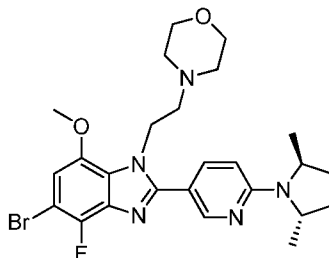
3-Fluoro-6-methoxy-N-(2-morpholinoethyl)-2-nitroaniline



To 1,3-difluoro-4-methoxy-2-nitrobenzene (1 g, 5.29 mmol) in DMSO (15 mL) were added 2-morpholinoethan-1-amine (0.688 g, 5.29 mmol) and K_2CO_3 (1.096 g, 7.93 mmol), and the reaction mixture was heated for 4 hours at 50 °C. Water (50 mL) was then added, and the resulting mixture was extracted with EtOAc (3 x 50mL). The organic extracts were then combined, washed with Brine, dried over MgSO_4 , filtered and concentrated. Purification by chromatography on SiO_2 with a gradient of 0 to 70% EtOAc in hexane to afforded 3-fluoro-6-methoxy-N-(2-morpholinoethyl)-2-nitroaniline (1.5 g, 5.01 mmol, 95 % yield) as a deep red oil. LC-MS (ES) m/z = 300 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 2.45 - 2.50 (m, 4H), 2.58 (dd, J = 6.3, 5.3 Hz, 2H), 3.26 (m, 2H), 3.73 - 3.77 (m, 4H), 3.90 (s, 3H), 6.06 (br. s., 1H), 6.50 (dd, J = 9.9, 9.1 Hz, 1H), 6.78 (dd, J = 9.0, 4.7 Hz, 1H).

Intermediate 3114-Bromo-3-fluoro-6-methoxy-N-(2-morpholinoethyl)-2-nitroaniline

To 3-fluoro-6-methoxy-N-(2-morpholinoethyl)-2-nitroaniline (940 mg, 3.14 mmol) in CH₂Cl₂ (45 mL) was added NBS (838 mg, 4.71 mmol), and the reaction mixture was stirred at room temperature for 1 hour. Additional NBS (838 mg, 4.71 mmol) was added, and the reaction mixture was stirred overnight. Water (50 mL) was then added, and the resulting mixture was extracted with EtOAc (4 x 30 mL). The organic extracts were combined and washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ with a gradient of 0 to 50% EtOAc in hexanes afforded 4-bromo-3-fluoro-6-methoxy-N-(2-morpholinoethyl)-2-nitroaniline (250 mg) as a bright red oil. LC-MS (ES) m/z = 379 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 2.33 (br. s., 4H), 2.44 - 2.48 (m, 2H), 3.10 (m, 2H), 3.52 - 3.57 (m, 4H), 3.89 (s, 3H), 6.19 (s, 1H), 7.30 (d, *J* = 6.3 Hz, 1H).

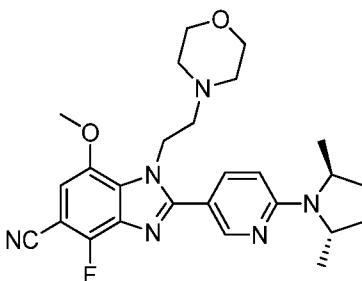
15 Intermediate 3124-(2-(5-Bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1H-benzo[d]imidazol-1-yl)ethyl)morpholine

To 4-bromo-3-fluoro-6-methoxy-N-(2-morpholinoethyl)-2-nitroaniline (360 mg, 0.952 mmol) in DMSO (10 mL) and water (2 mL) were added 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (214 mg, 1.047 mmol) and sodium hydrosulfite (585 mg, 2.86 mmol), and the reaction was heated at 97 °C for 2 hour. Water (20 mL) was then added, and the resulting mixture was extracted with EtOAc (4 x 20 mL). The organic extracts were combined and washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ with a gradient of 0 to 100% EtOAc in hexanes afforded 4-(2-

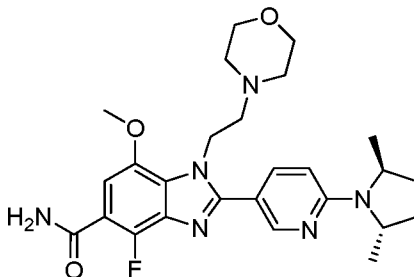
(5-bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1H-benzo[d]imidazol-1-yl)ethyl)morpholine (220 mg) as a slight beige solid. LC-MS (ES) m/z = 533 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.22 (d, J = 6.3 Hz, 6H), 1.76 (d, J = 5.6 Hz, 2H), 2.26 - 2.30 (m, 4H), 2.32 - 2.38 (m, 2H), 2.69 (m, 2H), 3.48 - 3.52 (m, 4H), 4.00 (s, 3H), 4.32 (br. s., 2H), 4.58 (m, 2H), 6.70 (d, J = 8.9 Hz, 1H), 6.97 (d, J = 4.8 Hz, 1H), 7.86 (dd, J = 9.0, 2.4 Hz, 1H), 8.45 - 8.48 (m, 1H).

Intermediate 313

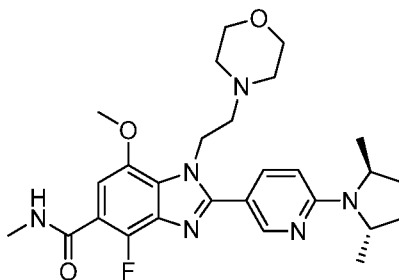
2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1-(2-morpholinoethyl)-1H-benzo[d]imidazole-5-carbonitrile



To 4-(2-(5-bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1H-benzo[d]imidazol-1-yl)ethyl)morpholine (110 mg, 0.207 mmol) in DMF (5 mL) was bubbled N_2 gas for 5 minutes. $Pd_2(dba)_3$ (56.8 mg, 0.062 mmol), Davephos (24.39 mg, 0.062 mmol), and zinc cyanide (48.3 mg, 0.413 mmol) were added, and the reaction mixture was capped and then heated over at 80 °C overnight. The reaction was filtered over celite, and the filtrate was diluted with water (30 mL) and extracted with EtOAc (3 x 30 mL). The organic extracts were combined and washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by chromatography on SiO_2 with a gradient of 0 to 40% (20:80 $CH_3OH:CH_2Cl_2$) in CH_2Cl_2 afforded 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1-(2-morpholinoethyl)-1H-benzo[d]imidazole-5-carbonitrile (90 mg) as a clear oil. LC-MS (ES) m/z = 479 $[M+H]^+$. ^1H NMR (400 MHz, $DMSO-d_6$): δ 1.14 (d, J = 6.1 Hz, 6H), 1.66 (d, J = 5.6 Hz, 2H), 2.13 - 2.21 (m, 4H), 2.25 (br. s., 2H), 2.53 - 2.63 (m, 2H), 3.34 - 3.41 (m, 4H), 3.99 (s, 3H), 4.26 (br. s., 2H), 4.45 - 4.54 (m, 2H), 6.62 - 6.67 (m, 1H), 7.20 (d, J = 4.1 Hz, 1H), 7.89 (dd, J = 8.9, 2.5 Hz, 1H), 8.51 (d, J = 2.0 Hz, 1H).

Example 224**2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1-(2-morpholinoethyl)-1H-benzo[d]imidazole-5-carboxamide**

5 To 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1-(2-morpholinoethyl)-1H-benzo[d]imidazole-5-carbonitrile (90 mg, 0.188 mmol) in DMSO (2 mL) was added K_2CO_3 (5.20 mg, 0.038 mmol) followed by hydrogen peroxide (0.192 mL, 1.881 mmol, 30% in water), and the reaction mixture was stirred overnight at room temperature. The reaction was filtered, and the filtrate was purified by reverse phase HPLC
 10 (30-85% CH_3CN in (0.1 % NH_4OH in water)) to afford 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1-(2-morpholinoethyl)-1H-benzo[d]imidazole-5-carboxamide (55 mg) as a white solid after freeze-drying. LC-MS (ES) m/z = 497 $[M+H]^+$. ^1H NMR (400 MHz, $DMSO-d_6$): δ 1.14 (d, J = 6.1 Hz, 6H), 2.17 (d, J = 4.1 Hz, 4H), 2.25 (br. s., 2H), 2.54 - 2.61 (m, 2H), 3.31 (s, 2H), 3.37 (d, J = 4.3 Hz, 4H), 3.96 (s, 3H), 4.26 (br. s.,
 15 2H), 4.49 (t, J = 6.2 Hz, 2H), 6.63 (d, J = 8.6 Hz, 1H), 7.04 (d, J = 4.6 Hz, 1H), 7.61 (d, J = 15.0 Hz, 2H), 7.88 (dd, J = 8.9, 2.5 Hz, 1H), 8.49 (d, J = 1.8 Hz, 1H).

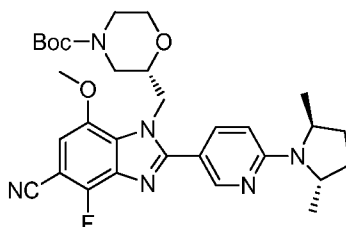
Example 225**2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-N-methyl-1-(2-morpholinoethyl)-1H-benzo[d]imidazole-5-carboxamide**

To NMP (2 mL) previously degassed with N_2 for 5 minutes were added potassium 2-ethoxy-2-oxoacetate (88 mg, 0.563 mmol), 4-(2-(5-bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1H-benzo[d]imidazol-1-yl)ethyl)morpholine (100 mg,
 25 0.188 mmol), 1,3-bis(diphenylphosphino)propane (23.24 mg, 0.056 mmol), and

palladium(II) trifluoroacetate (18.73 mg, 0.056 mmol), and the reaction mixture was heated under microwave conditions for 2 hours at 120 °C. The reaction was then filtered, and the filtrate was treated with 8N NaOH (0.235 mL, 1.878 mmol) and CH₃OH (1 mL). The resulting mixture was stirred at room temperature overnight. The reaction was concentrated under
 5 reduce pressure, and the resulting material was diluted with water (10 mL) and extracted with 20% isopropanol in CH₂Cl₂ (3 x 10 mL). The aqueous layer was partially concentrated to remove any volatile organic solvent, and then treated with 6N HCl until pH was slightly acidic. The resulting mixture was freeze dried to give crude 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1-(2-morpholinoethyl)-1H-
 10 benzo[d]imidazole-5-carboxylic acid (230 mg) as a brown solid. To this material in DMSO (2 mL) were added EDC (54.0 mg, 0.282 mmol), HOBT (43.1 mg, 0.282 mmol), methylamine hydrochloride (25.4 mg, 0.376 mmol), and N-methylmorpholine (0.145 mL, 1.315 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction was filtered, and the filtrate was purified by reverse phase HPLC (50-80% CH₃CN in (0.1%
 15 NH₄OH in water)) to afford 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-N-methyl-1-(2-morpholinoethyl)-1H-benzo[d]imidazole-5-carboxamide (10 mg) as an off-white solid after freeze-drying. LC-MS (ES) m/z = 511 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.14 (d, *J* = 6.1 Hz, 6H), 1.66 (d, *J* = 5.3 Hz, 2H), 2.17 (d, *J* = 4.1 Hz, 4H), 2.25 (br. s., 2H), 2.54 - 2.61 (m, 2H), 2.82 (d, *J* = 4.6 Hz, 3H), 3.35 - 3.40 (m, 4H), 3.95 (s,
 20 3H), 4.26 (br. s., 2H), 4.49 (t, *J* = 6.5 Hz, 2H), 6.63 (d, *J* = 8.9 Hz, 1H), 6.99 (d, *J* = 4.6 Hz, 1H), 7.87 (dd, *J* = 8.9, 2.5 Hz, 1H), 8.11 - 8.19 (m, 1H), 8.48 (d, *J* = 2.0 Hz, 1H).

Intermediate 314

tert-Butyl (R)-2-((5-cyano-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-
 25 methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate



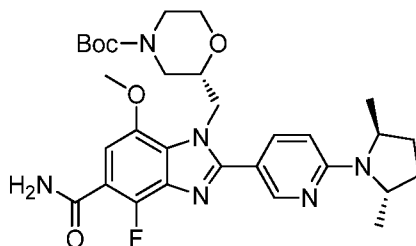
A mixture of tert-butyl (R)-2-((5-bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (2.10 g, 3.40 mmol), Zn(CN)₂ (0.797 g, 6.79 mmol), and N-methyl-2-pyrrolidone (10 mL) was
 30 degassed into a sealable vessel for 10 minutes by bubbling nitrogen. Pd(PPh₃)₄ (0.588 g, 0.509 mmol) was added, the vessel was sealed, and the reaction mixture was stirred at 110

°C for 18 hours. The mixture was cooled, quenched with water (30 mL,) and extracted with EtOAc (3x). The combined organic extract was dried (Na₂SO₄) and concentrated. The resulting residue was purified by column chromatography on silica gel (gradient: 0 to 80% EtOAc/heptane) to give the desired product (1.52 g) as a white solid. LC-MS (ES) m/z = 565 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.23 (d, J = 6.3 Hz, 6H), 1.42 - 1.56 (m, 9H), 1.69 - 1.84 (m, 2H), 2.29 - 2.45 (m, 2H), 2.70 (br. s., 1H), 2.95 (br. s., 1H), 3.77 - 3.92 (m, 3H), 3.94 - 4.12 (m, 4H), 4.25 - 4.48 (m, 3H), 4.62 (dd, J = 14.8, 2.7 Hz, 1H), 6.69 (d, J = 8.6 Hz, 1H), 7.07 (d, J = 4.1 Hz, 1H), 7.96 (dd, J = 8.9, 2.5 Hz, 1H), 8.58 (d, J = 2.0 Hz, 1H).

