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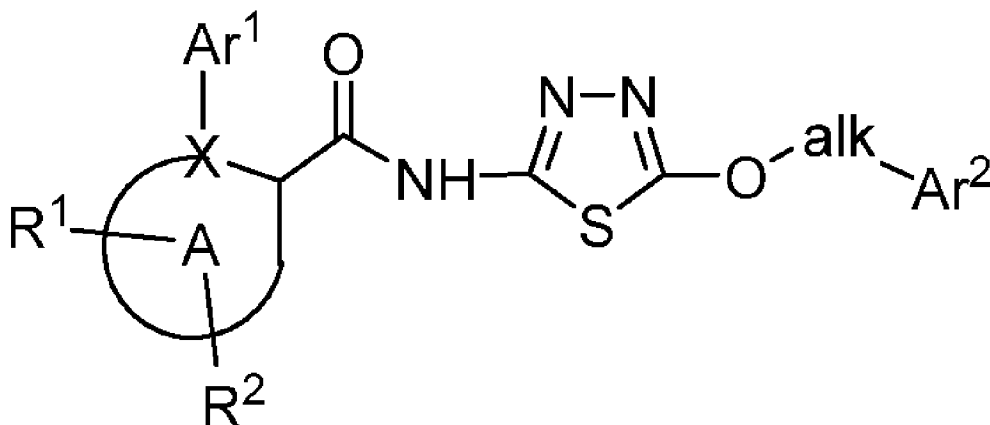
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(71) Demandeur/Applicant:
IDEAYA BIOSCIENCES, INC., US

(72) Inventeurs/Inventors:
BARSANTI, PAUL A., US;
BECK, HILARY PLAKE, US;
FLEURY, MELISSA, US;
KNOX, JOHN E., US; ...

(54) Titre : DERIVES DE THIADIAZOLYLE COMME INHIBITEURS DE L'ADN POLYMERASE THETA

(54) Title: THIADIAZOLYL DERIVATIVES AS DNA POLYMERASE THETA INHIBITORS



(I)

(57) Abrégé/Abstract:

Disclosed herein are certain thiadiazolyl derivatives Formula (I): that inhibit DNA Polymerase Theta (Polθ) activity, in particular inhibit Polθ activity by inhibiting ATP dependent helicase domain activity of Polθ. Also, disclosed are pharmaceutical compositions comprising such compounds and methods of treating and/or preventing diseases treatable by inhibition of Polθ such as cancer, including homologous recombination (HR) deficient cancers.

(72) **Inventeurs(suite)/Inventors(continued)**: MCSPADDEN, ETHAN DENARDO, US; JONES, BRIAN THOMAS, US;
MARTINEZ, LUISRUBEN P., US; PEI, ZHONGHUA, US; WANG, CHENBO, US

(74) **Agent**: BORDEN LADNER GERVAIS LLP

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(71) Applicant: **IDEAYA BIOSCIENCES, INC.** [US/US];
7000 Shoreline Court, Suite 350, South San Francisco, California 94080 (US).

(72) Inventors: **BARSANTI, Paul A.**; c/o Ideaya Biosciences, Inc., 7000 Shoreline Court, Suite 350, South San Francisco, California 94080 (US). **BECK, Hilary Plake**; c/o Ideaya Biosciences, Inc., 7000 Shoreline Court, Suite 350, South San Francisco, California 94080 (US). **FLEURY, Melissa**; c/o Ideaya Biosciences, Inc., 7000 Shoreline Court, Suite 350, South San Francisco, California 94080 (US). **KNOX, John E.**; c/o Ideaya Biosciences, Inc., 7000 Shoreline Court, Suite 350, South San Francisco, California 94080 (US). **MCSPADDEN, Ethan DeNardo**; c/o Ideaya Biosciences, Inc., 7000 Shoreline Court, Suite 350, South San Francisco, California 94080 (US). **JONES, Brian Thomas**; c/o Ideaya Biosciences, Inc., 7000 Shoreline Court, Suite 350, South San Francisco, California 94080 (US). **MARTINEZ, Luisruben P.**; c/o Ideaya Biosciences, Inc., 7000 Shoreline Court, Suite 350, South San Francisco, California 94080 (US). **PEI, Zhonghua**; c/o Ideaya Biosciences, Inc., 7000 Shoreline Court, Suite 350, South San Francisco, California 94080 (US). **WANG, Chenbo**; c/o Ideaya Biosciences, Inc., 7000 Shoreline Court, Suite 350, South San Francisco, California 94080 (US).

(74) Agent: **DOLAN, Gregory F.** et al.; MINTZ LEVIN COHN FERRIS GLOVSKY & POPEO, PC., One Financial Center, Boston, Massachusetts 02111 (US).

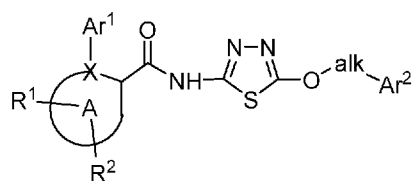
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(54) Title: THIADIAZOLYL DERIVATIVES AS DNA POLYMERASE THETA INHIBITORS



(I)

(57) Abstract: Disclosed herein are certain thiadiazolyl derivatives Formula (I): that inhibit DNA Polymerase Theta (Polθ) activity, in particular inhibit Polθ activity by inhibiting ATP dependent helicase domain activity of Polθ. Also, disclosed are pharmaceutical compositions comprising such compounds and methods of treating and/or preventing diseases treatable by inhibition of Polθ such as cancer, including homologous recombination (HR) deficient cancers.

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THIADIAZOLYL DERIVATIVES AS DNA POLYMERASE THETA INHIBITORS**CROSS-REFERENCES TO RELATED APPLICATIONS**

[0001] This application claims the benefit under 35 U.S.C. 119(e) of U.S. Provisional Application No. 62/855,495, filed on May 31, 2019 and U.S. Provisional Application No. 62/990,239, filed on March 16, 2020, the contents of each is hereby incorporated by reference in their entirety for all purposes.

**STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER
FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT**

[0002] NOT APPLICABLE

**REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER
PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK**

[0003] NOT APPLICABLE

Field:

[0004] Disclosed herein are certain thiadiazolyl derivatives that inhibit DNA Polymerase Theta (Pol θ) activity, in particular inhibit Pol θ activity by inhibiting the ATP dependent helicase domain activity of Pol θ . Also, disclosed are pharmaceutical compositions comprising such compounds and methods of treating and/or preventing diseases treatable by inhibition of Pol θ such as cancer, including homologous recombination deficient (HRD) cancers.

Background:

[0005] Targeting DNA repair deficiencies has become a proven and effective strategy in cancer treatment. However, DNA repair deficient cancers often become dependent on backup DNA repair pathways, which present an "Achilles heel" that can be targeted to eliminate cancer cells, and is the basis of synthetic lethality. Synthetic lethality is exemplified by the success of poly (ADP-ribose) polymerase (PARP) inhibitors in treating BRCA-deficient breast and ovarian cancers (Audeh M. W., et al., Lancet (2010); 376 (9737): 245-51).

[0006] DNA damage repair processes are critical for genome maintenance and stability, among which, double strand breaks (DSBs) are predominantly repaired by the nonhomologous end joining (NHEJ) pathway in G1 phase of the cell cycle and by homologous recombination (HR) in S-G2 phases. A less addressed alternative end-joining (alt-EJ), also known as microhomology-mediated end-joining (MMEJ) pathway, is commonly considered as a “backup” DSB repair pathway when NHEJ or HR are compromised. Numerous genetic studies have highlighted a role for DNA polymerase theta (Pol θ , encoded by *POLQ*) in stimulating MMEJ in higher organisms (Chan S. H., et al., PLoS Genet. (2010); 6: e1001005; Roerink S. F., et al., Genome research. (2014); 24: 954–962; Ceccaldi R., et. al., Nature (2015); 518: 258-62; and Mateos-Gomez P. A., et al., Nature (2015); 518: 254-57).

[0007] Pol θ is distinct among human DNA polymerases, exhibiting not only a C-terminal DNA polymerase domain but also an N-terminal helicase domain separated by a long and lesser-conserved central domain of unknown function beyond Rad51 binding (Seki et al., 2003, Shima et al 2003; Yousefzadeh and Wood 2013). The N-terminal ATPase/helicase domain belongs to the HELQ class of SF2 helicase super family. In homologous recombination deficient (HRD) cells, Pol θ can carry out error-prone DNA synthesis at DNA damage sites through alt-EJ pathway. It has been shown that the helicase domain of Pol θ causes suppression of HR pathway through disruption of Rad51 nucleoprotein complex formation involved in initiation of the HR-dependent DNA repair reactions following ionizing radiation. This anti-recombinase activity of Pol θ promotes the alt-EJ pathway. In addition, the helicase domain of Pol θ contributes to microhomology-mediated strand annealing (Chan SH et al., PLoS Genet. (2010); 6: e1001005; and Kawamura K et al., Int. J. Cancer (2004); 109: 9-16). Pol θ efficiently promotes end-joining in alt-EJ pathway by employing this annealing activity when ssDNA overhangs contain >2 bp of microhomology (Kent T., et al., Elife (2016); 5: e13740), and Kent T., et al., Nat. Struct. Mol. Biol. (2015); 22: 230–237). This reannealing activity is achieved through coupled actions of Rad51 interaction followed by ATPase-mediated displacement of Rad51 from DSB damage sites. Once annealed, the primer strand of DNA can be extended by the polymerase domain of Pol θ .

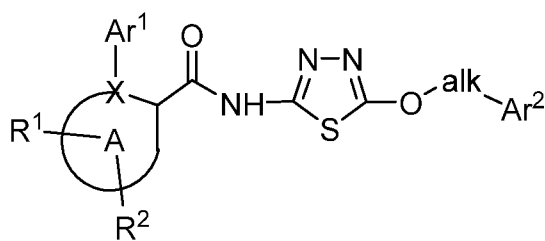
[0008] The expression of Pol θ is largely absent in normal cells but upregulated in breast, lung, and ovarian cancers (Ceccaldi R., et al., Nature (2015); 518, 258-62). Additionally, the increase

of Polθ expression correlates with poor prognosis in breast cancer (Lemee F et al., Proc Natl Acad Sci USA. (2010) ;107: 13390-5). It has been shown that cancer cells with deficiency in HR, NHEJ or ATM are highly dependent on Polθ expression (Ceccaldi R., et al., Nature (2015); 518: 258-62, Mateos-Gomez PA et al., Nature (2015); 518: 254-57, and Wyatt D.W., et al., Mol. Cell (2016); 63: 662-73). Therefore, Polθ is an attractive target for novel synthetic lethal therapy in cancers containing DNA repair defects.

Summary

[0009] Disclosed herein are certain thiadiazolyl derivatives that inhibit Polθ activity, in particular inhibit Polθ activity by inhibiting the ATP dependent helicase domain activity of Polθ. Also, disclosed are pharmaceutical compositions comprising such compounds and methods of treating and/or preventing diseases treatable by inhibition of Polθ such as cancer, including homologous recombination (HR) deficient cancers.

[0010] In a first aspect, provided is a compound of Formula (I):



(I)

wherein:

X is -N- or -C-;

alk is alkylene;

ring A is phenyl or a five to ten membered heteroaryl ring containing, inclusive of X, one to four heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ar¹ is phenyl, heteroaryl, heterocyclyl, bicyclic heterocyclyl, bridged heterocyclyl, or spiroheterocyclyl, wherein each of the aforementioned ring is substituted with R^a, R^b, and/or R^c, wherein R^a and R^b are independently selected from hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, cycloalkyloxy, acyl, acylamino, monoalkylamino, dialkylamino, alkylsulfonyl, cyano, and hydroxy; or R^a and R^b, when on adjacent ring vertices, combine to form a C₃₋₆

cycloalkyl or R^a and R^b, when on the same ring vertex, combine to form oxo, and R^c is selected from hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, heterocyclalkyl, heterocycloxy, aminocarbonyl;

Ar² is phenyl, heteroaryl, or cycloalkyl, wherein said phenyl and heteroaryl are substituted with R^d, R^e and/or R^f, wherein R^d and R^e are independently selected from hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, and cyano and R^f is selected from hydrogen, alkyl, cycloalkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, cyano, cyanomethyl, aminocarbonylmethyl, heteroaryl, and heterocycl, wherein said heteroaryl and heterocycl of R^f are unsubstituted or substituted with one, two, or three substituents independently selected from alkyl, halo, haloalkyl, and hydroxy;

R¹ is hydrogen, alkyl, halo, haloalkyl, haloalkoxy, alkoxy, hydroxy, cyano, cyanoalkyl, carboxy, alkoxy carbonyl, acylamino, aminocarbonyl; optionally substituted heteroaryl, hydroxyalkyl, cycloalkyl, hydroxyalkynyl, alkoxyalkyl, aminoalkyl, aminocarbonylalkyl, sulfonylalkyl, aminosulfonylalkyl, optionally substituted heteroalkyl, or optionally substituted heterocyclalkyl; and

R² is hydrogen, alkyl, halo, haloalkyl, haloalkoxy, or cyano; or
a pharmaceutically acceptable salt thereof.

[0011] In a second aspect, provided is a pharmaceutical composition comprising a compound of Formula (I) or a pharmaceutically acceptable thereof and at least one pharmaceutically acceptable excipient.

[0012] In a third aspect, provided is a method for treating and/or preventing a disease characterized by overexpression of Polθ in a patient comprising administering to the patient a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof (or an embodiment thereof disclosed herein). In first embodiment of the third aspect, the patient is in recognized need of such treatment. In second embodiment of the third aspect and first embodiment contained therein, the compound of Formula (I) (or an embodiment thereof disclosed herein), or a pharmaceutically acceptable salt thereof is administered in a pharmaceutical composition. In third embodiment of the third aspect and first and second embodiments contained therein, the disease is a cancer.

[0013] In a fourth aspect, provided is a method for treating and/or preventing a homologous recombination (HR) deficient cancer in a patient comprising administering to the patient a therapeutically effective amount of a compound of Formula (I) (or an embodiment thereof disclosed herein), or a pharmaceutically acceptable salt thereof. In first embodiment of the fourth aspect, the patient is in recognized need of such treatment. In second embodiment of the fourth aspect and first embodiment contained therein, the compound of Formula (I) (or an embodiment thereof disclosed herein), or a pharmaceutically acceptable salt thereof is administered in a pharmaceutical composition.

[0014] In a fifth aspect, provided is a method for inhibiting DNA repair by Pol θ in a cancer cell comprising contacting the cell with an effective amount of a compound of Formula (I) (or an embodiment thereof disclosed herein), or a pharmaceutically acceptable salt thereof. In a first embodiment, the cancer is HR deficient cancer.

[0015] In a sixth aspect, provided is a method for treating and/or preventing a cancer in a patient, wherein the cancer is characterized by a reduction or absence of BRCA gene expression, the absence of the BRAC gene, or reduced function of BRCA protein, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) (or an embodiment thereof disclosed herein), or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutical composition.

[0016] In a seventh aspect, provided is a compound of Formula (I) (or an embodiment thereof disclosed herein), or a pharmaceutically acceptable salt thereof for inhibiting DNA repair by Pol θ in a cell. In a first embodiment, the cell is HR deficient cell.

[0017] In an eighth aspect, provided is a compound of Formula (I) (or an embodiment thereof disclosed herein), or a pharmaceutically acceptable salt thereof for use in the treatment and/or prevention of a disease in a patient, wherein the disease is characterized by overexpression of Pol θ .

[0018] In a ninth aspect, provided is a compound of Formula (I) (or an embodiment thereof disclosed herein), or a pharmaceutically acceptable salt thereof for use in the treatment and/or prevention of a cancer in a patient, wherein the cancer is characterized by a reduction or absence of BRAC gene expression, the absence of the BRAC gene, or reduced function of BRAC protein.

[0019] In a tenth aspect, provided is a compound of Formula (I) (or an embodiment thereof disclosed herein), or a pharmaceutically acceptable salt thereof for use in the treatment and/or prevention of a HR deficient cancer in a patient.

[0020] In an eleventh aspect, provided is a compound of Formula (I) (or an embodiment thereof disclosed herein), or a pharmaceutically acceptable salt thereof for use in the treatment and/or prevention of a cancer that is resistant to poly(ADP-ribose) polymerase (PARP) inhibitor therapy in a patient. Examples of cancers resistant to PARP-inhibitors include, but are not limited to, breast cancer, ovarian cancer, lung cancer, bladder cancer, liver cancer, head and neck cancer, pancreatic cancer, gastrointestinal cancer, and colorectal cancer.

[0021] In any of the third to eleventh aspects, the cancer is lymphoma, soft tissue, rhabdoid, multiple myeloma, uterus, gastric, peripheral nervous system, rhabdomyosarcoma, bone, colorectal, mesothelioma, breast, ovarian, lung, fibroblast, central nervous system, urinary tract, upper aerodigestive, leukemia, kidney, skin, esophagus, and pancreas (data from large scale drop out screens in cancer cell lines indicate that some cell lines from the above cancers are dependent on polymerase theta for proliferation <https://depmap.org/portal/>).

[0022] In first embodiment, a HR-deficient cancer is breast cancer. Breast cancer includes, but is not limited to, lobular carcinoma *in situ* (LCIS), a ductal carcinoma *in situ* (DCIS), an invasive ductal carcinoma (IDC), inflammatory breast cancer, Paget disease of the nipple, Phyllodes tumor, Angiosarcoma, adenoid cystic carcinoma, low- grade adenosquamous carcinoma, medullary carcinoma, mucinous carcinoma, papillary carcinoma, tubular carcinoma, metaplastic carcinoma, micropapillary carcinoma, mixed carcinoma, or another breast cancer, including but not limited to triple negative, HER positive, estrogen receptor positive, progesterone receptor positive, HER and estrogen receptor positive, HER and progesterone receptor positive, estrogen and progesterone receptor positive, and HER and estrogen and progesterone receptor positive. In second embodiment, HR-deficient cancer is ovarian cancer. Ovarian cancer includes, but is not limited to, epithelial ovarian carcinomas (EOC), maturing teratomas, dysgerminomas, endodermal sinus tumors, granulosa-theca tumors, Sertoli-Leydig cell tumors, and primary peritoneal carcinoma.

Brief Description of The Drawings

[0023] NOT APPLICABLE

Detailed Description

[0024] Before the present invention is further described, it is to be understood that the invention is not limited to the particular embodiments set forth herein, and it is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

[0025] The singular forms “a,” “an,” and “the” as used herein and in the appended claims include plural referents unless the context clearly dictates otherwise. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology such as “solely,” “only” and the like in connection with the recitation of claim elements, or use of a “negative” limitation.

[0026] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges, and are also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

[0027] When needed, any definition herein may be used in combination with any other definition to describe a composite structural group. By convention, the trailing element of any such definition is that which attaches to the parent moiety. For example, the composite group alkoxyalkyl means that an alkoxy group is attached to the parent molecule through an alkyl group.

[0028] The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Further, the dates of publication provided may be different from the actual publication dates, which may need to be independently confirmed.

Definitions:

[0029] Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meaning:

[0030] “Alkyl” means a linear saturated monovalent hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbon atoms, e.g., methyl, ethyl, propyl, 2-propyl, butyl, pentyl, and the like. It will be recognized by a person skilled in the art that the term “alkyl” may include “alkylene” groups.

[0031] “Alkylene” means a linear saturated divalent hydrocarbon radical of one to six carbon atoms or a branched saturated divalent hydrocarbon radical of three to six carbon atoms unless otherwise stated e.g., methylene, ethylene, propylene, 1-methylpropylene, 2-methylpropylene, butylene, pentylene, and the like.

[0032] “Alkylsulfonyl” means a $-\text{SO}_2\text{R}$ radical where R is alkyl as defined above, e.g., methylsulfonyl, ethylsulfonyl, 2-propylsulfonyl, and the like.

[0033] “Alkoxy” means a $-\text{OR}$ radical where R is alkyl as defined above, e.g., methoxy, ethoxy, propoxy, or 2-propoxy, *n*-, *iso*-, or *tert*-butoxy, and the like.

[0034] “Alkoxycarbonyl” means a $-\text{COOR}$ radical where R is alkyl as defined above, e.g., methoxycarbonyl, ethoxycarbonyl, propoxy, or 2-propoxycarbonyl, *n*-, *iso*-, or *tert*-butoxycarbonyl, and the like.

[0035] “Alkoxyalkyl” means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbons substituted with one alkoxy group, as defined above, e.g., 2-methoxyethyl, 1-, 2-, or 3-methoxypropyl, 2-ethoxyethyl, and the like.

[0036] “Acyl” means a $-\text{C}(\text{O})\text{R}$ radical where R is alkyl as defined herein, e.g., methylcarbonyl, ethylcarbonyl, and the like.

[0037] “Acylamino” means a $-\text{NHC}(\text{O})\text{R}$ radical where R is alkyl as defined herein, e.g., methylcarbonylamino, ethylcarbonylamino, and the like.

[0038] “Amino” means a $-\text{NH}_2$.

[0039] “Aminoalkyl” means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbons substituted with –NR’R” where R’ and R” are independently hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, or acyl, each as defined herein, e.g., aminomethyl, aminoethyl, methylaminomethyl, and the like.

[0040] “Aminocarbonyl” means a –CONRR’ radical wherein R and R’ are independently hydrogen or alkyl as defined herein, e.g., –CONH₂, methylaminocarbonyl, dimethylaminocarbonyl, and the like.

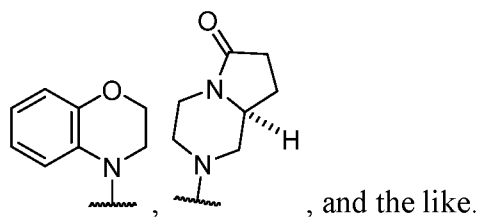
[0041] “Aminocarbonylalkyl” means alkyl radical as defined above that is substituted with –CONRR’ radical wherein R and R’ are independently hydrogen or alkyl as defined herein, e.g., –(CH₂)₂CONH₂, methylaminocarbonylmethyl, dimethylaminocarbonylethyl, and the like.

[0042] “Aminocarbonylmethyl” means a –CH₂CONRR’ radical wherein R and R’ are independently hydrogen or alkyl as defined herein, e.g., –CH₂CONH₂, methylaminocarbonylmethyl, dimethylaminocarbonylmethyl, and the like.

[0043] “Aminosulfonylalkyl” means alkyl radical as defined above that is substituted with –SO₂NRR’ radical wherein R and R’ are independently hydrogen or alkyl as defined herein, e.g., –(CH₂)₂SO₂NH₂, methylaminosulfonylmethyl, dimethylaminosulfonylethyl, and the like.

[0044] “Aryl” means a monovalent monocyclic or bicyclic aromatic hydrocarbon radical of 6 to 10 ring atoms e.g., phenyl or naphthyl.

[0045] "Bicyclic heterocyclyl" means a saturated monocyclic ring having 4 to 7 ring carbon ring atoms wherein one or two ring carbon atoms is(are) replaced by a heteroatom selected from N, O, or S(O)_n, (where n is an integer from 0 to 2) that is fused to phenyl, five or six-membered heteroaryl or heterocyclyl, each as defined herein. Exemplary bicyclic heterocyclyl groups include, but are not limited to,



[0046] "Bridged heterocyclyl" means a saturated monocyclic ring having 5 to 7 ring carbon atoms in which two non-adjacent ring atoms are linked by a (CRR')_n group where n is 1 to 3 and each R is independently H or methyl (also may be referred to herein as "bridging" group) and further wherein one or two ring carbon atoms, including an atom in the bridging group, is replaced by a heteroatom selected from N, O, or S(O)_n, where n is an integer from 0 to 2. Bridged heterocyclyl is optionally substituted with one or two substituents independently selected from alkyl, halo, alkoxy, hydroxy, or cyano. Examples include, but are not limited to, 2-azabicyclo[2.2.2]octane, quinuclidine, 7-oxabicyclo[2.2.1]heptane, and the like.

[0047] "Cycloalkyl" means a monocyclic monovalent hydrocarbon radical of three to six carbon atoms which may be saturated or contains one double bond. Cycloalkyl may be unsubstituted or substituted with one or two substituents independently selected from alkyl, halo, alkoxy, hydroxy, or cyano. Examples include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyanocycloprop-1-yl, 1-cyanomethylcycloprop-1-yl, 3-fluorocyclohexyl, and the like. When cycloalkyl contains a double bond, it may be referred to herein as cycloalkenyl.

[0048] "Cycloalkyloxy" means -O-R radical where R is cycloalkyl as defined above. Examples include, but are not limited to, cyclopropyloxy, cyclobutyloxy, and the like.

[0049] "Cyanoalkyl" means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbons substituted with one cyano, as defined above, e.g., cyanomethyl, 2-cyanoethyl, and the like.

[0050] "Deuteroalkyl" means an alkyl radical as defined above wherein one to six hydrogen atoms in the alkyl radical are replaced by deuterium, e.g., -CD₃, -CH₂CD₃, and the like.

[0051] "Dialkylamino" means -NRR' radical where R and R' are independently alkyl as defined herein.

[0052] "Halo" means fluoro, chloro, bromo, or iodo, preferably fluoro or chloro.

[0053] "Haloalkyl" means alkyl radical as defined above, which is substituted with one to five halogen atoms, such as fluorine or chlorine, including those substituted with different halogens,

e.g., $-\text{CH}_2\text{Cl}$, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{CF}_3$, $-\text{CF}_2\text{CF}_3$, $-\text{CF}(\text{CH}_3)_2$, and the like. When the alkyl is substituted with only fluoro, it can be referred to in this Application as fluoroalkyl.

[0054] “Haloalkoxy” means a $-\text{OR}$ radical where R is haloalkyl as defined above e.g., $-\text{OCF}_3$, $-\text{OCHF}_2$, and the like. When R is haloalkyl where the alkyl is substituted with only fluoro, it is referred to in this Application as fluoroalkoxy.

[0055] “Hydroxyalkyl” means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbons substituted with one or two hydroxy groups, provided that if two hydroxy groups are present, they are not both on the same carbon atom. Representative examples include, but are not limited to, hydroxymethyl, 2-hydroxy-ethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-(hydroxymethyl)-2-methylpropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxypropyl, 1-(hydroxymethyl)-2-hydroxyethyl, 2,3-dihydroxybutyl, 3,4-dihydroxybutyl and 2-(hydroxymethyl)-3-hydroxypropyl, preferably 2-hydroxyethyl, 2,3-dihydroxypropyl, and 1-(hydroxymethyl)-2-hydroxyethyl.

[0056] “Hydroxyalkynyl” means a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms that contains a triple bond and is substituted with a hydroxy group.

[0057] “Heteroaryl” means a monovalent monocyclic or bicyclic aromatic radical of 5 to 10 ring atoms, unless otherwise stated, where one or more, (in one embodiment, one, two, or three), ring atoms are heteroatom selected from N, O, or S, the remaining ring atoms being carbon, unless stated otherwise. Non-limiting examples of heteroaryl groups include pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, quinolynyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, benzotriazinyl, purinyl, benzimidazolyl, benzopyrazolyl, benzotriazolyl, benzoxazolyl, benzisoxazolyl, isobenzofuryl, isoindolyl, indolizynyl, benzotriazinyl, thienopyridinyl, thienopyrimidinyl, pyrazolopyrimidinyl, imidazopyridines, benzothiazolyl, benzothiadiazolyl, benzofuranyl, benzothienyl, indolyl, quinolyl, isoquinolyl, isothiazolyl, pyrazolyl, indazolyl, pteridinyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiadiazolyl, pyrrolyl, thiazolyl, furyl, thienyl, and the like. When the heteroaryl ring contains 5 or 6 ring atoms it is also referred to herein as five or six membered heteroaryl.

[0058] “Heterocyclyl” means a saturated or unsaturated monovalent monocyclic group of 4 to 8 ring atoms in which one or two ring atoms are heteroatom selected from N, O, or S(O)_n, where n is an integer from 0 to 2, the remaining ring atoms being C. Additionally, one or two ring carbon atoms in the heterocyclyl ring can optionally be replaced by a –CO– group. More specifically the term heterocyclyl includes, but is not limited to, azetidiny, oxetanyl, pyrrolidino, piperidino, homopiperidino, 2-oxopyrrolidinyl, 2-oxopiperidinyl, morpholino, piperazino, tetrahydro-pyranyl, thiomorpholino, and the like. When the heterocyclyl ring is unsaturated it can contain one or two ring double bonds provided that the ring is not aromatic.

[0059] “Heterocyclyloxy” means a –O-R radical where R is heterocyclyl, as defined above.

[0060] “Heterocyclylalkyl” means a –(alkylene)-R radical where R is heterocyclyl, each group as defined herein.

[0061] “Monoalkylamino” means a -NHR radical where R is alkyl as defined above, e.g., methylamino, ethylamino, propylamino, or 2-propylamino, and the like.

[0062] “Oxo,” as used herein, alone or in combination, refers to =(O).

[0063] “Optionally substituted heteroaralkyl” means -(alkylene)-heteroaryl, each as defined above, wherein heteroaryl is optionally substituted with one, two, or three substituents independently selected from alkyl, alkylsulfonyl, cycloalkyl, carboxy, alkoxycarbonyl, hydroxy, alkoxy, halo, haloalkyl, haloalkoxy, amino, alkylamino, dialkylamino, and cyano, unless stated otherwise.

[0064] “Optionally substituted heterocyclyl” means -(alkylene)-heterocyclyl, each as defined above, wherein heterocyclyl is optionally substituted with one, two, or three substituents independently selected from alkyl, alkylsulfonyl, cycloalkyl, carboxy, alkoxycarbonyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, aminoalkyl, halo, haloalkyl, haloalkoxy, and cyano, unless stated otherwise.

[0065] “Sulfonylalkyl” means alkyl radical as defined above that is substituted with -SO₂R radical wherein R is alkyl as defined herein, e.g., methylsulfonylmethyl, ethylsulfonylethyl, and the like.

[0066] "Spiroheterocyclyl" means a saturated bicyclic ring having 6 to 10 ring atoms in which one, two, or three ring atoms are heteroatom selected from N, O, or S(O)_n, where n is an integer from 0 to 2, the remaining ring atoms being C and the rings are connected through only one atom, the connecting atom is also called the spiroatom, most often a quaternary carbon ("spiro carbon"). Examples include, but are not limited to, 2,6-diazaspiro[3.3]heptane, 2,6-diazaspiro[3.4]octane, 4-oxa-7-azaspiro[2.5]octane, 2-azaspiro[3.4]octane, 2-azaspiro[3.5]nonane, 2,7-diazaspiro[4.4]nonane, and the like.

[0067] "Pharmaceutically acceptable salts" as used herein is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds disclosed herein contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of salts derived from pharmaceutically acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like. Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary and tertiary amines, including substituted amines, cyclic amines, naturally-occurring amines and the like, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogen carbonic, phosphoric, monohydrogen phosphoric, dihydrogen phosphoric, sulfuric, monohydrogen sulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also

included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S.M., et al, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, **1977**, *66*, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0068] The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound can differ from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

[0069] The present disclosure also includes protected derivatives of compounds of the present disclosure. For example, when compounds of the present disclosure contain groups such as hydroxy, carboxy, thiol or any group containing a nitrogen atom(s), these groups can be protected with a suitable protecting groups. A comprehensive list of suitable protective groups can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, 5th Ed., John Wiley & Sons, Inc. (2014), the disclosure of which is incorporated herein by reference in its entirety. The protected derivatives of compounds of the present disclosure can be prepared by methods well known in the art.

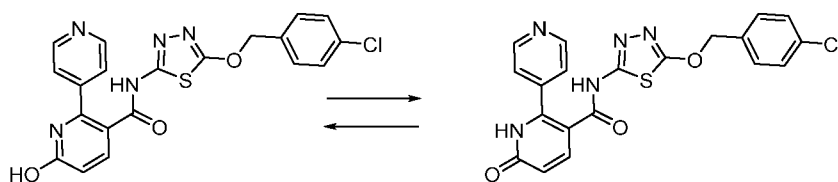
[0070] The present disclosure also includes prodrugs of the compound of Formula (I) (and any embodiment thereof disclosed herein including specific compounds) or a pharmaceutically acceptable salt thereof. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. An example, without limitation, of a prodrug would be a compound which is administered as an ester (the "prodrug"), but then is metabolically hydrolyzed to the carboxylic acid, the active entity. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

[0071] Certain compounds of Formulae (I) (and any embodiment thereof disclosed herein including specific compounds) can exist in unsolvated forms as well as solvated forms, including

hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain compounds of Formulae (I) may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present disclosure and are intended to be within the scope of the present disclosure.

[0072] Certain compounds of Formulae (I) (and any embodiment thereof disclosed herein including specific compounds) possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers, regioisomers and individual isomers (e.g., separate enantiomers) are all intended to be encompassed within the scope of the present invention. When a stereochemical depiction is shown, it is meant to refer to the compound in which one of the isomers is present and substantially free of the other isomer. ‘Substantially free of’ another isomer indicates at least an 80/20 ratio of the two isomers, more preferably 90/10, or 95/5 or more. In some embodiments, one of the isomers will be present in an amount of at least 99%.

[0073] Certain compounds of the present disclosure can exist as tautomers and/or geometric isomers. All possible tautomers and *cis* and *trans* isomers, as individual forms and mixtures thereof are within the scope of this disclosure. For example, certain hydroxy substituted compound of Formula (I) may exist as as tautomers as shown below:



[0074] The compounds of Formulae (I) (and any embodiment thereof disclosed herein including specific compounds) may also contain unnatural amounts of isotopes at one or more of the atoms that constitute such compounds. Unnatural amounts of an isotope may be defined as ranging from the amount found in nature to an amount 100% of the atom in question. that differ only in the presence of one or more isotopically enriched atoms. Exemplary isotopes that can be incorporated into compounds of the present invention, such as a compound of Formula (I) (and any embodiment thereof disclosed herein including specific compounds) include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, and iodine, such as

^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{32}P , ^{33}P , ^{35}S , ^{18}F , ^{36}Cl , ^{123}I , and ^{125}I , respectively. Isotopically labeled compounds (e.g., those labeled with ^3H and ^{14}C) can be useful in compound or substrate tissue distribution assays. Tritiated (i.e., ^3H) and carbon-14 (i.e., ^{14}C) isotopes can be useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements). In some embodiments, in compounds disclosed herein, including in Table 1 below one or more hydrogen atoms are replaced by ^2H or ^3H , or one or more carbon atoms are replaced by ^{13}C - or ^{14}C -enriched carbon. Positron emitting isotopes such as ^{15}O , ^{13}N , ^{11}C , and ^{15}F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Isotopically labeled compounds can generally be prepared by following procedures analogous to those disclosed in the Schemes or in the Examples herein, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

[0075] “Pharmaceutically acceptable carrier or excipient” means a carrier or an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier or an excipient that is acceptable for veterinary use as well as human pharmaceutical use. “A pharmaceutically acceptable carrier/excipient” as used in the specification and claims includes both one and more than one such excipient.

[0076] “About,” as used herein, is intended to qualify the numerical values which it modifies, denoting such a value as variable within a margin of error. When no particular margin of error, such as a standard deviation to a mean value given in a chart or table of data, is recited, the term “about” should be understood to mean that range which would encompass $\pm 10\%$, preferably $\pm 5\%$, the recited value and the range is included.

[0077] “Disease” as used herein is intended to be generally synonymous, and is used interchangeably with, the terms “disorder,” “syndrome,” and “condition” (as in medical condition), in that all reflect an abnormal condition of the human or animal body or of one of its parts that impairs normal functioning, is typically manifested by distinguishing signs and symptoms, and causes the human or animal to have a reduced duration or quality of life.

[0078] “Patient” is generally synonymous with the term “subject” and as used herein includes all mammals including humans. Examples of patients include humans, livestock such as cows, goats, sheep, pigs, and rabbits, and companion animals such as dogs, cats, rabbits, and horses. Preferably, the patient is a human.

[0079] “In need of treatment” as used herein means the patient is being treated by a physician or other caregiver after diagnoses of the disease. For example, the patient has been diagnosed as having a disease linked to overexpression of Polθ or a homologous recombination (HR)-deficient cancer.

[0080] “Administration”, “administer” and the like, as they apply to, for example, a patient, cell, tissue, organ, or biological fluid, refer to contact of, for example, a compound of Formula (I), a pharmaceutical composition comprising same, or a diagnostic agent to the subject, cell, tissue, organ, or biological fluid. In the context of a cell, administration includes contact (e.g., in vitro or ex vivo) of a reagent to the cell, as well as contact of a reagent to a fluid, where the fluid is in contact with the cell.

[0081] “Therapeutically effective amount” as used herein means the amount of a compound of Formula (I) (and any embodiment thereof disclosed herein including specific compounds) or a pharmaceutically acceptable salt thereof that, when administered to a patient for treating a disease either alone or as part of a pharmaceutical composition and either in a single dose or as part of a series of doses, is sufficient to affect such treatment for the disease. The “therapeutically effective amount” will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated. The therapeutically effective amount can be ascertained by measuring relevant physiological effects, and it can be adjusted in connection with the dosing regimen and diagnostic analysis of the subject’s condition, and the like. By way of example, measurement of the serum level of a compound of Formula (I) (or, e.g., a metabolite thereof) at a particular time post-administration may be indicative of whether a therapeutically effective amount has been used.

[0082] “Treating” or “treatment” of a disease includes:

(1) inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms; or

(2) relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

[0083] "Inhibiting", "reducing," or any variation of these terms in relation of Polθ, includes any measurable decrease or complete inhibition to achieve a desired result. For example, there may be a decrease of about, at most about, or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or more, or any range derivable therein, reduction of Polθ activity compared to its normal activity.

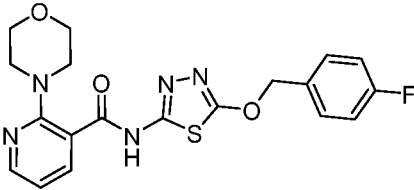
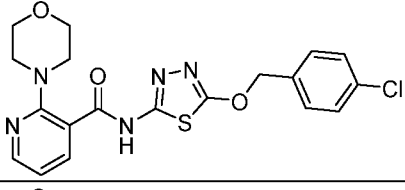
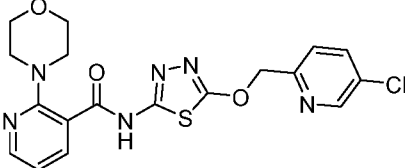
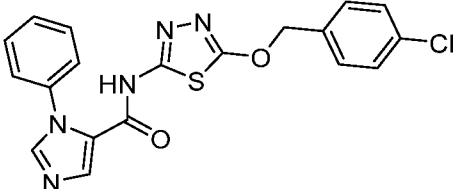
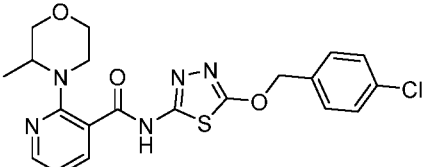
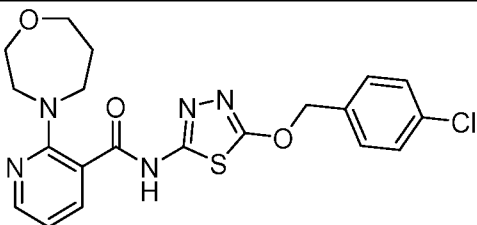
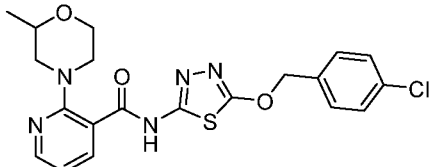
[0084] The term "preventing" refers to causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease.

[0085] The term "homologous recombination" refers to the cellular process of genetic recombination in which nucleotide sequences are exchanged between two similar or identical DNA.

[0086] The term "homologous recombination (HR) deficient cancer" refers to a cancer that is characterized by a reduction or absence of a functional HR repair pathway. HR deficiency may arise from absence of one or more HR-associated genes or presence of one or more mutations in one or more HR-associated genes. Examples of HR-associated genes include BRCA1, BRCA2, RAD54, RAD51B, CtIP (Choline Transporter-Like Protein), PALB2 (Partner and Localizer of BRCA2), XRCC2 (X-ray repair complementing defective repair in Chinese hamster cells 2), RECQL4 (RecQ Protein-Like 4), BLM (Bloom syndrome, RecQ helicase-like), WRN (Werner syndrome, one or more HR-associated genes) Nbs 1 (Nibrin), and genes encoding Fanconi anemia (FA) proteins or FA-like genes e.g. FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANJ (BRIP1), FANCL, FANCM, FANCN (RALB2), FANCP (SLX4), FANCS (BRCA1), RAD51C, and XPF.

[0087] The term "Polθ overexpression" refers to the increased expression or activity of Polθ in a diseases cell e.g., cancerous cell, relative to expression or activity of Polθ in a normal cell (e.g., non-diseased cell of the same kind). The amount of Polθ can be at least 2-fold, at least 3-fold, at least 4- fold, at least 5- fold, at least 10-fold, or more relative to the Polθ expression in a normal cell. Examples of Polθ cancers include, but are not limited to, breast, ovarian, cervical, lung, colorectal, gastric, bladder and prostate cancers.

[0088] Representative compound of Formula (I) are listed in Table 1 below:

Cpd #	Structure	Name
1		N-(5-((4-fluorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide
2		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide
3		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide
4		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-phenyl-1H-imidazole-5-carboxamide
5		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(3-methylmorpholino)nicotinamide
6		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(1,4-oxazepan-4-yl)nicotinamide
7		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2-methylmorpholino)nicotinamide

Cpd #	Structure	Name
8		N-(5-((6-chloropyridin-3-yl)methoxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide
9		(R)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(3-methylmorpholino)nicotinamide
10		(S)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(3-methylmorpholino)nicotinamide
11		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(1H-tetrazol-1-yl)nicotinamide
12		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(4-methoxyphenyl)-1H-imidazole-5-carboxamide
13		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-morpholinopyrimidine-5-carboxamide
14		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-2-morpholinonicotinamide
15		N-(5-((5-bromopyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide

Cpd #	Structure	Name
16		2-(4-acetylpiperazin-1-yl)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)nicotinamide
17		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(pyridin-3-yl)-1H-imidazole-5-carboxamide
18		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(pyridin-4-yl)-1H-imidazole-5-carboxamide
19		N-(5-((5-chloropyrazin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide
20		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-2-(4-hydroxypiperidin-1-yl)nicotinamide
21		N5-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-morpholinopyridine-2,5-dicarboxamide
22		(R)-N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-2-(3-methylmorpholino)nicotinamide

Cpd #	Structure	Name
23		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-2-(4-(methylsulfonyl)piperazin-1-yl)nicotinamide
24		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-1-phenyl-1H-pyrazole-5-carboxamide
25		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-1-phenyl-1H-1,2,3-triazole-5-carboxamide
26		1-(2-chlorophenyl)-N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-1H-imidazole-5-carboxamide
27		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(3-oxopiperazin-1-yl)nicotinamide-6-d
28		4-(3-((5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)carbamoyl)pyridin-2-yl)-N,N-dimethylpiperazine-1-carboxamide
29		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)-2-morpholinonicotinamide
30		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(4-oxa-7-azaspiro[2.5]octan-7-yl)nicotinamide

Cpd #	Structure	Name
31		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(2,4-dimethoxyphenyl)-1H-imidazole-5-carboxamide
32		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-6-cyano-2-morpholinonicotinamide
33		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-5-cyano-2-morpholinonicotinamide
34		N-(5-((4-chloro-3-methoxybenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide
35		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-4-morpholinonicotinamide
36		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-6-methoxy-4-morpholinonicotinamide
37		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-2-(1,1-dioxidothiomorpholino)nicotinamide

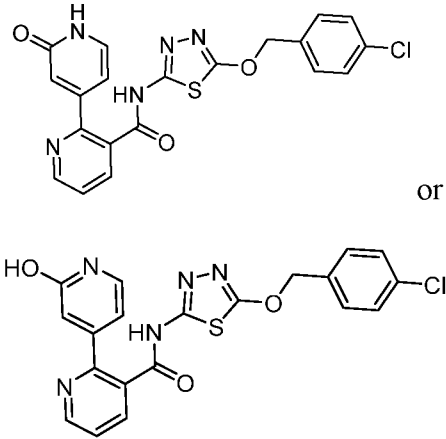
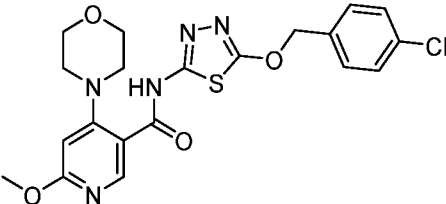
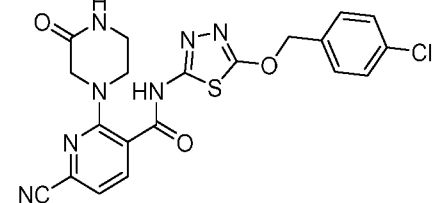
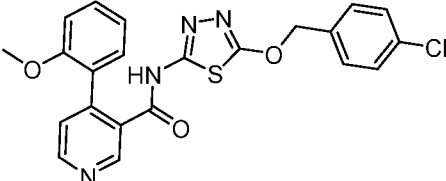
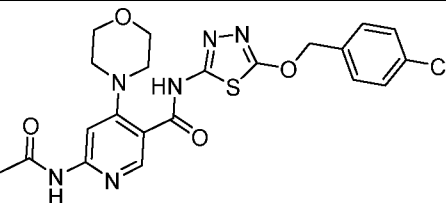
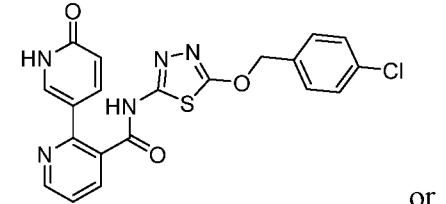
Cpd #	Structure	Name
38		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-1-(pyridin-2-yl)-1H-imidazole-5-carboxamide
39		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-2-(4,4-difluoropiperidin-1-yl)nicotinamide
40		N-(5-((4-bromobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide
41		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-morpholino-6-oxo-1,6-dihydropyridine-3-carboxamide or its tautomer N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-hydroxy-4-morpholinonicotinamide
42		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(2-chlorophenyl)-1H-imidazole-5-carboxamide
43		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(2-cyanophenyl)-1H-imidazole-5-carboxamide
44		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-2-(4-oxa-7-azaspiro[2.5]octan-7-yl)nicotinamide

Cpd #	Structure	Name
45		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(4-methyl-3-oxopiperazin-1-yl)nicotinamide
46		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(3-methyl-5-oxopiperazin-1-yl)nicotinamide
47		N-(5-((4-cyclopropylbenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide
48		N5-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-morpholinopyridine-2,5-dicarboxamide
49		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(3-methoxyphenyl)-1H-imidazole-5-carboxamide
50		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(2-methoxyphenyl)-1H-imidazole-5-carboxamide
51		2-(2-chlorophenyl)-N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)nicotinamide
52		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2-methyl-3-oxopiperazin-1-yl)nicotinamide

Cpd #	Structure	Name
53		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(3,6-dihydro-2H-pyran-4-yl)nicotinamide
54		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(tetrahydro-2H-pyran-4-yl)nicotinamide
55		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazole-5-carboxamide
56		2-morpholino-N-(5-((4-(oxetan-3-yl)benzyl)oxy)-1,3,4-thiadiazol-2-yl)nicotinamide-6-d
57		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(6-oxohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl-8a-d)nicotinamide
58		6-bromo-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide
59		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-morpholinoisonicotinamide
60		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2-methyl-5-oxopiperazin-1-yl)nicotinamide

Cpd #	Structure	Name
61		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(5-oxo-1,4-diazepan-1-yl)nicotinamide
62		N-(5-((4-cyclopropylbenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(2-methoxyphenyl)-1H-imidazole-5-carboxamide
63		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(3-oxo-1,4-diazepan-1-yl)nicotinamide
64		N ⁵ -(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-N ² -methyl-4-morpholinopyridine-2,5-dicarboxamide
65		2-morpholino-N-(5-((4-(oxazol-2-yl)benzyl)oxy)-1,3,4-thiadiazol-2-yl)benzyl)nicotinamide
66		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)nicotinamide
67		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2-methoxyphenyl)nicotinamide

Cpd #	Structure	Name
68		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(4-(2-hydroxyethyl)-3-oxopiperazin-1-yl)nicotinamide
69		(S)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(6-oxohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl-8a-d)nicotinamide
70		(R)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(6-oxohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl-8a-d)nicotinamide
71		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-2-(2-methoxyphenyl)nicotinamide
72		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-cyano-2-morpholinobenzamide
73		N5-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-N2,N2-dimethyl-4-morpholinopyridine-2,5-dicarboxamide

Cpd #	Structure	Name
74		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2'-oxo-1',2'-dihydro-[2,4'-bipyridine]-3-carboxamide or its tautomer N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2'-hydroxy-[2,4'-bipyridine]-3-carboxamide
75		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-methoxy-4-morpholinonicotinamide
76		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-2-(3-oxopiperazin-1-yl)nicotinamide
77		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)nicotinamide
78		6-acetamido-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-morpholinonicotinamide
79		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6'-oxo-1',6'-dihydro-[2,3'-bipyridine]-3-carboxamide or its tautomer N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6'-hydroxy-[2,3'-bipyridine]-3-carboxamide

Cpd #	Structure	Name
80		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1'-methyl-6'-oxo-1',6'-dihydro-[2,3'-bipyridine]-3-carboxamide
81		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-fluoro-5-(2-methoxyphenyl)-isonicotinamide
82		N-(5-((4-fluorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(2-methoxyphenyl)-1H-1,2,3-triazole-5-carboxamide
83		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-(4-(2-morpholinoethyl)-3-oxopiperazin-1-yl)nicotinamide
84		5-((5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)carbamoyl)-4-morpholinopicolinic acid
85		N-(5-((4-bromobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-2-(4-oxa-7-azaspiro[2.5]octan-7-yl)nicotinamide

Cpd #	Structure	Name
86		N-(5-((4-bromobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(2-methoxyphenyl)-1H-imidazole-5-carboxamide
87		N5-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-N2-methyl-4-(5-oxo-1,4-diazepan-1-yl)pyridine-2,5-dicarboxamide
88		N-(5-((4-bromobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-2-(3-oxopiperazin-1-yl)nicotinamide
89		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)nicotinamide
90		N-(5-(cyclopropylmethoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)nicotinamide
91		2-(2-chlorophenyl)-N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]pyridine-3-
92		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-4-(2-methoxyphenyl)nicotinamide
93		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-(2-cyclopropoxyphenyl)nicotinamide

Cpd #	Structure	Name
94		N-((5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-phenyl)nicotinamide
95		N-((5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(2-methoxyphenyl)isonicotinamide
96		N-((5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-6-cyano-4-(2-methoxyphenyl)nicotinamide
97		N-((5-((5-bromopyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)nicotinamide
98		N-((5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-(1H-imidazol-2-yl)-4-morpholinyl)nicotinamide
99		N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-3-(2-methoxyphenyl)pyridine-4-carboxamide
100		N-((5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(2-(difluoromethoxy)phenyl)isonicotinamide
101		N-[5-[(6-cyclopropylpyridin-3-yl)methoxy]-1,3,4-thiadiazol-2-yl]-3-(2-methoxyphenyl)pyridine-4-carboxamide

Cpd #	Structure	Name
102		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-(hydroxymethyl)-4-(2-methoxyphenyl)nicotinamide
103		3-(benzo[c][1,2,5]thiadiazol-4-yl)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)isonicotinamide
104		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-(difluoromethoxy)phenyl)-6-(hydroxymethyl)nicotinamide
105		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-(cyanomethyl)-4-(2-methoxyphenyl)nicotinamide
106		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-5-(2-methoxyphenyl)pyridazine-4-carboxamide
107		N-(5-((7-chloro-1H-indazol-4-yl)methoxy)-1,3,4-thiadiazol-2-yl)-3-(2-methoxyphenyl)isonicotinamide
108		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(5-cyano-2-(difluoromethoxy)phenyl)isonicotinamide
109		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(2-(difluoromethoxy)-6-fluorophenyl)isonicotinamide

Cpd #	Structure	Name
110		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-((3S,5S)-3,5-dimethylmorpholino)isonicotinamide
111		3-(benzo[d]oxazol-7-yl)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)isonicotinamide
112		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-5-(2-(difluoromethoxy)phenyl)pyridazine-4-carboxamide
113		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)-6-methylnicotinamide
114		N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-4-[2-(difluoromethoxy)phenyl]-6-methylpyridine-3-carboxamide
115		N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-[2-(difluoromethoxy)phenyl]-6-methylpyridine-3-carboxamide
116		N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(5-cyano-2-methoxyphenyl)-6-methylpyridine-3-carboxamide
117		N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(5-cyano-2-methoxyphenyl)-6-methylpyridine-3-carboxamide

Cpd #	Structure	Name
118		<i>N</i> -(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(4-methyl-1 <i>H</i> -pyrazol-5-yl)isonicotinamide
119		<i>N</i> -(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(1 <i>H</i> -indazol-4-yl)isonicotinamide
120		<i>N</i> -(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(3-oxo-3,4-dihydro-2 <i>H</i> -benzo[<i>b</i>][1,4]oxazin-8-yl)isonicotinamide
121		<i>N</i> -(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-4-yl)isonicotinamide
122		<i>N</i> -(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-methyl-6-oxo-1,6-dihydro-[3,4'-bipyridine]-3'-carboxamide
123		<i>N</i> -(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(5-cyano-2-methoxyphenyl)isonicotinamide
124		<i>N</i> -(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(2-fluoro-6-methoxyphenyl)isonicotinamide

Cpd #	Structure	Name
125		3-(2-chloro-6-methoxyphenyl)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)isonicotinamide
126		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(2-cyanophenyl)isonicotinamide
127		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(4-cyano-2-methoxyphenyl)isonicotinamide
128		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-(2,6-dimethoxyphenyl)nicotinamide
129		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-methoxy-[3,4'-bipyridine]-3'-carboxamide
130		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-(2-(trifluoromethoxy)phenyl)nicotinamide
131		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3'-methoxy-[3,4'-bipyridine]-4-carboxamide

Cpd #	Structure	Name
132		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-(2-(trifluoromethyl)phenyl)nicotinamide
133		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4'-methoxy-[3,3'-bipyridine]-4-carboxamide
134		N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-3-[2-(oxetan-3-yloxy)phenyl]pyridine-4-carboxamide
135		N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-3-(2-ethylphenyl)pyridine-4-carboxamide
136		N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-3-(3,4-dihydro-2H-1,4-benzoxazin-8-yl)pyridine-4-carboxamide
137		N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-2-(cyanomethyl)-5-(2-methoxyphenyl)pyridine-4-carboxamide
138		N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide

Cpd #	Structure	Name
139		N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-3-(4-methyl-2,3-dihydro-1,4-benzoxazin-8-yl)pyridine-4-carboxamide
140		N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-3-(3,5-dimethyl-1H-pyrazol-4-yl)pyridine-4-carboxamide
141		N-(5-[[4-(1-cyanocyclopropyl)phenyl]methoxy]-1,3,4-thiadiazol-2-yl)-3-(2-methoxyphenyl)pyridine-4-carboxamide
142		N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-3-[5H,6H,7H-pyrazolo[1,5-a]pyrimidin-4-yl]pyridine-4-carboxamide
143		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(2-fluoro-6-(oxetan-3-yloxy)phenyl)isonicotinamide
144		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-((3R,5R)-3,5-dimethylmorpholino)isonicotinamide
145		N-[5-(1H-1,3-benzodiazol-4-ylmethoxy)-1,3,4-thiadiazol-2-yl]-3-(2-methoxyphenyl)pyridine-4-carboxamide

Cpd #	Structure	Name
146		N-[5-[(7-chloro-1-methylindazol-4-yl)methoxy]-1,3,4-thiadiazol-2-yl]-3-(2-methoxyphenyl)pyridine-4-carboxamide
147		N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-5-[2-(difluoromethoxy)phenyl]-2-(3-hydroxyprop-1-yn-1-yl)pyridine-4-carboxamide
148		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-fluoro-5-(2-methoxyphenyl)isonicotinamide
149		N-(5-((4-cyclopropylbenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(2-methoxyphenyl)-1H-imidazole-5-carboxamide
150		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2-chlorophenyl)nicotinamide
151		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-cyano-5-(2-methoxyphenyl)isonicotinamide

Cpd #	Structure	Name
152		5-([5-[(4-bromophenyl)methoxy]-1,3,4-thiadiazol-2-yl]carbamoyl)-4-(2-methoxyphenyl)pyridine-2-carboxylic acid
153		N-[5-[(4-bromophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)pyridine-3-carboxamide
154		6-cyano-N-(5-(2-cyclopropylethoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)nicotinamide
155		N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(4-fluoro-2-methoxyphenyl)pyridine-3-carboxamide
156		N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-(trifluoromethyl)pyridine-3-carboxamide
157		N-(5-((3-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(2-methoxyphenyl)isonicotinamide
158		N-[5-[(3,4-dichlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-3-(2-methoxyphenyl)pyridine-4-carboxamide

Cpd #	Structure	Name
159		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(3-cyano-2-methoxyphenyl)isonicotinamide
160		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-methoxy-5-(2-methoxyphenyl)isonicotinamide
161		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-(2-methoxyphenyl)imidazo[1,2-a]pyridine-7-carboxamide
162		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(3-methyl-1H-pyrazol-4-yl)isonicotinamide
163		6-(3-amino-3-oxopropyl)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)nicotinamide
164		N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-6-(2-cyanoethyl)-4-(2-methoxyphenyl)pyridine-3-carboxamide
165		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(2-(3-hydroxycyclobutoxy)phenyl)isonicotinamide

Cpd #	Structure	Name
166		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-(2-hydroxyethyl)-4-(2-methoxyphenyl)nicotinamide
167a		(R)-N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-6-(1-hydroxyethyl)-4-(2-methoxyphenyl)pyridine-3-carboxamide
167b		(S)-N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-6-(1-hydroxyethyl)-4-(2-methoxyphenyl)pyridine-3-carboxamide
168		N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-3-[2-(difluoromethoxy)phenyl]imidazole-4-carboxamide
169		N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-3-(1,3-dimethylpyrazol-4-yl)pyridine-4-carboxamide
170		N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-6-(hydroxymethyl)-4-(2-methoxyphenyl)pyridine-3-carboxamide
171		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(2-(2-hydroxyethyl)phenyl)isonicotinamide
172		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(5-cyano-2-(oxetan-3-yloxy)phenyl)isonicotinamide

Cpd #	Structure	Name
173		N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-3-[4-oxa-7-azaspiro[2.5]octan-7-yl]pyridine-4-carboxamide
174		N-(5-(benzyloxy)-1,3,4-thiadiazol-2-yl)-3-(2-methoxyphenyl)isonicotinamide
175a		3-((1R,6S)-3-oxabicyclo[4.1.0]heptan-6-yl)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)isonicotinamide
175b		3-((1S,6R)-3-oxabicyclo[4.1.0]heptan-6-yl)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)isonicotinamide
176		N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-3-[3-oxa-8-azabicyclo[3.2.1]octan-8-yl]pyridine-4-carboxamide
177		N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-6-cyano-4-[4-oxa-7-azaspiro[2.5]octan-7-yl]pyridine-3-carboxamide
178a		3-((1R,6S)-2-oxa-5-azabicyclo[4.1.0]heptan-5-yl)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)isonicotinamide

Cpd #	Structure	Name
178b		3-((1S,6R)-2-oxa-5-azabicyclo[4.1.0]heptan-5-yl)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)isonicotinamide
179a		(S)-N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-3-(2-methyl-3-oxopiperazin-1-yl)isonicotinamide
179b		(R)-N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-3-(2-methyl-3-oxopiperazin-1-yl)isonicotinamide
180		N-[5-(3H-1,3-benzodiazol-4-ylmethoxy)-1,3,4-thiadiazol-2-yl]-3-(2-methoxyphenyl)pyridine-4-carboxamide
181		N-[5-(1H-indazol-4-ylmethoxy)-1,3,4-thiadiazol-2-yl]-3-(2-methoxyphenyl)pyridine-4-carboxamide
182		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-3-(2-(difluoromethoxy)-6-fluorophenyl)isonicotinamide
183		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-(2-fluoro-6-methoxyphenyl)-6-methylnicotinamide

Cpd #	Structure	Name
184		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-fluoro-6-methoxyphenyl)-6-methylnicotinamide
185		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-4-(2-fluoro-6-methoxyphenyl)nicotinamide
186		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-6-cyano-4-(2-fluoro-6-methoxyphenyl)nicotinamide
187		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-3-((3S,5S)-3,5-dimethylmorpholino)isonicotinamide
188		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-3-((3R,5R)-3,5-dimethylmorpholino)isonicotinamide
189		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-(2-(difluoromethoxy)-6-fluorophenyl)-6-methylnicotinamide
190		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-(difluoromethoxy)-6-fluorophenyl)-6-methylnicotinamide

Cpd #	Structure	Name
191		N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-5-(2-methoxyphenyl)-2-methylpyridine-4-carboxamide
192		N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-4-(2-(difluoromethoxy)-6-fluorophenyl)nicotinamide
193		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-6-cyano-4-(2-(difluoromethoxy)-6-fluorophenyl)nicotinamide
194		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-3'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide
195		N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-[3-(hydroxymethyl)-2-methoxyphenyl]-6-methylpyridine-3-carboxamide
196		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(3,5-dimethyl-1H-pyrazol-4-yl)-6methylnicotinamide
197		N-(5-(2-(5-chloropyridin-2-yl)ethoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)-6-methylnicotinamide

Cpd #	Structure	Name
198		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)-6-methylnicotinamide
199		N-(5-((4-fluoropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)-6-methylnicotinamide
200		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(5-(hydroxymethyl)-2-methoxyphenyl)-6-methylnicotinamide
201		<i>N</i> -[5-[(1 <i>R</i>)-1-(4-chlorophenyl)ethoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide
202		<i>N</i> -[5-[(1 <i>S</i>)-1-(4-chlorophenyl)ethoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide
203		N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-[2-(hydroxymethyl)phenyl]-6-methylpyridine-3-carboxamide
204		6-(aminomethyl)-N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)pyridine-3-carboxamide

Cpd #	Structure	Name
205		4-(2-methoxyphenyl)-6-methyl-N-(5-((5-methylpyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)nicotinamide
206		N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-fluoro-6-methoxyphenyl)-6-(hydroxymethyl)pyridine-3-carboxamide
207		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-6-(2-hydroxypropan-2-yl)-4-(2-methoxyphenyl)nicotinamide
208		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-6-methylnicotinamide
209		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-5-(2-methoxyphenyl)pyrimidine-4-carboxamide
210		N-[5-[(3-fluoropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide
211		N-[5-[(6-fluoropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide

Cpd #	Structure	Name
212		N-[5-[(5-chloropyrazin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide
213		N-[5-[(7-chloro-1H-indazol-4-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide
214		N-((5-(5-cyclopropylpyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)-6-methylnicotinamide
215		N-((5-(5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-5-fluoro-4-(2-methoxyphenyl)-6-methylnicotinamide
216		N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-6-cyclopropyl-4-(2-methoxyphenyl)pyridine-3-carboxamide
217		N-((5-(5-(1-cyanocyclopropyl)pyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-fluoro-6-methoxyphenyl)-6-methylnicotinamide
218		N-([5-[[5-(1-cyanocyclopropyl)pyridin-2-yl]methoxy]-1,3,4-thiadiazol-2-yl]-4-[2-(difluoromethoxy)phenyl])-6-methylpyridine-3-carboxamide

Cpd #	Structure	Name
219		N-(5-((5-cyanopyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)-6-methylnicotinamide
220		N-(5-[[5-(1-cyanocyclopropyl)pyridin-2-yl]methoxy]-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide
221		N-[5-[(5-fluoropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide
222		N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-6-methoxy-4-(2-methoxyphenyl)nicotinamide
223		N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-5-(2-methoxyphenyl)-[1,2,3]triazolo[1,5-a]pyridine-6-carboxamide
224		N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-7-(2-methoxyphenyl)imidazo[1,5-a]pyridine-6-carboxamide
225		N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-5-(2-methoxyphenyl)-1H-pyrrolo[3,2-b]pyridine-6-carboxamide

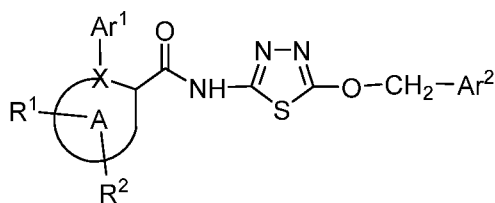
Cpd #	Structure	Name
226		N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-6-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridine-5-carboxamide
227		N-(5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl)-7-(2-methoxyphenyl)imidazo[1,2-a]pyridine-6-carboxamide
228		N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-5-(2-methoxyphenyl)pyrazolo[1,5-a]pyridine-6-carboxamide
229		N-(5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl)-6-(2-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyridine-7-carboxamide
230		N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-6-(2-methoxyphenyl)pyrazolo[1,5-a]pyridine-5-carboxamide
231		N-(5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl)-2-(2-methoxyphenyl)-1,6-naphthyridine-3-carboxamide
232		N-(5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl)-2-(2-methoxyphenyl)-1,7-naphthyridine-3-carboxamide

Embodiments:

[0089] In further embodiments 1 to 16 below, the present disclosure includes:

[0090] 1. In embodiment 1, provided is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, where R^1 , R^2 , X, alk, ring A, Ar^1 , and Ar^2 are as described in the Summary above. In a first subembodiment of embodiment 1, alk is methylene or ethylene. In a second subembodiment of embodiment 1, alk is C_{1-3} alkylene. In a third subembodiment of embodiment 1, alk is methylenemethylene.

[0091] 2. In embodiment 2, the compound of embodiment 1, or a pharmaceutically acceptable salt thereof is wherein the compound has a structure of formula (Ia):

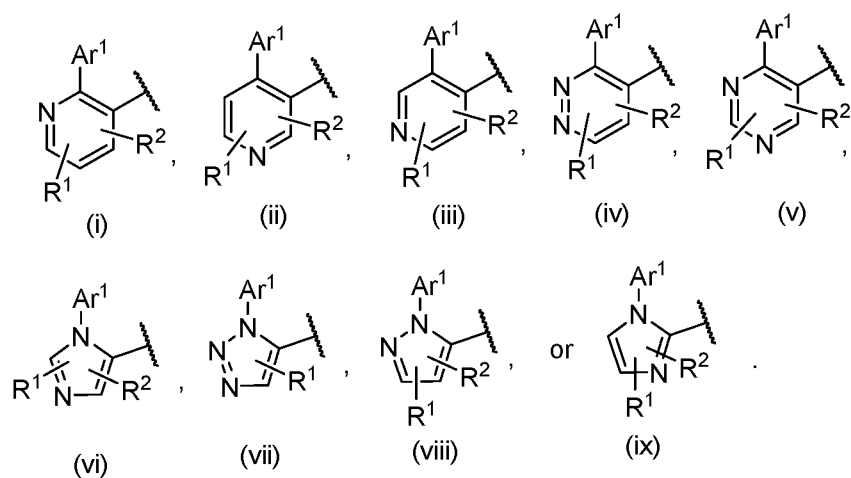


(Ia)

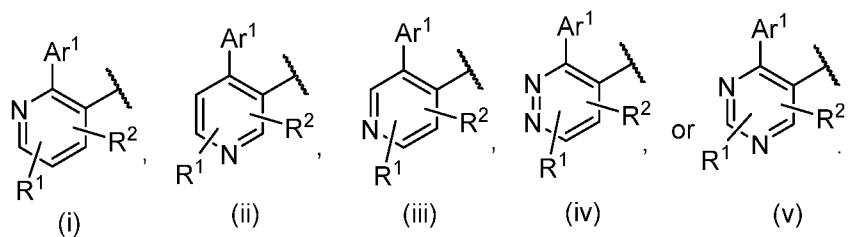
[0092] 3. In embodiment 3, the compound of embodiment 1 or 2 or embodiments contained therein, or a pharmaceutically acceptable salt thereof is wherein ring A is phenyl or a five or six membered heteroaryl ring. In a first subembodiment of embodiment 3, ring A is phenyl, pyridinyl, pyridazinyl, pyrimidinyl, imidazolyl, pyrazolyl, triazolyl or imidazo[1,2-a]pyridinyl. In a second subembodiment of embodiment 3, ring A is phenyl, pyridinyl, pyridazinyl, pyrimidinyl, imidazolyl, pyrazolyl, triazolyl, imidazo[1,2-a]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, imidazo[1,5-a]pyridinyl, pyrrolo[2,3-b]pyridinyl, pyrrolo[3,2-b]pyridinyl, pyrazolo[1,5-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, 1,6-naphthyridinyl, or 1,7-naphthyridinyl. In a subembodiment of embodiment 3, ring A is a nine or ten membered heteroaryl ring. In a subembodiment of embodiment 3, ring A is imidazo[1,2-a]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, imidazo[1,5-a]pyridinyl, pyrrolo[2,3-b]pyridinyl, pyrrolo[3,2-b]pyridinyl, pyrazolo[1,5-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, 1,6-naphthyridinyl, or 1,7-naphthyridinyl.

[0093] 4. In embodiment 4, the compound of embodiment 1 or 2 or embodiments contained therein, or a pharmaceutically acceptable salt thereof is wherein ring A is a five or six membered

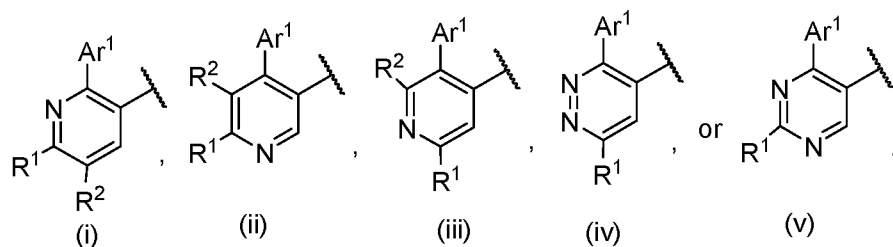
heteroaryl ring. In a first subembodiment of embodiment 4, ring A is pyridinyl, pyridazinyl, pyrimidinyl, imidazolyl, pyrazolyl, or triazolyl. In a second subembodiment of embodiment 4, ring A is:



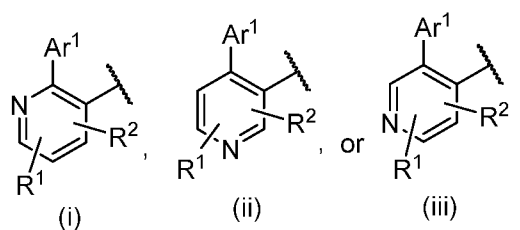
[0094] In a third subembodiment of embodiment 4, ring A is:



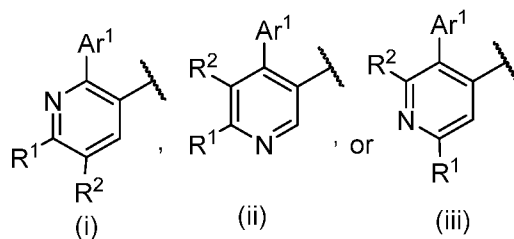
[0095] In a subembodiment of the third subembodiment, ring A is:



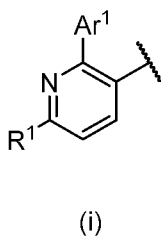
[0096] In a fourth subembodiment of embodiment 4, ring A is:



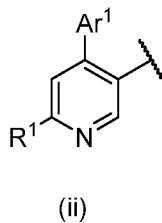
[0097] In a subembodiment of the fourth subembodiment, ring A is:



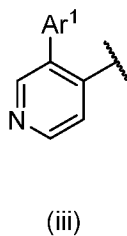
[0098] In a subembodiment of the fourth subembodiment, ring A is:



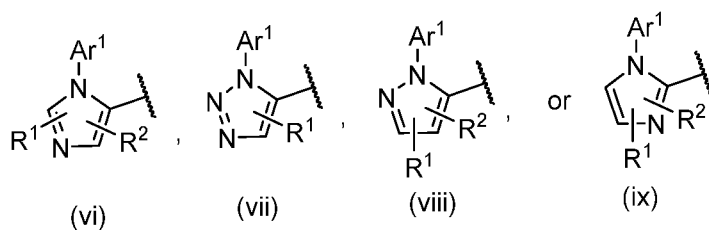
[0099] In a subembodiment of the fourth subembodiment, ring A is:



[0100] In a subembodiment of the fourth subembodiment, ring A is:



[0101] In a fifth subembodiment of embodiment 4, ring A is:



[0102] 5. In embodiment 4, the compound of any one of embodiments 1 to 4 and subembodiment contained therein, or a pharmaceutically acceptable salt thereof is wherein ring A is phenyl.

[0103] 6. In embodiment 6, the compound of any one of embodiments 1 to 5 and subembodiments contained therein, or a pharmaceutically acceptable salt thereof is wherein Ar¹ is heterocyclyl substituted with R^a, R^b, and/or R^c. In a first subembodiment of embodiment 6, Ar¹ is piperidinyl, piperazinyl, morpholinyl, homomorpholinyl, 2-oxopiperazinyl, 2-oxohomopiperazinyl, tetrahydropyranyl, 3,6-dihydro-2H-pyranyl, 2-oxo-1,2-dihydropyridinyl, thiomorpholinyl, or 1,1-dioxothiomorpholinyl substituted with R^a, R^b, and/or R^c. In a second subembodiment of embodiment 6, Ar¹ is piperidin-1-yl, piperazin-1-yl, morpholin-4-yl, homomorpholin-4-yl, 3-oxopiperazin-1-yl, 3-oxohomopiperazin-1-yl, 5-oxohomopiperazin-1-yl, tetrahydropyran-4-yl, 3,6-dihydro-2H-pyran-4-yl, 6-oxo-1,6-dihydropyridin-3-yl, 6-oxo-1,6-dihydropyridin-4-yl, thiomorpholin-4-yl, or 1,1-dioxothiomorpholin-4-yl substituted with R^a, R^b, and/or R^c. In a subembodiment of embodiment 6, Ar¹ is morpholin-4-yl substituted with R^a, R^b, and/or R^c. In a third subembodiment of embodiment 6 and first and second subembodiments contained therein, R^a is hydrogen or alkyl, R^b is hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, acyl, alkylsulfonyl, cyano, or hydroxy, and R^c is selected from alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, heterocyclylalkyl, and aminocarbonyl. In a subembodiment of embodiment 6, R^a and R^b, when on adjacent ring vertices, combine to form a cyclopropyl or cyclobutyl ring, and R^c is hydrogen. In a subembodiment of embodiment 6, R^a and R^b, when on adjacent ring vertices, combine to form a cyclopropyl ring, and R^c is hydrogen. In a fourth subembodiment of embodiment 6 and first and second subembodiments contained therein, Ar¹ is substituted with R^b and/or R^c wherein R^b is hydrogen, methyl, fluoro, cyano, methylsulfonyl, or methylcarbonyl and R^c is hydrogen, methyl, ethyl, fluoro, difluoromethyl, trifluoromethyl, trifluoroethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, hydroxy, 2-hydroxyethyl, 2-methoxyethyl, 2-aminoethyl, 2-morpholin-1-ylethyl, -CONH₂, methylaminocarbonyl, or dimethylaminocarbonyl. In a fifth subembodiment of embodiment 6, Ar¹ is morpholin-4-yl, homomorpholin-4-yl, 2-methylmorpholin-4-yl, 3-methylmorpholin-4-yl, 3R-methylmorpholin-4-yl, 3S-methylmorpholin-4-yl, 3-oxopiperazin-1-yl, 4-methyl-3-oxo-piperazin-1-yl, 2-methyl-3-oxopiperazin-1-yl, 6-methyl-3-oxopiperazin-1-yl, 5-methyl-3-oxopiperazin-1-yl, 3-

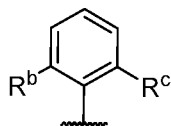
oxohomopiperazin-1-yl, 5-oxohomopiperazin-1-yl, 4-dimethylaminocarbonylpiperazin-1-yl, tetrahydropyran-4-yl, 3,6-dihydro-2H-pyran-4-yl, 4-(2-hydroxyethyl)-3-oxopiperazin-1-yl, 6-oxo-1,6-dihydropyridin-4-yl, 6-oxo-1,6-dihydropyridin-3-yl, 1-methyl-6-oxo-1,6-dihydropyridin-3-yl, 4-(2-morpholin-4-ylethyl)-3-oxopiperazin-1-yl, 4-methylcarbonylpiperazin-1-yl, 4-methylsulfonylpiperazin-1-yl, 1,1-dioxothiomorpholin-4-yl, or 4,4-difluoropiperidin-1-yl.

[0104] 7. In embodiment 7, the compound of any one of embodiments 1 to 6 and subembodiments contained therein, or a pharmaceutically acceptable salt thereof is wherein Ar¹ is bicyclic heterocyclyl substituted with R^a, R^b, and/or R^c. In a first subembodiment of embodiment 7, Ar¹ is 6-oxohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl or 2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl, each ring substituted with R^a, R^b, and/or R^c. In a subembodiment of embodiment 7, Ar¹ is selected from the group consisting of 6-oxohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl 3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl, benzo[d][1,3]dioxol-4-yl, (3,4-dihydro-2H-1,4-benzoxazin-8-yl), [5H,6H,7H-pyrazolo[1,5-a]pyrimidin-4-yl] and 2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl, each ring substituted with R^a, R^b, and/or R^c. In a second subembodiment of embodiment 7 and first subembodiment contained therein, R^a is hydrogen, R^b is hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, acyl, alkylsulfonyl, cyano, or hydroxy, and R^c is selected from alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, heterocyclalkyl, and aminocarbonyl. In a third subembodiment of embodiment 7 and first and second subembodiments contained therein, Ar¹ is substituted with R^b and/or R^c wherein R^b is hydrogen, methyl, fluoro, cyano, methylsulfonyl, or methylcarbonyl and R^c is hydrogen, methyl, ethyl, fluoro, difluoromethyl, trifluoromethyl, trifluoroethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, hydroxy, 2-hydroxyethyl, 2-methoxyethyl, 2-aminoethyl, 2-morpholin-1-ylethyl, -CONH₂, methylaminocarbonyl, or dimethylaminocarbonyl.

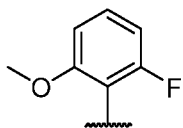
[0105] 8. In embodiment 8, the compound of any one of embodiments 1 to 7 and subembodiments contained therein, or a pharmaceutically acceptable salt thereof is wherein Ar¹ is spiroheterocyclyl substituted with R^a, R^b, and/or R^c. In a first subembodiment of embodiment 8, Ar¹ is 4-oxa-7-azaspiro[2.5]octan-7-yl substituted with R^a, R^b, and/or R^c. In a second subembodiment of embodiment 8 and first subembodiment contained therein, R^a is hydrogen, R^b is hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, acyl, alkylsulfonyl, cyano, or hydroxy,

and R^c is selected from alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, heterocyclalkyl, and aminocarbonyl. In a third subembodiment of embodiment 8 and first and second subembodiments contained therein, Ar^1 is substituted with R^b and/or R^c wherein R^b is hydrogen, methyl, fluoro, cyano, methylsulfonyl, or methylcarbonyl and R^c is hydrogen, methyl, ethyl, fluoro, difluoromethyl, trifluoromethyl, trifluoroethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, hydroxy, 2-hydroxyethyl, 2-methoxyethyl, 2-aminoethyl, 2-morpholin-1-ylethyl, $-CONH_2$, methylaminocarbonyl, or dimethylaminocarbonyl.

[0106] 9. In embodiment 9, the compound of any one of embodiments 1 to 8 and subembodiments contained therein, or a pharmaceutically acceptable salt thereof is wherein Ar^1 is phenyl substituted with R^a , R^b , and/or R^c . In a subembodiment of embodiment 9, wherein Ar^1 is



In a first subembodiment of embodiment 9, R^a is hydrogen or alkyl, R^b is hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, acyl, alkylsulfonyl, cyano, or hydroxy, and R^c is selected from alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, heterocyclalkyl, and aminocarbonyl. In a second subembodiment of embodiment 9, Ar^1 is substituted with R^b and/or R^c wherein R^b is hydrogen, methyl, fluoro, cyano, methylsulfonyl, or methylcarbonyl and R^c is hydrogen, methyl, ethyl, fluoro, difluoromethyl, trifluoromethyl, trifluoroethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, hydroxy, 2-hydroxyethyl, 2-methoxyethyl, 2-aminoethyl, 2-morpholin-1-ylethyl, $-CONH_2$, methylaminocarbonyl, or dimethylaminocarbonyl. In a subembodiment of embodiment 9, wherein Ar^1 is



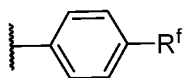
In a third subembodiment of embodiment 9, Ar^1 is phenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,4-dimethoxyphenyl, 2-chlorophenyl, 2-cyanophenyl, or 2-cyclopropyl-

oxyphenyl. In a third subembodiment of embodiment 9, Ar¹ is 2-methoxyphenyl. In a fourth subembodiment of embodiment 9, Ar¹ is 3-methoxyphenyl. In a fifth subembodiment of embodiment 9, Ar¹ is 2,4-dimethoxyphenyl.