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Intermediate 315

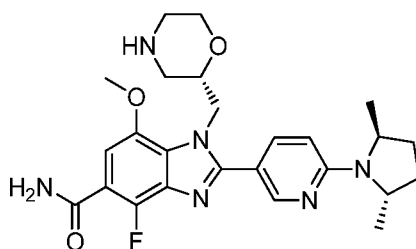
tert-Butyl (R)-2-((5-carbamoyl-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate



To a solution of tert-butyl (R)-2-((5-cyano-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (2.51 g, 4.45 mmol) in DMSO (13 mL) and ethanol (13 mL) was added aqueous NaOH (1N, 5.33 mL, 5.33 mmol), followed by the dropwise addition of H₂O₂ (30%, 0.817 mL, 8.00 mmol), and the reaction mixture was stirred for 1 hour at room temperature. Water (50 mL) was added, and the mixture was stirred for a few minutes and then filtered. The solid was washed with water and dried under vacuum to give the desired product (2.31 g) as a white solid. LC-MS (ES) m/z = 583 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.23 (d, J = 6.3 Hz, 6H), 1.43 - 1.54 (m, 9H), 1.70 - 1.83 (m, 2H), 2.27 - 2.43 (m, 2H), 2.63 - 2.79 (m, 3H), 2.96 (br. s., 1H), 3.03 (s, 1H), 3.78 - 3.94 (m, 3H), 3.95 - 4.13 (m, 4H), 4.25 (br. s., 1H), 4.39 (d, J = 8.4 Hz, 1H), 4.35 (d, J = 8.4 Hz, 2H), 4.60 (dd, J = 14.7, 2.8 Hz, 1H), 5.51 (s, 1H), 6.69 (d, J = 9.1 Hz, 1H), 7.28 (d, J = 4.8 Hz, 1H), 7.96 (dd, J = 9.0, 2.4 Hz, 1H), 8.57 (d, J = 2.0 Hz, 1H).

Intermediate 316

2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1-((S)-morpholin-2-ylmethyl)-1H-benzo[d]imidazole-5-carboxamide



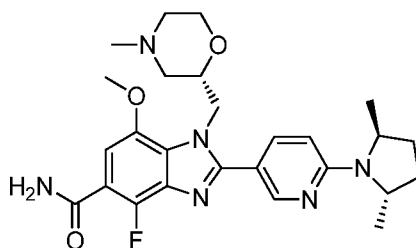
5

To a solution of tert-butyl (R)-2-((5-carbamoyl-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (2.3 g, 3.95 mmol) in CH₂Cl₂ (20 mL) was added TFA (6.0 mL, 78 mmol), and the reaction mixture was stirred at room temperature for 4 hours. The mixture was concentrated, and the resulting residue was dried under vacuum for 1 hour. The residue was treated with aqueous HCl (6N, 10 mL) and concentrated. The residue was treated with CH₂Cl₂ (30 mL) and saturated aqueous NaHCO₃ solution (50 mL), and the resulting mixture was extracted with 10% CH₃OH in CH₂Cl₂ (3x). The combined organic extract was dried (Na₂SO₄) and concentrated under vacuum to give the desired product (1.85 g) as a white solid. LC-MS (ES) m/z = 483 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.18 - 1.27 (m, 6H), 1.70 - 1.83 (m, 2H), 2.26 - 2.43 (m, 2H), 2.48 - 2.60 (m, 1H), 2.71 - 2.86 (m, 2H), 2.93 (dd, J = 12.4, 1.8 Hz, 1H), 3.38 - 3.48 (m, 1H), 3.80 (dd, J = 11.7, 2.0 Hz, 1H), 3.93 - 4.02 (m, 1H), 4.04 (s, 3H), 4.31 (dd, J = 14.7, 8.9 Hz, 3H), 4.49 - 4.58 (m, 1H), 6.68 (d, J = 8.9 Hz, 1H), 7.26 (d, J = 4.8 Hz, 1H), 7.92 - 7.99 (m, 1H), 8.54 - 8.61 (m, 1H).

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Example 226

2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1-(((S)-4-methylmorpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide

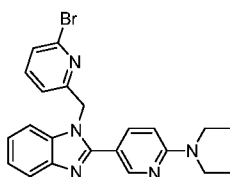


To a solution of 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1-(((S)-morpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide (1.83 g, 3.79 mmol) in 1,2-dichloroethane (24 mL) were added formaldehyde (36.5% in water, 1.431 mL, 18.96

mmol) and acetic acid (0.651 mL, 11.38 mmol), and the mixture was stirred at room temperature for 10 minutes. Sodium triacetoxyborohydride (2.81 g, 13.27 mmol) was added, and the reaction mixture was stirred at room temperature for 2 hours. The reaction was quenched with saturated aqueous NaHCO₃ (30 mL) followed by addition of saturated aqueous Na₂CO₃ until pH = 10, and extracted with CH₂Cl₂ (3x). The combined organic extract was dried over Na₂SO₄, filtered, and concentrated. The resulting residue was purified by column chromatography on silica gel (gradient: 0-100% (90:10:1 CH₂Cl₂:CH₃OH:NH₄OH)/heptane) to give the desired product (1.48 g) as a white solid. LC-MS (ES) m/z = 493 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): δ 1.23 - 1.32 (m, 6H), 1.79 - 1.96 (m, 2H), 2.00 - 2.27 (m, 4H), 2.32 (s, 3H), 2.67 (d, J = 11.7 Hz, 1H), 2.84 (d, J = 11.1 Hz, 1H), 3.39 - 3.54 (m, 4H), 3.61 - 3.70 (m, 1H), 3.82 (dd, J = 11.8, 1.9 Hz, 1H), 3.99 - 4.13 (m, 4H), 4.22 - 4.41 (m, 2H), 4.58 (dd, J = 14.4, 2.8 Hz, 1H), 6.67 (d, J = 8.9 Hz, 1H), 7.37 (d, J = 1.3 Hz, 1H), 7.79 (d, J = 1.5 Hz, 1H), 7.96 (dd, J = 9.0, 2.4 Hz, 1H), 8.54 (d, J = 2.5 Hz, 1H).

Example 227

5-(1-((6-Bromopyridin-2-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine

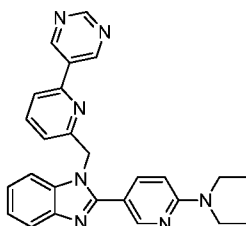


To a solution of 5-(1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (100 mg, 0.38 mmol) in DMF (3.7 mL) cooled to 0 °C was added NaH (60% dispersion in oil, 19.5 mg, 0.49 mmol). After 5 minutes, 2-bromo-6-(bromomethyl)pyridine (104 mg, 0.41 mmol) was added, and the reaction mixture was warmed to room temperature. After 30 minutes, the reaction was quenched with saturated aqueous NH₄Cl (2 mL) and diluted with EtOAc (20 mL) and water (20 mL). The phases were separated, and the aqueous layer was further extracted with EtOAc (2 x 20 mL). The combined organic extract was washed with water (20 mL) and brine (50 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 10 to 100% EtOAc/hexanes) to afford the desired product (130 mg) as a yellow film. LC-MS (ES) m/z = 438 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.37 (d, J = 2.0 Hz, 1H), 7.94 - 7.73 (m, 2H), 7.50 - 7.44 (m, 2H), 7.34 - 7.29 (m, 1H), 7.24 - 7.15 (m, 2H), 6.80 (dd, J = 6.7, 1.6 Hz, 1H),

6.58 (d, $J = 8.9$ Hz, 1H), 5.57 (s, 2H), 3.57 (q, $J = 7.1$ Hz, 4H), 1.23 (t, 3H), 1.45 - 1.28 (m, 6H).

Example 228

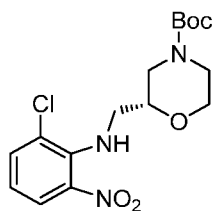
5 N,N-Diethyl-5-(1-((6-(pyrimidin-5-yl)pyridin-2-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine



To a suspension of 5-(1-((6-bromopyridin-2-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine (65 mg, 0.15 mmol), pyrimidin-5-ylboronic acid (22 mg, 0.18 mmol),
 10 and Cs_2CO_3 (146 mg, 0.447 mmol) in 10:1 THF/water (3 mL) under a nitrogen atmosphere was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (5.4 mg, 0.0074 mmol), and the reaction mixture was stirred in a sealed vessel at 100 °C for 4 hours. The reaction was then cooled to room temperature. Additional pyrimidin-5-yl boronic acid (22 mg, 0.18 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (5.4 mg,
 15 0.0074 mmol) were added, the vessel was resealed under a nitrogen atmosphere, and the reaction mixture was stirred at 80 °C for 16.5 hours. The reaction was then cooled to room temperature and concentrated. The resulting residue was purified by silica gel chromatography (eluting with 0 to 100% EtOAc/hexanes) to afford the desired product (30 mg) as a clear film. LC-MS (ES) $m/z = 436$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 9.34 (s, 2H), 9.30 (s, 1H), 8.45 (s, 1H), 7.93 (dd, $J = 9.1, 2.5$ Hz, 1H), 7.87 (d, $J = 7.9$ Hz, 1H), 7.81 - 7.72 (m, 2H), 7.33 (ddd, $J = 8.0, 5.1, 3.0$ Hz, 1H), 7.24-7.23 (m, 2H), 7.01 (d, $J = 7.4$ Hz, 1H), 6.59 (d, $J = 8.9$ Hz, 1H), 5.68 (s, 2H), 3.56 (q, $J = 7.1$ Hz, 4H), 1.21 (t, $J = 7.1$ Hz, 6H).

Intermediate 317

25 tert-Butyl (R)-2-(((2-chloro-6-nitrophenyl)amino)methyl)morpholine-4-carboxylate

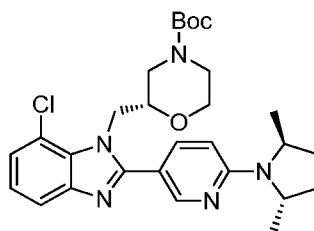


To 1-chloro-2-fluoro-3-nitrobenzene (150 mg, 0.854 mmol) in DMSO (10 mL) were added tert-butyl (R)-2-(aminomethyl)morpholine-4-carboxylate, hydrochloride (302 mg, 1.196

mmol), DIEA (0.298 mL, 1.709 mmol), and K_2CO_3 (236 mg, 1.709 mmol), and the reaction mixture was stirred at room temperature for 18 hours. The reaction was quenched with water (25 mL), and the product was extracted with EtOAc (3 x 75 mL). The organic extracts were combined, washed with brine, dried over $MgSO_4$, and concentrated. The mixture was
 5 purified by column chromatography on silica gel (gradient: 0 - 20% EtOAc/heptane) to give tert-butyl (R)-2-(((2-chloro-6-nitrophenyl)amino)methyl)morpholine-4-carboxylate (315 mg) as an orange oil. LCMS (ES) m/z = 372.2, 374.2 $[M+H]^+$. ^1H NMR (400 MHz, $DMSO-d_6$): δ 1.39 (s, 9H), 2.54 - 2.65 (m, 1H), 2.77 - 2.90 (m, 1H), 3.17 - 3.25 (m, 1H), 3.35 - 3.50 (m, 2H), 3.63 - 3.82 (m, 3H), 3.63 - 3.75 (m, 1H), 6.50 (t, J = 5.8 Hz, 1H), 6.94 (t, J = 8.0 Hz,
 10 1H), 7.72 (dd, J = 7.9, 1.5 Hz, 1H), 7.89 (dd, J = 8.5, 1.7 Hz, 1H).

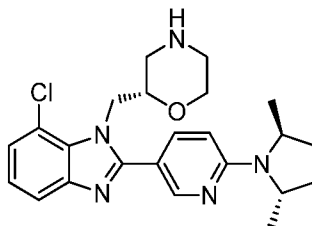
Intermediate 318

tert-Butyl (R)-2-((7-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate



To tert-butyl (R)-2-(((2-chloro-6-nitrophenyl)amino)methyl)morpholine-4-carboxylate (370 mg, 0.995 mmol) in DMSO (10 mL) were added 6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)nicotinaldehyde (224 mg, 1.095 mmol), sodium hydrosulfite (612 mg, 2.99 mmol, 85%), and water (2 mL), and the reaction mixture was stirred at 97 °C for 2 hours. The reaction
 20 was quenched with water (150 mL), and the product was extracted with EtOAc (4 x 75 mL). The organic extracts were combined, washed with brine, dried over $MgSO_4$, and concentrated. The mixture was purified by column chromatography on silica gel (gradient: 0 - 60% EtOAc/heptane) to give tert-butyl (R)-2-((7-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-
 25 carboxylate (264 mg) as a white solid. LCMS (ES) m/z = 526.6, 528.5 $[M+H]^+$. ^1H NMR (400 MHz, $DMSO-d_6$): δ 1.15 (d, J = 6.34 Hz, 6H), 1.36 (s, 9H), 1.66 (m, 2H), 2.20 - 2.29 (m, 2H), 2.55 - 2.64 (m, 1H), 2.83 (m, 1H), 3.17 (m, 1H), 3.56 - 3.80 (m, 4H), 4.14 - 4.34 (m, 2H), 4.48 (m, 1H), 4.66 (m, 1H), 6.62 (d, J = 8.9 Hz, 1H), 7.22 - 7.27 (m, 1H), 7.29 - 7.33 (m, 1H), 7.65 (dd, J = 7.9, 1.0 Hz, 1H), 7.90 (dd, J = 8.9, 2.3 Hz, 1H), 8.49 (d, J = 2.3 Hz, 1H).

30

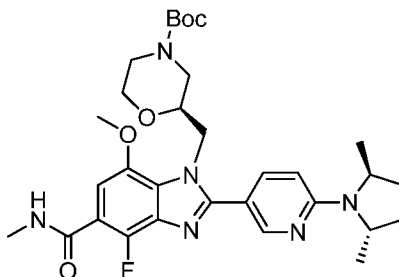
Example 229**(S)-2-((7-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine**

- 5 To tert-butyl (R)-2-((7-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (204 mg, 0.388 mmol) in CH₂Cl₂ (5 mL), was added TFA (2 mL, 26.0 mmol), and the reaction mixture was stirred at room temperature for 3 hours. The reaction was concentrated, and the remaining liquid was mixed with ethyl acetate and concentrated again. The remaining acid was neutralized using
- 10 saturated NaHCO₃ followed by saturated Na₂CO₃, and the resulting mixture was extracted with EtOAc (3 x 25 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, filtered, and concentrated. The product was dissolved in DMF and loaded onto a silica gel column for purification. The column was conditioned in hexanes, then run for 2 minutes at 100% hexanes followed by 2 minutes at 100% CH₂Cl₂, then eluted with a
- 15 0-10% gradient of CH₃OH/CH₂Cl₂. Water and acetonitrile were added in a 1:1 ratio (1 mL total) and the mixture was freeze-dried overnight to yield (S)-2-((7-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine (37 mg) as a white solid. LCMS (ES) m/z = 426.3, 428.3 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ
- 20 1.16 (d, *J* = 6.34 Hz, 6H), 1.59 - 1.71 (m, 2H), 2.18 - 2.36 (m, 4H), 2.57 - 2.71 (m, 2H), 2.58 - 2.72 (m, 1H), 3.17 - 3.25 (m, 1H), 3.60 (br d, *J* = 11.15 Hz, 1H), 3.65 - 3.79 (m, 1H), 4.17 - 4.34 (m, 2H), 4.42 (dd, *J* = 15.21, 8.36 Hz, 1H), 4.53 - 4.59 (m, 1H), 6.62 (d, *J* = 8.6 Hz, 1H), 7.20 - 7.25 (m, 1H), 7.28 - 7.32 (m, 1H), 7.62 - 7.66 (m, 1H), 7.90 (d, *J* = 8.9 Hz, 1H), 8.49 (d, *J* = 2.0 Hz, 1H).

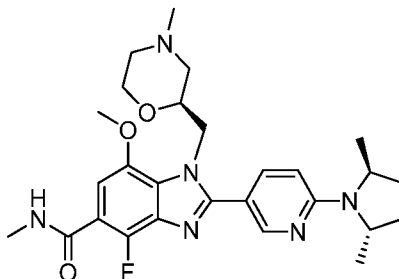
25

Intermediate 319

tert-Butyl (R)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-5-(methylcarbamoyl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate



- 5 To tert-butyl (R)-2-((5-cyano-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (1.3 g, 2.302 mmol) were added 8N NaOH (3 mL) and EtOH (15mL), and the reaction mixture was heated to reflux for 20 hours. The reaction was concentrated, water (10mL) was then added, and the resulting mixture was extracted with EtOAc (3 x 10 mL). The organic extracts were
- 10 combined and extracted with 1N NaOH solution (10 mL). The aqueous layer was then acidified by addition of 6N HCl solution and freeze-dried overnight. To the resulting light brown solid were added EDC (0.441 g, 2.302 mmol), HOBt (0.353 g, 2.302 mmol), methylamine hydrochloride (0.233 g, 3.45 mmol), DMSO (5 mL), and N-methylmorpholine (2.53 mL, 23.02 mmol), and the reaction mixture was stirred overnight. The reaction was
- 15 quenched with water (10 mL) and extracted with EtOAc (4 x 5 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, filtered, and concentrated. The resulting material was dissolved in DMSO (1.5 mL) and purified by reverse phase HPLC (50 – 99% CH₃CN in (0.1 % NH₄OH in water)) to give tert-butyl (R)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-5-(methylcarbamoyl)-1H-
- 20 benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (24 mg) as a very light gray solid after freeze-drying. LC-MS (ES) m/z = 597 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.15 (d, *J* = 6.1 Hz, 6H), 1.40 (s, 9H), 1.66 (d, *J* = 5.8 Hz, 2H), 2.24 (br. s., 2H), 2.46 - 2.48 (m, 2H), 2.82 (d, *J* = 4.6 Hz, 3H), 3.18 - 3.26 (m, 1H), 3.63 - 3.81 (m, 4H), 3.96 (s, 3H), 4.17 - 4.38 (m, 3H), 4.50 (d, *J* = 12.7 Hz, 1H), 6.62 (d, *J* = 9.1 Hz, 1H), 7.00 (d, *J* = 4.6 Hz, 1H),
- 25 7.93 (dd, *J* = 9.0, 2.4 Hz, 1H), 8.14 - 8.19 (m, 1H), 8.54 (d, *J* = 2.3 Hz, 1H).

Example 230**2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-N-methyl-1-(((S)-4-methylmorpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide**

5 To tert-butyl (R)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-5-(methylcarbamoyl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (24 mg, 0.040 mmol) in CH₂Cl₂ (1 mL) was added TFA (600 µl, 7.79 mmol), and the reaction mixture was stirred for 1 hour at room temperature. The reaction was concentrated and then neutralized with saturated aqueous NaHCO₃ solution until basic followed by addition

10 of saturated aqueous Na₂CO₃ (2 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL), and the organic extracts were then combined, washed with brine, dried over MgSO₄, filtered, and concentrated. The resulting a clear oil was dissolved in 1,2-dichloroethane (1000 µl), formaldehyde 36% in water (15.39 µl, 0.201 mmol) and acetic acid (6.91 µl, 0.121 mmol) were added, and the resulting mixture was and stirred at room

15 temperature for 15 minutes. NaBH(OAc)₃ (29.8 mg, 0.141 mmol) was then added, and the reaction mixture was stirred for 1 hour at room temperature. The reaction was concentrated and then quenched with saturated aqueous NaHCO₃ solution until basic followed by addition of saturated aqueous Na₂CO₃ (2 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL), and the organic extracts were then combined, washed with brine, dried

20 over MgSO₄, filtered, and concentrated. Purification by chromatography on SiO₂ (gradient: of 0 to 50% (80:20 CH₂Cl₂:CH₃OH)/CH₂Cl₂) to afford 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-N-methyl-1-(((S)-4-methylmorpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide (14.6 mg) as a white solid after freeze-drying. LC-MS (ES) m/z = 511 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.15 (d, *J* = 6.1 Hz, 6H), 1.63 -

25 1.74 (m, 3H), 1.90 - 1.98 (m, 1H), 2.15 (s, 3H), 2.25 (br. s., 2H), 2.60 (d, *J* = 10.4 Hz, 1H), 2.82 (d, *J* = 4.6 Hz, 3H), 3.25 - 3.31 (m, 2H), 3.66 (d, *J* = 10.4 Hz, 1H), 3.75 - 3.83 (m, 1H), 3.96 (s, 3H), 4.21 - 4.38 (m, 3H), 4.43 - 4.50 (m, 1H), 6.62 (d, *J* = 8.9 Hz, 1H), 6.99 (d, *J* = 4.6 Hz, 1H), 7.93 (dd, *J* = 9.0, 2.4 Hz, 1H), 8.13 - 8.19 (m, 1H), 8.52 (d, *J* = 2.3 Hz, 1H).

30

Example 231 - Capsule Composition

An oral dosage form for administering the present invention is produced by filling a standard two piece hard gelatin capsule with the ingredients in the proportions shown in Table I, below.

5

Table I

<u>INGREDIENTS</u>	<u>AMOUNTS</u>
N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine (Compound of Example 1)	7 mg
Lactose	53 mg
Talc	16 mg
Magnesium Stearate	4 mg

Example 232 - Injectable Parenteral Composition

An injectable form for administering the present invention is produced by stirring 1.7% by weight of 5-(1-((1-Ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-dipropylpyridin-2-amine (Compound of Example 2) in 10% by volume propylene glycol in water.

10

Example 233 - Tablet Composition

The sucrose, calcium sulfate dihydrate and a compound of the invention as shown in Table II below, are mixed and granulated in the proportions shown with a 10% gelatin solution. The wet granules are screened, dried, mixed with the starch, talc and stearic acid, screened and compressed into a tablet.

15

Table II

<u>INGREDIENTS</u>	<u>AMOUNTS</u>
N-Ethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N-propylpyridin-2-amine (Compound of Example 3)	12 mg
calcium sulfate dihydrate	30 mg
Sucrose	4 mg
Starch	2 mg
Talc	1 mg
stearic acid	0.5 mg

20

Example 234: c-MYC Cell Based Assay

Cellular c-MYC Detection Assay

MYC levels in COLO320HSR cells (ATCC, Cat # CCL-220.1) were measured using the human c-MYC Homogeneous Time-Resolved Fluorescence (HTRF) assay kit (Cisbio, Cat#

63ADK053PEC) following the manufacturer's instructions. In brief, 1536 well pre-stamped compound plates were seeded with COLO320HSR cells (4000 cells/well) in a culture media (RPMI Media w/ L-glutamine +10% FBS) containing 0.01% CHAPS. The plated were incubated at 37°C overnight. After the incubation the cells were lysed using cell kinase lysis
5 buffer (CisBio, Cat # 64KL1FDF) supplemented with protease inhibitor (Sigma, Cat # P8340-5 ml) for 1 h at room temperature. The donor and the acceptor antibodies were added to the plate and incubated for another 4 h at room temperature. The plates were read in the HTRF mode (excitation 320 nm and emission 665 nm and 620 nm) using the BMG
10 PHERAstar FS (BMG LABTECH Inc., Cary, NC). The ratio of 665/620 is measured as the assay signal. This assay produces a positive signal for the presence of MYC.

Compounds of the invention are tested for activity against c-MYC in the above assay.

15 The compounds of the Examples were tested generally according to the above c-MYC Cell Based Assay and in at least one experimental run exhibited a pIC₅₀ value, or in a set of two or more experimental runs exhibited an average pIC₅₀ value, of: ≥ 5.7 against c-MYC.

20 The compound of Example 5 was tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC₅₀ value of 5.7 against c-MYC.

The compound of Example 9 was tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC₅₀
25 value of 7 against c-MYC.

The compound of Example 20 was tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC₅₀ value of 6.5 against c-MYC.

The compound of Example 25 was tested generally according to the above c-MYC
30 Cell Based Assay and in at least one set of experimental runs exhibited an average pIC₅₀ value of 6.4 against c-MYC.

The compound of Example 44 was tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC₅₀ value of 6.8 against c-MYC.

The compound of Example 51 was tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC₅₀ value of 6.5 against c-MYC.

5 The compound of Example 61 was tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC₅₀ value of 6.2 against c-MYC.

The compound of Example 68 was tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC₅₀ value of 7.3 against c-MYC.

10 The compound of Example 75 was tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC₅₀ value of 6.3 against c-MYC.

The compound of Example 86 was tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC₅₀ value of 5.9 against c-MYC.

15 The compound of Example 99 was tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC₅₀ value of 7.2 against c-MYC.

20 The compound of Example 116 was tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC₅₀ value of 5.8 against c-MYC.

The compound of Example 121 was tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC₅₀ value of 6.4 against c-MYC.

25 The compound of Example 132 was tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC₅₀ value of 6.6 against c-MYC.

30 The compound of Example 136 was tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC₅₀ value of 6.7 against c-MYC.

The compound of Example 145 was tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC₅₀ value of 6.3 against c-MYC.

The compound of Example 158 was tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC₅₀ value of 5.9 against c-MYC.

5 The compound of Example 164 was tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC₅₀ value of 6.8 against c-MYC.

The compound of Example 174 was tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC₅₀ value of 7.4 against c-MYC.

10 The compound of Example 180 was tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC₅₀ value of 7.2 against c-MYC.

The compound of Example 191 was tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC₅₀ value of 6.6 against c-MYC.

15 The compound of Example 195 was tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC₅₀ value of 7.5 against c-MYC.

20 The compound of Example 210 was tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC₅₀ value of 6.8 against c-MYC.

The compound of Example 223 was tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC₅₀ value of 7.3 against c-MYC.

25 The compound of Example 226 was tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC₅₀ value of 7.7 against c-MYC.

The compound of Example 229 was tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC₅₀ value of 6.8 against c-MYC.