[0107] 10. In embodiment 10, the compound of any one of embodiments 1 to 9 and subembodiments contained therein, or a pharmaceutically acceptable salt thereof is wherein Ar¹ is heteroaryl substituted with R^a, R^b, and/or R^c. In a subembodiment of embodiment 10, Ar¹ is benzo[c][1,2,5]thiadiazolyl, benzo[d]oxazolyl, 1*H*-indazolyl, substituted with R^a, R^b, and/or R^c where R^a is hydrogen or alkyl, R^b is hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, acyl, alkylsulfonyl, cyano, or hydroxy, and R^c is selected from hydrogen alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, heterocyclalkyl, and aminocarbonyl. In a first subembodiment of embodiment 10, Ar¹ is pyridinyl, pyrimidinyl, pyrazolyl, pyrrolyl, imidazolyl, or triazolyl substituted with R^a, R^b, and/or R^c where R^a is hydrogen or alkyl, R^b is hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, acyl, alkylsulfonyl, cyano, or hydroxy, and R^c is selected from alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, heterocyclalkyl, and aminocarbonyl. In a second subembodiment of embodiment 10, Ar¹ is substituted with R^b and/or R^c wherein R^b is hydrogen, methyl, fluoro, cyano, methylsulfonyl, or methylcarbonyl and R^c is hydrogen, methyl, ethyl, fluoro, difluoromethyl, trifluoromethyl, trifluoroethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, hydroxy, 2-hydroxyethyl, 2-methoxyethyl, 2-aminoethyl, 2-morpholin-1-ylethyl, -CONH₂, methylaminocarbonyl, or dimethylaminocarbonyl.

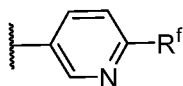
[0108] 11. In embodiment 11, the compound of any one of embodiments 1 to 10 and subembodiments contained therein, or a pharmaceutically acceptable salt thereof is wherein Ar² is phenyl substituted with R^d, R^e and/or R^f. In a first subembodiment of embodiment 11, R^d is hydrogen, R^e is hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, or cyano and R^f is selected from hydrogen, alkyl, cycloalkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, cyano, cyanomethyl, aminocarbonylmethyl, heteroaryl, and heterocycl, wherein said heteroaryl and heterocycl of R^f are unsubstituted or substituted with one, two, or three substituents independently selected from alkyl, halo, haloalkyl, and hydroxy. In a subembodiment of embodiment 11, R^f is cycloalkyl optionally substituted with cyano. In a first subembodiment of embodiment 11, Ar² is phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-methoxyphenyl, 2-chloro-4-

fluorophenyl, 4-cyanophenyl, 4-bromophenyl, 4-oxetan—3-ylphenyl, 4-chloro-3-methoxyphenyl, 4-cyclopropylphenyl, or 4-oxazol-2-ylphenyl. In a subembodiment of embodiment 11, Ar² is

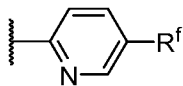


In a third subembodiment of embodiment 11, Ar² is 4-fluorophenyl. In a fourth subembodiment of embodiment 11, Ar² is 4-chlorophenyl.

[0109] 12. In embodiment 12, the compound of any one of embodiments 1 to 11 and subembodiments contained therein, or a pharmaceutically acceptable salt thereof is wherein Ar² is heteroaryl substituted with R^d, R^e and/or R^f. In a first subembodiment of embodiment 12, R^d is hydrogen, R^e is hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, or cyano and R^f is selected from hydrogen, alkyl, cycloalkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, cyano, cyanomethyl, aminocarbonylmethyl, heteroaryl, and heterocyclyl, wherein said heteroaryl and heterocyclyl of R^f are unsubstituted or substituted with one, two, or three substituents independently selected from alkyl, halo, haloalkyl, and hydroxy. In a subembodiment of embodiment 12, R^f is cycloalkyl optionally substituted with cyano. In a second subembodiment of embodiment 12 and first subembodiment contained therein Ar² is heteroaryl selected from pyridinyl or pyrimidinyl. In a subembodiment of embodiment 12 and subembodiments contained therein Ar² is



In a subembodiment of embodiment 12 and subembodiments contained therein Ar² is



In a third subembodiment of embodiment 11, Ar² is 6-chloropyridin-3-yl, 6-bromopyridin-3-yl, or 5-chloropyrazin-2-yl.

[0110] 13. In embodiment 13, the compound of any one of embodiments 1 to 12 and subembodiments contained therein, or a pharmaceutically acceptable salt thereof is wherein Ar² is cycloalkyl. In a first subembodiment of embodiment 13, Ar² is cycloalkyl is selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

[0111] 14. In embodiment 14, the compound of any one of embodiments 1 to 13 and subembodiments contained therein, or a pharmaceutically acceptable salt thereof is wherein R¹ is hydrogen, cyano, -CONH₂, methylaminocarbonyl, dimethylaminocarbonyl, imidazol-2-yl, methoxy, hydroxy, bromo, carboxy, or fluoro. In a subembodiment of embodiment 14, R¹ is hydrogen, alkyl, halo, haloalkyl, or cyano.

[0112] 15. In embodiment 15, the compound of any one of embodiments 1 to 14 and subembodiments contained therein, or a pharmaceutically acceptable salt thereof is wherein R¹ is hydroxyalkyl, alkoxyalkyl, aminoalkyl, aminocarbonylalkyl, sulfonylalkyl, aminosulfonylalkyl, optionally substituted heteroaralkyl, or optionally substituted heterocyclalkyl.

[0113] 16. In embodiment 16, the compound of any one of embodiments 1 to 14 and subembodiments contained therein, or a pharmaceutically acceptable salt thereof is wherein R² is hydrogen, cyano, or fluoro, preferably hydrogen.

[0114] It is understood that the embodiments set forth above include combinations of one or more of embodiments and/or subembodiments listed therein. For example, the Ar¹ group listed in embodiment 10 and subembodiment therein, can independently combine with one or more of the embodiments 1-9, and 11-16 and/or subembodiments contained therein.

Assay

[0115] The ability of compounds of the disclosure to inhibit Polθ can be measured as described in Biological Example 1 below.

Pharmaceutical Composition

[0116] The compounds of Formula (I), or a pharmaceutically acceptable salt thereof, provided herein may be in the form of compositions suitable for administration to a subject. In general, such compositions are pharmaceutical compositions comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable or physiologically acceptable excipients. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is present in a therapeutically effective amount. The pharmaceutical compositions may be used in the methods disclosed herein; thus, for example,

the pharmaceutical compositions can be administered *ex vivo* or *in vivo* to a subject in order to practice the therapeutic methods and uses described herein.

[0117] The pharmaceutical compositions can be formulated to be compatible with the intended method or route of administration; exemplary routes of administration are set forth herein. Furthermore, the pharmaceutical compositions may be used in combination with other therapeutically active agents or compounds as described herein in order to treat the diseases, disorders and conditions contemplated by the present disclosure.

[0118] The pharmaceutical compositions containing the active ingredient (e.g., a compound of Formula (I), a pharmaceutically acceptable salt thereof) may be in a form suitable for oral use, for example, as tablets, capsules, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups, solutions, microbeads or elixirs. Pharmaceutical compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents such as, for example, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets, capsules and the like contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets, capsules, and the like. These excipients may be, for example, diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc.

[0119] The tablets, capsules and the like suitable for oral administration may be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action. For example, a time-delay material such as glyceryl monostearate or glyceryl di-stearate may be employed. The tablets may also be coated by techniques known in the art to form osmotic therapeutic tablets for controlled release. Additional agents include biodegradable or biocompatible particles or a polymeric substance such as polyesters, polyamine acids, hydrogel, polyvinyl pyrrolidone, polyanhydrides, polyglycolic acid, ethylene-vinyl acetate, methylcellulose, carboxymethylcellulose, protamine

sulfate, or lactide and glycolide copolymers, polylactide and glycolide copolymers, or ethylene vinyl acetate copolymers in order to control delivery of an administered composition. For example, the oral agent can be entrapped in microcapsules prepared by coacervation techniques or by interfacial polymerization, by the use of hydroxymethyl cellulose or gelatin-microcapsules or poly (methyl methacrylate) microcapsules, respectively, or in a colloid drug delivery system. Colloidal dispersion systems include macromolecule complexes, nanocapsules, microspheres, microbeads, and lipid-based systems, including oil-in-water emulsions, micelles, mixed micelles, and liposomes. Methods for the preparation of the above-mentioned formulations are known in the art.

[0120] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate, kaolin or microcrystalline cellulose, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

[0121] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture thereof. Such excipients can be suspending agents, for example sodium carboxymethylcellulose, methylcellulose, (hydroxypropyl)methyl cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents, for example a naturally-occurring phosphatide (e.g., lecithin), or condensation products of an alkylene oxide with fatty acids (e.g., poly-oxyethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols (e.g., for heptdecaethyleneoxycetanol), or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol (e.g., polyoxyethylene sorbitol monooleate), or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides (e.g., polyethylene sorbitan monooleate). The aqueous suspensions may also contain one or more preservatives.

[0122] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation.

[0123] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified herein.

[0124] The pharmaceutical compositions may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example, liquid paraffin, or mixtures of these. Suitable emulsifying agents may be naturally occurring gums, for example, gum acacia or gum tragacanth; naturally occurring phosphatides, for example, soy bean, lecithin, and esters or partial esters derived from fatty acids; hexitol anhydrides, for example, sorbitan monooleate; and condensation products of partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate.

[0125] The pharmaceutical compositions typically comprise a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipient. Suitable pharmaceutically acceptable excipients include, but are not limited to, antioxidants (e.g., ascorbic acid and sodium bisulfate), preservatives (e.g., benzyl alcohol, methyl parabens, ethyl or n-propyl, p-hydroxybenzoate), emulsifying agents, suspending agents, dispersing agents, solvents, fillers, bulking agents, detergents, buffers, vehicles, diluents, and/or adjuvants. For example, a suitable vehicle may be physiological saline solution or citrate buffered saline, possibly supplemented with other materials common in pharmaceutical compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. Those skilled in the art will readily recognize a variety of buffers that can be used in the pharmaceutical compositions and dosage forms contemplated herein. Typical buffers include, but are not limited to, pharmaceutically acceptable weak acids, weak bases, or mixtures thereof. As an example, the buffer components can be water soluble materials such as phosphoric acid, tartaric acids, lactic acid, succinic acid, citric acid, acetic acid, ascorbic acid, aspartic acid, glutamic acid, and salts thereof. Acceptable buffering agents include, for example, a Tris buffer, N-(2-Hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid) (HEPES), 2-(N-Morpholino)ethanesulfonic acid (MES), 2-(N-Morpholino)ethanesulfonic acid sodium salt (MES), 3-(N-Morpholino)propanesulfonic acid (MOPS), and N-tris[Hydroxymethyl]methyl-3-aminopropanesulfonic acid (TAPS).

[0126] After a pharmaceutical composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or dehydrated or lyophilized powder. Such formulations may be stored either in a ready-to-use form, a lyophilized form requiring reconstitution prior to use, a liquid form requiring dilution prior to use, or other acceptable form. In some embodiments, the pharmaceutical composition is provided in a single-use container (e.g., a single-use vial, ampoule, syringe, or autoinjector (similar to, e.g., an EpiPen®)), whereas a multi-use container (e.g., a multi-use vial) is provided in other embodiments.

[0127] Formulations can also include carriers to protect the composition against rapid degradation or elimination from the body, such as a controlled release formulation, including liposomes, hydrogels, prodrugs and microencapsulated delivery systems. For example, a time delay material such as glyceryl monostearate or glyceryl stearate alone, or in combination with a wax, may be employed. Any drug delivery apparatus may be used to deliver a compound of Formula (I), or a pharmaceutically acceptable salt thereof, including implants (e.g., implantable pumps) and catheter systems, slow injection pumps and devices, all of which are well known to the skilled artisan.

[0128] Depot injections, which are generally administered subcutaneously or intramuscularly, may also be utilized to release the compound of Formula (I), or a pharmaceutically acceptable salt thereof disclosed herein over a defined period of time. Depot injections are usually either solid- or oil-based and generally comprise at least one of the formulation components set forth herein. One of ordinary skill in the art is familiar with possible formulations and uses of depot injections.

[0129] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. The suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents mentioned herein. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Acceptable diluents, solvents and dispersion media that may be employed include water, Ringer's solution, isotonic sodium chloride solution, Cremophor EL™ (BASF, Parsippany, NJ) or phosphate buffered saline (PBS), ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. In addition, sterile, fixed oils are

conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. Moreover, fatty acids such as oleic acid, find use in the preparation of injectables. Prolonged absorption of particular injectable formulations can be achieved by including an agent that delays absorption (e.g., aluminum monostearate or gelatin).

[0130] A compound of Formula (I), or a pharmaceutically acceptable salt thereof may also be administered in the form of suppositories for rectal administration or sprays for nasal or inhalation use. The suppositories can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include, but are not limited to, cocoa butter and polyethylene glycols.

Routes of Administration

[0131] Compounds of Formula (I), or a pharmaceutically acceptable salt thereof and compositions containing the same may be administered in any appropriate manner. Suitable routes of administration include oral, parenteral (e.g., intramuscular, intravenous, subcutaneous (e.g., injection or implant), intraperitoneal, intracisternal, intraarticular, intraperitoneal, intracerebral (intraparenchymal) and intracerebroventricular), nasal, vaginal, sublingual, intraocular, rectal, topical (e.g., transdermal), buccal and inhalation. Depot injections, which are generally administered subcutaneously or intramuscularly, may also be utilized to administer the compounds of Formula (I), or a pharmaceutically acceptable salt thereof over a defined period of time. Particular embodiments of the present invention contemplate oral administration.

Combination Therapy

[0132] The present invention contemplates the use of compounds of Formula (I), or a pharmaceutically acceptable salt thereof in combination with one or more active therapeutic agents (e.g., chemotherapeutic agents) or other prophylactic or therapeutic modalities (e.g., radiation). In such combination therapy, the various active agents frequently have different, complementary mechanisms of action. Such combination therapy may be especially advantageous by allowing a dose reduction of one or more of the agents, thereby reducing or eliminating the adverse effects associated with one or more of the agents. Furthermore, such

combination therapy may have a synergistic therapeutic or prophylactic effect on the underlying disease, disorder, or condition.

[0133] As used herein, “combination” is meant to include therapies that can be administered separately, for example, formulated separately for separate administration (e.g., as may be provided in a kit), and therapies that can be administered together in a single formulation (i.e., a “co-formulation”).

[0134] In certain embodiments, the compounds of Formula (I), or a pharmaceutically acceptable salt thereof are administered or applied sequentially, e.g., where one agent is administered prior to one or more other agents. In other embodiments, the compounds of Formula (I), or a pharmaceutically acceptable salt thereof are administered simultaneously, e.g., where two or more agents are administered at or about the same time; the two or more agents may be present in two or more separate formulations or combined into a single formulation (i.e., a co-formulation). Regardless of whether the two or more agents are administered sequentially or simultaneously, they are considered to be administered in combination for purposes of the present disclosure.

[0135] The compounds of Formula (I), or a pharmaceutically acceptable salt thereof may be used in combination with at least one other (active) agent in any manner appropriate under the circumstances. In one embodiment, treatment with the at least one active agent and at least one compound of Formula (I), or a pharmaceutically acceptable salt thereof is maintained over a period of time. In another embodiment, treatment with the at least one active agent is reduced or discontinued (e.g., when the subject is stable), while treatment with the compound of Formula (I), or a pharmaceutically acceptable salt thereof is maintained at a constant dosing regimen. In a further embodiment, treatment with the at least one active agent is reduced or discontinued (e.g., when the subject is stable), while treatment with a compound of Formula (I), or a pharmaceutically acceptable salt thereof is reduced (e.g., lower dose, less frequent dosing or shorter treatment regimen). In yet another embodiment, treatment with the at least one active agent is reduced or discontinued (e.g., when the subject is stable), and treatment with the compound of Formula (I), or a pharmaceutically acceptable salt thereof is increased (e.g., higher dose, more frequent dosing or longer treatment regimen). In yet another embodiment, treatment with the at least one active agent is maintained and treatment with the compound of Formula (I),

or a pharmaceutically acceptable salt thereof is reduced or discontinued (e.g., lower dose, less frequent dosing or shorter treatment regimen). In yet another embodiment, treatment with the at least one active agent and treatment with the compound of Formula (I), or a pharmaceutically acceptable salt thereof are reduced or discontinued (e.g., lower dose, less frequent dosing or shorter treatment regimen).

[0136] The present disclosure provides methods for treating cancer with a compound of Formula (I), or a pharmaceutically acceptable salt thereof and at least one additional therapeutic or diagnostic agent.

[0137] In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered in combination with at least one additional therapeutic agent, selected from Temozolomide, Pemetrexed, Pegylated liposomal doxorubicin (Doxil), Eribulin (Halaven), Ixabepilone (Ixempra), Protein-bound paclitaxel (Abraxane), Oxaliplatin, Irinotecan, Venatoclax (bcl2 inhibitor), 5-azacytadine, Anti-CD20 therapeutics, such as Rituxan and obinutuzumab, Hormonal agents (anastrozole, exemestand, letrozole, zoladex, lupon eligard), CDK4/6 inhibitors, Palbociclib, Abemaciclib, CPI (Avelumab, Cemiplimab-rwlc, and Bevacizumab.

[0138] In certain embodiments, the present disclosure provides methods for treating cancer comprising administration of a compound of Formula (I), or a pharmaceutically acceptable salt thereof described herein in combination with a signal transduction inhibitor (STI) to achieve additive or synergistic suppression of tumor growth. As used herein, the term “signal transduction inhibitor” refers to an agent that selectively inhibits one or more steps in a signaling pathway. Examples of signal transduction inhibitors (STIs) useful in methods described herein include, but are not limited to: (i) bcr/abl kinase inhibitors (e.g., GLEEVEC); (ii) epidermal growth factor (EGF) receptor inhibitors, including kinase inhibitors and antibodies; (iii) her-2/neu receptor inhibitors (e.g., HERCEPTIN); (iv) inhibitors of Akt family kinases or the Akt pathway (e.g., rapamycin); (v) cell cycle kinase inhibitors (e.g., flavopiridol); and (vi) phosphatidyl inositol kinase inhibitors. Agents involved in immunomodulation can also be used in combination with one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof described herein for the suppression of tumor growth in cancer patients.

[0139] In certain embodiments, the present disclosure provides methods for treating cancer comprising administration of a compound of Formula (I), or a pharmaceutically acceptable salt

thereof described herein in combination with a chemotherapeutic agents. Examples of chemotherapeutic agents include, but are not limited to, alkylating agents such as thiotepa and cyclophosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethio-phosphoramide and trimethylolomelamine; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabycin, caminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogs such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, 5-FU; androgens such as calusterone, dromostanolone propionate, epitiolesterol, mepitiolesterol, testosterone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside (Ara-C); cyclophosphamide; thiotepa; taxoids, e.g., paclitaxel and doxetaxel; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum and platinum coordination complexes such as cisplatin and carboplatin; vinblastine; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine;

navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; CPT11; topoisomerase inhibitors; difluoromethylornithine (DMFO); retinoic acid; esperamicins; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. In a particular embodiment, compounds of the present disclosure are coadministered with a cytostatic compound selected from the group consisting of cisplatin, doxorubicin, taxol, taxotere and mitomycin C. In a particular embodiment, the cytostatic compound is doxorubicin.

[0140] Chemotherapeutic agents also include anti-hormonal agents that act to regulate or inhibit hormonal action on tumors such as anti-estrogens, including for example tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, onapristone, and toremifene; and antiandrogens such as flutamide, nilutamide, bicalutamide, enzalutamide, apalutamide, abiraterone acetate, leuprolide, and goserelin; and pharmaceutically acceptable salts, acids or derivatives of any of the above. In certain embodiments, combination therapy comprises administration of a hormone or related hormonal agent.

[0141] The present disclosure also contemplates the use of the compounds of Formula (I), or a pharmaceutically acceptable salt thereof described herein in combination with immune checkpoint inhibitors. The tremendous number of genetic and epigenetic alterations that are characteristic of all cancers provides a diverse set of antigens that the immune system can use to distinguish tumor cells from their normal counterparts. In the case of T cells, the ultimate amplitude (e.g., levels of cytokine production or proliferation) and quality (e.g., the type of immune response generated, such as the pattern of cytokine production) of the response, which is initiated through antigen recognition by the T-cell receptor (TCR), is regulated by a balance between co-stimulatory and inhibitory signals (immune checkpoints). Under normal physiological conditions, immune checkpoints are crucial for the prevention of autoimmunity (i.e., the maintenance of self-tolerance) and also for the protection of tissues from damage when the immune system is responding to pathogenic infection. The expression of immune checkpoint proteins can be dysregulated by tumors as an important immune resistance mechanism. Examples of immune checkpoint inhibitors include but are not limited to CTLA-4, PD-1, PD-L1, BTLA, TIM3, LAG3, OX40, 41BB, VISTA, CD96, TGF β , CD73, CD39, A2AR, A2BR, IDO1, TDO2, Arginase, B7-H3, B7-H4. Cell-based modulators of anti-cancer immunity are also

contemplated. Examples of such modulators include but are not limited to chimeric antigen receptor T-cells, tumor infiltrating T-cells and dendritic-cells.

[0142] The present disclosure contemplates the use of compounds of Formula (I), or a pharmaceutically acceptable salt thereof described herein in combination with inhibitors of the aforementioned immune-checkpoint receptors and ligands, for example ipilimumab, abatacept, nivolumab, pembrolizumab, atezolizumab, nivolumab, and durvalumab.

[0143] Additional treatment modalities that may be used in combination with a compound of Formula (I), or a pharmaceutically acceptable salt thereof disclosed herein include radiotherapy, a monoclonal antibody against a tumor antigen, a complex of a monoclonal antibody and toxin, a T-cell adjuvant, bone marrow transplant, or antigen presenting cells (e.g., dendritic cell therapy).

[0144] The present disclosure contemplates the use of compounds of Formula (I), or a pharmaceutically acceptable salt thereof described herein for the treatment of glioblastoma either alone or in combination with radiation and/or temozolomide (TMZ), avastin or lomustine.

[0145] The present disclosure encompasses pharmaceutically acceptable salts, acids or derivatives of any of the above.

Dosing

[0146] The compounds of Formula (I), or a pharmaceutically acceptable salt thereof provided herein may be administered to a subject in an amount that is dependent upon, for example, the goal of administration (e.g., the degree of resolution desired); the age, weight, sex, and health and physical condition of the subject to which the formulation is being administered; the route of administration; and the nature of the disease, disorder, condition or symptom thereof. The dosing regimen may also take into consideration the existence, nature, and extent of any adverse effects associated with the agent(s) being administered. Effective dosage amounts and dosage regimens can readily be determined from, for example, safety and dose-escalation trials, in vivo studies (e.g., animal models), and other methods known to the skilled artisan.

[0147] In general, dosing parameters dictate that the dosage amount be less than an amount that could be irreversibly toxic to the subject (the maximum tolerated dose (MTD)) and not less than an amount required to produce a measurable effect on the subject. Such amounts are

determined by, for example, the pharmacokinetic and pharmacodynamic parameters associated with ADME, taking into consideration the route of administration and other factors.

[0148] An effective dose (ED) is the dose or amount of an agent that produces a therapeutic response or desired effect in some fraction of the subjects taking it. The “median effective dose” or ED₅₀ of an agent is the dose or amount of an agent that produces a therapeutic response or desired effect in 50% of the population to which it is administered. Although the ED₅₀ is commonly used as a measure of reasonable expectance of an agent’s effect, it is not necessarily the dose that a clinician might deem appropriate taking into consideration all relevant factors. Thus, in some situations the effective amount is more than the calculated ED₅₀, in other situations the effective amount is less than the calculated ED₅₀, and in still other situations the effective amount is the same as the calculated ED₅₀.

[0149] In addition, an effective dose of a compound of Formula (I), or a salt thereof, as provided herein, may be an amount that, when administered in one or more doses to a subject, produces a desired result relative to a healthy subject. For example, for a subject experiencing a particular disorder, an effective dose may be one that improves a diagnostic parameter, measure, marker and the like of that disorder by at least about 5%, at least about 10%, at least about 20%, at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or more than 90%, where 100% is defined as the diagnostic parameter, measure, marker and the like exhibited by a normal subject.

[0150] In certain embodiments, the compounds of Formula (I), or a pharmaceutically acceptable salt thereof disclosed herein may be administered (e.g., orally) at dosage levels of about 0.01 mg/kg to about 50 mg/kg, or about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[0151] For administration of an oral agent, the compositions can be provided in the form of tablets, capsules and the like containing from 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 3.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient.

[0152] In certain embodiments, the dosage of the compound of Formula (I), or a pharmaceutically acceptable salt thereof is contained in a “unit dosage form”. The phrase “unit dosage form” refers to physically discrete units, each unit containing a predetermined amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, either alone or in combination with one or more additional agents, sufficient to produce the desired effect. It will be appreciated that the parameters of a unit dosage form will depend on the particular agent and the effect to be achieved.

Kits

[0153] The present invention also contemplates kits comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and pharmaceutical compositions thereof. The kits are generally in the form of a physical structure housing various components, as described below, and may be utilized, for example, in practicing the methods described above.

[0154] A kit can include one or more of the compound of Formula (I), or a pharmaceutically acceptable salt thereof disclosed herein (provided in, e.g., a sterile container), which may be in the form of a pharmaceutical composition suitable for administration to a subject. The compound of Formula (I), or a pharmaceutically acceptable salt thereof can be provided in a form that is ready for use (e.g., a tablet or capsule) or in a form requiring, for example, reconstitution or dilution (e.g., a powder) prior to administration. When the compounds of Formula (I), or a pharmaceutically acceptable salt thereof are in a form that needs to be reconstituted or diluted by a user, the kit may also include diluents (e.g., sterile water), buffers, pharmaceutically acceptable excipients, and the like, packaged with or separately from the compounds of Formula (I), or a pharmaceutically acceptable salt thereof. When combination therapy is contemplated, the kit may contain the several agents separately or they may already be combined in the kit. Each component of the kit may be enclosed within an individual container, and all of the various containers may be within a single package. A kit of the present invention may be designed for conditions necessary to properly maintain the components housed therein (e.g., refrigeration or freezing).

[0155] A kit may contain a label or packaging insert including identifying information for the components therein and instructions for their use (e.g., dosing parameters, clinical pharmacology

of the active ingredient(s), including mechanism of action, pharmacokinetics and pharmacodynamics, adverse effects, contraindications, etc.). Labels or inserts can include manufacturer information such as lot numbers and expiration dates. The label or packaging insert may be, e.g., integrated into the physical structure housing the components, contained separately within the physical structure, or affixed to a component of the kit (e.g., an ampule, tube or vial).

[0156] Labels or inserts can additionally include, or be incorporated into, a computer readable medium, such as a disk (e.g., hard disk, card, memory disk), optical disk such as CD- or DVD-ROM/RAM, DVD, MP3, magnetic tape, or an electrical storage media such as RAM and ROM or hybrids of these such as magnetic/optical storage media, FLASH media or memory-type cards. In some embodiments, the actual instructions are not present in the kit, but means for obtaining the instructions from a remote source, e.g., via the internet, are provided.

Examples

[0157] The following examples and references (intermediates) are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention, nor are they intended to represent that the experiments below were performed or that they are all of the experiments that may be performed. It is to be understood that exemplary descriptions written in the present tense were not necessarily performed, but rather that the descriptions can be performed to generate data and the like of a nature described therein. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.), but some experimental errors and deviations should be accounted for.

[0158] Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Celsius (°C), and pressure is at or near atmospheric. Standard abbreviations are used, including the following: μg = microgram; μl or μL = microliter; mM = millimolar; μM = micromolar; THF = tetrahydrofuran; DIEA = diisopropylethylamine; EtOAc = ethyl acetate; NMP = N-methylpyridine, TFA = trifluoroacetic acid; DCM = dichloromethane; Cs_2CO_3 = cesium carbonate; XPhos Pd G3 = 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl][2-(2'-amino-1,1'-biphenyl)]palladium-(II) methanesulfonate; LiCl = lithium chloride; POCl_3 = phosphoryl chloride; PE = petroleum

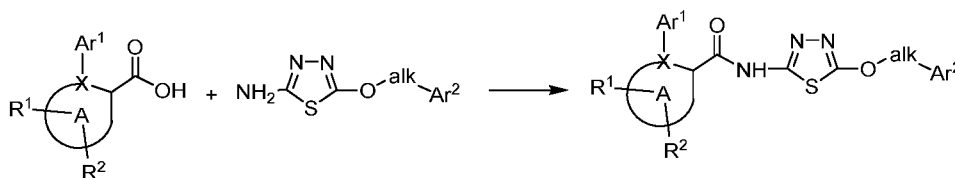
ether; DMSO = dimethylsulfoxide; HCl = hydrochloric acid; Na₂SO₄ = sodium sulfate; DMF = dimethylformamide; NaOH = sodium hydroxide; K₂CO₃ = potassium carbonate; MeCN = acetonitrile; BOC = tert-butoxycarbonyl; MTBE = methyl tert-butyl ether; MeOH = methanol; NaHCO₃ = sodium bicarbonate; NaBH₃CN = sodium cyanoborohydride; EtOH = ethanol; PCl₅ = phosphorus pentachloride; NH₄OAc = ammonium acetate; Et₂O = ether; HOAc = acetic acid; Ac₂O = acetic anhydride; *i*-PrOH = isopropanol; NCS = N-chlorosuccinimide; K₃PO₄ = potassium phosphate; Pd(dtbpf)Cl₂ = 1,1'-Bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II); Zn(CN)₂ = Zinc cyanide; Pd(PPh₃)₄ = tetrakis(triphenylphosphine)palladium(0); Et₃N = triethylamine; CuCN = copper cyanide; *t*-BuONO = tert-butyl nitrite; HATU = 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate; DBU = 1,8-diazabicyclo(5.4.0)undec-7-ene; LiAlH₄ = lithium aluminium hydride; NH₃ = ammonia; H₂SO₄ = sulfuric acid; H₂O₂ = hydrogen peroxide; EDCI = N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride; HOBT = 1-hydroxybenzotriazole hydrate; DHP = dihydropyran; TsOH = p-Toluenesulfonic acid; FA = formic acid; TCFH = N,N,N,N'-tetramethylchloroformamidinium hexafluorophosphate; NMI = N-methylimidazole; Pd(dppf)Cl₂ = [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II); Pd(dppf)Cl₂-DCM = [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane.

Synthetic Examples

General Procedures

General Procedure A

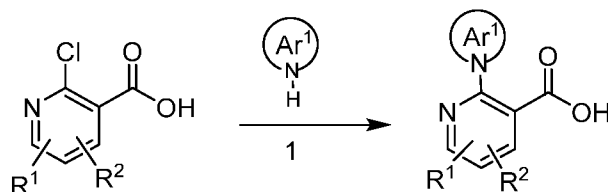
Amide formation using HATU



[0159] To a solution of carboxylic acid (1 eq.) and amine (1 eq.) in DMF (0.5 M) was added DIEA (2 eq.) and HATU (1.5 eq.). The mixture was stirred overnight at room temperature under nitrogen.

General Procedure B

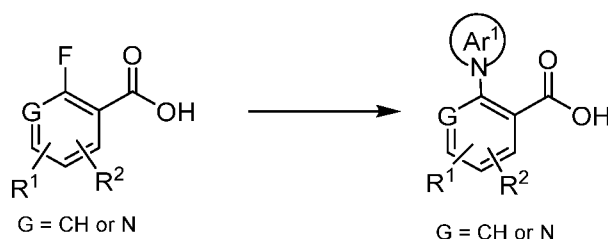
Amination of 2-chloropyridine



[0160] To a solution of 2-chloropyridine-3-carboxylic acid (1 eq.) in NMP (0.6 M) was added heterocyclyl of formula 1 (1 eq.) and DIEA (3 eq.) at room temperature under nitrogen. The mixture was stirred for 5 h at 80 °C.

General Procedure C

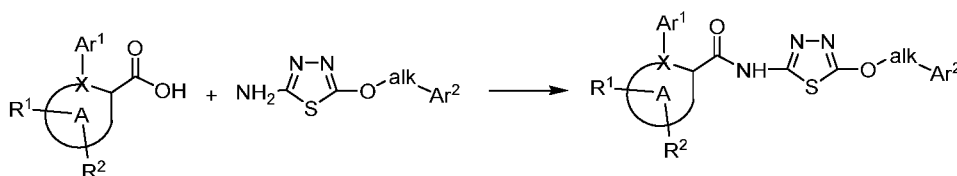
Amination of 2-fluorobenzene and 2-fluoropyridine



[0161] To a solution of aryl-carboxylic acid (1 eq.) in MeCN (0.7 M) was added heterocyclyl of formula 1 above (1.5 eq.) and DIEA (2 eq.) at room temperature under nitrogen. The mixture was stirred at 80 °C overnight.

General Procedure D

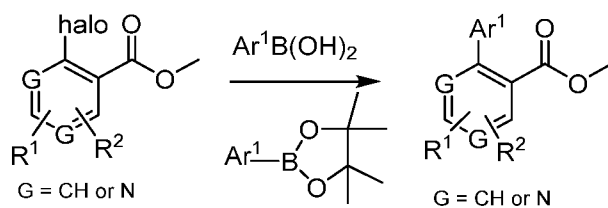
Amide formation using Propylphosphonic anhydride



[0162] To a solution of carboxylic acid (1 eq.) and amine (1 eq.) in THF (0.5 M) was added T3P (1.5 eq.) and DIEA (2 eq.) under nitrogen. The mixture was stirred at 50 °C overnight.

General Procedure E

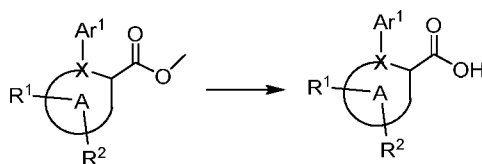
Arylation using Suzuki coupling



[0163] To a solution of aryl halogen (1 eq.) in dioxane:water (5:1, 0.4 M) was added boronic acid or boronic ester (1.5eq.), Pd(dppf)Cl₂ (0.2eq.) and K₂CO₃ (2 eq.). Mixture was stirred at 100 °C overnight.

General Procedure F

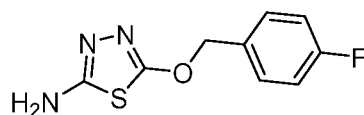
Ester hydrolysis



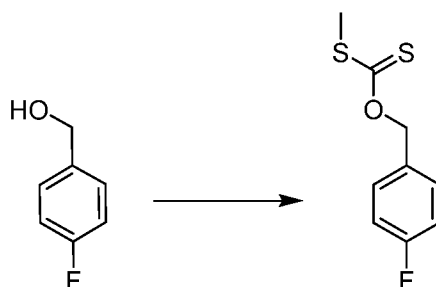
[0164] To a solution of ester (1 eq.) in methanol:water (1:1, 0.2 M) was added NaOH (5 eq). The mixture was stirred at room temperature for 1 h.

Intermediate A

Synthesis of 5-((4-fluorobenzyl)oxy)-1,3,4-thiadiazol-2-amine

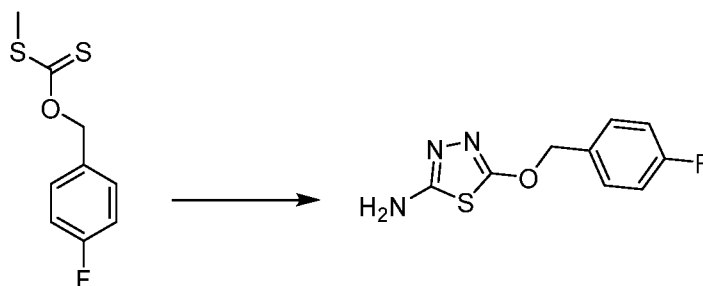


Step 1. Preparation of O-(4-fluorobenzyl) S-methyl carbonodithioate



[0165] To a solution of (4-fluorophenyl)methanol (2.0 g, 15.9 mmol) in THF (20 mL) at 0 °C was added NaH (0.63 g, 15.9 mmol, 60% dispersion in oil). CS₂ (1.21 g, 15.9 mmol) was added dropwise over 5 min at 0 °C and the mixture was stirred for additional 30 min at 0 °C. CH₃I (2.25 g, 15.9 mmol) was added dropwise over 5 min at 0 °C. The mixture was stirred for additional 6 h at 0 °C and then quenched with water. The aqueous layer was extracted with EtOAc and the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE to afford the title compound as yellow oil.

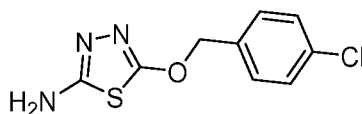
Step 2. Preparation of 5-((4-fluorobenzyl)oxy)-1,3,4-thiadiazol-2-amine



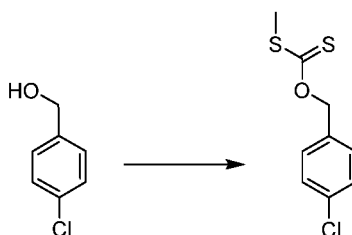
[0166] A mixture of O-(4-fluorobenzyl) S-methyl carbonodithioate (1.20 g, 5.548 mmol) and hydrazine hydrate (2.9 g, 5.8 mmol) in MeOH (12 mL) was stirred for 3 h at room temperature under nitrogen and then Et₃N (1.1 g, 11.1 mmol) was added. BrCN (0.88 g, 8.308 mmol) was added and the reaction mixture was stirred for 3 h. The mixture was diluted with water and solids were collected by filtration and washed with MeOH to provide the title compound as a red solid.

Intermediate B

Synthesis of 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine

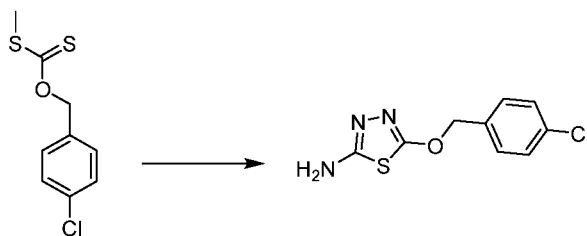


Step 1. Preparation of O-(4-chlorobenzyl) S-methyl carbonodithioate



[0167] To a solution of (4-chlorophenyl)methanol (20 g, 140 mmol) in THF (200 mL) under nitrogen was added NaOH (11.2 g, 280 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min and then CS₂ (12.8 g, 168 mmol) was added. The mixture was stirred at 0 °C for additional 30 min and then MeI (23.9 g, 168 mmol) was added. After 30 min water was added and the mixture was extracted with EtOAc. The combined organic layers were concentrated under reduce pressure to afford the title compound as a yellow oil.

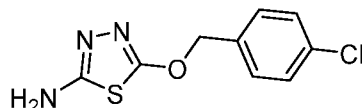
Step 2. Preparation of 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine



[0168] To a solution of O-(4-chlorobenzyl) S-methyl carbonodithioate (15 g, 64 mmol) in methanol (450 mL) under nitrogen was added hydrazine hydrate (3.2 g, 64 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min and then concentrated under reduced pressure. The residue was diluted with MeOH and then Et₃N (14 g, 139 mmol) and BrCN (8 g, 77 mmol) were added. The mixture was stirred for 30 min at room temperature. The solids were collected by filtration and washed with MeOH to afford the title compound as a yellow solid.

Additional synthesis of Intermediate B

Synthesis of 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine



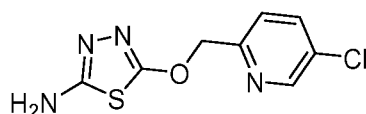
Step 1. Preparation of 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine

[0169] To a solution of NaH (42.0 g, 1.05 mol, 60.0% purity) in THF (750 mL) was added a solution of (4-chlorophenyl)methanol (100 g, 701 mmol) in THF (250 mL) dropwise at 5 °C. The mixture was stirred at 5 °C for 4 h. Then 2-amino-5-bromo-1,3,4-thiadiazole (152 g, 842

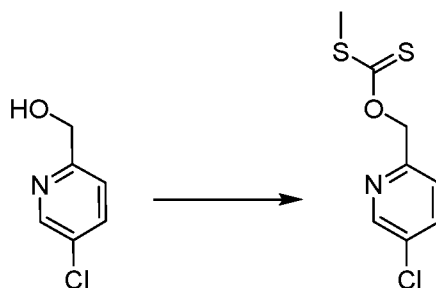
mmol) was added to the mixture at 5 °C. The mixture was stirred at 5 °C for 3 h. The mixture was poured into H₂O and extracted with EtOAc (3x). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduce pressure. The crude was purified by silica gel column chromatography, eluted with 9% - 66% EtOAc in PE to afford a residue. The residue was diluted with MeOH and the slurry was stirred at 25 °C for 0.5 h. The solids were collected and diluted with MeOH. The slurry was stirred at 80 °C for 16 h. The solids were collected to afford the title compound (61.0 g, 18% yield) as a grey solid.

Intermediate C

Synthesis of 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine

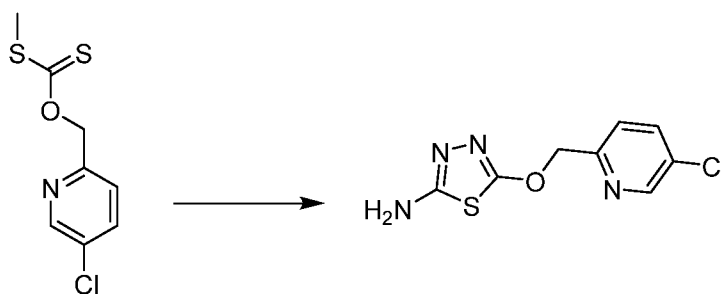


Step 1. O-((5-chloropyridin-2-yl)methyl) S-methyl carbonodithioate



[0170] To a solution (5-chloropyridin-2-yl)methanol (3.0 g, 21 mmol) in THF (30 mL) at 0°C was added NaOH (1.3 g, 31.5 mmol) under nitrogen. The mixture was stirred at 0°C for 15 min. Then CS₂ (1.8 g, 23 mmol) was added and the mixture was stirred for 30 min at 0°C. Then MeI (3.3 g, 23 mmol) was added and the mixture was stirred for 30 min at 0°C. Then sat. NH₄Cl (30 mL) was added and mixture warmed to room temperature. The aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 1% EtOAc in PE to afford O-((5-chloropyridin-2-yl)methyl) S-methyl carbonodithioate as a yellow oil.

Step 2. Preparation of 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine

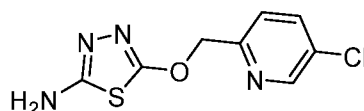


[0171] To a solution of O-((5-chloropyridin-2-yl)methyl) S-methyl carbonodithioate (1.8 g, 7.7 mmol) in MeOH (18 mL) was added hydrazine hydrate (387 mg, 7.7 mmol) under nitrogen. The mixture was stirred for 15 min at room temperature. Then BrCN (819 mg, 7.7 mmol) and Et₃N (1638 mg, 15 mmol) were added. The mixture was stirred for 15 min at room temperature. A solid formed and the solid was collected by filtration. The solid was washed with MeOH (3 x 5 mL) to afford 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine as a gray solid.

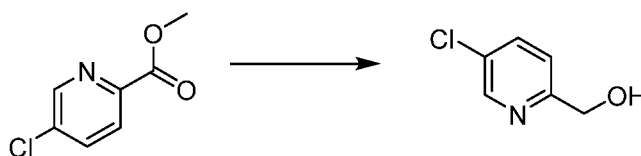
Additional synthesis of Intermediate C

Intermediate C

Synthesis of 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine

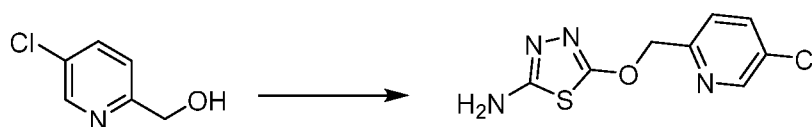


Step 1. Preparation of (5-chloropyridin-2-yl)methanol



[0172] To a solution of methyl 5-chloropyridinate (95 g, 554 mmol) in MeOH (950 mL) was added NaBH₄ (42.0 g, 1.11 mol) in portions at 0 °C. Then the mixture was stirred at rt for 2 h. The mixture was poured into H₂O. Mixture was cooled to 0 °C and 6 N HCl was added until pH of solution was 1 ~ 2. The temperature of the solution was 0 - 10 °C. Then the mixture was concentrated under reduce pressure to remove MeOH. 6 N NaOH was added until the pH of the solution was 8 ~ 10. The mixture was extracted with EtOAc (3x). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduce pressure to afford the title compound (158 g) as a yellow oil, which was used in the next step without further purification.

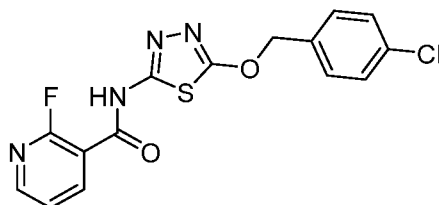
Step 2. Preparation of 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine



[0173] To a solution of NaH (65.7 g, 1.64 mol, 60.0% purity) in THF (1.20 L) was added a solution of (5-chloropyridin-2-yl)methanol (158 g, 1.10 mol) in THF (400 mL) at 5 °C dropwise. The mixture was stirred at 5 °C for 1 h. Then 2-amino-5-bromo-1,3,4-thiadiazole (237 g, 1.31 mol) was added in portions at 5 °C. The mixture was stirred at 5 °C for 4 h. The mixture was poured into H₂O and extracted with EtOAc (4x). The combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduce pressure. The residue was diluted with MeOH and slurry was stirred at 25 °C for 0.5 h. The solids were collected and diluted with MeOH. The slurry was stirred at 80 °C for 2 h. The solids were collected to afford the title compound (57.6 g, 21% yield) as a grey solid.

Intermediate D

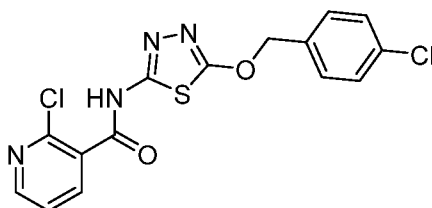
Synthesis of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-2-fluoropyridine-3-carboxamide



[0174] To a solution of 2-fluoropyridine-3-carboxylic acid (1 g, 7.1 mmol) in SOCl₂ (1052 mg, 7.8 mmol) was added DMF (51.80 mg, 0.709 mmol) under nitrogen. The mixture was stirred 2 h at room temperature. The mixture was concentrated under reduced pressure. The residue was diluted with DCM (10 mL) and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (1679 mg, 6.9 mmol, Intermediate B) and Et₃N (1434 mg, 14.2 mmol) were added. The mixture was stirred for 2 h at room temperature. The mixture was diluted with DCM (10 mL) and water (10 mL). The organic layer was concentrated under reduce pressure. The residue was re-crystallized from MeOH:water, 10:1 to afford N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-2-fluoropyridine-3-carboxamide as an off-white solid.

Intermediate E

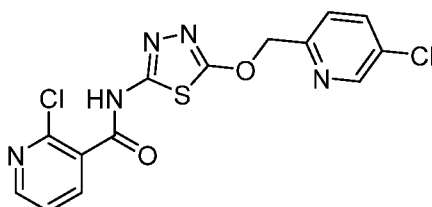
Synthesis of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-2-chloropyridine-3-carboxamide



[0175] The title compound was prepared using General Procedure D employing 2-chloropyridine-3-carboxylic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B).

Intermediate F

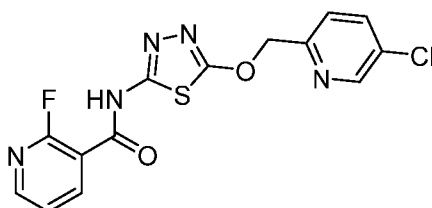
N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-2-chloronicotinamide



[0176] The title compound was prepared using General Procedure D employing 2-chloropyridine-3-carboxylic acid and 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C). The mixture was stirred at room temperature for 2 h. The mixture was diluted with ice water. The mixture was filtered and the solid was washed with ice water to give the desired product as an off-white solid.

Intermediate G

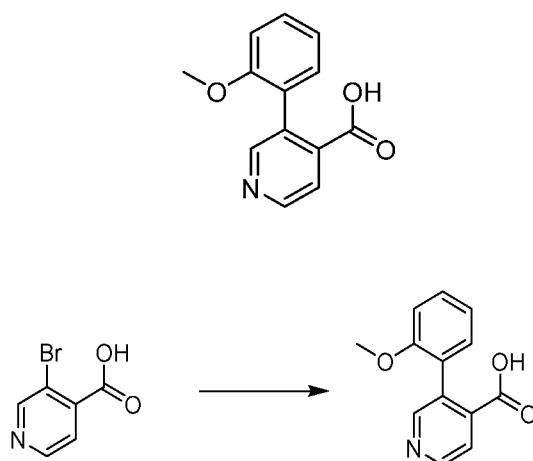
N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-2-fluoronicotinamide



[0177] The title compound was prepared using similar procedure as Intermediate F, replacing 2-chloropyridine-3-carboxylic acid with 2-fluoropyridine-3-carboxylic acid.

Intermediate H

3-(2-methoxyphenyl) pyridine-4-carboxylic acid

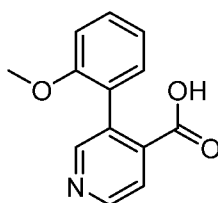


[0178] To a solution of 3-bromopyridine-4-carboxylic acid (2.0 g, 9.9 mmol) in dioxane (10 mL) and water (10 mL) was added 2-methoxyphenylboronic acid (2.3 g, 14.9 mmol), Na_2CO_3 (1.1 g, 9.9 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (1.1 g, 0.99 mmol) at room temperature under nitrogen. The mixture was stirred at 100 °C overnight. The mixture was cooled to room temperature and diluted with water. The mixture was extracted with EtOAc (2 x). The aqueous layer was acidified to pH 6 with HCl (1 M). A solid formed and mixture was filtered to afford title compound as a white solid.

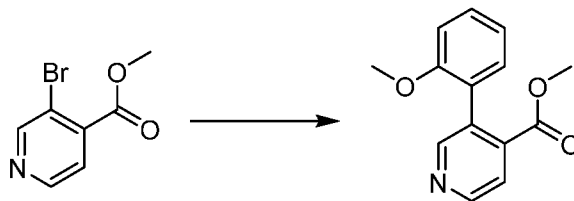
Additional synthesis of Intermediate H

Intermediate H

3-(2-methoxyphenyl) pyridine-4-carboxylic acid

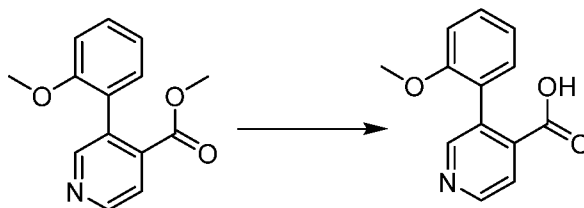


Step 1. Preparation of methyl 3-(2-methoxyphenyl)isonicotinate



[0179] To a solution of methyl 3-bromoisonicotinate (150 g, 694 mmol) in dioxane (1.5 L) and H₂O (150 mL) was added K₂CO₃ (95.9 g, 694 mmol), Pd(dppf)Cl₂ (25.4 g, 34.7 mmol) and compound 2-methoxyphenylboronic acid (126 g, 833 mmol). The mixture was stirred at 85 °C for 16 h. The mixture was poured into H₂O and extracted with EtOAc (3x). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography, eluted with 9 – 100% EtOAc in PE to afford a residue. The residue was diluted with MTBE and the slurry was stirred at rt for 0.5 h to afford the title compound (94.0 g, 83% yield) as a white solid.

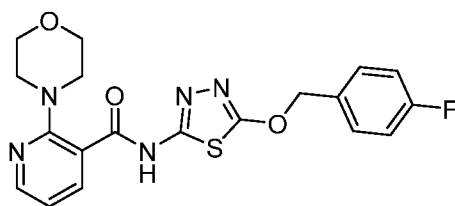
Step 2. Preparation of 3-(2-methoxyphenyl) pyridine-4-carboxylic acid



[0180] To a solution of methyl 3-(2-methoxyphenyl)isonicotinate (108 g, 444 mmol) in MeOH (648 mL) and H₂O (648 mL) was added NaOH (53.2 g, 1.33 mol). The mixture was stirred at 50 °C for 2 h. The mixture was concentrated under reduced pressure. The residue was diluted with 2 N HCl until pH was 2 – 3. The mixture was filtered. The solid was washed with H₂O (3x). The solid was dried under vacuum to afford the title compound (70.0 g, 79% yield) as a white solid, which was used to next step without further purification.

Example 1

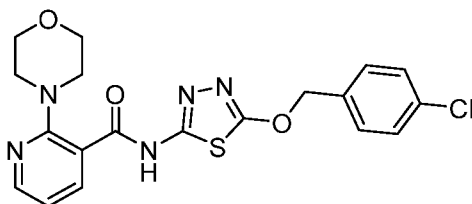
Synthesis of N-(5-((4-fluorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide



[0181] The title compound was prepared using General Procedure A employing 2-(morpholin-4-yl)pyridine-3-carboxylic acid and 5-((4-fluorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate A). The mixture was diluted with water (6 mL) and extracted with EtOAc (2 x 3 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 100:1) to afford N-(5-((4-fluorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide as a white solid. ^1H NMR (300MHz; DMSO- d_6): δ 3.21-3.24 (t, 4H), 3.65-3.68 (t, 4H), 5.49 (s, 2H), 6.98-7.02 (m, 1H), 7.22-7.30 (m, 2H), 7.57-7.61 (m, 2H), 7.90-7.93 (m, 1H), 8.35-8.37 (m, 1H), 12.87 (s, 1H). m/z 416 ($\text{M}+\text{H}^+$).

Example 2

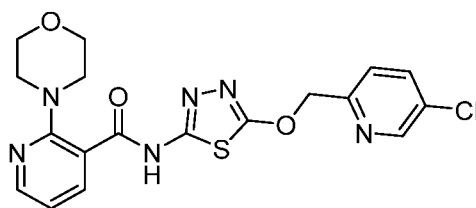
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide



[0182] The title compound was prepared using General Procedure A employing 2-(morpholin-4-yl)pyridine-3-carboxylic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was diluted with water and extracted with EtOAc (2 x). The combined organic layers were concentrated under reduced pressure. The residue was triturated with MeOH to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide as a white solid. ^1H NMR (300MHz; DMSO- d_6): δ 3.17-3.25 (m, 4H), 3.65-3.68 (t, 4H), 5.51 (s, 2H), 6.98-7.02 (m, 1H), 7.48-7.58 (m, 4H), 7.90-7.93 (m, 1H), 8.35-8.38 (m, 1H), 12.89 (s, 1H) ppm. m/z 432 ($\text{M}+\text{H}^+$).

Example 3

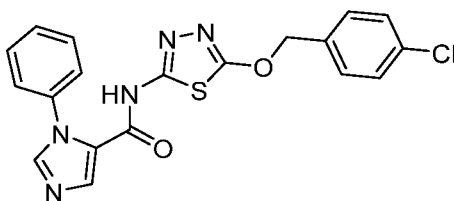
Synthesis of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-2-(morpholin-4-yl)benzamide



[0183] The title compound was prepared using General Procedure A employing 2-(morpholin-4-yl)pyridine-3-carboxylic acid and 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C). The mixture was diluted with water (2 mL) and the mixture was extracted with EtOAc (4 x 2 mL). The combined organic layers were concentrated under reduced pressure. The residue was triturated with 3 mL MeOH to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide as a white solid. ^1H NMR (300MHz; DMSO- d_6): δ 3.21-3.24 (t, 4H), 3.64-3.68 (t, 4H), 5.61 (s, 2H), 6.98-7.02 (m, 1H), 7.62-7.64 (d, 1H), 7.90-7.94 (m, 1H), 8.00-8.04 (m, 1H), 8.32-8.38 (m, 1H), 8.66-8.69 (m, 1H), 12.91 (s, 1H) ppm. m/z 433 ($\text{M}+\text{H}^+$).

Example 4

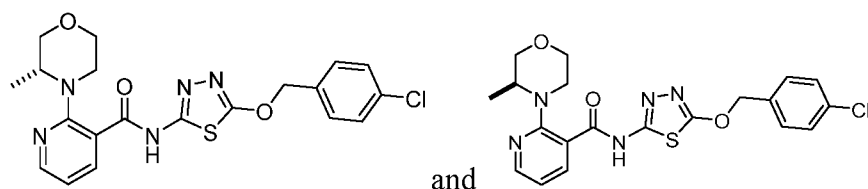
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-phenyl-1H-imidazole-5-carboxamide



[0184] The title compound was prepared according to General Procedure D using 1-phenyl-1H-imidazole-5-carboxylic acid and intermediate B to give N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-phenyl-1H-imidazole-5-carboxamide (20 mg, 6% yield). ^1H NMR (400 MHz, DMSO- d_6) δ 12.82 (s, 1H), 8.15 (s, 1H), 8.10 (s, 1H), 7.53 – 7.45 (m, 7H), 7.41 (d, J = 6.6 Hz, 2H), 5.46 (s, 2H) ppm. m/z 412 ($\text{M}+\text{H}^+$).

Example 5

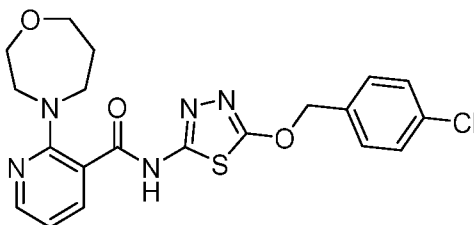
Synthesis of (R) N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(3-methylmorpholino)-nicotinamide and (S)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(3-methylmorpholino)nicotinamide



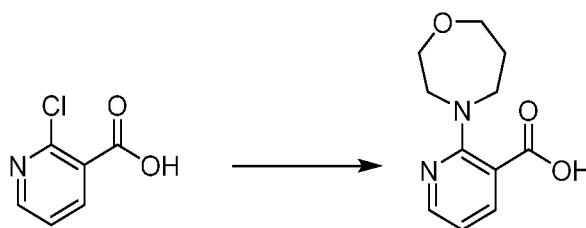
[0185] To a vial equipped with stir bar was added 2-chloro-*N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)nicotinamide Intermediate E (100 mg, 1 eq.) followed by addition of racemic 3-methylmorpholine (79 mg, 3 eq.) and THF (1.3 mL). DIPEA (0.274 mL, 6 eq.) was then added and the reaction was heated to 75° C and allowed to stir for 8 h. Upon reaction completion, the mixture was diluted with water, and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude residue was purified by column chromatography (silica gel, hexanes/ethyl acetate 0 – 100%) to give racemic mixture of (R) *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(3-methylmorpholino)nicotinamide and (S) *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(3-methylmorpholino)nicotinamide as a racemic mixture (12 mg, 10% yield) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.55 (d, *J* = 4.0 Hz, 1H), 8.49 (d, *J* = 7.7 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.32 – 7.25 (m, 1H), 5.49 (s, 2H), 4.04 (t, *J* = 8.5 Hz, 3H), 3.27 (td, *J* = 11.4, 10.6, 4.5 Hz, 1H), 3.23 – 3.09 (m, 2H), 2.98 (t, *J* = 11.3 Hz, 1H), 1.23 (d, *J* = 6.2 Hz, 3H) ppm. *m/z* 446 (M+H⁺).

Example 6

Synthesis of *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(1,4-oxazepan-4-yl)nicotinamide

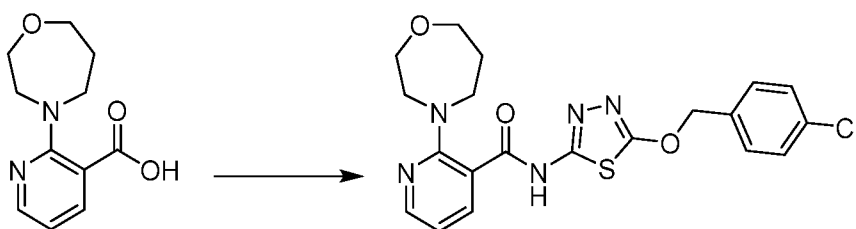


Step 1. Preparation of 2-(1,4-oxazepan-4-yl)nicotinic acid



[0186] The title compound was prepared using General Procedure B employing 1, 4-oxazepane. The mixture was concentrated under reduced pressure. The residue was purified by reverse phase chromatography (column C₁₈ silica gel; mobile phase, with 5-100% MeCN in water). The residue was further purified using reverse phase Prep-HPLC[(XBridge Prep OBD C₁₈ column; gradient elution 2 to 15% ACN in (0.16% NH₄HCO₃ in water)] to afford 2-(1,4-oxazepan-4-yl)nicotinic acid as a light yellow solid.

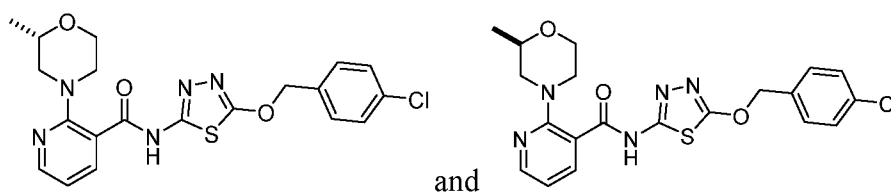
Step 2. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(1,4-oxazepan-4-yl)nicotinamide



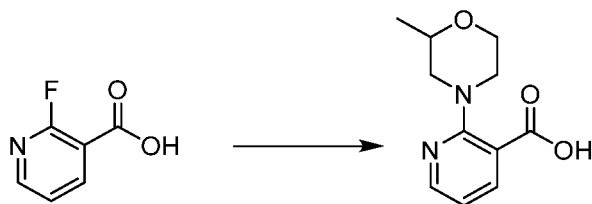
[0187] The title compound was prepared using General Procedure A employing 2-(1,4-oxazepan-4-yl)nicotinic acid and 5-((4-fluorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate A). The mixture was stirred for 2 days at room temperature. The mixture was diluted with water (5 mL). The mixture was extracted with EtOAc (3 x 3 mL) and the combined organic layers were concentrated under reduce pressure. The residue was purified by Prep-TLC (EtOAc:hexanes, 1:1) to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(1,4-oxazepan-4-yl)nicotinamide as a white solid. ¹H NMR (300MHz; DMSO-d₆): δ 1.80-1.90 (m, 2H), 3.46-3.52 (m, 2H), 3.53-3.60 (m, 4H), 3.73-3.74 (d, 2H), 5.49 (s, 2H), 6.73-6.77 (m, 1H), 7.48-7.56 (m, 4H), 7.75-7.78 (m, 1H), 8.22-8.24 (m, 1H), 12.82 (s, 1H) ppm. *m/z* 446 (M+H⁺).

Example 7

Synthesis of (R)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2-methylmorpholino)nicotinamide and (S)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2-methylmorpholino)nicotinamide

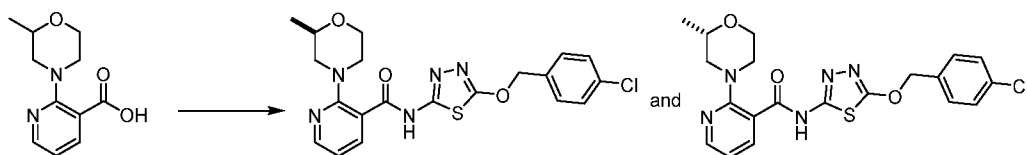


Step 1. Preparation of racemic 2-(2-methylmorpholin-4-yl)pyridine-3-carboxylic acid



[0188] The title compound was prepared using General Procedure C employing racemic 2-methylmorpholine. The mixture was diluted with water. The aqueous layer was extracted with EtOAc (3 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 20:1) to afford racemic 2-(2-methylmorpholin-4-yl)pyridine-3-carboxylic acid as a white solid.

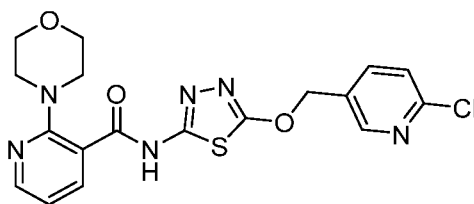
Step 2. Preparation of (R)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2-methylmorpholino)nicotinamide and (S)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2-methylmorpholino)nicotinamide



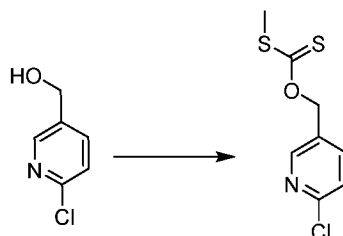
[0189] The title compounds were prepared using General Procedure A employing racemic 2-(2-methylmorpholin-4-yl)pyridine-3-carboxylic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was diluted with water and extracted with EtOAc. The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 35:1) to afford as a racemic mixture of (R)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2-methylmorpholino)nicotinamide and (S)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2-methylmorpholino)nicotinamide as a white solid. ^1H NMR (300MHz; DMSO- d_6): δ 1.27 (s, 3H), 2.96-3.33 (m, 4H), 4.03-4.15 (m, 3H), 5.52 (s, 2H), 7.30-7.34 (m, 1H), 7.38-7.48 (m, 4H), 8.52-8.60 (m, 2H), 13.51 (s, 1H) ppm. m/z 446 ($M+H^+$).

Example 8

Synthesis of N-(5-((6-chloropyridin-3-yl)methoxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide

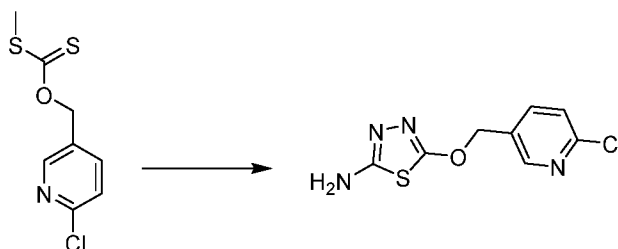


Step 1. Preparation of [(6-chloropyridin-3-yl)methoxy](methylsulfanyl)methanethione



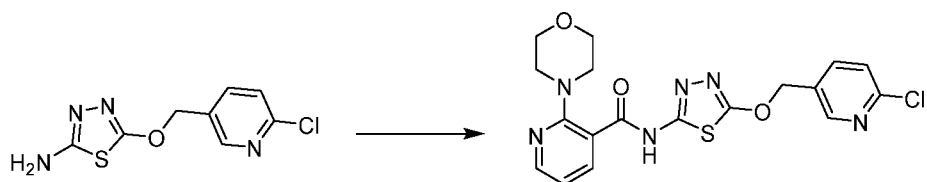
[0190] The title compound was prepared using a similar procedure as Intermediate B, Step 1 replacing (4-chlorophenyl)methanol with (6-chloropyridin-3-yl)methanol. The residue was purified by silica gel column chromatography, eluted with 1% EtOAc in PE to afford [(6-chloropyridin-3-yl)methoxy](methylsulfanyl)methanethione as yellow oil.

Step 2. Preparation of 5-[(6-chloropyridin-3-yl)methoxy]-1,3,4-thiadiazol-2-amine



[0191] The title compound was prepared using a similar procedure as Intermediate B, Step 2 replacing O-(4-chlorobenzyl) S-methyl carbonodithioate with [(6-chloropyridin-3-yl)methoxy]-(methylsulfanyl)methanethione. The mixture was concentrated under reduce pressure. The residue with triturated with MeOH to afford 5-[(6-chloropyridin-3-yl)methoxy]-1,3,4-thiadiazol-2-amine as a white solid.

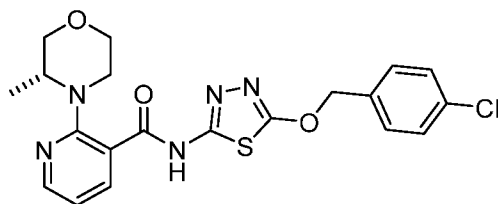
Step 3. Preparation of N-(5-((6-chloropyridin-3-yl)methoxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide



[0192] The title compound was prepared using General Procedure A employing 5-[(6-chloropyridin-3-yl)methoxy]-1,3,4-thiadiazol-2-amine and 2-(morpholin-4-yl)pyridine-3-carboxylic acid. The mixture was diluted with water. The aqueous layer was extracted with EtOAc (3 x). The combined organic layers were concentrated under reduce pressure. The residue was purified by Prep-TLC (DCM:MeOH, 35:1). The residue was further purified by Prep-HPLC [column, XBridge Prep OBD C₁₈; mobile phase 15-25% ACN in (0.05% NH₄OH in water)] to afford N-(5-((6-chloropyridin-3-yl)methoxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide as a white solid. ¹H NMR (400 MHz; DMSO-*d*₆): δ 3.23 (t, 4H), 3.66 (t, 4H), 5.56 (s, 2H), 6.97-7.01 (m, 1H), 7.59-7.62 (m, 1H), 7.90-7.92 (m, 1H), 8.03-8.06 (m, 1H), 8.35-8.36 (m, 1H), 8.59 (d, 1H), 12.90 (s, 1H) ppm. *m/z* 433 (M+H⁺).

Example 9

Synthesis of (R)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(3-methylmorpholino)nicotinamide

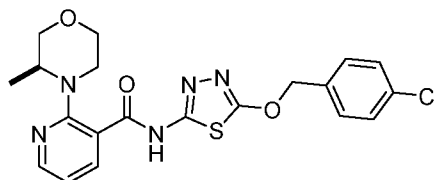


[0193] To a vial equipped with stir bar was added 2-chloro-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)nicotinamide Intermediate E (200 mg, 1 eq.) followed by addition of (R)-3-methylmorpholine (159 mg, 3 eq.) and THF (2.6 mL). DIPEA (0.548 mL, 6 eq.) was then added and the reaction was heated to 75° C and allowed to stir for 8 h. Upon reaction completion, the mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, hexanes/ethyl acetate 0 – 100%) to give the title compound (28 mg, 12% yield) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.55 (d, J = 4.8 Hz, 1H), 8.50 (d, J = 7.7 Hz, 1H), 7.44 (d, J = 7.6 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 7.32 –

7.24 (m, 1H), 5.49 (s, 2H), 4.08 – 4.00 (m, 3H), 3.28 (td, $J = 11.6, 4.3$ Hz, 1H), 3.16 (dd, $J = 23.0, 12.2$ Hz, 2H), 2.98 (t, $J = 11.2$ Hz, 1H), 1.23 (d, $J = 6.1$ Hz, 3H) ppm. m/z 446 ($M+H^+$).

Example 10

Synthesis of (S)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(3-methylmorpholino)nicotinamide

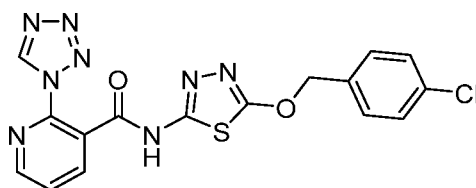


[0194] Proceeding analogously as described in Example 9 above but substituting (R)-3-methylmorpholine with (S)-3-methylmorpholine gave the title compound as a white solid.

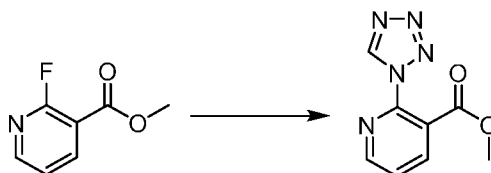
LC/MS $[M+H]^+$ 445.92. ^1H NMR (400 MHz, Chloroform- d) δ 8.55 (d, $J = 4.7$ Hz, 1H), 8.49 (d, $J = 7.8$ Hz, 1H), 7.43 (d, $J = 8.0$ Hz, 2H), 7.37 (d, $J = 8.0$ Hz, 2H), 7.32 – 7.24 (m, 1H), 5.49 (s, 2H), 4.11 – 3.93 (m, 3H), 3.26 (td, $J = 11.4, 10.8, 4.6$ Hz, 1H), 3.22 – 3.07 (m, 2H), 2.97 (t, $J = 11.3$ Hz, 1H), 1.23 (d, $J = 6.0$ Hz, 3H) ppm. m/z 446 ($M+H^+$).

Example 11

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(1H-tetrazol-1-yl)nicotinamide



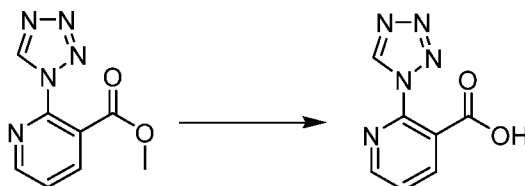
Step 1. Preparation of methyl 2-(1H-tetrazol-1-yl)nicotinate



[0195] To a solution of tetrazole (0.68 g, 9.7 mmol) in NMP (15 mL) at 0 °C was added NaH (0.58 g, 14.5 mmol, 60% dispersion in oil) in portions under nitrogen. The mixture was stirred at 0 °C for 30 min then methyl 2-fluoropyridine-3-carboxylate (1.50 g, 9.7 mmol) was added. The

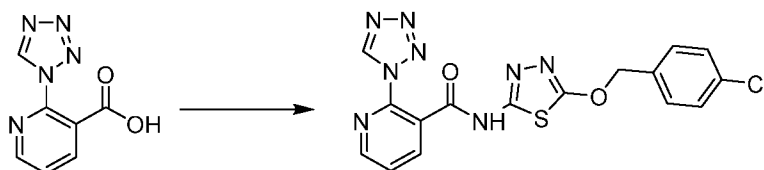
mixture was heated to 80 °C and stirred at 80 °C for overnight. The mixture was cooled to room temperature and quenched with sat. NH₄Cl. The mixture was extracted with EtOAc (3 x) and the combined organic layers were concentrated under reduce pressure. The residue was purified by reverse phase chromatography (column, C₁₈ silica gel; mobile phase, with 5-100% MeCN in water) to afford methyl 2-(1H-tetrazol-1-yl)nicotinate as white solid.

Step 2. Preparation of 2-(1H-tetrazol-1-yl)nicotinic acid



[0196] To a solution of methyl 2-(1H-tetrazol-1-yl)nicotinate (620 mg, 2.9 mmol) in MeOH (30mL) was added a solution of NaOH (234 mg, 5.8 mmol) in H₂O (6 mL). The mixture was stirred at room temperature for 4 h. HCl (1 M) was added until the pH of the mixture was 5. The mixture was concentrated under reduced pressure. The residue was purified by reverse phase chromatography (column, C₁₈ silica gel; mobile phase, with 5-100% MeCN in water) to afford 2-(1H-tetrazol-1-yl)nicotinic acid as a white solid.

Step 3. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(1H-tetrazol-1-yl)nicotinamide

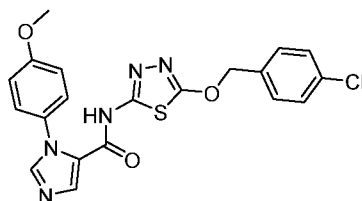


[0197] To a solution of 2-(1H-tetrazol-1-yl)nicotinic acid (200 mg, 1.0 mmol) in DMF (5 mL) was added 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (253 mg, 1.0 mmol, Intermediate B), EDCI (301 mg, 1.6 mmol) and HOBt (212 mg, 1.6 mmol). The mixture was stirred at 50 °C overnight. The mixture was diluted with sat. NaCl (20 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were concentrated under reduce pressure. The residue was re-crystallization from DCM: MeOH, 30:1 to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(1H-tetrazol-1-yl)nicotinamide as a white solid. ¹H NMR (300 MHz; DMSO-d₆): δ 5.50

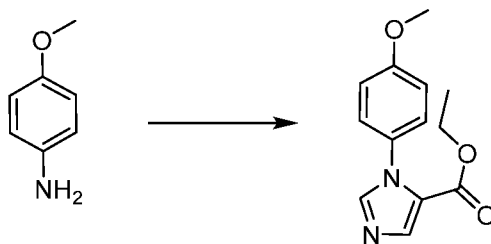
(s, 2H), 7.47-7.56 (m, 4H), 7.82-7.93 (m, 1H), 8.39-8.49 (m, 1H), 8.83-8.88 (m, 1H), 10.21 (s, 1H), 13.05 (s, 1H) ppm. m/z 415 ($M+H^+$).

Example 12

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(4-methoxyphenyl)-1H-imidazole-5-carboxamide

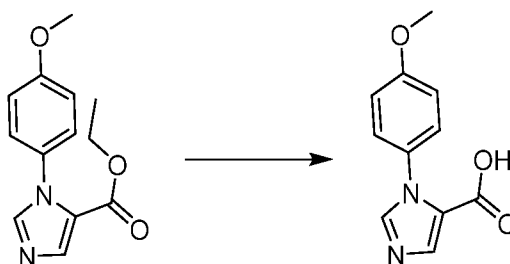


Step 1. Preparation of ethyl 1-(4-methoxyphenyl)-1H-imidazole-5-carboxylate



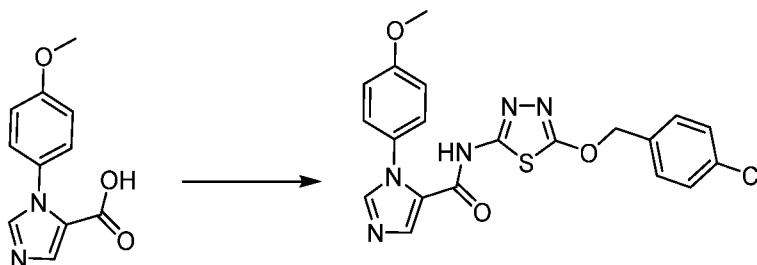
[0198] To a solution of p-Anisidine (3.0 g, 24.4 mmol) and ethyl glyoxylate (5.0 g, 24.4 mmol, 50% in toluene) in toluene (30 mL) under nitrogen was added sodium sulfate (17.3 g, 122 mmol). The mixture was stirred for 1 h at 120 °C. The mixture was filtered and the filtration was concentrated under reduce pressure. The mixture was diluted with EtOH (30 mL) and purged with nitrogen. Then K_2CO_3 (2.2 g, 16.2 mmol) and p-toluenesulfonylmethyl isocyanide (2.4 g, 12.2 mmol) were added. The mixture was stirred at 50 °C for 4 h. The mixture was cooled to room temperature and quenched with water (30 mL). The mixture was extracted with EtOAc (6 x 30 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 2% MeOH in DCM to afford ethyl 1-(4-methoxyphenyl)-1H-imidazole-5-carboxylate as a yellow solid.

Step 2. Preparation of 3-(4-methoxyphenyl)imidazole-4-carboxylic acid



[0199] To a solution of ethyl 3-(4-methoxyphenyl)imidazole-4-carboxylate (400 mg, 1.6 mmol) in THF (4 mL) and water (4 mL) was added NaOH (130 mg, 3.2 mmol). The mixture was stirred at room temperature for 2 h. The mixture was diluted with water (15 mL). The mixture was acidified to pH 6 with HOAc. The mixture was extracted with EtOAc (2 x 5 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure to afford 3-(4-methoxyphenyl)imidazole-4-carboxylic acid as a white solid.

Step 3. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(4-methoxyphenyl)-1H-imidazole-5-carboxamide

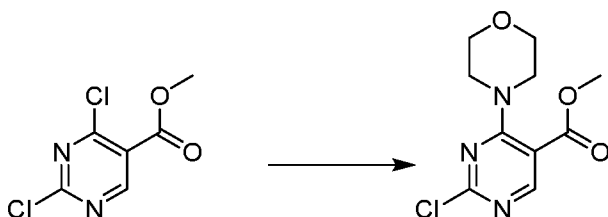


[0200] The title compound was prepared using General Procedure D employing 3-(4-methoxyphenyl)imidazole-4-carboxylic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was cooled to room temperature and quenched with water. The aqueous layer was extracted with EtOAc (2 x). The combining organic layer were concentrated under reduce pressure and the residue was triturated with MeOH to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(4-methoxyphenyl)-1H-imidazole-5-carboxamide as a brown solid. ¹H NMR (300 MHz; DMSO-d₆): δ 3.81 (s, 3H), 5.46 (s, 2H), 7.00-7.03 (m, 2H), 7.27-7.34 (m, 2H), 7.45-7.53 (m, 4H), 8.04-8.16 (m, 2H), 12.63-12.80 (br s, 1H) ppm. *m/z* 442 (M+H⁺).