30 The compound of Example 230 was tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC₅₀ value of 7.7 against c-MYC.

The compounds of Examples 2, 3, 4, 5, 8, 10, 12, 14, 16, 17, 22, 28 to 41, 48, 58, 61, 63, 64, 77 to 80, 82, 83, 85 to 87, 89, 90, 93, 94, 95, 104, 108, 110, 112, 114 to 117, 122, 124, 130, 133, 134, 138, 140, 142, 143, 146 to 148, 157 to 159, 161, 167, 176, 179, 181, 227 and 228 were tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC50 value: ≥ 5.7 and ≤ 6.2 against c-MYC.

The compounds of Examples 1, 7, 11, 13, 15, 18 to 21, 23 to 27, 42 to 45, 47, 49 to 55, 57, 59, 60, 65 to 67, 69, 70, 72 to 75, 81, 84, 91, 92, 96 to 98, 101 to 103, 105 to 107, 109, 111, 114 to 117, 120, 121, 123, 125, 127, 128, 131, 132, 135, 136, 141, 144, 145, 149, 150, 152 to 156, 160, 164 to 172, 175, 183, 184, 186, 189 to 193, 196, 197, 200, 202, 205, 206, 208 to 218, 220, 222, 224 and 229 were tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC50 value: ≥ 6.3 and ≤ 6.8 against c-MYC.

The compounds of Examples 6, 9, 46, 56, 68, 71, 76, 88, 99, 100, 113, 118, 119, 126, 129, 137, 139, 151, 162, 163, 173, 174, 177, 178, 180, 182, 185, 187, 188, 194, 195, 198, 199, 201, 203, 204, 207, 211, 219, 221, 223, 225, 226 and 230 were tested generally according to the above c-MYC Cell Based Assay and in at least one set of experimental runs exhibited an average pIC50 value: ≥ 6.9 against c-MYC.

Example 235: p300 Acetyltransferase Radioactivity/SPA - pIC50 Assay

Biochemical measurement of p300 acetyltransferase activity was analyzed in a radioactive SPA assay. 96 well plates (Corning 3884) were stamped with 500 nL of compound per well (11-point, 3-fold serial dilution in DMSO) with positive and negative control wells stamped with 500 nL DMSO (Sigma D8418). 8 μ L of 1.5x substrate mix was added to each well. Negative control wells were then prequenched with the addition of 12 μ L formic acid (12.5% JT Baker 0129-01) followed by the addition of 4 μ L of 3x enzyme mix to initiate the reaction in all wells. After a 30 minute incubation with shaking, reaction wells were quenched with 12 μ L formic acid (12.5% JT Baker 0129-01). SPA beads were then added (12 μ L per well, 3 mg/mL Perkin Elmer RPNQ0007) and incubated with shaking for 30 minutes. Plates were read on a MicroBeta2 (Perkin Elmer) following a ≥ 200 minute delay. Assay conditions prior to quench were as follows, 0.8 nM full-length wild-type p300 (Active Motif 31124), 1 μ M Acetyl Coenzyme A (Sigma A2056), 1 μ M ^{3} H- Acetyl Coenzyme A (Perkin Elmer NET2902250UC), 0.2 μ M H3-21 peptide (Anaspec AS-61702), 50 mM Tris pH 8.0 (Invitrogen 1566025), 1 mM DTT (Invitrogen P2325), 0.1 mM EDTA (Gibco 15575-038), 0.04% Pluronic Acid F127 (Life Technologies P6866) and 10% glycerol (Em Science GX0185-6).

A representative sample of compounds described in this application were tested in the above p300 Acetyltransferase Radioactivity/SPA assay and found to inhibit p300/CBP histone acetyltransferase activity.

5 The compound of Example 6 was tested generally according to the above p300 Acetyltransferase Radioactivity/SPA assay and in at least one set of experimental runs exhibited an average pIC50 value of 7.29 against p300/CBP histone acetyltransferase activity.

10 The compound of Example 21 was tested generally according to the above p300 Acetyltransferase Radioactivity/SPA assay and in at least one set of experimental runs exhibited an average pIC50 value of 6.4 against p300/CBP histone acetyltransferase activity.

15 The compound of Example 39 was tested generally according to the above p300 Acetyltransferase Radioactivity/SPA assay and in at least one set of experimental runs exhibited an average pIC50 value of 6.9 against p300/CBP histone acetyltransferase activity.

20 The compound of Example 57 was tested generally according to the above p300 Acetyltransferase Radioactivity/SPA assay and in at least one set of experimental runs exhibited an average pIC50 value of 7.4 against p300/CBP histone acetyltransferase activity.

 The compound of Example 69 was tested generally according to the above p300 Acetyltransferase Radioactivity/SPA assay and in at least one set of experimental runs exhibited an average pIC50 value of 7.3 against p300/CBP histone acetyltransferase activity.

25 The compound of Example 76 was tested generally according to the above p300 Acetyltransferase Radioactivity/SPA assay and in at least one set of experimental runs exhibited an average pIC50 value of 6.3 against p300/CBP histone acetyltransferase activity.

30 The compound of Example 82 was tested generally according to the above p300 Acetyltransferase Radioactivity/SPA assay and in at least one set of experimental runs exhibited an average pIC50 value of 6.8 against p300/CBP histone acetyltransferase activity.

35 The compound of Example 126 was tested generally according to the above p300 Acetyltransferase Radioactivity/SPA assay and in at least one set of experimental runs exhibited an average pIC50 value of 6.8 against p300/CBP histone acetyltransferase activity.

The compound of Example 133 was tested generally according to the above p300 Acetyltransferase Radioactivity/SPA assay and in at least one set of experimental runs exhibited an average pIC50 value of 6.2 against p300/CBP histone acetyltransferase activity.

5 The compound of Example 141 was tested generally according to the above p300 Acetyltransferase Radioactivity/SPA assay and in at least one set of experimental runs exhibited an average pIC50 value of 6.3 against p300/CBP histone acetyltransferase activity.

10 The compound of Example 149 was tested generally according to the above p300 Acetyltransferase Radioactivity/SPA assay and in at least one set of experimental runs exhibited an average pIC50 value of 6.2 against p300/CBP histone acetyltransferase activity.

15 The compound of Example 164 was tested generally according to the above p300 Acetyltransferase Radioactivity/SPA assay and in at least one set of experimental runs exhibited an average pIC50 value of 6.3 against p300/CBP histone acetyltransferase activity.

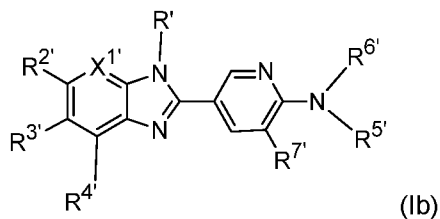
20 The compound of Example 167 was tested generally according to the above p300 Acetyltransferase Radioactivity/SPA assay and in at least one set of experimental runs exhibited an average pIC50 value of 6.1 against p300/CBP histone acetyltransferase activity.

While the preferred embodiments of the invention are illustrated by the above, it is to be understood that the invention is not limited to the precise instructions herein disclosed and that the right to all modifications coming within the scope of the following claims is reserved.

25

What is claimed is:

1. A compound according to Formula Ib:



where:

R' is C₁-6alkyl, substituted with from 1 to 3 substituents independently selected from:

fluoro,
 oxo,
 aryl substituted by heteroaryl,
 heterocyclyl,
 heterocyclyl substituted with from 1 to 4 substituents independently selected from:

fluoro,
 chloro,
 bromo,
 oxo,
 -OH,
 heteroaryl,
 C₁-6alkyl, and

C₁-6alkyl substituted with from 1 to 5 substituents independently selected from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH and -NH₂,

heteroaryl,
 heteroaryl substituted with from 1 to 4 substituents independently selected from:

fluoro,
 chloro,

- bromo,
-OH,
heteroaryl,
C1-6alkyl, and
- 5 C1-6alkyl substituted with from 1 to 5 substituents
independently selected from: fluoro, chloro,
bromo, iodo, oxo, -CN, -OH and -NH₂,
- C1-6alkoxy,
C1-6alkoxy substituted with from 1 to 9 substituents independently
10 selected from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and
-N(CH₃)₂,
-Ocyaloalkyl, and
-Ocyaloalkyl substituted with from 1 to 4 substituents independently
selected from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and
15 -N(CH₃)₂;
- X^{1'} is selected from: CR^{1'} and N,
where,
R^{1'} is selected from:
- 20 hydrogen,
fluoro,
chloro,
bromo,
iodo,
25 -OH,
-NH₂,
-NHCH₃,
-N(CH₃)₂,
-CN,
30 C1-4alkoxy,
C1-4alkoxy substituted with from 1 to 7 substituents independently selected
from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and -N(CH₃)₂,
C1-6alkyl,
C1-6alkyl substituted with from 1 to 7 substituents independently selected
35 from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH, -OC1-5alkyl,

heterocyclyl, $-\text{COOH}$, $-\text{S(O)}_2\text{H}$, $-\text{S(O)}_2\text{R}^{\text{X}}$ where R^{X} is selected from C1-3alkyl and C1-3alkyl substituted from one to 3 times by fluoro, heterocyclyl, and $-\text{NR}^{\text{a}}\text{R}^{\text{b}}$,

where R^{a} and R^{b} are independently selected form:

5

hydrogen,

C1-5alkoxy,

C1-5alkoxy substituted with from 1 to 4 substituents

independently selected from: fluoro, oxo, $-\text{OH}$,

$-\text{OC1-5alkyl}$, cycloalkyl, cycloalkyl substituted

10

by $-\text{OH}$, $-\text{COOH}$, $-\text{NH}_2$, $-\text{S(O)}_2\text{H}$, and

$-\text{S(O)}_2\text{CH}_3$,

C1-5alkyl,

C1-5alkyl substituted with from 1 to 4 substituents

independently selected from: fluoro, oxo, $-\text{OH}$,

15

$-\text{OC1-5alkyl}$, cycloalkyl, cycloalkyl substituted

by $-\text{OH}$, $-\text{COOH}$, $-\text{NH}_2$, $-\text{S(O)}_2\text{H}$, and

$-\text{S(O)}_2\text{R}^{\text{X}}$ where R^{X} is selected from C1-3alkyl

and C1-3alkyl substituted from one to 3 times

by fluoro,

20

cycloalkyl, and

cycloalkyl substituted with from 1 to 4 substituents

independently selected from: fluoro, oxo, $-\text{OH}$,

$-\text{O1-5alkyl}$, $-\text{COOH}$, and $-\text{NH}_2$,

heteroaryl, and

25

heteroaryl substituted with from 1 to 4 substituents independently selected from:

fluoro,

chloro,

C1-6alkyl, and

C1-6alkyl substituted with from 1 to 5 substituents independently
selected from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH and
-NH₂;

5

R^{2'}, R^{3'}, and R^{4'} are independently selected from:

hydrogen,
fluoro,
chloro,
10 bromo,
iodo,
-OH
boronic acid,
1,3,6,2-dioxazaborocane-4,8-dione,
15 -CN,
-NR^cR^d,

where R^c and R^d are independently selected from:

hydrogen,

C1-5alkyl,

20

C1-5alkyl substituted with from 1 to 4 substituents

independently selected from: fluoro, oxo, -OH,

-OC1-5alkyl, cycloalkyl, -COOH, -NH₂,

-N(H)C1-4alkyl, -N(C1-4alkyl)₂, -N(H)C1-4alkyl where
alkyl is substituted from one to 3 times by fluoro,

25

N(C1-4alkyl)₂ where each alkyl is substituted from

one to 3 times by fluoro, -S(O)₂H, and -S(O)₂R^x

where R^x is selected from C1-3alkyl and C1-3alkyl
substituted from one to 3 times by fluoro,

-S(O)₂H,

30

-S(O)₂R^{x'} where R^{x'} is selected from C1-3alkyl and C1-3alkyl
substituted from one to 3 times by fluoro,

- aryl,
 aryl, substituted with from 1 to 4 substituents
 independently selected from: fluoro, oxo, -OH,
 -O1-5alkyl, -COOH, and -NH₂,
- 5 heteroaryl,
 heteroaryl, substituted with from 1 to 4 substituents
 independently selected from: fluoro, oxo, -OH,
 -O1-5alkyl, -COOH, and -NH₂,
- 10 heterocyclyl,
 heterocyclyl, substituted with from 1 to 4 substituents
 independently selected from: fluoro, oxo, -OH,
 -O1-5alkyl, -COOH, and -NH₂,
- cycloalkyl, and
 cycloalkyl substituted with from 1 to 4 substituents
 independently selected from: fluoro, oxo, -OH,
 -O1-5alkyl, -COOH, and -NH₂,
- 15 heterocyclyl,
 C1-4alkoxy,
 C1-4alkoxy substituted with from 1 to 7 substituents independently selected
 from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and -N(CH₃)₂,
- 20 C1-6alkyl,
 C1-6alkyl substituted with from 1 to 7 substituents independently selected
 from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH, -OC1-5alkyl,
 heterocyclyl, -COOH, -S(O)₂H, -S(O)₂R^x where R^x is selected from
- 25 C1-3alkyl and C1-3alkyl substituted from one to 3 times by fluoro,
 and -NR^aR^b,
 where R^a and R^b are independently selected from:
 hydrogen,
 C1-5alkyl,
- 30 C1-5alkyl substituted with from 1 to 4 substituents

independently selected from: fluoro, oxo, -OH,
 -OC₁₋₅alkyl, cycloalkyl, -COOH, -NH₂,
 -S(O)₂H, and -S(O)₂R^X where R^X is selected
 from C₁₋₃alkyl and C₁₋₃alkyl substituted from
 one to 3 times by fluoro,
 aryl,
 aryl, substituted with from 1 to 4 substituents
 independently selected from: fluoro, oxo, -OH,
 -O₁₋₅alkyl, -COOH, and -NH₂,
 heteroalkyl,
 heteroalkyl, substituted with from 1 to 4 substituents
 independently selected from: fluoro, oxo, -OH,
 -O₁₋₅alkyl, -COOH, and -NH₂,
 heterocycle,
 heteroalkyl, substituted with from 1 to 4 substituents
 independently selected from: fluoro, oxo, -OH,
 -O₁₋₅alkyl, -COOH, and -NH₂,
 cycloalkyl, and
 cycloalkyl substituted with from 1 to 4 substituents
 independently selected from: fluoro, oxo, -OH,
 -O₁₋₅alkyl, -COOH, and -NH₂,
 aryl,
 aryl substituted with from 1 to 4 substituents independently selected
 from:
 fluoro,
 chloro,
 C₁₋₆alkyl, and
 C₁₋₆alkyl substituted with from 1 to 5 substituents independently
 selected from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH and
 -NH₂,

cycloalkyl,
cycloalkyl substituted with from 1 to 4 substituents independently selected
from:

5 fluoro,
chloro,
C1-6alkyl, and

C1-6alkyl substituted with from 1 to 5 substituents independently
selected from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH and
-NH₂.

10 heterocycle,
heterocycle substituted with from 1 to 4 substituents independently selected
from:

fluoro,
chloro,
C1-6alkyl, and

C1-6alkyl substituted with from 1 to 5 substituents independently
selected from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH and
-NH₂,

heteroaryl, and
20 heteroaryl substituted with from 1 to 4 substituents independently selected from:

fluoro,
chloro,
C₁₋₆alkyl, and

25 C1-6alkyl substituted with from 1 to 5 substituents independently
selected from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH and
-NH₂.

or 2 adjacent members of R^{1'}, R^{2'}, R^{3'}, and R^{4'} are taken together to form a non-aromatic ring containing 3 to 6 member atoms independently selected from: carbon, nitrogen, sulphur, oxygen and boron, to form an oxaborolyl, heterocyclyl, cycloalkyl, or heteroaryl, in which each

of said oxaborolyl, heterocyclyl, cycloalkyl, and heteroaryl is optionally substituted with from 1 to 3 substituents independently selected from: fluoro, chloro, -OH, oxo, C₁-6alkyl, and -NH₂;

5 R^{5'} and R^{6'} are independently selected from:

C₁-4alkyl,

C₁-4alkyl substituted with from 1 to 6 substituents

independently selected from: fluoro, oxo, -NH₂, C₁-4alkoxy, and -OH,

10

cycloalkyl,

cycloalkyl substituted with from 1 to 5 substituents independently selected from:

fluoro,

chloro,

15

-OH, and

C₁-6alkyl,

R^{5'} and R^{6'} are taken together with the nitrogen to which they are attached, and optionally from 1 to 3 additional heteroatoms, to form a heterocyclyl, which is optionally substituted with from 1 to 5 substituents independently selected from:

20

fluoro,

chloro,

C₁-6alkyl,

C₁-6alkyl substituted with from 1 to 9 substituents

25

independently selected from: fluoro, chloro,

C₁-4alkoxy, oxo, -OH, -NH₂, -N(H)C₁-4alkyl,

-N(C₁-4alkyl)₂, and -CN,

C₁-4alkoxy,

C₁-4alkoxy substituted with from 1 to 4 substituents

independently selected from: fluoro, oxo, -OH,
-COOH, -NH₂, and -CN,

oxo,

-NH₂,

5

-N(H)C₁₋₄alkyl, and

-N(C₁₋₄alkyl)₂, or

one of R^{5'} and R^{6'} is taken together with R^{7'}, and optionally from 1 to 3
additional heteroatoms, to form a heterocyclyl, which is optionally
substituted with from 1 to 5 substituents independently selected from:
10 fluoro, chloro, -OH, oxo, C₁₋₄alkyl, C₁₋₄alkoxy, and -NH₂; and

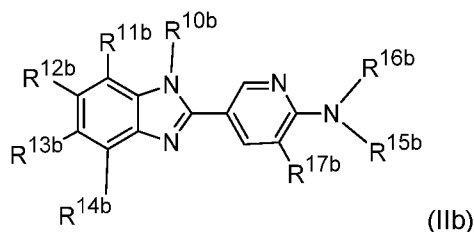
R^{7'} is selected from: hydrogen and fluoro,

or one of R^{5'} and R^{6'} is taken together with R^{7'}, and optionally from 1 to 3
additional heteroatoms, to form a heterocyclyl, which is optionally
15 substituted with from 1 to 5 substituents independently selected from:
fluoro, chloro, -OH, oxo, C₁₋₄alkyl, C₁₋₄alkoxy, and -NH₂;

or a pharmaceutically acceptable salt thereof.

20

2. The compound of Claim 1 represented by the following Formula (IIb):



where:

25

R^{10b} is C₁₋₄alkyl, substituted with from 1 to 3 substituents independently selected
from:
oxo,

- phenyl substituted by pyrimidinyl,
heterocyclyl,
heterocyclyl substituted with from 1 to 4 substituents independently
selected from:
- 5 fluoro,
chloro,
bromo,
oxo,
heteroaryl,
- 10 C1-6alkyl, and
- C1-6alkyl substituted with from 1 to 5 substituents
independently selected from: fluoro, chloro,
bromo, iodo, oxo, -CN, -OH and -NH₂,
heteroaryl,
- 15 heteroaryl substituted with from 1 to 4 substituents independently
selected from:
- fluoro,
chloro,
bromo,
heteroaryl,
- 20 C1-6alkyl, and
- C1-6alkyl substituted with from 1 to 5 substituents
independently selected from: fluoro, chloro,
bromo, iodo, oxo, -CN, -OH and -NH₂,
- 25 C1-6alkoxy,
C1-6alkoxy substituted with from 1 to 9 substituents independently
selected from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and
-N(CH₃)₂,
- Ocyloalkyl, and
- 30 -Ocyloalkyl substituted with from 1 to 4 substituents independently
selected from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and
-N(CH₃)₂;

R^{11b} is selected from:

- hydrogen,
 fluoro,
 chloro,
 bromo,
 iodo,
 -OH,
 -NH₂,
 -CN,
 C1-4alkoxy,
 C1-4alkoxy substituted with from 1 to 7 substituents independently selected
 from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and -N(CH₃)₂,
 C1-6alkyl,
 C1-6alkyl substituted with from 1 to 7 substituents independently selected
 from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH, -OC1-5alkyl,
 heterocyclyl, -COOH, -S(O)₂H, -S(O)₂R^{x1'} where R^{x1'} is selected
 from C1-3alkyl and C1-3alkyl substituted from one to 3 times by
 fluoro, and -NR^{a1'}R^{b1'},
 where R^{a1'} and R^{b1'} are independently selected from:
 hydrogen,
 C1-5alkoxy,
 C1-5alkyl,
 C1-5alkyl substituted with from 1 to 4 substituents
 independently selected from: fluoro, oxo, -OH,
 -OC1-5alkyl, cycloalkyl, cycloalkyl substituted
 by -OH, -COOH, -NH₂, -S(O)₂H, and
 -S(O)₂CH₃,
 cycloalkyl, and
 cycloalkyl substituted with from 1 to 4 substituents
 independently selected from: fluoro, oxo, -OH,
 -O1-5alkyl, -COOH, and -NH₂,

heteroaryl, and

heteroaryl substituted with from 1 to 4 substituents independently selected

from:

fluoro,

5

chloro,

C1-6alkyl, and

C1-6alkyl substituted with from 1 to 5 substituents independently

selected from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH and

-NH₂;

10

R^{12b}, R^{13b}, and R^{14b} are independently selected from:

hydrogen,

fluoro,

chloro,

15

bromo,

iodo,

-OH,

boronic acid,

1,3,6,2-dioxazaborocane-4,8-dione,

20

-CN,

-NR^{c1'}R^{d1'},

where R^{c1'} and R^{d1'} are independently selected from:

hydrogen,

C1-5alkyl,

25

C1-5alkyl substituted with from 1 to 4 substituents

independently selected from: fluoro, oxo, -OH,

-OC1-5alkyl, cycloalkyl, -COOH, -NH₂,

-N(H)C1-4alkyl, -N(H)C1-4alkyl where alkyl is

substituted from one to 3 times by fluoro, and

30

-S(O)₂H,

-S(O)₂H,

-S(O)₂C1-3alkyl,

- heterocyclyl,
 C1-4alkoxy,
 C1-4alkoxy substituted with from 1 to 7 substituents independently selected
 from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and -N(CH₃)₂,
 5 C1-6alkyl,
 C1-6alkyl substituted with from 1 to 7 substituents independently selected
 from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH, -OC1-5alkyl,
 heterocyclyl, -COOH, -S(O)₂H, -S(O)₂R^{X1'} where R^{X1'} is selected
 from C1-3alkyl and C1-3alkyl substituted from one to 3 times by
 10 fluoro, and -NR^{a1'}R^{b1'},
 where R^{a1'} and R^{b1'} are independently selected from:
 hydrogen,
 C1-5alkoxy,
 C1-5alkyl,
 15 C1-5alkyl substituted with from 1 to 4 substituents
 independently selected from: fluoro, oxo, -OH,
 -OC1-5alkyl, cycloalkyl, -COOH, -NH₂,
 -S(O)₂H, and -S(O)₂R^{X1'} where R^{X1'} is
 selected from C1-3alkyl and C1-3alkyl
 20 substituted from one to 3 times by fluoro;
 cycloalkyl, and
 cycloalkyl substituted with from 1 to 4 substituents
 independently selected from: fluoro, oxo, -OH,
 -O1-5alkyl, -COOH, and -NH₂,
 25 heteroaryl, and
 heteroaryl substituted with from 1 to 3 substituents independently selected
 from:
 fluoro,
 chloro,

C1-6alkyl, and

C1-6alkyl substituted with from 1 to 5 substituents independently
selected from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH and
-NH₂,

5 or 2 adjacent members of R^{12b}, R^{13b}, and R^{14b} are taken together to form
a non-aromatic ring containing 3 to 6 member atoms independently
selected from: carbon, nitrogen, sulphur, oxygen and boron, to form
an oxaborolyl, heterocyclyl, cycloalkyl, or heteroaryl, in which each
of said oxaborolyl, heterocyclyl, cycloalkyl, and heteroaryl is
10 optionally substituted with from 1 to 3 substituents independently
selected from: fluoro, chloro, -OH, oxo, C1-6alkyl, and -NH₂;

R^{15b} and R^{16b} are independently selected from:

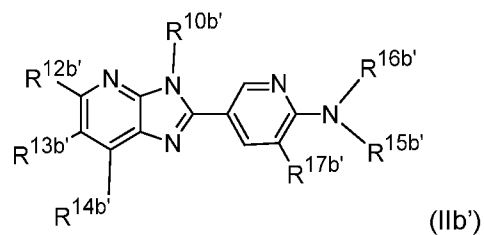
C1-4alkyl,

15 C1-4alkyl substituted with from 1 to 6 substituents
independently selected from: fluoro, oxo, -NH₂, C1-4alkoxy, and
-OH,
cycloalkyl, and
cycloalkyl substituted with from 1 to 5 substituents independently
20 selected from:
fluoro,
chloro,
-OH, and
C1-6alkyl,

25 R^{15b} and R^{16b} are taken together with the nitrogen to which they are
attached, and optionally from 1 to 3 additional heteroatoms, to form
a heterocyclyl, which is optionally substituted with from 1 to 5
substituents independently selected from:
fluoro,
30 chloro,

- C1-6alkyl,
C1-6alkyl substituted with from 1 to 9 substituents
independently selected from: fluoro, chloro,
C1-4alkoxy, oxo, -OH, -NH₂, -N(H)C1-4alkyl,
5 -N(C1-4alkyl)₂, and -CN,
C1-4alkoxy,
C1-4alkoxy substituted with from 1 to 4 substituents
independently selected from: fluoro, oxo, -OH,
-COOH, -NH₂, and -CN,
10 oxo,
-NH₂,
-N(H)C1-4alkyl, and
-N(C1-4alkyl)₂, or
one of R^{15b} and R^{16b} is taken together with R^{17b}, and optionally from 1 to 3
15 additional heteroatoms, to form a heterocyclyl, which is optionally
substituted with from 1 to 3 substituents independently selected from:
fluoro, -OH, C1-4alkyl, and C1-4alkoxy; and
R^{17b} is selected from: hydrogen and fluoro,
20 or one of R^{15b} and R^{16b} is taken together with R^{17b}, and optionally from 1 to
3 additional heteroatoms, to form a heterocyclyl, which is
optionally substituted with from 1 to 3 substituents independently
selected from: fluoro, -OH, C1-4alkyl, and C1-4alkoxy;
25 or a pharmaceutically acceptable salt thereof.