Example 13

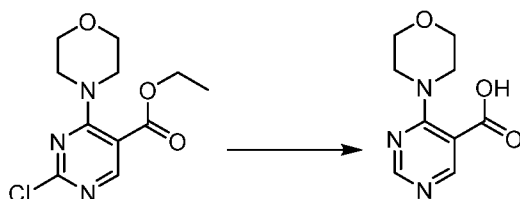
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)- 4-morpholinopyrimidine-5-carboxamide

Step 1. Preparation of methyl 2-chloro-4-(morpholin-4-yl)pyrimidine-5-carboxylate



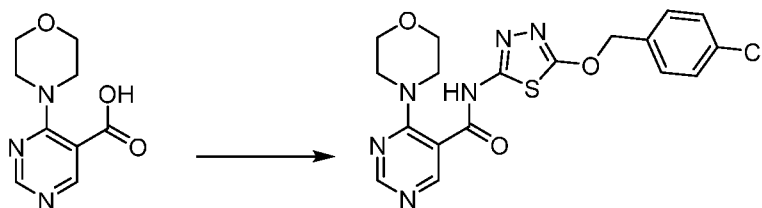
[0201] To a solution of methyl 2,4-dichloropyrimidine-5-carboxylate (1.0 g, 4.8 mmol) in NMP (10 mL) at 0 °C was added DIEA (1.25 g, 9.7 mmol) under nitrogen. Then morpholine (0.42 g, 4.8 mmol) was added in portions. The mixture was stirred at 0 °C for 3 h. The mixture was diluted with EtOAc (10 mL) washed with water (3 x 10 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were concentrated under reduce pressure. The residue was purified by Prep-TLC (PE:EtOAc, 2:1) to afford methyl 2-chloro-4-(morpholin-4-yl)pyrimidine-5-carboxylate as a yellow solid.

Step 2. Preparation of 4-(morpholin-4-yl)pyrimidine-5-carboxylic acid



[0202] To a solution of methyl 2-chloro-4-(morpholin-4-yl)pyrimidine-5-carboxylate (400 mg, 1.6 mmol) in MeOH was added 10 % Pd/C (40 mg) and NaOH (311 mg, 7.8 mmol) and water (4 mL). The mixture was stirred at room temperature for 3 h under the of H₂ (g). The mixture was filtered through celite and the filtrate was concentrated under reduced pressure to afford 4-(morpholin-4-yl)pyrimidine-5-carboxylic acid as a white solid.

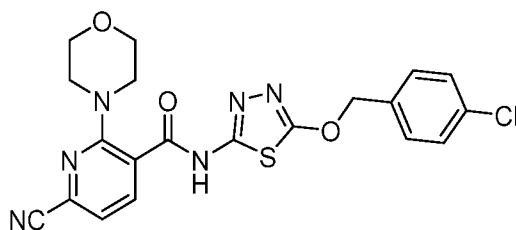
Step 3. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)- 4-morpholinopyrimidine-5-carboxamide



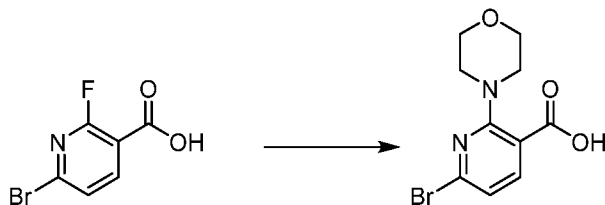
[0203] The title compound was prepared using General Procedure D employing 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) and 4-(morpholin-4-yl)pyrimidine-5-carboxylic acid. The mixture was cooled to room temperature and diluted with EtOAc. The mixture was washed with water (3 x). The aqueous layer was extracted with EtOAc. The organic layer was concentrated under reduce pressure and the residue was purified by Prep-TLC (DCM:MeOH, 50:1) to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-morpholinopyrimidine-5-carboxamide as a white solid. ^1H NMR (300 MHz; DMSO- d_6): δ 3.48-3.50 (m, 4H), 3.61-3.64 (m, 4H), 5.51 (s, 2H), 7.48-7.51 (m, 2H), 7.54-7.56 (m, 2H), 8.47 (s, 1H), 8.61 (s, 1H), 13.01 (s, 1H) ppm. m/z 433 ($M+H^+$).

Example 14

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-2-morpholinonicotinamide



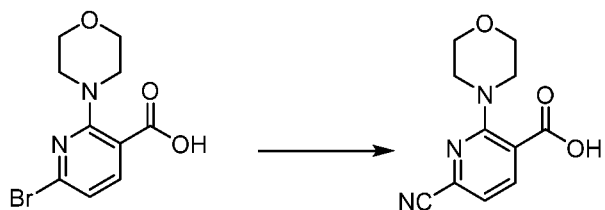
Step 1. Preparation of 6-bromo-2-morpholinonicotinic acid



[0204] To a solution of 6-bromo-2-fluoropyridine-3-carboxylic acid (5.0 g, 22.7 mmol) in MeCN (50 mL) was added morpholine (4.0 g, 45.5 mmol), and DIEA (5.9 g, 45.4 mmol) under nitrogen. The mixture was stirred at 50 °C overnight. The mixture was concentrated under reduce pressure and the residue was purified by reverse flash chromatography (column, C_{18} silica gel;

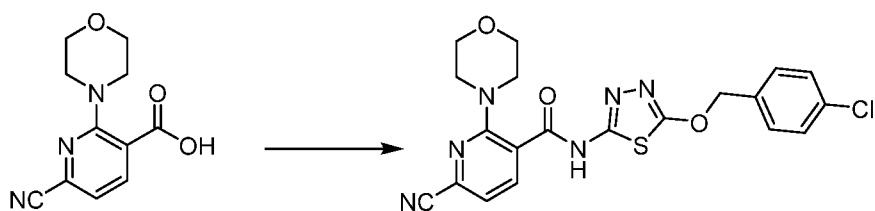
mobile phase, 5 – 40% MeCN in water to afford 6-bromo-2-morpholinonicotinic acid as a brown solid.

Step 2. Preparation of 6-cyano-2-morpholinonicotinic acid



[0205] To a solution of 6-bromo-2-morpholinonicotinic acid (3.2 g, 11.1 mmol) in DMSO (32mL) was added CuCN (5.0 g, 55.7 mmol) under nitrogen. The mixture was stirred at 120 °C for 4 h. Then the mixture was cooled to room temperature and diluted with EtOAc (20 mL). The mixture was filtered and the filtrate was concentrated under reduce pressure. The residue was purified by reverse flash chromatography (column, C₁₈ silica gel; mobile phase, 5 – 30% MeCN) in water to afford 6-cyano-2-morpholinonicotinic acid as a yellow green solid.

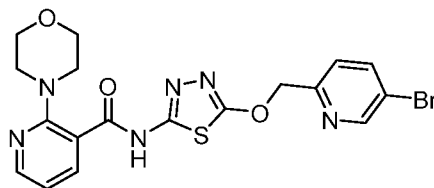
Step 3. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-2-morpholinonicotinamide



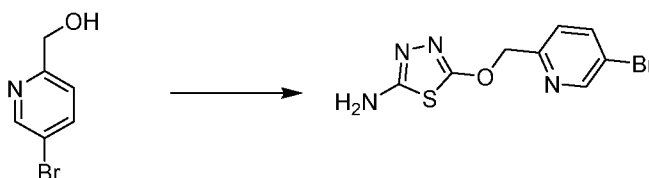
[0206] To a solution of 6-cyano-2-morpholinonicotinic acid (170 mg, 0.73 mmol) and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (211 mg, 0.88 mmol, Intermediate B) in DMF (2 mL) was added EDCI (210 mg, 1.09 mmol) and HOBt (148 mg, 1.1 mmol) under nitrogen. The mixture was stirred at 50 °C overnight. The mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were concentrated under reduce pressure and the residue was triturated with 1 mL MeOH to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-2-morpholinonicotinamide as a light yellow solid. ¹H NMR (300 MHz; DMSO-d₆): δ 3.31-3.32 (m, 4H), 3.61-3.63 (m, 4H), 5.46-5.51 (m, 2H), 7.46-7.57 (m, 5H), 8.00-8.02 (m, 1H), 13.03 (s, 1H) ppm. *m/z* 457 (M+H⁺).

Example 15

Synthesis of N-[5-[(5-bromopyridin-3-yl)oxy]-1,3,4-thiadiazol-2-yl]-2-(morpholin-4-yl)pyridine-3-carboxamide

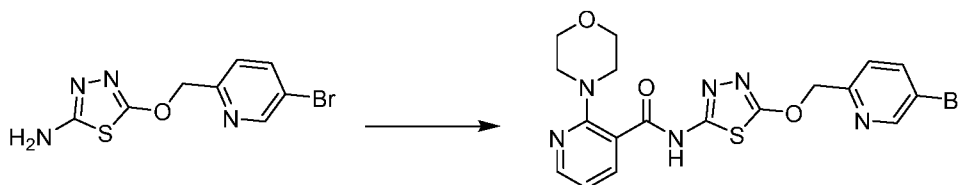


Step 1. Preparation of 5-((5-bromopyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine



[0207] The title compound was prepared using similar procedure as Intermediate C replacing (5-chloropyridin-2-yl)methanol in Step 1 with (5-bromopyridin-2-yl) methanol.

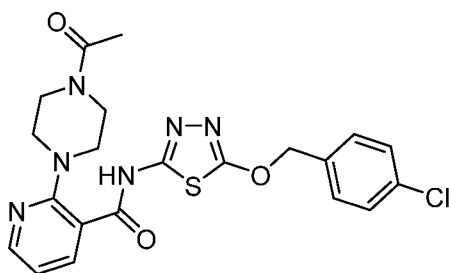
Step 2. Preparation of N-[5-[(5-bromopyridin-3-yl)oxy]-1,3,4-thiadiazol-2-yl]-2-(morpholin-4-yl)pyridine-3-carboxamide



[0208] The title compound was prepared using General Procedure A employing 5-((5-bromopyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine and 2-morpholinonicotinic acid. The mixture was diluted with water and filtered. The filtrate was concentrated and the residue was purified by Prep-TLC (DCM:MeOH, 50:1) to afford N-[5-[(5-bromopyridin-3-yl)oxy]-1,3,4-thiadiazol-2-yl]-2-(morpholin-4-yl)pyridine-3-carboxamide as a white solid. ^1H NMR (300 MHz; DMSO- d_6): δ 3.22-3.24 (m, 4H), 3.65-3.67 (m, 4H), 5.55 (s, 2H), 6.98-7.01 (m, 1H), 7.56-7.58 (m, 1H), 7.90-7.93 (m, 1H), 8.12-8.15 (m, 1H), 8.35-8.36 (m, 1H), 8.73-8.74 (m, 1H), 12.90 (s, 1H) ppm. m/z 479 ($M+H^+$).

Example 16

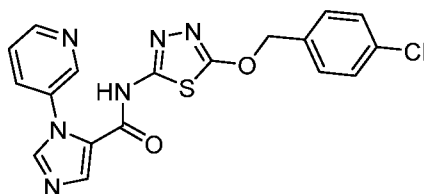
Synthesis of 2-(4-acetylpiperazin-1-yl)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)nicotinamide



[0209] Proceeding analogously as described in Example 9 but substituting (R)-3-methylmorpholine with 1-(piperazin-1-yl)ethan-1-one gave crude product. The crude residue was purified via Prep-HPLC (column, C18 silica gel; mobile phase, 45 - 85% MeCN in water, with both eluents containing 0.1% FA) to the title compound as a white solid. LC/MS $[M+H]^+$ 472.95. ^1H NMR (400 MHz, DMSO- d_6) δ 8.34 (d, $J = 4.6$ Hz, 1H), 7.90 (d, $J = 7.4$ Hz, 1H), 7.55 (d, $J = 8.2$ Hz, 2H), 7.49 (d, $J = 8.1$ Hz, 2H), 6.98 (dd, $J = 7.4, 4.9$ Hz, 1H), 5.49 (s, 2H), 3.64 – 3.45 (m, 4H), 3.30 – 3.15 (m, 4H), 2.00 (s, 3H) ppm. m/z 473 ($M+H^+$).

Example 17

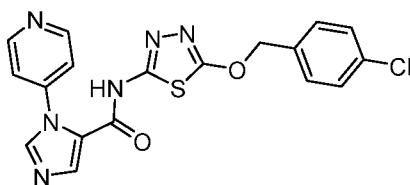
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(pyridin-3-yl)-1H-imidazole-5-carboxamide



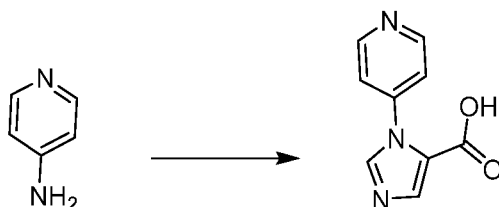
[0210] The title compound was prepared using similar procedure as Example 12, replacing p-Anisidine in Step 1 with 3-aminopyridine to provide N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(pyridin-3-yl)-1H-imidazole-5-carboxamide as a white solid. ^1H NMR (300 MHz; DMSO- d_6): δ 5.47 (s, 2H), 7.45-7.58 (m, 5H), 7.92-7.95 (m, 1H), 8.21-8.25 (m, 2H), 8.66-8.67 (m, 2H), 12.87-12.95 (br s, 1H) ppm. m/z 413 ($M+H^+$).

Example 18

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(pyridin-4-yl)-1H-imidazole-5-carboxamide

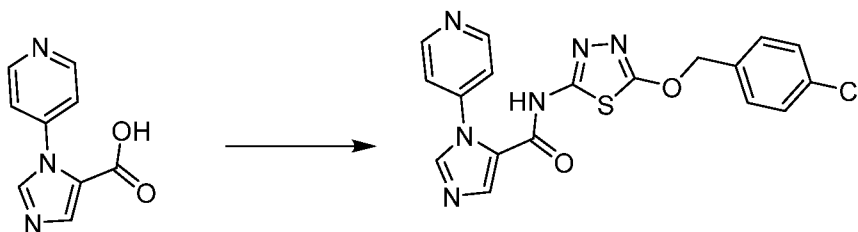


Step 1. Preparation of 3-(pyridin-4-yl)imidazole-4-carboxylic acid



[0211] The title compound was prepared using similar procedure as Example 12, Step 1 and 2 replacing p-Anisidine in Step 1 with 4-aminopyridine.

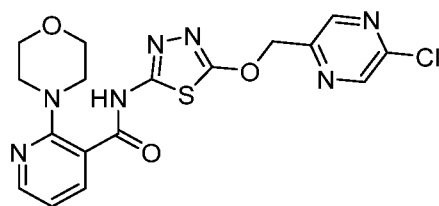
Step 2. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(pyridin-4-yl)-1H-imidazole-5-carboxamide



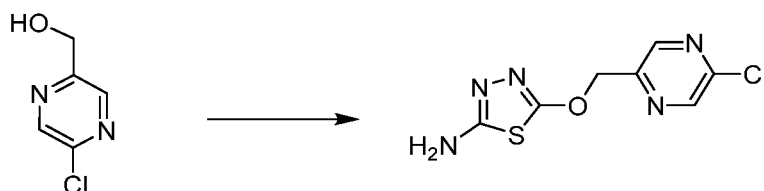
[0212] The title compound was prepared using General Procedure A employing 3-(pyridin-4-yl)imidazole-4-carboxylic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was stirred at 50 °C for 4 h. The mixture was cooled to room temperature and diluted with water (10 mL) at room temperature. The mixture was extracted with EtOAc (2 x 5 mL). The combined organic layers were concentrated under reduced pressure and the residue triturated MeOH (2 mL) to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(pyridin-4-yl)-1H-imidazole-5-carboxamide as a white solid. ¹H NMR (300 MHz; DMSO-d₆): δ 5.47 (s, 2H), 7.45-7.57 (m, 6H), 8.15-8.25 (m, 2H), 8.69-8.71 (m, 2H), 12.81-13.15 (br s, 1H) ppm. *m/z* 413 (M+H⁺).

Example 19

Synthesis of N-[5-[(5-chloropyrazin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-2-(morpholin-4-yl)pyridine-3-carboxamide

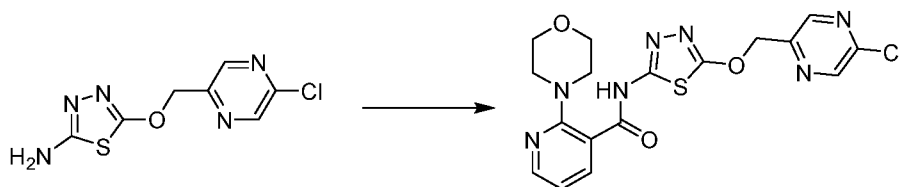


Step 1. Preparation of 5-[(5-chloropyrazin-2-yl)methoxy]-1,3,4-thiadiazol-2-amine



[0213] The title compound was prepared using similar procedure as Intermediate C replacing (5-chloropyridin-2-yl)methanol in Step 1 with (5-chloropyrazin-2-yl)methanol.

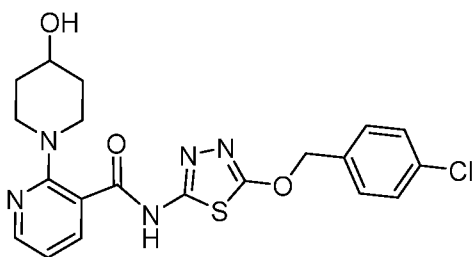
Step 2. Preparation of N-[5-[(5-chloropyrazin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-2-(morpholin-4-yl)pyridine-3-carboxamide



[0214] The title compound was prepared using General Procedure A employing 5-[(5-chloropyrazin-2-yl)methoxy]-1,3,4-thiadiazol-2-amine and 2-morpholinonicotinic acid. The mixture was diluted with water (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were concentrated under reduced pressure. The residue was triturated with MeOH (1 mL) to afford N-[5-[(5-chloropyrazin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-2-(morpholin-4-yl)pyridine-3-carboxamide as a yellow solid. ^1H NMR (300 MHz; DMSO- d_6): δ 3.22-3.25 (m, 4H), 3.61-3.68 (m, 4H), 5.67 (s, 2H), 6.98-7.03 (m, 1H), 7.91-7.96 (m, 1H), 8.36-8.38 (m, 1H), 8.75 (s, 1H), 8.86-8.87 (m, 1H), 12.92 (s, 1H) ppm. m/z 434 ($\text{M}+\text{H}^+$).

Example 20

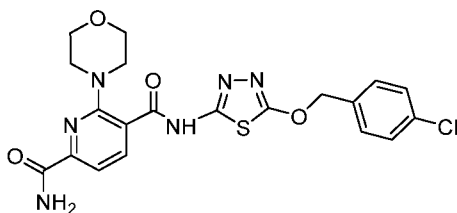
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(4-hydroxypiperidin-1-yl)nicotinamide



[0215] Proceeding analogously as described in Example 22 but replacing (R)-3-methylmorpholine with 4-piperidinol gave crude product. The crude product was purified by reverse phase HPLC (water (0.1% formic acid) and MeCN (0.1% formic acid)) to afford the title compound as a white solid. ^1H NMR (400 MHz, DMSO- d_6): δ 12.98 (s, 1H), 8.66 (s, 1H), 8.33 (d, J = 4.7 Hz, 1H), 8.08 – 7.95 (m, 1H), 7.90 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.06 – 6.81 (m, 1H), 5.57 (s, 2H), 4.71 (d, J = 4.0 Hz, 1H), 3.79 – 3.57 (m, 1H), 3.57 – 3.40 (m, 3H), 2.98 (t, J = 11.2 Hz, 2H), 1.85 – 1.63 (m, 2H), 1.55 – 1.37 (m, 2H) ppm. m/z 447 ($\text{M}+\text{H}^+$).

Example 21

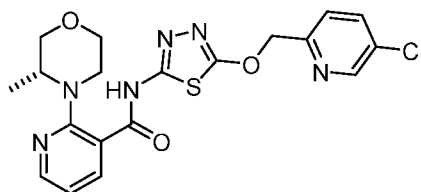
Synthesis of N^5 -(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-morpholinopyridine-2,5-dicarboxamide



[0216] To a solution of N^5 -(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-2-morpholino-nicotinamide (55 mg, 0.12 mmol, Example 14) in MeOH (3 mL) was added H_2O_2 (1.5 mL, 30% in water), water (0.6 mL) and NaOH (3.5 mg, 0.087 mmol). The mixture was stirred overnight at room temperature. The mixture was diluted with water (6 mL) and extracted with EtOAc (2 x 3 mL). The combining organic layers were concentrated under reduce pressure. The residue was purified by Prep-TLC (DCM:MeOH, 10:1). The residue was triturated with MeOH (1 mL) to afford N^5 -(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-morpholinopyridine-2,5-dicarboxamide as a white solid. ^1H NMR (300 MHz; DMSO- d_6): δ 3.62 (s, 4H), 5.36-4.82 (m, 6H), 6.08 (s, 1H), 7.37-7.34 (m, 1H), 7.53-7.45 (m, 5H), 7.86-7.76 (m, 2H) ppm. m/z 475 ($\text{M}+\text{H}^+$).

Example 22

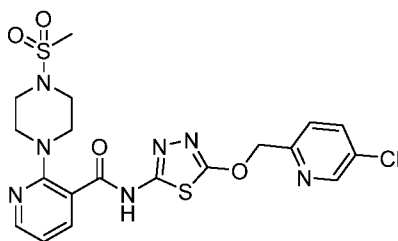
Synthesis of (R)-N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-2-(3-methylmorpholino)nicotinamide



[0217] To a vial equipped with stir bar was added 2-chloro-N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)nicotinamide Intermediate F (200 mg, 1 eq.) followed by addition of (R)-3-methylmorpholine (158 mg, 3 eq.) and THF (2.6 mL). DIPEA (0.546 mL, 6 eq.) was then added and the reaction was heated to 75° C and allowed to stir for 8 h. Upon reaction completion the mixture was diluted with water, and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The crude residue was purified via reverse phase chromatography conditions (40%-80% MeCN/H₂O) to give the title compound (30 mg, 12% yield) as a white solid. ¹H NMR (400 MHz, Chloroform-d) δ 8.60 (s, 1H), 8.56 (d, J = 4.8 Hz, 1H), 8.50 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 8.3 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.32 – 7.25 (m, 1H), 5.61 (s, 2H), 4.10 – 3.98 (m, 3H), 3.27 (td, J = 11.3, 10.4, 4.8 Hz, 1H), 3.15 (dd, J = 22.2, 12.2 Hz, 2H), 2.98 (t, J = 11.3 Hz, 1H), 1.23 (d, J = 6.2 Hz, 3H) ppm. *m/z* 447 (M+H⁺).

Example 23

Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-2-(4-(methylsulfonyl)piperazin-1-yl)nicotinamide

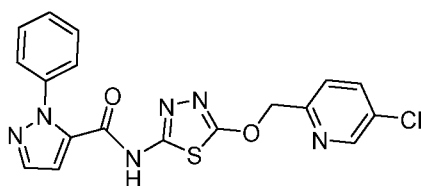


[0218] Proceeding analogously as described in Example 22, employing (methylsulfonyl)piperazine, hydrogen chloride and N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-

thiadiazol-2-yl)-2-fluoronicotinamide (Intermediate G) gave crude product. The residue was purified by Prep-HPLC (column, C₁₈ silica gel; mobile phase, 45%-85% MeCN in water, with both eluents containing 0.1% FA) to give the title compound. ¹H NMR (400 MHz; DMSO-d₆): δ 12.85 (br s, 1H), 8.66 (s, 1H), 8.35 (d, 1H), 8.01 (dd, 1H), 7.91 (d, 1H), 7.62 (d, 1H), 7.00-6.97 (m, 1H), 5.57 (s, 2H), 3.37-3.31 (m, 4H), 3.20-3.18 (m, 4H), 2.89 (s, 3H) ppm. *m/z* 510 (M+H⁺).

Example 24

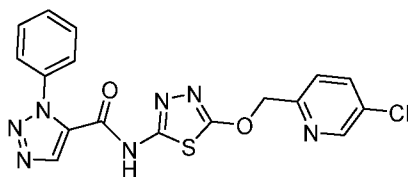
Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-1-phenyl-1H-pyrazole-5-carboxamide



[0219] The title compound was prepared using General Procedure D employing 1-phenyl-1H-pyrazole-5-carboxylic acid and 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C). The mixture was diluted with water and extracted with EtOAc. The combined organic layers were concentrated under reduce pressure. The residue was purified by reverse phase HPLC (column, C₁₈ silica; mobile phase 0 - 100% MeCN in water, with both eluents containing 0.1% FA water) to afford N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-1-phenyl-1H-pyrazole-5-carboxamide as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 13.05 (s, 1H), 8.65 (d, J = 2.3 Hz, 1H), 8.04 – 7.94 (m, 1H), 7.85 (s, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.44 (td, J = 15.8, 14.5, 10.2 Hz, 7H), 5.55 (s, 2H) ppm. *m/z* 413 (M+H⁺).

Example 25

Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-1-phenyl-1H-1,2,3-triazole-5-carboxamide

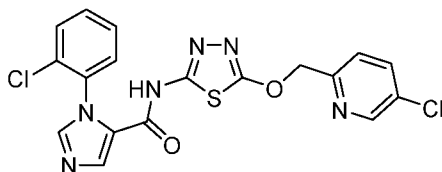


[0220] The title compound was prepared using General Procedure D employing 1-phenyl-1H-1,2,3-triazole-5-carboxylic acid and 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine

(Intermediate C). The mixture was diluted with water and extracted with EtOAc (3 x). The combined organic layers were concentrated under reduce pressure. The residue was purified by reverse phase HPLC (column, C₁₈ silica; mobile phase 0 - 100% MeCN in water, with both eluents containing 0.1% FA water) to afford N-(5-((5-chloropyridin-2-yl)methoxy))-1,3,4-thiadiazol-2-yl)-1-phenyl-1H-pyrazole-5-carboxamide as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 13.38 (s, 1H), 8.64 (d, J = 2.2 Hz, 1H), 7.99 (dd, J = 8.3, 2.4 Hz, 1H), 7.58 (s, 6H), 5.55 (s, 2H) ppm. *m/z* 414 (M+H⁺).

Example 26

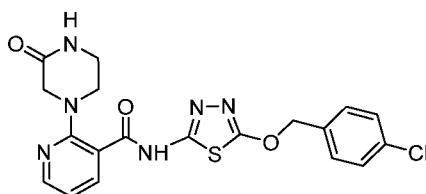
Synthesis of 3-(2-chlorophenyl)-N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]imidazole-4-carboxamide



[0221] The title compound was prepared using similar procedure as Example 18, replacing 4-aminopyridine with 2-chloroaniline in Step 1 and employing (5-((5-chloropyridin-2-yl)methoxy))-1,3,4-thiadiazol-2-amine, Intermediate C) in Step 2. The mixture was stirred at 50 °C overnight and then cooled to room temperature and diluted with water. The mixture was extracted with EtOAc (3 x) and the combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 15:1) to afford 3-(2-chlorophenyl)-N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]imidazole-4-carboxamide as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆): δ 5.53 (s, 2H), 7.48-7.58 (m, 4H), 7.65-7.67 (m, 1H), 7.97-8.00 (m, 1H), 8.10 (s, 1H), 8.25 (s, 1H), 8.63-8.64 (m, 1H), 12.85 (s, 1H) ppm. *m/z* 447 (M+H⁺).

Example 27

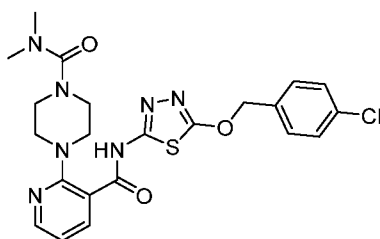
Synthesis of N-(5-((4-chlorobenzyl)oxy))-1,3,4-thiadiazol-2-yl)-2-(3-oxopiperazin-1-yl)nicotinamide



[0222] The title compound was prepared using General Procedure C, employing piperazin-2-one. Followed by General Procedure D employing 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was diluted with EtOAc and washed with brine (2 x). The aqueous layer was extracted with EtOAc. The combined organic layers were concentrated and the residue was purified by Prep-TLC (DCM:MeOH, 20:1). The residue was triturated with MeOH to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(3-oxopiperazin-1-yl)nicotinamide as a white solid. ^1H NMR (400 MHz; DMSO- d_6): δ 3.22 (s, 2H), 3.44-3.47 (m, 2H), 3.78 (s, 2H), 5.50 (s, 2H), 6.94-6.97 (m, 1H), 7.48-7.56 (m, 4H), 7.87-7.89 (m, 1H), 8.02 (s, 1H), 8.32-8.33 (m, 1H), 12.84 (s, 1H) ppm. m/z 445 ($M+H^+$).

Example 28

Synthesis of 4-(3-((5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)carbamoyl)pyridin-2-yl)-N,N-dimethylpiperazine-1-carboxamide

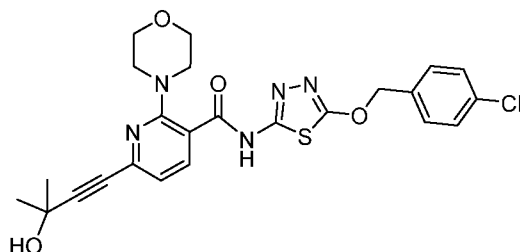


[0223] The title compound was prepared using General Procedure C, employing N,N-dimethylpiperazine-1-carboxamide. Followed by General Procedure A employing 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was stirred at 50 °C for overnight. The mixture was cooled to room temperature and diluted with water. The mixture was extracted with EtOAc (2 x). The combined organic layers were concentrated and the residue was purified by Prep-TLC (DCM:MeOH, 20:1). The residue was purified by Prep-HPLC [column, C₁₈ silica gel; mobile phase, 50-63% ACN in (0.16% NH₄HCO₃ in water)] to afford 4-(3-((5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)carbamoyl)pyridin-2-yl)-N,N-dimethylpiperazine-1-carboxamide as a white solid. ^1H NMR (400 MHz; DMSO- d_6): δ 2.76 (s,

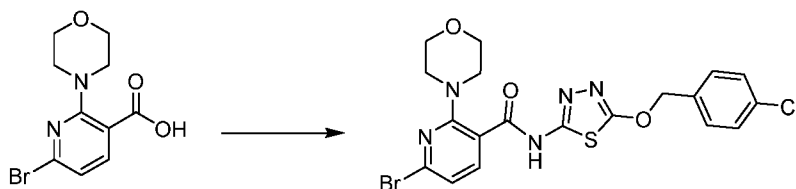
6H), 3.19-3.26 (m, 8H), 5.51 (s, 2H), 6.98-7.02 (m, 1H), 7.49-7.57 (m, 4H), 7.91-7.93 (m, 1H), 8.35-8.37 (m, 1H), 12.87 (s, 1H) ppm. m/z 502 ($M+H^+$).

Example 29

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)-2-morpholinonicotinamide

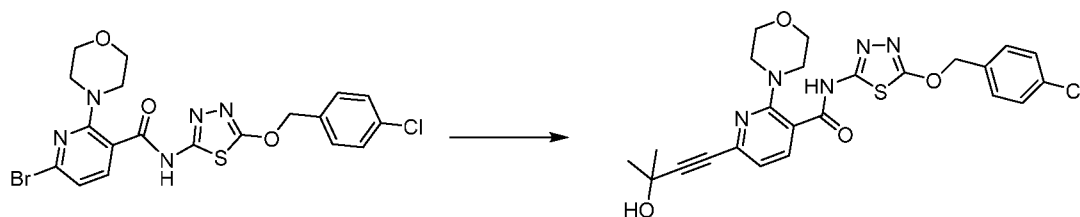


Step 1. Preparation of 6-bromo-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide



[0224] The title compound was prepared using General Procedure A employing 6-bromo-2-morpholinonicotinic acid (Step 1, Example 14) and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was diluted with water and extracted with EtOAc (3 x). The combined organic layers were concentrated under reduce pressure. The residue was triturated with DCM:MeOH, 10:1 to afford 6-bromo-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide as a white solid.

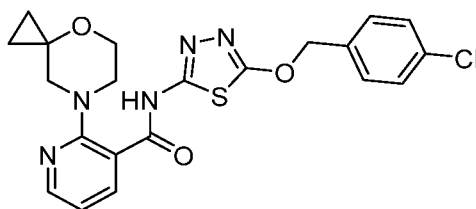
Step 2. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)-2-morpholinonicotinamide



[0225] To a solution of 6-bromo-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide (150 mg, 0.29 mmol) in DME (5 mL) was added 2-methyl-3-butyn-2-ol (37 mg, 0.44 mmol, 1.50), PPh₃ (123 mg, 0.47 mmol), CuI (22 mg, 0.12 mmol), and 10 % Pd/C (15 mg, 10%) under nitrogen. The mixture was stirred at 80 °C for 3 h. The mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (EtOAc:hexanes, 1:1) to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4- thiadiazol-2-yl)-6-(3-hydroxy-3-methylbut-1-yn-1-yl)-2-morpholinonicotinamide as a white solid. ¹H NMR (400 MHz; DMSO-d₆): δ 1.47 (s, 6H), 3.21-3.23 (d, 4H), 3.63-3.65 (m, 4H), 5.50-5.62 (m, 3H), 7.00-7.03 (m, 1H), 7.47-7.56 (m, 4H), 7.84-7.87 (m, 1H), 12.84 (s, 1H) ppm. *m/z* 433 (M+H⁺).

Example 30

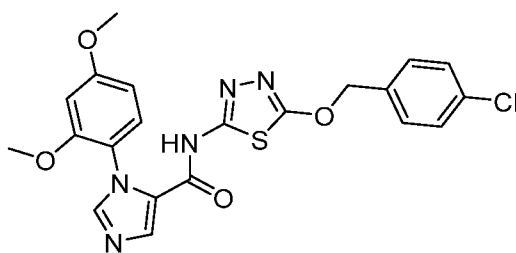
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(4-oxa-7-azaspiro[2.5]octan-7-yl)nicotinamide



[0226] The title compound was prepared using General Procedure C, employing 4-oxa-7-azaspiro[2.5]octane. Followed by General Procedure A employing 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was diluted with water and extracted with EtOAc (4 x). The combined organic layers were concentrated under reduced pressure. The residue was triturated with MeOH to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(4-oxa-7-azaspiro[2.5]octan-7-yl)nicotinamide as a white solid. ¹H NMR (300 MHz; DMSO-d₆): δ 0.50-0.55 (m, 2H), 0.66-0.70 (m, 2H), 3.23 (s, 2H), 3.27-3.32 (m, 2H), 3.72-3.76 (m, 2H), 5.50 (s, 2H), 7.00-7.05 (m, 1H), 7.47-7.57 (m, 4H), 7.93-7.96 (m, 1H), 8.36-8.38 (m, 1H), 13.00 (s, 1H) ppm. *m/z* 458 (M+H⁺).

Example 31

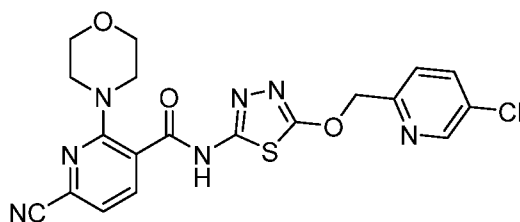
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(2,4-dimethoxyphenyl)-1H-imidazole-5-carboxamide



[0227] The title compound was prepared using similar procedure as Example 18, replacing 4-aminopyridine with 2,4-dimethoxyaniline in Step 1 and employing (5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) in Step 2. The mixture was stirred at 50 °C overnight and then cooled to room temperature and diluted with water. The mixture was extracted with EtOAc and the combined organic layers were concentrated under reduced pressure. The residue was triturated with MeOH to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(2,4-dimethoxyphenyl)-1H-imidazole-5-carboxamide as a white solid. ¹H NMR (300 MHz; DMSO-d₆): δ 3.65 (s, 3H), 3.83 (s, 3H), 5.46 (s, 2H), 6.58-6.62 (m, 1H), 6.70-6.71 (m, 1H), 7.25-7.28 (m, 1H), 7.45-7.53 (m, 4H), 7.92 (s, 1H), 8.11 (s, 1H), 12.68 (s, 1H) ppm. *m/z* 472 (M+H⁺).

Example 32

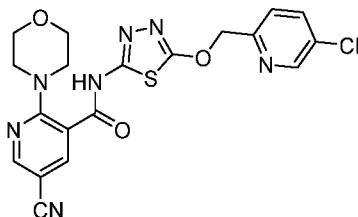
Synthesis of N-{5-[(5-chloro(2-pyridyl))methoxy](1,3,4-thiadiazol-2-yl)}(6-cyano-2-morpholin-4-yl)nicotinamide



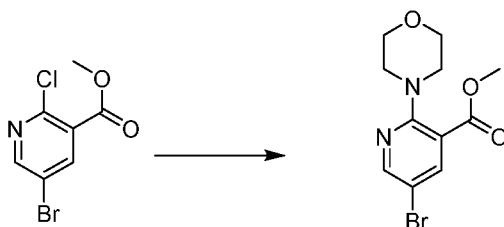
[0228] The title compound was prepared using General Procedure A employing 6-cyano-2-morpholinonicotinic acid (Example 14, Step 3) and 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C). The mixture was cooled to room temperature and filtered. The solid was washed with EtOAc to give N-{5-[(5-chloro(2-pyridyl))methoxy](1,3,4-thiadiazol-2-yl)}(6-cyano-2-morpholin-4-yl(3-pyridyl))carboxamide as a tan solid. ¹H NMR (400 MHz; DMSO-d₆): δ 13.04 (br s, 1H), 8.66 (s, 1H), 8.01 (d, 2H), 7.63 (d, 1H), 7.47 (d, 1H), 5.57 (s, 2H), 3.64-3.61 (m, 4H), 3.33-3.30 (m, 4H), ppm. *m/z* 458 (M+H⁺).

Example 33

Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-5-cyano-2-morpholinonicotinamide

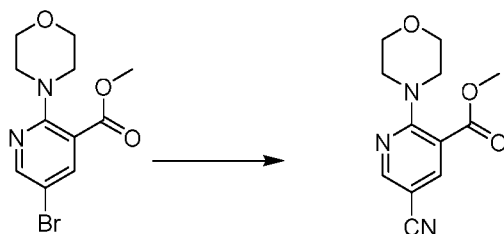


Step 1. Preparation of methyl 5-bromo-2-morpholinonicotinate



[0229] To a solution of methyl 5-bromo-2-chloropyridine-3-carboxylate (1.0 g, 4.0 mmol) in DMF (10 mL) was added morpholine (0.70 g, 8.0 mmol), DIEA (1.0 g, 8.0 mmol) under nitrogen. The mixture was stirred at 100 °C overnight. The mixture was cooled to room temperature and diluted with water. The mixture was extracted with EtOAc (2 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 9% EtOAc in PE to afford methyl 5-bromo-2-morpholinonicotinate as yellow oil.

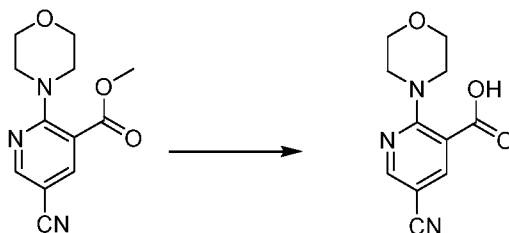
Step 2. Preparation of methyl 5-cyano-2-morpholinonicotinate



[0230] To a solution of methyl 5-bromo-2-morpholinonicotinate (1.1 g, 3.6 mmol) in DMF (11 mL) was added $\text{Zn}(\text{CN})_2$ (0.84 g, 7.2 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (0.41 g, 0.36 mmol) under nitrogen. The mixture was stirred at 100 °C for overnight. The mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layers were concentrated under

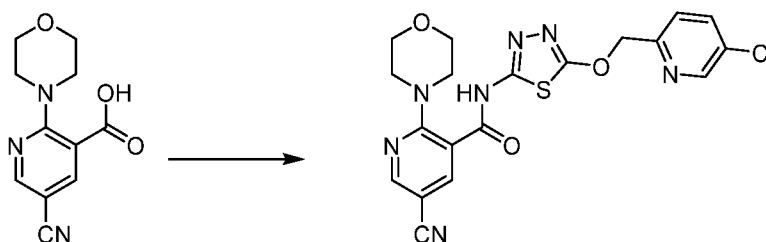
reduced pressure. The residue was purified by silica gel column chromatography, eluted with 33% EtOAc in PE to afford methyl 5-cyano-2-morpholinonicotinate as an off-white solid.

Step 3. Preparation of 5-cyano-2-morpholinonicotinic acid



[0231] To a solution of methyl 5-cyano-2-morpholinonicotinate (770. mg, 3.1 mmol) in THF (7.7 mL) was added water (2 mL) and LiOH (179 mg, 7.5 mmol). The mixture was stirred overnight at room temperature. The mixture was diluted with water (20 mL) and was extracted with EtOAc (2 x 10 mL). Formic acid was added to the aqueous layer until pH was 3. The aqueous phase was concentrated under reduced pressure. The residue was purified by reverse phase chromatography (column, C₁₈ silica gel; mobile phase, with 0-40% MeCN in water) to afford 5-cyano-2-morpholinonicotinic acid as a white solid.

Step 4. Preparation of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-5-cyano-2-morpholinonicotinamide

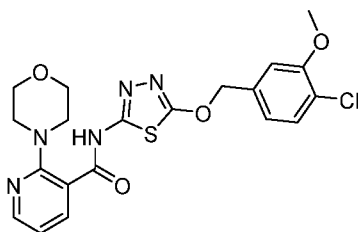


[0232] To a solution of 5-cyano-2-morpholinonicotinic acid (460 mg, 2.0 mmol) in DMF (5 mL) was added 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (718 mg, 3.0 mmol, Intermediate C), EDCI (567 mg, 3.0 mmol) and HOBT (400 mg, 3.0 mmol) under nitrogen. The mixture was stirred overnight at room temperature and then was diluted with water (20 mL). The mixture was extracted with EtOAc (5 x 20 mL). The combining organic layer was concentrated under reduce pressure. The residue was diluted with MeOH (10 mL) and the mixture was filtered. The solid was washed with MeOH (1 x 3 mL) to afford N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-5-cyano-2-morpholinonicotinamide as a

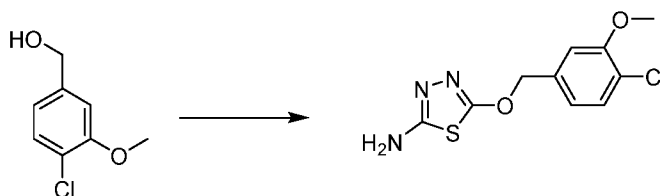
white solid. ^1H NMR (300 MHz; DMSO- d_6): δ 3.46-3.49 (m, 4H), 3.61-3.64 (m, 4H), 5.57 (s, 2H), 7.61-7.64 (m, 1H), 8.00-8.04 (m, 1H), 8.23-8.24 (m, 1H), 8.63-8.67 (m, 2H), 12.99 (s, 1H) ppm. m/z 458 ($M+H^+$).

Example 34

Synthesis of N-(5-((4-chloro-3-methoxybenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide

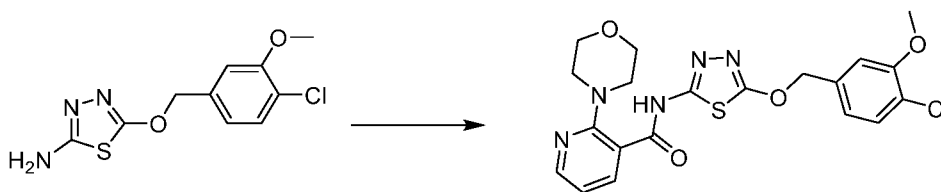


Step 1. Preparation of 5-[(4-chloro-3-methoxyphenyl)methoxy]-1,3,4-thiadiazol-2-amine



[0233] The title compound was prepared using similar procedure as Intermediate C replacing (5-chloropyridin-2-yl)methanol in Step 1 with (4-chloro-3-methoxyphenyl)methanol.

Step 2. Preparation of N-(5-((4-chloro-3-methoxybenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide

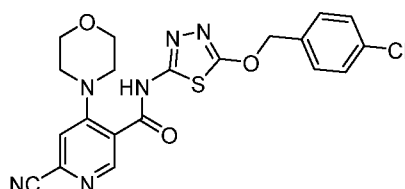


[0234] The title compound was prepared using General Procedure D employing 5-[(4-chloro-3-methoxyphenyl)methoxy]-1,3,4-thiadiazol-2-amine and 2-morpholinonicotinic acid. The mixture was diluted with water. The aqueous layer was extracted with EtOAc (3 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 35:1) to afford N-(5-((4-chloro-3-methoxybenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide as a white solid ^1H NMR (300 MHz; DMSO- d_6): δ

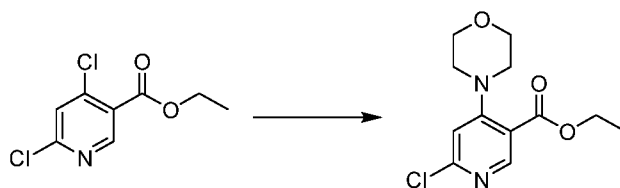
3.22-3.25 (m, 4H), 3.66-3.69 (m, 4H), 3.89 (s, 3H), 5.50 (s, 2H), 6.98-7.03 (m, 1H), 7.10-7.13 (m, 1H), 7.33-7.34 (m, 1H), 7.46-7.49 (m, 1H), 7.91-7.94 (m, 1H), 8.36-8.38 (m, 1H), 12.88 (s, 1H) ppm. m/z 462 ($M+H^+$).

Example 35

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-4-morpholinonicotinamide

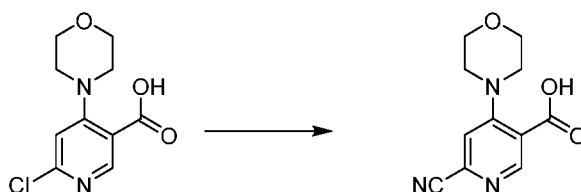


Step 1. Preparation of ethyl 6-chloro-4-morpholinonicotinate



[0235] To a solution of morpholine (871 mg, 10 mmol) and Et_3N (1.8 g, 18 mmol) in MeCN (20 mL) was added ethyl 4,6-dichloropyridine-3-carboxylate (2.0 g, 9.1 mmol) under nitrogen. The mixture was stirred overnight at room temperature. The mixture was concentrated under reduce pressure. The residue was triturated with PE:EtOAc, 30:1 to afford ethyl 6-chloro-4-morpholinonicotinate as a white solid.

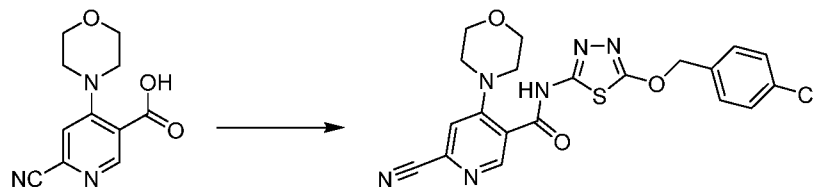
Step 2. Preparation of 6-cyano-4-(morpholin-4-yl)pyridine-3-carboxylic acid



[0236] To a solution of 6-chloro-4-(morpholin-4-yl)pyridine-3-carboxylic acid (400 mg, 1.6 mmol) in DMF (4 mL) was added $Zn(CN)_2$ (387 mg, 3.3 mmol), Zn powder (323 mg, 4.9 mmol) and $Pd(dppf)Cl_2$ (181 mg, 0.25 mmol) under nitrogen. The mixture was stirred at 100 °C for 2 h. The mixture was cooled to room temperature and filtered. The solid was washed with DMF (2 x 2 mL). The filtrate was concentrated under reduce pressure and the residue was purified by

reverse phase chromatography (column, C₁₈ silica gel; mobile phase, 0-100% MeCN in water) to afford 6-cyano-4-(morpholin-4-yl)pyridine-3-carboxylic acid as a yellow solid.

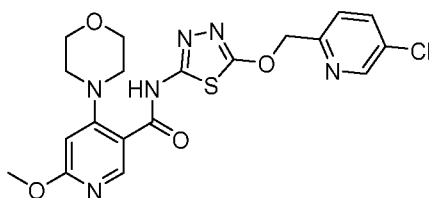
Step 3. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-4-morpholinonicotinamide



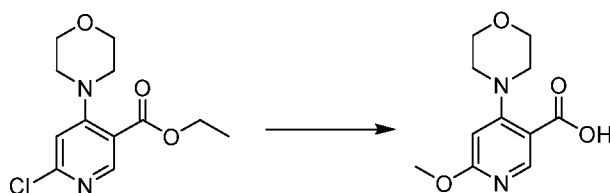
[0237] The title compound was prepared using General Procedure A employing 6-cyano-4-(morpholin-4-yl)pyridine-3-carboxylic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was diluted with water and extracted with EtOAc (3 x). The combined organic layers concentrated under reduce pressure. The residue was triturated with MeOH to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-4-morpholinonicotinamide as a yellow solid. ¹H NMR (300 MHz; DMSO-d₆): δ 3.26 (s, 4H), 3.64 (s, 4H), 5.51 (s, 2H), 7.48-7.57 (m, 4H), 7.70 (s, 1H), 8.47 (s, 1H), 13.04 (s, 1H) ppm. *m/z* 457 (M+H⁺).

Example 36

Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-6-methoxy-4-morpholinonicotinamide

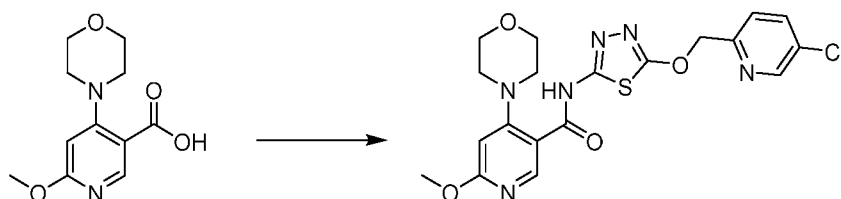


Step 1. Preparation of 6-methoxy-4-(morpholin-4-yl)pyridine-3-carboxylic acid



[0238] To a solution of ethyl 6-chloro-4-(morpholin-4-yl)pyridine-3-carboxylate (810 mg, 3.1 mmol, Example 35, Step 1) in MeOH (10 mL) at 0 °C was added sodium methoxide (199 mg, 3.7 mmol) under nitrogen. The mixture was stirred at 60 °C for overnight. Then NaOH (1.5 mL, 6.1 mmol, 4 M) was added and the mixture was stirred for 5 h at room temperature. The mixture was acidified to pH 6 with HOAc. The mixture was concentrated and the residue was purified by reverse phase chromatography (column, C₁₈ silica gel; mobile phase, with 10-50% MeCN in water) to afford 6-methoxy-4-(morpholin-4-yl)pyridine-3-carboxylic acid as a white solid.

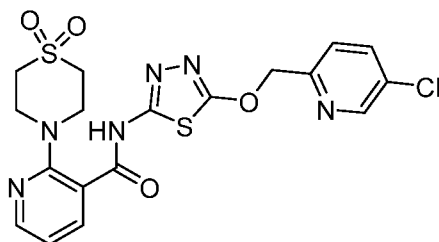
Step 2. Preparation of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-6-methoxy-4-morpholinonicotinamide



[0239] The title compound was prepared using General Procedure A employing 6-methoxy-4-(morpholin-4-yl)pyridine-3-carboxylic acid and 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C). The mixture was stirred at 50 °C overnight. The mixture was diluted with water and extracted with EtOAc (2 x). The combined organic layers were concentrated under reduced pressure. The residue was triturated with MeOH (2 mL) to afford N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-6-methoxy-4-morpholinonicotinamide as a brown solid. ¹H NMR (300 MHz; DMSO-d₆): δ 3.02-3.05 (m, 4H), 3.66-3.69 (m, 4H), 3.88 (s, 3H), 5.57 (s, 2H), 6.37 (s, 1H), 7.62-7.65 (m, 1H), 8.00-8.04 (m, 1H), 8.26 (s, 1H), 8.66-8.67 (m, 1H), 12.65 (s, 1H) ppm. *m/z* 463 (M+H⁺).

Example 37

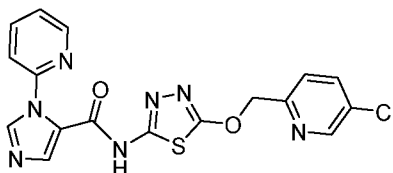
Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-2-(1,1-dioxidothiomorpholino)nicotinamide



[0240] To a vial equipped with stir bar was added N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-2-fluoronicotinamide Intermediate G (100 mg, 1 eq.) followed by addition of thiomorpholine 1,1-dioxide (110 mg, 3 eq.) and DMF (1.2 mL). DIPEA (0.280 mL, 6 eq.) was then added and the reaction was heated to 75° C and allowed to stir for 48 hours. Upon reaction completion the mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with a 10% by weight solution of LiCl in H₂O, then brine, and dried over Na₂SO₄ and concentrated in vacuo. The crude residue was purified via reverse phase chromatography conditions (column, C18 silica gel; mobile phase, 40 - 80% MeCN in water, with both eluents containing 0.1% FA) to afford to give the title compound (7 mg, 5% yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.66 (s, 1H), 8.32 (d, J = 4.7 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 7.5 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.01 (t, J = 6.2 Hz, 1H), 5.55 (s, 2H), 3.72 (bs, 4H), 3.18 (bs, 4H) ppm. *m/z* 481 (M+H⁺).

Example 38

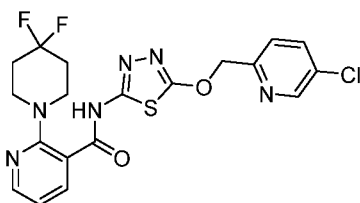
Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-1-(pyridin-2-yl)-1H-imidazole-5-carboxamide



[0241] The title compound was prepared using General Procedure D employing 1-(pyridin-2-yl)-1H-imidazole-5-carboxylic acid and 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C). The mixture was diluted with water and extracted with EtOAc (3 x). The combined organic layers were concentrated under reduce pressure. The residue was purified by Prep-HPLC (column, C₁₈ silica gel; mobile phase, 0-100% MeCN in water, both containing 0.1% formic acid) to afford N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-1-phenyl-1H-pyrazole-5-carboxamide as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 12.94 (s, 1H), 8.64 (d, J = 2.2 Hz, 1H), 8.59 – 8.44 (m, 1H), 8.34 – 8.19 (m, 1H), 8.09 – 7.87 (m, 2H), 7.66 – 7.55 (m, 2H), 7.57 – 7.43 (m, 1H), 6.52 (s, 1H), 5.52 (s, 2H) ppm. *m/z* 414 (M+H⁺).

Example 39

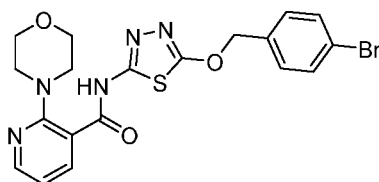
Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-2-(4,4-difluoropiperidin-1-yl)nicotinamide



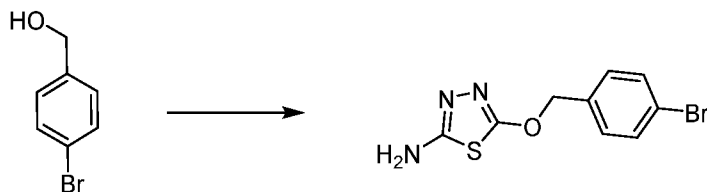
[0242] Proceeding analogously as described in Example 22, but using N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-2-fluoronicotinamide Intermediate G and 4,4-difluoropiperidine gave crude product. Purification by reverse phase chromatography (column, C18 silica gel; mobile phase, 40 - 80% MeCN in water, with both eluents containing 0.1% FA) gave the title compound as a white solid. ¹H NMR (400 MHz, Chloroform-d) δ 8.61 (s, 1H), 8.54 (d, J = 4.5 Hz, 1H), 8.48 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.32 – 7.26 (m, 1H), 5.63 (s, 2H), 3.44 (s, 4H), 2.31 (dt, J = 13.5, 7.2 Hz, 4H) ppm. *m/z* 467 (M+H⁺).

Example 40

Synthesis of N-(5-((4-bromobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide

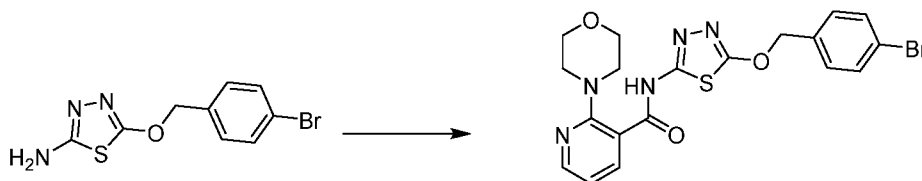


Step 1. Preparation of 5-((4-bromobenzyl)oxy)-1,3,4-thiadiazol-2-amine



[0243] The title compound was prepared using similar procedure as Intermediate C replacing (5-chloropyridin-2-yl)methanol in Step 1 with p-bromobenzyl alcohol.

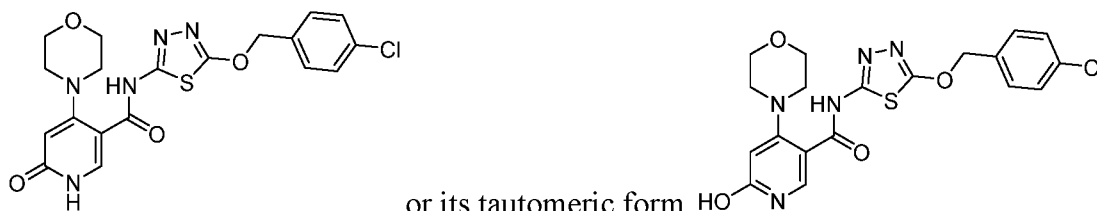
Step 2. Preparation of N-(5-((4-bromobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide



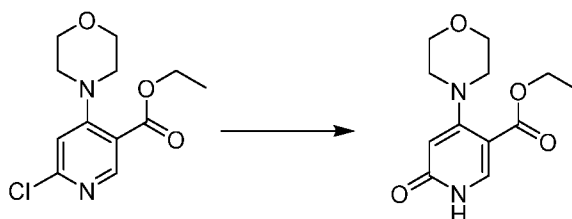
[0244] The title compound was prepared using General Procedure A employing 5-((4-bromobenzyl)-oxy)-1,3,4-thiadiazol-2-amine and 2-morpholinonicotinic acid. The mixture was diluted with water. The aqueous layer was extracted with EtOAc (3 x). The combined organic layer was concentrated under reduced pressure. The residue was triturated with MeOH to afford N-(5-((4-bromobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide as a pink solid. ¹H NMR (400 MHz; DMSO-d₆): δ 3.22-3.25 (m, 4H), 3.66-3.68 (m, 4H), 5.45 (s, 2H), 7.00-7.02 (m, 1H), 7.48-7.52 (m, 2H), 7.62-7.65 (m, 2H), 7.91-7.93 (m, 1H), 8.36-8.37 (m, 1H), 12.88 (s, 1H) ppm. *m/z* 476 (M+H⁺).

Example 41

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-morpholino-6-oxo-1,6-dihydropyridine-3-carboxamide or its tautomer N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-hydroxy-4-morpholinonicotinamide

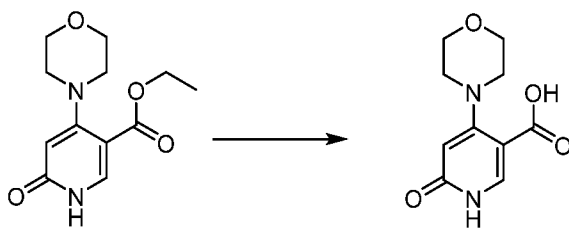


Step 1. Preparation of ethyl 4-(morpholin-4-yl)-6-oxo-1H-pyridine-3-carboxylate



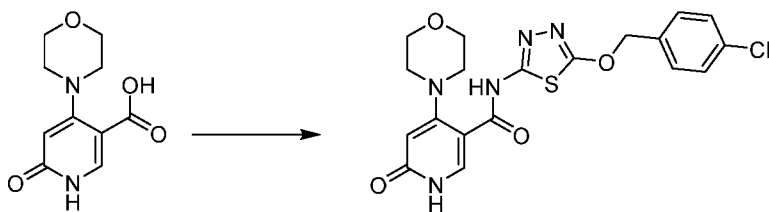
[0245] A solution of ethyl 6-chloro-4-(morpholin-4-yl)pyridine-3-carboxylate (1.0 g, 3.7 mmol, Example 35, Step 1) in HOAc (10 mL) was stirred at 100 °C overnight. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted by with sat. NaHCO₃ (10 mL) and the mixture was extracted with EtOAc (5 x 10 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 5% MeOH in DCM to afford ethyl 4-(morpholin-4-yl)-6-oxo-1H-pyridine-3-carboxylate as a white solid.

Step 2. Preparation of 4-morpholino-6-oxo-5,6-dihydropyridine-3-carboxylic acid



[0246] To a solution of ethyl 4-(morpholin-4-yl)-6-oxo-1H-pyridine-3-carboxylate (430 mg, 1.7 mmol) in MeOH (4.3 mL) was added NaOH (136 mg, 3.4 mmol) and water (1.7 mL). The mixture was stirred at 100 °C for 48 h. The mixture was acidified to pH 6 with HCl (1 M). The mixture was concentrated under reduce pressure. The residue was purified by reverse phase chromatography (column, C₁₈ silica gel; mobile phase, with 0-50% MeCN in water, with both eluents containing 0.05% TFA). The residue was further purified by reverse phase chromatography 9column, Prep T3 OBD Column; mobile phase, with 2-10% MeCN in water, with water containing 0.05% TFA0 to afford 4-morpholino-6-oxo-5,6-dihydropyridine-3-carboxylic acid as a white solid.

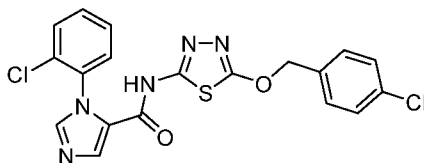
Step 3. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-morpholino-6-oxo-1,6-dihydropyridine-3-carboxamide



[0247] The title compound was prepared using General Procedure A employing and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was stirred at 50 °C overnight under nitrogen. The mixture was cooled room temperature and diluted with water. The mixture was extracted with EtOAc (2 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 25:1) to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-morpholino-6-oxo-1,6-dihydropyridine-3-carboxamide as a white solid. ¹H NMR (300 MHz; DMSO-d₆): δ 2.92 (s, 4H), 3.65-3.69 (m, 4H), 5.48 (s, 2H), 5.71 (s, 1H), 7.47-7.56 (m, 4H), 7.77 (s, 1H), 11.62 (s, 1H), 12.38 (s, 1H) ppm. *m/z* 448 (M+H⁺).

Example 42

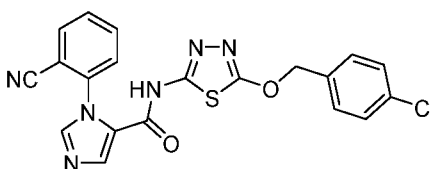
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(2-chlorophenyl)-1H-imidazole-5-carboxamide



[0248] The title compound was prepared using similar procedure as Example 18, replacing 4-aminopyridine with 2-chloroaniline in Step 1 and employing 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) in Step 2. The mixture was diluted with water and extracted with EtOAc (2 x). The combined organic layers were concentrated under reduce pressure. The residue was purified Prep-TLC with (DCM:MeOH, 35:1) to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(2-chlorophenyl)-1H-imidazole-5-carboxamide as a white solid. ¹H NMR (300 MHz; DMSO-d₆): δ 5.44-5.47 (m, 2H), 7.45-7.60 (m, 7H), 7.65-7.68 (m, 1H), 8.11 (s, 1H), 8.27 (s, 1H), 12.85 (s, 1H) ppm. *m/z* 446 (M+H⁺).

Example 43

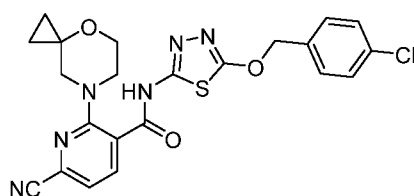
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(2-cyanophenyl)-1H-imidazole-5-carboxamide



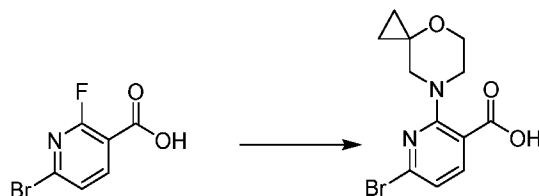
[0249] The title compound was prepared using similar procedure as Example 12, replacing p-Anisidine with 2-aminobenzonitrile and employing 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) in Step 2. The mixture was diluted with water and extracted with EtOAc (2 x). The combined organic layers were concentrated under reduce pressure. The residue was triturated with to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(2-cyanophenyl)-1H-imidazole-5-carboxamide as a light yellow solid. ¹H NMR (300 MHz; DMSO-d₆): δ 5.47 (s, 2H), 7.46-7.54 (m, 4H), 7.70-7.75 (m, 2H), 7.83-7.93 (m, 1H), 8.04-8.07 (m, 1H), 8.27-8.32 (m, 2H), 12.96-13.04 (br s, 1H) ppm. *m/z* 437 (M+H⁺).

Example 44

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-2-(4-oxa-7-azaspiro[2.5]octan-7-yl)nicotinamide

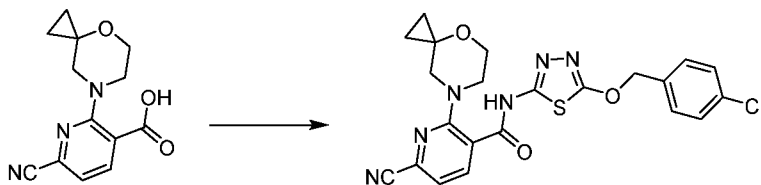


Step 1. Preparation of 6-cyano-2-(4-oxa-7-azaspiro[2.5]octan-7-yl)nicotinic acid



[0250] The title compound was prepared using similar procedure as Example 14, Steps 1-2, replacing morpholine with 4-oxa-7-azaspiro[2.5]octane in Step 1.

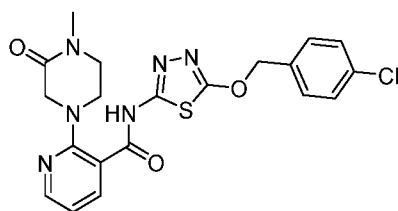
Step 2. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-2-(4-oxa-7-azaspiro[2.5]octan-7-yl)nicotinamide



[0251] The title compound was prepared using General Procedure A employing 6-cyano-2-(4-oxa-7-azaspiro[2.5]octan-7-yl)nicotinic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was diluted with water and extracted with EtOAc (3 x). The combined organic layers were concentrated under reduced pressure. The residue was triturated with MeOH to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-2-(4-oxa-7-azaspiro[2.5]octan-7-yl)nicotinamide as a yellow green solid. ^1H NMR (400 MHz; DMSO- d_6): δ 0.53-0.56 (m, 2H), 0.66-0.69 (m, 2H), 3.31-3.32 (m, 2H), 3.35-3.37 (m, 2H), 3.68-3.70 (m, 2H), 5.51 (s, 2H), 7.47-7.50 (m, 3H), 7.54-7.56 (m, 2H), 8.00-8.02 (m, 1H), 13.04 (s, 1H) ppm. m/z 483 ($\text{M}+\text{H}^+$).

Example 45

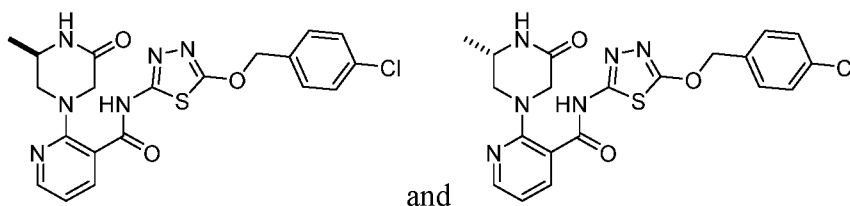
Synthesis of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-2-(4-methyl-3-oxopiperazin-1-yl)pyridine-3-carboxamide



[0252] To a solution of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-2-fluoropyridine-3-carboxamide (100 mg, 0.27 mmol, Intermediate D) in MeCN (1.0 mL), was added 1-methylpiperazin-2-one (34 mg, 0.3 mmol) and Et₃N (55 mg, 0.55 mmol) under nitrogen. The mixture was stirred at 80 °C overnight. The mixture was cooled to room temperature and concentrated under reduce pressure. The residue was triturated with MeOH to afford N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-2-(4-methyl-3-oxopiperazin-1-yl)pyridine-3-carboxamide as a yellow solid. ¹H NMR (400 MHz; DMSO-d₆): δ 2.82-2.85 (m, 3H), 3.32-3.34 (m, 2H), 3.54-3.57 (m, 2H), 3.83 (s, 2H), 5.51 (s, 2H), 6.95-6.98 (m, 1H), 7.48-7.56 (m, 4H), 7.88-7.90 (m, 1H), 8.32-8.34 (m, 1H), 12.74 (s, 1H) ppm. *m/z* 459 (M+H⁺).

Example 46

Synthesis of (R) N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(3-methyl-5-oxopiperazin-1-yl)nicotinamide and (S) N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(3-methyl-5-oxopiperazin-1-yl)nicotinamide

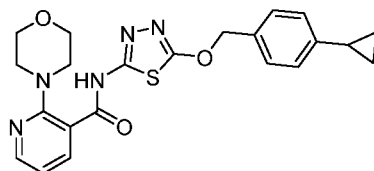


[0253] To a solution of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-2-fluoropyridine-3-carboxamide (100 mg, 0.27 mmol, Intermediate D) in NMP (1 mL) was added racemic 6-methylpiperazin-2-one (125 mg, 1.1 mmol) and DIEA (74 mg, 0.55 mmol) under nitrogen. The mixture was stirred for 12 h at room temperature. The mixture was diluted with EtOAc (2 mL) and washed with water (2 x). The organic layer was concentrated under reduce pressure. The residue was triturated with MeOH (2 mL) to afford a racemic mixture of (R) N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(3-methyl-5-oxopiperazin-1-yl)nicotinamide and (S) N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(3-methyl-5-oxopiperazin-1-yl)nicotinamide as a white solid. ¹H NMR (400 MHz; DMSO-d₆): δ 1.00-1.02 (m, 3H), 3.00-

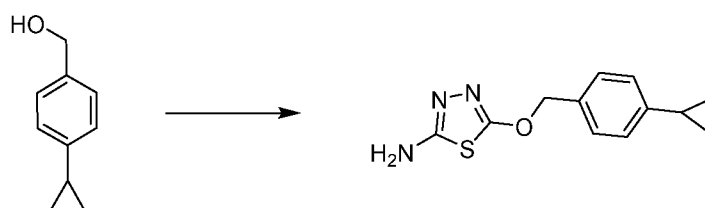
3.05 (m, 1H), 3.55 (s, 1H), 3.65-3.79 (m, 3H), 5.51 (s, 2H), 6.93-6.96 (m, 1H), 7.48-7.56 (m, 4H), 7.86-7.89 (m, 1H), 8.07 (s, 1H), 8.32-8.33 (m, 1H), 12.84 (s, 1H) ppm. m/z 459 ($M+H^+$).

Example 47

Synthesis of N-(5-((4-cyclopropylbenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide

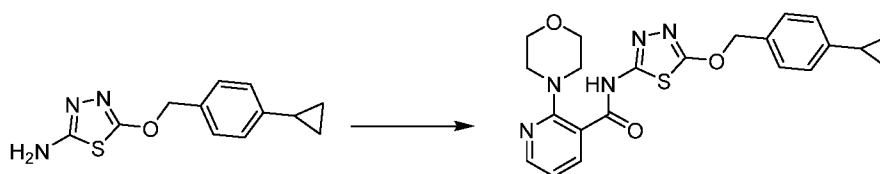


Step 1. Preparation of 5-[(4-cyclopropylphenyl)methoxy]-1,3,4-thiadiazol-2-amine



[0254] The title compound was prepared using similar procedure as Intermediate C replacing (5-chloropyridin-2-yl)methanol in Step 1 with (4-cyclopropylphenyl)methanol.

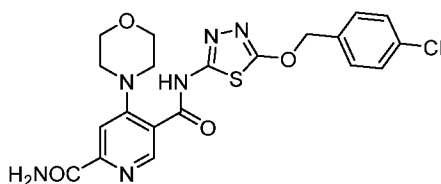
Step 2. Preparation of N-(5-((4-cyclopropylbenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide



[0255] The title compound was prepared using General Procedure A employing 5-[(4-cyclopropylphenyl)methoxy]-1,3,4-thiadiazol-2-amine and 2-morpholinonicotinic acid. The mixture was diluted with water. The aqueous layer was extracted with EtOAc (3 x). The combined organic layer was concentrated under reduced pressure. The residue was triturated with MeOH to afford N-(5-((4-cyclopropylbenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide as off-white solid. ^1H NMR (300 MHz; DMSO- d_6): δ 0.61-0.71 (m, 2H), 0.96-0.99 (m, 2H), 1.89-1.98 (m, 1H), 3.21-3.24 (m, 4H), 3.65-3.68 (m, 4H), 5.43 (s, 2H), 6.97-7.01 (m, 1H), 7.10-7.13 (m, 2H), 7.37-7.40 (m, 2H), 7.89-7.92 (m, 1H), 8.34-8.37 (m, 1H), 12.85 (s, 1H) ppm. m/z 438 ($M+H^+$).

Example 48

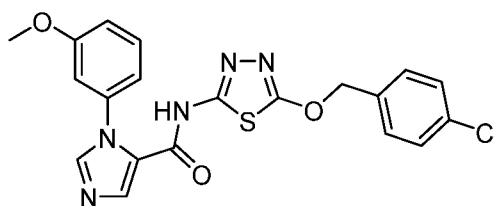
Synthesis of N⁵-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-morpholinopyridine-2,5-dicarboxamide



[0256] The title compound was prepared using similar procedure as Example 21 employing N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-4-morpholinonicotinamide, Example 35. The mixture was stirred at room temperature for 2 h. The mixture was cooled room temperature and diluted with water. The mixture was extracted with EtOAc (3 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC with (DCM:MeOH, 35:1) to afford N⁵-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-morpholinopyridine-2,5-dicarboxamide as a yellow solid. ¹H NMR (400 MHz; DMSO-d₆): δ 3.20 (s, 4H), 3.67 (s, 4H), 5.51 (s, 2H), 7.49-7.58 (m, 5H), 7.70-7.73 (m, 1H), 8.14-8.19 (m, 1H), 8.45 (s, 1H), 12.92-13.00 (br s, 1H) ppm. *m/z* 475 (M+H⁺).

Example 49

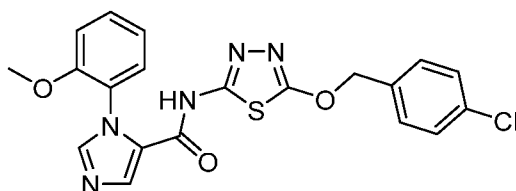
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(3-methoxyphenyl)-1H-imidazole-5-carboxamide



[0257] The title compound was prepared using similar procedure as Example 18, replacing 4-aminopyridine with 3-methoxyaniline in Step 1 and employing 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) in Step 2. The mixture was diluted with EtOAc and washed with water (2 x). The organic layer was concentrated under reduced pressure. The residue was triturated with MeOH to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(3-methoxyphenyl)-1H-imidazole-5-carboxamide as an off-white solid. ¹H NMR (300 MHz; DMSO-d₆): δ 3.78 (s, 3H), 5.47 (s, 2H), 6.95-7.01 (m, 3H), 7.36-7.53 (m, 5H), 8.12-8.16 (m, 2H), 12.80 (s, 1H) ppm. *m/z* 442 (M+H⁺).

Example 50

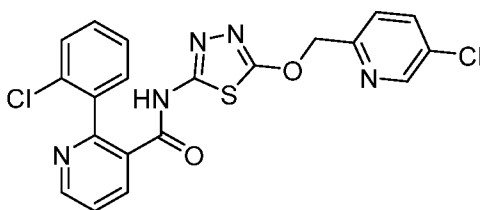
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(2-methoxyphenyl)-1H-imidazole-5-carboxamide



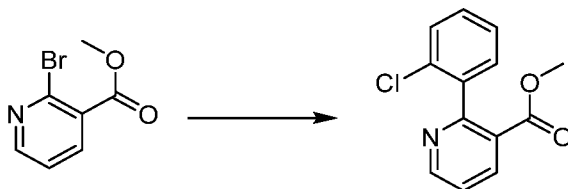
[0258] The title compound was prepared using similar procedure as Example 18, replacing 4-aminopyridine with 2-methoxyaniline in Step 1 and employing 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) in Step 2. The mixture was diluted with water and filtered. The solid was triturated with MeOH to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(2-methoxyphenyl)-1H-imidazole-5-carboxamide as an off-white solid. ¹H NMR (400 MHz; DMSO-d₆): δ 3.64-3.66 (m, 3H), 5.44 (s, 2H), 7.02-7.07 (m, 1H), 7.15-7.17 (m, 1H), 7.34-7.36 (m, 1H), 7.41-7.52 (m, 5H), 7.97 (s, 1H), 8.09 (s, 1H), 12.71 (s, 1H) ppm. *m/z* 442 (M+H⁺).

Example 51

Synthesis of 2-(2-chlorophenyl)-N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]pyridine-3-carboxamide



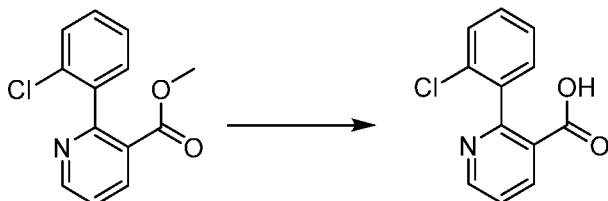
Step 1. Preparation of methyl 2-(2-chlorophenyl)pyridine-3-carboxylate



[0259] The title compound was prepared using General Procedure E employing methyl 2-bromopyridine-3-carboxylate and 2-chlorophenylboronic acid. The mixture was cooled to rt and diluted with water. The mixture was extracted with EtOAc (3 x). The combined organic layer was concentrated under reduce pressure. The residue was purified by silica gel column

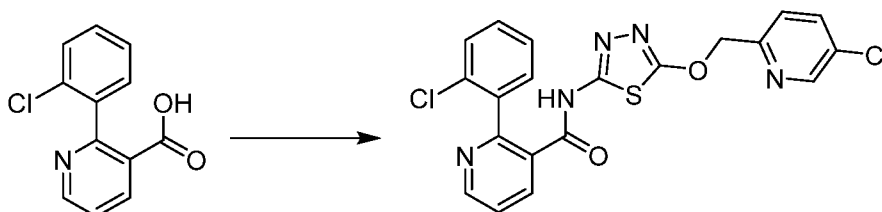
chromatography, eluted with 16% EtOAc in hexanes to afford methyl 2-(2-chlorophenyl)pyridine-3-carboxylate as a yellow solid.

Step 2. Preparation of 2-(2-chlorophenyl)pyridine-3-carboxylic acid



[0260] The title compound was prepared using General Procedure F employing methyl 2-(2-chlorophenyl)pyridine-3-carboxylate. The mixture was diluted with water and extracted with EtOAc (5 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 50:1) to afford 2-(2-chlorophenyl)pyridine-3-carboxylic acid as a white solid.