3. A compound of Claim 1 represented by the following Formula (IIb'):



where:

5

$R^{10b'}$ is C1-4alkyl, substituted with from 1 to 3 substituents independently selected from:

10

oxo,
phenyl substituted by pyrimidinyl,
heterocyclyl,
heterocyclyl substituted with from 1 to 4 substituents independently selected from:

15

fluoro,
chloro,
bromo,
oxo,
heteroaryl,
C1-6alkyl, and

20

C1-6alkyl substituted with from 1 to 5 substituents independently selected from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH and -NH₂,

heteroaryl,
heteroaryl substituted with from 1 to 4 substituents independently selected from:

25

fluoro,
chloro,
bromo,
heteroaryl,
C1-6alkyl, and

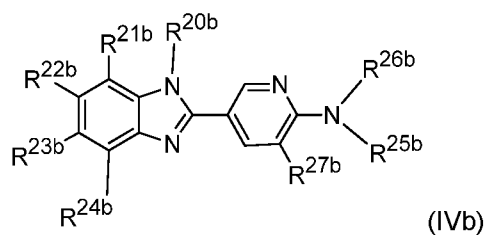
- C1-6alkyl substituted with from 1 to 5 substituents
independently selected from: fluoro, chloro,
bromo, iodo, oxo, -CN, -OH and -NH₂,
- C1-6alkoxy,
- 5 C1-6alkoxy substituted with from 1 to 9 substituents independently
selected from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and
-N(CH₃)₂,
-Ocycloalkyl, and
-Ocycloalkyl substituted with from 1 to 4 substituents independently
10 selected from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and
-N(CH₃)₂;
- R^{12b'}, R^{13b'}, and R^{14b'} are independently selected from:
- 15 hydrogen,
fluoro,
chloro,
bromo,
iodo,
-OH,
20 boronic acid,
1,3,6,2-dioxazaborocane-4,8-dione,
-CN,
-NR^{c1b}R^{d1b},
- where R^{c1b} and R^{d1b} are independently selected from:
- 25 hydrogen,
C1-5alkyl,
C1-5alkyl substituted with from 1 to 4 substituents
independently selected from: fluoro, oxo, -OH,
-OC1-5alkyl, cycloalkyl, -COOH, -NH₂,
30 -N(H)C1-4alkyl, -N(H)C1-4alkyl where alkyl is
substituted from one to 3 times by fluoro, and
-S(O)₂H,
-S(O)₂H,

- S(O)₂C₁₋₃alkyl,
heterocyclyl,
C₁₋₄alkoxy,
C₁₋₄alkoxy substituted with from 1 to 7 substituents independently selected
5 from: fluoro, chloro, oxo, -OH, -NH₂, -NHCH₃, and -N(CH₃)₂,
C₁₋₆alkyl,
C₁₋₆alkyl substituted with from 1 to 7 substituents independently selected
from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH, -OC₁₋₅alkyl,
heterocyclyl, -COOH, -S(O)₂H, -S(O)₂R^{x1a} where R^{x1a} is selected
10 from C₁₋₃alkyl and C₁₋₃alkyl substituted from one to 3 times by
fluoro, and -NR^{a1b}R^{b1b},
where R^{a1b} and R^{b1b} are independently selected from:
hydrogen,
C₁₋₅alkoxy,
15 C₁₋₅alkyl,
C₁₋₅alkyl substituted with from 1 to 4 substituents
independently selected from: fluoro, oxo, -OH,
-OC₁₋₅alkyl, cycloalkyl, -COOH, -NH₂,
-S(O)₂H, and -S(O)₂R^{x1b} where R^{x1b} is
20 selected from C₁₋₃alkyl and C₁₋₃alkyl
substituted from one to 3 times by fluoro;
cycloalkyl, and
cycloalkyl substituted with from 1 to 4 substituents
independently selected from: fluoro, oxo, -OH,
25 -O₁₋₅alkyl, -COOH, and -NH₂,
heteroaryl, and
heteroaryl substituted with from 1 to 3 substituents independently selected
from:
fluoro,

- chloro,
C1-6alkyl, and
C1-6alkyl substituted with from 1 to 5 substituents independently
selected from: fluoro, chloro, bromo, iodo, oxo, -CN, -OH and
5 -NH₂,
or 2 adjacent members of R^{12b'}, R^{13b'}, and R^{14b'} are taken together to form
a non-aromatic ring containing 3 to 6 member atoms independently
selected from: carbon, nitrogen, sulphur, oxygen and boron, to form
an oxaborolyl, heterocyclyl, cycloalkyl, or heteroaryl, in which each
10 of said oxaborolyl, heterocyclyl, cycloalkyl, and heteroaryl is
optionally substituted with from 1 to 3 substituents independently
selected from: fluoro, chloro, -OH, oxo, C1-6alkyl, and -NH₂;
- R^{15b'} and R^{16b'} are independently selected from:
- 15 C1-4alkyl,
C1-4alkyl substituted with from 1 to 6 substituents
independently selected from: fluoro, oxo, -NH₂, C1-4alkoxy, and
-OH,
cycloalkyl, and
20 cycloalkyl substituted with from 1 to 5 substituents independently
selected from:
fluoro,
chloro,
-OH, and
25 C1-6alkyl,
R^{15b'} and R^{16b'} are taken together with the nitrogen to which they are
attached, and optionally from 1 to 3 additional heteroatoms, to form
a heterocyclyl, which is optionally substituted with from 1 to 5
substituents independently selected from:
30 fluoro,

- chloro,
C1-6alkyl,
C1-6alkyl substituted with from 1 to 9 substituents
independently selected from: fluoro, chloro,
5 C1-4alkoxy, oxo, -OH, -NH₂, -N(H)C1-4alkyl,
-N(C1-4alkyl)₂, and -CN,
C1-4alkoxy,
C1-4alkoxy substituted with from 1 to 4 substituents
independently selected from: fluoro, oxo, -OH,
10 -COOH, -NH₂, and -CN,
oxo,
-NH₂,
-N(H)C1-4alkyl, and
-N(C1-4alkyl)₂, or
15 one of R^{15b'} and R^{16b'} is taken together with R^{17b'}, and optionally from 1 to
3 additional heteroatoms, to form a heterocyclyl, which is optionally
substituted with from 1 to 3 substituents independently selected from:
fluoro, -OH, C1-4alkyl, and C1-4alkoxy; and
20 R^{17b'} is selected from: hydrogen and fluoro,
or one of R^{15b'} and R^{16b'} is taken together with R^{17b'}, and optionally from 1
to 3 additional heteroatoms, to form a heterocyclyl, which is
optionally substituted with from 1 to 3 substituents independently
selected from: fluoro, -OH, C1-4alkyl, and C1-4alkoxy;
25 or a pharmaceutically acceptable salt thereof.

4. A compound of Claim 1 or 2 represented by the following Formula (IVb):



where:

5

R^{20b} is C1-2alkyl substituted by:

- phenyl substituted by pyrimidinyl,
- pyrazolyl,
- pyrazolyl substituted by C1-3alkyl,
- 10 pyrazinyl,
- pyrazinyl substituted by C1-3alkyl,
- piperazinyl,
- piperazinyl substituted by oxo,
- piperazinyl substituted by C1-3alkyl,
- 15 oxazolyl,
- oxazolyl substituted by C1-3alkyl,
- imidazolyl,
- imidazolyl substituted by C1-3alkyl,
- morpholinyl,
- 20 morpholinyl substituted 1 or 2 times by C1-3alkyl,
- morpholinyl substituted by oxo,
- dioxanyl,
- dioxanyl substituted by C1-3alkyl,
- 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine;
- 25 triazolyl,
- triazolyl substituted by C1-3alkyl,
- thiazolyl,
- thiazolyl substituted by C1-3alkyl,
- Ocyclopentyl,
- 30 C1-6alkoxy,
- C1-6alkoxy substituted from 1 to 6 times by fluoro,
- C1-6alkoxy substituted by hydroxy,
- tetrahydrofuran,
- pyridyl,

pyridyl substituted by bromo, or
pyridyl substituted by pyrimidinyl;

R^{21b} is selected from:

5	hydrogen, fluoro, chloro, bromo, -OH, -CN, -NH ₂ , -C(O)NHCH ₃ , -C(O)NHCH ₂ CH ₂ OH, -C(O)NHCH ₂ CH ₂ SO ₂ CH ₃ , -C(O)NHOCH ₃ , -C(O)NH ₂ , -C(O)OCH ₃ , -C(O)NHCH ₂ cyclopropyl, -C(O)NHcyclobutyl, optionally substituted by hydroxy, -CH ₂ morpholinyl, -CH ₂ OH, -CH ₂ NHCH ₂ CF ₃ , -CH ₂ NHCH ₂ CH ₂ SO ₂ CH ₃ , -CH ₂ SO ₂ CH ₃ , -CH(OH)CF ₃ , -CH ₃ , -CF ₃ , -OCH ₃ , methoxy-d ₃ , pyrazolyl, oxazolyl, and oxazolyl substituted once or twice by methyl;

R^{22b} , R^{23b} , and R^{24b} are independently selected from:

35 hydrogen,
fluoro,
chloro,
bromo,
-OH,

- boronic acid,
 1,3,6,2-dioxazaborocane-4,8-dione,
 -CN,
 -C(O)NHCH₃,
 5 -C(O)NHCH₂CH₃,
 -C(O)NHCH₂CF₂H,
 -C(O)NHCH₂CH₂OH,
 -C(O)NHCH₂CH₂SO₂CH₃,
 -C(O)NHOCH₃,
 10 -C(O)NH₂,
 -C(O)OCH₃,
 -C(O)NHCH₂cyclopropyl,
 -C(O)NHcyclobutyl, optionally substituted by hydroxy,
 -CH₂morpholinyl,
 15 -CH₂OH,
 -CH₂NHCH₂CF₃,
 -CH₂NHCH₂CH₂SO₂CH₃,
 -CH₂SO₂CH₃,
 -CH(OH)CF₃,
 20 -CH₃,
 -CF₃,
 -OCH₃,
 methoxy-d₃,
 -NHC(O)CH₃,
 25 -NH₂,
 -NHSO₂CH₃,
 morpholinyl
 pyrazolyl,
 oxazolyl, and
 30 oxazolyl substituted once or twice by methyl,
 or R^{23b} and R^{24b} are taken together with the carbon atoms to which they
 are attached to form oxaborolyl, optionally substituted by hydroxy;

R^{25b} and R^{26b} are independently selected from:

- 35 C1-3alkyl,
 C1-3alkyl substituted from 1 to 3 times by fluoro, and

cyclopropyl,

R^{25b} and R^{26b} are taken together with the nitrogen to which they are attached to form:

azetidinyl,

pyrrolidinyl,

each of which is optionally substituted one or two times by:

C1-3alkyl or C1-3alkyl substituted from 1 to 3 times by fluoro,

or

one of R^{25b} and R^{26b} is taken together with R^{27b} , and optionally 1

additional heteroatom, to form:

pyrrolidinyl, or

morpholinyl,

each of which are optionally substituted from 1 to 4 times by

C1-3alkyl; and

R^{27b} is selected from: hydrogen and fluoro;

or one of R^{25b} and R^{26b} is taken together with R^{27b} , and optionally 1

additional heteroatom, to form:

pyrrolidinyl, or

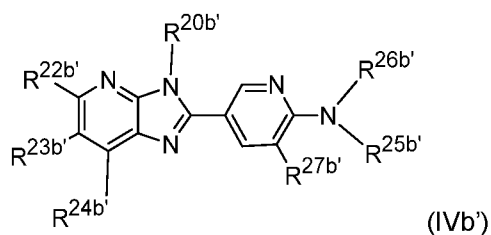
morpholinyl,

each of which are optionally substituted from 1 to 4 times by

C1-3alkyl;

or a pharmaceutically acceptable salt thereof.