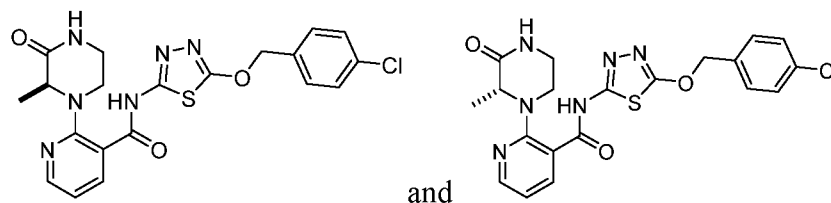
Step 3. Preparation of 2-(2-chlorophenyl)-N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]pyridine-3-carboxamide



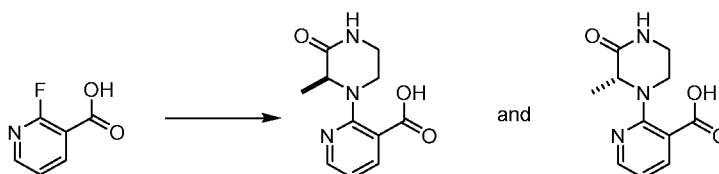
[0261] To a solution of 2-(2-chlorophenyl)pyridine-3-carboxylic acid (140 mg, 0.51 mmol) in DCM (1.4 mL) was added oxalyl chloride (98 mg, 0.77 mmol) and DMF (4 mg, 0.05 mmol) at room temperature. The mixture was stirred for 1 h. The mixture was concentrated under reduced pressure. The residue was dissolved in DCM (1.2 mL) and Et₃N (130 mg, 1.3 mmol) and 5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-amine (149 mg, 0.62 mmol, Intermediate C) were added. The mixture was stirred for 3 h at room temperature. The mixture was diluted with DCM was washed with water. The aqueous layer was extracted with EtOAc (3 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 50:1) to afford 2-(2-chlorophenyl)-N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]pyridine-3-carboxamide as a white solid. ¹H NMR (300 MHz; DMSO-d₆): δ 5.54 (s, 2H), 7.40-7.49 (m, 4H), 7.58-7.63 (m, 2H), 7.98-8.01 (m, 1H), 8.21-8.24 (m, 1H), 8.64-8.65 (m, 1H), 8.81-8.83 (m, 1H), 13.00 (s, 1H) ppm. *m/z* 458 (M+H⁺).

Example 52

Synthesis of (R) N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2-methyl-3-oxopiperazin-1-yl)nicotinamide and (S) N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2-methyl-3-oxopiperazin-1-yl)nicotinamide

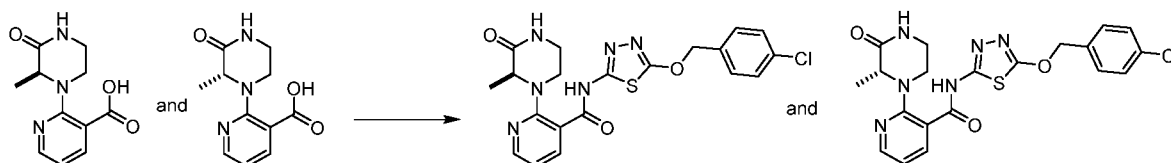


Step 1. Preparation of (R) 2-(2-methyl-3-oxopiperazin-1-yl)pyridine-3-carboxylic acid and (S) 2-(2-methyl-3-oxopiperazin-1-yl)pyridine-3-carboxylic acid



[0262] To a solution of 2-fluoropyridine-3-carboxylic acid (1.0 g, 7.1 mmol) in MeCN (10 mL) was added racemic 3-methylpiperazin-2-one (1618 mg, 14.2 mmol) and Et₃N (1434 mg, 14.2 mmol). The mixture was stirred at 80 °C for 3 days. The mixture was cooled to room temperature and concentrated under reduce pressure. The residue was triturated with MeOH (5 mL) to afford a racemic mixture of (R) 2-(2-methyl-3-oxopiperazin-1-yl)pyridine-3-carboxylic acid and (S) 2-(2-methyl-3-oxopiperazin-1-yl)pyridine-3-carboxylic acid as a yellow solid.

Step 2. Preparation of (R) N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2-methyl-3-oxopiperazin-1-yl)nicotinamide and (S) N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2-methyl-3-oxopiperazin-1-yl)nicotinamide

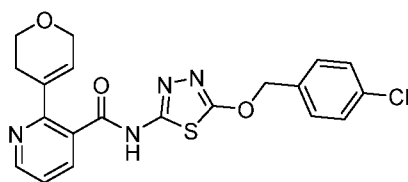


[0263] The title compound was prepared using General Procedure A employing a racemic mixture of (R) 2-(2-methyl-3-oxopiperazin-1-yl)pyridine-3-carboxylic acid and (S) 2-(2-methyl-3-oxopiperazin-1-yl)pyridine-3-carboxylic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was stirred at 50 °C 4 h. The mixture was cooled room temperature and diluted with water. The mixture was extracted with EtOAc (3 x). The combined

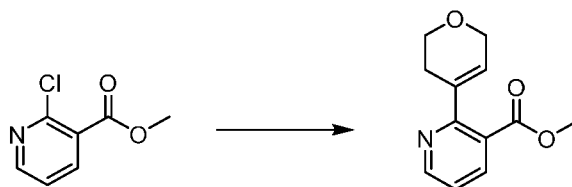
organic layers were concentrated under reduced pressure. The residue was triturated with MeOH to afford a racemic mixture of (R) N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2-methyl-3-oxopiperazin-1-yl)nicotinamide and (S) N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2-methyl-3-oxopiperazin-1-yl)nicotinamide as a yellow solid. ^1H NMR (300 MHz; DMSO- d_6): δ 1.24-1.32 (m, 3H), 3.10-3.14 (m, 1H), 3.35-3.41 (m, 2H), 3.51-3.57 (m, 1H), 4.25-4.32 (m, 1H), 5.51 (s, 2H), 6.93-6.98 (m, 1H), 7.48-7.57 (m, 4H), 7.86-7.89 (m, 2H), 8.32-8.35 (m, 1H), 12.97 (s, 1H) ppm. m/z 459 ($M+H^+$).

Example 53

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(3,6-dihydro-2H-pyran-4-yl)nicotinamide

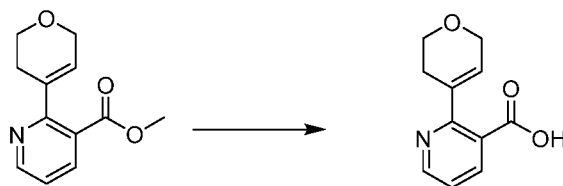


Step 1. Preparation of methyl 2-(3,6-dihydro-2H-pyran-4-yl)pyridine-3-carboxylate



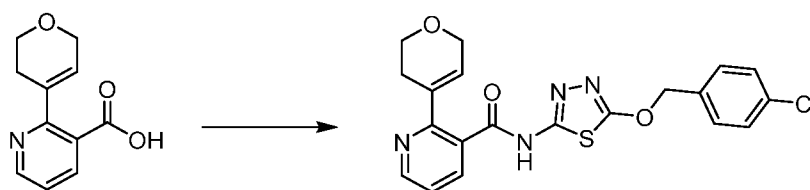
[0264] The title compound was prepared using General Procedure E employing methyl 2-chloropyridine-3-carboxylate and 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. The mixture was stirred at 100 °C for 3 h. The mixture was cooled room temperature and diluted with water. The mixture was extracted with EtOAc (4 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 33% EtOAc in PE to afford methyl 2-(3,6-dihydro-2H-pyran-4-yl)pyridine-3-carboxylate as yellow oil.

Step 2. Preparation of 2-(3,6-dihydro-2H-pyran-4-yl)nicotinic acid



[0265] The title compound was prepared using General Procedure F employing methyl 2-(3,6-dihydro-2H-pyran-4-yl)pyridine-3-carboxylate. The mixture was stirred at room temperature for 5 h and then diluted with water. The mixture was extracted with EtOAc (3 x). The aqueous layer was neutralized to pH 6 with HOAc and the mixture was extracted with EtOAc (5 x). The combined organic layers were concentrated under reduced pressure. The residue was purified using Prep-HPLC (column, C₁₈ silica gel; mobile phase, 10-50% MeCN in water, with both eluents containing 0.05% TFA) to afford 2-(3,6-dihydro-2H-pyran-4-yl)nicotinic acid as light-yellow oil.

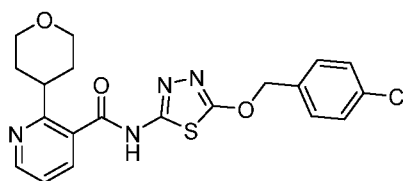
Step 3. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(3,6-dihydro-2H-pyran-4-yl)nicotinamide



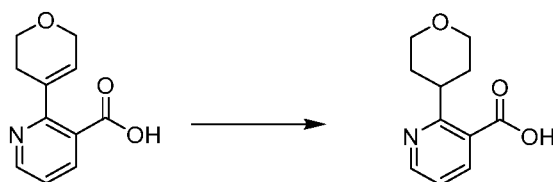
[0266] The title compound was prepared using General Procedure A employing 2-(3,6-dihydro-2H-pyran-4-yl)nicotinic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was diluted with water. The mixture was extracted with EtOAc (2 x). The combined organic layers were concentrated under reduced pressure. The residue was triturated with MeOH to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(3,6-dihydro-2H-pyran-4-yl)nicotinamide as a white solid. ¹H NMR (400 MHz; DMSO-d₆): δ 2.51-2.54 (m, 2H), 3.75-3.78 (m, 2H), 4.06-4.07 (m, 2H), 5.50 (s, 2H), 5.92 (s, 1H), 7.39-7.43 (m, 1H), 7.46-7.57 (m, 4H), 7.93-7.96 (m, 1H), 8.66-8.69 (m, 1H), 12.89 (s, 1H) ppm. *m/z* 429 (M+H⁺).

Example 54

Synthesis of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-2-(oxan-4-yl)pyridine-3-carboxamide

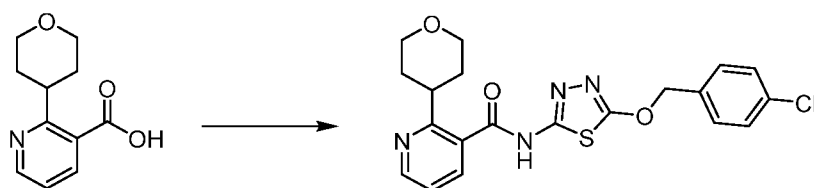


Step 1. Preparation of 2-(oxan-4-yl)pyridine-3-carboxylic acid



[0267] To a solution of 2-(3,6-dihydro-2H-pyran-4-yl)nicotinic acid (180 mg, 0.88 mmol, Example 53, Step 2), in MeOH (22 mL) was added 20% Pd/C (36 mg). The mixture was stirred at room temperature under hydrogen for 9 h. The mixture was filtered over celite and the filtrate was concentrated under reduced pressure to afford 2-(oxan-4-yl)pyridine-3-carboxylic acid as light-yellow oil.

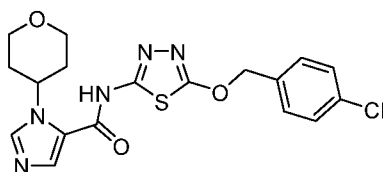
Step 2. Preparation of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-2-(oxan-4-yl)pyridine-3-carboxamide



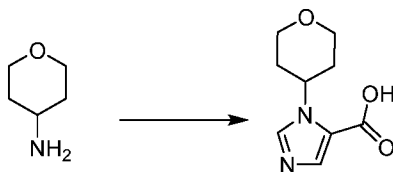
[0268] The title compound was prepared using General Procedure A employing 2-(oxan-4-yl)pyridine-3-carboxylic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was diluted with water. The mixture was extracted with EtOAc (2 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 100:1) to afford N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-2-(oxan-4-yl)pyridine-3-carboxamide as a white solid. ^1H NMR (300 MHz; DMSO- d_6): δ 1.62-1.65 (m, 2H), 1.84-1.98 (m, 2H), 3.17-3.22 (m, 1H), 3.37-3.40 (m, 2H), 3.89-3.94 (m, 2H), 5.52 (s, 2H), 7.35-7.40 (m, 1H), 7.49-7.58 (m, 4H), 7.94-7.97 (m, 1H), 8.68-8.71 (m, 1H), 12.98 (s, 1H) ppm. m/z 431 ($\text{M}+\text{H}^+$).

Example 55

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazole-5-carboxamide

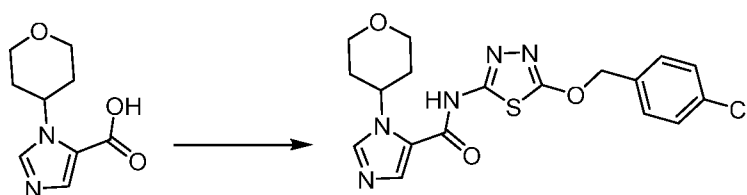


Step 1. Preparation of 1-(tetrahydro-2H-pyran-4-yl)-1H-imidazole-5-carboxylic acid



[0269] The title compound was prepared using similar procedure as Example 12, Steps 1 - 2 replacing p-Anisidine in Step 1 with oxan-4-amine.

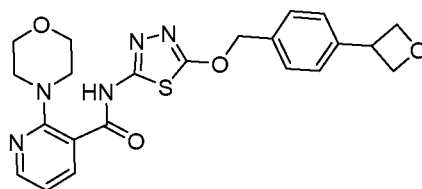
Step 2. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazole- 5-carboxamide



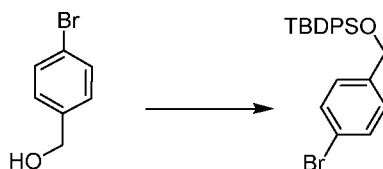
[0270] To a solution of 1-(tetrahydro-2H-pyran-4-yl)-1H-imidazole-5-carboxylic acid (110 mg, 0.61 mmol) in DCM (1.1 mL) was added DMF (4.5 mg, 0.06 mmol) and then oxalyl chloride (85 mg, 0.63 mmol) was added dropwise at room temperature under nitrogen. Following the addition, the mixture was concentrated under reduce pressure. The yellow solid was diluted with DCM (1.2 mL) and Et₃N (113 mg, 1.1 mmol) and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (120 mg, 0.56 mmol, Intermediate B) were added at room temperature under nitrogen. The mixture was stirred at room temperature for 4 h. The mixture was diluted with water. The mixture was extracted with EtOAc (2 x). The combined organic layers were concentrated under reduced pressure. The residue was triturated with MeOH (1 mL) to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(tetrahydro-2H-pyran-4-yl)-1H-imidazole- 5-carboxamide as a white solid. ¹H NMR (300 MHz; DMSO-d₆): δ 1.89-1.98 (m, 4H), 3.40-3.49 (m, 2H), 3.95-3.99 (m, 2H), 5.05-5.10 (m, 1H), 5.50 (s, 2H), 7.47-7.56 (m, 4H), 8.10 (s, 1H), 8.23 (s, 1H), 12.67-12.79 (br s, 1H) ppm. *m/z* 420 (M+H⁺).

Example 56

Synthesis of 2-morpholino-N-(5-((4-(oxetan-3-yl)benzyl)oxy)-1,3,4-thiadiazol-2-yl)nicotinamide

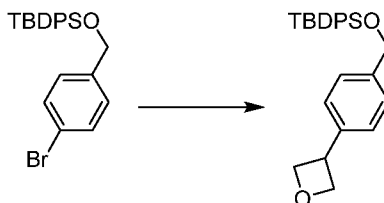


Step 1. Preparation of ((4-bromobenzyl)oxy)(tert-butyl)diphenylsilane



[0271] To a solution of p-bromobenzyl alcohol (5 g, 26.88 mmol) in THF (10 mL) was added imidazole (182.0 mg, 0.2688 mmol) and TBDPSCl (8.08 g, 29.57 mmol) under nitrogen. The mixture was stirred at room temperature overnight. The mixture was diluted with water and extracted with DCM (3 x). The combined organic layers were concentrated under reduced pressure to afford ((4-bromobenzyl)oxy)(tert-butyl)diphenylsilane as a solid. The material was used in the next step without further purification.

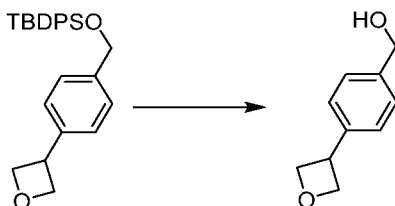
Step 2. Preparation of tert-butyl((4-(oxetan-3-yl)benzyl)oxy)diphenylsilane



[0272] ((4-Bromobenzyl)oxy)(tert-butyl)diphenylsilane (500 mg, 1.2 mmol), 3-iodooxetane (732 mg, 5.3 mmol), [Ir(dtbbpy)(ppy)₂][PF₆] (43 mg, 0.047 mmol), tris(trimethylsilyl)silane (532 mg, 2.4 mmol) and Na₂CO₃ (450 mg, 4.2 mmol) were combined and purged with nitrogen. Then DME (20 mL) was added. In a separate vial 4,4'-Di-tert-butyl-2,2'-bipyridine (12 mg, 0.043 mmol), nickel(II) chloride (5 mg, 0.036 mmol) and 1,2-dimethoxyethane (9 mg, 0.039 mmol) were combined and purged with nitrogen and diluted with DME (10 mL). The mixture was stirred at room temperature for 20 min and then added into the Ir solution. The mixture was degassed with bubbling nitrogen for 10 minutes and then sealed. The mixture was stirred under 50 W blue LED lamp (7 cm away, with cooling fan to maintain 25°C) for 3.5 days. The mixture was diluted with EtOAc (50 mL) and washed with water (20 mL x 2). The organic layer was

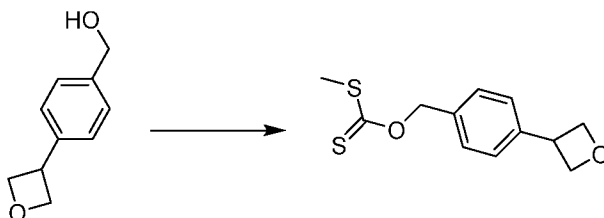
concentrated under reduce pressure and the residue was purified by Prep-TLC (PE:EtOAc, 4:1) to afford tert-butyl((4-(oxetan-3-yl)benzyl)oxy)diphenylsilane as a light yellow solid.

Step 3. Preparation of (4-(oxetan-3-yl)phenyl)methanol



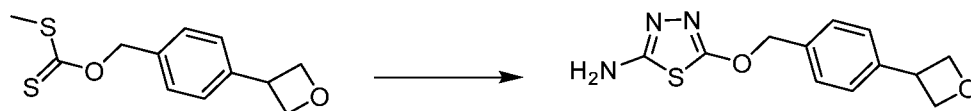
[0273] To a solution of tert-butyl([4-(oxetan-3-yl)phenyl]methoxy)diphenylsilane (300 mg, 0.72 mmol) in THF (6 mL) was added TBAF (564 mg, 2.2 mmol). The mixture was stirred at room temperature for 40 minutes. The mixture was diluted with EtOAc (30 mL), washed with brine (3 x 5 mL) and concentrated under reduce pressure. The residue was purified by Prep-TLC (PE:EtOAc, 1:1) to afford (4-(oxetan-3-yl)phenyl)methanol as colorless oil.

Step 4. Preparation of S-methyl O-(4-(oxetan-3-yl)benzyl) carbonodithioate



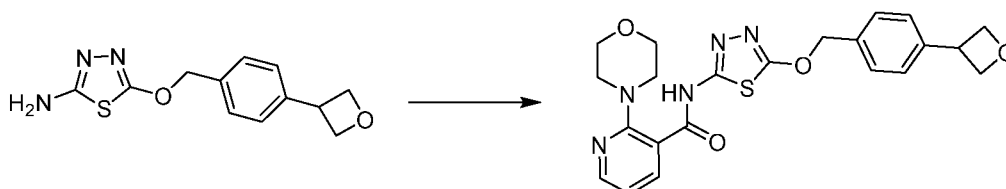
[0274] To a solution of (4-(oxetan-3-yl)phenyl)methanol (80 mg, 0.49 mmol) in THF (5 mL) at 0 °C was added NaH (39 mg, 0.97 mmol, 60% dispersion in oil). The mixture was stirred at 0 °C for 20 min and then CS₂ (45 mg, 0.59 mmol) was added. The mixture was stirred at 0 °C for 10 min and then MeI (83 mg, 0.59 mmol) was added. The mixture was diluted with sat. NH₄Cl (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 9% EtOAc in hexanes to afford S-methyl O-(4-(oxetan-3-yl)benzyl) carbonodithioate as a white solid.

Step 5. Preparation of 5-((4-(oxetan-3-yl)benzyl)oxy)-1,3,4-thiadiazol-2-amine



[0275] The title compound was prepared using similar procedure as Intermediate B, Step 2, replacing O-(4-chlorobenzyl) S-methyl carbonodithioate with S-methyl O-(4-(oxetan-3-yl)benzyl) carbonodithioate

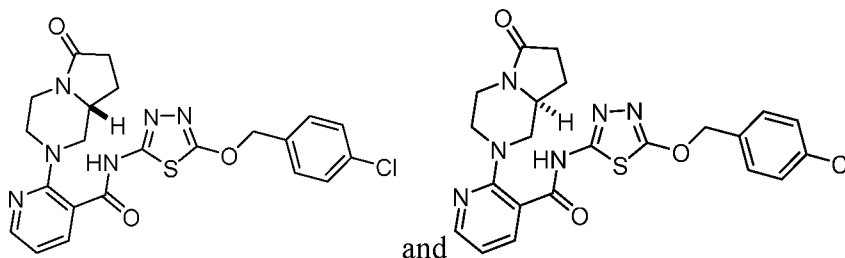
Step 6. Preparation of 2-morpholino-N-(5-((4-(oxetan-3-yl)benzyl)oxy)-1,3,4-thiadiazol-2-yl)nicotinamide



[0276] The title compound was prepared using General Procedure A employing 2-(morpholin-4-yl)pyridine-3-carboxylic acid and 5-((4-(oxetan-3-yl)benzyl)oxy)-1,3,4-thiadiazol-2-amine. The mixture was diluted with water and extracted with DCM (3 x). The combined organic layers were purified by Prep-HPLC [column, XBridge Prep OBD C₁₈; mobile phase, 20 - 40% MeCN in (0.05 % NH₄OH in water)] to afford 2-morpholino-N-(5-((4-(oxetan-3-yl)benzyl)oxy)-1,3,4-thiadiazol-2-yl)nicotinamide as a white solid. ¹H NMR (400 MHz; DMSO-d₆): δ 3.22-3.25 (m, 4H), 3.66-3.68 (m, 4H), 4.24-4.32 (m, 1H), 4.61-4.64 (m, 2H), 4.94-4.97 (m, 2H), 5.50 (s, 2H), 6.98-7.01 (m, 1H), 7.45-7.54 (m, 4H), 7.90-7.92 (m, 1H), 8.35-8.37 (m, 1H), 12.88 (s, 1H) ppm. *m/z* 454 (M+H⁺).

Example 57

Synthesis of (R) N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(6-oxohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)nicotinamide and (S) N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(6-oxohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)nicotinamide

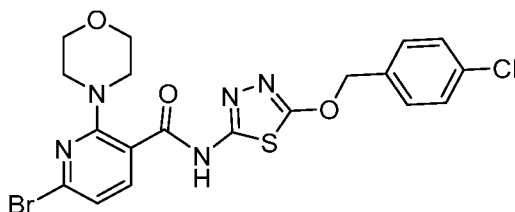


[0277] To a solution of racemic hexahydro-1H-pyrrolo[1,2-a]pyrazin-6-one (110 mg, 0.78 mmol) and N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-2-fluoropyridine-3-

carboxamide (200 mg, 0.55 mmol, Intermediate D) in NMP (1.5 mL) was added DIEA (202 mg, 1.6 mmol) under nitrogen. The mixture was stirred at 60 °C overnight. The mixture was diluted with water. The mixture was extracted with EtOAc (2 x). The combined organic layers were washed with water (2 x) and concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH,20:1) to afford a racemic mixture of (R) N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(6-oxohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)nicotinamide and (S) N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(6-oxohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)nicotinamide as a white solid. ¹H NMR (300 MHz; DMSO-d₆): δ 1.52-1.59 (m, 1H), 2.03-2.09 (m, 1H), 2.22-2.30 (m, 2H), 2.61-2.68 (m, 1H), 2.73-2.85 (m, 2H), 3.61-3.68 (m, 2H), 3.78-3.84 (m, 2H), 5.51 (s, 2H), 6.99-7.03 (m, 1H), 7.48-7.58 (m, 4H), 7.91-7.94 (m, 1H), 8.35-8.37 (m, 1H), 12.85 (s, 1H) ppm. *m/z* 485 (M+H⁺).

Example 58

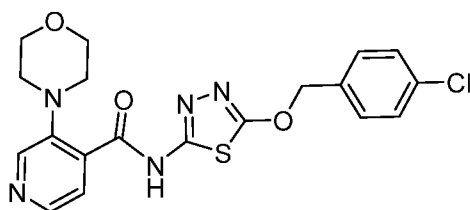
Synthesis of 6-bromo-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide



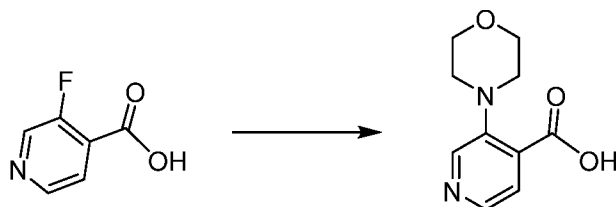
[0278] The title compound was prepared using General Procedure A employing 6-bromo-2-morpholinonicotinic acid (Step 1, Example 14) and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was diluted with water and extracted with EtOAc (3 x). The combined organic layers were concentrated under reduce pressure. The residue was triturated with DCM:MeOH, 10:1 to afford 6-bromo-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-morpholinonicotinamide as a white solid. ¹H NMR (300 MHz; DMSO-d₆): δ 3.26-3.32 (m, 4H), 3.61-3.64 (m, 4H), 5.50 (s, 2H), 7.06-7.09 (m, 1H), 7.47-7.56 (m, 4H), 7.72-7.75 (m, 1H), 12.83 (s, 1H) ppm. *m/z* 512 (M+H⁺).

Example 59

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-morpholinoisonicotinamide

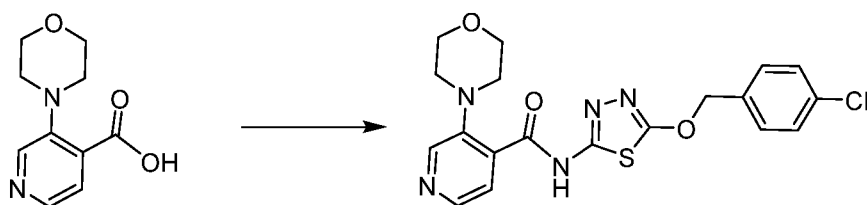


Step 1: Preparation of 3-morpholinoisonicotinic acid



[0279] To a solution of 3-fluoroisonicotinic acid (1 eq.) and morpholine (1.2 eq.) in THF at -78°C was slowly added a solution of LiHMDS (3 eq., 1 M in THF). The mixture was slowly warm to room temperature and stirred for an additional 18 h. The mixture was quenched with 4M HCl in dioxane and the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography, eluted with 0-12% MeOH in DCM to afford 3-morpholinoisonicotinic acid an orange solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 14.11 (s, 1H), 8.55 (d, $J = 1.7$ Hz, 1H), 8.34 (dd, $J = 4.9, 1.7$ Hz, 1H), 7.53 (dd, $J = 4.9, 1.7$ Hz, 1H), 3.80 – 3.68 (m, 4H), 3.16 – 3.03 (m, 4H).

Step 2. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-morpholinoisonicotinamide

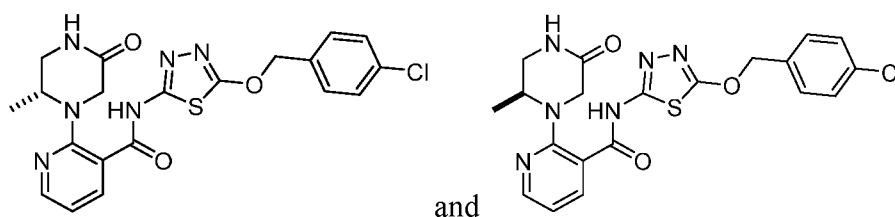


[0280] The title compound was prepared using General Procedure D employing 3-morpholinoisonicotinic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was diluted with water and extracted with EtOAc (3 x). The combined organic layers were concentrated under reduce pressure. The residue was purified by reverse phase HPLC (column, C18 silica gel; mobile phase, 0 - 100% MeCN in water, with both eluents containing 0.1% FA) to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-

morpholinoisonicotinamide as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 13.48 (s, 1H), 8.65 (s, 1H), 8.54 – 8.36 (m, 1H), 7.69 – 7.60 (m, 1H), 7.56 (dd, J = 8.5, 1.9 Hz, 2H), 7.49 (dd, J = 8.6, 2.0 Hz, 2H), 5.51 (s, 2H), 3.73 (t, J = 4.3 Hz, 4H), 3.08 (t, J = 4.2 Hz, 4H) ppm. m/z 432 ($\text{M}+\text{H}^+$).

Example 60

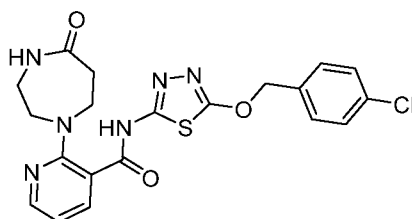
Synthesis of (R) N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2-methyl-5-oxopiperazin-1-yl)nicotinamide and (S) N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2-methyl-5-oxopiperazin-1-yl)nicotinamide



[0281] The title compound was prepared using similar procedure as Example 7, Steps 1-2, replacing racemic 2-methylmorpholine in Step 1 with racemic 5-methylpiperazin-2-one hydrochloride. The mixture was diluted with water. The mixture was extracted with EtOAc (2 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 50:1) to afford a racemic mixture of (R) N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2-methyl-5-oxopiperazin-1-yl)nicotinamide and (S) N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2-methyl-5-oxopiperazin-1-yl)nicotinamide as a white solid. ^1H NMR (300 MHz; DMSO-d_6): δ 1.09-1.11 (m, 3H), 2.97-3.06 (m, 1H), 3.36-3.42 (m, 1H), 3.66-3.81 (m, 2H), 4.08-4.10 (m, 1H), 5.50 (s, 2H), 6.92-7.02 (m, 1H), 7.47-7.57 (m, 4H), 7.86-7.96 (m, 2H), 8.31-8.38 (m, 1H), 12.86 (s, 1H) ppm. m/z 459 ($\text{M}+\text{H}^+$).

Example 61

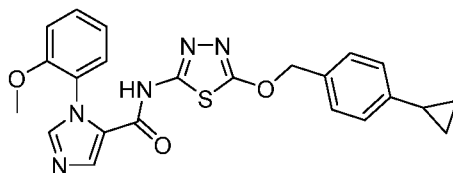
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(5-oxo-1,4-diazepan-1-yl)nicotinamide



[0282] To a solution of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-2-fluoropyridine-3-carboxamide (200 mg, 0.55 mmol, Intermediate D) in MeCN (2.0 mL), was added 1,4-diazepan-5-one (69 mg, 0.60 mmol) and Et₃N (111 mg, 1.1 mmol) under nitrogen. The mixture was stirred at 60 °C overnight. The mixture was cooled to room temperature and diluted with water. The mixture was filtered and the solid was washed with MeOH (2 mL) to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(5-oxo-1,4-diazepan-1-yl)nicotinamide as a white solid. ¹H NMR (400 MHz; DMSO-d₆): δ 2.56-2.58 (m, 4H), 3.20-3.25 (m, 2H), 3.51 (s, 2H), 5.50 (s, 2H), 6.87-6.91 (m, 1H), 7.45-7.57 (m, 5H), 7.83-7.88 (m, 1H), 8.28-8.30 (m, 1H), 12.84 (s, 1H) ppm. *m/z* 459 (M+H⁺).

Example 62

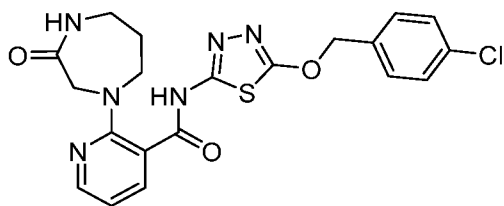
Synthesis of N-(5-((4-cyclopropylbenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(2-methoxyphenyl)-1H-imidazole-5-carboxamide



[0283] The title compound was prepared using similar procedure as Example 50 employing 5-[(4-cyclopropylphenyl)methoxy]-1,3,4-thiadiazol-2-amine (Example 47, Step 1) in Step 2. The mixture was diluted with water and extracted with DCM. The combined organic layers were concentrated under reduced pressure. The residue was triturated with MeOH to afford N-(5-((4-cyclopropylbenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(2-methoxyphenyl)-1H-imidazole-5-carboxamide as a white solid. ¹H NMR (300 MHz; DMSO-d₆): δ 0.62-0.66 (m, 2H), 0.94-0.98 (m, 2H), 1.87-1.96 (m, 1H), 3.66 (s, 3H), 5.39 (s, 2H), 7.03-7.11 (m, 3H), 7.16-7.18 (m, 1H), 7.33-7.37 (m, 3H), 7.42-7.48 (m, 1H), 7.95-7.98 (m, 1H), 8.10 (s, 1H), 12.62-12.71 (br s, 1H) ppm. *m/z* 448 (M+H⁺).

Example 63

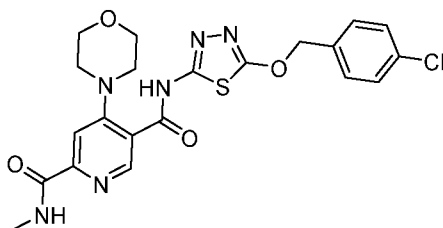
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(3-oxo-1,4-diazepan-1-yl)nicotinamide



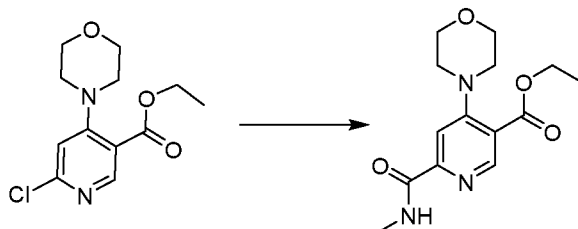
[0284] The title compound was prepared using similar procedure as Example 61, replacing 1,4-diazepan-5-one with 1,4-diazepan-2-one. The mixture was cooled room temperature and diluted with EtOAc. The mixture was washed with water. The combined organic layer was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 10:1). The residue was further triturated with MeOH to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(3-oxo-1,4-diazepan-1-yl)nicotinamide as a white solid. ^1H NMR (400 MHz; DMSO- d_6): δ 1.90 (s, 2H), 2.96-2.97 (m, 2H), 3.36-3.39 (m, 2H), 4.02 (s, 2H), 5.49 (s, 2H), 6.82-6.86 (m, 1H), 7.41 (s, 1H), 7.47-7.56 (m, 4H), 7.78-7.84 (m, 1H), 8.22-8.27 (m, 1H), 12.74 (s, 1H) ppm. m/z 459 ($M+H^+$).

Example 64

Synthesis of N⁵-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-N²-methyl-4-morpholinopyridine-2,5-dicarboxamide



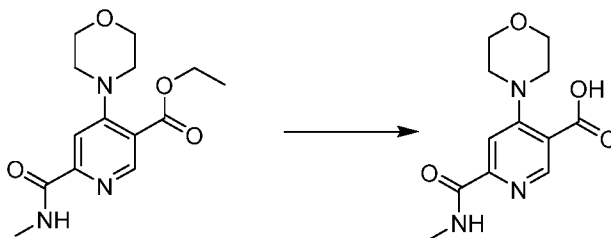
Step 1. Preparation of ethyl 6-(methylcarbamoyl)-4-morpholinonicotinate



[0285] To a solution of ethyl 6-chloro-4-(morpholin-4-yl)pyridine-3-carboxylate (1.5 g, 5.5 mmol, Example 35, Step 1) in THF (15 mL) was added Et₃N (1.1 g, 11.1 mmol), methylamine (2.80 mL, 5.6 mmol, 2 M in THF) and Pd(dppf)Cl₂ (405 mg, 0.55 mmol). The mixture was

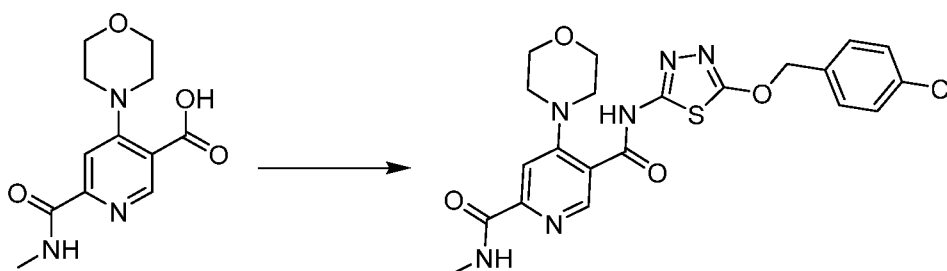
stirred at 110 °C for 4 h under CO (20 atm) . The mixture was cooled room temperature and diluted with water. The mixture was extracted with EtOAc (5 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 50:1) to afford ethyl 6-(methylcarbamoyl)-4-morpholinonicotinate as a red solid.

Step 2. Preparation of 6-(methylcarbamoyl)-4-morpholinonicotinic acid



[0286] To a solution of ethyl 6-(methylcarbamoyl)-4-morpholinonicotinate (310 mg, 1.0 mmol) in MeOH (3 mL) and water (3 mL) was added NaOH (204 mg, 5.1 mmol). The mixture was stirred at room temperature overnight. The mixture was acidified to pH 6 with HCl (1 M). The mixture was concentrated under reduced pressure. The residue was purified by reverse phase chromatography (column, C₁₈ silica gel; mobile phase, with 10-50% MeOH in water) to afford 6-(methylcarbamoyl)-4-morpholinonicotinic acid as a colorless solid.

Step 3. Preparation of N⁵-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-N2-methyl-4-morpholinopyridine-2,5-dicarboxamide

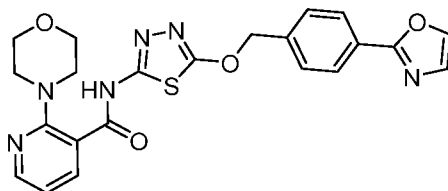


[0287] The title compound was prepared using General Procedure A employing 6-(methylcarbamoyl)-4-morpholinonicotinic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was diluted with water. The mixture was extracted with EtOAc (2 x). The combined organic layers were concentrated under reduced pressure. The residue was triturated with MeOH to afford N⁵-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-N2-methyl-4-morpholinopyridine-2,5-dicarboxamide as a white solid. ¹H NMR (400 MHz;

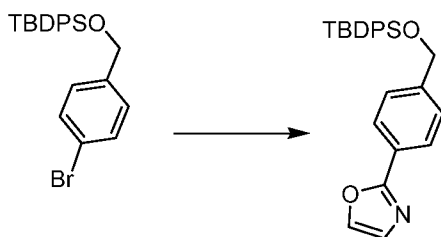
DMSO- d_6): δ 2.81-2.82 (m, 3H), 3.18-3.21 (m, 4H), 3.60-3.69 (m, 4H), 5.52 (s, 2H), 7.49-7.58 (m, 5H), 8.46 (s, 1H), 8.80-8.82 (m, 1H), 12.93 (s, 1H) ppm. m/z 489 ($M+H^+$).

Example 65

Synthesis of 2-morpholino-N-(5-(((4-(oxazol-2-yl)benzyl)oxy)-1,3,4-thiadiazol-2-yl)nicotinamide

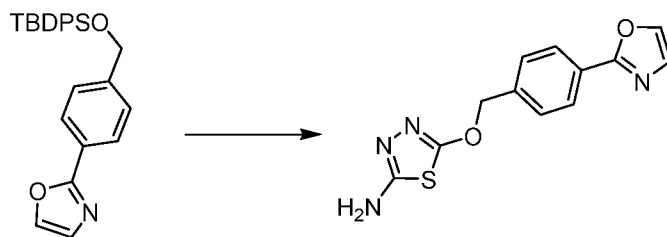


Step 1. Preparation of 2-(4-(((tert-butyl)dimethylsilyl)oxy)methyl)phenyl)oxazole



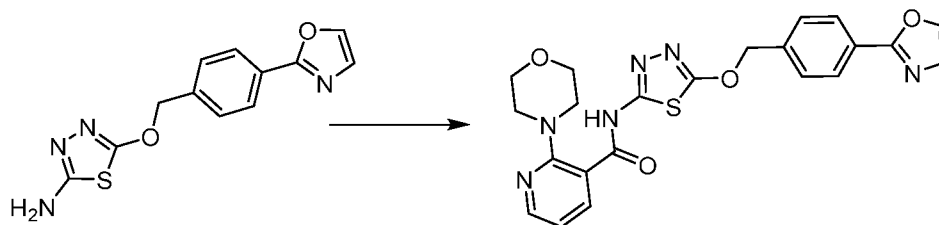
[0288] To a solution of ((4-bromobenzyl)oxy)(tert-butyl)dimethylsilane (1.5 g, 3.5 mmol, Example 56, step 1), in toluene (15 mL) was added 2-(tributylstannyl)-1,3-oxazole (1.9 g, 5.3 mmol) and $Pd(PPh_3)_4$ (0.4 g, 0.35 mmol) under nitrogen. The mixture was stirred at 110 °C for overnight. The mixture was cooled to room temperature and diluted with water. The mixture was extracted with DCM (3 x) and the combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 9% EtOAc in hexanes to afford 2-(4-(((tert-butyl)dimethylsilyl)oxy)methyl)phenyl)oxazole as yellow oil.

Step 2. Preparation of 5-(((4-(oxazol-2-yl)benzyl)oxy)-1,3,4-thiadiazol-2-amine



[0289] The title compound was prepared using similar procedure as Example 56, Step 3, 4 and 5 replacing tert-butyl([4-(oxetan-3-yl)phenyl]methoxy)diphenylsilane in Step 3 with 2-(4-(((tert-butyl)diphenylsilyl)oxy)methyl)phenyl)oxazole

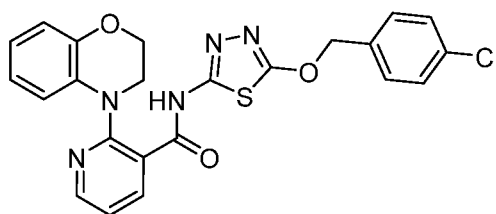
Step 3. Preparation of 2-morpholino-N-(5-((4-(oxazol-2-yl)benzyl)oxy)-1,3,4-thiadiazol-2-yl)nicotinamide



[0290] The title compound was prepared using General Procedure A employing 2-(morpholin-4-yl)pyridine-3-carboxylic acid and 5-((4-(oxazol-2-yl)benzyl)oxy)-1,3,4-thiadiazol-2-amine. The mixture was diluted with water and mixture was filtered. Solid was triturated with MeOH to afford 2-morpholino-N-(5-((4-(oxazol-2-yl)benzyl)oxy)-1,3,4-thiadiazol-2-yl)nicotinamide as a white solid. ^1H NMR (400 MHz; DMSO- d_6): δ 3.18-3.25 (m, 4H), 3.66-3.69 (m, 4H), 5.59 (s, 2H), 6.98-7.02 (m, 1H), 7.42 (s, 1H), 7.67-7.70 (m, 2H), 7.91-7.94 (m, 1H), 8.00-8.06 (m, 2H), 8.26 (s, 1H), 8.36-8.38 (m, 1H), 12.89 (s, 1H) ppm. m/z 465 ($M+H^+$).

Example 66

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)nicotinamide

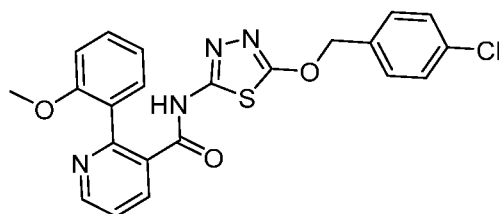


[0291] The title compound was prepared according to General Procedure D using Intermediate B and 2-(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)nicotinic acid, prepared according to General procedure C with 3,4-dihydro-2H-benzo[b][1,4]oxazine, to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)nicotinamide (14 mg, 15% yield.) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.48 (d, J = 4.7 Hz, 1H), 7.95 (d, J =

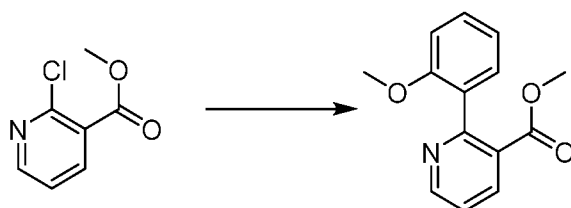
7.5 Hz, 1H), 7.49 (q, $J = 8.2$ Hz, 4H), 7.17 (t, $J = 6.0$ Hz, 1H), 6.73 (d, $J = 8.0$ Hz, 2H), 6.67 (t, $J = 7.7$ Hz, 1H), 6.52 (t, $J = 7.7$ Hz, 1H), 5.43 (s, 2H), 4.31 (s, 2H), 3.81 (s, 2H) ppm. m/z 480 ($M+H^+$).

Example 67

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2-methoxyphenyl)nicotinamide

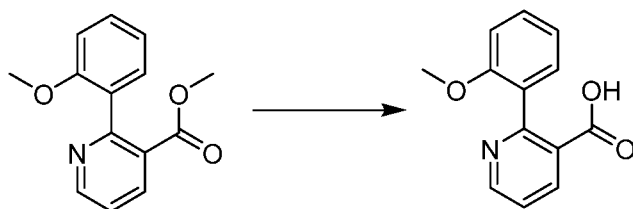


Step 1. Preparation of methyl 2-(2-methoxyphenyl)pyridine-3-carboxylate



[0292] The title compound was prepared using General Procedure E employing methyl 2-chloropyridine-3-carboxylate and 2-methoxyphenylboronic acid. The mixture was cooled room temperature and diluted with water. The mixture was extracted with EtOAc (3 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 17% EtOAc in PE to afford methyl 2-(2-methoxyphenyl)pyridine-3-carboxylate (as a white solid).

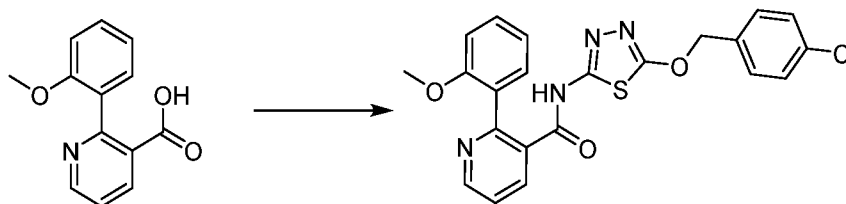
Step 2. Preparation of 2-(2-methoxyphenyl)pyridine-3-carboxylic acid



[0293] The title compound was prepared using General Procedure F employing methyl 2-(2-methoxyphenyl)pyridine-3-carboxylate. The mixture was stirred at 50 °C for 4 h. The mixture was acidified to pH 6 with HCl (1 M) and extracted with EtOAc (4 x). The combined organic

layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 33% EtOAc in PE to afford 2-(2-methoxyphenyl)pyridine-3-carboxylic acid as a white solid

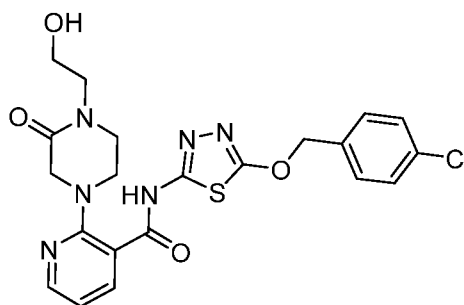
Step 3. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2-methoxyphenyl)nicotinamide



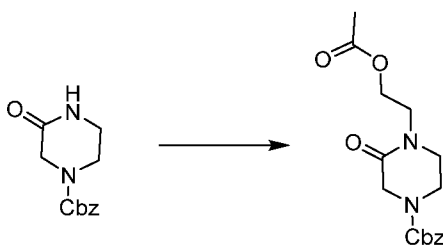
[0294] The title compound was prepared using General Procedure A employing 2-(2-methoxyphenyl)pyridine-3-carboxylic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was diluted with water. The mixture was extracted with EtOAc (2 x). The combined organic layers were concentrated under reduced pressure. The residue was triturated with MeOH. The residue was further purified by Prep-TLC (DCM:MeOH, 20:1) to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2-methoxyphenyl)nicotinamide (90.8 mg, 22.98%) as a white solid. ¹H NMR (400 MHz; DMSO-d₆): δ 3.49 (s, 3H), 5.47 (s, 2H), 6.93-6.95 (m, 1H), 7.05-7.13 (m, 1H), 7.36-7.40 (m, 1H), 7.47-7.54 (m, 6H), 8.03-8.04 (m, 1H), 8.77-8.78 (m, 1H), 12.70 (s, 1H) ppm. *m/z* 453 (M+H⁺).

Example 68

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(4-(2-hydroxyethyl)-3-oxopiperazin-1-yl)nicotinamide

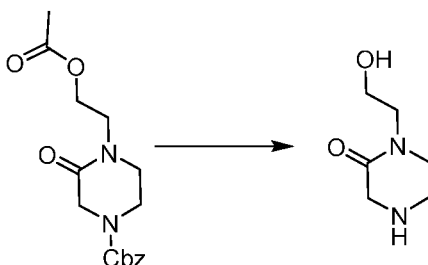


Step 1. Preparation of benzyl 4-(2-acetoxyethyl)-3-oxopiperazine-1-carboxylate



[0295] To a solution of benzyl 3-oxopiperazine-1-carboxylate (3.0 g, 12.8 mmol) in DMF (30 mL) was added 2-bromoethyl acetate (2.1 g, 12.8 mmol) dropwise under nitrogen. Then NaH (1.3 g, 32 mmol, 60% dispersion in oil) was added. The mixture was stirred overnight at room temperature. The mixture was diluted with sat. NH_4Cl . The mixture was extracted with EtOAc (2 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 0.5% MeOH in DCM to afford benzyl 4-(2-acetoxyethyl)-3-oxopiperazine-1-carboxylate as a yellow solid.

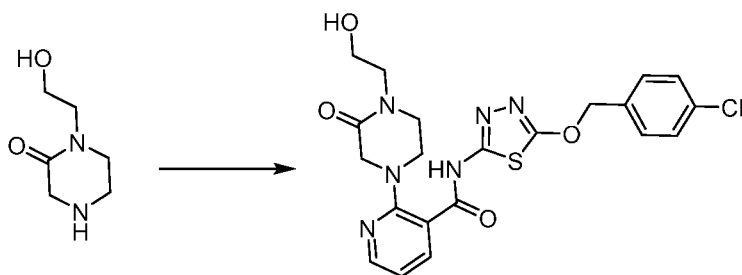
Step 2. Preparation of 1-(2-hydroxyethyl)piperazin-2-one



[0296] To a solution of benzyl 4-[2-(acetyloxy)ethyl]-3-oxopiperazine-1-carboxylate (2.4 g, 7.5 mmol) in MeOH (24 mL) and water (10 mL) was added K_2CO_3 (2.1 g, 15.0 mmol). The mixture was stirred for 2 h at room temperature. The mixture was diluted with CHCl_3 (24 mL).

[0297] The mixture was washed with brine (3 x). The mixture was concentrated under reduced pressure. The residue was dissolved in MeOH (10 mL) and 10% Pd/C (100 mg) was added. The mixture was stirred for 2 h at room temperature under hydrogen. The mixture was filtered through celite. The filtrate was concentrated under reduced pressure to afford 1-(2-hydroxyethyl)piperazin-2-one as a white solid.

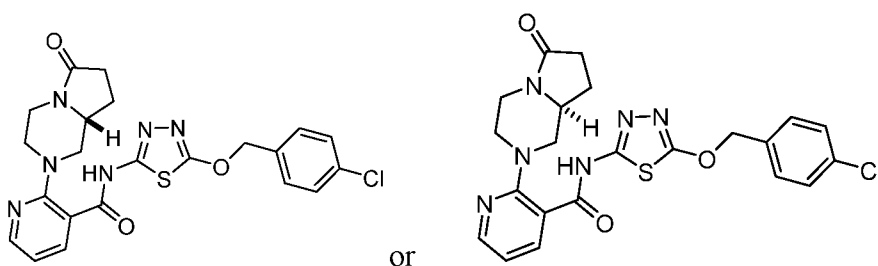
Step 3. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(4-(2-hydroxyethyl)-3-oxopiperazin-1-yl)nicotinamide



[0298] The title compound was prepared using similar procedure as Example 61, replacing 1,4-diazepan-5-one with 1-(2-hydroxyethyl)piperazin-2-one. The mixture was cooled to room temperature and diluted with EtOAc. The mixture was washed with water (3 x). The organic layer was concentrated under reduced pressure. The residue was triturated with MeOH to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(4-(2-hydroxyethyl)-3-oxopiperazin-1-yl)nicotinamide as a white solid. ^1H NMR (400 MHz; DMSO- d_6): δ 3.35-3.38 (m, 2H), 3.44-3.52 (m, 4H), 3.55-3.58 (m, 2H), 3.83 (s, 2H), 4.68-4.71 (m, 1H), 5.51 (s, 2H), 6.92-6.95 (m, 1H), 7.48-7.50 (m, 2H), 7.54-7.56 (m, 2H), 7.87-7.89 (m, 1H), 8.31-8.33 (m, 1H), 12.82 (s, 1H) ppm. m/z 489 ($\text{M}+\text{H}^+$).

Example 69

Synthesis of (R)- N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(6-oxohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)nicotinamide or (S)- N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(6-oxohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)nicotinamide

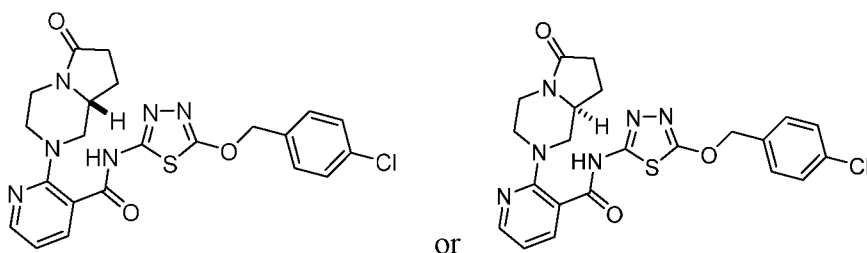


[0299] The racemic mixture (R) N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(6-oxohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)nicotinamide and (S)- N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(6-oxohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)nicotinamide (Example 57) was purified using Prep-HPLC (column: CHIRALPAK IF-3; mobile phase A: 25% DCM in hexanes containing (0.1% Et₂NH), mobile phase B: EtOH, isocratic 30% B in A) to afford the

title compound as a white solid, as the first eluting isomer. ^1H NMR (300 MHz; DMSO- d_6): δ 1.51-1.58 (m, 1H), 2.03-2.07 (m, 1H), 2.21-2.29 (m, 2H), 2.60-2.64 (m, 1H), 2.77-2.84 (m, 2H), 3.60-3.67 (m, 2H), 3.77-3.84 (m, 2H), 5.50 (s, 2H), 6.98-7.03 (m, 1H), 7.48-7.57 (m, 4H), 7.91-7.94 (m, 1H), 8.34-8.36 (m, 1H), 12.82 (s, 1H) ppm. m/z 485 ($M+H^+$).

Example 70

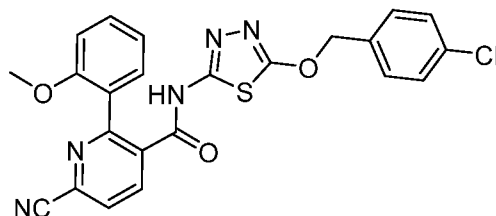
Synthesis of (R)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(6-oxohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)nicotinamide or (S)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(6-oxohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)nicotinamide



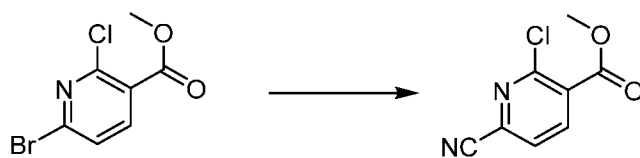
[0300] Further elution of Example 69 afforded to title compound as the second eluting isomer. ^1H NMR (300 MHz; DMSO- d_6): δ 1.52-1.59 (m, 1H), 2.03-2.07 (m, 1H), 2.21-2.30 (m, 2H), 2.60-2.68 (m, 1H), 2.73-2.84 (m, 2H), 3.61-3.68 (m, 2H), 3.77-3.84 (m, 2H), 5.51 (s, 2H), 6.99-7.03 (m, 1H), 7.48-7.58 (m, 4H), 7.91-7.94 (m, 1H), 8.35-8.37 (m, 1H), 12.82 (s, 1H) ppm. m/z 485 ($M+H^+$).

Example 71

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-2-(2-methoxyphenyl)nicotinamide

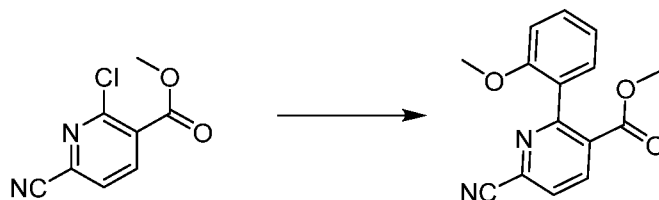


Step 1. Preparation of methyl 2-chloro-6-cyanonicotinate



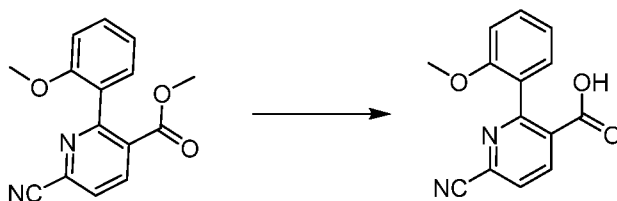
[0301] To a solution of methyl 6-bromo-2-chloropyridine-3-carboxylate (1 g, 4.0 mmol) in DMF (10 mL) was added $\text{Zn}(\text{CN})_2$ (516 mg, 4.4 mmol). The solution was degassed with bubbling nitrogen for 3 minutes and then $\text{Pd}(\text{PPh}_3)_4$ (461 mg, 0.40 mmol) was added. The solution was degassed with bubbling with nitrogen for 3 minutes. The mixture was stirred at 80 °C for 14 h. The mixture was cooled to room temperature and diluted with water. The mixture was extracted with EtOAc (3 x). The combined organic layers were washed with brine (3 x) and concentrated under reduce pressure. The residue was purified by silica gel column chromatograph eluted with 3-9% EtOAc in PE to afford methyl 2-chloro-6-cyanonicotinate as light yellow oil.

Step 2. Preparation of methyl 6-cyano-2-(2-methoxyphenyl)nicotinate



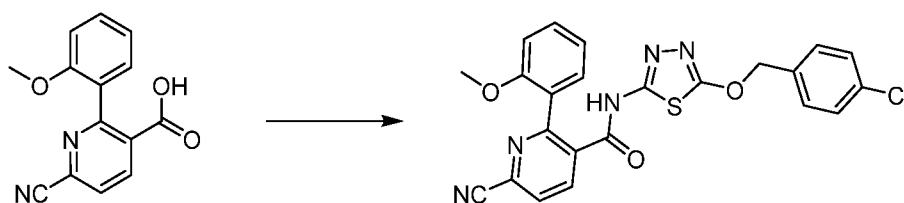
[0302] The title compound was prepared using General Procedure E employing methyl 2-chloro-6-cyanopyridine-3-carboxylate and 2-methoxyphenylboronic acid. The mixture was stirred at 80 °C for 4 h. The mixture was cooled to room temperature and diluted with EtOAc. The mixture was washed with brine (2 x) and concentrated under reduce pressure. The residue was purified by Prep-TLC (PE:EtOAc, 2:1) to afford methyl 6-cyano-2-(2-methoxyphenyl)nicotinate as a white solid.

Step 3. Preparation of 6-cyano-2-(2-methoxyphenyl)nicotinic acid



[0303] To a solution of methyl 6-cyano-2-(2-methoxyphenyl)pyridine-3-carboxylate (215 mg, 0.80 mmol) in THF (4 mL) was added a solution of LiOH (19 mg, 0.80 mmol) in water (0.8 mL). The mixture was stirred at room temperature for 16 h. The mixture was diluted with EtOAc and washed with brine (2 x). The combined aqueous layers were acidified by to pH 3 with HCl (1 M). The mixture was extracted with EtOAc (2 x). The combined organic layers were concentrated under reduce pressure to afford 6-cyano-2-(2-methoxyphenyl)nicotinic acid as a white solid.

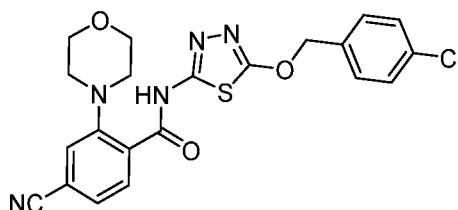
Step 4. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-2-(2-methoxyphenyl)nicotinamide



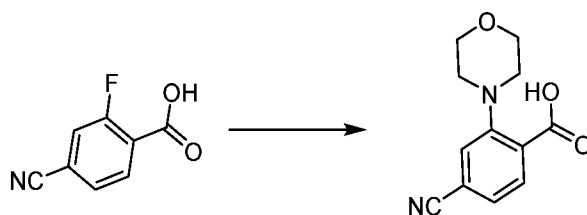
[0304] The title compound was prepared using General Procedure A employing 6-cyano-2-(2-methoxyphenyl)nicotinic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was diluted with EtOAc and washed with brine (2 x). The organic layer was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 80:1). The residue was further purified by trituration with MeOH to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-2-(2-methoxyphenyl)nicotinamide as a white solid. ^1H NMR (300 MHz; DMSO- d_6): δ 3.51 (s, 3H), 5.48 (s, 2H), 6.98-7.01 (m, 1H), 7.08-7.13 (m, 1H), 7.42-7.56 (m, 6H), 8.15-8.18 (m, 1H), 8.30-8.33 (m, 1H), 13.00 (s, 1H) ppm. m/z 478 ($\text{M}+\text{H}^+$).

Example 72

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-cyano-2-morpholinobenzamide

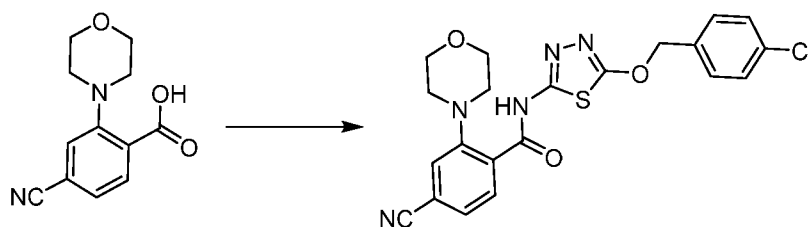


Step 1. Preparation of 4-cyano-2-morpholinobenzoic acid



[0305] The title compound was prepared using General Procedure C employing 4-cyano-2-fluorobenzoic acid. The mixture was cooled to room temperature and concentrated under reduce pressure. The residue was purified by silica gel column eluted with 0.9 – 2% MeOH in (0.05% AcOH in DCM). The residue was further purified by triturating with DCM give 4-cyano-2-morpholinobenzoic acid as a white solid.

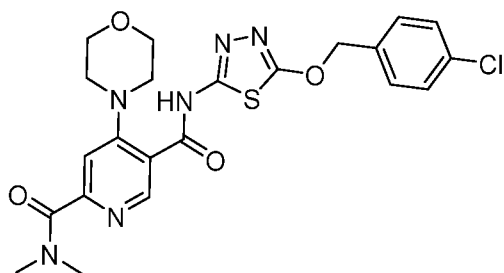
Step 2. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-cyano-2-morpholinobenzamide



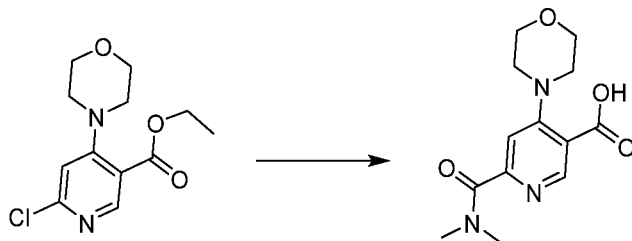
[0306] The title compound was prepared using General Procedure A employing and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was diluted with water and stirred at room temperature for 5 minutes. The mixture was filtered and the solid was washed with water (2 x). The solid was triturated with MeOH to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-cyano-2-morpholinobenzamide as a light yellow solid. ¹H NMR (300 MHz; DMSO-d₆): δ 3.00-3.03 (m, 4H), 3.70-3.73 (m, 4H), 5.52 (s, 2H), 7.48-7.51 (m, 2H), 7.55-7.58 (m, 2H), 7.63-7.66 (m, 1H), 7.77-7.78 (m, 1H), 7.83-7.86 (m, 1H), 13.38 (s, 1H) ppm. *m/z* 456 (M+H⁺).

Example 73

Synthesis of N⁵-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-N²,N²-dimethyl- 4-morpholinopyridine-2,5-dicarboxamide

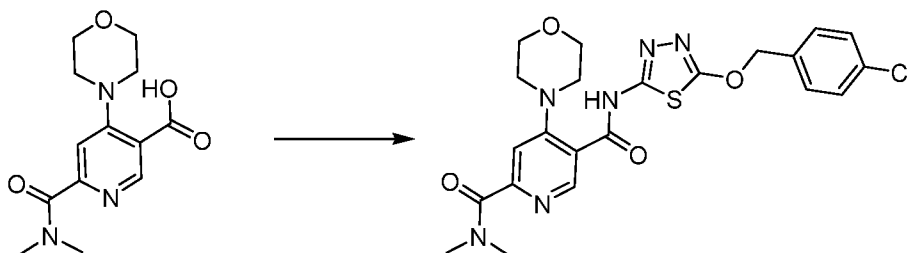


Step 1. Preparation of 6-(dimethylcarbamoyl)-4-(morpholin-4-yl)pyridine-3-carboxylic acid



[0307] The title compound was prepared using similar procedure as Example 64, Steps 1-2, replacing methylamine with dimethylamine in Step 1.

Step 2. Preparation of N⁵-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-N₂,N₂-dimethyl- 4-morpholinopyridine-2,5-dicarboxamide

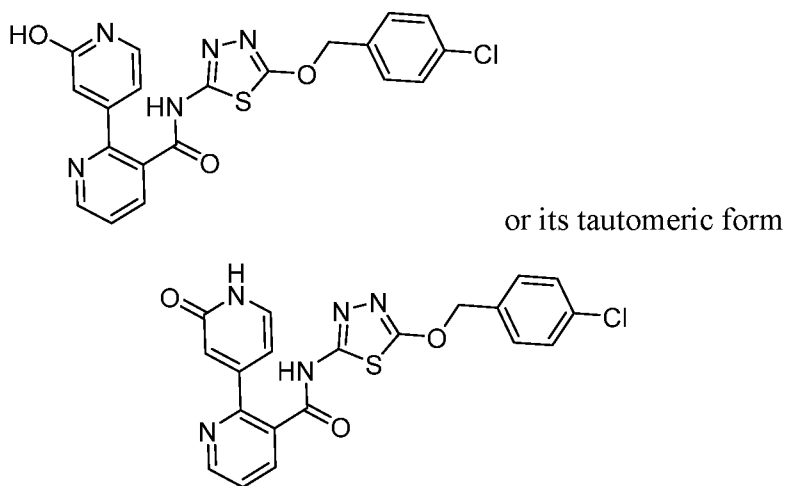


[0308] To a solution of 6-(dimethylcarbamoyl)-4-(morpholin-4-yl)pyridine-3-carboxylic acid (100 mg, 0.36 mmol) in DCM (1 mL) was added DMF (5 mg, 0.72 mmol) and oxalyl chloride (68 mg, 0.54 mmol). The mixture was stirred at room temperature for 1 h. The mixture was concentrated under reduced pressure. Then a solution of 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (87 mg, 0.36 mmol, Intermediate B) and Et₃N (72 mg, 0.72 mmol) in DCM (1 mL) was added. The mixture was stirred at room temperature for 2 h. The mixture was concentrated under reduce pressure. The residue was triturated with MeOH (1 mL). The residue was further purified by Prep-HPLC with the following condition [column: XBridge Prep OBD

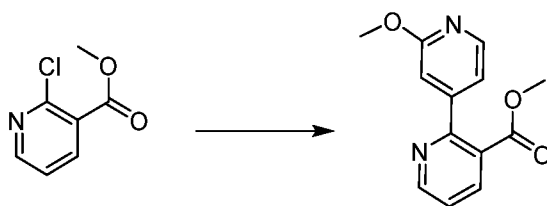
C₁₈; mobile phase, 13 – 33% MeCN in (0.05% NH₄OH in water)] to afford N⁵-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-N₂,N₂-dimethyl-4-morpholinopyridine-2,5-dicarboxamide as a white solid. ¹H NMR (300 MHz; DMSO-d₆): δ 2.92 (s, 3H), 2.99 (s, 3H), 3.16 (s, 4H), 3.63-3.65 (m, 4H), 5.50 (s, 2H), 7.08 (s, 1H), 7.47-7.57 (m, 4H), 8.41 (s, 1H), 12.85 (s, 1H) ppm. *m/z* 503 (M+H⁺).

Example 74

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2'-hydroxy-[2,4'-bipyridine]-3-carboxamide or its tautomer N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2'-oxo-1',2'-dihydro-[2,4'-bipyridine]-3-carboxamide

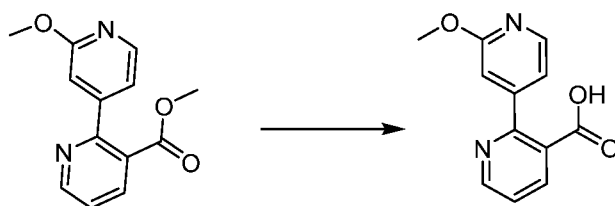


Step 1. Preparation of methyl 2'-methoxy-[2,4'-bipyridine]-3-carboxylate



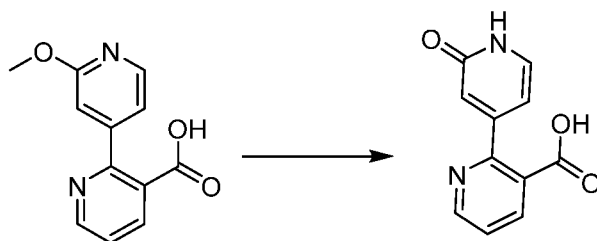
[0309] The title compound was prepared using General Procedure D employing methyl 2-chloropyridine-3-carboxylate and 2-methoxypyridin-4-ylboronic acid. The mixture was cooled to room temperature and diluted with EtOAc. The mixture was washed with water (3 x) and the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 9% EtOAc in PE to afford methyl 2'-methoxy-[2,4'-bipyridine]-3-carboxylate as a white solid.

Step 2. Preparation of 2'-methoxy-[2,4'-bipyridine]-3-carboxylic acid



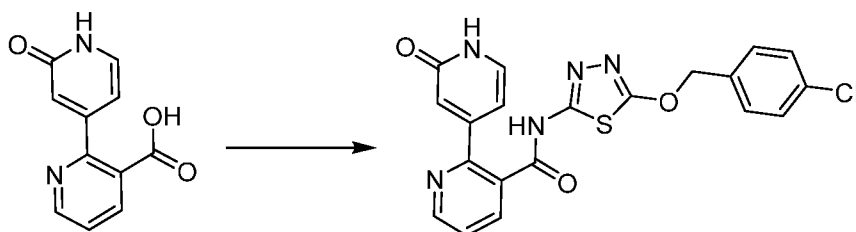
[0310] To a solution of methyl 2'-methoxy-[2,4'-bipyridine]-3-carboxylate (1.9 g, 7.8 mmol) in DCM (20 mL) was added BBr_3 (19 g, 78 mmol) at 0°C under nitrogen. The mixture was warmed to room temperature and stirred at room temperature overnight. The mixture was diluted with sat. NaHCO_3 (20 mL). The mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 17% MeOH in DCM to afford 2'-methoxy-[2,4'-bipyridine]-3-carboxylic acid as a white solid.

Step 3. Preparation of 2'-oxo-1',2'-dihydro-[2,4'-bipyridine]-3-carboxylic acid



[0311] To a solution of 2-methoxy-[2,4-bipyridine]-3-carboxylic acid (780 mg, 3.4 mmol) and PTSA (886 mg, 5.1 mmol) in DMF was added LiCl (218 mg, 5.1 mmol). The mixture was stirred for 1 h at 100°C under nitrogen. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by Prep-HPLC (column, C_{18} ; mobile phase, 0 – 100% MeCN in water) to afford 2'-oxo-1',2'-dihydro-[2,4'-bipyridine]-3-carboxylic acid as a white solid.

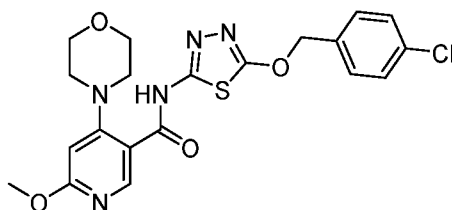
Step 4. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2'-oxo-1',2'-dihydro-[2,4'-bipyridine]-3-carboxamide



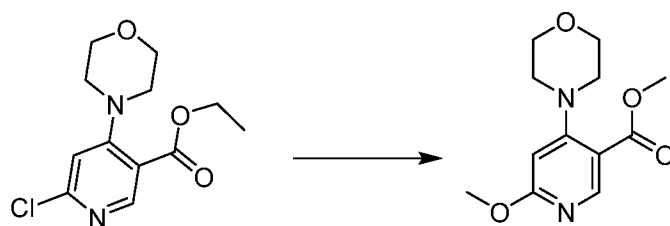
[0312] The title compound was prepared using General Procedure A employing 2'-oxo-1',2'-dihydro-[2,4'-bipyridine]-3-carboxylic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was diluted with EtOAc and washed with water (2 x). The organic layer was concentrated under reduce pressure and the residue was triturated with MeOH to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2'-oxo-1',2'-dihydro-[2,4'-bipyridine]-3-carboxamide as a white solid. ¹H NMR (400 MHz; DMSO-d₆): δ 5.49 (s, 2H), 6.30-6.37 (m, 2H), 7.41-7.61 (m, 6H), 8.10-8.13 (m, 1H), 8.79-8.81 (m, 1H), 11.58-11.73 (br s, 1H), 13.01-13.11 (br s, 1H) ppm. *m/z* 440 (M+H⁺).

Example 75

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-methoxy-4-morpholino-nicotinamide

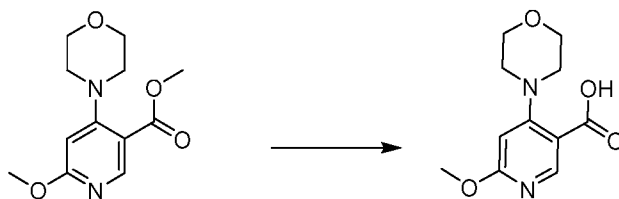


Step 1. Preparation of methyl 6-methoxy-4-morpholinonicotinate



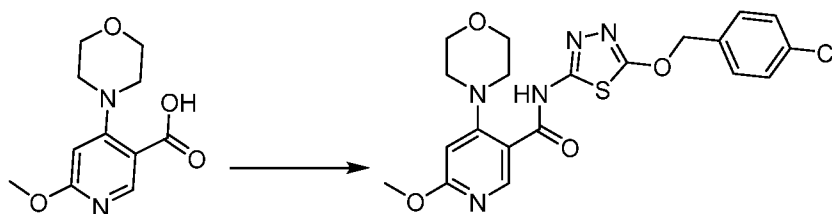
[0313] To a solution of ethyl 6-chloro-4-(morpholin-4-yl)pyridine-3-carboxylate (500 mg, 1.8 mmol, Example 35, Step 1) in DMF (5 mL) and MeOH (3.8 mL) was added MeONa (998 mg, 18.5 mmol). The mixture was stirred at 60 °C overnight. The mixture was cooled to room temperature and diluted with sat NH₄Cl (15 mL). The mixture was extracted with EtOAc (3 x) and the combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (PE:EtOAc, 5:1) to afford methyl 6-methoxy-4-morpholinonicotinate as an off-white oil.

Step 2. Preparation of 6-methoxy-4-morpholinonicotinic acid



[0314] The title compound was prepared using General Procedure F employing methyl 6-methoxy-4-morpholinonicotinate. The mixture was acidified to pH 3 with HCl (1 M). The mixture was concentrated. The residue was purified by Prep-HPLC (column, C₁₈; mobile phase, 10 – 50% MeCN and water, with both eluents containing 0.05% TFA) to afford 6-methoxy-4-morpholinonicotinic acid as an off-white oil.

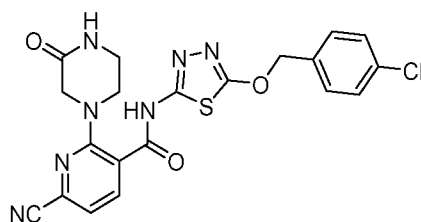
Step 3. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-methoxy-4-morpholinonicotinamide



[0315] The title compound was prepared using General Procedure A employing 6-methoxy-4-morpholinonicotinic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was diluted with EtOAc and washed with water (2 x). The mixture was concentrated under reduce pressure. The residue was triturated with MeOH to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-methoxy-4-morpholinonicotinamide as a white solid. ¹H NMR (300 MHz; DMSO-d₆): δ 3.02-3.05 (m, 4H), 3.64-3.69 (m, 4H), 3.88 (s, 3H), 5.50 (s, 2H), 6.37 (s, 1H), 7.48-7.57 (m, 4H), 8.26 (s, 1H), 12.62 (s, 1H) ppm. *m/z* 462 (M+H⁺).

Example 76

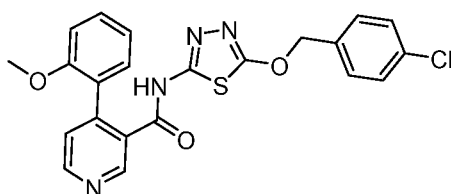
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-2-(3-oxopiperazin-1-yl)nicotinamide



[0316] The title compound was prepared using similar procedure as Example 14, Step 1-3, replacing morpholine with piperazin-2-one in Step 1. The mixture was purified by Prep-HPLC [column C₁₈ Spherical; mobile phase, 35 – 55% MeCN in (0.16% NH₄HCO₃ in water)] to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-2-(3-oxopiperazin-1-yl)nicotinamide as a white solid. ¹H NMR (300 MHz; DMSO-*d*₆): δ 3.24 (s, 2H), 3.51-3.55 (m, 2H), 3.81 (s, 2H), 5.51 (s, 2H), 7.46-7.56 (m, 5H), 8.02-8.05 (m, 1H), 8.13 (s, 1H), 13.11 (s, 1H) ppm. *m/z* 470 (M+H⁺).

Example 77

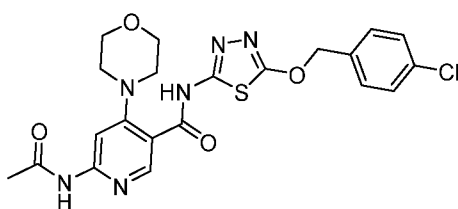
Synthesis of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)pyridine-3-carboxamide



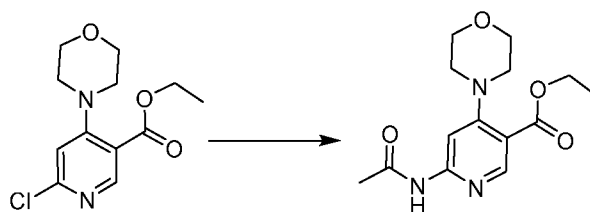
[0317] The title compound was prepared using similar procedure as Example 67, Steps 1 - 3, replacing methyl 2-chloropyridine-3-carboxylate with methyl 4-chloropyridine-3-carboxylate in Step 1. The residue was purified by Prep-TLC (DCM:MeOH, 15:1) to afford N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)pyridine-3-carboxamide as a white solid. ¹H NMR (400 MHz; DMSO-*d*₆): δ 3.52 (s, 3H), 5.48 (s, 2H), 6.98-7.00 (m, 1H), 7.06-7.09 (m, 1H), 7.34-7.44 (m, 3H), 7.47-7.54 (m, 4H), 8.75-8.79 (m, 2H), 12.78 (s, 1H) ppm. *m/z* 453 (M+H⁺).

Example 78

Synthesis of 6-acetamido-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-morpholinonicotinamide

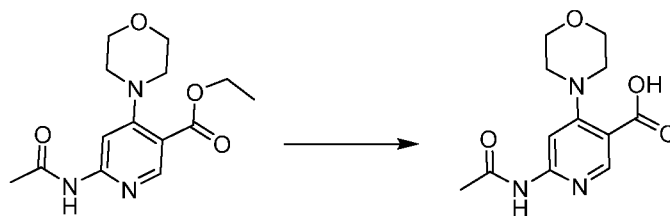


Step 1. Preparation of ethyl 6-acetamido-4-morpholinonicotinate



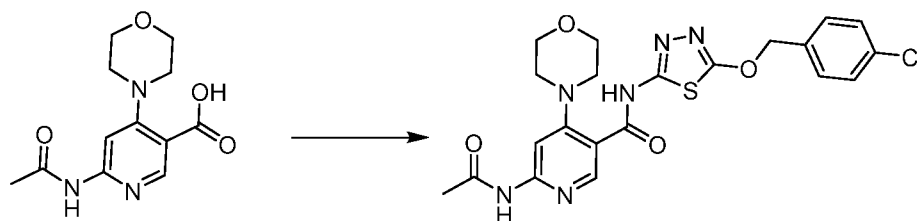
[0318] To a stirred solution of ethyl 6-chloro-4-(morpholin-4-yl)pyridine-3-carboxylate (1.0 g, 3.7 mmol, Example 35, Step 1) in dioxane (10 mL) was added acetamide (436 mg, 7.4 mmol), Pd(OAc)₂ (124 mg, 0.55 mmol), dppf (204 mg, 0.37 mmol) and Cs₂CO₃ (2.4 g, 7.4 mmol) at room temperature under nitrogen. The mixture was stirred at 100 °C for 4 h. The mixture was diluted with EtOAc (10 mL) and was washed with water (3 x 10 mL). The organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 3% EtOAc in PE to afford ethyl 6-acetamido-4-morpholinonicotinate as an off-white solid.

Step 2. Preparation of 6-acetamido-4-morpholinonicotinic acid



[0319] To a solution of ethyl 6-acetamido-4-morpholinonicotinate (300 mg, 1.0 mmol) in DCM (3 mL) was added BBr₃ (512 mg, 2.0 mmol) at room temperature under nitrogen. The mixture was stirred for 30 min at room temperature. The mixture was diluted with sat. NaHCO₃. The mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC (column, C₁₈ silica gel; mobile phase, 0 – 5% MeCN in water) to afford 6-acetamido-4-morpholinonicotinic acid as a white solid.

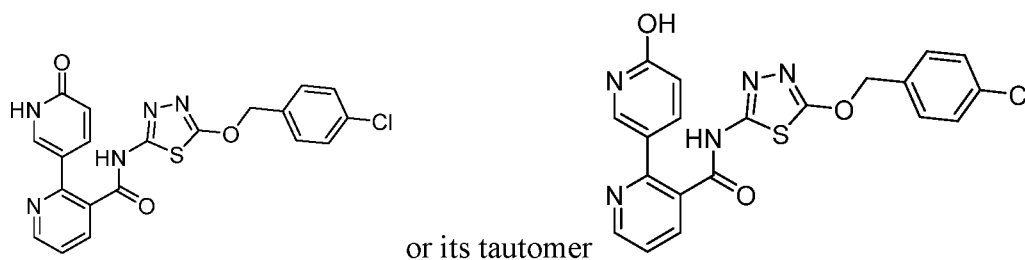
Step 3. Preparation of 6-acetamido-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-morpholinonicotinamide



[0320] The title compound was prepared using General Procedure A employing 6-acetamido-4-morpholinonicotinic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was diluted with EtOAc and washed with water (3 x). The organic layer concentrated under reduced pressure. The residue was purified by Prep-TLC (PE:EtOAc, 2:1). The residue was further purified by triturating with MeOH to afford 6-acetamido-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-morpholinonicotinamide as a white solid. ^1H NMR (300 MHz; DMSO- d_6): δ 2.11(s, 3H), 3.05 (s, 4H), 3.69 (s, 4H), 5.50 (s, 2H), 7.47-7.57 (m, 4H), 7.79 (s, 1H), 8.31 (s, 1H), 10.61 (s, 1H), 12.59 (s, 1H) ppm. m/z 489 ($\text{M}+\text{H}^+$).

Example 79

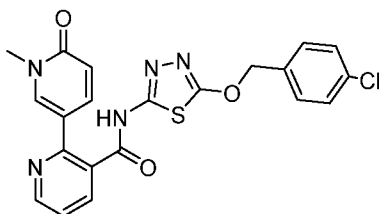
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6'-oxo-1',6'-dihydro-[2,3'-bipyridine]-3-carboxamide or its tautomer N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6'-hydroxy-[2,3'-bipyridine]-3-carboxamide



[0321] The title compound was prepared using similar procedure as Example 67, Steps 1 - 3, replacing 2-methoxyphenylboronic acid with 6-oxo-1H-pyridin-3-ylboronic acid in Step 1. The mixture was diluted with water and extracted with EtOAc (2 x). The combined organic layers concentrated under reduced pressure. The residue was triturated with MeOH to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6'-oxo-1',6'-dihydro-[2,3'-bipyridine]-3-carboxamide as a light green solid. ^1H NMR (300 MHz; DMSO- d_6): δ 5.51 (s, 2H), 6.31-6.40 (m, 1H), 7.29-7.65 (m, 7H), 8.03-8.04 (m, 1H), 8.74 (s, 1H), 11.65-11.96 (br s, 1H), 12.73-13.11 (br s, 1H) ppm. m/z 440 ($\text{M}+\text{H}^+$).

Example 80

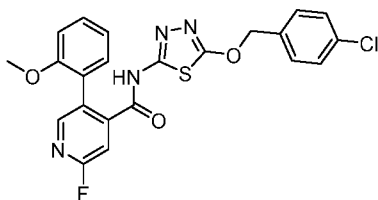
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1'-methyl-6'-oxo-1',6'-dihydro-[2,3'-bipyridine]-3-carboxamide



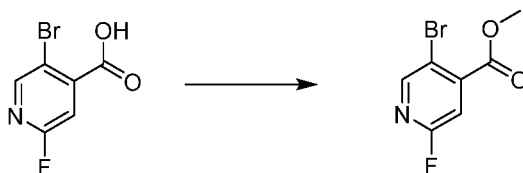
[0322] The title compound was prepared using similar procedure as Example 67, Steps 1 - 3, replacing 2-methoxyphenylboronic acid with 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-one in Step 1. The mixture was diluted with water and extracted with EtOAc (2 x). The combined organic layers concentrated under reduced pressure. The residue was triturated with MeOH to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1'-methyl-6'-oxo-1',6'-dihydro-[2,3'-bipyridine]-3-carboxamide as a white solid. ¹H NMR (400 MHz; DMSO-d₆): δ 3.48 (s, 3H), 5.50 (s, 2H), 6.38-6.40 (m, 1H), 7.45-7.48 (m, 4H), 7.50-7.56 (m, 2H), 8.05-8.07 (m, 2H), 8.73-8.74 (m, 1H), 12.94 (s, 1H) ppm. *m/z* 440 (M+H⁺).

Example 81

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-fluoro-5-(2-methoxyphenyl)isonicotinamide



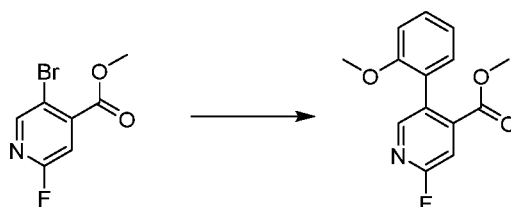
Step 1. Preparation of methyl 5-bromo-2-fluoroisonicotinate



[0323] To a solution of 5-bromo-2-fluoropyridine-4-carboxylic acid (1.0 g, 4.5 mmol) in THF (10 mL) was added Ph₃P (2.4 g, 9.1 mmol) and MeOH (0.7 g, 22.7 mmol) at 0 °C. The mixture was stirred at 0 °C for 5 min then DIAD (1.8 g, 9.1 mmol) was added and the mixture was

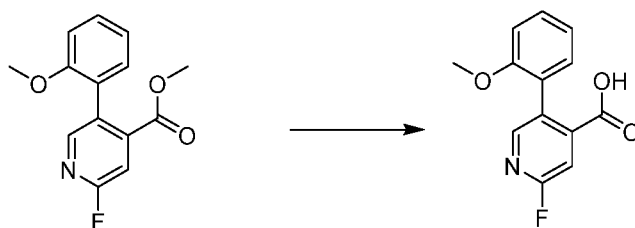
warmed to room temperature and stirred for 30 min at room temperature. The mixture was concentrated under reduce pressure. The residue was purified by silica gel column chromatography, eluted with 3% EtOAc in PE to afford methyl 5-bromo-2-fluoroisonicotinate as a white solid.

Step 2. Preparation of methyl 2-fluoro-5-(2-methoxyphenyl)isonicotinate



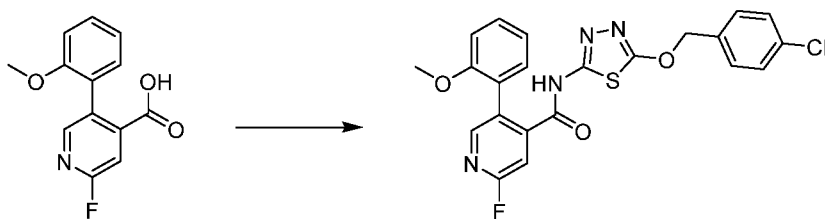
[0324] The title compound was prepared using General Procedure E employing methyl 5-bromo-2-fluoroisonicotinate and 2-methoxyphenylboronic acid. The mixture was cooled room temperature and diluted with water. The mixture was extracted with EtOAc (2 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 3% EtOAc in PE to afford methyl 2-fluoro-5-(2-methoxyphenyl)isonicotinate as a white solid.

Step 3. Preparation of 2-fluoro-5-(2-methoxyphenyl)pyridine-4-carboxylic acid



[0325] The title compound was prepared using General Procedure F employing methyl 2-fluoro-5-(2-methoxyphenyl)isonicotinate. The mixture was acidified to pH 6 with HCl (1 M). The mixture was extracted with EtOAc (3 x) and the combined organic layers were concentrated under reduced pressure to afford 2-fluoro-5-(2-methoxyphenyl)pyridine-4-carboxylic acid as a white solid.

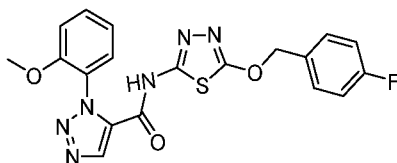
Step 4. Preparation of N-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-fluoro-5-(2-methoxyphenyl)isonicotinamide



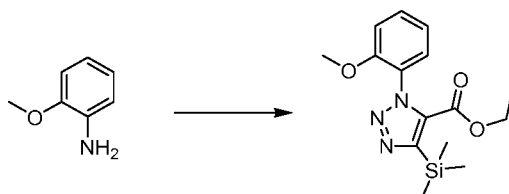
[0326] The title compound was prepared using General Procedure A employing 2-fluoro-5-(2-methoxyphenyl)pyridine-4-carboxylic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was diluted with water and extracted with EtOAc (2 x). The combined organic layers were concentrated under reduced pressure. The residue was re-crystallized from MeOH:water (10:1) to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-fluoro-5-(2-methoxyphenyl)isonicotinamide as a white solid. ^1H NMR (300 MHz; DMSO- d_6): δ 3.51 (s, 3H), 5.48 (s, 2H), 6.97-7.08 (m, 2H), 7.34-7.41 (m, 2H), 7.46-7.55 (m, 5H), 8.27 (s, 1H), 12.97 (s, 1H) ppm. m/z 471 ($\text{M}+\text{H}^+$).

Example 82

Synthesis of N-(5-((4-fluorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(2-methoxyphenyl)-1H-1,2,3-triazole-5-carboxamide



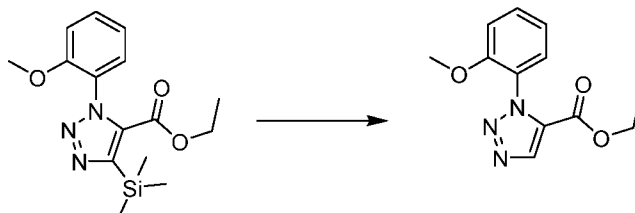
Step 1. Preparation of ethyl 3-(2-methoxyphenyl)-5-(trimethylsilyl)-1,2,3-triazole-4-carboxylate



[0327] To a solution of 2-methoxyaniline (3 g, 24.4 mmol) in 4 M HCl (30 mL) was added a solution of NaNO_2 (1.9 g, 26.8 mmol) in water (10 mL) dropwise at 0 °C. The mixture was stirred for 30 min. Then azidosodium (1.9 g, 29.2 mmol) was added in portions. The mixture was slowly warmed to room temperature and stirred 1 h at room temperature. The mixture was extracted with MTBE (3 x). The combined organic layers were dried over Na_2SO_4 and

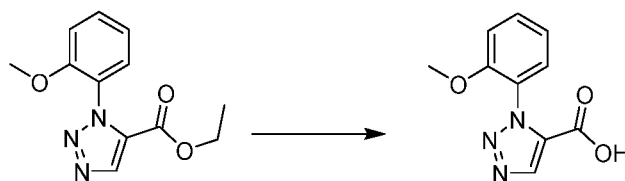
concentrated under reduced pressure. The residue was diluted with toluene (8 mL) and ethyl 3-(trimethylsilyl)prop-2-ynoate (1.0 g, 5.9 mmol) was added under nitrogen. The mixture was stirred at 80°C overnight. The mixture was cooled to room temperature and concentrated under reduced pressure to afford ethyl 3-(2-methoxyphenyl)-5-(trimethylsilyl)-1,2,3-triazole-4-carboxylate as brown oil, which was used in the next step without further purification.

Step 2. Preparation of ethyl 3-(2-methoxyphenyl)-1, 2, 3-triazole-4-carboxylate



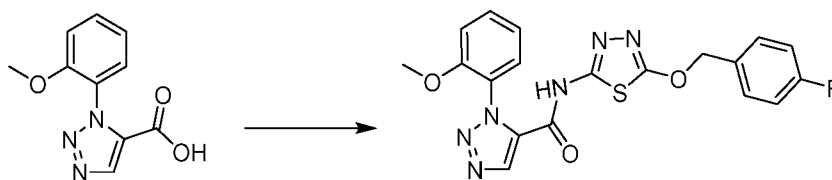
[0328] To a solution of ethyl 3-(2-methoxyphenyl)-5-(trimethylsilyl)-1, 2, 3-triazole-4-carboxylate (1.7 g, 5.3 mmol) in THF (20 mL) was added TBAF (2.1 g, 8.0 mmol) under nitrogen. The mixture was stirred at room temperature for 3 h. The mixture was diluted with water (20 mL) and extracted with DCM (3 x). The combined organic layers were concentrated under reduced pressure and the residue was purified by Prep-TLC (hexanes:EtOAc, 3:1) to afford ethyl 3-(2-methoxyphenyl)-1, 2, 3-triazole-4-carboxylate as brown oil.

Step 3. Preparation of 3-(2-methoxyphenyl)-1, 2, 3-triazole-4-carboxylic acid



[0329] The title compound was prepared using General Procedure F employing ethyl 3-(2-methoxyphenyl)-1, 2, 3-triazole-4-carboxylate. The mixture was diluted with water and acidified to pH 6 with HCl (1 M). The mixture was extracted with EtOAc (2 x) and the combined organic layers were concentrated under reduced pressure. The residue was triturated with MeOH to afford 3-(2-methoxyphenyl)-1, 2, 3-triazole-4-carboxylic acid as a white solid.

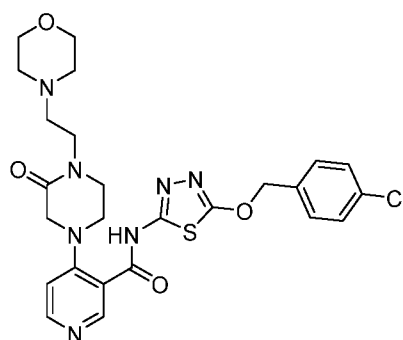
Step 4. Preparation of N-(5-((4-fluorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(2-methoxyphenyl)-1H-1,2,3-triazole-5-carboxamide



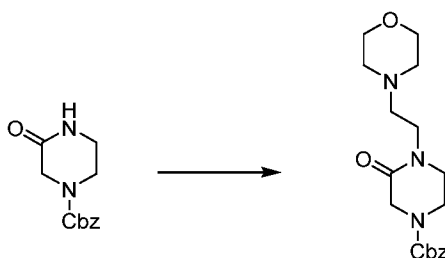
[0330] The title compound was prepared using General Procedure A employing 3-(2-methoxyphenyl)-1,2,3-triazole-4-carboxylic acid and 5-((4-fluorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate A). The mixture was diluted with water and extracted with EtOAc (2 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 10:1). The residue was further purified by triturating with MeOH to afford N-(5-((4-fluorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(2-methoxyphenyl)-1H-1,2,3-triazole-5-carboxamide as a white solid. ^1H NMR (300 MHz; DMSO- d_6): δ 3.66 (s, 3H), 5.47-5.52 (m, 2H), 7.13-7.28 (m, 4H), 7.52-7.59 (m, 4H), 8.57-8.62 (m, 1H), 13.28-13.37 (br s, 1H) ppm. m/z 427 ($\text{M}+\text{H}^+$).

Example 83

Synthesis of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-4-[4-[2-(morpholin-4-yl)ethyl]-3-oxopiperazin-1-yl]pyridine-3-carboxamide

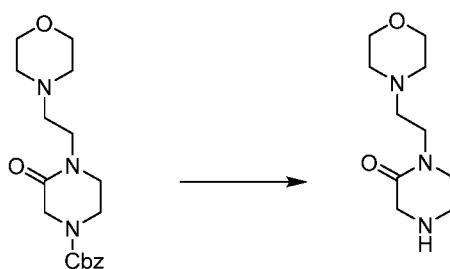


Step 1. Preparation of benzyl 4-[2-(morpholin-4-yl)ethyl]-3-oxopiperazine-1-carboxylate



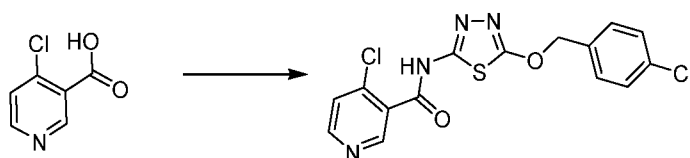
[0331] To a solution of benzyl 3-oxopiperazine-1-carboxylate (2.0 g, 8.5 mmol) in DMF (20 mL) was added NaH (0.68 g, 17.1 mmol, 60% dispersion in oil) under nitrogen at 0 °C. The mixture was stirred at 0 °C for 1 h and then 4-(2-bromoethyl)morpholine (1.7 g, 8.5 mmol) was added. The mixture was warmed to room temperature and stirred at room temperature for 3 h. The mixture was diluted with sat. NH₄Cl (60 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were concentrated under reduce pressure. The residue was purified by silica gel column chromatography, eluted with 25% EtOAc in PE to afford benzyl 4-[2-(morpholin-4-yl)ethyl]-3-oxopiperazine-1-carboxylate as a yellow solid.

Step 2. Preparation of 1-[2-(morpholin-4-yl)ethyl]piperazin-2-one



[0332] To a solution of benzyl 4-[2-(morpholin-4-yl)ethyl]-3-oxopiperazine-1-carboxylate (500 mg, 1.4 mmol) in MeOH (10 mL) was added 20% Pd/C (100 mg). The mixture was stirred at room temperature for 2 h under an of hydrogen. The mixture was filtered over celite. The filtrate was concentrated under reduce pressure to afford 1-[2-(morpholin-4-yl)ethyl]piperazin-2-one as a yellow solid.

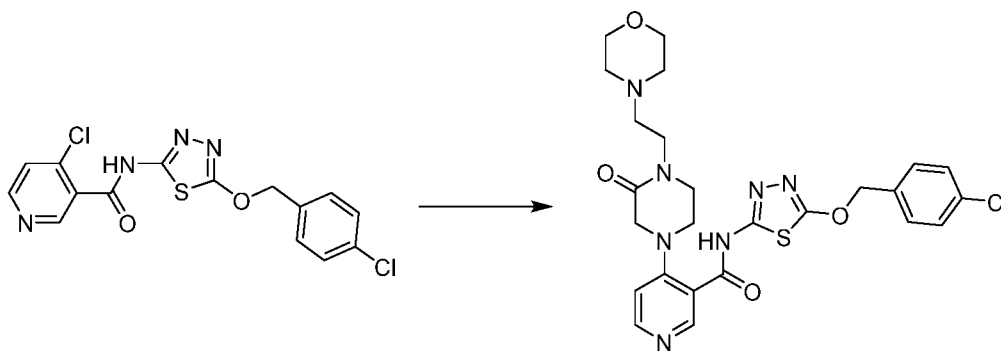
Step 3. Preparation of 4-chloro-N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]pyridine-3-carboxamide



[0333] A solution of 4-chloropyridine-3-carboxylic acid (2.0 g, 12.7 mmol) in SOCl₂ (20 mL) was stirred at 85 °C for 3 h under nitrogen. The mixture cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in DCM (20 mL) and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (3.1 g, 12.7 mmol, Intermediate B) and Et₃N (2.6 g, 25.4 mmol) were added under nitrogen. The mixture was stirred for 3 h at room temperature.

The mixture was diluted with water and extracted with EtOAc (3 x). The combined organic layers were concentrated under reduced pressure. The residue was triturated with EtOAc to afford 4-chloro-N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]pyridine-3-carboxamide as a yellow solid.

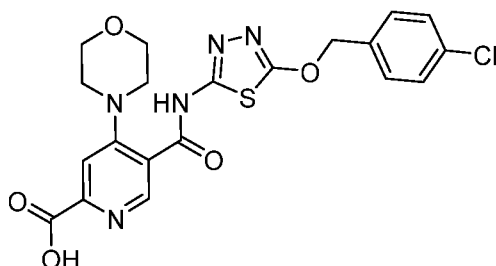
Step 4. Preparation of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-4-[4-[2-(morpholin-4-yl)ethyl]-3-oxopiperazin-1-yl]pyridine-3-carboxamide



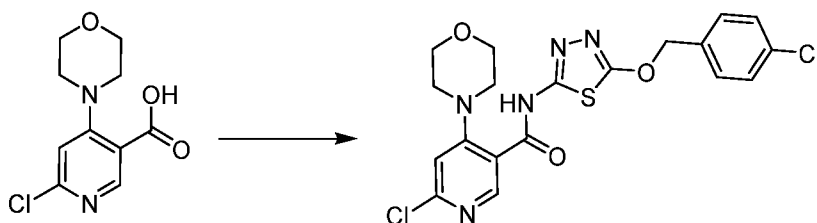
[0334] To a solution of 1-[2-(morpholin-4-yl)ethyl]piperazin-2-one (180 mg, 0.84 mmol, Step 2) in MeCN (2 mL) was added 4-chloro-N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]pyridine-3-carboxamide (322 mg, 0.84 mmol, Step 3), DIEA (218 mg, 1.7 mmol) under nitrogen. The mixture was stirred at 80 °C for 6 h. The mixture was cooled room temperature and diluted with water. The mixture was extracted with EtOAc (3 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 5:1) to afford N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-4-[4-[2-(morpholin-4-yl)ethyl]-3-oxopiperazin-1-yl]pyridine-3-carboxamide as a white solid. ¹H NMR (300 MHz; DMSO-d₆): δ 2.35-2.39 (m, 4H), 2.42-2.44 (m, 2H), 3.40-3.50 (m, 6H), 3.52 (s, 4H), 3.78 (s, 2H), 5.51 (s, 2H), 6.92-6.97 (m, 1H), 7.48-7.57 (m, 4H), 8.33-8.35 (m, 1H), 8.42 (s, 1H), 12.80-13.03 (br s, 1H) ppm. *m/z* 558 (M+H⁺).

Example 84

Synthesis of 5-((5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)carbamoyl)-4-morpholinopicolinic acid

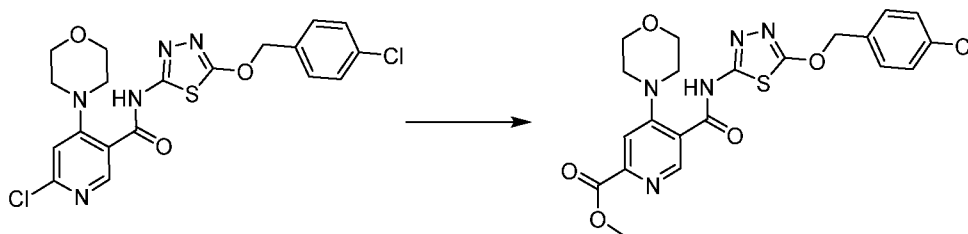


Step 1. Preparation of 6-chloro-N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(morpholin-4-yl)pyridine-3-carboxamide



[0335] The title compound was prepared using General Procedure A employing 6-chloro-4-(morpholin-4-yl)pyridine-3-carboxylic acid (Example 35, Step 1) and 5-((4-chlorobenzyl)-oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was diluted with EtOAc and washed with water (2 x). The organic layer was concentrated under reduced pressure. The residue was re-crystallized from MeOH/water (10:1) to afford 6-chloro-N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(morpholin-4-yl)pyridine-3-carboxamide as a white solid.

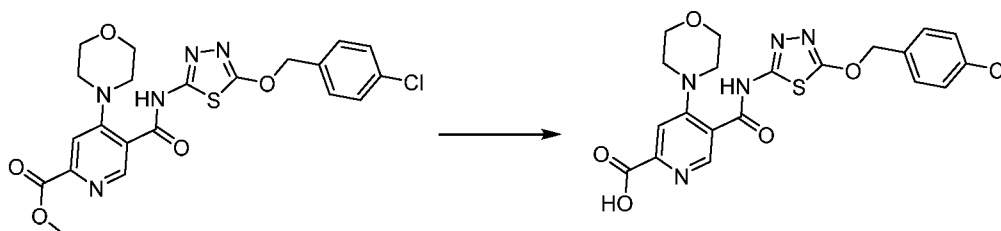
Step 2. Preparation of methyl 5-((5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)carbamoyl)-4-morpholinopicolinate



[0336] To a solution of 6-chloro-N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(morpholin-4-yl)pyridine-3-carboxamide (5.0 g, 10.7 mmol) in MeOH (300) was added Et₃N (2.2 g, 21.4 mmol), Xantphos (0.3 g, 0.54 mmol) and Pd(dppf)Cl₂ (0.4 g, 0.54 mmol) at room temperature. The mixture was stirred at 80 °C for 12 h under 30 atm of carbon monoxide. The mixture was cooled to room temperature and diluted with EtOAc (500 mL). The resulting

mixture was washed with water (3 x). The organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 0.3% MeOH in DCM to afford methyl 5-((5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)carbamoyl)-4-morpholinopicolinate as a white solid.

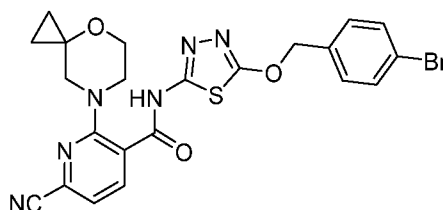
Step 3. Preparation of 5-((5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)carbamoyl)-4-morpholinopicolinic acid



[0337] To a solution of methyl 5-((5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)carbamoyl)-4-morpholinopicolinate (1.2 g, 2.5 mmol) in MeOH (7 mL) and H₂O (7 mL) was added NaOH (0.2 g, 5.1 mmol). The mixture was stirred for 1 h at room temperature. The mixture was acidified to pH 7 with HCl (1 M). The mixture was extracted with EtOAc (3 x). The combined organic layers were concentrated under reduced pressure. The residue was re-crystallized from (MeOH:water, 12:1) to afford 5-((5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)carbamoyl)-4-morpholinopicolinic acid as an off-white solid. ¹H NMR (300 MHz; DMSO-*d*₆): δ 3.24-3.26 (m, 4H), 3.65-3.68 (m, 4H), 5.49 (s, 2H), 7.47-7.56 (m, 5H), 8.44 (s, 1H) ppm. *m/z* 476 (M+H⁺).

Example 85

Synthesis of N-(5-((4-bromobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-2-(4-oxa-7-azaspiro[2.5]octan-7-yl)nicotinamide

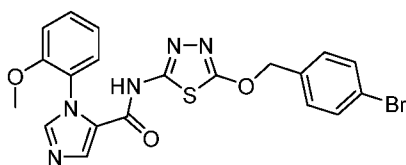


[0338] The title compound was prepared using General Procedure A employing 6-cyano-2-(4-oxa-7-azaspiro[2.5]octan-7-yl)nicotinic acid (Example 44, Step 1) and 5-((4-bromobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Example 40, Step 1). The mixture was diluted with EtOAc washed

with water (2 x). The organic layer was concentrated under reduced pressure. The residue was triturated with MeOH to afford N-(5-((4-bromobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-2-(4-oxa-7-azaspiro[2.5]octan-7-yl)nicotinamide as a yellow solid. ^1H NMR (300 MHz; DMSO- d_6): δ 0.48-0.55 (m, 2H), 0.60-0.69 (m, 2H), 3.35-3.38 (m, 4H), 3.68-3.71 (m, 2H), 5.49 (s, 2H), 7.47-7.49 (m, 3H), 7.61-7.64 (m, 2H), 8.00-8.02 (m, 1H), 13.03 (s, 1H) ppm. m/z 527 ($\text{M}+\text{H}^+$).

Example 86

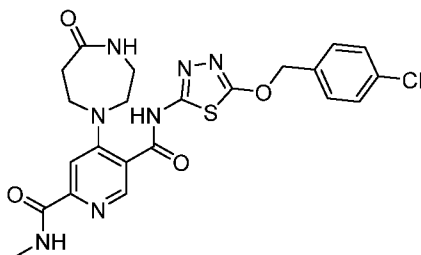
Synthesis of N-(5-((4-bromobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(2-methoxyphenyl)-1H-imidazole-5-carboxamide



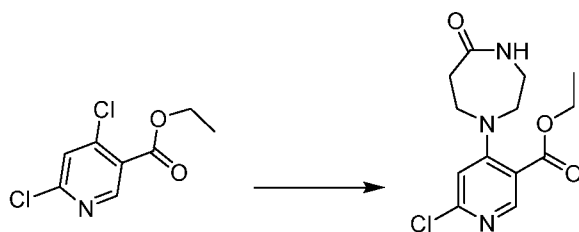
[0339] The title compound was prepared using similar procedure as Example 18, replacing 4-aminopyridine with 2-methoxyaniline in Step 1 and employing 5-((4-bromobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Example 40, Step 1) in Step 2. The mixture was diluted with water and extracted with EtOAc (2 x). The combined organic layers were concentrated under reduced pressure. The residue was triturated with MeOH to afford N-(5-((4-bromobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(2-methoxyphenyl)-1H-imidazole-5-carboxamide as a pink solid. ^1H NMR (300 MHz; DMSO- d_6): δ 3.68 (s, 3H), 5.44 (s, 2H), 7.03-7.08 (m, 1H), 7.16-7.19 (m, 1H), 7.35-7.38 (m, 1H), 7.43-7.48 (m, 3H), 7.59-7.62 (m, 2H), 7.98 (s, 1H), 8.10 (s, 1H), 12.71 (s, 1H) ppm. m/z 486 ($\text{M}+\text{H}^+$).

Example 87

Synthesis of N⁵-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-N²-methyl-4-(5-oxo-1,4-diazepan-1-yl)pyridine-2,5-dicarboxamide

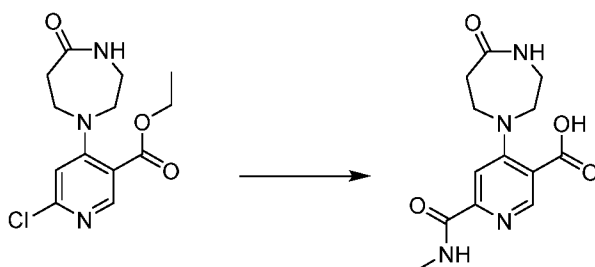


Step 1. Preparation of ethyl 6-chloro-4-(5-oxo-1,4-diazepan-1-yl)nicotinate



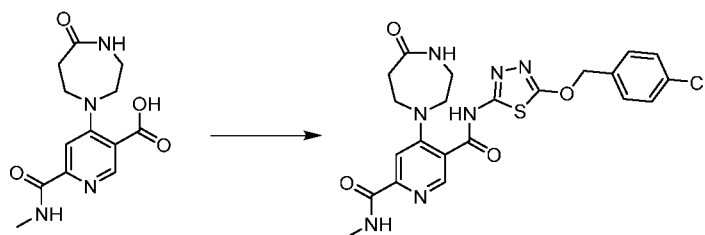
[0340] The title compound was prepared using similar procedure as Example 35, Step 1 replacing morpholine with 1,4-diazepan-5-one.

Step 2. Preparation of 6-(methylcarbamoyl)-4-(5-oxo-1,4-diazepan-1-yl)nicotinic acid



[0341] The title compound was prepared using similar procedure as Example 64, Steps 1 and 2, replacing ethyl 6-chloro-4-(morpholin-4-yl)pyridine-3-carboxylate in Step 1 with ethyl 6-chloro-4-(5-oxo-1,4-diazepan-1-yl)nicotinate.

Step 3. Preparation of N⁵-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-N2-methyl-4-(5-oxo-1,4-diazepan-1-yl)pyridine-2,5-dicarboxamide

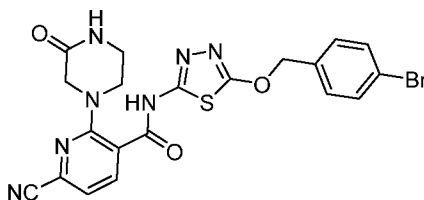


[0342] The title compound was prepared using General Procedure D employing 6-(methylcarbamoyl)-4-(5-oxo-1,4-diazepan-1-yl)nicotinic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was stirred overnight at room temperature. The mixture was diluted with EtOAc and washed with water (3 x). The aqueous layer was extracted with EtOAc (3 x). The combined organic layers were concentrated under reduce pressure and residue was purified by Prep-TLC (DCM:MeOH, 20:1) to afford N⁵-(5-((4-

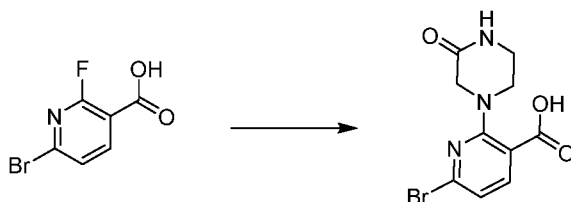
chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)- N2-methyl-4-(5-oxo-1,4-diazepan-1-yl)pyridine-2,5-dicarboxamide as a white solid. ^1H NMR (400 MHz; DMSO- d_6): δ 2.62-2.68 (m, 2H), 2.80-2.82 (m, 3H), 3.29-3.34 (m, 4H), 3.50-3.51 (m, 2H), 5.51 (s, 2H), 7.49-7.61 (m, 6H), 8.42 (s, 1H), 8.79-8.81 (m, 1H), 12.96 (s, 1H) ppm. m/z 516 ($\text{M}+\text{H}^+$).

Example 88

Synthesis of N-(5-((4-bromobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-2-(3-oxopiperazin-1-yl)nicotinamide

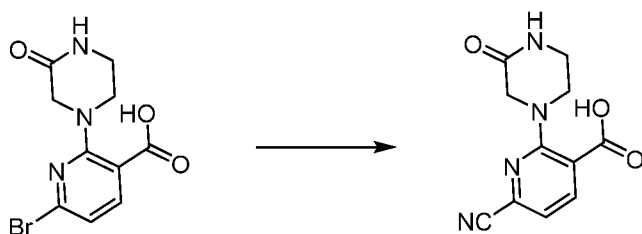


Step 1. Preparation of 6-bromo-2-(3-oxopiperazin-1-yl)nicotinic acid



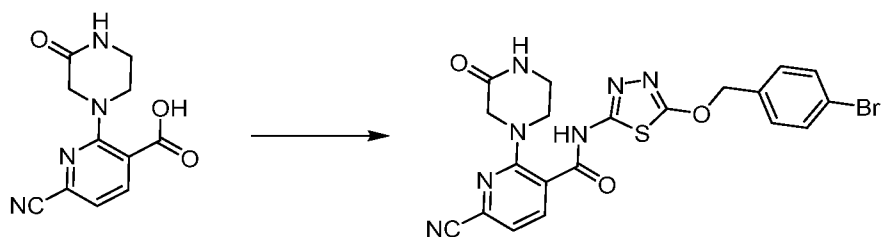
[0343] The title compound was prepared using similar procedure as Example 14, Step 1 replacing morpholine with piperazin-2-one

Step 2. Preparation of 6-cyano-2-(3-oxopiperazin-1-yl)pyridine-3-carboxylic acid



[0344] The title compound was prepared using similar procedure as Example 35, Step 2 replacing 6-chloro-4-(morpholin-4-yl)pyridine-3-carboxylic acid with 6-bromo-2-(3-oxopiperazin-1-yl)nicotinic acid

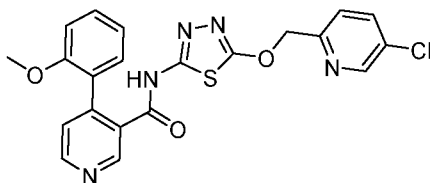
Step 3. Preparation of N-(5-((4-bromobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-2-(3-oxopiperazin-1-yl)nicotinamide



[0345] The title compound was prepared using General Procedure A employing 6-cyano-2-(3-oxopiperazin-1-yl)pyridine-3-carboxylic acid and 5-((4-bromobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Example 40, Step 1). The mixture was diluted with EtOAc and washed with water (2 x). The organic layer was concentrated under reduce pressure. The residue was triturated with MeOH to afford N-(5-((4-bromobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-2-(3-oxopiperazin-1-yl)nicotinamide as a yellow solid. ^1H NMR (400 MHz; DMSO- d_6): δ 3.24-3.28 (m, 2H), 3.52-3.54 (m, 2H), 3.81 (s, 2H), 5.49 (s, 2H), 7.46-7.52 (m, 3H), 7.58-7.64 (m, 2H), 8.02-8.04 (m, 1H), 8.12 (s, 1H), 13.10 (s, 1H) ppm. m/z 514 ($\text{M}+\text{H}^+$).

Example 89

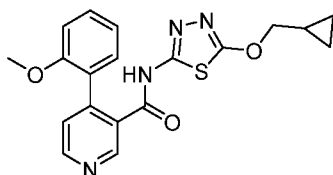
Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)nicotinamide



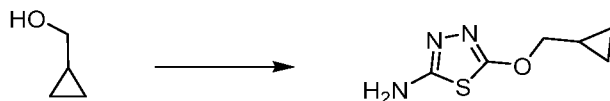
[0346] The title compound was prepared using similar procedure as Example 77, replacing 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) with 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C). ^1H NMR (300 MHz; DMSO- d_6): δ 3.52 (s, 3H), 5.54 (s, 2H), 6.98-7.01 (m, 1H), 7.05-7.10 (m, 1H), 7.34-7.44 (m, 3H), 7.59-7.62 (m, 1H), 7.98-8.02 (m, 1H), 8.65-8.66 (m, 1H), 8.74-8.79 (m, 2H), 12.82 (s, 1H) ppm. m/z 454 ($\text{M}+\text{H}^+$).

Example 90

Synthesis of N-(5-(cyclopropylmethoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)nicotinamide

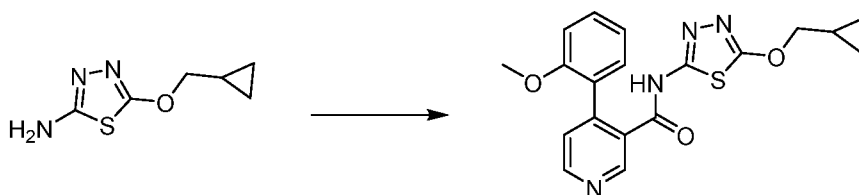


Step 1. Preparation of 5-(cyclopropylmethoxy)-1,3,4-thiadiazol-2-amine



[0347] The title compound was prepared using similar procedure as Intermediate A, replacing (4-fluorophenyl)methanol with cyclopropylmethanol in Step 1.

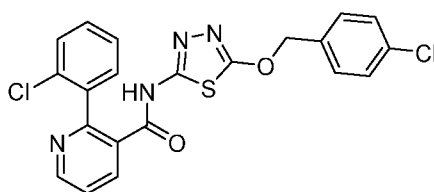
Step 2. Preparation of N-(5-(cyclopropylmethoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)nicotinamide



[0348] The title compound was prepared using General Procedure A employing 5-(cyclopropylmethoxy)-1,3,4-thiadiazol-2-amine and 4-(2-methoxyphenyl)pyridine-3-carboxylic acid (Example 77). The mixture was diluted with water and extracted with EtOAc (2 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 20:1). The residue was further purified by trituration with MeOH to afford N-(5-(cyclopropylmethoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)nicotinamide as a white solid. ^1H NMR (300 MHz; CD_3OD): δ 0.38-0.41 (m, 2H), 0.68-0.69 (m, 2H), 1.31-1.40 (m, 1H), 3.00 (s, 1H), 3.63 (s, 3H), 4.25-4.31 (m, 2H), 6.98-7.01 (m, 1H), 7.07-7.12 (m, 1H), 7.39-7.42 (m, 2H), 7.45-7.50 (m, 1H), 8.71-8.72 (m, 1H), 8.79 (s, 1H) ppm. m/z 383 ($\text{M}+\text{H}^+$).

Example 91

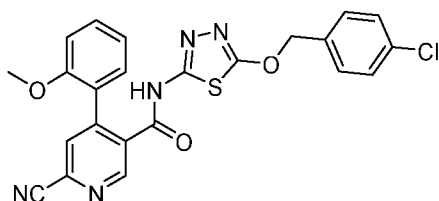
Synthesis of Synthesis of 2-(2-chlorophenyl)-N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]pyridine-3-carboxamide



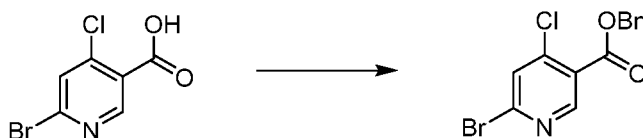
[0349] The title compound was prepared using similar procedure as Example 51 employing 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). ^1H NMR (300 MHz; DMSO- d_6): δ 5.54 (s, 2H), 7.40-7.49 (m, 8H), 7.58-7.63 (m, 1H), 8.20-8.23 (m, 1H), 8.81-8.83 (m, 1H), 13.00 (s, 1H) ppm. m/z 457 ($M+H^+$).

Example 92

N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-4-(2-methoxyphenyl)nicotinamide

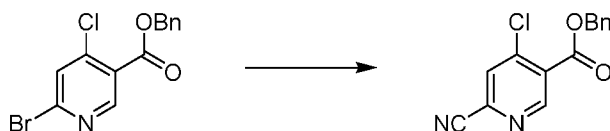


Step 1. Preparation of benzyl 6-bromo-4-chloropyridine-3-carboxylate



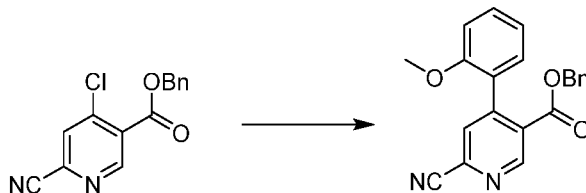
[0350] To a solution of 6-bromo-4-chloropyridine-3-carboxylic acid (1.5 g, 6.3 mmol) in DMF (20 mL) was added (bromomethyl)benzene (1.2 g, 7.0 mmol), K_2CO_3 (1.8 g, 12.7 mmol). The mixture was stirred at 60 °C for 10 min. The mixture was cooled to room temperature, diluted with water and extracted with EtOAc. The combined organic layers were concentrated under reduced pressure and the residue was purified by silica gel column chromatography, eluted with 8% EtOAc in hexane to afford benzyl 6-bromo-4-chloropyridine-3-carboxylate as a white solid.

Step 2. Preparation of benzyl 4-chloro-6-cyanopyridine-3-carboxylate



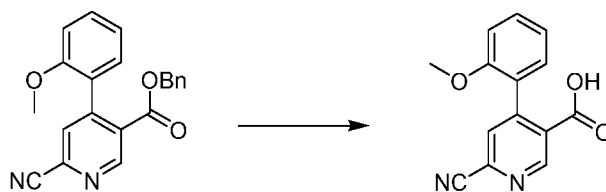
[0351] The title compound was prepared using similar procedure as Example 33, Step 2 replacing methyl 5-bromo-2-morpholinonicotinate with benzyl 6-bromo-4-chloropyridine-3-carboxylate.

Step 3. Preparation of benzyl 6-cyano-4-(2-methoxyphenyl)pyridine-3-carboxylate



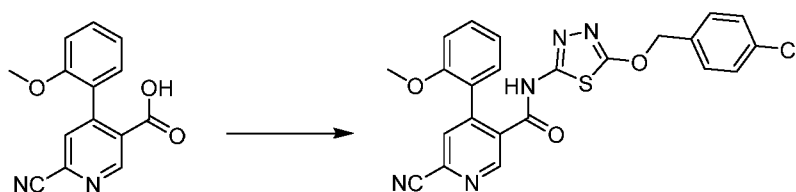
[0352] The title compound was prepared using similar procedure as Example 67, Step 1, replacing methyl 2-chloropyridine-3-carboxylate with benzyl 4-chloro-6-cyanopyridine-3-carboxylate in Step 1.

Step 4. Preparation of 6-cyano-4-(2-methoxyphenyl)pyridine-3-carboxylic acid



[0353] To a solution of benzyl 6-cyano-4-(2-methoxyphenyl)pyridine-3-carboxylate (530 mg, 1.5 mmol) in THF (12 mL) was added 10% Pd/C (106 mg). The mixture was stirred under hydrogen at room temperature for 6 h. The mixture was filtered over celite and the filtrate was concentrated under reduced pressure to afford 6-cyano-4-(2-methoxyphenyl)pyridine-3-carboxylic acid as an off-white solid.

Step 5. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-4-(2-methoxyphenyl)nicotinamide

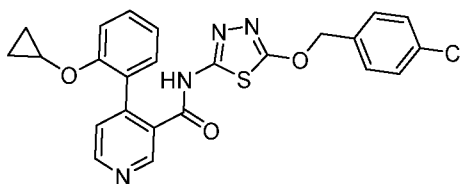


[0354] The title compound was prepared using General Procedure D employing 6-cyano-4-(2-methoxyphenyl)pyridine-3-carboxylic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-

amine (Intermediate B). The mixture was stirred at room temperature overnight and diluted with water. The mixture was extracted with EtOAc (2 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 12:1) to afford N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-4-(2-methoxyphenyl)nicotinamide as a light yellow solid. ^1H NMR (300 MHz; DMSO- d_6): δ 3.54 (s, 3H), 5.48 (s, 2H), 7.02-7.13 (m, 2H), 7.42-7.55 (m, 6H), 8.14 (s, 1H), 8.96 (s, 1H), 13.07 (s, 1H) ppm. m/z 478 ($\text{M}+\text{H}^+$).

Example 93

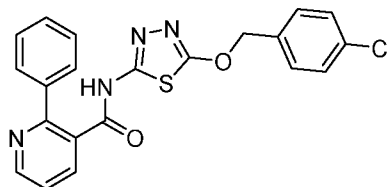
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-(2-cyclopropoxyphenyl)nicotinamide



[0355] The title compound was prepared using similar procedure as Example 77, replacing 2-methoxyphenylboronic acid with 2-(2-cyclopropoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. ^1H NMR (300 MHz; DMSO- d_6): δ 0.32-0.55 (m, 4H), 3.49-3.57 (m, 1H), 5.53 (s, 2H), 7.06-7.10 (m, 1H), 7.17-7.66 (m, 8H), 8.70-8.80 (m, 2H), 12.66-12.96 (br s, 1H) ppm. m/z 479 ($\text{M}+\text{H}^+$).

Example 94

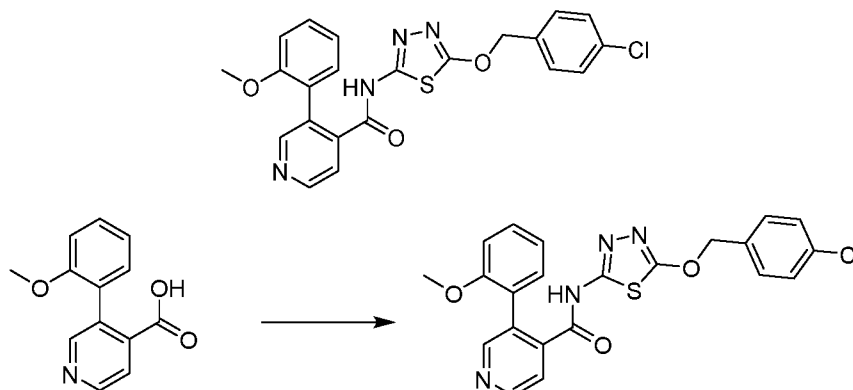
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-phenylnicotinamide



[0356] The title compound was prepared using similar procedure as Example 67, replacing 2-methoxyphenylboronic acid in Step 1 with phenyl boronic acid. ^1H NMR (400 MHz; DMSO- d_6): δ 5.48 (s, 2H), 7.38 (s, 3H), 7.40-7.58 (m, 7H), 8.05-8.08 (m, 1H), 8.79-8.81 (m, 1H), 12.88 (s, 1H) ppm. m/z 423 ($\text{M}+\text{H}^+$).

Example 95

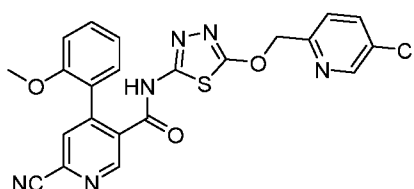
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(2-methoxyphenyl)isonicotinamide



[0357] The title compound was prepared using General Procedure A employing 3-(2-methoxyphenyl) pyridine-4-carboxylic acid (Intermediate H) and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was diluted with water and extracted with EtOAc (2 x). The combined organic layers were concentrated under reduced pressure. The residue was triturated with MeOH to afford *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(2-methoxyphenyl)isonicotinamide as an off-white solid. ^1H NMR (300 MHz; DMSO- d_6): δ 3.51 (s, 3H), 5.47 (s, 2H), 6.97-7.00 (m, 1H), 7.04-7.09 (m, 1H), 7.35-7.41 (m, 2H), 7.47-7.54 (m, 4H), 7.62-7.63 (m, 1H), 8.61 (s, 1H), 8.70-8.72 (m, 1H), 12.84 (s, 1H) ppm. m/z 453 ($M+H^+$).

Example 96

Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-6-cyano-4-(2-methoxyphenyl)nicotinamide

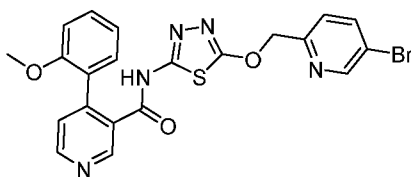


[0358] The title compound was prepared using General Procedure D employing 6-cyano-4-(2-methoxyphenyl)pyridine-3-carboxylic acid (Example 92, Step 4) and 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C). The mixture was stirred at room

temperature overnight and diluted with water. The mixture was extracted with EtOAc (2 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 12:1) to afford N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-6-cyano-4-(2-methoxyphenyl)nicotinamide as a white solid. ¹H NMR (300 MHz; DMSO-d₆): δ 3.54 (s, 3H), 5.54 (s, 2H), 7.02-7.12 (m, 2H), 7.42-7.47 (m, 2H), 7.59-7.62 (m, 1H), 7.98-8.02 (m, 1H), 8.13 (s, 1H), 8.64-8.65 (m, 1H), 8.96 (s, 1H), 13.08 (s, 1H) ppm. *m/z* 479 (M+H⁺).

Example 97

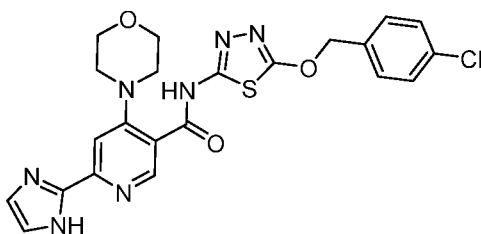
Synthesis of N-(5-((5-bromopyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)nicotinamide



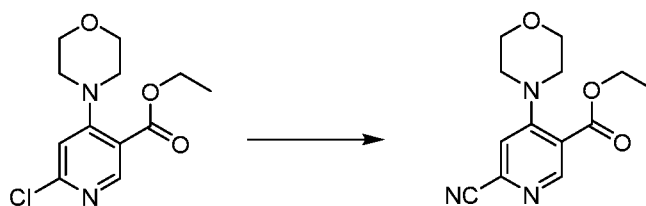
[0359] The title compound was prepared using similar procedure as Example 77, replacing 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) with 5-((5-bromopyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Example 15, Step 1). ¹H NMR (300 MHz; DMSO-d₆): δ 3.52 (s, 3H), 5.52 (s, 2H), 6.98-7.01 (m, 1H), 7.05-7.10 (m, 1H), 7.34-7.44 (m, 3H), 7.53-7.56 (m, 1H), 8.11-8.14 (m, 1H), 8.73-8.76 (m, 2H), 8.79 (s, 1H), 12.84 (s, 1H) ppm. *m/z* 498 (M+H⁺).

Example 98

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-(1H-imidazol-2-yl)-4-morpholinonicotinamide

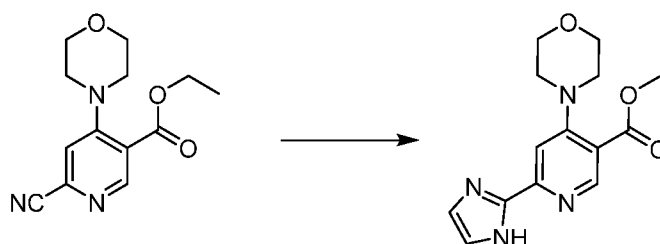


Step 1. Preparation of ethyl 6-cyano-4-(morpholin-4-yl)pyridine-3-carboxylate



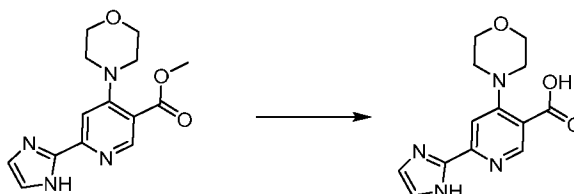
[0360] The title compound was prepared using similar procedure as Example 35, Steps 2 replacing 6-chloro-4-(morpholin-4-yl)pyridine-3-carboxylic acid with ethyl 6-chloro-4-(morpholin-4-yl)pyridine-3-carboxylate.

Step. Preparation of methyl 6-(1H-imidazol-2-yl)-4-morpholinonicotinate



[0361] To a solution of ethyl 6-cyano-4-(morpholin-4-yl)pyridine-3-carboxylate (360 mg, 1.38 mmol) in MeOH (4 mL) was added NaOMe (15 mg, 0.28 mmol). The mixture was stirred at 50 °C for 1.5 h, then HOAc (147 mg, 2.4 mmol) and 2,2-dimethoxyethanamine (1289 mg, 1.2 mmol) were added. The mixture was stirred at 50 °C for 2 h. Then HCl (133.97 mg, 3.7 mmol, concentrated) was added. The mixture was stirred at 50 °C for 13 h. The mixture was cooled to room temperature and diluted with sat. NaHCO₃ (10 mL). The mixture was extracted with EtOAc (4 x) and the combined organic layers were concentrated under reduce pressure. The residue was purified by Prep-TLC (DCM:MeOH, 30:1) to afford methyl 6-(1H-imidazol-2-yl)-4-morpholinonicotinate as a white solid.

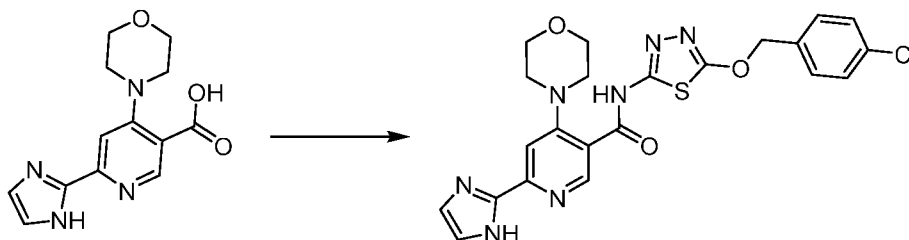
Step 2. Preparation of 6-(1H-imidazol-2-yl)-4-morpholinonicotinic acid



[0362] The title compound was prepared using General Procedure F employing methyl 6-(1H-imidazol-2-yl)-4-morpholinonicotinate. The mixture was stirred overnight at room temperature

and then acidified to pH 6 with HCl (1M). The mixture was concentrated and the residue was purified by reverse phase chromatography (column, C₁₈ silica gel; mobile phase, 0 – 50% MeCN in water) to afford 6-(1H-imidazol-2-yl)-4-morpholinonicotinic acid as a white solid.

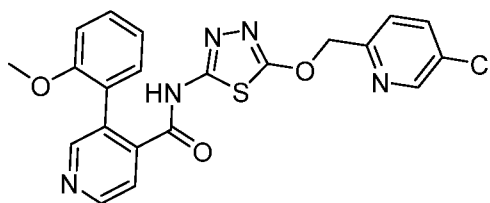
Step 3. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-(1H-imidazol-2-yl)-4-morpholinonicotinamide



[0363] The title compound was prepared using General Procedure A employing 6-(1H-imidazol-2-yl)-4-morpholinonicotinic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was diluted with EtOAc and washed with water (3 x). The organic layer was concentrated under reduced pressure and the residue was triturated with MeOH to afford in N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-(1H-imidazol-2-yl)-4-morpholinonicotinamide as a light yellow solid. ¹H NMR (300 MHz; DMSO-d₆): δ 3.17 (s, 4H), 3.69-3.70 (m, 4H), 5.51 (s, 2H), 7.19 (s, 2H), 7.48-7.61 (m, 5H), 8.51 (s, 1H), 12.81-12.93 (m, 2H) ppm. *m/z* 498 (M+H⁺).

Example 99

Synthesis of *N*-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-3-(2-methoxyphenyl)pyridine-4-carboxamide

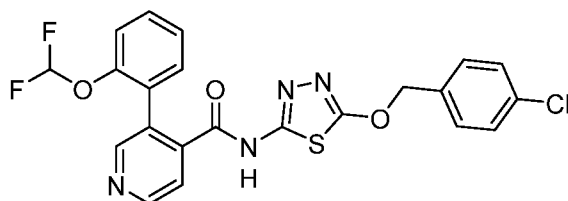


[0364] The title compound was prepared using General Procedure A employing 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C) and 3-(2-methoxyphenyl)pyridine-4-carboxylic acid (Intermediate H). The mixture was diluted with water and extracted with EtOAc (3x). The combined organic layers were dried over Na₂SO₄ and

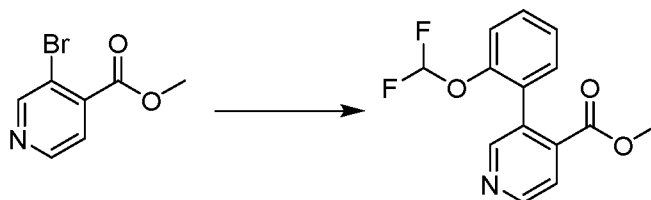
concentrated under reduced pressure. The residue was triturated with EtOAc (2x) to give the title compound. ^1H NMR (300 MHz; DMSO- d_6): δ 12.91 (s, 1H), 8.72-8.61 (m, 3H), 8.00 (d, 1H), 7.65-7.60 (m, 2H), 7.42-7.36 (m, 2H), 7.10-6.99 (m, 2H), 5.55 (s, 2H), 3.52 (s, 3H) ppm. m/z 454 ($M+H^+$).

Example 100

Synthesis of *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(2-(difluoromethoxy)phenyl)isonicotinamide

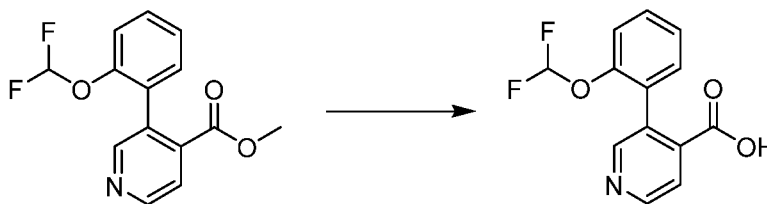


Step 1. Preparation of methyl 3-[2-(difluoromethoxy)phenyl]pyridine-4-carboxylate



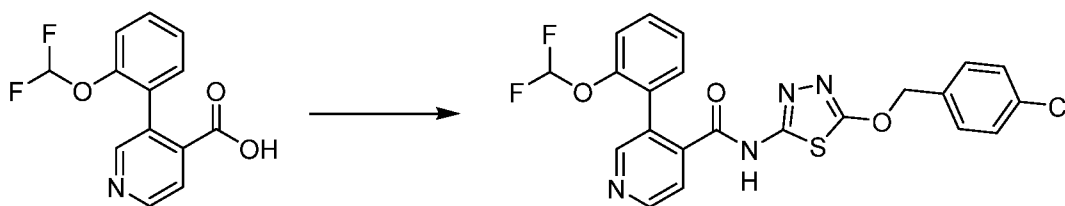
[0365] The title compound was prepared using General Procedure E employing methyl 3-bromopyridine-4-carboxylate and 2-(difluoromethoxy)phenylboronic acid. The mixture was stirred at 80 °C for 1 h. The mixture was cooled to rt and diluted with EtOAc. The mixture was washed with water (3x). The organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 50% EtOAc in PE to afford the title compound as a yellow oil.

Step 2. Preparation of 3-[2-(difluoromethoxy)phenyl]pyridine-4-carboxylic acid



[0366] The title compound was prepared using General Procedure F employing methyl 3-[2-(difluoromethoxy)phenyl]pyridine-4-carboxylate. The mixture was stirred at 50 °C for 3 h. The mixture was diluted with water and washed with EtOAc. 2 M HCl was added to the aqueous layer to adjust the pH to 5-6. The precipitate was filtered and the solid was dried in an oven to afford the title compound as a white solid. The residue was purified by Prep-TLC (DCM:MeOH, 20:1) to afford the title compound as a white solid.

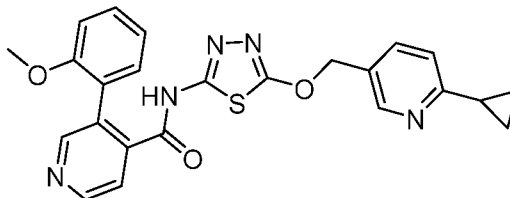
Step 3. Preparation of *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(2-(difluoromethoxy)phenyl)isonicotinamide



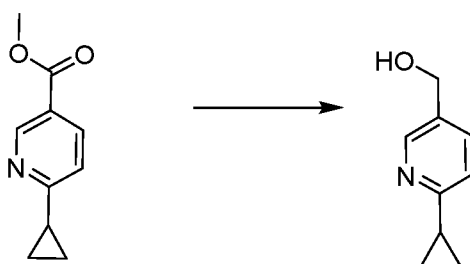
[0367] The title compound was prepared using General Procedure A employing 3-[2-(difluoromethoxy)phenyl]pyridine-4-carboxylic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was diluted with EtOAc and washed with water (2x). The organic layer was concentrated under reduced pressure. ¹H NMR (300 MHz; DMSO-d₆): δ 13.06 (s, 1H), 8.78 (d, 1H), 8.63 (s, 1H), 7.74 (d, 1H), 7.51 - 7.42 (m, 6H), 6.80-7.35 (m, 3H), 5.47 (s, 2H) ppm. m/z 489 (M+H⁺).

Example 101

Synthesis of *N*-[5-[(6-cyclopropylpyridin-3-yl)methoxy]-1,3,4-thiadiazol-2-yl]-3-(2-methoxyphenyl)pyridine-4-carboxamide

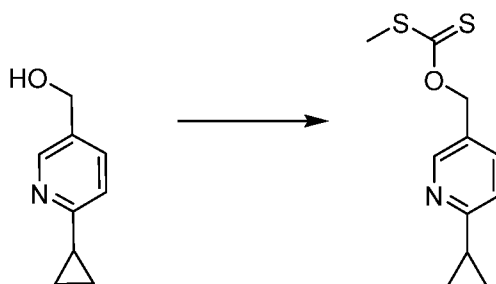


Step 1. Preparation of (6-cyclopropylpyridin-3-yl)methanol



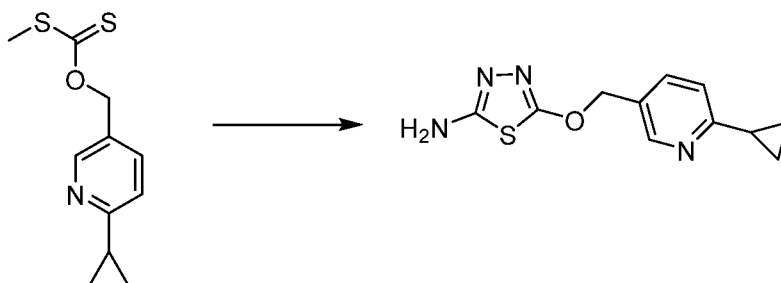
[0368] To a solution of methyl 6-cyclopropylpyridine-3-carboxylate (2.0 g, 11.3 mmol) in THF (20 mL) at 0 °C was added LiAlH₄ (0.86 g, 22.660 mmol, 2.01 equiv). The mixture was stirred at 0 °C for 1 h. The mixture was warmed to rt and a solution of NH₄Cl (aq.) was added. The mixture was extracted with EtOAc (3 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 25% EtOAc in PE to afford the title compound (1.4 g, 79% yield) as a yellow liquid.

Step 2. Preparation of [(6-cyclopropylpyridin-3-yl)methoxy](methylsulfanyl)methanethione



[0369] The title compound was prepared using similar procedure as Intermediate A, Step 1, replacing (4-fluorophenyl)methanol with (6-cyclopropylpyridin-3-yl)methanol.

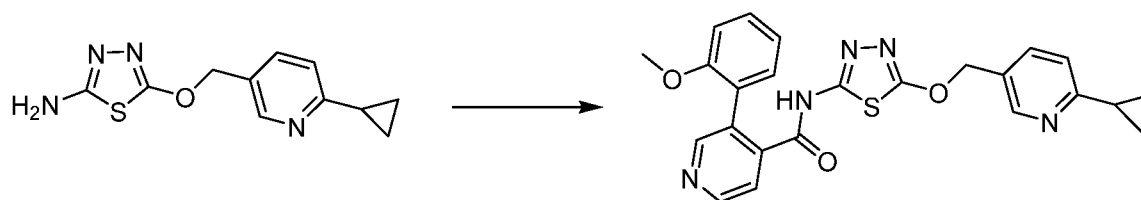
Step 3. Preparation of 5-[(6-cyclopropylpyridin-3-yl)methoxy]-1,3,4-thiadiazol-2-amine



[0370] To a solution of [(6-cyclopropylpyridin-3-yl)methoxy](methylsulfanyl)methanethione (920 mg, 3.8 mmol) in MeOH (10 mL) at 0 °C was added hydrazine hydrate (196 mg, 3.9 mmol). The mixture was stirred at 0 °C for 0.5 h. The mixture was filtered and the solid was washed

with MeOH (2 x). The filtrate was concentrated under reduced pressure to afford a white solid. The solid was diluted with MeOH (7 mL) cooled to 0 °C. Then Et₃N (625 mg, 6.2 mmol) and BrCN (393 mg, 3.7 mmol) were added. The mixture was stirred at 0 °C for 1 h. The mixture was filtered and the solid was washed with MeOH (2 x) to give the title compound as a yellow solid.

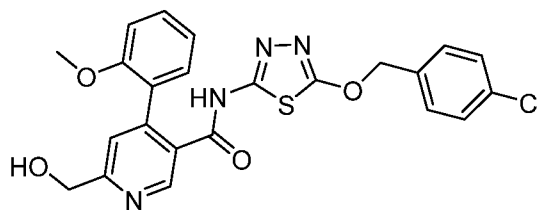
Step 4. Preparation of *N*-[5-[(6-cyclopropylpyridin-3-yl)methoxy]-1,3,4-thiadiazol-2-yl]-3-(2-methoxyphenyl)pyridine-4-carboxamide



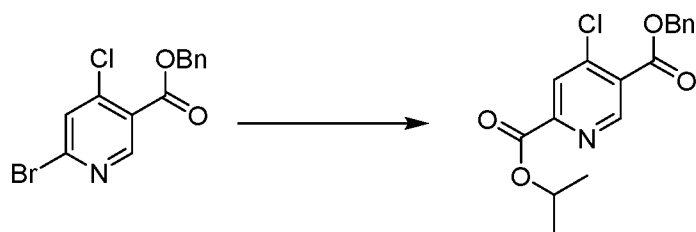
[0371] The title compound was prepared using General Procedure A employing 3-(2-methoxyphenyl) pyridine-4-carboxylic acid (Intermediate H) and 5-[(6-cyclopropylpyridin-3-yl)methoxy]-1,3,4-thiadiazol-2-amine. The mixture was stirred for 1 h at rt. The mixture was diluted with EtOAc and washed with water (2 x). The organic layer was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 20:1) to afford the title compound as a white solid. ¹H NMR (300 MHz; DMSO-d₆): δ 12.87 (s, 1H), 8.71 (d, 1H), 8.60 (s, 1H), 8.52 - 8.51 (m, 1H), 7.79-7.76 (m, 1H), 7.63 (d, 1H), 7.37-7.32 (m, 3H), 7.09-7.06 (m, 1H), 6.98 (d, 1H), 5.44 (s, 2H), 3.51 (s, 3H), 2.11-2.07 (m, 1H), 0.98 -0.90 (m, 4H) ppm. m/z 460 (M+H⁺).

Example 102

Synthesis of *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-(hydroxymethyl)-4-(2-methoxyphenyl)nicotinamide

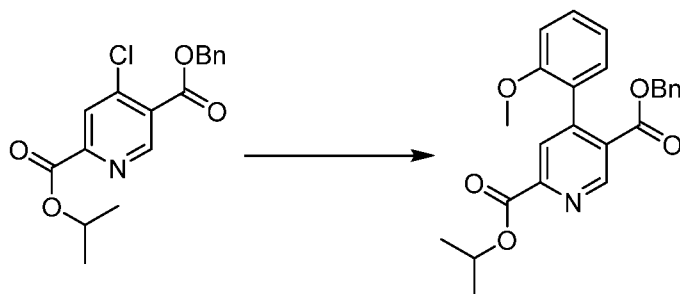


Step 1: Preparation of 5-benzyl 2-isopropyl 4-chloropyridine-2,5-dicarboxylate



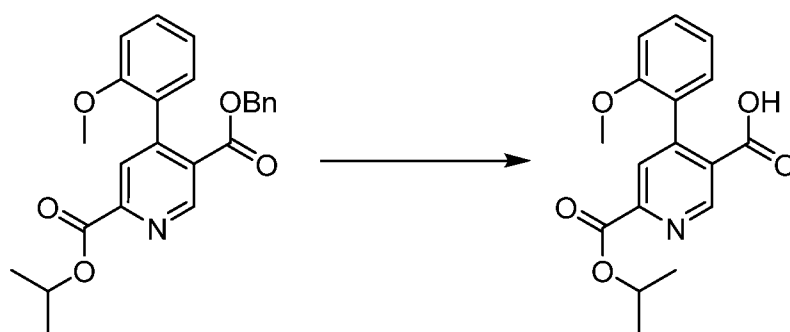
[0372] A solution of benzyl 6-bromo-4-chloropyridine-3-carboxylate (8.0 g, 24.5 mmol), Et₃N (5.0 g, 49.0 mmol) and Pd(dppf)Cl₂ (2.7 g, 3.7 mmol) in propan-2-ol (1.50 L) was added to 2L pressure tank reactor. Mixture was purged with CO (30 atm) and stirred at 60 °C overnight under atmosphere of CO (30 atm). The mixture was diluted with water and extracted with DCM (3x). The combined organic layers were concentrated and the residue was purified by silica gel column chromatography, eluted with 9% EtOAc in hexanes to afford the title compound (6.8 g, 75% yield) as a white solid.

Step 2: Preparation of 5-benzyl 2-isopropyl 4-(2-methoxyphenyl)pyridine-2,5-dicarboxylate



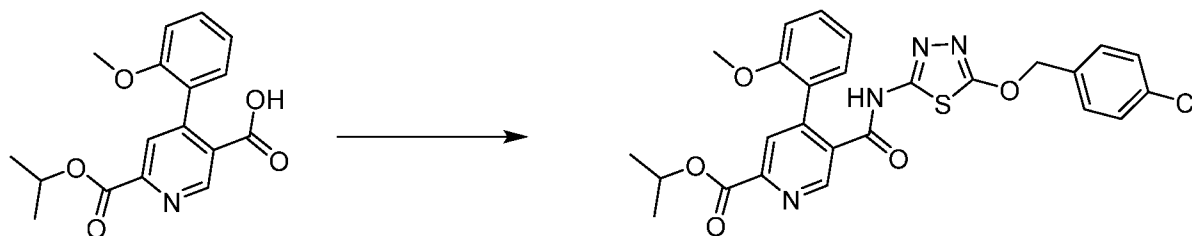
[0373] The title compound was prepared using General Procedure E employing 5-benzyl 2-isopropyl 4-chloropyridine-2,5-dicarboxylate and 2-methoxyphenylboronic acid. The mixture was diluted with water and extracted with DCM (3x). The combined organic layers were washed with 1 N NaOH (2x), dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 14% EtOAc in PE to the title compound (4.4 g, 49% yield) as a light yellow solid.

Step 3: Preparation of 6-(isopropoxycarbonyl)-4-(2-methoxyphenyl)pyridine-3-carboxylic acid



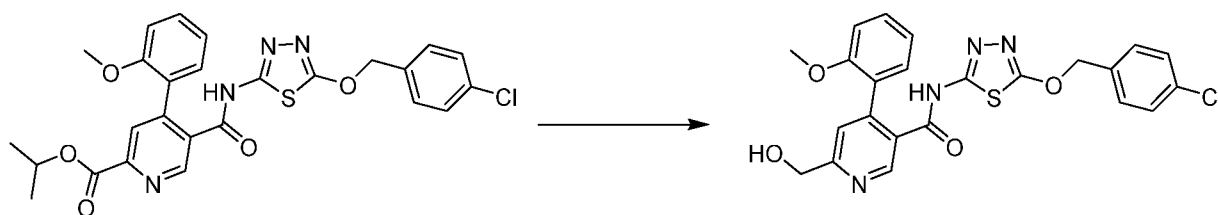
[0374] To a solution of 5-benzyl 2-isopropyl 4-(2-methoxyphenyl)pyridine-2,5-dicarboxylate (4.4 g) in THF (180 mL) was added 10% Pd/C (0.80 g). The mixture was stirred for 2 h at room temperature under the atmosphere of H₂. The mixture was filtered and the filtration was concentrated under reduced pressure to afford the title compound (3.6 g) as a light yellow solid which was used without further purification.

Step 4: Preparation of isopropyl 5-((5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)carbamoyl)-4-(2-methoxyphenyl)picolinate



[0375] A reaction vial was charged with 6-(isopropoxycarbonyl)-4-(2-methoxyphenyl)pyridine-3-carboxylic acid (200 mg, 0.634 mmol), THF (3 mL), 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) (153 mg, 0.634 mmol), DIEA (163 mg, 1.26 mmol) and propylphosphonic anhydride (50 wt. % in EtOAc, 605 mg, 0.951 mmol) at room temperature. The resulting mixture was stirred for 3 h at room temperature under nitrogen atmosphere. The resulting mixture was diluted with water (15 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic extracts were concentrated under vacuum. The crude product was triturated with MeOH (5 mL) to afford the title compound (230 mg, 63% yield) as a white solid.

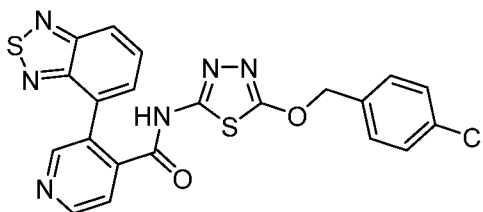
Step 5: Preparation of *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-(hydroxymethyl)-4-(2-methoxyphenyl)nicotinamide



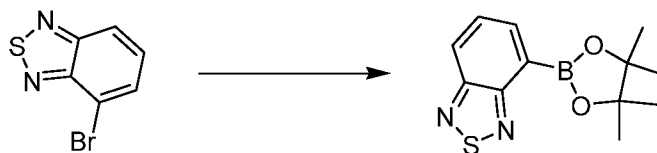
[0376] A round bottom flask was charged with isopropyl 5-((5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)carbamoyl)-4-(2-methoxyphenyl)picolinate (210 mg, 0.390 mmol), MeOH (2 mL, 49 mmol) and NaBH₄ (29 mg, 0.779 mmol) at room temperature. The resulting mixture was stirred for 30 minutes at room temperature under a nitrogen atmosphere. The reaction was quenched by the addition of sat. NH₄Cl (aq.) (25mL) at room temperature. The aqueous layer was extracted with EtOAc (4 x 10 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (eluent: 10% MeOH in DCM) to afford the title compound (33 mg, 17% yield) as a yellow solid. ¹H NMR (400 MHz; DMSO *d*₆): δ 12.78 (s, 1H), 8.69 (s, 1H), 7.54-7.42 (m, 5H), 7.40-7.38 (m, 1H), 7.35-7.33 (m, 1H), 7.11-7.07 (m, 1H), 6.99 (d, 1H), 5.59 (d, 1H), 5.47(s, 2H), 4.66 (d, 1H), 3.51 (s, 3H). *m/z* 483 (M+H⁺).

Example 103

Synthesis of 3-(benzo[*c*][1,2,5]thiadiazol-4-yl)-*N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)isonicotinamide



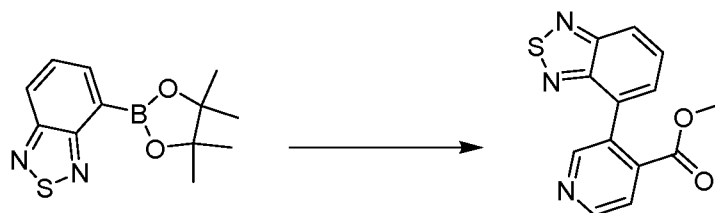
Step 1: Preparation of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*c*][1,2,5]thiadiazole



[0377] A round bottom flask under a nitrogen atmosphere was charged with 4-bromo-2,1,3-benzothiadiazole (1.00 g, 4.65 mmol), 1,4-dioxane (10 mL), bis(pinacolato)diboron (1.77 g, 6.97 mmol), KOAc (912 mg, 9.29 mmol), Pd(dppf)Cl₂ (340 mg, 0.465 mmol). The resulting solution was stirred for 4 hours at 80 °C. The resulting mixture was diluted with water (50 mL). The aqueous layer was extracted with EtOAc (50 mL). The combined organic extracts were

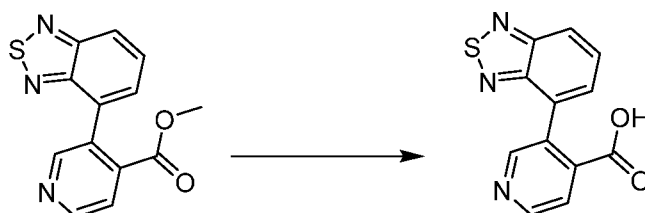
concentrated under vacuum. The residue was purified by silica gel column chromatography (eluent: 3% EtOAc in PE) to afford the title compound (850 mg, 48% yield) as a yellow solid.

Step 2: Preparation of methyl 3-(benzo[*c*][1,2,5]thiadiazol-4-yl)isonicotinate



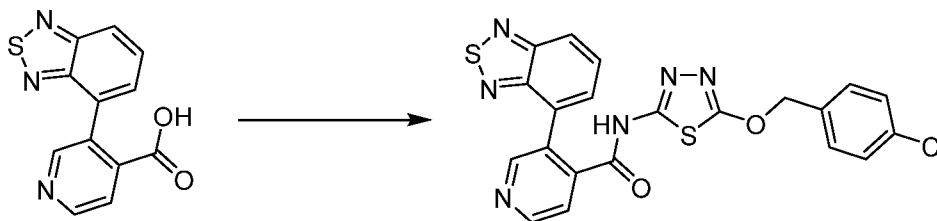
[0378] A round bottom flask under a nitrogen atmosphere was charged with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*c*][1,2,5]thiadiazole (830 mg, 3.16 mmol), 1,4-dioxane (8.30 mL), methyl 3-bromopyridine-4-carboxylate (752 mg, 3.48 mmol), H₂O (2.10 mL), K₂CO₃ (875 mg, 6.33 mmol), Pd(dppf)Cl₂ (231 mg, 0.317 mmol). The resulting solution was stirred for 1.5 hours at 100 °C. The resulting mixture was diluted with water (30 mL). The aqueous layer was extracted with EtOAc (40 mL). The combined organic extracts were concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 25% EtOAc in PE) to afford the title compound (490 mg, 54% yield) as a yellow solid.