5. A compound of Claim 1 or 3 represented by the following Formula (IVb'):



where:

$R^{20b'}$ is C1-2alkyl substituted by:

- phenyl substituted by pyrimidinyl,
- pyrazolyl,
- 5 pyrazolyl substituted by C1-3alkyl,
- pyrazinyl,
- pyrazinyl substituted by C1-3alkyl,
- piperazinyl,
- piperazinyl substituted by oxo,
- 10 piperazinyl substituted by C1-3alkyl,
- oxazolyl,
- oxazolyl substituted by C1-3alkyl,
- imidazolyl,
- imidazolyl substituted by C1-3alkyl,
- 15 morpholinyl,
- morpholinyl substituted 1 or 2 times by C1-3alkyl,
- morpholinyl substituted by oxo,
- dioxanyl,
- dioxanyl substituted by C1-3alkyl,
- 20 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine;
- triazolyl,
- triazolyl substituted by C1-3alkyl,
- thiazolyl,
- thiazolyl substituted by C1-3alkyl,
- 25 -Ocyclopentyl,
- C1-6alkoxy,
- C1-6alkoxy substituted from 1 to 6 times by fluoro,
- C1-6alkoxy substituted by hydroxy,
- tetrahydrofuran,
- 30 pyridyl,
- pyridyl substituted by bromo, or
- pyridyl substituted by pyrimidinyl;

$R^{22b'}$, $R^{23b'}$, and $R^{24b'}$ are independently selected from:

- 35 hydrogen,
- fluoro,
- chloro,
- bromo,
- OH,
- 40 boronic acid,

- 1,3,6,2-dioxazaborocane-4,8-dione,
 -CN,
 -C(O)NHCH₃,
 -C(O)NHCH₂CH₃,
 5 -C(O)NHCH₂CF₂H,
 -C(O)NHCH₂CH₂OH,
 -C(O)NHCH₂CH₂SO₂CH₃,
 -C(O)NHOCH₃,
 -C(O)NH₂,
 10 -C(O)OCH₃,
 -C(O)NHCH₂cyclopropyl,
 -C(O)NHcyclobutyl, optionally substituted by hydroxy,
 -CH₂morpholinyl,
 -CH₂OH,
 15 -CH₂NHCH₂CF₃,
 -CH₂NHCH₂CH₂SO₂CH₃,
 -CH₂SO₂CH₃,
 -CH(OH)CF₃,
 -CH₃,
 20 -CF₃,
 -OCH₃,
 methoxy-d₃,
 -NHC(O)CH₃,
 -NH₂,
 25 -NHSO₂CH₃,
 morpholinyl
 pyrazolyl,
 oxazolyl, and
 oxazolyl substituted once or twice by methyl,
 30 or R^{23b'} and R^{24b'} are taken together with the carbon atoms to which they
 are attached to form oxaborolyl, optionally substituted by hydroxy;

R^{25b'} and R^{26b'} are independently selected from:

- C1-3alkyl,
 35 C1-3alkyl substituted from 1 to 3 times by fluoro, and
 cyclopropyl,

$R^{25b'}$ and $R^{26b'}$ are taken together with the nitrogen to which they are attached to form:

azetidinyl,

pyrrolidinyl,

each of which is optionally substituted one or two times by:

C1-3alkyl or C1-3alkyl substituted from 1 to 3 times by fluoro,

or

one of $R^{25b'}$ and $R^{26b'}$ is taken together with $R^{27b'}$, and optionally 1 additional heteroatom, to form:

pyrrolidinyl, or

morpholinyl,

each of which are optionally substituted from 1 to 4 times by

C1-3alkyl; and

$R^{27b'}$ is selected from: hydrogen and fluoro;

or one of $R^{25b'}$ and $R^{26b'}$ is taken together with $R^{27b'}$, and optionally 1

additional heteroatom, to form:

pyrrolidinyl, or

morpholinyl,

each of which are optionally substituted from 1 to 4 times by

C1-3alkyl;

or a pharmaceutically acceptable salt thereof.

6. A compound of claim 1 selected from:

N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;

5-(1-((1-Ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-dipropylpyridin-2-amine;

N-Ethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N-propylpyridin-2-amine;

- 1-((1-Ethyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;
- N-Ethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N-isopropylpyridin-2-amine;
- 5 2-(6-(Diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- (S)-1-((1-Ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide;
- 10 2-(6-((2S,5R)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-(Cyclopropyl(ethyl)amino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 15 2-(6-(Diethylamino)-5-fluoropyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- (S)-1-((1-Ethyl-1H-pyrazol-3-yl)methyl)-2-(5-fluoro-6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 20 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)-5-fluoropyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-N-(2-hydroxyethyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 25 (S)-1-((1-Ethyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5R)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 5-(4-Chloro-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 30 N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-4-methyl-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole;

- 5-(7-Chloro-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 5-Bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole;
- 5 (2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-(1H-pyrazol-3-yl)-1H-benzo[d]imidazole;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-(1H-pyrazol-4-yl)-1H-benzo[d]imidazole;
- 10 5-(4,5-Dichloro-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-fluoro-1H-benzo[d]imidazole;
- 15 N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-methoxy-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-6-methyl-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 2-(6-(Diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-7-carbonitrile;
- 20 2-(6-(Diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carbonitrile;
- 2-(6-(Diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-4-carbonitrile;
- 25 2-(6-(Diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-4-carboxamide;
- N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-5-methyl-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 5-(5-Chloro-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 30 N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-7-methyl-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- N,N-Diethyl-5-(1-((1-ethyl-1H-pyrazol-3-yl)methyl)-4-methoxy-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;

- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-4-(trifluoromethyl)-1H-benzo[d]imidazole;
- (2-(6-(Diethylamino)pyridin-3-yl)-1-((1-ethyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 5 (S)-1-(2-(Tert-butoxy)ethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;
- 1-(2-(Tert-butoxy)ethyl)-2-(6-((2S,5R)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;
- Methyl 1-(2-(tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxylate;
- 10 1-(2-(Tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide;
- 1-(2-(Tert-butoxy)ethyl)-N-(cyclopropylmethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide;
- 15 1-(2-(Tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-N-(2-hydroxyethyl)-1H-benzo[d]imidazole-5-carboxamide;
- 5-(1-(2-(Tert-butoxy)ethyl)-4-chloro-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 5-(1-(2-(Tert-butoxy)ethyl)-4-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 20 5-(5-Bromo-1-(2-(tert-butoxy)ethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- (1-(2-(Tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 25 5-(1-(2-(Tert-butoxy)ethyl)-5-(1H-pyrazol-3-yl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 5-(1-(2-(tert-butoxy)ethyl)-5-fluoro-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 5-(1-(2-(Tert-butoxy)ethyl)-4-fluoro-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 30 1-(2-(Tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazole-4-carbonitrile;
- 1-(2-(Tert-butoxy)ethyl)-2-(6-(diethylamino)pyridin-3-yl)-1H-benzo[d]imidazole-4-carboxamide;
- 35 N,N-Diethyl-5-(1-(2-isopropoxyethyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;

- 5-(4-Chloro-1-(2-isopropoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 2-(6-(Diethylamino)pyridin-3-yl)-1-(2-isopropoxyethyl)-1H-benzo[d]imidazole-5-carboxamide;
- 5 (S)-1-(2-Isopropoxyethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide;
- (S)-1-(2-Isopropoxyethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide;
- 4-Chloro-2-(6-(diethylamino)pyridin-3-yl)-1-(2-isopropoxyethyl)-1H-benzo[d]imidazole-5-carboxamide;
- 10 5-(4-Chloro-1-(2-isopropoxyethyl)-5-(morpholinomethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole;
- 15 2-(6-((2S,5R)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole;
- (S)-1-(2-Ethoxyethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;
- 1-(2-Ethoxyethyl)-2-(1-ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-benzo[d]imidazole;
- 20 7-(1-(2-Ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-4-ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine;
- 5-(1-(2-Ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N-ethyl-N-(2,2,2-trifluoroethyl)pyridin-2-amine;
- 25 5-(4-Chloro-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- (2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-4-methyl-1H-benzo[d]imidazol-5-yl)boronic acid;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-3H-[1,2]oxaborolo[4',3':3,4]benzo[1,2-d]imidazol-6(8H)-ol;
- 30 4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-5-fluoro-1H-benzo[d]imidazole;

- 5-(5-Bromo-4-chloro-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
(4-Chloro-2-(6-(diethylamino)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 5 5-Bromo-4-chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole;
(4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 10 5-(5-Bromo-4-chloro-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethyl-3-fluoropyridin-2-amine;
(4-Chloro-2-(6-(diethylamino)-5-fluoropyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-4-(trifluoromethyl)-1H-benzo[d]imidazole;
- 15 5-(5-Bromo-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
(2-(6-(Diethylamino)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
(S)-(1-(2-Ethoxyethyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 20 5-Bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole;
(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 25 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-5,6-difluoro-1H-benzo[d]imidazole;
(S)-1-(2-Ethoxyethyl)-4-fluoro-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;
Methyl 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole-5-carboxylate;
- 30 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
(S)-1-(2-Ethoxyethyl)-6-fluoro-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;
- 35 5-(3-(2-Ethoxyethyl)-3H-imidazo[4,5-b]pyridin-2-yl)-N,N-diethylpyridin-2-amine;

- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-N-methyl-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-7-methyl-3H-imidazo[4,5-b]pyridine;
- 5 (2-(6-(Diethylamino)pyridin-3-yl)-3-(2-ethoxyethyl)-3H-imidazo[4,5-b]pyridin-6-yl)boronic acid;
- (2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-3H-imidazo[4,5-b]pyridin-6-yl)boronic acid;
- (2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-(2-ethoxyethyl)-7-methyl-3H-imidazo[4,5-b]pyridin-6-yl)boronic acid;
- 10 5-(4-Chloro-1-(2-propoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 5-(4-Chloro-1-(2-(cyclopentyloxy)ethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 15 5-Bromo-4-chloro-1-(2-(2,2-difluoroethoxy)ethyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;
- (4-Chloro-1-(2-(2,2-difluoroethoxy)ethyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 4-Chloro-1-(2-(2,2-difluoroethoxy)ethyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;
- 20 N,N-Diethyl-5-(1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 4-Ethyl-7-(1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine;
- 25 4-Ethyl-7-(1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine;
- 2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)-4-ethyloxazole;
- 4-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)-2-ethyloxazole;
- 30 2-(4-Ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-1-((2-ethyloxazol-4-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;

- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- (2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-5-yl)methanol;
- 5 N-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-5-yl)methyl)-2,2,2-trifluoroethanamine;
- (S)-1-((1-Methyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;
- N,N-Diethyl-5-(1-((2-ethyl-1H-imidazol-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 10 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyl-1H-imidazol-4-yl)methyl)-1H-benzo[d]imidazole;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((4-ethyl-1H-imidazol-2-yl)methyl)-1H-benzo[d]imidazole;
- 15 N,N-Diethyl-5-(1-((3-ethyl-1H-1,2,4-triazol-5-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- N,N-Diethyl-5-(1-((2-ethylthiazol-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- N,N-Diethyl-5-(1-(oxazol-2-ylmethyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 20 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(4-Ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 25 ((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(4-Ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 30 2-(1-Ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(1-Ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-methyl-1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 35

- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-N-methyl-1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 5 5-Bromo-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-4-fluoro-1H-benzo[d]imidazole;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-4-fluoro-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- (2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)methanol;
- 10 2-(6-(Diethylamino)pyridin-3-yl)-N-methyl-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-methyl-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 15 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 2-(1-Ethyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-methyl-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((3-ethyl-1H-1,2,4-triazol-5-yl)methyl)-1H-benzo[d]imidazole;
- 20 4-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-5-((methylsulfonyl)methyl)-1H-benzo[d]imidazol-1-yl)methyl)-2-ethyloxazole;
- 2-(4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione;
- 25 1-(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-5-yl)-2,2,2-trifluoroethanol;
- N-(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)acetamide;
- (R)-2-(4-ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-N-methyl-3-((2-methyloxazol-4-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 30 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-methyl-3-((2-methyloxazol-4-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- (4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-5-yl)boronic acid;

- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-N-((1R,3S)-3-hydroxycyclobutyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-N-methoxy-1H-benzo[d]imidazole-5-carboxamide;
- 5 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-N-(2-hydroxyethyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-N-(2-(methylsulfonyl)ethyl)-1H-benzo[d]imidazole-5-carboxamide;
- 10 N-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)methyl)-2-(methylsulfonyl)ethanamine;
- 4-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)methyl)morpholine;
- (4-Chloro-1-(2-ethoxyethyl)-2-(4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 15 5-(1-(2-Ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- 5-(1-(2-Ethoxyethyl)-7-methoxy-1H-benzo[d]imidazol-2-yl)-N,N-diethylpyridin-2-amine;
- N,N-Diethyl-5-(1-((2-methyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-
- 20 amine;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-amine;
- N-(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazol-5-yl)methanesulfonamide;
- 25 4-(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridin-6-yl)morpholine;
- (R)-2-(4-Ethyl-3-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-N-methyl-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-methyloxazol-4-
- 30 yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((2-methyloxazol-4-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 2-(4-Ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-N-methyl-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;

- (4-Chloro-2-(4-ethyl-3,3-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- (4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((2-ethyloxazol-4-yl)methyl)-1H-benzo[d]imidazol-5-yl)boronic acid;
- 5 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((2-methyl-1H-imidazol-4-yl)methyl)-3H-imidazo[4,5-b]pyridine;
- 10 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-6-fluoro-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine;
- 15 2-(6-(Diethylamino)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-(Diethylamino)pyridin-3-yl)-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- N,N-Diethyl-5-(1-((tetrahydrofuran-2-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-
- 20 amine;
- (S)-N,N-Diethyl-5-(1-((tetrahydrofuran-2-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- N,N-Diethyl-5-(1-(3-(pyrimidin-5-yl)benzyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 25 2-(6-(Diethylamino)pyridin-3-yl)-N-methyl-1-(3-(pyrimidin-5-yl)benzyl)-1H-benzo[d]imidazole-5-carboxamide;
- (S)-2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine;
- (S)-2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-4-methylmorpholine;
- 30 (S)-2-((4-Fluoro-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine;
- (S)-2-((2-(6-((2S,4S)-2,4-Dimethylazetidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine;

- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1-(((S)-4-methylmorpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-N-methyl-1-(((S)-4-methylmorpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 5 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-ethyl-7-methoxy-1-(((S)-morpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-ethyl-7-methoxy-1-(((S)-4-methylmorpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 10 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-1-(((S)-morpholin-2-yl)methyl)-1H-benzo[d]imidazol-7-ol;
- (S)-2-((4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine;
- (S)-2-((4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)-4-methylmorpholine;
- 15 (S)-2-((7-Methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl);
- (S)-2-((2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine;
- (2S,6S)-2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-6-methylmorpholine;
- 20 (2S,6S)-2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-4,6-dimethylmorpholine;
- 1-(((2S,6S)-4,6-Dimethylmorpholin-2-yl)methyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-N-methyl-1H-benzo[d]imidazole-5-
- 25 carboxamide;
- 1-(((2S,6S)-4,6-Dimethylmorpholin-2-yl)methyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazole-5-carboxamide;
- (S)-2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-fluoro-1H-benzo[d]imidazol-1-yl)methyl)morpholine;
- 30 (S)-2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-fluoro-1H-benzo[d]imidazol-1-yl)methyl)-4-methylmorpholine;
- (S)-2-((4-Chloro-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)methyl)morpholine;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-ethyl-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 35