Step 3: Preparation of 3-(benzo[*c*][1,2,5]thiadiazol-4-yl)isonicotinic acid



[0379] The title compound was prepared according to General Procedure F employing methyl 3-(benzo[*c*][1,2,5]thiadiazol-4-yl)isonicotinate (470 mg, 1.73 mmol), MeOH (5 mL), H₂O (1.25 mL), NaOH (138 mg, 3.46 mmol). The resulting mixture was diluted with water (20 mL). The aqueous layer was extracted with EtOAc (20 mL). The pH of aqueous solution was adjusted to 5 with HCl (1 M). The aqueous layer was extracted with EtOAc (20 mL). The combined organic extracts were concentrated under reduced pressure to afford the title compound (330 mg, 71% yield) as a white solid.

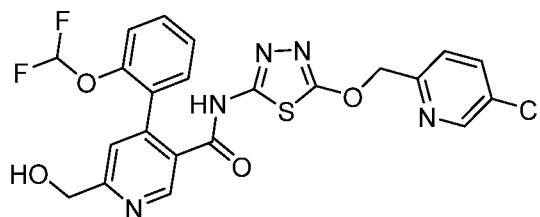
Step 4: Preparation of 3-(benzo[*c*][1,2,5]thiadiazol-4-yl)-*N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)isonicotinamide



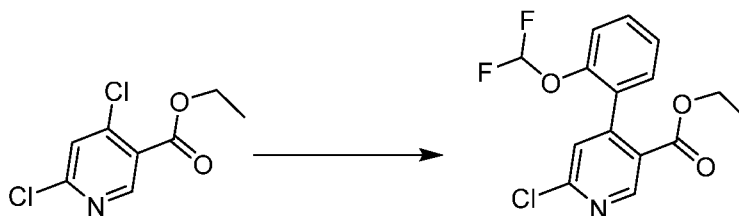
[0380] A reaction vial was charged with 3-(benzo[*c*][1,2,5]thiadiazol-4-yl)isonicotinic acid (150 mg, 0.583 mmol), DMF (1.50 mL), 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) (140 mg, 0.583 mmol), EDCI (167 mg, 0.875 mmol), HOBT (118 mg, 0.875 mmol). The resulting solution was stirred overnight at room temperature. The precipitated solids were collected by filtration and washed with water (3 mL) followed by MeOH (3 mL) to afford the title compound (167 mg, 58% yield) as an off-white solid. ¹H NMR (400 MHz; DMSO *d*₆): δ 13.19 (s, 1H), 8.91 (d, 2H), 8.15 (dd, 1H), 7.85-7.79 (m, 3H), 7.51-7.45 (m, 4H), 5.44 (s, 2H); *m/z* 481 [M+H⁺].

Example 104

Synthesis of *N*-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-(difluoromethoxy)phenyl)-6-(hydroxymethyl)nicotinamide



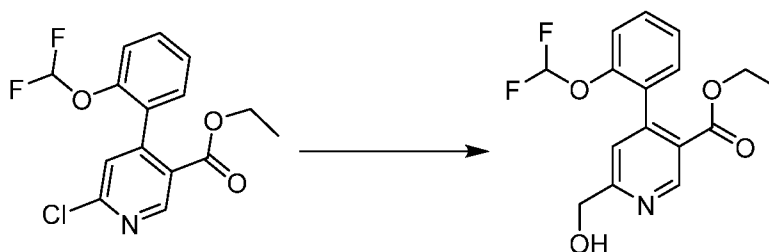
Step 1: Preparation of ethyl 6-chloro-4-(2-(difluoromethoxy)phenyl)nicotinate



[0381] A reaction vial under a nitrogen atmosphere was charged with 2-(difluoromethoxy)phenylboronic acid (460 mg, 2.44 mmol), 1,4-dioxane (4.60 mL), ethyl 4,6-dichloropyridine-3-carboxylate (807 mg, 3.67 mmol), H₂O (1.10 mL), K₂CO₃ (676 mg, 4.89

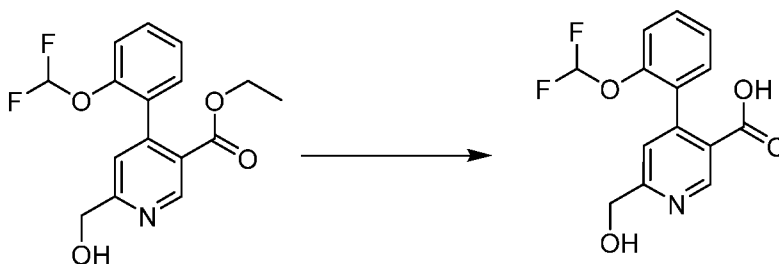
mmol), Pd(dtbpf)Cl₂ (159 mg, 0.245 mmol). The resulting solution was stirred for 4 hours at 80 °C. The resulting mixture was diluted with water (20 mL). The aqueous layer was extracted with EtOAc (20 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (40% EtOAc in PE) to afford the title compound (730 mg, 60% yield) as a white solid.

Step 2: Preparation of ethyl 4-(2-(difluoromethoxy)phenyl)-6-(hydroxymethyl)nicotinate



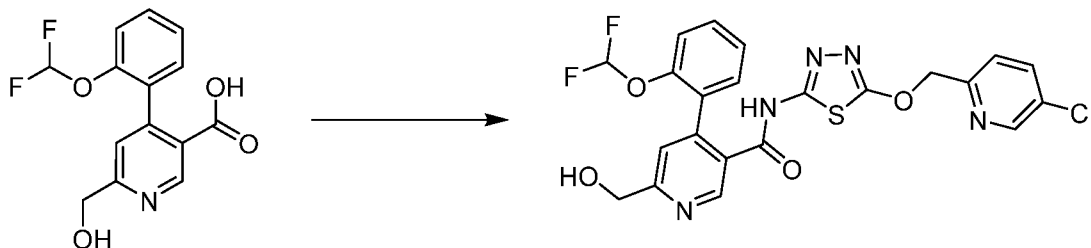
[0382] A round bottom flask under an atmosphere of nitrogen was charged with ethyl 6-chloro-4-(2-(difluoromethoxy)phenyl)nicotinate (690 mg, 2.10 mmol), PhMe (7 mL), (tributylstannyl)methanol (1.01 g, 3.15 mmol), Pd(PPh₃)₄ (243 mg, 0.211 mmol). The resulting solution was stirred for 4 hours at 80 °C. The resulting mixture was diluted with water (20 mL). The aqueous layer was extracted with EtOAc (20 mL). The residue was purified by Prep-TLC (40% EtOAc in PE) to afford the title compound (160 mg, 24% yield) as a yellow oil.

Step 3: Preparation of 4-(2-(difluoromethoxy)phenyl)-6-(hydroxymethyl)nicotinic acid



[0383] A reaction vial was charged with ethyl 4-(2-(difluoromethoxy)phenyl)-6-(hydroxymethyl)nicotinate (150 mg, 0.464 mmol), EtOH (1.50 mL), H₂O (0.4 mL), NaOH (37 mg, 0.928 mmol). The resulting solution was stirred for 1.5 hours at room temperature. The resulting mixture was diluted with water (10 mL). The aqueous layer was extracted with EtOAc (10 mL). The pH of aqueous solution was adjusted to 5 using HCl (1 M). The aqueous layer was extracted with EtOAc (10 mL). The resulting mixture was concentrated under reduced pressure to afford the title compound (120 mg, 86% yield) as a white solid.

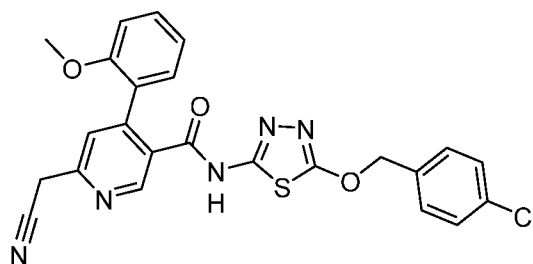
Step 4: Preparation of *N*-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-(difluoromethoxy)phenyl)-6-(hydroxymethyl)nicotinamide



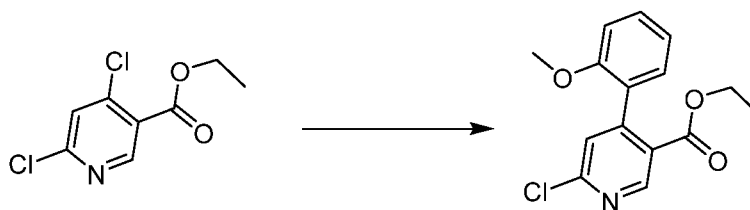
[0384] A reaction vial was charged with 4-(2-(difluoromethoxy)phenyl)-6-(hydroxymethyl)nicotinic acid (100 mg, 0.339 mmol), DMF (1 mL), 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C) (82 mg, 0.339 mmol), EDCI (97 mg, 0.508 mmol), HOBT (68 mg, 0.508 mmol). The resulting solution was stirred overnight at room temperature. The precipitated solids were collected by filtration and washed with water (3 mL) followed by MeOH (2 mL) to afford the title compound (25 mg, 14% yield) as an off-white solid. ¹H NMR (400 MHz; DMSO *d*₆): δ 12.98 (s, 1H), 8.85 (s, 1H), 8.66 (s, 1H), 8.02-8.00 (m, 1H), 7.62 (d, 1H), 7.52 (d, 2H), 7.43-7.36 (m, 2H), 7.24-6.88 (m, 2H), 5.64 (t, 1H), 5.55 (s, 2H), 4.69 (d, 2H); *m/z* 520 (M+H⁺).

Example 105

Synthesis of *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-(cyanomethyl)-4-(2-methoxyphenyl)pyridine-3-carboxylate

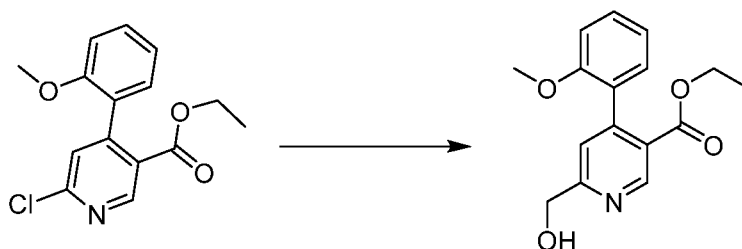


Step 1: Preparation of ethyl 6-chloro-4-(2-methoxyphenyl)pyridine-3-carboxylate



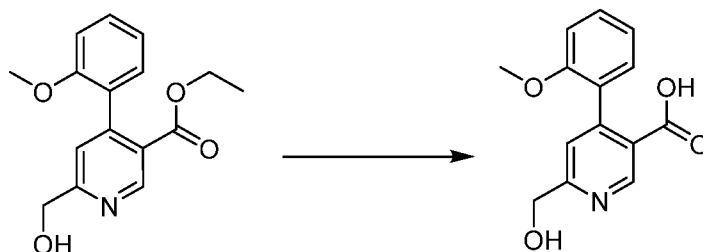
[0385] The title compound was prepared using General Procedure E employing ethyl 4,6-dichloropyridine-3-carboxylate and 2-methoxyphenylboronic acid and replacing Pd(dppf)Cl₂ (0.2eq) with Pd(dtbpf)Cl₂ (0.1 equiv). The mixture was diluted with water and extracted with EtOAc (2x). The combined organic layers were concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with 6% EtOAc in PE to afford the title compound as a yellow solid.

Step 2: Preparation of ethyl 6-(hydroxymethyl)-4-(2-methoxyphenyl)pyridine-3-carboxylate



[0386] To a stirred solution of ethyl 6-chloro-4-(2-methoxyphenyl)pyridine-3-carboxylate (480 mg, 1.6 mmol) and (tributylstannyl)methanol (792 mg, 2.5 mmol) in toluene was added Pd(dppf)Cl₂ (120 mg, 0.17 mmol) at room temperature under nitrogen atmosphere. The mixture was stirred for 2h at 100 °C under nitrogen atmosphere. The mixture was diluted with water. The aqueous layer was extracted with EtOAc (3x). The combined organic layers were concentrated under vacuum. The residue was purified by Prep-TLC (PE:EtOAc, 1:1) to afford the title compound (300 mg, 63% yield) as a white solid.

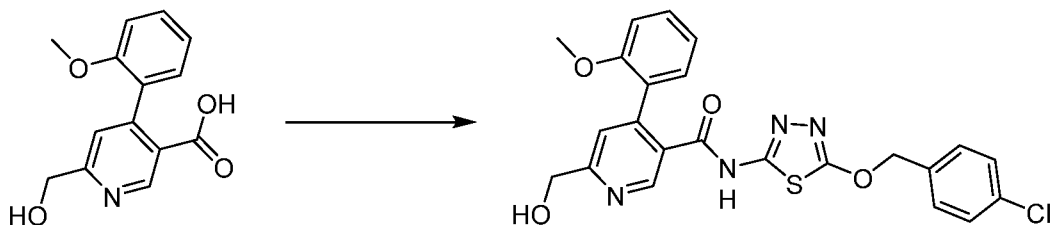
Step 3: Preparation of 6-(hydroxymethyl)-4-(2-methoxyphenyl)pyridine-3-carboxylic acid



[0387] To a solution of ethyl 6-(hydroxymethyl)-4-(2-methoxyphenyl)pyridine-3-carboxylate (287 mg, 1.0 mmol) in EtOH(5 mL) and water (1 mL) was added LiOH (84 mg, 2.0 mmol). The mixture was stirred at rt overnight. The mixture was acidified to pH 5 with HCl (1 M). The mixture was concentrated under vacuum. The residue was purified by reverse phase

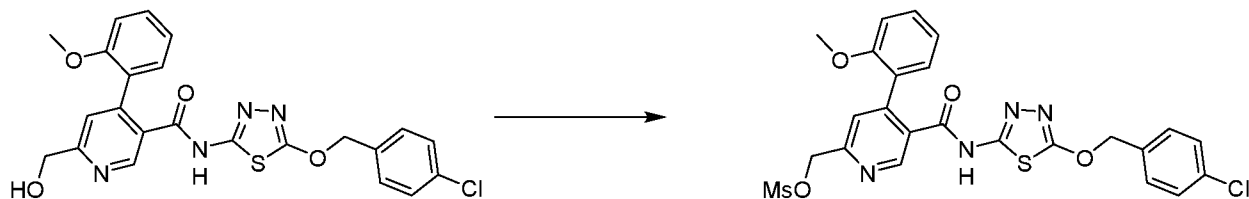
chromatography (column, C18 silica gel; mobile phase, with 0-100% MeCN in water) to afford the title compound (77 mg, 30% yield) as a white solid.

Step 4: Preparation of *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-(hydroxymethyl)-4-(2-methoxyphenyl)nicotinamide



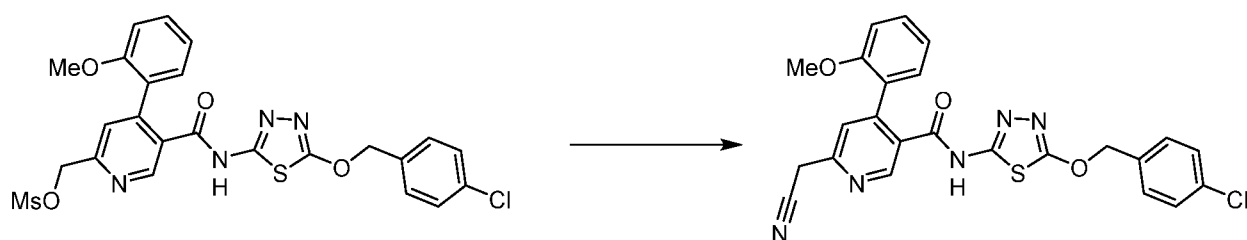
[0388] The title compound was prepared according to General Procedure A using 6-(hydroxymethyl)-4-(2-methoxyphenyl)pyridine-3-carboxylic acid (540 mg, 2.08 mmol) and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was stirred for 3 h at room temperature. The mixture was diluted with water. The aqueous layer was extracted with EtOAc (2 x). The residue was purified by Prep-TLC (5% MeOH in DCM) to afford the title compound (300 mg, 27% yield) as a brown solid.

Step 5: Preparation of (5-((5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)carbamoyl)-4-(2-methoxyphenyl)pyridin-2-yl)methyl methanesulfonate



[0389] To a solution of *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-(hydroxymethyl)-4-(2-methoxyphenyl)nicotinamide (290 mg, 0.600 mmol) and Et₃N (121 mg, 1.20 mmol) in DCM was added MsCl (82.54 mg, 0.721 mmol) dropwise at room temperature under nitrogen atmosphere. The mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The mixture was concentrated under vacuum. The residue was purified by Prep-TLC (5% MeOH in DCM) to afford the title compound (110 mg, 29% yield) as an off-white solid.

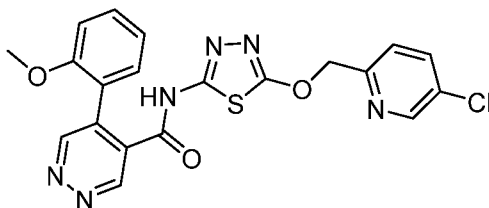
Step 6: Preparation of *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-(cyanomethyl)-4-(2-methoxyphenyl)nicotinamide



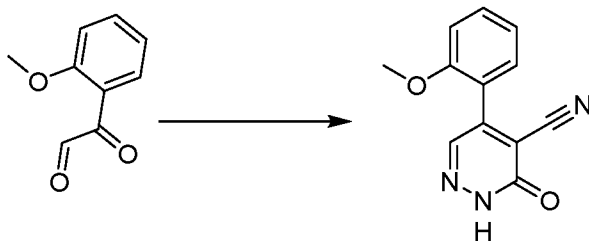
[0390] To a solution of [5-([5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]carbamoyl)-4-(2-methoxyphenyl)pyridin-2-yl)methyl methanesulfonate (100 mg, 0.178 mmol) in DMSO (2 mL) was added NaCN (34 mg, 0.713 mmol). The mixture was stirred for 2 hours at room temperature. The mixture was diluted with water and extracted with EtOAc (2 x). The mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (2% MeOH in DCM) to afford the title compound (37 mg, 40% yield) as an off-white solid. ^1H NMR (300 MHz, DMSO- d_6) δ 12.88 (s, 1H), 8.79 (s, 1H), 7.59 - 7.31 (m, 7H), 7.12-7.00 (m, 2H), 5.48 (s, 2H), 4.35 (s, 2H), 3.52 (s, 3H); m/z : $[\text{M}+\text{H}]^+$ 492.

Example 106

Synthesis of *N*-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-5-(2-methoxyphenyl)pyridazine-4-carboxamide



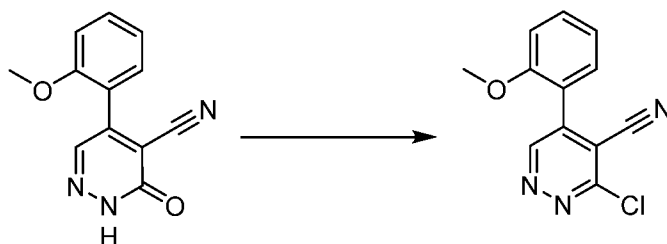
Step 1: Preparation of 5-(2-methoxyphenyl)-3-oxo-2,3-dihydropyridazine-4-carbonitrile



[0391] To a solution of 2-(2-methoxyphenyl)-2-oxoacetaldehyde (1.90 g, 11.5 mmol) in EtOH (60 mL) was added cyacetamide (1.14 g, 11.5 mmol) and Na_2SO_4 (3.28 g, 23.1 mmol). The mixture was stirred for 5 hours at room temperature under an inert atmosphere of nitrogen. The mixture was filtered and washed with EtOAc (3x). The mixture was concentrated to afford a brown solid. The residue was dissolved in EtOH (60 mL). In a separate flask, sodium metal (2.66

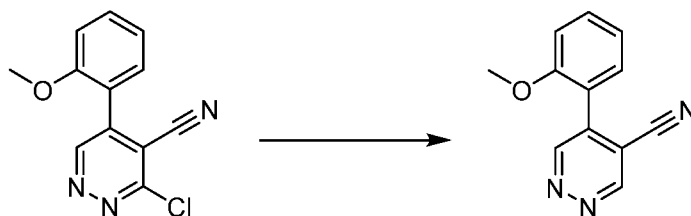
g, 11.5 mmol) was added to EtOH (60 mL) and the mixture was cooled 0 °C under nitrogen atmosphere. The brown mixture was added to the sodium ethoxide mixture dropwise at 0 °C. The mixture was then stirred at 80 °C overnight. The mixture was cooled to rt and diluted with water. The mixture was concentrated under reduced pressure to half volume. The precipitated were collected by filtration and washed with water and then washed with EtOAc to afford the title compound (1.5 g, 56% yield) as a grey solid.

Step 2: Preparation of 3-chloro-5-(2-methoxyphenyl)pyridazine-4-carbonitrile



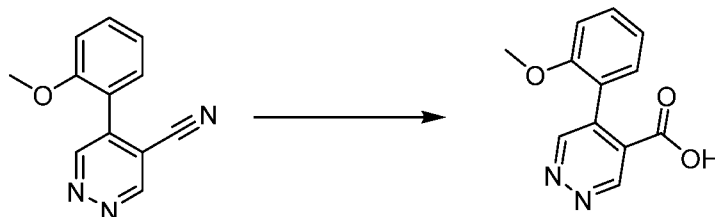
[0392] A round bottom flask was charged with 5-(2-methoxyphenyl)-3-oxo-2,3-dihydropyridazine-4-carbonitrile (1.50 g, 6.60 mmol), and POCl₃ (15 mL). The mixture was stirred at 100 °C overnight. The mixture was cooled to rt and concentrated under reduced pressure. The residue was cooled to 0 °C and ice water was added (50 mL). The aqueous layer was extracted with EtOAc (50 mL). The organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluent: 17% EtOAc in PE to afford the title compound (780 mg, 47% yield) as a brown solid.

Step 3: Preparation of 5-(2-methoxyphenyl)pyridazine-4-carbonitrile



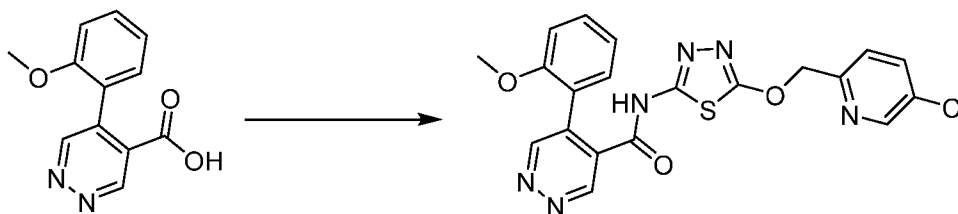
[0393] To a solution of 3-chloro-5-(2-methoxyphenyl)pyridazine-4-carbonitrile (720 mg, 2.93 mmol) in THF (72 mL) was added 10% Pd/C (72 mg) and Et₃N (889 mg, 8.79 mmol). The mixture was purged with H₂ and stirred under an atmosphere of H₂ for 30 mins at room temperature. The mixture was filtered, and the filter cake was washed with THF. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (eluent: 25% EtOAc in PE) to afford the title compound (300 mg, 45% yield) as a grey solid.

Step 4: Preparation of 5-(2-methoxyphenyl)pyridazine-4-carboxylic acid



[0394] To a solution of 5-(2-methoxyphenyl)pyridazine-4-carbonitrile (285 mg, 1.34 mmol) in water H₂O (2 mL) was added H₂SO₄ (1.20 mL, 60% w/w). The mixture was stirred at 100 °C for 5 hours. The mixture was cooled to rt and saturated NaHCO₃ (aq.) was added until mixture was pH 5. The mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (eluent: 5% MeOH in DCM) to afford the title compound (100 mg, 31%) as an off-white solid.

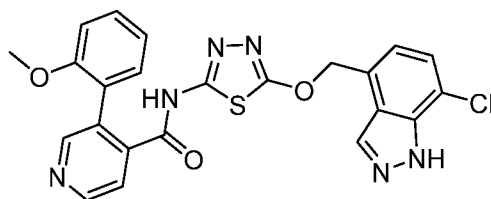
Step 5: Preparation of *N*-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-5-(2-methoxyphenyl)pyridazine-4-carboxamide



[0395] To a solution of 5-(2-methoxyphenyl)pyridazine-4-carboxylic acid (90 mg, 0.391 mmol) in DMF (1 mL) was added EDCI (112 mg, 0.586 mmol), HOBT (79 mg, 0.586 mmol) and 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C) (94 mg, 0.391 mmol). The mixture was stirred for 4 hours at room temperature. The mixture was diluted with water. The aqueous layer was extracted with EtOAc. The organic layer was concentrated under reduced pressure. The residue was triturated with MeOH to afford the title compound (26.7 mg, 14% yield) as a white solid. ¹H NMR (300 MHz; DMSO *d*₆): δ 13.17 (s, 1H), 9.41 (dd, 2H), 8.66 (d, 1H), 8.01 (dd, 1H), 7.62 (d, 1H), 7.51-7.46 (m, 2H), 7.16-7.06 (m, 2H), 5.56 (s, 2H), 3.55 (s, 3H); *m/z* 455 (M+H⁺).

Example 107

Synthesis of *N*-(5-((7-chloro-1*H*-indazol-4-yl)methoxy)-1,3,4-thiadiazol-2-yl)-3-(2-methoxyphenyl)isonicotinamide

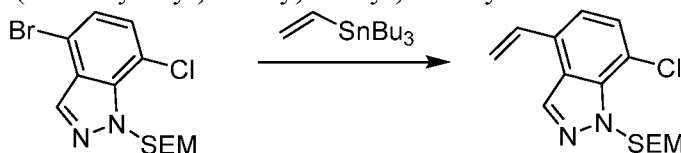


Step 1: Preparation of 4-bromo-7-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole



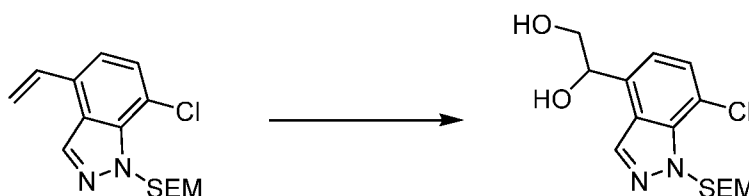
[0396] To a solution of 4-bromo-7-chloro-1*H*-indazole (1.50 g, 6.48 mmol) in DMF (32 mL) was added sodium hydride (as a 60% dispersion in mineral oil, 518 mg, 12.9 mmol) portion wise at 0 °C. The mixture was stirred for 40 min and then SEM-Cl (2.16 g, 12.9 mmol) was added to the mixture and stirred for 4 h. The mixture was diluted with water and extracted with EtOAc (3 x). The combined organic layers were concentrated under vacuum. The residue was purified by silica gel column chromatography, eluent: 1% EtOAc in PE to afford the title compound (1.8g, 76% yield) as a yellow oil.

Step 2: 7-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-4-vinyl-1*H*-indazole



[0397] To a solution of 4-bromo-7-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]indazole (1.80 g, 4.97 mmol) in toluene (15 mL) was added tributyl(ethenyl)stannane (1.89 g, 5.97 mmol) and Pd(PPh₃)₄ (862 mg, 0.746 mmol) at room temperature. The mixture was stirred for 4 h at 110 °C under nitrogen atmosphere. The mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluent: 100 % DCM to afford the title compound (1.3 g, 84% yield) as a yellow oil.

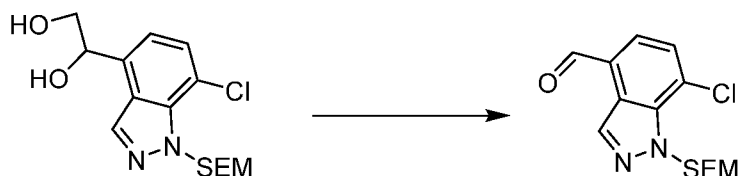
Step 3: 1-(7-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-4-yl)ethane-1,2-diol



[0398] To a solution of 7-chloro-4-ethenyl-1-[[2-(trimethylsilyl)ethoxy] methyl]indazole (1.30 g, 4.20 mmol) in THF (12 mL) was added OsO₄ (107 mg, 0.421 mmol) at room temperature.

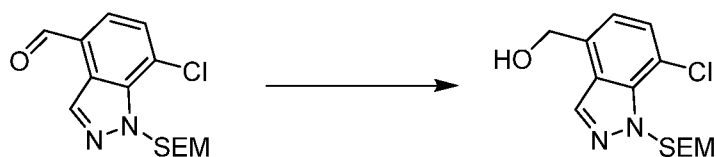
Then a solution of NMO (986 mg, 8.41 mmol) in H₂O (1 mL) was added at room temperature. The mixture was stirred for 2 h at room temperature. The mixture was diluted with H₂O water and extracted with EtOAc (3 x). The combined organic extracts were concentrated under vacuum. The residue was purified by Prep-TLC (5 % MeOH in DCM) to afford the title compound (660 mg, 45% yield) as a yellow oil.

Step 4: Preparation of 7-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole-4-carbaldehyde



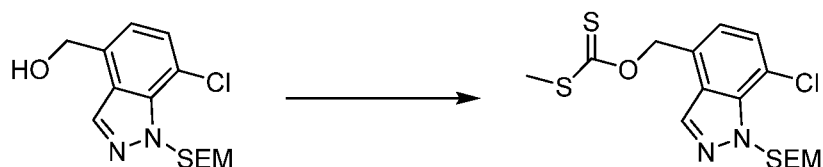
[0399] To a solution of 1-(7-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-4-yl)ethane-1,2-diol (650 mg, 1.89 mmol) in MeOH (5 mL) was added NaIO₄ (810 mg, 3.79 mmol) at room temperature. The mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The mixture was diluted with water and extracted with EtOAc (5 x). The combined organic extracts were concentrated under vacuum. The residue was purified by Prep-TLC (eluent: 17% EtOAc in PE) to afford the title compound (560 mg, 87% yield) as a yellow solid.

Step 5: (7-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-4-yl)methanol



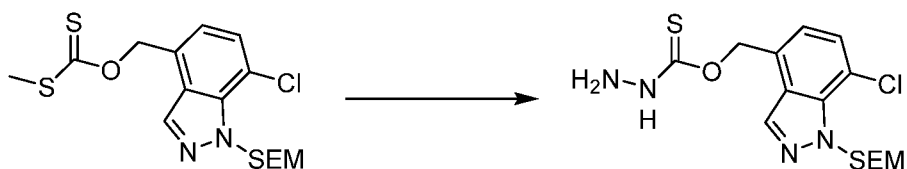
[0400] To a solution of 7-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]indazole-4-carbaldehyde (560 mg, 1.80 mmol) in MeOH (5 mL) was added NaBH₄ (136 mg, 3.60 mmol) at room temperature. The mixture was stirred for 30 min at room temperature. Then sat. NH₄Cl (aq.) was added and the mixture was extracted with EtOAc (3 x). The combined organic extracts were concentrated under vacuum. The residue was purified by Prep-TLC (eluent: 5% MeOH in DCM) to afford the title compound (520 mg, 84% yield) as a yellow solid.

Step 6: Preparation of *O*-((7-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-4-yl)methyl) *S*-methyl carbonodithioate



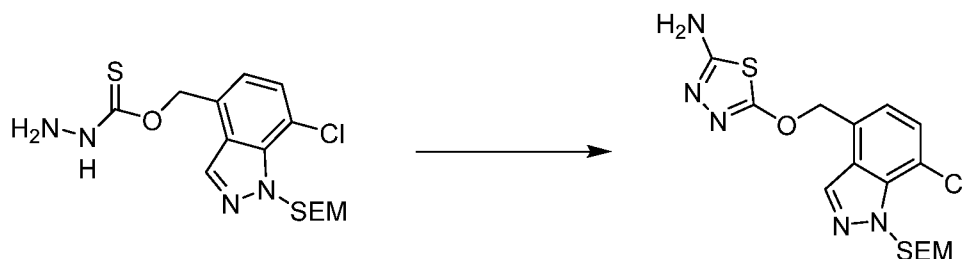
[0401] To a solution of (7-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-4-yl)methanol (510 mg, 1.63 mmol) in THF (0.5 ml) at 0 °C was added NaH (as a 60% dispersion in mineral oil, 130 mg, 3.25 mmol). The mixture was stirred for 30 min at 0 °C, then MeI (254 mg, 1.79 mmol) was added at 0 °C. The mixture was stirred for 5 min, then CS₂ (5 mg, 0.070 mmol) was then added. The mixture was warmed to room temperature and stirred for 30 min. A sat. NH₄Cl (aq.) solution was added and the was diluted with water. The mixture was extracted with EtOAc (3 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (eluent: 20% EtOAc in PE) to afford the title compound (445 mg, 67%) as a yellow solid.

Step 7: Preparation of *O*-((7-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-4-yl)methyl) *S*-methyl carbonodithioate



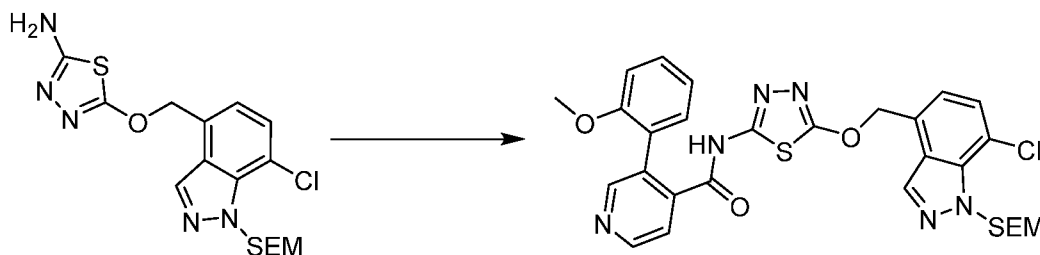
[0402] To a solution of *O*-((7-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-4-yl)methyl) *S*-methyl carbonodithioate (445 mg, 1.10 mmol) in MeOH (5 ml) at 0 °C was added hydrazine hydrate (55mg, 1.10 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 15 min at rt. The mixture was diluted with EtOAc. The mixture was washed with water (5 x). The organic layer was concentrated under reduced pressure. The residue was purified by Prep-TLC (eluent: 50% EtOAc in PE) to afford the title compound (370 mg, 86% yield) as a yellow oil.

Step 8: 5-((7-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-4-yl)methoxy)-1,3,4-thiadiazol-2-amine



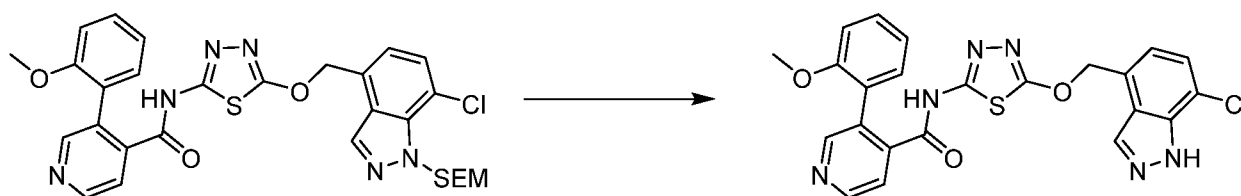
[0403] To a solution of *O*-((7-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-4-yl)methyl) hydrazinecarbothioate (370 mg, 0.956 mmol) in MeOH (4 mL) at 0 °C was added Et₃N (193 mg, 1.91 mmol) and BrCN (111 mg, 1.05 mmol) at 0 °C. The mixture was stirred for 30 min. The mixture was diluted with water. The aqueous layer was extracted with EtOAc (3 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (eluent: 7% MeOH in DCM) to afford the title compound (210 mg, 52% yield) as a yellow oil.

Step 9: *N*-5-((7-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-4-yl)methoxy)-1,3,4-thiadiazol-2-yl)-3-(2-methoxyphenyl)isonicotinamide



[0404] The title compound was prepared according to General Procedure A employing 3-(2-methoxyphenyl)pyridine-4-carboxylic acid (Intermediate H) and 5-((7-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-4-yl)methoxy)-1,3,4-thiadiazol-2-amine. The mixture was diluted with EtOAc (25 mL). The mixture was washed with water (3 x). The organic layer was concentrated under vacuum. The residue was purified by Prep-TLC (eluent: 5% EtOAc in PE) to afford the title compound (260 mg, 81%) as an off-white solid.

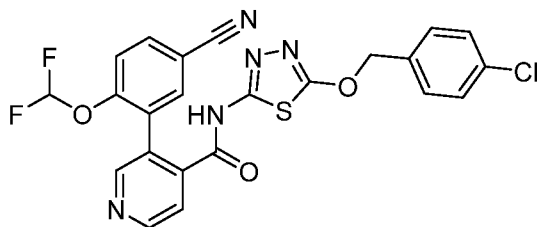
Step 10: *N*-5-((7-chloro-1*H*-indazol-4-yl)methoxy)-1,3,4-thiadiazol-2-yl)-3-(2-methoxyphenyl)isonicotinamide



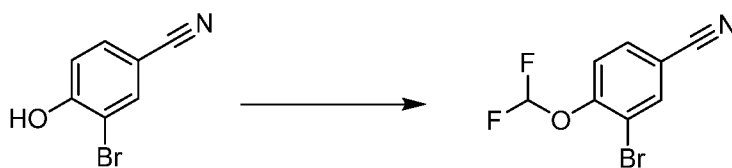
[0405] To a solution of *N*-[5-[(7-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-4-yl)methoxy]-1,3,4-thiadiazol-2-yl]-3-(2-methoxyphenyl)pyridine-4-carboxamide *N*-(5-((7-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazol-4-yl)methoxy)-1,3,4-thiadiazol-2-yl)-3-(2-methoxyphenyl)isonicotinamide (150 mg, 0.241 mmol) in THF (2 mL) was added TBAF (2 M in THF, 0.722 mL, 1.44 mmol) and CsF (365 mg, 2.40 mmol) at room temperature. The mixture was stirred at 60 °C overnight under nitrogen atmosphere. The mixture was diluted with EtOAc. The mixture was washed with water (4 x). The organic layer was concentrated under reduced pressure. The residue was purified by Prep-TLC (eluent: 7% MeOH in DCM) to afford the title compound (50 mg, 42% yield) as a white solid. ¹H NMR (400 MHz, DMSO *d*₆): δ 13.76 (s, 1H), 12.87 (s, 1H), 8.72 (d, 1H), 8.61 (s, 1H), 8.45 (s, 1H), 7.63 (d, 1H), 7.48 (d, 1H), 7.40-7.35 (m, 2H), 7.26 (d, 1H), 7.08-7.04 (m, 1H), 6.99-6.97 (m, 1H), 5.81 (s, 2H), 3.50 (s, 3H); *m/z* 493 (M+H⁺).

Example 108

Synthesis of *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(5-cyano-2-(difluoromethoxy)phenyl)isonicotinamide



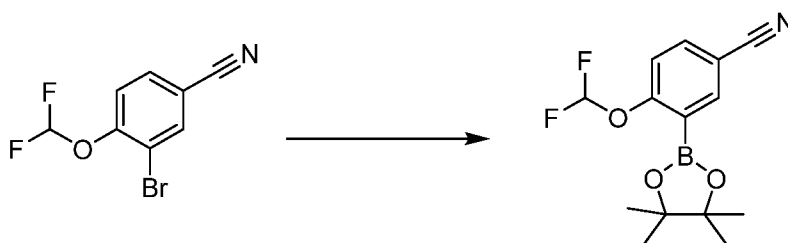
Step 1: Preparation of 3-bromo-4-(difluoromethoxy)benzonitrile



[0406] To a solution of 3-bromo-4-hydroxybenzonitrile (5.00 g, 25.2 mmol), (bromodifluoromethyl)trimethylsilane (10.2 g, 50.4 mmol) in DCM (20 mL) at 0 °C was added a

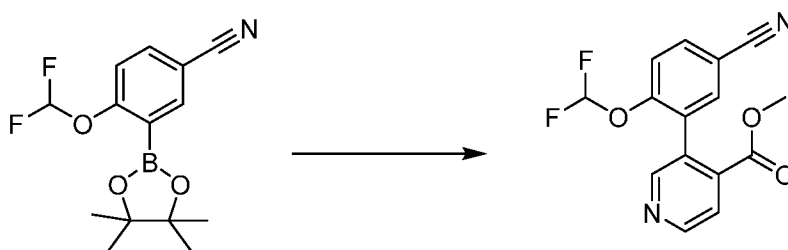
solution of KOH (8.50 g, 151.5 mmol) in water (35 mL) was added at 0 °C. The mixture was stirred overnight at room temperature. The mixture was diluted with water. The aqueous layer was extracted with EtOAc (3 x). The combined organic layers were concentrated under vacuum. The residue was purified by silica gel column chromatography, eluent: 75% EtOAc in PE to afford the title compound (4 g, 63% yield) as a white solid.

Step 2: 4-(difluoromethoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile



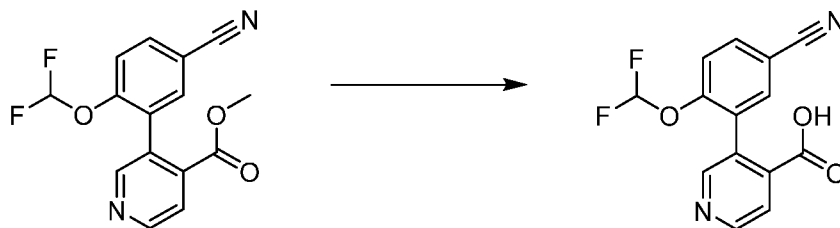
[0407] To a solution of 3-bromo-4-(difluoromethoxy)benzonitrile (2.00 g, 8.06 mmol), bis(pinacolato)diboron (2.46 g, 9.67 mmol) in 1,4-dioxane (20 mL) was added KOAc (1.58 g, 16.1 mmol), and Pd(dppf)Cl₂ (1.18 g, 1.61 mmol) at room temperature. The mixture was stirred at 80 °C overnight under a nitrogen atmosphere. The mixture was diluted with water and extracted with EtOAc (3 x). The combined organic layers were concentrated under vacuum. The residue was purified by silica gel column chromatography, eluent: 33% EtOAc in PE to afford the title compound (400 mg, 16%) as an off-white solid.

Step 3: Preparation of methyl 3-(5-cyano-2-(difluoromethoxy)phenyl)isonicotinate

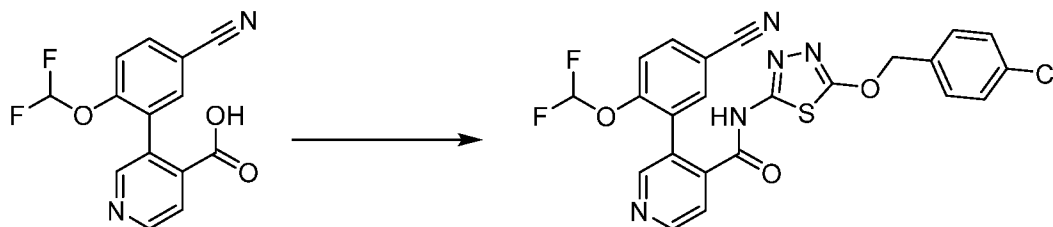


[0408] The title compound was prepared according to General Procedure E employing 4-(difluoromethoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile and methyl 3-bromopyridine-4-carboxylate. The mixture was diluted with water and extracted with EtOAc (3 x). The combined organic layers were concentrated under vacuum. The residue was purified by Prep-TLC (eluent: 25% EtOAc in PE) to afford the title compound (143 mg, 34% yield) as an off-white solid.

Step 4: Preparation of 3-(5-cyano-2-(difluoromethoxy)phenyl)isonicotinic acid



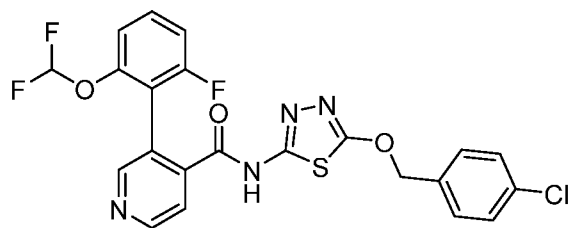
[0409] The title compound was prepared according to General Procedure F employing methyl 3-(5-cyano-2-(difluoromethoxy)phenyl)isonicotinate (50 mg, 0.164 mmol) and replacing NaOH (5 eq) with LiOH (1.5 eq). The mixture was acidified with HCl (1 M) to pH 5 and extracted with EtOAc (2 x). The combined organic layers were concentrated under vacuum. The residue was purified by reverse phase chromatography (column, C18 silica gel; mobile phase, with 0-100% MeCN in water) to afford the title compound as a white solid.

Step 5: *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(5-cyano-2-(difluoromethoxy)phenyl)isonicotinamide

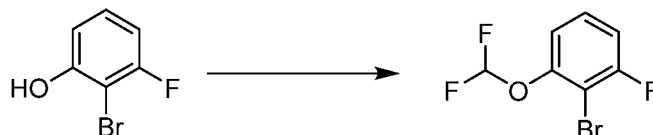
[0410] The title compound was prepared according to General Procedure A employing 3-(5-cyano-2-(difluoromethoxy)phenyl)isonicotinic acid and 5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-amine 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was diluted with water and extracted with EtOAc (2 x). The combined organic layers were concentrated under vacuum. The residue was purified by Prep-TLC (eluent: 3% MeOH in DCM) to afford the title compound (10 mg, 18%) as a white solid. ^1H NMR (300 MHz, DMSO d_6): δ 13.12 (s, 1H), 8.84 (d, 1H), 8.69 (s, 1H), 8.03-7.99 (m, 2H), 7.80 (d, 1H), 7.55-7.01 (m, 6H), 5.48 (s, 2H); m/z 514 ($\text{M}+\text{H}^+$).

Example 109

Synthesis of *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(2-(difluoromethoxy)-6-fluorophenyl)isonicotinamide

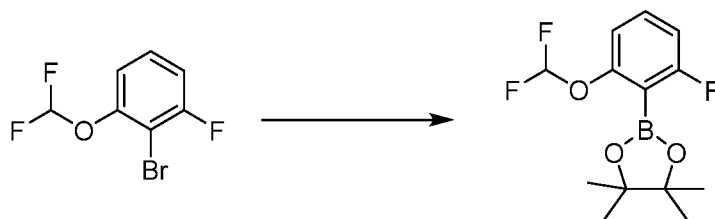


Step 1: Preparation of 2-bromo-1-(difluoromethoxy)-3-fluorobenzene



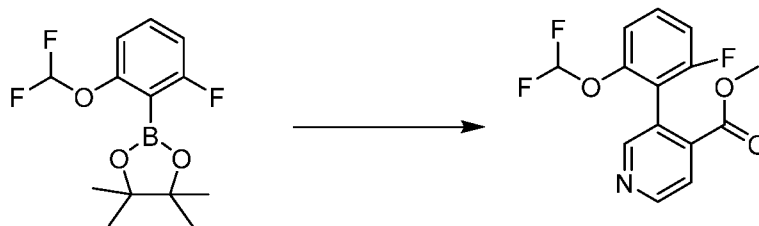
[0411] To a solution of 2-bromo-3-fluorophenol (5 g, 26.1 mmol) and (bromodifluoromethyl)trimethylsilane (10.6 g, 52.3 mmol) in DCM (100 mL) was added a solution of KOH (8.81 g, 157.0 mmol) in water (35 mL) dropwise. The mixture was stirred overnight at room temperature. The mixture was diluted with water (300 mL). The aqueous layer was extracted with DCM (3 x 100 mL). The combined organic extracts were concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 10% EtOAc in PE) to afford the title compound (4 g, 63% yield) as a yellow oil.

Step 2: Preparation of 2-(2-(difluoromethoxy)-6-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



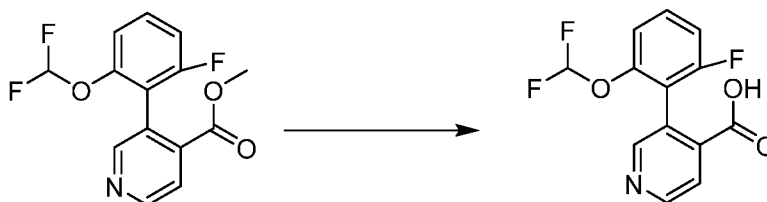
[0412] To a solution of 2-bromo-1-(difluoromethoxy)-3-fluorobenzene (2.00 g, 8.29 mmol) in 1,4-dioxane (20 mL) was added bis(pinacolato)diboron (3.16 g, 12.4 mmol), KOAc (1.63 g, 16.5 mmol) and Pd(dppf)Cl₂ (0.61 g, 0.830 mmol). The mixture was stirred at 80 °C overnight under nitrogen atmosphere. The mixture was diluted with water and extracted with EtOAc (3 x). The mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluent: 10% EtOAc in PE to afford the title compound (900 mg, 37% yield) as a yellow oil.

Step 3: Preparation of methyl 3-(2-(difluoromethoxy)-6-fluorophenyl)isonicotinate



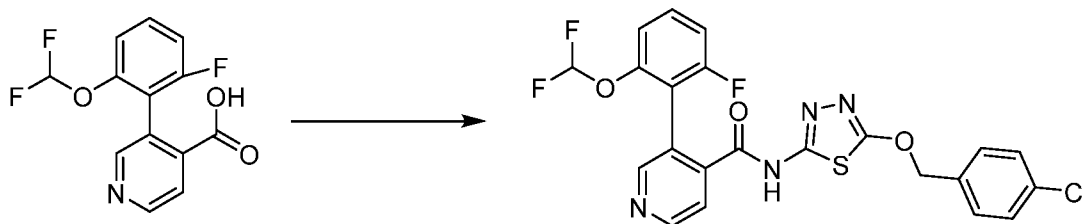
[0413] To a solution of 2-(2-(difluoromethoxy)-6-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (840 mg, 2.91 mmol), in 1,4-dioxane (4 mL) and water (1 mL) was added methyl 3-bromopyridine-4-carboxylate (944 mg, 4.374 mmol), K_2CO_3 (806 mg, 5.83 mmol) and $Pd(dtbpf)Cl_2$ (380 mg, 0.583 mmol) at room temperature. The mixture was stirred at 100 °C overnight under a nitrogen atmosphere. The mixture was diluted with water and extracted with EtOAc (3 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (eluent: 10% EtOAc in PE) to afford the title compound (140 mg, 16% yield) as a white solid.

Step 4: Preparation of 3-(2-(difluoromethoxy)-6-fluorophenyl)isonicotinic acid



[0414] To a solution of methyl 3-(2-(difluoromethoxy)-6-fluorophenyl)isonicotinate (130 mg, 0.437 mmol) in MeOH (2 mL) was added an aqueous solution of LiOH (2 M, 0.44 mL, 0.880 mmol) dropwise at room temperature. The mixture was stirred overnight at room temperature. The mixture was diluted with water and washed with EtOAc. HCl (1 M) was added to the aqueous layer until pH was 5. The solid was collected by filtration and washed with water (3 x) to afford the title compound (60 mg, 47% yield) as a white solid.

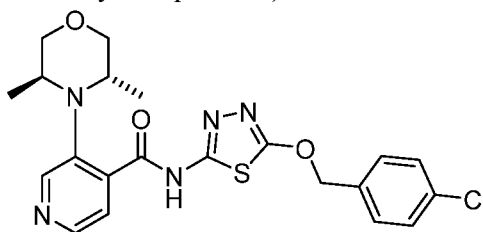
Step 5: Preparation of *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(2-(difluoromethoxy)-6-fluorophenyl)isonicotinamide



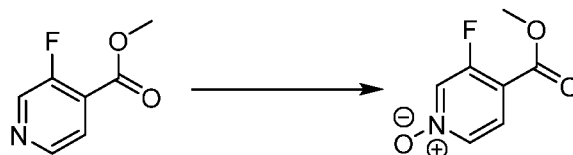
[0415] The title compound was prepared according to General Procedure A employing 3-(2-(difluoromethoxy)-6-fluorophenyl)isonicotinic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was diluted with water and extracted with EtOAc (2 x). The combined organic extracts were concentrated under reduced pressure. The residue was purified by Prep-TLC (eluent: 5% MeOH in DCM) to afford the title compound (53 mg, 59% yield) as a light yellow solid. ^1H NMR (300 MHz; DMSO d_6): δ 13.13 (s, 1H), 8.83 (d, 1H), 8.66 (s, 1H), 7.84 (d, 1H), 7.54 -7.46 (m, 5H), 7.38-6.89 (m, 3H), 5.47 (s, 2H); m/z 507 ($\text{M}+\text{H}^+$).

Example 110

Synthesis of *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-((3*S*,5*S*)-3,5-dimethylmorpholino)isonicotinamide

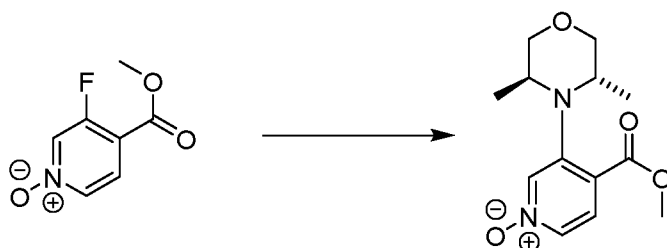


Step 1: Preparation of 3-fluoro-4-(methoxycarbonyl)pyridine 1-oxide



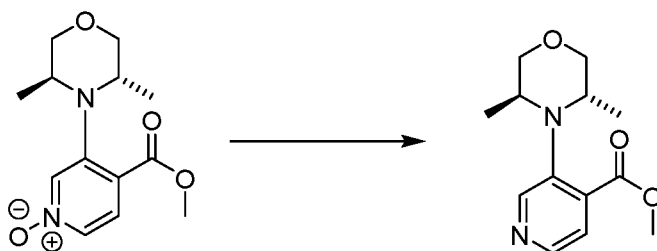
[0416] To a solution of methyl 3-fluoropyridine-4-carboxylate (800 mg, 5.2 mmol) in chloroform (8 mL) under and atmosphere of nitrogen was added *m*-CPBA (85%, 10474 mg, 5.2 mmol). The mixture was stirred for 5 h at room temperature. A solution of sat. NH_4Cl (aq.) was added and the mixture was extracted with DCM (3x). The mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 5% MeOH in DCM to afford the title compound.

Step 2: Preparation of 3-((3*S*,5*S*)-3,5-dimethylmorpholino)-4-(methoxycarbonyl)pyridine 1-oxide



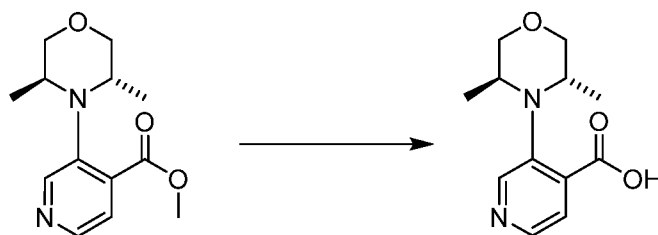
[0417] To a solution of 3-fluoro-4-(methoxycarbonyl)pyridine 1-oxide (770 mg, 4.50 mmol) in MeCN (7.70 mL) was added (3*S*,5*S*)-3,5-dimethylmorpholine hydrochloride (407 mg, 2.70 mmol) and DIEA (1.04 g, 8.09 mmol). The mixture was stirred at 100 °C for 3 days. The mixture was diluted with water and concentrated under reduced pressure to half volume. The mixture was diluted with EtOAc and the layer were separated. The organic layer was concentrated under vacuum. The residue was purified by Prep-TLC (eluent: 4% MeOH in DCM) to afford the title compound (130 mg, 8% yield) as a yellow oil.

Step 3: Preparation of methyl 3-((3*S*,5*S*)-3,5-dimethylmorpholino)isonicotinate



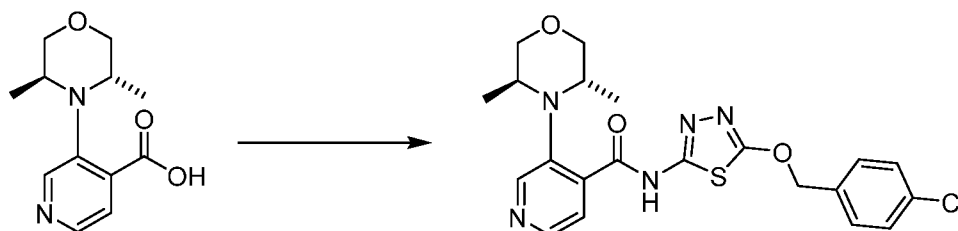
[0418] To a solution of 3-((3*S*,5*S*)-3,5-dimethylmorpholino)-4-(methoxycarbonyl)pyridine 1-oxide (120 mg, 0.451 mmol) in MeOH (1.20 mL) was added 10% Pd/C (12 mg) and HCO₂NH₄ (142 mg, 2.25 mmol). The mixture was stirred for 2 hours at room temperature. The mixture was diluted with MeOH. The solid was removed by filtration and washed with MeOH (2 x). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (eluent: 20% EtOAc in PE) to afford the title compound (78 mg, 67%) as a colorless oil.

Step 4: Preparation of 3-((3*S*,5*S*)-3,5-dimethylmorpholino)isonicotinic acid



[0419] To a solution of methyl 3-((3*S*,5*S*)-3,5-dimethylmorpholino)isonicotinate (78 mg, 0.312 mmol) in MeOH (0.80 mL) and water (0.20 mL) was added NaOH (24 mg, 0.623 mmol). The mixture was stirred for 2 hours at room temperature. The mixture was diluted with water and washed with EtOAc. HCl (1 M) was added to aqueous layer until pH was 5. The aqueous layer was extracted with EtOAc (8 x). The combined organic layers were concentrated under reduced pressure to afford the title compound (70 mg, 94% yield) as a white solid which was used without further purification.

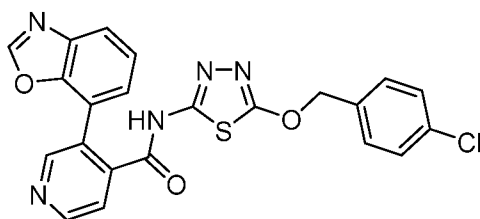
Step 5: *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-((3*S*,5*S*)-3,5-dimethylmorpholino)isonicotinamide



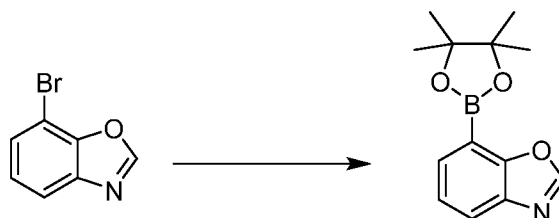
[0420] The title compound was prepared according to General Procedure A employing 3-((3*S*,5*S*)-3,5-dimethylmorpholino)isonicotinic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The resulting was stirred for 2 h at room temperature. The mixture was diluted with water. The solid was collected by filtration and washed with water. The solid was purified by trituration with MeOH to afford the title compound (61 mg, 43% yield) as a light pink solid. ¹H-NMR (300 MHz, DMSO-*d*₆): δ 14.24 (s, 1H), 8.74 (s, 1H), 8.62 (d, 1H), 7.90 (d, 1H), 7.57-7.55 (m, 2H), 7.51-7.48 (m, 2H), 5.52 (s, 2H), 3.95 (s, 3H), 3.74 (s, 1H), 3.17 (s, 2H), 1.06 (s, 3H), 0.81 (s, 3H); *m/z* [M+H]⁺ 460.

Example 111

Synthesis of 3-(benzo[*d*]oxazol-7-yl)-*N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)isonicotinamide

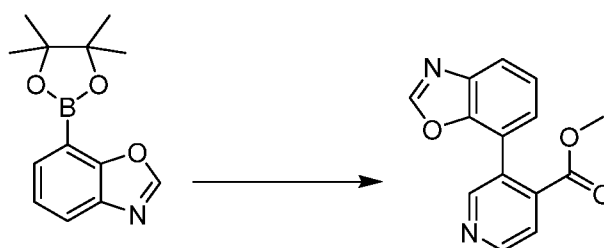


Step 1: Preparation of 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]oxazole



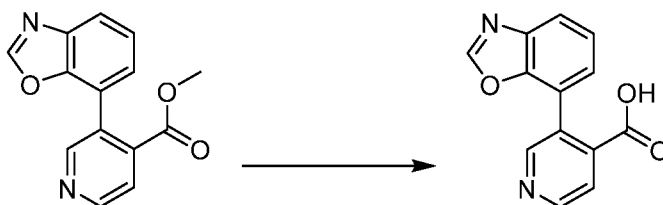
[0421] To a solution of 7-bromo-1,3-benzoxazole (2.00 g, 10.1 mmol) in 1,4-dioxane (20 mL) was added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)-1,3,2-dioxaborolane (3.88 g, 15.1 mmol), KOAc (1.98 g, 20.2 mmol), Pd(dppf)Cl₂ (740 mg, 1.01 mmol). The mixture was stirred at 80 °C for 2 h. The mixture was cooled to rt and diluted with water. The mixture was extracted with EtOAc (3 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluent: 2% EtOAc in PE to afford the title compound (2 g, 71% yield) as a white solid.

Step 2: Preparation of methyl 3-(benzo[d]oxazol-7-yl)isonicotinate



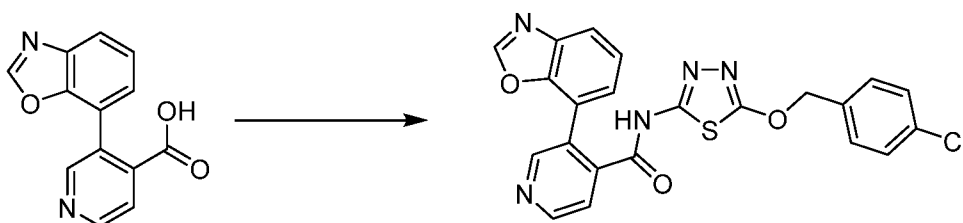
[0422] To a solution of 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]oxazole (1.00 g, 4.08 mmol) in 1,4-dioxane (10 mL) and water (2 mL) was added methyl 3-bromopyridine-4-carboxylate (1.32 g, 6.12 mmol), K₂CO₃ (1.13 g, 8.16 mmol) and Pd(dppf)Cl₂ (0.30 g, 0.408 mmol). The mixture was stirred at 80 °C for 2 h. The mixture was diluted with water and extracted with EtOAc (3x). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluent: 3% EtOAc in PE to afford the title compound (700 mg, 64% yield) as a white solid.

Step 3: Preparation of 3-(benzo[d]oxazol-7-yl)isonicotinic acid



[0423] The title compound was prepared according to General Procedure F employing methyl 3-(benzo[d]oxazol-7-yl)isonicotinate. The mixture was acidified to pH 6 with AcOH. The mixture was concentrated under reduced pressure. The residue was purified by reverse phase chromatography (column, C18 silica gel; mobile phase, with 0-10% MeCN in water) to afford the title compound (270 mg, 37% yield) as a yellow solid.

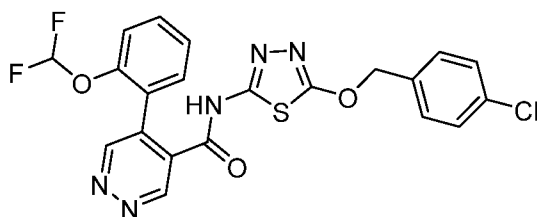
Step 4: Preparation of 3-(benzo[d]oxazol-7-yl)-*N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)isonicotinamide



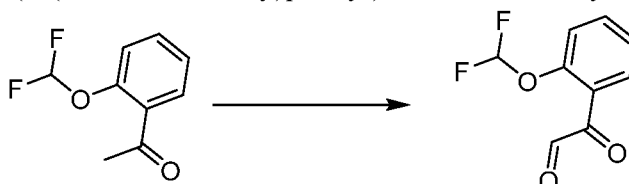
[0424] The title compound was prepared according to General Procedure A employing 3-(benzo[d]oxazol-7-yl)isonicotinic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was diluted with water and extracted with EtOAc (2 x). The combined organic extracts were concentrated under reduced pressure. The residue was purified by Prep-TLC (eluent: 5% MeOH in DCM) to afford the title compound (15 mg, 7% yield) as a white solid. ¹H NMR (300 MHz, DMSO-*d*₆): δ 13.13 (s, 1H), 8.93 (s, 1H), 8.85 (d, 1H), 8.72 (s, 1H), 7.85 - 7.80 (m, 2H), 7.54 - 7.46 (m, 6H), 5.46 (s, 2H); *m/z* 464 (M+H⁺).

Example 112

Synthesis of *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-5-(2-(difluoromethoxy)phenyl)pyridazine-4-carboxamide

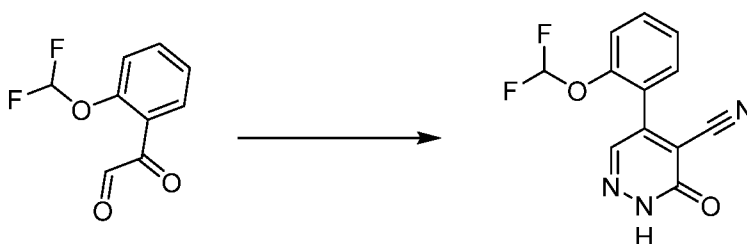


Step 1: Preparation of 2-(2-(difluoromethoxy)phenyl)-2-oxoacetaldehyde



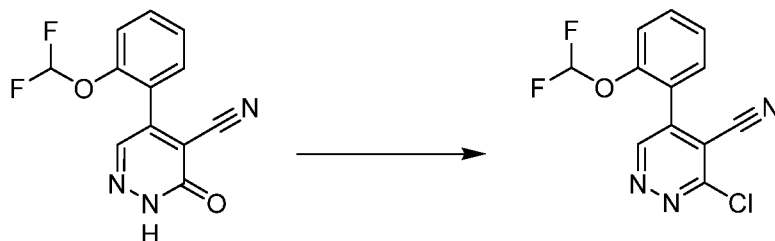
[0425] To a solution of 1-[2-(difluoromethoxy)phenyl]ethanone (5.00 g, 26.8 mmol) in 1,4-dioxane (27 mL) and water (3 mL) was added SeO_2 (4.47 g, 40.2 mmol). The mixture was stirred at 100 °C overnight. The mixture was diluted with water and extracted with EtOAc. The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 20% EtOAc in PE) to afford the title compound (3.6 g, 26% yield) as a colorless oil.

Step 2: Preparation of 5-(2-(difluoromethoxy)phenyl)-3-oxo-2,3-dihydropyridazine-4-carbonitrile



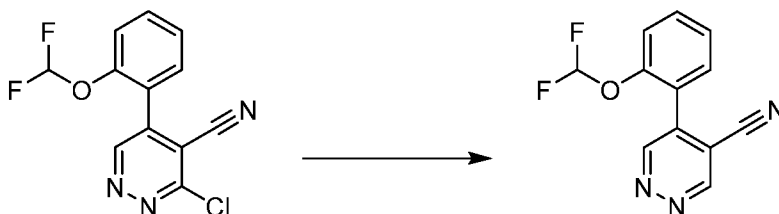
[0426] To a solution of 2-(2-(difluoromethoxy)phenyl)-2-oxoacetaldehyde (3.60 g, 17.9 mmol) in EtOH (108 mL) was added Na_2SO_4 (5.11 g, 35.9 mmol) and cyacetamide (1.78 g, 17.9 mmol). The mixture was stirred for 5 hours at room temperature. The mixture was filtered and washed with EtOAc (3 x). The filtrate was concentrated under vacuum to give a residue. The residue was dissolved in EtOH to give solution A. In a separate flask, a solution of sodium metal (413 mg, 17.9 mmol) in EtOH was cooled to 0 °C under nitrogen atmosphere. The solution A was added to the sodium ethoxide mixture dropwise at 0 °C. The mixture was then stirred at 80 °C overnight. The mixture was cooled to rt and diluted with water. The mixture was concentrated under reduced pressure. The precipitated solids were collected by filtration and washed with water followed by EtOAc to afford the title compound (1.14 g, 23% yield) as a brown solid.

Step 3: Preparation 3-chloro-5-(2-(difluoromethoxy)phenyl)pyridazine-4-carbonitrile



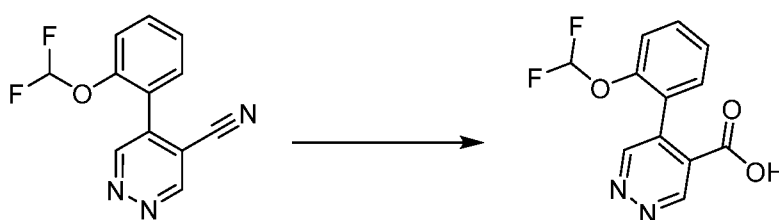
[0427] 5-(2-(difluoromethoxy)phenyl)-3-oxo-2,3-dihydropyridazine-4-carbonitrile (1.10 g, 4.17 mmol) was diluted with POCl₃ (11 mL). The mixture was stirred at 100 °C overnight. The mixture was cooled to 0 °C and ice water was added. The mixture was extracted with EtOAc and the organic layer was concentrated under reduced pressure. During concentration, precipitated solid form. The solid was collected by filtration and washed with MeOH to afford the title compound (780 mg, 63% yield) as a brown solid.

Step 4: Preparation of 5-(2-(difluoromethoxy)phenyl)pyridazine-4-carbonitrile



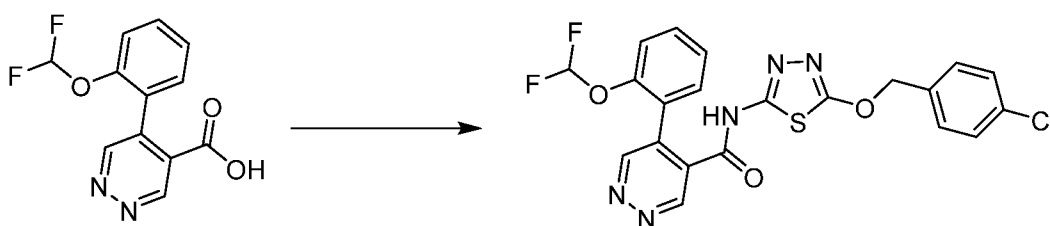
[0428] To a solution of 3-chloro-5-(2-(difluoromethoxy)phenyl)pyridazine-4-carbonitrile (340 mg, 1.20 mmol) in MeOH (3.50 mL) and THF (1.70 mL) was added 10% Pd/C (35 mg) and HCO₂NH₄ (380 mg, 6.03 mmol). The mixture was stirred at 60 °C overnight. The solids were filtered and washed with MeOH (3 x). The mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (eluent: 3% MeOH in DCM) to afford the title compound (130 mg, 41% yield) as a colorless oil.

Step 5: Preparation of 5-(2-(difluoromethoxy)phenyl)pyridazine-4-carboxylic acid



[0429] To a solution of 5-(2-(difluoromethoxy)phenyl)pyridazine-4-carbonitrile (110 mg, 0.445 mmol) in EtOH (1.10 mL) was added KOH (99 mg, 1.78 mmol). The mixture was stirred at 100 °C for 3 h. The mixture was diluted with water and washed with EtOAc. AcOH was added to the aqueous layer until the pH was 5. The mixture was extracted with EtOAc. The organic layer was concentrated under reduced pressure to afford the title compound (55 mg, 45% yield) as a yellow solid.

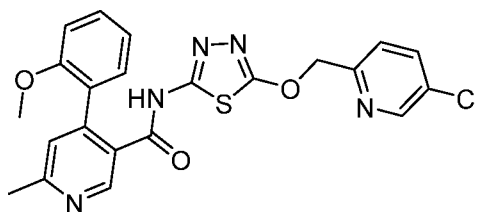
Step 6: Preparation of *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-5-(2-(difluoromethoxy)phenyl)pyridazine-4-carboxamide



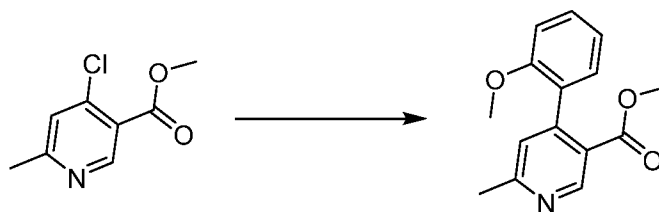
[0430] To a solution of 5-(2-(difluoromethoxy)phenyl)pyridazine-4-carboxylic acid (45 mg, 0.169 mmol) in DMF (0.50 mL) was added 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) (40 mg, 0.169 mmol), EDCI (48 mg, 0.254 mmol) and HOBt (34 mg, 0.254 mmol). The mixture was stirred overnight at room temperature. The mixture was diluted with water and extracted with EtOAc. The organic layer was concentrated under reduced pressure. The residue was purified by Prep-TLC (eluent: 3% MeOH in DCM) to afford the title compound (16 mg, 19% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.31 (s, 1H), 9.55 (s, 1H), 9.40 (s, 1H), 7.58-7.46 (m, 6H), 7.41-6.85 (m, 3H), 5.47 (s, 2H); *m/z* 490 (M+H⁺).

Example 113

Synthesis of *N*-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)-6-methylnicotinamide

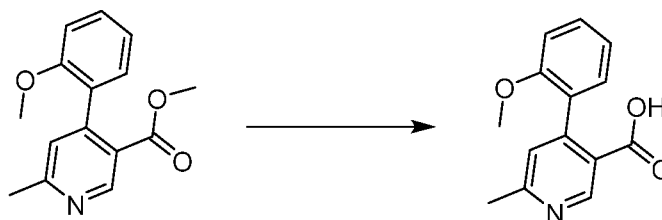


Step 1: Preparation of methyl 4-(2-methoxyphenyl)-6-methylnicotinate



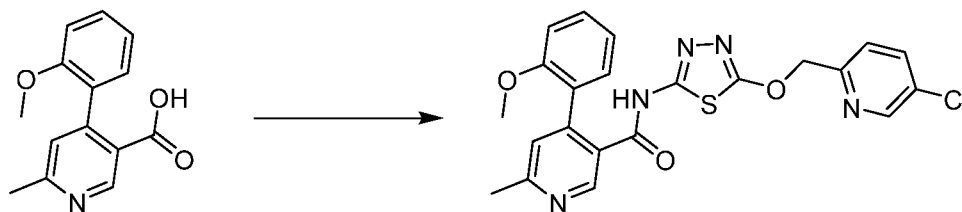
[0431] To a solution of methyl 4-chloro-6-methylpyridine-3-carboxylate (300 mg, 1.61 mmol) in 1,4-dioxane (4 mL) and water (0.5 mL), was added 2-methoxyphenylboronic acid (491 mg, 3.23 mmol), K_2CO_3 (446 mg, 3.23 mmol), $Pd(dtbpf)Cl_2$ (105 mg, 0.162 mmol). The mixture was stirred for 2 h at 80 °C. The mixture was diluted with water and extracted with EtOAc (3 x). The combined organic extracts were concentrated under reduced pressure. The residue was purified by Prep-TLC (eluent: 10% MeOH in DCM) to afford the title compound (330 mg, 72% yield) as a brown oil.

Step 2: Preparation of 4-(2-methoxyphenyl)-6-methylnicotinic acid



[0432] The title compound was prepared according to General Procedure F employing methyl 4-chloro-6-methylpyridine-3-carboxylate. The mixture was diluted with water and MeOH was removed under reduced pressure. The mixture was acidified to pH 5 with HCl (1 M). The precipitated solids were collected by filtration and washed with water (2 x) to afford the title compound (140 mg, 41% yield) as a white solid.

Step 3: Preparation of *N*-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)-6-methylnicotinamide

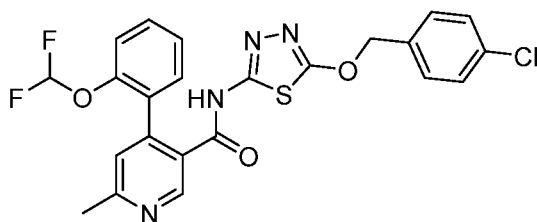


[0433] The title compound was prepared according to General Procedure A employing 4-(2-methoxyphenyl)-6-methylnicotinic acid and 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-

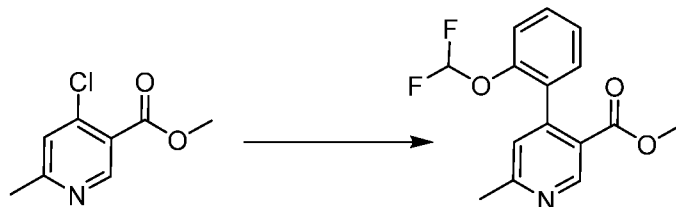
2-amine (Intermediate C). The mixture was diluted with water. The mixture was extracted with EtOAc (3 x). The combined organic extracts were concentrated under reduced pressure. The residue was purified by Prep-TLC (eluent: 3% MeOH in DCM) to afford the title compound (55 mg, 27%) as a white solid. ^1H NMR (300 MHz, DMSO- d_6): δ 12.76 (s, 1H), 8.66 (s, 2H), 8.00 (d, 1H), 7.60 (d, 1H), 7.39-7.33 (m, 2H), 7.30 (s, 1H), 7.08 (t, 1H), 6.96 (d, 1H), 5.54 (s, 2H), 3.51 (s, 3H), 2.57 (s, 3H); m/z 468 ($\text{M}+\text{H}^+$).

Example 114

Synthesis of *N*-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-4-[2-(difluoromethoxy)phenyl]-6-methylpyridine-3-carboxamide

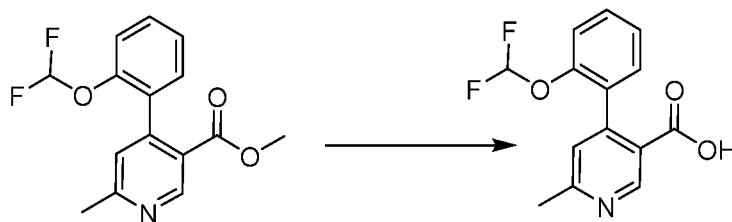


Step 1: Preparation of methyl 4-[2-(difluoromethoxy)phenyl]-6-methylpyridine-3-carboxylate



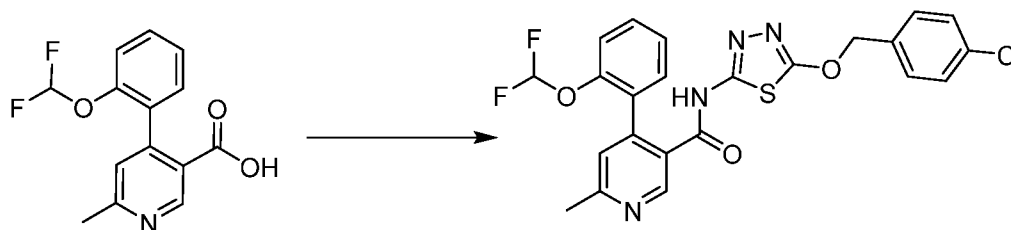
[0434] The title compound was prepared using General Procedure E employing methyl 4-chloro-6-methylpyridine-3-carboxylate and 2-[2-(difluoromethoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. The mixture was stirred at 60 °C for 2 h. The mixture was cooled to rt and diluted with water. The mixture was extracted with EtOAc (2x) and the combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EtOAc 5:1) to afford the title compound as a yellow oil.

Step 2: Preparation of 4-[2-(difluoromethoxy)phenyl]-6-methylpyridine-3-carboxylic acid



[0435] The title compound was prepared according to General Procedure F employing methyl 4-[2-(difluoromethoxy)phenyl]-6-methylpyridine-3-carboxylate. The mixture was stirred at 50°C for 3 h. The mixture was cooled to rt and diluted with water. The MeOH removed by vacuum. The mixture was acidified to pH 6 with HCl (1 M). The mixture was extracted with EtOAc (3x5). The combined organic layers were concentrated under reduced pressure to afford the title compound as a white solid which was used without further purification.

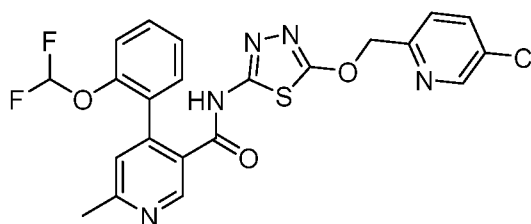
Step 3: Preparation of *N*-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-4-[2-(difluoromethoxy)phenyl]-6-methylpyridine-3-carboxamide



[0436] To a solution of 4-[2-(difluoromethoxy)phenyl]-6-methylpyridine-3-carboxylic acid (100 mg, 0.36 mmol) in DMF (1.00 mL) was added 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) (87 mg, 0.36 mmol), HOBt (73 mg, 0.54 mmol) and EDCI (103 mg, 0.54 mmol). The mixture was stirred for at rt for 12 h. The mixture was diluted with water and extracted with EtOAc (2x). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 20:1) to afford the title compound (88 mg, 47% yield) as a white solid. ¹H NMR (300 MHz, DMSO-*d*₆): δ 12.90 (s, 1H), 8.80 (s, 1H), 7.54 -7.45 (m, 5H), 7.45 -7.43 (m, 1H), 7.42 -7.39 (m, 2H), 7.32 - 7.17 (m, 1H), 7.03 - 6.78 (m, 1H), 5.47 (s, 2H), 2.58 (s, 3H); *m/z* 503 (M+H⁺).

Example 115

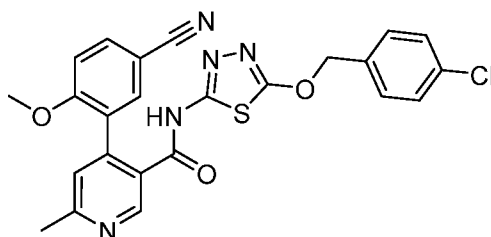
Synthesis of *N*-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-[2-(difluoromethoxy)phenyl]-6-methylpyridine-3-carboxamide



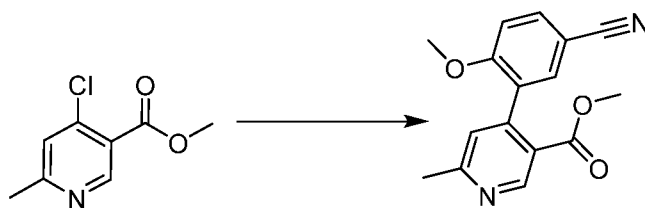
[0437] The title compound was prepared using similar procedure as Example 114, Step 3 replacing 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) with 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C). The residue was purified by Prep-TLC (DCM:MeOH, 20:1) to afford the title compound as a white solid. ¹H NMR (300 MHz, DMSO-*d*₆): δ 12.93 (s, 1H), 8.81 (s, 1H), 8.65 (s, 1H), 8.02 - 7.98 (m, 1H), 7.61 - 7.58 (d, 1H), 7.51 - 7.46 (m, 1H), 7.46 - 7.42 (m, 1H), 7.40 - 7.28 (m, 2H), 7.20 - 6.79 (m, 2H), 5.54 (s, 2H), 2.58 (s, 3H); *m/z* 504 (M+H⁺).

Example 116

Synthesis of *N*-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(5-cyano-2-methoxyphenyl)-6-methylpyridine-3-carboxamide

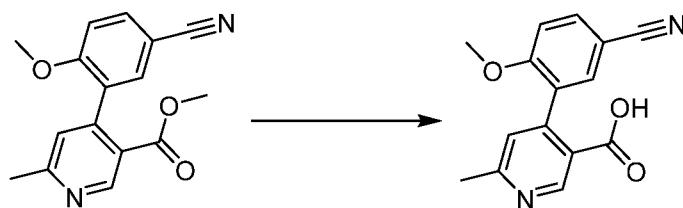


Step 1. Preparation of methyl 4-(5-cyano-2-methoxyphenyl)-6-methylpyridine-3-carboxylate



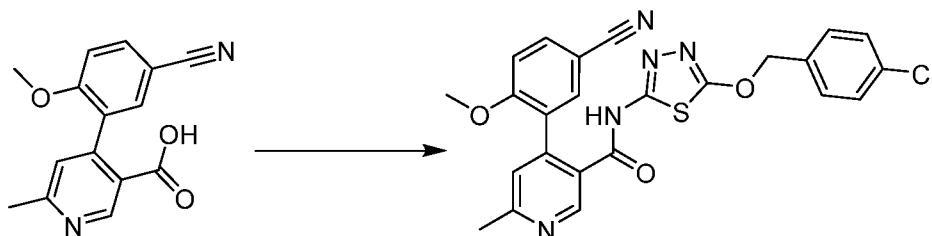
[0438] A reaction vial under a nitrogen atmosphere was charged with 5-cyano-2-methoxyphenylboronic acid (1525 mg, 8.6 mmol), 1,4-dioxane (8 mL), methyl 4-chloro-6-methylpyridine-3-carboxylate (800 mg, 4.3 mmol), H₂O (2 mL), K₂CO₃ (1191 mg, 8.6 mmol), Pd(dtbpf)Cl₂ (281 mg, 0.43 mmol). The mixture was stirred at 80 °C for 4 h. The mixture was cooled to rt and diluted with water. The mixture was extracted with EtOAc (3x) and the combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 20:1) to afford the title compound as a yellow oil.

Step 2. Preparation of 4-(5-cyano-2-methoxyphenyl)-6-methylpyridine-3-carboxylic acid



[0439] To a solution of methyl 4-(5-cyano-2-methoxyphenyl)-6-methylpyridine-3-carboxylate (600.00 mg, 2.125 mmol) in THF (20 mL), and water (4 mL) was added LiOH (102 mg, 4.3 mmol). The mixture was stirred at rt for 2 h. The mixture was diluted with water and acidified with HCl (1 M) to pH 5. The mixture was extracted with EtOAc (3x) and the combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 8:1) to afford the title compound (360 mg, 60% yield) as a brown solid.

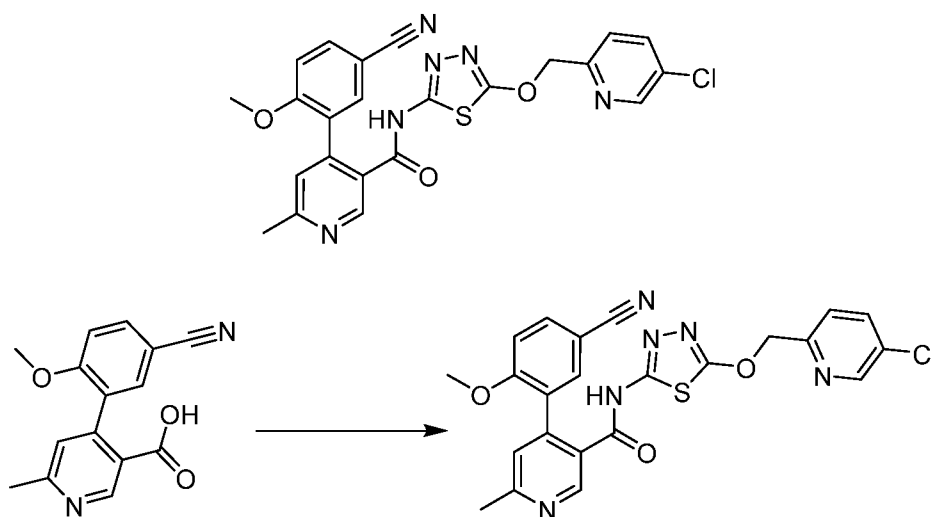
Step 3. Preparation of *N*-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(5-cyano-2-methoxyphenyl)-6-methylpyridine-3-carboxamide



[0440] The title compound was prepared using General Procedure A employing 4-(5-cyano-2-methoxyphenyl)-6-methylpyridine-3-carboxylic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). The mixture was diluted with water and extracted with EtOAc (3x). The combined organic layers were concentrated under reduced pressure. The residue was triturated with MeOH to afford the title compound as a red solid. ¹H NMR (300 MHz, DMSO-*d*₆): δ 12.88 (s, 1H), 8.82 (s, 1H), 8.08-7.73 (m, 2H), 7.54-7.47 (m, 4H), 7.39 (s, 1H), 7.26-7.16 (d, 1H), 5.38 (s, 2H), 3.59 (s, 3H), 2.58 (s, 3H); *m/z* 492 (M+H⁺).

Example 117

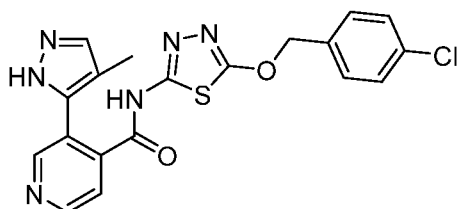
Synthesis of *N*-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(5-cyano-2-methoxyphenyl)-6-methylpyridine-3-carboxamide



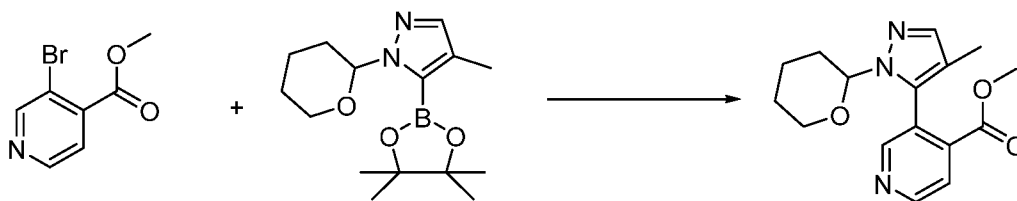
[0441] The title compound was prepared using General Procedure A employing 4-(5-cyano-2-methoxyphenyl)-6-methylpyridine-3-carboxylic acid (Example 116, Step 2) and 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C). The mixture was diluted with water and extracted with EtOAc (3x). The combined organic layers were concentrated under reduced pressure. The residue was triturated with MeOH to afford the title compound as a red solid. ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 12.81 (s, 1H), 8.73 (s, 1H), 8.65 (s, 1H), 8.02-7.95 (m, 1H), 7.92-7.84 (m, 2H), 7.62-7.54 (d, 1H), 7.39 (s, 1H), 7.19-7.16 (d, 1H), 5.54 (s, 2H), 3.59 (s, 3H), 2.58 (s, 3H); m/z 493 ($\text{M}+\text{H}^+$).

Example 118

Synthesis of *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(4-methyl-1*H*-pyrazol-5-yl)isonicotinamide

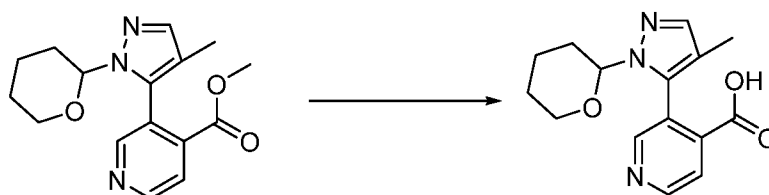


Step 1: Preparation of methyl 3-(4-methyl-1-(tetrahydro-2H-pyran-2-yl)-1*H*-pyrazol-5-yl)isonicotinate



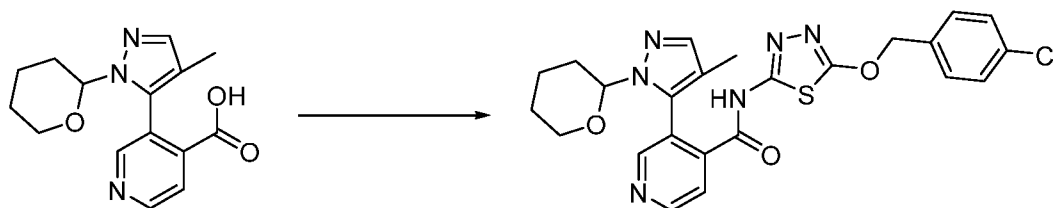
[0442] A reaction vial under an atmosphere of nitrogen was charged with methyl 3-bromoisonicotinate (250 mg, 1.15 mmol), 4-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (405 mg, 1.38 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (128 mg, 0.173 mmol), K₂CO₃ (319 mg, 2.31 mmol) and 6 mL of a 9:1 dioxane/water solution. The mixture was sealed under nitrogen and heated to 80 °C for 18 h. The mixture was diluted with water (5 mL), extracted with EtOAc (3 x 5 mL), dried over Na₂SO₄. The combined organic extracts were concentrated under reduced pressure. The residue was purified via silica gel column chromatography (eluent: 0% - 100% EtOAc in hexanes) to afford the title compound (125 mg, 36% yield) as a yellow oil.

Step 2: Preparation of 3-(4-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-5-yl)isonicotinic acid



[0443] The title compound was prepared according to General Procedure F employing methyl 3-(4-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-5-yl)isonicotinate (122 mg, 0.404 mmol). The resulting mixture was diluted with water (5 mL). The aqueous layer was extracted with EtOAc (3 x 8 mL). The pH of aqueous solution was adjusted to 5 with HCl (1 M). The aqueous layer was extracted with EtOAc (20 mL). The combined organic extracts were concentrated under reduced pressure to afford the title compound which was taken forward crude without further purification.

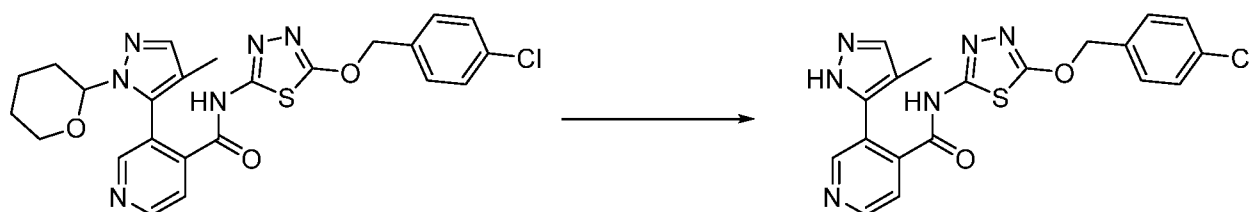
Step 3: Preparation of *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(4-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-5-yl)isonicotinamide



[0444] The title compound was prepared according to General Procedure A employing 3-(4-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-5-yl)isonicotinic acid (120 mg, 0.417 mmol),

and 5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-amine (Intermediate B) (100 mg, 0.417 mmol). The resulting solution was stirred for 2 hours at room temperature. The mixture was diluted with water (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were concentrated under reduced pressure. The residue was purified using silica gel chromatography (eluent: 0% - 100% EtOAc hexanes) to afford the title compound (108 mg, 50% yield) as a yellow oil.

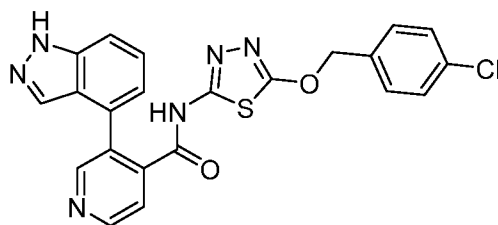
Step 4: Preparation of *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(4-methyl-1*H*-pyrazol-5-yl)isonicotinamide



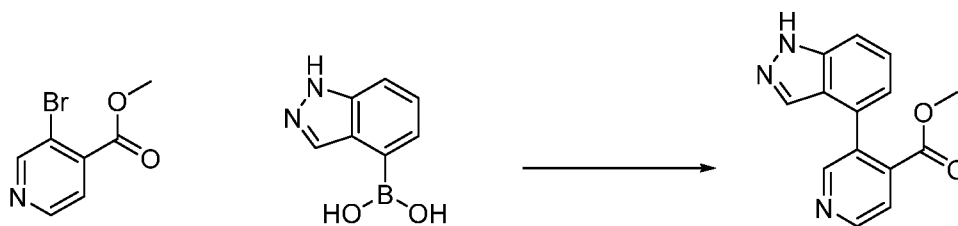
[0445] A reaction vial was charged with *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(4-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-5-yl)isonicotinamide (108 mg, 211 mmol), TFA (0.048 mL, 0.634 mmol) and DCM (1 mL) the mixture was stirred for 1 hour at room temperature. The mixture was concentrated under reduced pressure. The residue was purified via reverse phase HPLC (C18 column, 15%-50% MeCN in water) to afford the title compound as a white powder (2 mg, 2% yield). *m/z* 427 [M+H]⁺

Example 119

Synthesis of *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(1*H*-indazol-4-yl)isonicotinamide

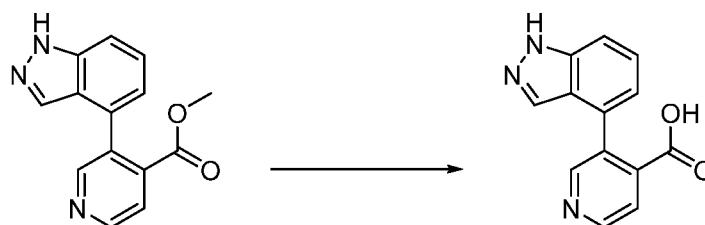


Step 1: Preparation of methyl 3-(1*H*-indazol-4-yl)isonicotinate



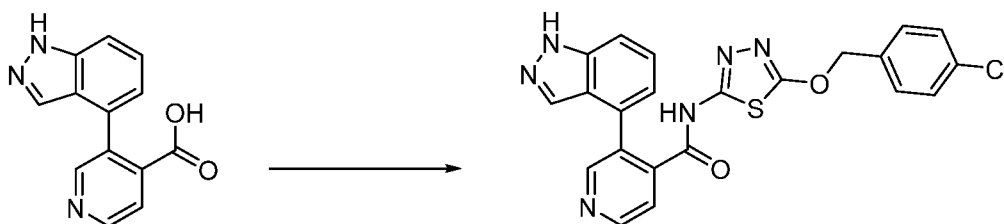
[0446] A reaction vial under an atmosphere of nitrogen was charged with methyl 3-bromoisonicotinate (190 mg, 0.879 mmol), 1,4-dioxane (6.9 mL), (1*H*-indazol-4-yl)boronic acid (170 mg, 1.05 mmol), K₂CO₃ (243 mg, 1.75 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (97 mg, 0.131 mmol). The resulting solution was stirred overnight at 85 °C. The mixture was diluted with water (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 0 -100% EtOAc hexanes) to afford the title compound (90 mg, 40% yield) as a white solid.

Step 2: Preparation of 3-(1*H*-indazol-4-yl)isonicotinic acid



[0447] The title compound was prepared according to General Procedure F employing methyl 3-(1*H*-indazol-4-yl)isonicotinate (90 mg, 0.355 mmol). The resulting mixture was diluted with water (5 mL). The aqueous layer was extracted with EtOAc (3 x 8 mL). The pH of aqueous solution was adjusted to 5 with HCl (1 M). The aqueous layer was extracted with EtOAc (20 mL). The combined organic extracts were concentrated under reduced pressure to afford the title compound which was taken forward crude without further purification.

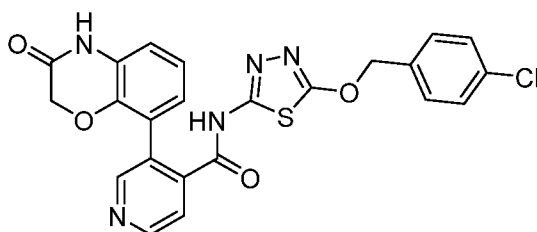
Step 3: Preparation of *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(1*H*-indazol-4-yl)isonicotinamide



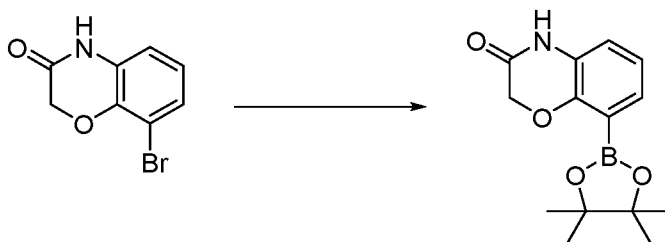
[0448] The title compound was prepared according to General Procedure A employing 3-(1*H*-indazol-4-yl)isonicotinic acid (85 mg, 0.355 mmol), and 5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-amine (Intermediate B) (85 mg, 0.355 mmol). The mixture was diluted with water (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were concentrated under reduced pressure. The residue was purified using silica gel chromatography (eluent: 0% - 100% EtOAc hexanes) to afford the title compound (1 mg, 1% yield) as a clear oil. *m/z* 463 [M+H]⁺

Example 120

Synthesis of *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-8-yl)isonicotinamide



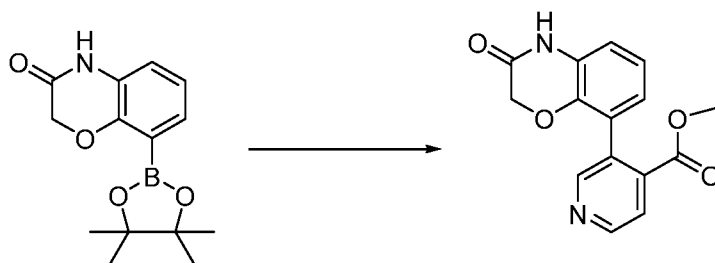
Step 1: Preparation of 8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one



[0449] A round bottom flask under an atmosphere of nitrogen was charged with (500 mg, 2.19 mmol), Bis(pinacolato) diboron (1.11 mg, 4.38 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II):DCM (181 mg, 0.219 mmol), NaOAc

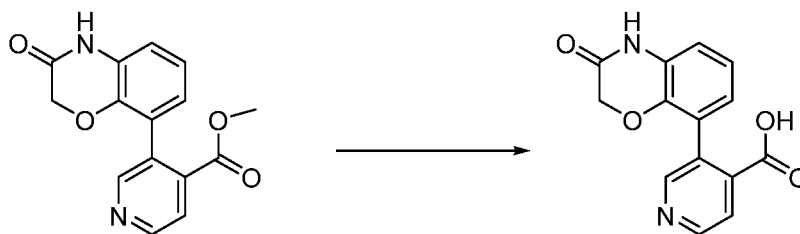
(645 mg, 6.57 mmol) and 1,4-dioxane (11 mL). The mixture was sealed under nitrogen and heated to 100 °C for 2 h. The mixture was diluted with water (5 mL), extracted with EtOAc (3 x 5 mL), dried over Na₂SO₄. The combined organic extracts were concentrated under reduced pressure. The residue was purified via silica gel column chromatography (eluent: 0% - 100% EtOAc in hexanes) to afford the title compound (536 mg, 88% yield) as a yellow oil.

Step 2: Preparation of methyl 3-(3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-8-yl)isonicotinate



[0450] A reaction vial under an atmosphere of nitrogen was charged with methyl 3-bromoisonicotinate (274 mg, 1.27 mmol), 1,4-dioxane (6.4 mL), 8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (350 mg, 1.27 mmol), K₂CO₃ (351 mg, 2.54 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (141 mg, 0.190 mmol). The resulting solution was stirred overnight at 85 °C. The mixture was diluted with water (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 0 -100% EtOAc hexanes) to afford the title compound (176 mg, 48% yield) as a yellow oil.

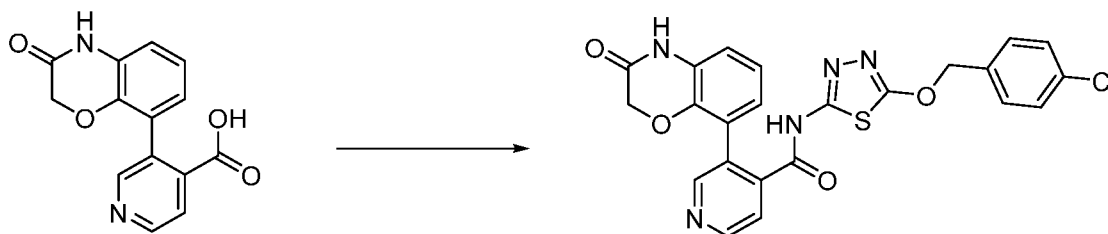
Step 3: 3-(3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-8-yl)isonicotinic acid



[0451] The title compound was prepared according to General Procedure F employing methyl 3-(3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-8-yl)isonicotinate (88 mg, 0.309 mmol). The resulting mixture was diluted with water (5 mL). The aqueous layer was extracted with EtOAc (3 x 8 mL). The pH of aqueous solution was adjusted to 5 with HCl (1 M). The aqueous layer was

extracted with EtOAc (20 mL). The combined organic extracts were concentrated under reduced pressure to afford the title compound which was taken forward crude without further purification.

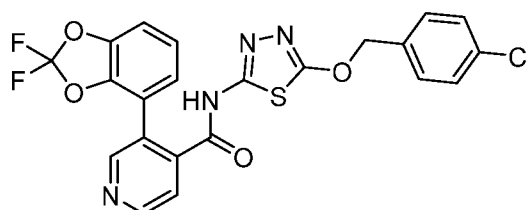
Step 4: Preparation of *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-8-yl)isonicotinamide



[0452] The title compound was prepared according to General Procedure A employing 3-(3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-8-yl)isonicotinic acid (83 mg, 0.307 mmol), and 5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-amine (Intermediate B) (74 mg, 0.307 mmol). The mixture was diluted with water (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were concentrated under reduced pressure. The residue was purified using silica gel chromatography (eluent: 0% - 100% EtOAc hexanes) to afford the title compound (15 mg, 10% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.05 (s, 1H), 10.82 (s, 1H), 8.74 (d, 1H), 8.66 (s, 1H), 7.69 (d, 1H), 7.58 – 7.42 (m, 4H), 7.10 – 6.89 (m, 3H), 5.48 (s, 2H), 4.26 (s, 2H). *m/z* 494 [M+H]⁺

Example 121

Synthesis of *N*-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-4-yl)isonicotinamide

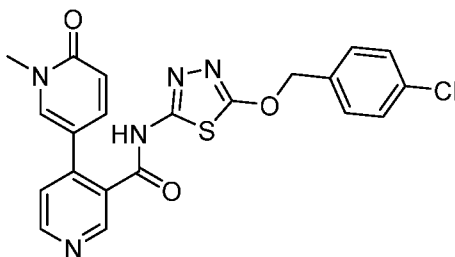


[0453] The title compound was prepared using General Procedures E, F and A employing methyl 3-bromoisonicotinate and (2,2-difluorobenzo[*d*][1,3]dioxol-4-yl)boronic acid in General procedure E and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) in General

procedures A. ^1H NMR (400 MHz, DMSO-d_6) δ 13.24 (s, 1H), 8.86 - 8.83 (m, 2H), 7.79 (d, 1H), 7.59 - 7.50 (m, 2H), 7.50 - 7.46 (m, 3H), 7.35 - 7.30 (m, 2H), 5.49 (s, 2H). m/z 503 $[\text{M}+\text{H}]^+$

Example 122

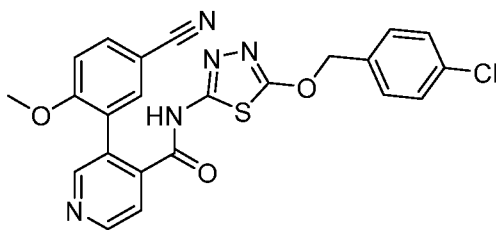
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-methyl-6-oxo-1,6-dihydro-[3,4'-bipyridine]-3'-carboxamide



[0454] The title compound was prepared using General Procedures E, F and A. Methyl 4-chloronicotinate and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one were employed in General Procedure E and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) was replaced with $\text{Pd}(\text{PPh}_3)_4$ in General Procedure E. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. m/z 454 $[\text{M}+\text{H}]^+$

Example 123

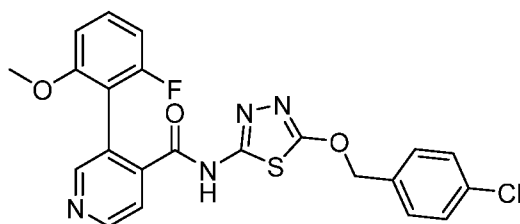
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(5-cyano-2-methoxyphenyl)isonicotinamide



[0455] The title compound was prepared using General Procedures E, F and A. Methyl 3-bromoisonicotinate and (5-cyano-2-methoxyphenyl)boronic acid were employed in General Procedures E. For General Procedure F, NaOH was replaced with LiOH. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. ^1H NMR (400 MHz, DMSO-d_6) δ 12.95 (s, 1H), 8.78 (s, 1H), 8.68 (s, 1H), 7.89 (s, 2H), 7.70 (s, 1H), 7.62 - 7.44 (m, 4H), 7.18 (d, 1H), 5.48 (s, 2H), 3.59 (d, 3H). m/z 478 $[\text{M}+\text{H}]^+$

Example 124

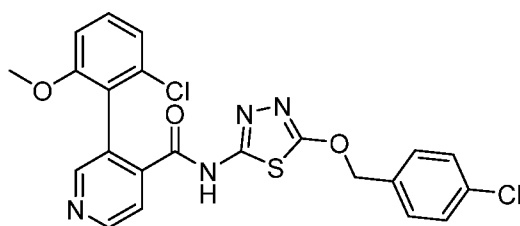
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(2-fluoro-6-methoxyphenyl)isonicotinamide



[0456] The title compound was prepared using General Procedures E, F and A. Methyl 3-bromoisonicotinate and 2-fluoro-6-methoxyphenylboronic acid were employed in General Procedures E and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) was replaced with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane. For General Procedure F, NaOH was replaced with LiOH. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. ^1H NMR (400 MHz, DMSO- d_6) δ 13.03 (s, 1H), 8.76 (d, 1H), 8.63 (s, 1H), 7.74 (s, 1H), 7.66 – 7.46 (m, 4H), 7.41 (q, 1H), 7.06 – 6.82 (m, 2H), 5.48 (s, 2H), 3.58 (d, 3H). m/z 471 $[\text{M}+\text{H}]^+$

Example 125

Synthesis of 3-(2-chloro-6-methoxyphenyl)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)isonicotinamide

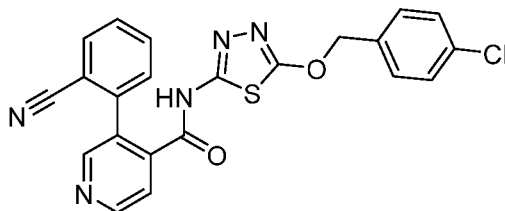


[0457] The title compound was prepared using General Procedures E, F and A. Methyl 3-bromoisonicotinate and 2-chloro-6-methoxyphenylboronic acid were employed in General Procedures E and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) was replaced with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane. For General Procedure F, NaOH was replaced with LiOH. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. ^1H NMR (400 MHz, DMSO- d_6) δ 13.04 (s, 1H), 8.82 – 8.67 (m, 1H), 8.54 (s, 1H), 7.76 (d, 1H),

7.57 – 7.43 (m, 4H), 7.42 – 7.32 (m, 1H), 7.14 (d, 1H), 7.03 (d, 1H), 5.46 (s, 2H), 3.58 (d, 3H).
 m/z 487 $[M+H]^+$

Example 126

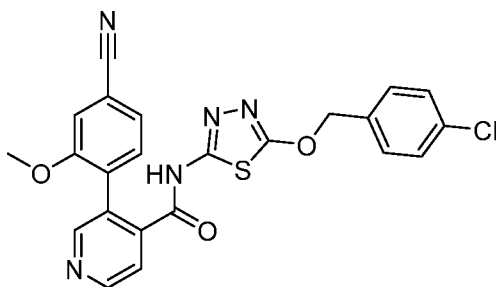
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(2-cyanophenyl)isonicotinamide



[0458] The title compound was prepared using General Procedures E, F and A. Methyl 3-bromoisonicotinate and 2-cyanophenylboronic acid were employed in General Procedures E and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) was replaced with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane. For General Procedure F, NaOH was replaced with LiOH. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. ^1H NMR (400 MHz, DMSO- d_6) δ 13.28 (s, 1H), 8.98 – 8.83 (m, 1H), 8.76 (s, 1H), 7.96 (d, 1H), 7.86 (d, 1H), 7.76 (t, 1H), 7.62 (t, 1H), 7.56 – 7.45 (m, 5H), 5.47 (d, 2H). m/z 448 $[M+H]^+$

Example 127

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(4-cyano-2-methoxyphenyl)isonicotinamide

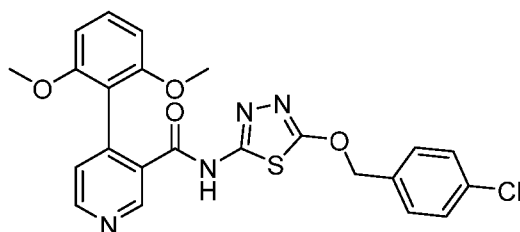


[0459] The title compound was prepared using General Procedures E, F and A. Methyl 3-bromoisonicotinate and 4-cyano-2-methoxycyanophenylboronic acid were employed in General Procedures E and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) was replaced with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane. For General Procedure F, NaOH was replaced with LiOH. For General

Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. ^1H NMR (400 MHz, DMSO- d_6) δ 13.00 (s, 1H), 8.79 (d, 1H), 8.64 (d, 1H), 7.69 (t, 2H), 7.62 – 7.43 (m, 6H), 5.48 (s, 2H), 3.57 (s, 3H). m/z 478 $[\text{M}+\text{H}]^+$

Example 128

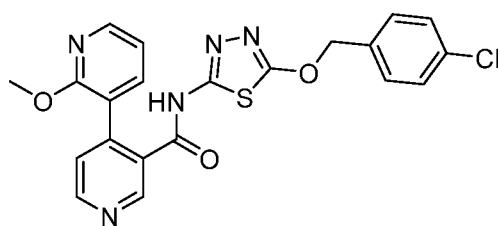
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-(2,6-dimethoxyphenyl)nicotinamide



[0460] The title compound was prepared using General Procedures E and A. 4-bromonicotinic acid and 2,6-dimethoxyphenylboronic acid were employed in General Procedures E and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) was replaced with $\text{Pd}(\text{PPh}_3)_4$. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used and HATU was replaced with propylphosphonic anhydride. m/z 483 $[\text{M}+\text{H}]^+$.

Example 129

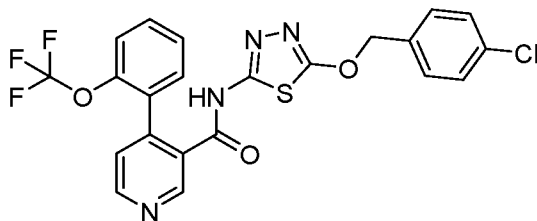
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-methoxy-[3,4'-bipyridine]-3'-carboxamide



[0461] The title compound was prepared using General Procedures E and A. 4-bromonicotinic acid and 2-methoxypyridine-3-boronic acid were employed in General Procedures E and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) was replaced with $\text{Pd}(\text{PPh}_3)_4$. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used and HATU was replaced with propylphosphonic anhydride. m/z 454 $[\text{M}+\text{H}]^+$.

Example 130

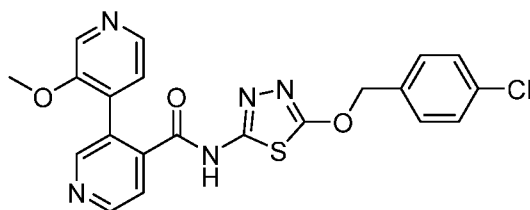
Synthesis N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-(2-(trifluoromethoxy)phenyl)nicotinamide



[0462] The title compound was prepared using General Procedures E, F and A. Methyl 4-chloronicotinate and (2-(trifluoromethoxy)phenyl)boronic acid were employed in General Procedures E and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) was replaced with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane. For General Procedure F, NaOH was replaced with LiOH. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. m/z 507 $[M+H]^+$.

Example 131

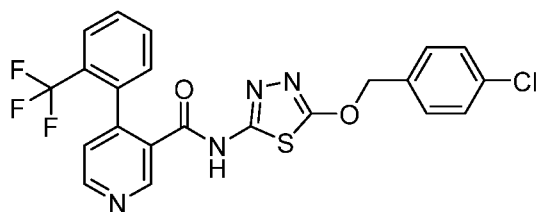
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3'-methoxy-[3,4'-bipyridine]-4-carboxamide



[0463] The title compound was prepared using General Procedures E, F and A. methyl 3-bromoisonicotinate and (3-methoxypyridin-4-yl)boronic acid were employed in General Procedures E. [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) was replaced with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane in General procedure E. For General Procedure F, NaOH was employed instead of LiOH. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. m/z 454 $[M+H]^+$.

Example 132

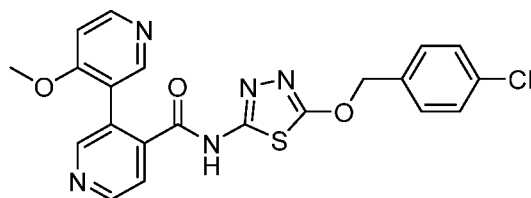
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-(2-(trifluoromethyl)phenyl)nicotinamide



[0464] The title compound was prepared using General Procedures E and A. 4-bromonicotinic acid and 2-(trifluoromethyl)phenyl boronic acid were employed in General Procedures E [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) was replaced with Pd(PPh₃)₄ in General procedure E. For General Procedure A 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. *m/z* 491 [M+H]⁺.

Example 133

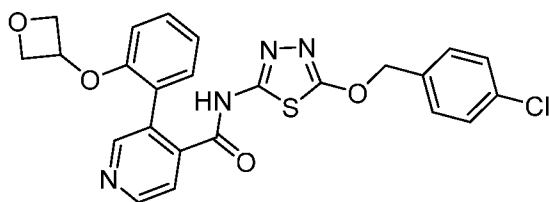
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4'-methoxy-[3,3'-bipyridine]-4-carboxamide



[0465] The title compound was prepared using General Procedures E, F and A methyl 3-bromoisonicotinate and (4-methoxypyridin-3-yl)boronic acid were employed in General Procedures E. [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) was replaced with Pd(PPh₃)₄ in General procedure E. For General Procedure A 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. *m/z* 454 [M+H]⁺.

Example 134

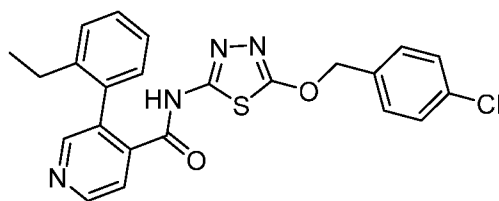
Synthesis of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-3-[2-(oxetan-3-yloxy)phenyl]pyridine-4-carboxamide



[0466] The title compound was prepared using General Procedures E, F and A methyl 3-bromopyridine-4-carboxylate and 4,4,5,5-tetramethyl-2-[2-(oxetan-3-yloxy)phenyl]-1,3,2-dioxaborolane were employed in General Procedures E. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used and HATU was replaced with T3P (50% in EtOAc) solution. ¹H NMR (300 MHz, DMSO-d₆): δ 12.99 (s, 1H), 8.75 (d, 1H), 8.61 (s, 1H), 7.69 (d, 1H), 7.54-7.46 (m, 4H), 7.42-7.35 (m, 1H), 7.32-7.29 (m, 1H), 7.13-7.08 (m, 1H), 6.50 (d, 1H), 5.51 (s, 2H), 5.02-4.95 (m, 1H), 4.66 (t, 2H), 4.35 (t, 2H) ppm *m/z* 495 [M+H]⁺

Example 135

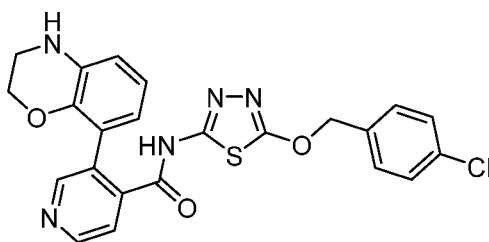
Synthesis of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-3-(2-ethylphenyl)pyridine-4-carboxamide



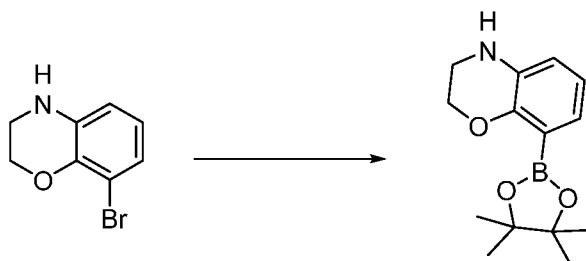
[0467] The title compound was prepared using General Procedures E, F and A. For General Procedure E, methyl 3-bromopyridine-4-carboxylate and 2-ethylphenylboronic acid were employed. For General procedures A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used and HATU was replaced with T₃P solution (50% in EtOAc). ¹H NMR (400 MHz, DMSO-d₆): δ 12.97 (s, 1H), 8.74 (d, 1H), 8.52 (s, 1H), 7.71 (d, 1H), 7.51-7.45 (m, 4H), 7.33 - 7.28 (m, 2H), 7.19-7.17 (m, 1H), 7.12 (d, 1H), 5.44 (s, 2H), 2.42 - 2.33 (m, 2H), 0.99 (t, 3H). *m/z* 451 [M+H]⁺.

Example 136

Synthesis of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-3-(3,4-dihydro-2H-1,4-benzoxazin-8-yl)pyridine-4-carboxamide

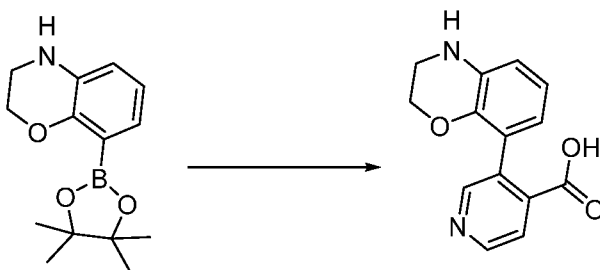


Step 1. Preparation of 8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-2H-1,4-benzoxazine



[0468] To a solution of 8-bromo-3,4-dihydro-2H-1,4-benzoxazine (94 mg, 4.4 mmol) in dioxane (10 mL) was added KOAc (867 mg, 8.8 mmol), bis(pinacolato)diboron (1.7 g, 6.6 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (323 mg, 0.44 mmol). The mixture was stirred for 2 h at 80 °C under nitrogen atmosphere. The mixture was diluted with water and extracted with EtOAc (3 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 9% EtOAc in PE to afford the title compound (930 mg, 69% yield) as a yellow oil.

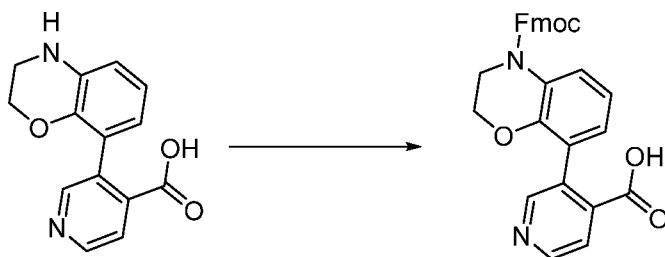
Step 2. Preparation of 3-(3,4-dihydro-2H-1,4-benzoxazin-8-yl)pyridine-4-carboxylic acid



[0469] To a solution of 8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-2H-1,4-benzoxazine (900 mg, 3.4 mmol) in dioxane (8 mL) and water (2 mL) was added K_3PO_4 (49 mg, 0.23 mmol), methyl 3-bromopyridine-4-carboxylate (745 mg, 3.4 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (252 mg, 0.35 mmol) at room temperature. The mixture was stirred for 4 h at 80 °C under nitrogen atmosphere. The mixture

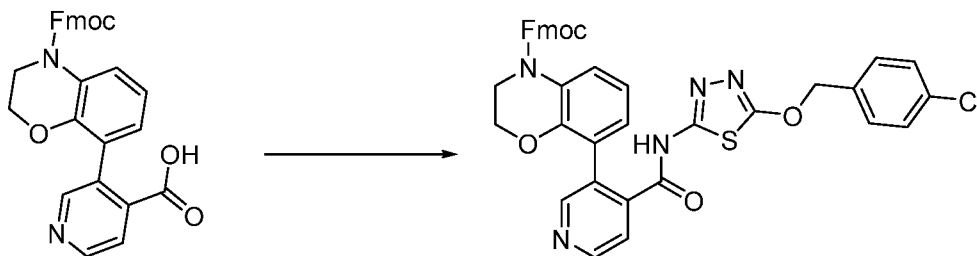
was diluted with water and extracted with EtOAc (3 x). The residue was purified by silica gel column chromatography, eluted with 6% EtOAc in hexane to afford methyl 3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)isonicotinate as a yellow oil. The title compound was prepared following General Procedure F employing methyl 3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)isonicotinate.

Step 3. Preparation of 3-[4-[(9H-fluoren-9-ylmethoxy)carbonyl]-2,3-dihydro-1,4-benzoxazin-8-yl]pyridine-4-carboxylic acid



[0470] To a solution of 3-(3,4-dihydro-2H-1,4-benzoxazin-8-yl)pyridine-4-carboxylic acid (740 mg, 2.89 mmol) in water (2 mL) and dioxane (2 mL) was added NaHCO_3 (485 mg, 5.8 mmol) and 9-fluorenylmethyl chloroformate (1122 mg, 4.3 mmol) at room temperature. The mixture was stirred for 2 h at room temperature under hydrogen atmosphere. The reaction was diluted with water and acidified to pH 6 with HCl (2 M). The mixture was extracted with EtOAc (3 x). The combined organic layers were concentrated under vacuum. The residue was purified by reverse phase chromatography (column, C18 silica gel; mobile phase, with 10-50% MeCN in water) to afford the title compound (180 mg, 13% yield) as an off-white solid.

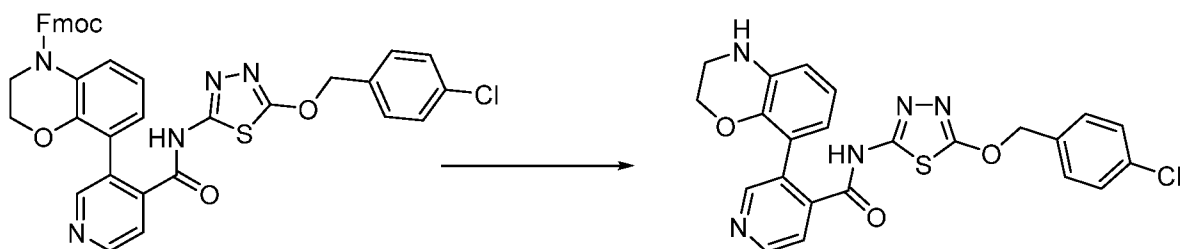
Step 4. Preparation of (9H-fluoren-9-yl)methyl 8-(4-((5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)carbamoyl)pyridin-3-yl)-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate



[0471] To a solution of 3-[4-[(9H-fluoren-9-ylmethoxy)carbonyl]-2,3-dihydro-1,4-benzoxazin-8-yl]pyridine-4-carboxylic acid (160 mg, 0.33 mmol) in DMF (2 mL) was added EDCI (96 mg, 0.50 mmol), HOBt (50 mg, 0.37 mmol), 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (81

mg, 0.33 mmol, Intermediate B). The mixture was stirred for 1 h at rt. The mixture was diluted with water and extracted with EtOAc (3 x). The mixture was concentrated under reduced pressure and the residue was triturated with MeOH to afford the title compound (180 mg, 77% yield) as a white solid.

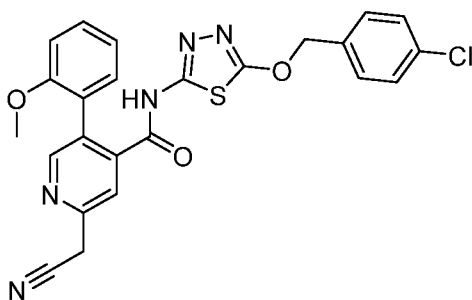
Step 5. Preparation of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-3-(3,4-dihydro-2H-1,4-benzoxazin-8-yl)pyridine-4-carboxamide



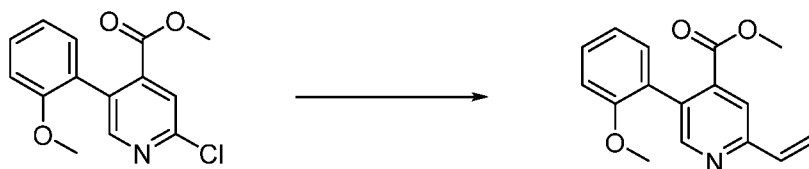
[0472] To a solution of 9H-fluoren-9-ylmethyl 8-[4-[(5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]carbamoyl)pyridin-3-yl]-2,3-dihydro-1,4-benzoxazine-4-carboxylate (170 mg, 0.24 mmol) in DCM (2 mL) was added piperidine (41 mg, 0.48 mmol) at room temperature. The mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The mixture was diluted with DCM and washed with water (4 x). The mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM:MeOH, 20:1) to afford the title compound (24 mg, 21% yield) as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6): δ 2.07 (s, 1H), 3.13 (s, 3H), 3.80 (s, 2H), 5.48 (s, 2H), 5.82 (s, 1H), 6.54-6.59 (m, 2H), 6.74-6.78 (m, 1H), 8.58 (s, 1H), 8.67 (d, 4H), 12.85 (s, 1H). m/z 480 $[\text{M}+\text{H}^+]$.

Example 137

Synthesis of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-2-(cyanomethyl)-5-(2-methoxyphenyl)pyridine-4-carboxamide

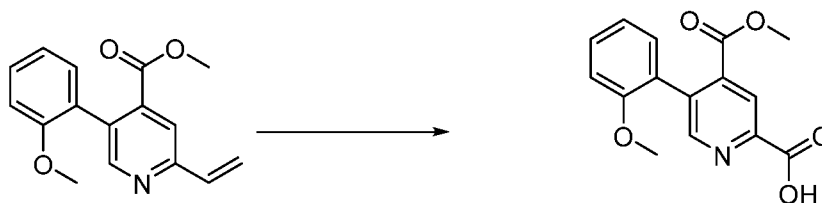


Step 1. Preparation of methyl 2-ethenyl-5-(2-methoxyphenyl)pyridine-4-carboxylate



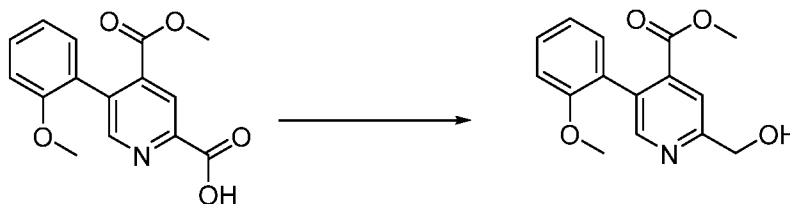
[0473] To a solution of methyl 2-chloro-5-(2-methoxyphenyl)pyridine-4-carboxylate (1.9 g, 6.8 mmol, Example 191, Step 1) and tributyl(ethenyl)stannane (3.3 g, 0.010 mmol) in DMF (20 mL) was added and $\text{Pd}(\text{PPh}_3)_4$ (0.79 g, 0.001 mmol) at room temperature under nitrogen atmosphere. The mixture was stirred overnight at 100 °C under nitrogen atmosphere. The mixture was diluted with water and extracted with EtOAc (2 x). The residue was purified by silica gel column chromatography, eluted with 5% EtOAc in hexanes to afford the title compound (1.42 g) as a white solid.

Step 2. Preparation of 4-(methoxycarbonyl)-5-(2-methoxyphenyl)pyridine-2-carboxylic acid



[0474] To a solution of methyl 2-ethenyl-5-(2-methoxyphenyl)pyridine-4-carboxylate (1.4 g, 5.2 mmol) in THF (20 mL) and water (4 mL) was added NMO (2.4 g, 20.8 mmol) and OsO_4 (0.40 g, 1.6 mmol) at room temperature. The mixture was stirred for 2 h at rt. The mixture was diluted with water and extracted with EtOAc. The mixture was concentrated under vacuum. The residue was purified by reverse phase chromatography (column, C18 silica gel; mobile phase, with 0-100% MeCN in water) to afford the title compound (580 mg, 39% yield) as a colorless oil.

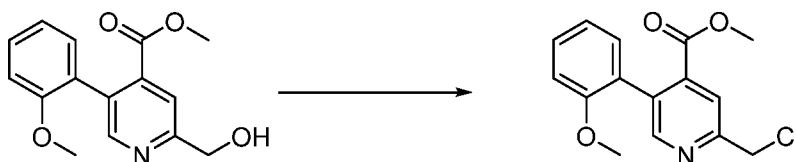
Step 3. Preparation of methyl 2-(hydroxymethyl)-5-(2-methoxyphenyl)pyridine-4-carboxylate



[0475] To a solution of 4-(methoxycarbonyl)-5-(2-methoxyphenyl)pyridine-2-carboxylic acid (540 mg, 1.9 mmol) in THF was added BH_3 (1 M in THF, 3.8 mL, 3.8 mmol) was dropwise at

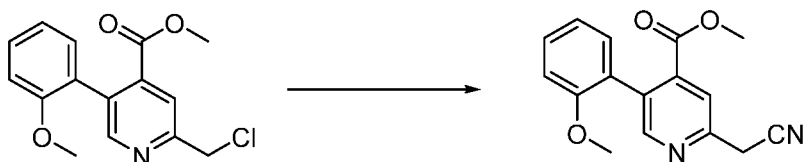
room temperature. The mixture was stirred overnight at 60 °C. The mixture was diluted with water and extracted with EtOAc (2 x). The mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM:MeOH, 20:1) to afford the title compound (320 mg, 62% yield) as a white solid.

Step 4. Preparation of methyl 2-(chloromethyl)-5-(2-methoxyphenyl)pyridine-4-carboxylate



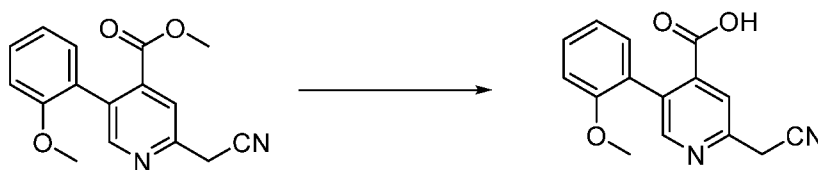
[0476] To a solution of methyl 2-(hydroxymethyl)-5-(2-methoxyphenyl)pyridine-4-carboxylate (310 mg, 1.1 mmol) in DCM was added SOCl_2 (675 mg, 5.7 mmol). The mixture was stirred for 2 h at room temperature. The mixture was quenched by the addition of NaHCO_3 (aq.). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x). The combined organic layers were concentrated under vacuum. The residue was purified by Prep-TLC (DCM:MeOH, 15:1) to afford the title compound (300 mg, 91% yield) as a yellow solid.

Step 5. Preparation of methyl 2-(cyanomethyl)-5-(2-methoxyphenyl)pyridine-4-carboxylate



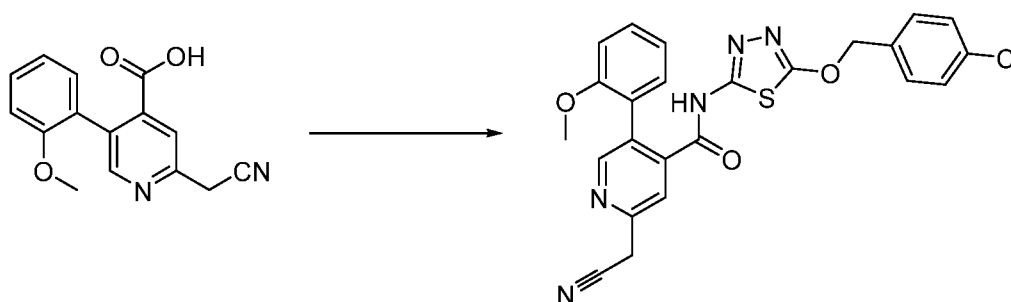
[0477] To a solution of methyl 2-(chloromethyl)-5-(2-methoxyphenyl)pyridine-4-carboxylate (240 mg, 0.82 mmol) in DMSO (5 mL) was added NaCN (81 mg, 1.6 mmol) at room temperature. The mixture was stirred overnight at 60 °C. The mixture was diluted with water and extracted with EtOAc (2 x). The combined organic layers were concentrated under vacuum. The residue was purified by Prep-TLC (DCM:MeOH, 20:1) to afford the title compound (190 mg, 82% yield) as a white solid.

Step 6. Preparation of 2-(cyanomethyl)-5-(2-methoxyphenyl)pyridine-4-carboxylic acid



[0478] To a solution of methyl 2-(cyanomethyl)-5-(2-methoxyphenyl)pyridine-4-carboxylate (160 mg, 0.57 mmol) water (0.5 mL) and MeOH (2.00 mL) was added LiOH (47mg, 1.1 mmol) at room temperature. The mixture was stirred for 1 h at 60 °C. The solution was acidified to pH 5 with HCl (2 M). The mixture was concentrated under vacuum. The residue was purified by reverse phase chromatography (column, C18 silica gel; mobile phase, with 0-30% MeCN in water) to afford the title compound (65 mg, 43% yield) as a white solid.

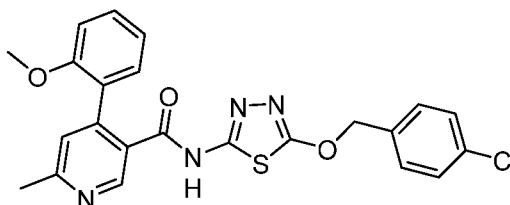
Step 7. Preparation of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-2-(cyanomethyl)-5-(2-methoxyphenyl)pyridine-4-carboxamide



[0479] The title compound was prepared using General Procedure A employing 2-(cyanomethyl)-5-(2-methoxyphenyl)pyridine-4-carboxylic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). ¹H NMR (400 MHz, DMSO-d₆): δ 12.91 (s, 1H), 8.60 (s, 1H), 7.67 (s, 1H), 7.54-7.46 (m, 4H), 7.38 (d, 2H), 7.08 (d, 1H), 6.99 (d, 1H), 5.47 (s, 2H), 4.34 (s, 2H), 3.51 (s, 3H). m/z 492 [M+H⁺].

Example 138

Synthesis of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide

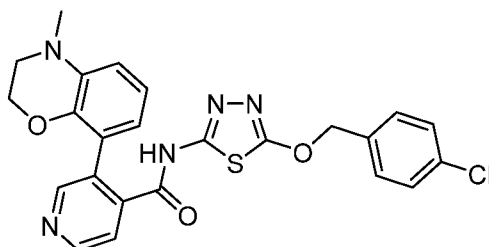


[0480] The title compound was prepared using General Procedure A employing 4-(2-methoxyphenyl)-6-methylnicotinic acid (Example 113, Step 2) and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). ¹H NMR (300 MHz, DMSO-d₆): δ 12.75 (s, 1H),

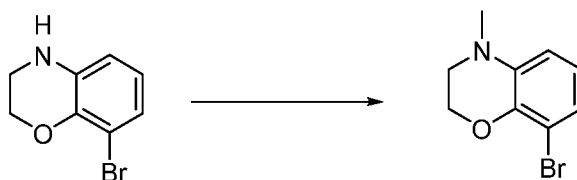
8.66 (s, 1H), 7.55 - 7.47 (m, 4H), 7.42 - 7.30 (m, 3H), 7.08 (t, 1H), 7.04-6.98 (m, 1H), 5.48 (s, 2H), 3.50 (s, 3H), 2.57 (s, 3H). m/z 467 $[M+H]^+$.

Example 139

Synthesis of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-3-(4-methyl-2,3-dihydro-1,4-benzoxazin-8-yl)pyridine-4-carboxamide

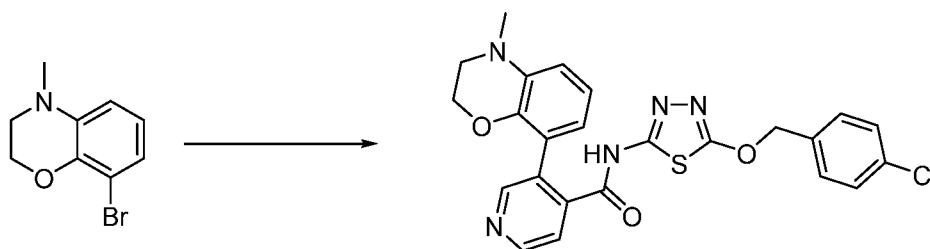


Step 1. Preparation of 8-bromo-4-methyl-2,3-dihydro-1,4-benzoxazine



[0481] To a solution of 8-bromo-3,4-dihydro-2H-1,4-benzoxazine (900 mg, 4.2 mmol) in THF (10 ml) at 0 °C was added sodium hydride (60% dispersion in oil, 202 mg, 5.0 mmol). The mixture was stirred for 40 min at 0 °C. Then MeI (656 mg, 4.63 mmol) was added. The mixture was stirred for 40 min and then warmed to rt and quenched with NH_4Cl (aq.). The mixture was extracted with EtOAc (3 x). The mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with 1% EtOAc in PE to afford the title compound (845 mg, 88% yield) as a light-yellow oil.

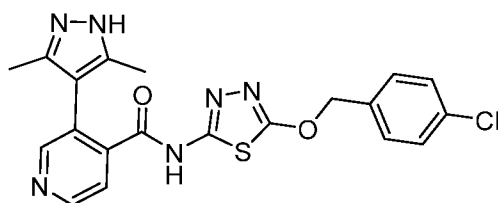
Step 2. Preparation of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-3-(4-methyl-2,3-dihydro-1,4-benzoxazin-8-yl)pyridine-4-carboxamide



[0482] The title compound was prepared using similar procedure as Example 136, Steps 1, 2 and 4 replacing 8-bromo-3,4-dihydro-2H-1,4-benzoxazine with 8-bromo-4-methyl-2,3-dihydro-1,4-benzoxazine in Step 1. ¹H NMR (300 MHz, DMSO-d₆): δ 2.80 (s, 3H), 3.07- 3.17 (m, 2H), 3.86 - 3.94 (m, 2H), 5.48 (s, 2H), 6.64-6.74 (m, 2H), 6.85-6.90 (m, 1H), 7.47-7.60 (m, 5H), 8.59 (s, 1H), 8.68 (d, 1H), 12.86 (s, 1H). m/z 494 [M+H⁺].

Example 140

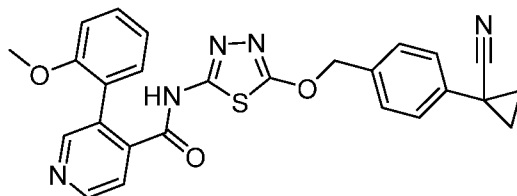
Synthesis of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-3-(3,5-dimethyl-1H-pyrazol-4-yl)pyridine-4-carboxamide



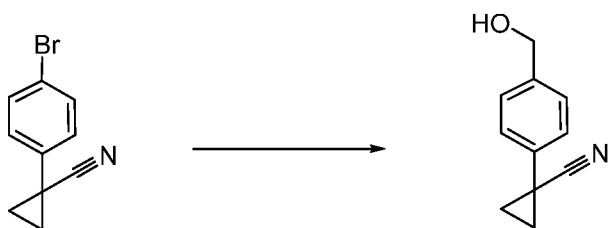
[0483] The title compound was prepared using General Procedure E, F and A. 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole and methyl 3-bromopyridine-4-carboxylate were employed for General Procedure E. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. ¹H NMR (300MHz; DMSO-d₆): δ 12.82 (s, 1H), 12.32 (s, 1H), 8.66 (d, 1H), 8.53 (s, 1H), 7.64 (d, 1H), 7.54 -7.47 (m, 4H), 5.48 (s, 2H), 2.01 (s, 6H). m/z 441 [M+H⁺].

Example 141

Synthesis of N-(5-[[4-(1-cyanocyclopropyl)phenyl]methoxy]-1,3,4-thiadiazol-2-yl)-3-(2-methoxyphenyl)pyridine-4-carboxamide

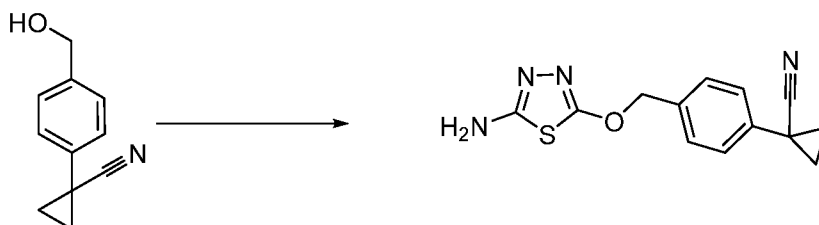


Step 1. Preparation of 1-[4-(hydroxymethyl)phenyl]cyclopropane-1-carbonitrile



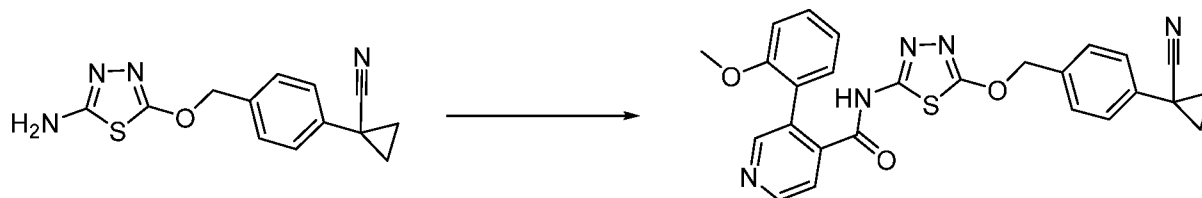
[0484] To a solution of 1-(4-bromophenyl)cyclopropane-1-carbonitrile (1.0 g, 4.5 mmol), in DMF (10 mL) was added (tributylstannyl)methanol (2.2 g, 0.007 mmol) and Pd(PPh₃)₄ (0.52 g, 0.000 mmol) under nitrogen atmosphere. The solution was stirred overnight at 100 °C. The mixture was diluted with water and extracted with EtOAc (3 x). The mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (hexane:EtOAc, 3:1) to afford the title compound (150 mg, 17% yield) as an off-white oil.

Step 2. Preparation of 1-(4-[[5-amino-1,3,4-thiadiazol-2-yl]oxy]methyl]phenyl) cyclopropane-1-carbonitrile



[0485] The title compound was prepared using similar procedures as the synthesis of Intermediate C, replacing (5-chloropyridin-2-yl)methanol with 1-[4-(hydroxymethyl)phenyl]cyclopropane-1-carbonitrile in Step 1.

Step 3. Preparation of N-(5-[[4-(1-cyanocyclopropyl)phenyl]methoxy]-1,3,4-thiadiazol-2-yl)-3-(2-methoxyphenyl)pyridine-4-carboxamide

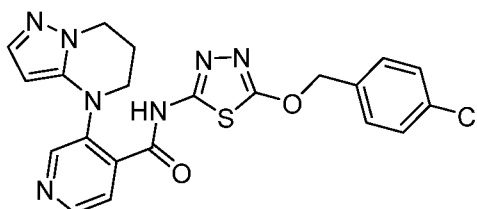


[0486] The title compound was prepared using General Procedure A employing 1-(4-[[5-amino-1,3,4-thiadiazol-2-yl]oxy]methyl]phenyl) cyclopropane-1-carbonitrile and 3-(2-methoxyphenyl) pyridine-4-carboxylic acid (Intermediate H). ¹H NMR (300MHz; DMSO-d₆): δ12.85 (s, 1H), 8.72 - 8.70 (d, 1H), 8.61 (s, 1H), 7.63 (d, 1H), 7.52 (d, 2H), 7.41 - 7.35 (m, 4H),

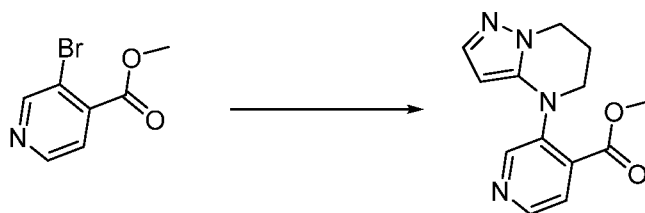
7.09-7.04 (m, 1H), 7.00 - 6.97 (m, 1H), 5.47 (s, 2H), 3.51 (s, 3H), 1.78 (t, 2H), 1.52 (t, 2H). m/z 484 [M+H⁺].

Example 142

Synthesis of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-3-[5H,6H,7H-pyrazolo[1,5-a]pyrimidin-4-yl]pyridine-4-carboxamide

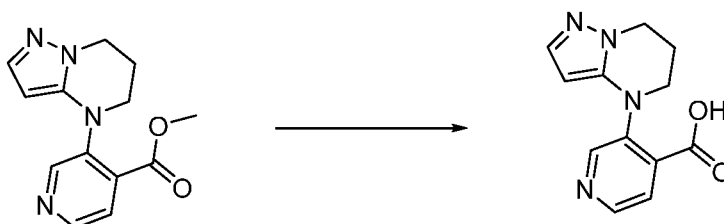


Step 1. Preparation of methyl 3-[5H,6H,7H-pyrazolo[1,5-a]pyrimidin-4-yl]pyridine-4-carboxylate



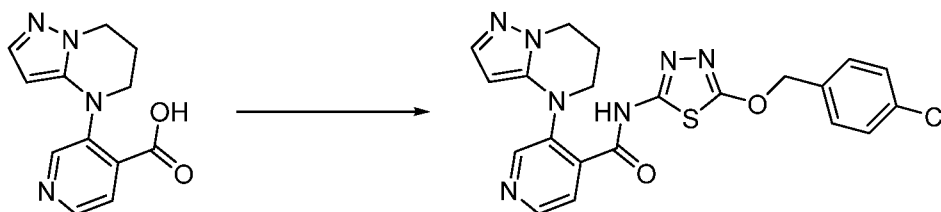
[0487] Into a 50-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed To a solution of methyl 3-bromopyridine-4-carboxylate (1.0 g, 4.6 mmol) in DMF (10 mL) was added 4H,5H,6H,7H-pyrazolo[1,5-a]pyrimidine (684 mg, 5.6 mmol), Cs₂CO₃ (3016 mg, 9.3 mmol), Xantphos (536 mg, 0.93 mmol) and Pd₂(dba)₃CHCl₃ (479 mg, 0.46 mmol) under an atmosphere of nitrogen. The mixture was stirred for 5 hours at 80 °C. The mixture was diluted with water and extracted with EtOAc. The organic layer was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 30:1) to afford the title compound (420 mg, 33% yield) as a black oil.

Step 2. Preparation of 3-[5H,6H,7H-pyrazolo[1,5-a]pyrimidin-4-yl]pyridine-4-carboxylic acid



[0488] The title compound was prepared using General Procedures F using methyl 3-[5H,6H,7H-pyrazolo[1,5-a]pyrimidin-4-yl]pyridine-4-carboxylate.

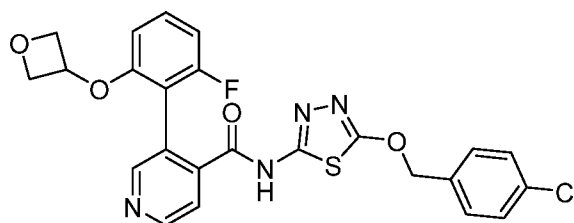
Step 3. Preparation of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-3-[5H,6H,7H-pyrazolo[1,5-a]pyrimidin-4-yl]pyridine-4-carboxamide



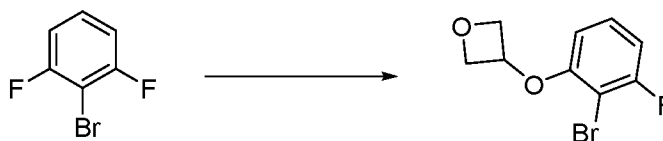
[0489] To a solution of 3-[5H,6H,7H-pyrazolo[1,5-a]pyrimidin-4-yl]pyridine-4-carboxylic acid (100 mg, 0.41 mmol) in DMF (1.0 mL) was added EDCI (118 mg, 0.61 mmol), HOBT (83 mg, 0.61 mmol) and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (99 mg, 0.41 mmol, Intermediate B). The mixture was stirred overnight at room temperature. The mixture was diluted with water and extracted with EtOAc. The organic layer was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 15:1) to afford the title compound (10.6 mg, 6% yield) as a light yellow solid. ¹H NMR (300 MHz, DMSO-d₆): δ 12.93 (s, 1H), 8.75 (s, 1H), 8.53 (s, 1H), 7.74-7.49 (m, 5H), 7.04 (s, 1H), 5.47 (s, 2H), 5.11 (s, 1H), 4.12-4.05 (m, 2H), 3.65-3.55 (m, 2H), 2.39-2.19 (m, 2H). m/z 468 [M+H⁺].

Example 143

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(2-fluoro-6-(oxetan-3-yloxy)phenyl)isonicotinamide

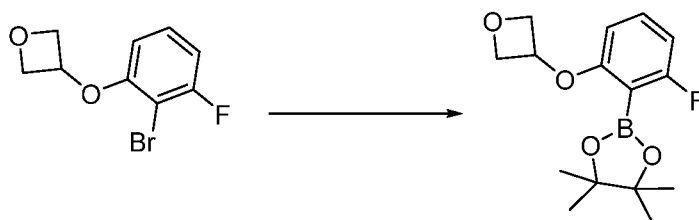


Step 1. Preparation of 3-(2-bromo-3-fluorophenoxy)oxetane



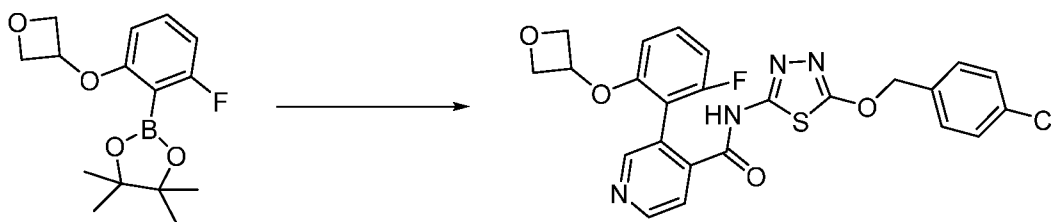
[0490] To a solution of 2-bromo-1,3-difluorobenzene (5.0 g, 25.9 mmol) in DMF (50 mL) was added oxetan-3-ol (2.9g, 38.9 mmol) and K_2CO_3 (7.2 g, 51.8 mmol) at room temperature under nitrogen atmosphere. The mixture was stirred overnight at 140 °C under nitrogen atmosphere. The mixture was diluted with water and extracted with EtOAc (4 x). The mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 1% EtOAc in PE to afford the title compound (1.6 g, 25% yield) as a yellow solid.

Step 2. Preparation of 2-(2-fluoro-6-(oxetan-3-yloxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



[0491] To a solution of 3-(2-bromo-3-fluorophenoxy)oxetane (1.5 g, 6.1 mmol) and dioxane (13 mL), was added bis(pinacolato)diboron (1.5 g, 6.1 mmol), KOAc (1.2 g, 12.1 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.89 g, 1.2 mmol) at room temperature under nitrogen atmosphere. The mixture was stirred overnight at 100 °C under nitrogen atmosphere. The mixture was diluted with water and extracted with EtOAc (3 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 17% EtOAc in PE to afford the title compound (960 mg, 54% yield) as a yellow oil.

Step 3. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(2-fluoro-6-(oxetan-3-yloxy)phenyl)isonicotinamide

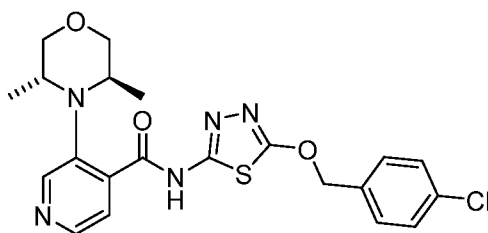


[0492] The title compound was prepared using General Procedures E, F and A. For General Procedure E, 2-(2-fluoro-6-(oxetan-3-yloxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and methyl 3-bromopyridine-4-carboxylate were employed. For General Procedure A, 5-((4-

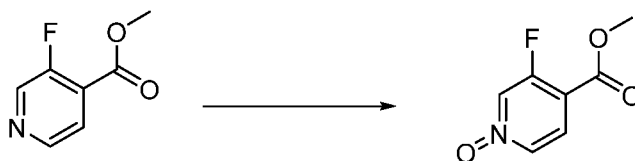
chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 13.13 (s, 1H), 8.79 (d, 1H), 8.66 (s, 1H), 7.80 (s, 1H), 7.54 -7.47 (m, 4H), 7.39-7.33 (m, 1H), 7.02-6.98 (m, 1H), 6.44 (d, 1H), 5.49 (t, 2H), 5.10-5.04 (m, 1H), 4.75 (t, 1H), 4.62 (t, 1H), 4.45-4.42 (m, 1H), 4.22-4.19 (m, 1H). m/z 513 $[\text{M}+\text{H}^+]$.

Example 144

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-((3R,5R)-3,5-dimethylmorpholino)isonicotinamide

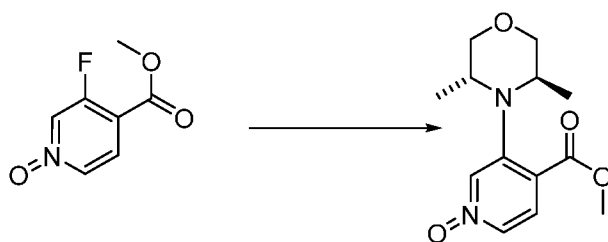


Step 1. Preparation of methyl 3-fluoro-1-oxo-1 λ 5-pyridine-4-carboxylate



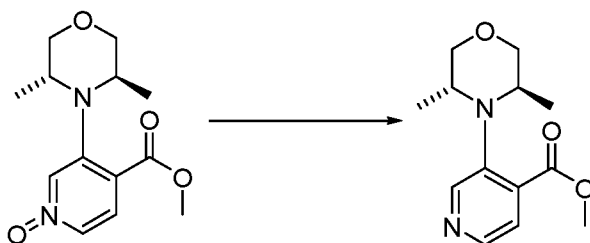
[0493] Into a 50-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed To a solution of methyl 3-fluoropyridine-4-carboxylate (800 mg, 5.2 mmol) in chloroform (8 mL) was added m-CPBA (85%, 1047 mg, 5.2 mmol) under nitrogen atmosphere. The mixture was stirred for 5 hours at room temperature. The mixture was quenched by the addition of sat. NH_4Cl (aq.) at room temperature. The layers were separated, and the aqueous layer was extracted with DCM (3 x). The mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 5% MeOH in DCM to afford the title compound (900 mg, 99% yield) as a white solid.

Step 2. Preparation of 3-((3R,5R)-3,5-dimethylmorpholino)-4-(methoxycarbonyl)pyridine 1-oxide



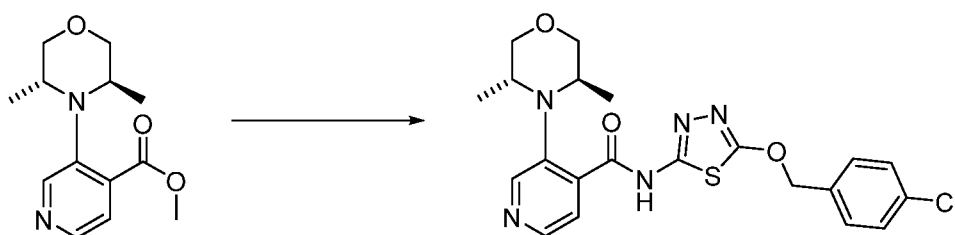
[0494] To a solution of methyl 3-fluoro-1-oxo-1λ5-pyridine-4-carboxylate (1.2 g, 7.0 mmol) in MeCN (12 mL) was added (3R,5R)-3,5-dimethylmorpholine hydrochloride (635 mg, 4.2 mmol) and DIEA (1631 mg, 12.6 mmol). The mixture was stirred for 3 days at 100 °C. The mixture was cooled to rt, diluted with water and extracted with EtOAc. The organic layer was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 25:1) to afford the title compound (180 mg, 8% yield) as a yellow oil.

Step 3. Preparation of methyl 3-((3R,5R)-3,5-dimethylmorpholino)isonicotinate



[0495] To a solution of 3-((3R,5R)-3,5-dimethylmorpholino)-4-(methoxycarbonyl)pyridine 1-oxide (170 mg, 0.64 mmol) in MeOH (2.00 mL) was added Pd/C (10%, 17 mg,) and HCOONH₄ (201 mg, 3.2 mmol). The mixture was stirred for 2 hours at room temperature. The mixture was diluted with MeOH and filtered out. The solids were washed with MeOH (2 x). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE:EtOAc, 4:1) to afford the title compound (110 mg, 67% yield) as a yellow oil.

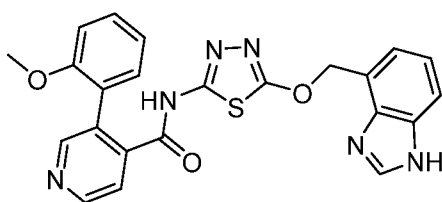
Step 4. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-((3R,5R)-3,5-dimethylmorpholino)isonicotinamide



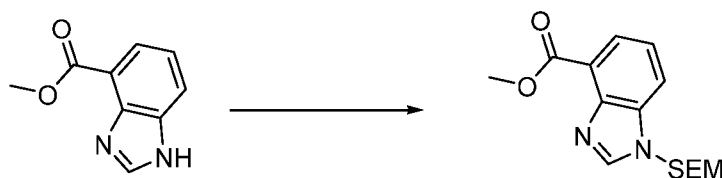
[0496] The title compound was prepared using General Procedures F and A. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. ¹H NMR (300 MHz, DMSO-*d*₆): δ 14.24 (s, 1H), 8.74 (s, 1H), 8.61 (d, 1H), 7.89 (d, 1H), 7.58-7.48 (m, 4H), 5.52 (s, 2H), 4.10-3.65 (m, 4H), 3.32 - 3.24 (m, 2H), 1.23 - 0.81 (m, 6H). *m/z* 460 [M+H⁺].