- N-(2,2-Difluoroethyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-3-((1-methyl-1H-pyrazol-3-yl)methyl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;
- 1-(((R)-1,4-Dioxan-2-yl)methyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-(methoxy-d3)-1H-benzo[d]imidazole;
- 5 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-(methoxy-d3)-1-(pyrazin-2-ylmethyl)-1H-benzo[d]imidazole;
- N-Ethyl-7-methoxy-1-(((S)-4-methylmorpholin-2-yl)methyl)-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide;
- 1-(2-Ethoxyethyl)-2-(6-(ethyl(2,2,2-trifluoroethyl)amino)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazole-5-carboxamide;
- 10 1-(2-Ethoxyethyl)-2-(6-(ethyl(2,2,2-trifluoroethyl)amino)pyridin-3-yl)-7-methoxy-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 1-(2-Ethoxyethyl)-2-(6-(ethyl(2,2,2-trifluoroethyl)amino)pyridin-3-yl)-7-hydroxy-1H-benzo[d]imidazole-5-carboxamide;
- 15 1-(2-Ethoxyethyl)-2-(6-(ethyl(2,2,2-trifluoroethyl)amino)pyridin-3-yl)-7-hydroxy-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- N,N-Diethyl-5-(5-methoxy-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;
- 2-(6-(Diethylamino)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-5-ol;
- 20 4-(2-(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1H-benzo[d]imidazol-1-yl)ethyl)piperazin-2-one;
- 4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-(((S)-morpholin-2-yl)methyl)-1H-benzo[d]imidazol-7-ol;
- 25 (R)-6-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholin-3-one;
- 2-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine;
- (R)-7-Methoxy-1-((1-methyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-(trifluoromethyl)pyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole;
- 30 (R)-1-((1-Methyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-(trifluoromethyl)pyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-7-ol;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-ethyl-4-fluoro-7-methoxy-1-(((S)-morpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;

- N-ethyl-4-fluoro-7-methoxy-1-(((S)-4-methylmorpholin-2-yl)methyl)-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide;
1-(((R)-1,4-Dioxan-2-yl)methyl)-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-N-methyl-1H-benzo[d]imidazole-5-carboxamide;
- 5 4-(2-(4-Chloro-2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)ethyl)piperazin-2-one;
- N-Ethyl-4-fluoro-7-methoxy-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1-(((S)-morpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide;
- 3-((2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)methyl)morpholine;
- 10 (R)-7-Methoxy-N-methyl-1-((1-methyl-1H-pyrazol-3-yl)methyl)-2-(6-(2-(trifluoromethyl)pyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide;
- (S)-2-(6-(4,4-Difluoro-2-methylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole;
- 15 2-(6-((2S,4S)-4-Fluoro-2-methylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole;
- 2-(6-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazole;
- 4-(2-(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)ethyl)morpholine;
- 20 2-(2-(2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-7-methoxy-1H-benzo[d]imidazol-1-yl)ethoxy)ethan-1-ol;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-benzo[d]imidazol-7-amine;
- 25 4-Fluoro-7-methoxy-1-(((S)-4-methylmorpholin-2-yl)methyl)-2-(6-((S)-2-methylpyrrolidin-1-yl)pyridin-3-yl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1-(2-morpholinoethyl)-1H-benzo[d]imidazole-5-carboxamide;
- 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-N-methyl-1-(2-morpholinoethyl)-1H-benzo[d]imidazole-5-carboxamide;
- 30 2-(6-((2S,5S)-2,5-Dimethylpyrrolidin-1-yl)pyridin-3-yl)-4-fluoro-7-methoxy-1-(((S)-4-methylmorpholin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxamide; and
- N,N-Diethyl-5-(1-((6-(pyrimidin-5-yl)pyridin-2-yl)methyl)-1H-benzo[d]imidazol-2-yl)pyridin-2-amine;

or a pharmaceutically acceptable salt thereof.

5 7. A pharmaceutical composition comprising a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

10 8. A method of treating cancer and pre-cancerous syndromes, in a mammal in need thereof, which comprises administering to such mammal a therapeutically effective amount of a compound as described in any one claims 1 to 6 or a pharmaceutically acceptable salt thereof.

15 9. The method of claim 8 wherein the mammal is a human.

20 10. The method according to claim 9 wherein said cancer is selected from: brain (gliomas), glioblastomas, astrocytomas, glioblastoma multiforme, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, adenocarcinoma, ductal adenocarcinoma, adenosquamous carcinoma, acinar cell carcinoma, glucagonoma, insulinoma, metastatic melanoma, prostate, sarcoma and thyroid.

25 11. Use of a compound of Formula (Ib), as described in claim 1 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in treating cancer.

30 12. The method of decreasing MYC protein (c-MYC) in cells and/or inhibiting p300/CBP histone acetyltransferase in a mammal in need thereof, which comprises administering to such mammal a therapeutically effective amount of a compound of Formula Ib, as described in claim 1 or a pharmaceutically acceptable salt thereof.

35 13. The method of claim 12 wherein the mammal is a human.

14. A method of treating cancer in a mammal in need thereof, which comprises:
administering to such mammal a therapeutically effective amount of

- 5 a) a compound of Formula (Ib), as described in claim 1 or a pharmaceutically acceptable salt thereof; and
 b) at least one anti-neoplastic agent.

10 15. The method claim 14, wherein the at least one anti-neoplastic agent is selected from the group consisting of anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, hormones and hormonal analogues, signal transduction pathway inhibitors; non-receptor tyrosine kinase angiogenesis inhibitors;
15 immunotherapeutic agents; proapoptotic agents; cell cycle signaling inhibitors; proteasome inhibitors; and inhibitors of cancer metabolism.

 16. The method of claim 14, wherein the at least one anti-neoplastic agent is an
20 anti-microtubule agent selected from diterpenoids and vinca alkaloids.

 17. The method of claim 14, wherein the at least one anti-neoplastic agent is a
25 diterpenoid.

 18. The method of claim 14, wherein the at least one anti-neoplastic agent is a
vinca alkaloid.

30 19. The method of claim 14, wherein the at least one anti-neoplastic agent is a platinum coordination complex.

35 20. The method of claim 14, wherein the at least one anti-neoplastic agent is paclitaxel, carboplatin, or vinorelbine.

21. The method of claim 14, wherein the at least one anti-neoplastic agent is paclitaxel.

5 22. The method of claim 14, wherein the at least one anti-neoplastic agent is carboplatin.

10 23. The method of claim 14, wherein the at least one anti-neoplastic agent is vinorelbine.

15 24. The method of claim 14, wherein the at least one anti-neoplastic agent is a signal transduction pathway inhibitor.

20 25. The method of claim 24, wherein the signal transduction pathway inhibitor is an inhibitor of a growth factor receptor kinase selected from the group consisting of VEGFR2, TIE2, PDGFR, BTK, IGFR-1, TrkA, TrkB, TrkC, and c-fms.

25 26. The method of claim 24, wherein the signal transduction pathway inhibitor is an inhibitor of a serine/threonine kinase selected from the src family of kinases.

30 27. The method of claim 26, wherein the signal transduction pathway inhibitor is an inhibitor of c-src.

35 28. The method of claim 24, wherein the signal transduction pathway inhibitor is an inhibitor of Ras oncogene selected from inhibitors of farnesyl transferase and geranylgeranyl transferase.

 29. The method of claim 24, wherein the signal transduction pathway inhibitor is an inhibitor of a serine/threonine kinase selected from the group consisting of PI3K, MEK and BRaf.

30. The method of claim 14, wherein the at least one anti-neoplastic agent is a cell cycle signaling inhibitor.

5 31. The method of claim 30, wherein the cell cycle signaling inhibitor is selected from inhibitors of the group CDK2, CDK4, and CDK6.

10 32. A pharmaceutical combination as claimed in claim 14 for use in therapy.

33. The use of a pharmaceutical combination as claimed in claim 14 for the preparation of a medicament useful in the treatment of cancer.

15 34. The method according to claim 8 wherein said cancer is selected from: brain (gliomas), glioblastomas, astrocytomas, glioblastoma multiforme, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, inflammatory breast cancer, Wilm's tumor, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, 20 colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, adenocarcinoma, ductal adenocarcinoma, adenosquamous carcinoma, acinar cell carcinoma, glucagonoma, insulinoma, metastatic melanoma, prostate, sarcoma, osteosarcoma, giant cell tumor of bone, thyroid,

25 Lymphoblastic T cell leukemia, Chronic myelogenous leukemia, Chronic lymphocytic leukemia, Hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, Chronic neutrophilic leukemia, Acute lymphoblastic T cell leukemia, Plasmacytoma, Immunoblastic large cell leukemia, Mantle cell leukemia, Multiple myeloma Megakaryoblastic leukemia, multiple myeloma, acute megakaryocytic leukemia, promyelocytic leukemia, Erythroleukemia,

30 malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma, neuroblastoma, bladder cancer, urothelial cancer, lung cancer, vulval cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharyngeal cancer, buccal 35 cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor) and testicular cancer.

35. The method of claim 34 wherein the mammal is a human.

36. A process for preparing a pharmaceutical composition containing a
5 pharmaceutically acceptable excipient and an effective amount of a compound of Formula
(Ib) as described in claim 1 or a pharmaceutically acceptable salt thereof, which process
comprises bringing the compound of Formula (Ib) or a pharmaceutically acceptable salt
thereof into association with a pharmaceutically acceptable excipient.

10

37. The method according to claim 8 wherein said pre-cancerous syndrome is
selected from: cervical intraepithelial neoplasia, monoclonal gammopathy of unknown
significance (MGUS), myelodysplastic syndrome, aplastic anemia, cervical lesions, skin
nevi (pre-melanoma), prostatic intraepithelial (intraductal) neoplasia (PIN), Ductal
15 Carcinoma in situ (DCIS), colon polyps and severe hepatitis or cirrhosis.

38. The method of claim 14, wherein the at least one anti-neoplastic agent is
pazopanib.

20

39. A method of treating ocular diseases in a human in need thereof, which
comprises administering to such human a therapeutically effective amount of a compound
of Formula Ib, as described in claim 1 or a pharmaceutically acceptable salt thereof.

25

40. A pharmaceutical composition comprising from 0.5 to 1,000 mg of a
compound or pharmaceutically acceptable salt thereof as defined in any one of claims 1 to
4, and from 0.5 to 1,000 mg of a pharmaceutically acceptable excipient.

30

41. The method of inhibiting p300/CBP histone acetyltransferase activity in a
mammal in need thereof, which comprises administering to such mammal a therapeutically
effective amount of a compound of Formula Ib, as described in claim 1 or a
35 pharmaceutically acceptable salt thereof.

42. The method of claim 41 wherein the mammal is a human.

5

43. A method of treating a disease state selected from: cardiac hypertrophy, diabetes, obesity & nonalcoholic fatty liver disease, HIV, polycystic kidney disease, inflammatory diseases, ankylosing spondylitis, psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease, and multiple sclerosis, in a mammal in need thereof, which
10 comprises administering to such mammal a therapeutically effective amount of a compound as described in any one claims 1 to 6 or a pharmaceutically acceptable salt thereof.

44. The method of claim 43 wherein the mammal is a human.

15

45. A method of treating a disease state selected from: cardiac hypertrophy, diabetes, obesity & nonalcoholic fatty liver disease, HIV, polycystic kidney disease, inflammatory diseases, ankylosing spondylitis, psoriasis, psoriatic arthritis, rheumatoid
20 arthritis, Crohn's disease, and multiple sclerosis, in a subject in need thereof, which comprises: administering to such subject a therapeutically effective amount of

- a) a compound of Formula (Ib), as described in claim 1 or a pharmaceutically acceptable salt thereof; and
- b) at least one further active compound.

25

46. The method of decreasing MYC protein (c-MYC) in cells in a mammal in need thereof, which comprises administering to such mammal a therapeutically effective amount of a compound of Formula Ib, as described in claim 1 or a pharmaceutically acceptable salt
30 thereof.

47. The method of claim 41 wherein the mammal is a human.

35

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2018/056806

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/04 C07D471/04 A61K31/4439 A61K31/437 A61P35/00
ADD.

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

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.
X	WO 2011/119565 A1 (SIEMENS MEDICAL SOLUTIONS [US]) 29 September 2011 (2011-09-29) page 105, paragraph [00338]; compound T487 -----	1-7
A	CN 106 977 443 A (UNIV NANCHANG) 25 July 2017 (2017-07-25) abstract page 3, paragraph [0017]; table 1 page 4, paragraph [0018]; table 2 claims 1-3 -----	1-47
A	WO 2016/197078 A1 (SYROS PHARMACEUTICALS INC [US]) 8 December 2016 (2016-12-08) example 150 claims 1, 32, 36 ----- -/--	1-47

☒ 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

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"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

15 November 2018

Date of mailing of the international search report

26/11/2018

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2018/056806

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

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