Example 145

Synthesis of N-[5-(1H-1,3-benzodiazol-4-ylmethoxy)-1,3,4-thiadiazol-2-yl]-3-(2-methoxyphenyl)pyridine-4-carboxamide

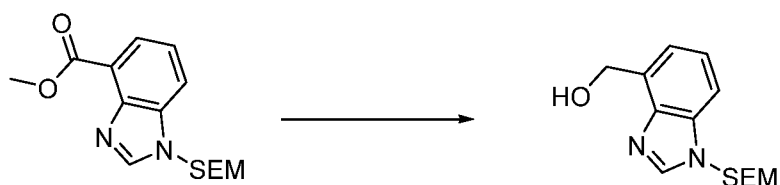


Step 1. Preparation of methyl 1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole-4-carboxylate



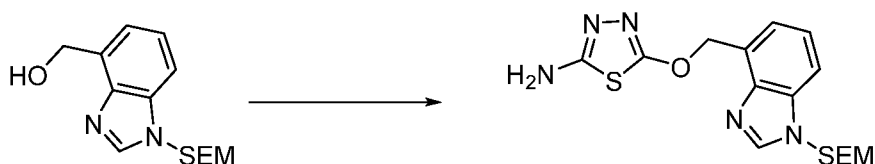
[0497] To a solution of methyl 1H-1,3-benzodiazole-4-carboxylate (3.0 g, 17.0 mmol) in DMF (30 mL) at 0 °C was added NaH (60% dispersion in oil, 1.0 g, 25.5 mmol). The mixture was stirred for 40 min at 0 °C. Then 2-(trimethylsilyl)ethoxymethyl chloride (2.8 g, 17.0 mmol) was added and the mixture was warmed to rt and stirred overnight. The mixture was quenched by NH₄Cl (aq.) and extracted with EtOAc (5 x). The combined organic layers were concentrated under vacuum. The residue was purified by reverse phase chromatography (column, C18 silica gel; mobile phase, with 5-80% MeCN in water) to afford the title compound (3.1 g, 56% yield) as a brown oil.

Step 2. Preparation of (1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-4-yl)methanol



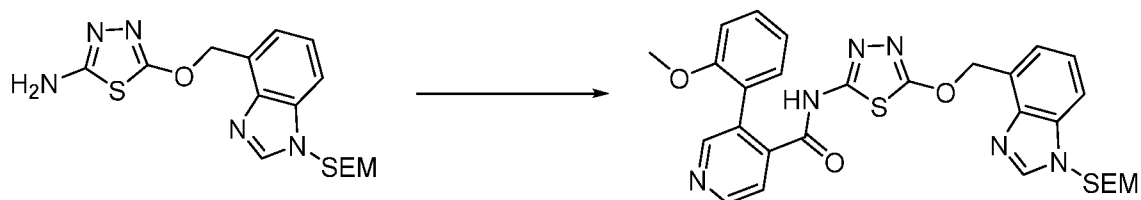
[0498] To a solution of methyl 1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole-4-carboxylate (1.1 g, 3.4 mmol) in THF (15 mL) was added LiAlH₄ (259 mg, 6.8 mmol) at room temperature under nitrogen atmosphere. The mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The mixture was cooled to 0 °C and was quenched by the addition of NH₄Cl (aq.) The mixture was extracted with EtOAc (3 x). The combined organic layers were concentrated under vacuum. The residue was purified by silica gel column chromatography, 17% EtOAc in PE to afford the title compound (840 mg, 84% yield) as a yellow oil.

Step 3. Preparation of 5-[(1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-4-yl)methoxy]-1,3,4-thiadiazol-2-amine



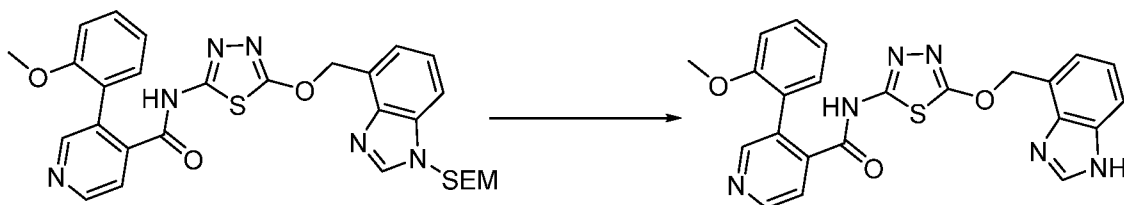
[0499] The title compound was prepared using similar procedures as the synthesis of Intermediate C, replacing (5-chloropyridin-2-yl)methanol with (1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-4-yl)methanol in Step 1.

Step 4. Preparation of 3-(2-methoxyphenyl)-N-[5-[(1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-4-yl)methoxy]-1,3,4-thiadiazol-2-yl]pyridine-4-carboxamide



[0500] The title compound was prepared using General Procedure A employing 3-(2-methoxyphenyl) pyridine-4-carboxylic acid (Intermediate H) and 5-[(1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-4-yl)methoxy]-1,3,4-thiadiazol-2-amine.

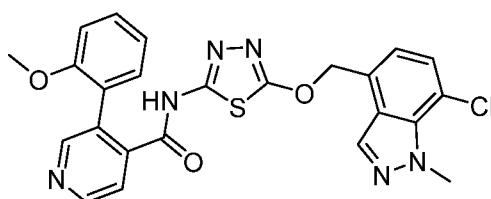
Step 5. Preparation of N-[5-(1H-1,3-benzodiazol-4-ylmethoxy)-1,3,4-thiadiazol-2-yl]-3-(2-methoxyphenyl)pyridine-4-carboxamide



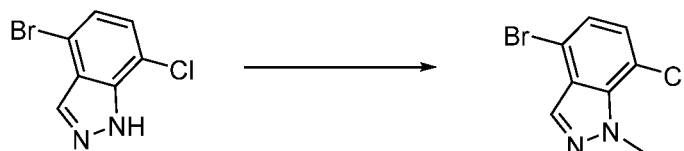
[0501] To a solution of 3-(2-methoxyphenyl)-N-[5-[(1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-4-yl)methoxy]-1,3,4-thiadiazol-2-yl]pyridine-4-carboxamide (200 mg, 0.34 mmol) in THF (3 mL) was added TBAF (1 M in THF, 1.7 mL, 1.7 mmol) and CsF (1032 mg, 6.80 mmol) at room temperature. The mixture was stirred for 4 h at 70 °C under nitrogen atmosphere. The mixture was diluted with water and extracted with EtOAc (3 x). The combined organic layers were concentrated vacuum. The residue was purified by Prep-TLC (DCM:MeOH, 10:1) to afford the title compound (52 mg, 33% yield) as an off-white solid. ¹H NMR (300 MHz, DMSO-*d*₆): δ 12.86-12.61 (m, 2H), 8.72 (d, 1H), 8.61 (s, 1H), 8.27 (s, 1H), 7.65-7.63 (m, 2H), 7.38-7.33 (m, 3H), 7.30-7.20 (m, 1H), 7.09-6.98 (m, 2H), 5.80 (d, 2H), 3.53 (s, 3H). *m/z* 459 [M+H⁺].

Example 146

Synthesis of N-[5-[(7-chloro-1-methylindazol-4-yl)methoxy]-1,3,4-thiadiazol-2-yl]-3-(2-methoxyphenyl)pyridine-4-carboxamide



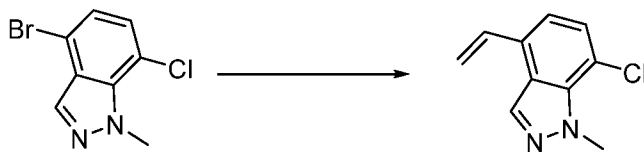
Step 1. Preparation of 4-bromo-7-chloro-1-methylindazole



[0502] To a solution of 4-bromo-7-chloro-1H-indazole (3.0 g, 13.0 mmol) in DMF (30 mL) at 0 °C was added NaH (60% dispersion in oil, 1.04 g, 26.0 mmol). The mixture was stirred for 40 min at 0 °C. Then MeI (1840 mg, 13.0 mmol) was added and the mixture warm to rt and stirred at rt overnight. The mixture was quenched by the addition of NH₄Cl (aq.) and extracted with EtOAc (3 x). The combined organic layers were concentrated under vacuum. The residue was

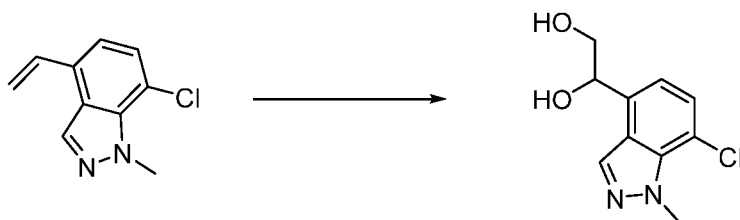
purified by silica gel column chromatography, eluted with 3% EtOAc in PE to afford the title compound (1.8 g, 57% yield) as an off-white solid.

Step 2. Preparation of 7-chloro-4-ethenyl-1-methylindazole



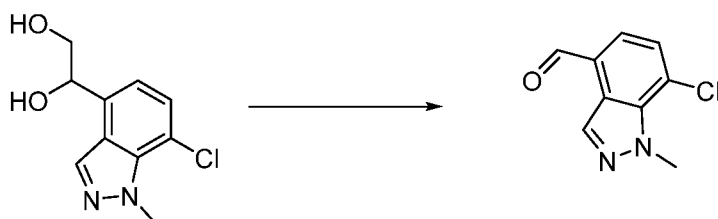
[0503] To a solution of 4-bromo-7-chloro-1-methylindazole (1.8 g, 7.3 mmol) in toluene (20 mL) was added tributyl(ethenyl)stannane (5813 mg, 18.3 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (847 mg, 0.73 mmol) at room temperature. The mixture was stirred for 2 h at 110 °C under nitrogen atmosphere. The mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with 9% EtOAc in PE to afford the title compound (1 g, 71% yield) as an off-white solid.

Step 3. Preparation of 1-(7-chloro-1-methylindazol-4-yl)ethane-1,2-diol



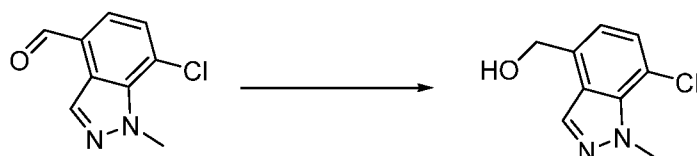
[0504] To a solution of 7-chloro-4-ethenyl-1-methylindazole (980 mg, 5.1 mmol) in THF (10 mL) was added OsO_4 (129 mg, 0.51 mmol) at room temperature. Then a solution of NMO (1192 mg, 10.2 mmol) in water (5 mL) was added. The mixture was stirred for 2 h and then diluted with water. The mixture was extracted with EtOAc (3 x). The combined organic layers were concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with 50% EtOAc in DCM to afford the title compound (730 mg, 63% yield) as a black solid.

Step 4. Preparation of 7-chloro-1-methylindazole-4-carbaldehyde



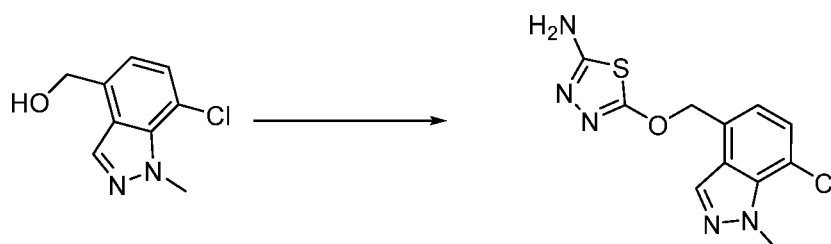
[0505] To a solution of 1-(7-chloro-1-methylindazol-4-yl)ethane-1,2-diol (710 mg, 3.1 mmol) in MeOH (7 mL) was added NaIO₄ (1340 mg, 6.3 mmol) at room temperature. The mixture was stirred for 4 h at room temperature under nitrogen atmosphere. The mixture was diluted with water and extracted with EtOAc (3 x). The combined organic layers were concentrated under vacuum. The residue was purified by Prep-TLC (PE:EtOAc, 5:1) to afford the title compound (560 mg, 92% yield) as a white solid.

Step 5. Preparation of (7-chloro-1-methylindazol-4-yl) methanol



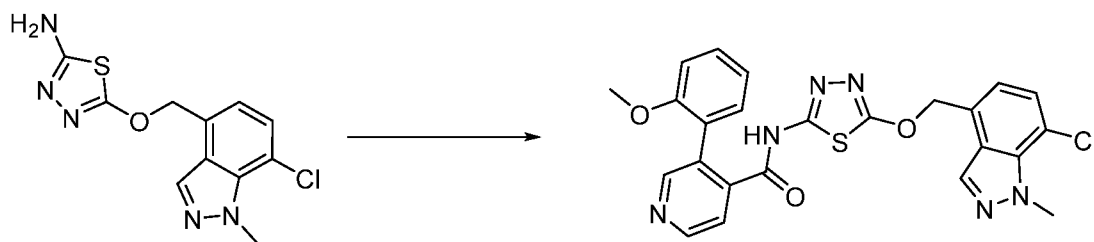
[0506] To a solution of 7-chloro-1-methylindazole-4-carbaldehyde (560 mg, 2.9 mmol) in MeOH (10 mL) was added NaBH₄ (218 mg, 5.8 mmol) at room temperature. The mixture was stirred for 30 min at room temperature under nitrogen atmosphere. The mixture was quenched by the addition of water at room temperature. The mixture was extracted with EtOAc (3 x). The combined organic layers were concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with 17% EtOAc in DCM to afford the title compound (530 mg, 94% yield) as a white solid.

Step 6. Preparation of 5-[(7-chloro-1-methylindazol-4-yl)methoxy]-1,3,4-thiadiazol-2-amine



[0507] The title compound was prepared using similar procedures as the synthesis of Intermediate C, replacing (5-chloropyridin-2-yl)methanol with (7-chloro-1-methylindazol-4-yl) methanol in Step 1.

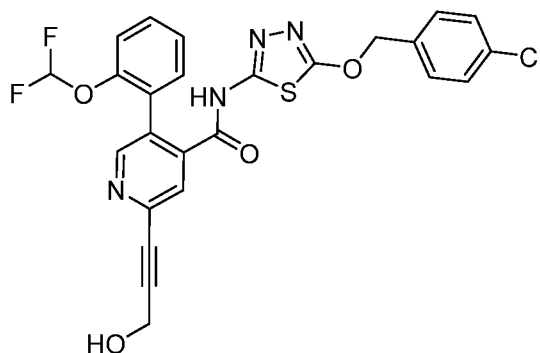
Step 7. Preparation of N-[5-[(7-chloro-1-methylindazol-4-yl)methoxy]-1,3,4-thiadiazol-2-yl]-3-(2-methoxyphenyl)pyridine-4-carboxamide



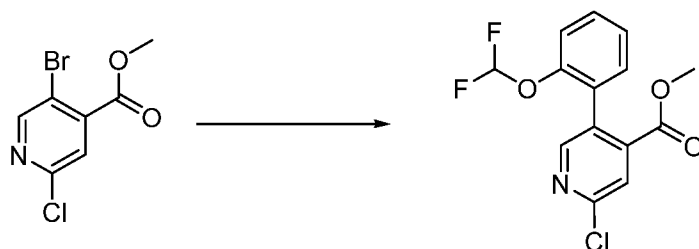
[0508] The title compound was prepared using General Procedure A employing 5-[(7-chloro-1-methylindazol-4-yl)methoxy]-1,3,4-thiadiazol-2-amine and 3-(2-methoxyphenyl) pyridine-4-carboxylic acid (Intermediate H). ^1H NMR (300 MHz, DMSO- d_6): δ 12.86 (s, 1H), 8.72 (d, 1H), 8.61 (s, 1H), 8.29 (s, 1H), 7.63 (d, 1H), 7.49 (d, 1H), 7.41-7.36 (m, 2H), 7.26-7.24 (m, 1H), 7.09-6.98 (m, 2H), 5.80 (s, 2H), 4.34 (s, 3H), 3.52 (s, 3H). m/z 507 $[\text{M}+\text{H}^+]$.

Example 147

Synthesis of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-5-[2-(difluoromethoxy)phenyl]-2-(3-hydroxyprop-1-yn-1-yl)pyridine-4-carboxamide

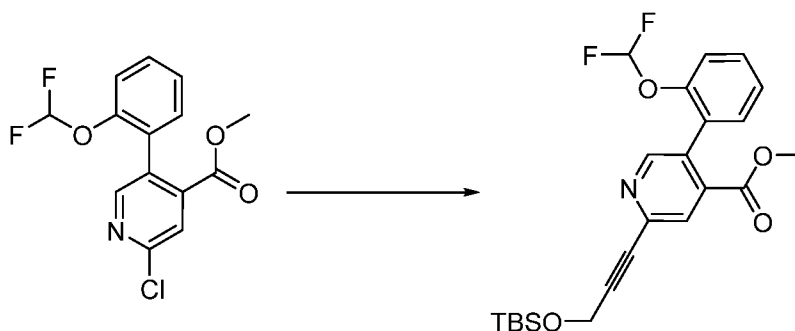


Step 1. Preparation of methyl 2-chloro-5-(2-(difluoromethoxy)phenyl)isonicotinate



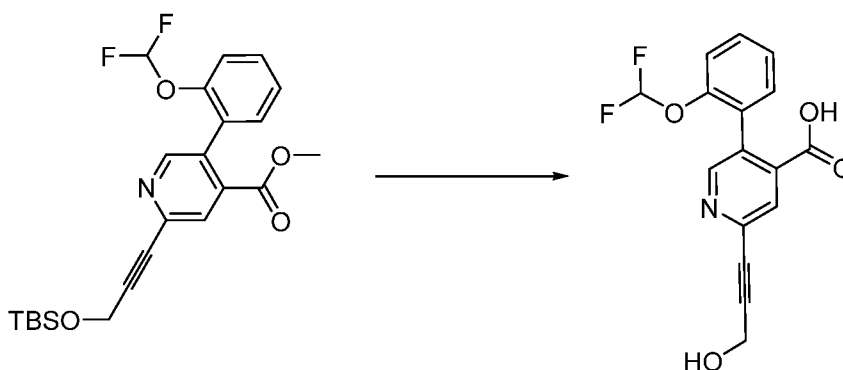
[0509] The title compound was prepared using General Procedure E employing methyl 5-bromo-2-chloropyridine-4-carboxylate and 2-[2-(difluoromethoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

Step 2. Preparation of methyl 2-[3-[(tert-butyldimethylsilyl)oxy]prop-1-yn-1-yl]-5-[2-(difluoromethoxy)phenyl]pyridine-4-carboxylate



[0510] To a solution of methyl 2-chloro-5-[2-(difluoromethoxy)phenyl]pyridine-4-carboxylate (320 mg, 1.0 mmol) in DMF (12 mL) was added diisopropylamine (516 mg, 5.1 mmol), CuI (78 mg, 0.41 mmol), Pd/C (10%, 64 mg) and tert-butyldimethyl(prop-2-yn-1-yloxy)silane (869 mg, 5.1 mmol) at room temperature. The mixture was irradiated with microwave radiation for 40 min at 140 °C. The mixture was cooled room temperature. The solids were filtered, and the filtrate was diluted with water and extracted with EtOAc (3 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (PE:EtOAc, 2:1) to afford the title compound (300 mg, 66% yield) as a yellow oil.

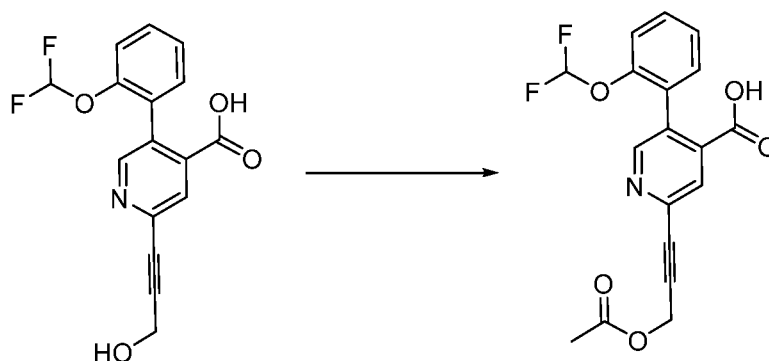
Step 3. Preparation of 5-[2-(difluoromethoxy)phenyl]-2-(3-hydroxyprop-1-yn-1-yl)pyridine-4-carboxylic acid



[0511] To a solution of methyl 2-[3-[(tert-butyldimethylsilyl)oxy]prop-1-yn-1-yl]-5-[2-(difluoromethoxy)phenyl]pyridine-4-carboxylate (280 mg, 0.63 mmol) in MeOH (3.0 mL) and water (1.0 mL) was added NaOH (51 mg, 1.3 mmol) at room temperature. The mixture was stirred for 30 min at room temperature under nitrogen atmosphere. The mixture was diluted with water and acidified to pH 5 with HCl (1M). The mixture was extracted with EtOAc (5 x). The

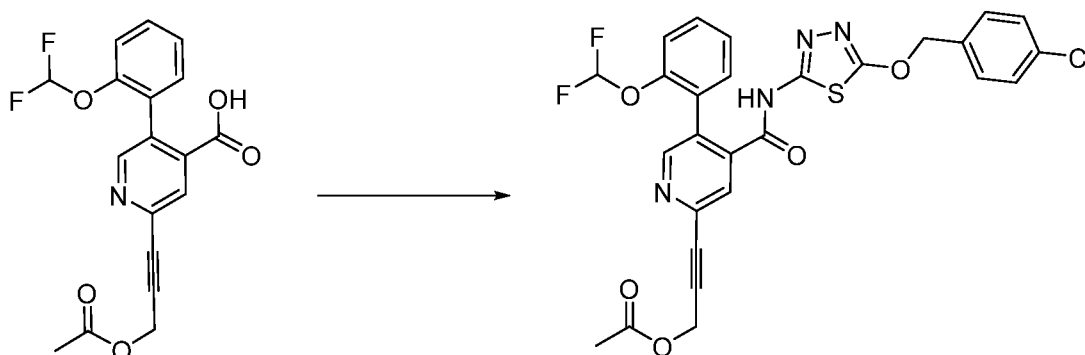
combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 10:1) to afford the title compound (140 mg, 71% yield) as a white solid.

Step 4. Preparation of 2-[3-(acetyloxy)prop-1-yn-1-yl]-5-[2-(difluoromethoxy)phenyl]pyridine-4-carboxylic acid



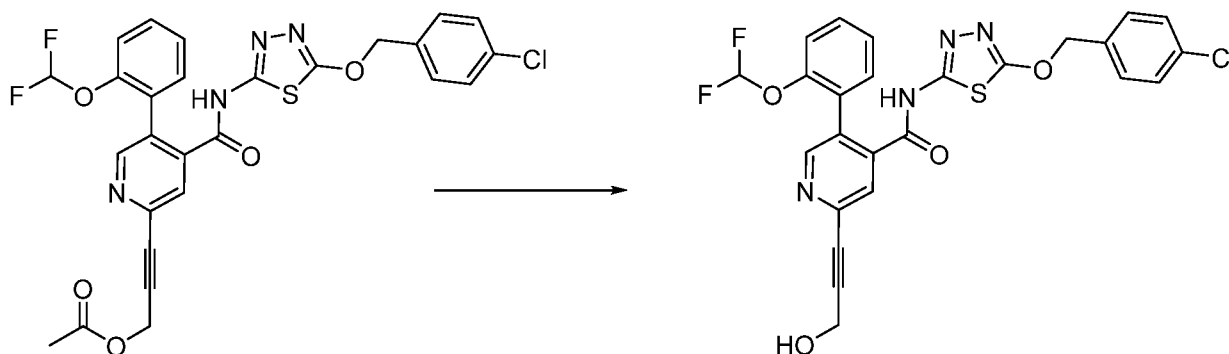
[0512] To a solution of 5-[2-(difluoromethoxy)phenyl]-2-(3-hydroxyprop-1-yn-1-yl)pyridine-4-carboxylic acid (135 mg, 0.42 mmol) in DCM (2 mL) was added DIEA (109 mg, 0.85 mmol) and AcCl (33 mg, 0.42 mmol) at 0 °C. The mixture was stirred for 30 min at room temperature under nitrogen atmosphere. The mixture was diluted with water and extracted with EtOAc (3 x). The combined organic layers were concentrated under vacuum. The residue was purified by Prep-TLC (DCM:MeOH, 15:1) to afford (80 mg, 52% yield) as a white semi-solid.

Step 5. Preparation of 3-[4-([5-[2-(difluoromethoxy)phenyl]pyridin-2-yl]carbonyl)-1,3,4-thiadiazol-2-yl]prop-2-yn-1-yl acetate



[0513] The title compound was prepared using General Procedure A employing 2-[3-(acetyloxy)prop-1-yn-1-yl]-5-[2-(difluoromethoxy)phenyl]pyridine-4-carboxylic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B).

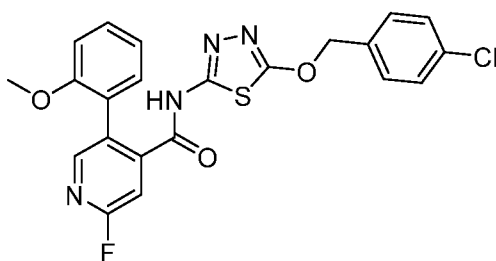
Step 6. Preparation of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-5-[2-(difluoromethoxy)phenyl]-2-(3-hydroxyprop-1-yn-1-yl)pyridine-4-carboxamide



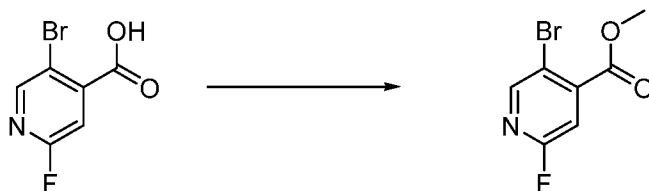
[0514] To a solution of 3-[4-([5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]carbamoyl)-5-[2-(difluoromethoxy)phenyl]pyridin-2-yl]prop-2-yn-1-yl acetate (95 mg, 0.16 mmol) in MeOH (2 mL) and water (0.5 mL) was added LiOH.H₂O (14 mg, 0.33 mmol) at room temperature. The mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The mixture was diluted with water and acidified to pH 5 with HCl (1 M). The mixture was extracted with EtOAc (3 x) and the combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 20:1) to afford the title compound (16 mg, 19% yield) as a white solid. ¹H NMR (400 MHz, CD₃OD): δ 8.56 (s, 1H), 7.84 (s, 1H), 7.48-7.30 (m, 7H), 7.20 (d, 1H), 6.92-6.43 (m, 1H), 5.44 (s, 2H), 4.47 (s, 2H). m/z 543 [M+H⁺].

Example 148

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-fluoro-5-(2-methoxyphenyl)isonicotinamide

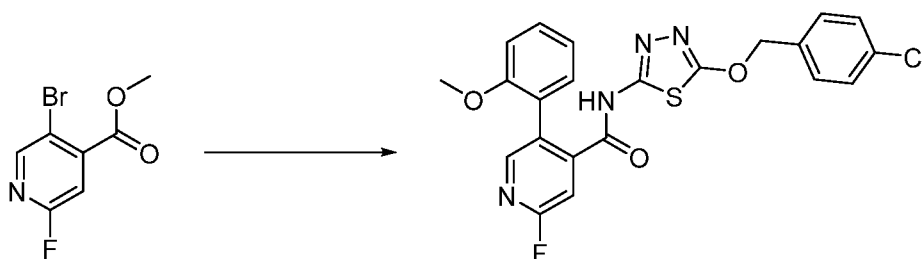


Step 1. Preparation of methyl 5-bromo-2-fluoroisonicotinate



[0515] To a solution of 5-bromo-2-fluoropyridine-4-carboxylic acid (1.0 g, 4.5 mmol) in THF (10 mL) was added Ph_3P (2.4 g, 9.1 mmol) and MeOH (0.73 g, 22.7 mmol) at 0 °C. The mixture was stirred for 5 min and then DIAD (1.8 g, 9.1 mmol) was added. The mixture was warmed to rt and stirred at rt for 30 min. The mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with 3% EtOAc in PE to afford the title compound (0.95 g, 88% yield) as a white solid.

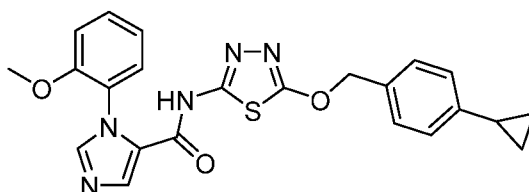
Step 2. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-fluoro-5-(2-methoxyphenyl)isonicotinamide



[0516] The title compound was prepared using General Procedures E, F and A. For General Procedure E, methyl 5-bromo-2-fluoropyridine-4-carboxylate and 2-methoxyphenylboronic acid were employed. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 3.51 (s, 3H), 5.48 (s, 2H), 6.97-7.08 (m, 2H), 7.34-7.41 (m, 2H), 7.46-7.55 (m, 5H), 8.27 (s, 1H), 12.97 (s, 1H). m/z 471 $[\text{M}+\text{H}^+]$.

Example 149

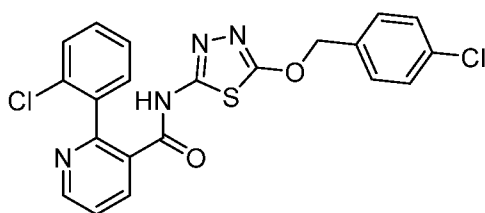
Synthesis of N-(5-((4-cyclopropylbenzyl)oxy)-1,3,4-thiadiazol-2-yl)-1-(2-methoxyphenyl)-1H-imidazole-5-carboxamide



[0517] The title compound was prepared using similar procedures as the synthesis of Example 50 replacing 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) with 5-[(4-cyclopropylphenyl)methoxy]-1,3,4-thiadiazol-2-amine (Example 47, Step 1). ¹H NMR (300 MHz, DMSO-d₆): δ 0.62-0.66 (m, 2H), 0.94-0.98 (m, 2H), 1.87-1.96 (m, 1H), 3.66 (s, 3H), 5.39 (s, 2H), 7.03-7.11 (m, 3H), 7.17 (d, 1H), 7.33-7.37 (m, 3H), 7.42-7.48 (m, 1H), 7.97 (d, 1H), 8.10 (s, 1H), 12.68 (br s, 1H). m/z 448 [M+H⁺].

Example 150

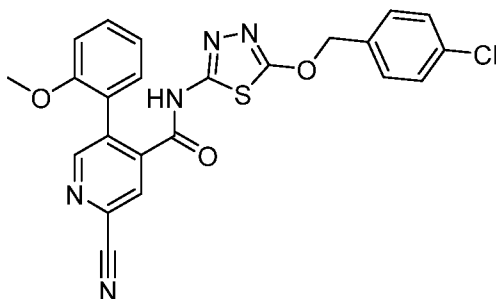
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-(2-chlorophenyl)nicotinamide



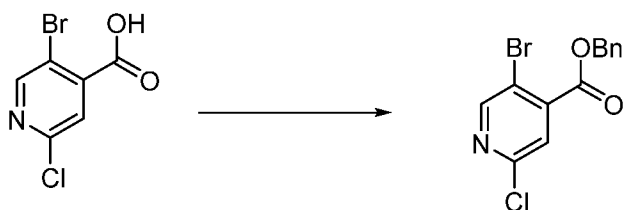
[0518] The title compound was prepared using General Procedures E, F and A. For General Procedure E, methyl 2-bromopyridine-3-carboxylate and 2-chlorophenylboronic acid were employed. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. ¹H NMR (300 MHz, DMSO-d₆): δ 5.54 (s, 2H), 7.40-7.63 (m, 8H), 7.98-8.01 (m, 1H), 8.21-8.24 (m, 1H), 8.81-8.83 (m, 1H), 13.00 (s, 1H). m/z 457 [M+H⁺].

Example 151

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-cyano-5-(2-methoxyphenyl)isonicotinamide

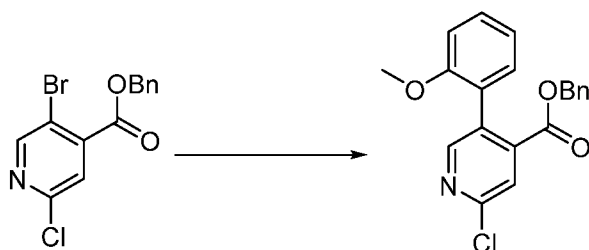


Step 1. Preparation of benzyl 5-bromo-2-chloropyridine-4-carboxylate



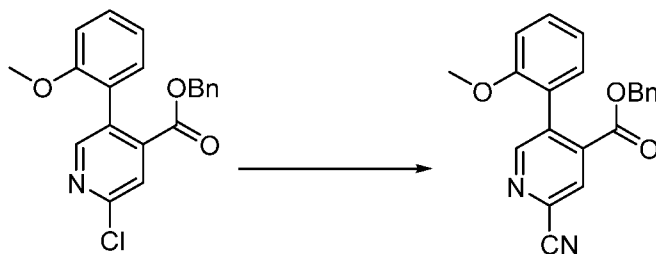
[0519] To a solution of 5-bromo-2-chloropyridine-4-carboxylic acid (3 g, 12.7 mmol) and benzyl bromide (2.6 g, 15.2 mmol) in DMF (10 mL) was added K_2CO_3 (1.2 g, 8.5 mmol) at room temperature. The mixture was stirred for 2 h at 50 °C. The mixture was diluted with EtOAc and washed with (3 x). The organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 14% EtOAc in PE to afford the title compound (4 g, 93% yield) as a white solid.

Step 2. Preparation of benzyl 2-chloro-5-(2-methoxyphenyl)pyridine-4-carboxylate



[0520] The title compound was prepared using General Procedure E employing benzyl 5-bromo-2-chloropyridine-4-carboxylate and 2-methoxyphenylboronic acid.

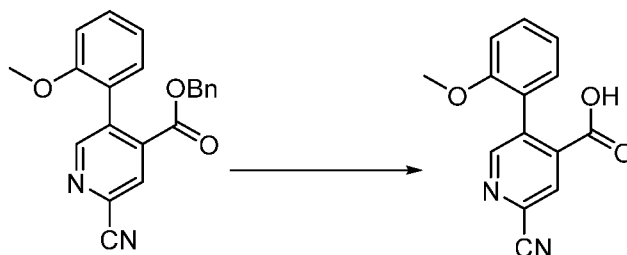
Step 3. Preparation of benzyl 2-cyano-5-(2-methoxyphenyl)pyridine-4-carboxylate



[0521] To a solution of benzyl 2-chloro-5-(2-methoxyphenyl)pyridine-4-carboxylate (3.4 g, 9.7 mmol) in DMF (34 mL) was added $Zn(CN)_2$ (5.7 g, 48.6 mmol) at room temperature. The mixture was stirred for 2 h at 80 °C under nitrogen atmosphere. The mixture was cooled to rt, diluted with EtOAc and washed with water. The organic layer was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with 17% EtOAc in PE to

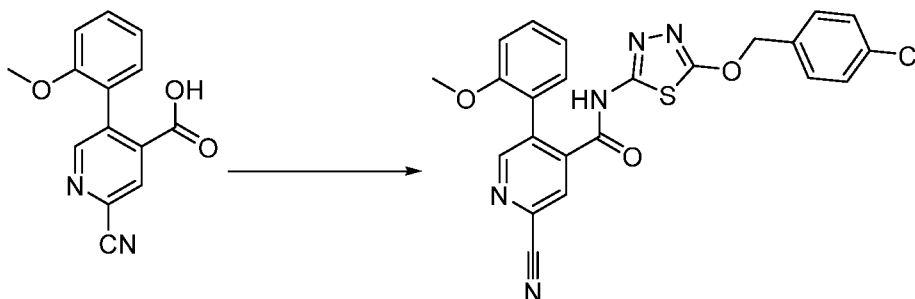
afford the title compound (2 g, 57% yield) as a white solid.

Step 4. Preparation of 2-cyano-5-(2-methoxyphenyl)pyridine-4-carboxylic acid



[0522] To a solution of benzyl 2-cyano-5-(2-methoxyphenyl)isonicotinate (1 g, 2.9 mmol) in MeOH was added Pd/C (10%, 0.09 g) at room temperature. The mixture was stirred for 8 h at room temperature under hydrogen atmosphere. The mixture was filtered, and the solid was washed with MeOH (3 x). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 7:1) to afford the title compound (140 mg, 17% yield) as a yellow oil.

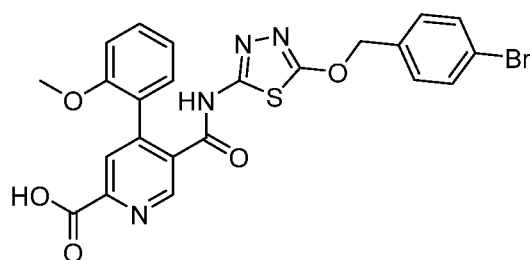
Step 5. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-cyano-5-(2-methoxyphenyl)isonicotinamide



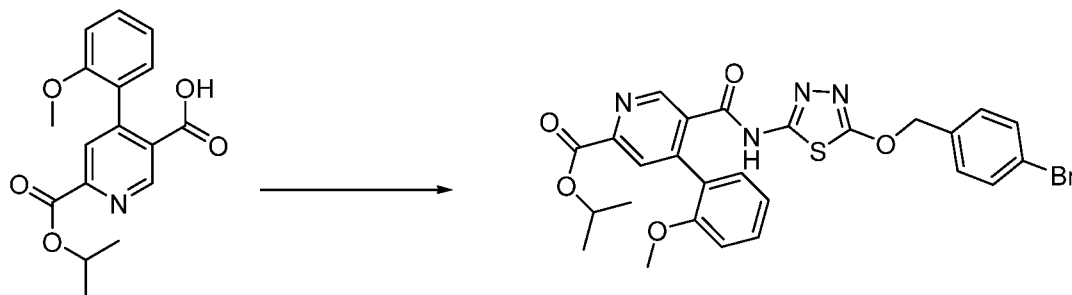
[0523] The title compound was prepared using General Procedure A employing 2-cyano-5-(2-methoxyphenyl)pyridine-4-carboxylic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). ¹H NMR (300 MHz, DMSO-d₆): δ 3.58 (s, 3H), 5.48 (s, 2H), 7.02 - 7.12 (m, 2H), 7.41 - 7.55 (m, 6H), 8.36 (s, 1H), 8.82 (s, 1H), 13.05 (s, 1H). m/z 478 [M+H⁺].

Example 152

Synthesis of 5-([5-[(4-bromophenyl)methoxy]-1,3,4-thiadiazol-2-yl]carbamoyl)-4-(2-methoxyphenyl)pyridine-2-carboxylic acid

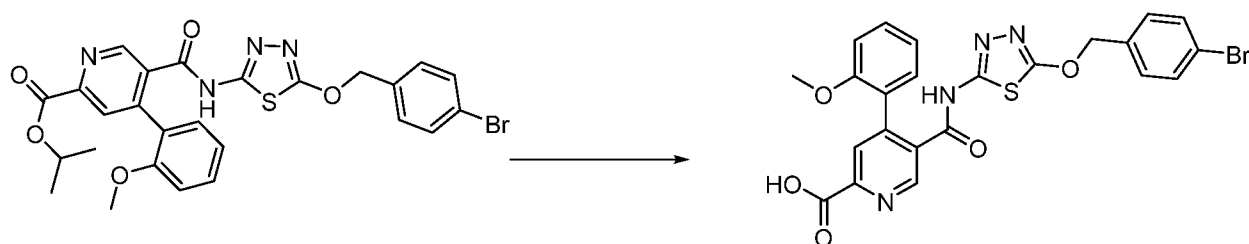


Step 1. Preparation of isopropyl 5-([5-[(4-bromophenyl)methoxy]-1,3,4-thiadiazol-2-yl]carbamoyl)-4-(2-methoxyphenyl)pyridine-2-carboxylate



[0524] The title compound was prepared using General Procedure A employing 6-(isopropoxycarbonyl)-4-(2-methoxyphenyl)pyridine-3-carboxylic acid (Example 102, Step 3) and 5-((4-bromobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Example 40, Step 1).

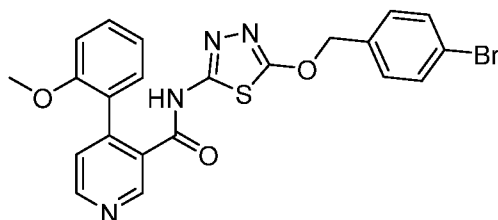
Step 2. Preparation of 5-([5-[(4-bromophenyl)methoxy]-1,3,4-thiadiazol-2-yl]carbamoyl)-4-(2-methoxyphenyl)pyridine-2-carboxylic acid



[0525] To a solution of isopropyl 5-([5-[(4-bromophenyl)methoxy]-1,3,4-thiadiazol-2-yl]carbamoyl)-4-(2-methoxyphenyl)pyridine-2-carboxylate (2.0 g, 3.4 mmol) in MeOH (50 mL) was added LiOH.H₂O (0.57 g, 13.8 mmol) and water (10 mL) at room temperature. The mixture was stirred for 2 hours. The mixture was diluted with water and MeOH was removed under reduced pressure. The pH of the mixture was adjusted pH 6~7 with formic acid. The solid was collected by filtration to afford the title compound (1.1 g, 57% yield) as an off-white solid. ¹H NMR (300 MHz, DMSO-d₆): δ 8.81 (s, 1H), 7.87 (s, 1H), 7.60 (d, 2H), 7.47 - 7.31 (m, 4H), 7.07-6.93 (m, 2H), 5.42 (s, 2H), 3.53 (s, 3H). m/z 541 [M+H⁺].

Example 153

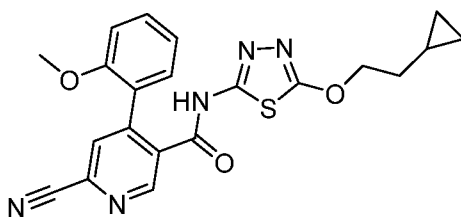
Synthesis of N-[5-[(4-bromophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)pyridine-3-carboxamide



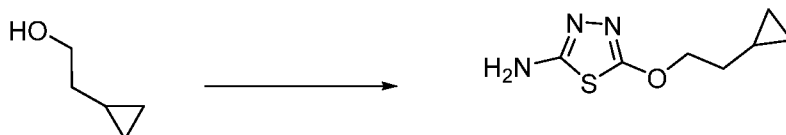
[0526] The title compound was prepared using similar procedures as Example 77, replacing 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) with 5-((4-bromobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Example 40, Step 1). ¹H NMR (300 MHz, DMSO-d₆): δ 3.52 (s, 3H), 5.45 (s, 2H), 7.00 (d, 1H) 7.05-7.09 (m, 1H) 7.34-7.40 (m, 1H), 7.42-7.47 (m, 4H), 7.59-7.62 (m, 2H), 8.74 (s, 1H), 8.75 (s, 1H), 12.79 (s, 1H). m/z 497 [M+H⁺].

Example 154

Synthesis of 6-cyano-N-(5-(2-cyclopropylethoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)nicotinamide

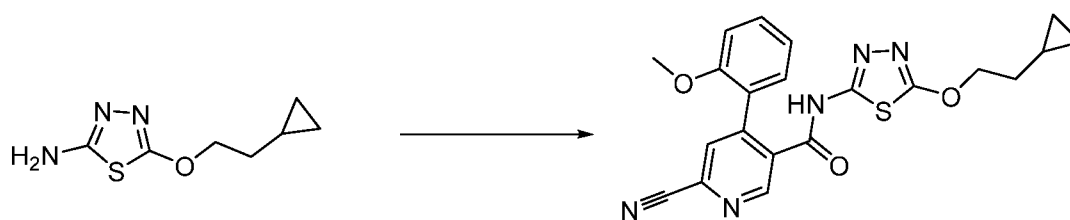


Step 1. Preparation of 5-(2-cyclopropylethoxy)-1,3,4-thiadiazol-2-amine



[0527] The title compound was prepared using similar procedures as the synthesis of Intermediate C, replacing (5-chloropyridin-2-yl)methanol with 2-cyclopropylethanol in Step 1.

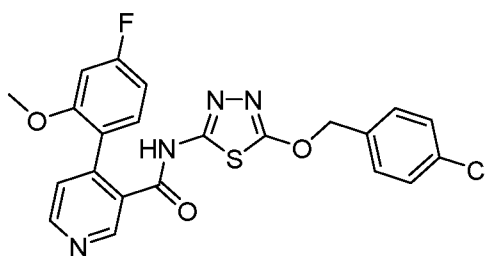
Step 2. Preparation of 6-cyano-N-(5-(2-cyclopropylethoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)nicotinamide



[0528] The title compound was prepared using General Procedure A employing 5-((2-cyclopropylethoxy)-1,3,4-thiadiazol-2-yl)-1,3,4-thiadiazol-2-amine and 6-cyano-4-(2-methoxyphenyl)pyridine-3-carboxylic acid (Example, 92, Step 4). ^1H NMR (300 MHz, DMSO-d_6): δ 13.02 (s, 1H), 8.95 (s, 1H), 8.14 (s, 1H), 7.45 (d, 2H), 7.10 - 7.01 (m, 2H), 4.46 (t, 2H), 3.73 (s, 3H), 1.70 - 1.57 (m, 2H), 0.89 - 0.74 (m, 1H), 0.46 - 0.39 (m, 2H), 0.13 - 0.10 (m, 2H). m/z 422 $[\text{M}+\text{H}^+]$.

Example 155

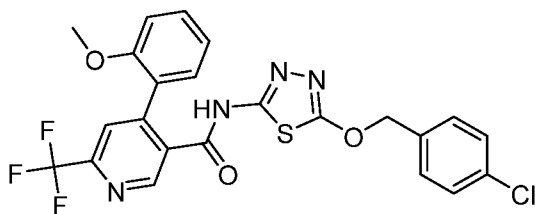
Synthesis of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(4-fluoro-2-methoxyphenyl)pyridine-3-carboxamide



[0529] The title compound was prepared using General Procedures E, F and A. For General Procedure E, methyl 4-chloropyridine-3-carboxylate and 4-fluoro-2-methoxyphenylboronic acid were employed. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. ^1H NMR (300 MHz, DMSO-d_6): δ 12.84 (s, 1H), 8.77 (d, 2H), 7.55 - 7.47 (m, 4H), 7.43 - 7.36 (m, 2H), 6.90 (d, 2H), 5.48 (s, 2H), 3.53 (s, 3H). m/z 471 $[\text{M}+\text{H}^+]$.

Example 156

Synthesis of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-(trifluoromethyl)pyridine-3-carboxamide

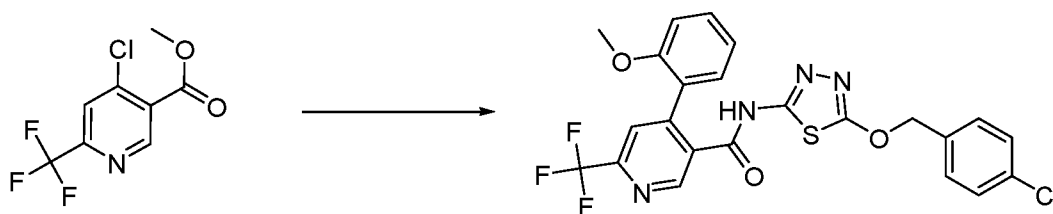


Step 1. Preparation of methyl 4-chloro-6-(trifluoromethyl)pyridine-3-carboxylate



[0530] To a solution of 4-chloro-6-(trifluoromethyl)pyridine-3-carboxylic acid (480 mg, 2.1 mmol) in THF (5 mL) was added Ph_3P (2791 mg, 10.6 mmol) and MeOH (682 mg, 21.3 mmol) at 0 °C. The mixture was stirred for 2 min at 0 °C and then DIAD (2152 mg, 10.6 mmol) was added and the mixture warmed to rt and stirred for 1 h. The mixture was diluted with water and extracted with EtOAc (3 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 2% EtOAc in PE to afford the title compound (415 mg, 81% yield) as a white solid.

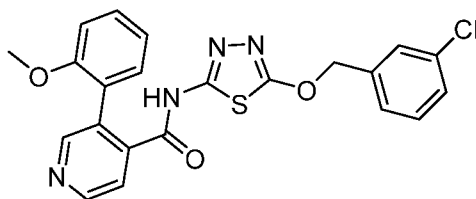
Step 2. Preparation of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-(trifluoromethyl)pyridine-3-carboxamide



[0531] The title compound was prepared using General Procedures E, F and A. For General Procedure E, methyl 4-chloro-6-(trifluoromethyl)pyridine-3-carboxylate and 4-fluoro-2-methoxyphenylboronic acid were employed. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. ^1H NMR (300 MHz, DMSO- d_6): δ 13.04 (s, 1H), 9.00 (s, 1H), 7.92 (s, 1H), 7.56 - 7.43 (m, 6H), 7.13 - 7.02 (m, 2H), 5.49 (s, 2H), 3.54 (s, 3H). m/z 521 $[\text{M}+\text{H}]^+$.

Example 157

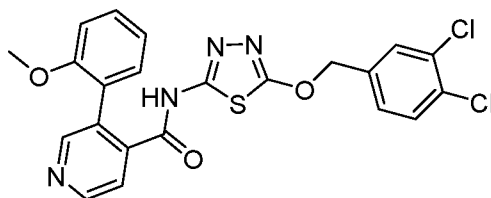
Synthesis of N-(5-((3-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(2-methoxyphenyl)isonicotinamide



[0532] The title compound was prepared using similar procedures as the synthesis of Example 141, Step 2 and 3, replacing 1-[4-(hydroxymethyl)phenyl]cyclopropane-1-carbonitrile with m-chlorobenzyl alcohol in Step 2. ¹H NMR (300 MHz, DMSO-d₆): δ12.88 (s, 1H), 8.72 (d, 1H), 8.61 (s, 1H), 7.63-7.59 (m, 1H), 7.59 (s, 1H), 7.45-7.44 (m, 3H), 7.40-7.35 (m, 2H), 7.09-7.04 (m, 1H), 6.99 (d, 1H), 5.48 (s, 2H), 3.51 (s, 3H). m/z 453 [M+H⁺].

Example 158

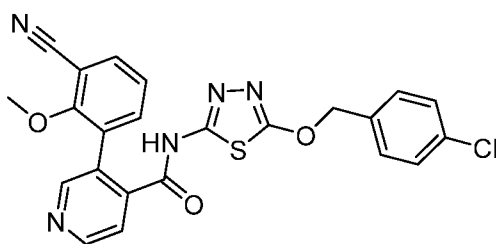
Synthesis of N-[5-[(3,4-dichlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-3-(2-methoxyphenyl)pyridine-4-carboxamide



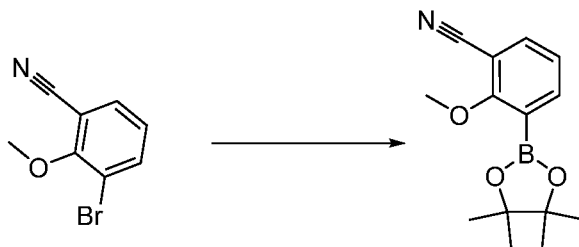
[0533] The title compound was prepared using similar procedures as the synthesis of Example 141, Step 2 and 3, replacing 1-[4-(hydroxymethyl)phenyl]cyclopropane-1-carbonitrile with 3,4-dichlorobenzyl alcohol in Step 2. ¹H NMR (400 MHz, DMSO-d₆): δ12.86 (s, 1H), 8.71 (d, 1H), 8.61 (s, 1H), 7.80 (d, 1H), 7.69 (d, 1H), 7.63-7.62 (m, 1H), 7.52-7.49 (m, 1H), 7.40-7.35 (m, 2H), 7.06 (t, 1H), 6.99 (d, 1H), 5.48 (s, 2H), 3.51 (s, 3H). m/z 487 [M+H⁺].

Example 159

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(3-cyano-2-methoxyphenyl)isonicotinamide

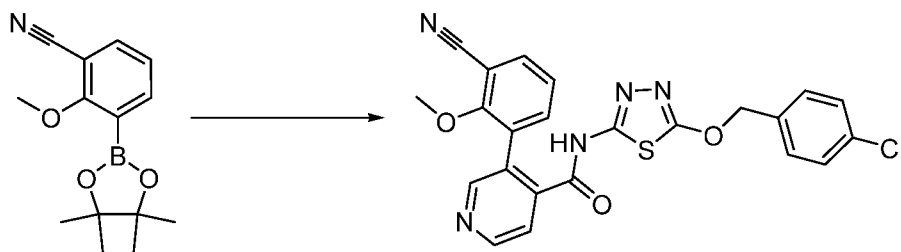


Step 1. Preparation of 2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile



[0534] To a solution of 3-bromo-2-methoxybenzonitrile (200 mg, 0.94 mmol) in dioxane (3.0 mL) was added bis(pinacolato)diboron (287 mg, 1.1 mmol), K_3PO_4 (400 mg, 1.9 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (69 mg, 0.09 mmol) at room temperature. The mixture was stirred for 4 h at 80 °C under nitrogen atmosphere. The mixture was cooled to room temperature, diluted with water and extracted with EtOAc (2 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (PE:EtOAc, 5:1) to afford the title compound (56 mg, 23% yield) as a yellow oil.

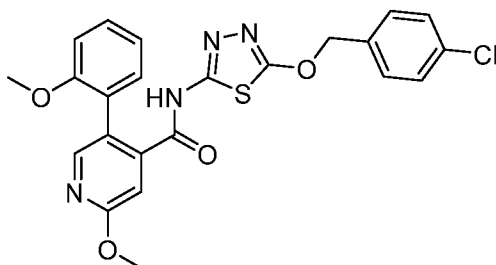
Step 2. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(3-cyano-2-methoxyphenyl)isonicotinamide



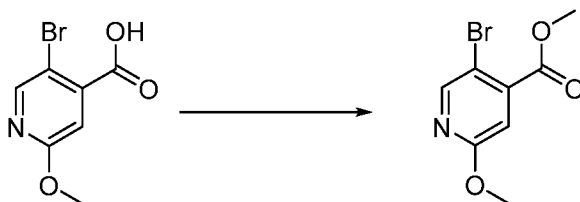
[0535] The title compound was prepared using General Procedures E, F and A. For General Procedure E, 2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile and methyl 3-bromopyridine-4-carboxylate were employed. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. ^1H NMR (300 MHz, DMSO- d_6): δ 13.10 (s, 1H), 8.79 (d, 1H), 8.64 (s, 1H), 7.83 - 7.77 (m, 2H), 7.67 (d, 1H), 7.54 - 7.45 (m, 4H), 7.35 (t, 1H), 5.45 (s, 2H), 3.55 (s, 3H). m/z 478 $[M+H]^+$.

Example 160

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-methoxy-5-(2-methoxyphenyl)isonicotinamide

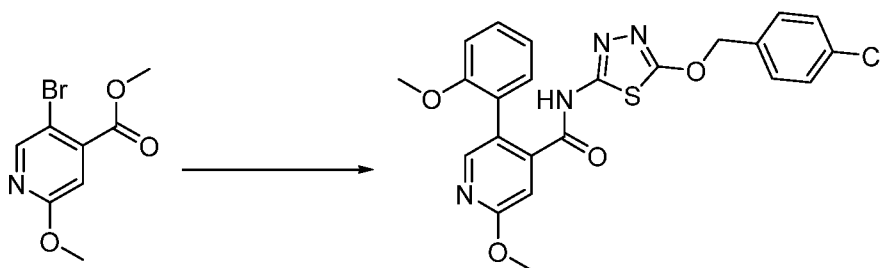


Step 1. Preparation of methyl 5-bromo-2-methoxypyridine-4-carboxylate



[0536] To a solution of 5-bromo-2-methoxypyridine-4-carboxylic acid (800 mg, 3.4 mmol) in THF (8.0 mL) was added MeOH (221 mg, 6.9 mmol), PPh₃ (1809 mg, 6.9 mmol) and DIAD (1046 mg, 5.2 mmol) at 0 °C. The mixture was stirred for 1 hour at 0 °C. The mixture was diluted with water and extracted with EtOAc. The organic layer was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE:EtOAc, 20:1) to afford the title compound (800 mg, 94% yield) as a white solid.

Step 2. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-2-methoxy-5-(2-methoxyphenyl)isonicotinamide

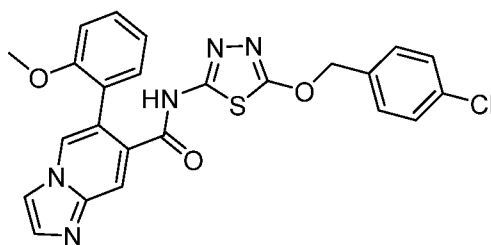


[0537] The title compound was prepared using General Procedures E, F and A. For General Procedure E, methyl 5-bromo-2-methoxypyridine-4-carboxylate and 2-methoxyphenylboronic acid were employed. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-

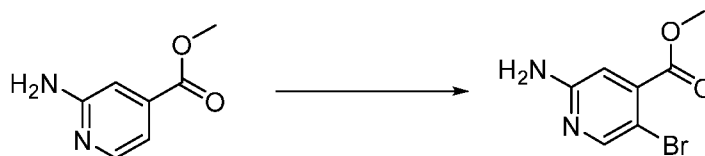
amine (Intermediate B) was used. ^1H NMR (300 MHz, DMSO- d_6): δ 12.83 (s, 1H), 8.17 (s, 1H), 7.55 - 7.47 (m, 4H), 7.37 - 7.31 (m, 2H), 7.09 (s, 1H), 7.06-7.01 (m, 1H), 6.95 (d, 1H), 5.48 (s, 2H), 3.95 (s, 3H), 3.49 (s, 3H). m/z 483 $[\text{M}+\text{H}^+]$.

Example 161

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-(2-methoxyphenyl)imidazo[1,2-a]pyridine-7-carboxamide



Step 1. Preparation of methyl 2-amino-5-bromopyridine-4-carboxylate



[0538] To a solution of methyl 2-aminopyridine-4-carboxylate (5.0 g, 32.9 mmol) in DMF (50 mL) was added NBS (6.3 g, 36.1 mmol) at rt. The mixture was stirred for 2h at rt under nitrogen atmosphere. The mixture was diluted with water and extracted with EtOAc (3 x). The combined organic layers were concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with 100% CH_2Cl_2 to afford the title compound (3.5 g, 46% yield) as a yellow oil.

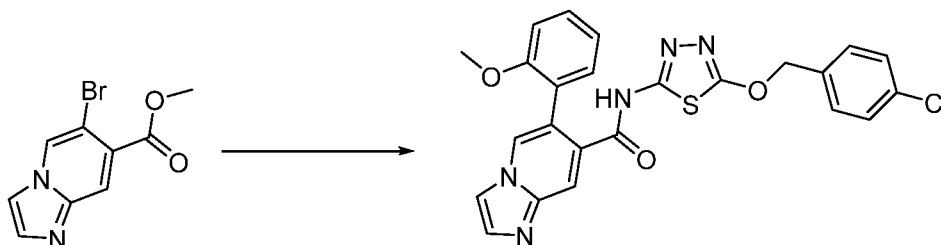
Step 2. Preparation of methyl 6-bromoimidazo[1,2-a]pyridine-7-carboxylate



[0539] To a solution of methyl 2-amino-5-bromopyridine-4-carboxylate (3.3 g, 14.3 mmol) in EtOH (35 mL), was added NaHCO_3 (2.0 g, 24.3 mmol) and chloroacetaldehyde (5.05 g, 64.3 mmol) at room temperature. The mixture was stirred for overnight at 80 $^\circ\text{C}$ under nitrogen atmosphere. The mixture was diluted with water and extracted with EtOAc (3 x). The combined

organic layers were concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with 100% CH₂Cl₂ to afford the title compound (3.9 g, 96% yield) as a yellow oil.

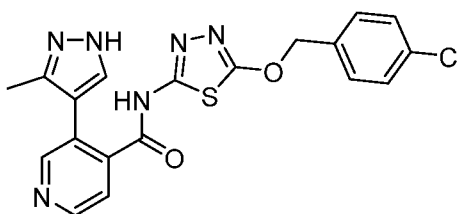
Step 3. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-(2-methoxyphenyl)imidazo[1,2-a]pyridine-7-carboxamide



[0540] The title compound was prepared using General Procedures E, F and A. For General Procedure E, methyl 6-bromoimidazo[1,2-a]pyridine-7-carboxylate and 2-methoxyphenylboronic acid were employed. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. ¹H NMR (400 MHz, DMSO-d₆): δ 12.81 (s, 1H), 8.56 (s, 1H), 8.05 (s, 1H), 7.92 (s, 1H), 7.73 (s, 1H), 7.54 - 7.47 (m, 4H), 7.39 - 7.33 (m, 2H), 7.06 - 7.03 (m, 1H), 6.95 - 6.93 (m, 1H), 5.47 (s, 2H), 3.49 (s, 3H). m/z 492 [M+H⁺].

Example 162

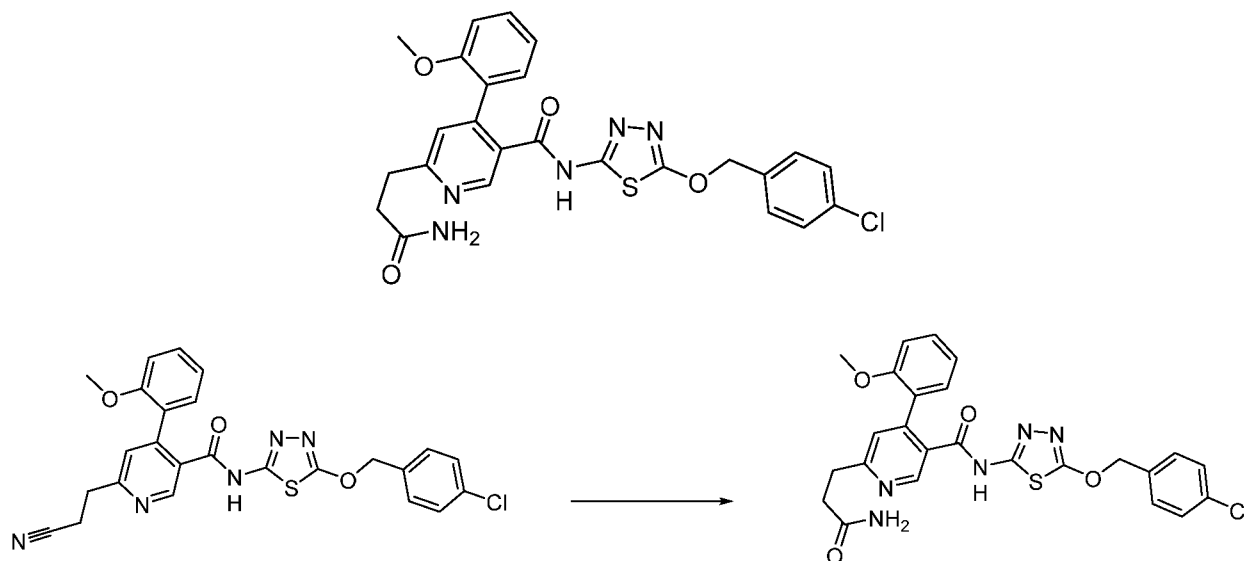
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(3-methyl-1H-pyrazol-4-yl)isonicotinamide



[0541] The title compound was prepared using General Procedures E, F and A. For General Procedure E, methyl 3-bromopyridine-4-carboxylate and 3-methyl-1H-pyrazol-4-ylboronic acid were employed. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. ¹H NMR (300 MHz, DMSO-d₆): δ 12.80 (s, 2H), 8.65 - 8.58 (m, 2H), 7.61 - 7.47 (m, 6H), 5.48 (s, 2H), 2.18 (s, 3H). m/z 427 [M+H⁺].

Example 163

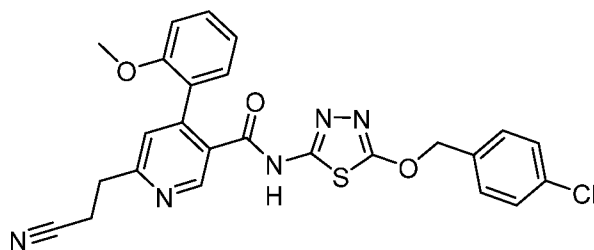
Synthesis of 6-(3-amino-3-oxopropyl)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)nicotinamide



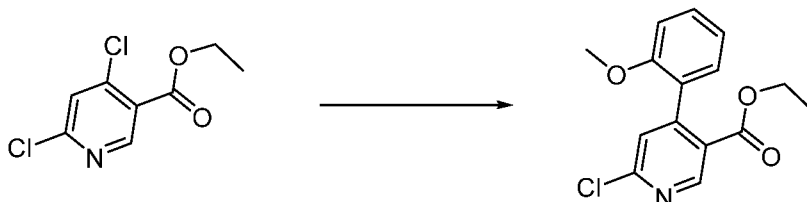
[0542] To a solution of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-6-(2-cyanoethyl)-4-(2-methoxyphenyl)pyridine-3-carboxamide (24 mg, 0.047 mmol, Example 164,) in H₂O₂ (30%, 21 mg, 0.190 mmol) and EtOH (2 mL) was added a solution of LiOH (2.3 mg, 0.095 mmol) in water (1.0 mL) dropwise at room temperature under air atmosphere. The mixture was stirred for 3h at 70 °C. The mixture was cooled to rt, diluted with water, and extracted with EtOAc (2 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 15:1) to afford the title compound (12 mg, 46% yield) as a white solid. ¹H NMR (300 MHz, DMSO-d₆): δ 12.75 (s, 1H), 8.68 (s, 1H), 7.55 - 7.49 (m, 4H), 7.42 - 7.35 (m, 3H), 7.30 (s, 1H), 7.10 (t, 1H), 6.98 (d, 1H), 6.81 (s, 1H), 5.47 (s, 2H), 3.50 (s, 3H), 3.05 (t, 2H), 2.59 - 2.56 (m, 2H). m/z 524 [M+H⁺].

Example 164

Synthesis of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-6-(2-cyanoethyl)-4-(2-methoxyphenyl)pyridine-3-carboxamide

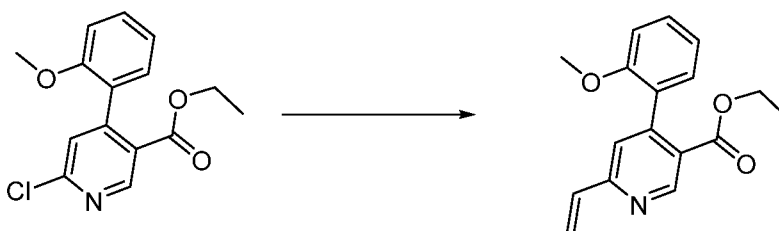


Step 1. Preparation of ethyl 6-chloro-4-(2-methoxyphenyl)pyridine-3-carboxylate



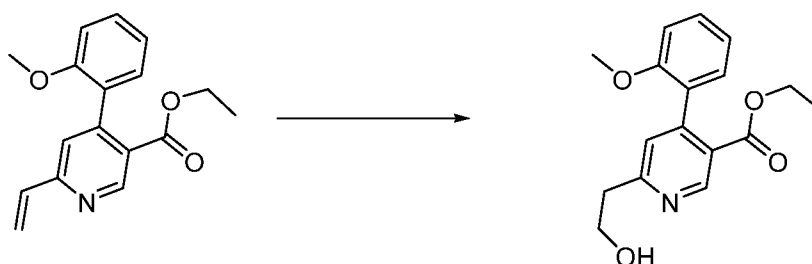
[0543] To a solution of ethyl 4,6-dichloropyridine-3-carboxylate (10 g, 45.4 mmol) in dioxane (100 mL) and water (20 mL) was added 2-methoxyphenylboronic acid (6.9 g, 45.5 mmol), K_2CO_3 (12.6 g, 90.9 mmol) and $Pd(DTBPF)Cl_2$ (3.0 g, 4.5 mmol) under nitrogen atmosphere. The solution was stirred for 3 hr at 80 °C. The mixture was cooled to rt, diluted with water and extracted with EtOAc (2 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 6% EtOAc in PE to afford the title compound (4.5g, 32% yield) as a yellow solid.

Step 2. Preparation of ethyl 6-ethenyl-4-(2-methoxyphenyl)pyridine-3-carboxylate



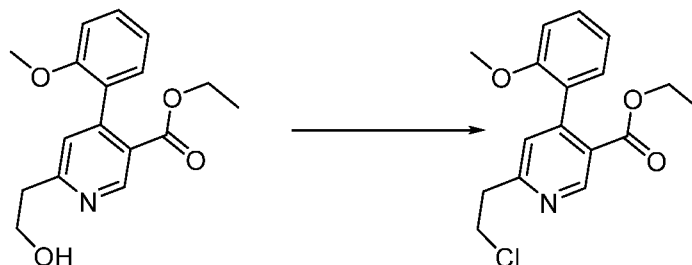
[0544] To a solution of ethyl 6-chloro-4-(2-methoxyphenyl)pyridine-3-carboxylate (2 g, 6.9 mmol) in DMF (20 mL) was added tributyl(ethenyl)stannane (2.6 g, 8.2 mmol) and $Pd(PPh_3)_4$ (0.79 g, 0.684 mmol) under nitrogen atmosphere. The solution was stirred for 3 hr at 100 °C. The mixture was cooled to rt, diluted with water and extracted with EtOAc (2 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 9% EtOAc in PE to afford the title compound (2 g, 99.9% yield) as a yellow oil.

Step 3. Preparation of ethyl 6-(2-hydroxyethyl)-4-(2-methoxyphenyl)pyridine-3-carboxylate



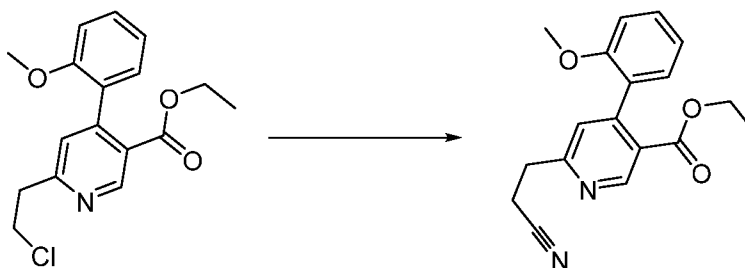
[0545] To a solution of ethyl 6-ethenyl-4-(2-methoxyphenyl)pyridine-3-carboxylate (2 g, 7.1 mmol) in THF was added BH_3 (1M in THF, 23 mL, 23 mmol) dropwise at room temperature. The mixture was heated to 55 °C for 1h. The mixture was cooled to 0 °C and then K_2CO_3 (1M in water, 24 mL, 24 mmol) was added dropwise followed by H_2O_2 (30%, 20 mL, 858 mmol). The mixture was stirred for 2h at room temperature. The mixture was diluted with water and extracted with EtOAc (2 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 17% EtOAc in hexanes to afford the title compound (400mg, 17% yield) as a light-yellow oil.

Step 4. Preparation of ethyl 6-(2-chloroethyl)-4-(2-methoxyphenyl)pyridine-3-carboxylate



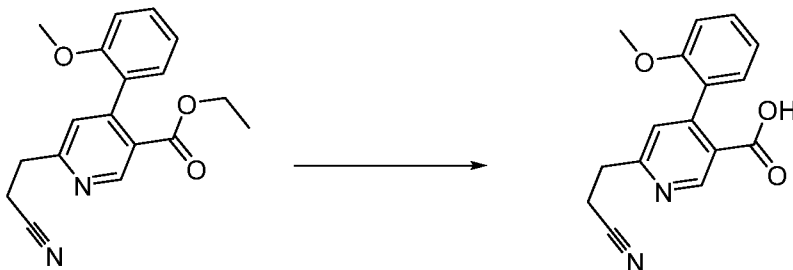
[0546] To a solution of ethyl 6-(2-hydroxyethyl)-4-(2-methoxyphenyl)pyridine-3-carboxylate (400 mg, 1.3 mmol) in DCM was added SOCl_2 (1579 mg, 13.3 mmol). The mixture was stirred overnight at room temperature. The mixture was quenched with water and extracted with DCM (2 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 30:1) to afford the title compound (300 mg, 67% yield) as a light-yellow oil.

Step 5. Preparation of ethyl 6-(2-cyanoethyl)-4-(2-methoxyphenyl)pyridine-3-carboxylate



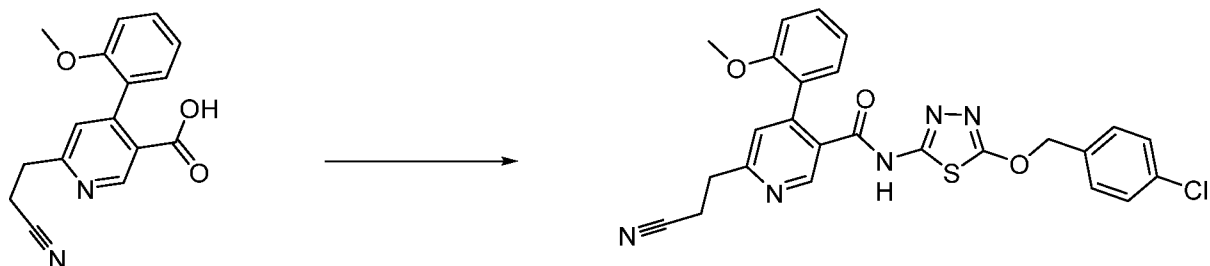
[0547] To a solution of ethyl 6-(2-chloroethyl)-4-(2-methoxyphenyl)pyridine-3-carboxylate (300 mg, 0.94 mmol) in DMSO (5 mL) was added NaCN (230 mg, 4.7 mmol). The mixture was stirred for 2 hr at 90 °C. The mixture was cooled to rt, diluted with water and extracted with EtOAc (3 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (hexanes:EtOAc, 5:1) to afford the title compound (180 mg, 59% yield) as a light brown oil.

Step 6. Preparation of 6-(2-cyanoethyl)-4-(2-methoxyphenyl)pyridine-3-carboxylic acid



[0548] To a solution of ethyl 6-(2-cyanoethyl)-4-(2-methoxyphenyl)pyridine-3-carboxylate (150 mg, 0.48 mmol) in ethanol (3 mL) were added a solution of LiOH.H₂O (40 mg, 0.97 mmol) in water (1 mL) dropwise at room temperature. The mixture was stirred for 3hr at 60 °C. The mixture was acidified to pH 5 with HCl (2 M). The mixture was concentrated under reduced pressure. The residue was purified by reverse phase chromatography (column, C18 silica gel; mobile phase, with 10-30% MeCN in water) to afford the title compound (80mg, 56% yield) as an off-white solid.

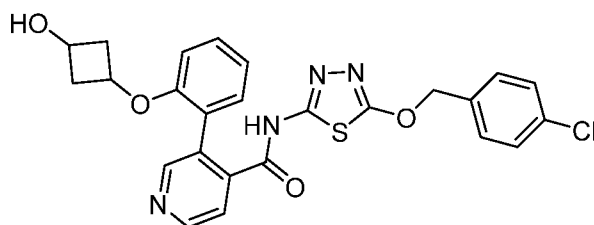
Step 7. Preparation of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-6-(2-cyanoethyl)-4-(2-methoxyphenyl)pyridine-3-carboxamide



[0549] The title compound was prepared using General Procedure A employing 6-(2-cyanoethyl)-4-(2-methoxyphenyl)pyridine-3-carboxylic acid and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B). ^1H NMR (300 MHz, DMSO- d_6): δ 12.82 (s, 1H), 8.74 (s, 1H), 7.56 - 7.47 (m, 4H), 7.43 - 7.36 (m, 3H), 7.10 (t, 1H), 7.00 (d, 1H), 5.48 (s, 2H), 3.51 (s, 3H), 3.19 (t, 2H), 3.00 (t, 2H). m/z 506 $[\text{M}+\text{H}^+]$.

Example 165

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(2-(3-hydroxycyclobutoxy)phenyl)isonicotinamide

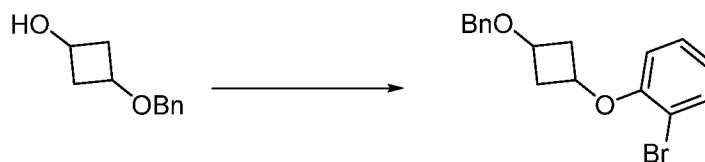


Step 1. Preparation of 3-(benzyloxy)cyclobutan-1-ol



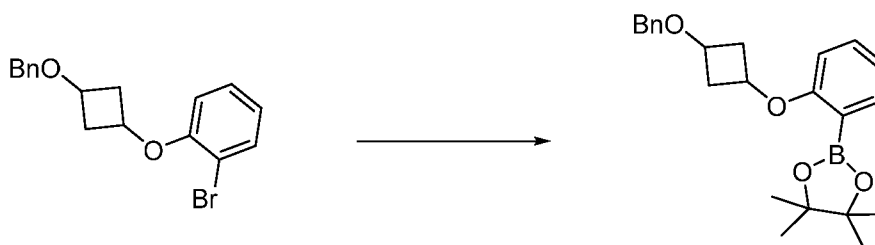
[0550] To a solution of 3-(benzyloxy)cyclobutan-1-one (7 g, 39.7 mmol) in MeOH (70 mL) was added NaBH_4 (3.0 g, 79.4 mmol) in portions at 0 °C under air atmosphere. The mixture was stirred for overnight at 0 °C under air atmosphere. The mixture was warmed to rt and quenched by the addition of NH_4Cl (aq.) The mixture was extracted with EtOAc (3 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, 9% eluted with EtOAc in PE to afford the title compound (4.2g, 59% yield) as a yellow oil.

Step 2. Preparation of 1-(3-(benzyloxy)cyclobutoxy)-2-bromobenzene



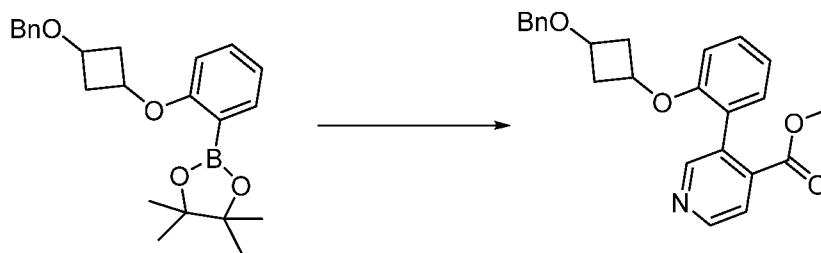
[0551] To a solution of 3-(benzyloxy)cyclobutan-1-ol (4.2 g, 23.6 mmol) in THF (45 mL) was added 2-bromophenol (6.2 g, 35.3 mmol) and PPh_3 (15.5 g, 58.9 mmol) at 0 °C under nitrogen atmosphere. Then DIAD (9.5 g, 47.1 mmol) was added at 0 °C in in portions over 20 min. The mixture was stirred for overnight at 60 °C. The mixture was cooled to rt and diluted with water. The mixture was extracted with EtOAc (3 x). The organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 1% EtOAc in PE to afford the title compound (5.2 g, 62% yield) as a light yellow solid.

Step 3. Preparation of 2-(2-(3-(benzyloxy)cyclobutoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



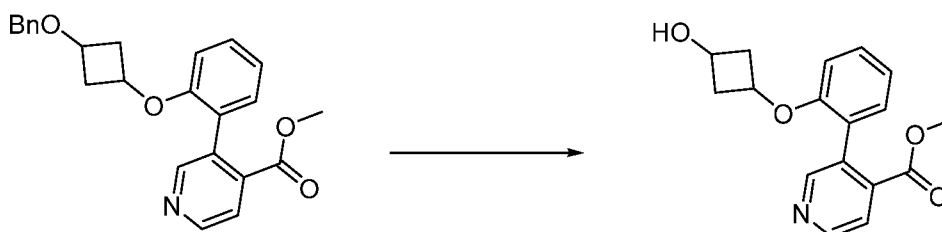
[0552] To a solution of 1-(3-(benzyloxy)cyclobutoxy)-2-bromobenzene (1 g, 31 mmol) in dioxane (10 mL) was added and bis(pinacolato)diboron (1.5 g, 6.0 mmol), KOAc (0.6 g, 62 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.22 g, 0.300 mmol) under nitrogen atmosphere. The mixture was stirred for overnight at 80 °C. The mixture was cooled room temperature and diluted with water. The mixture was extracted with EtOAc (3 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 2% EtOAc in PE to afford the title compound (900 mg, 79% yield) as a light brown solid.

Step 4. Preparation of methyl 3-(2-(3-(benzyloxy)cyclobutoxy)phenyl)isonicotinate



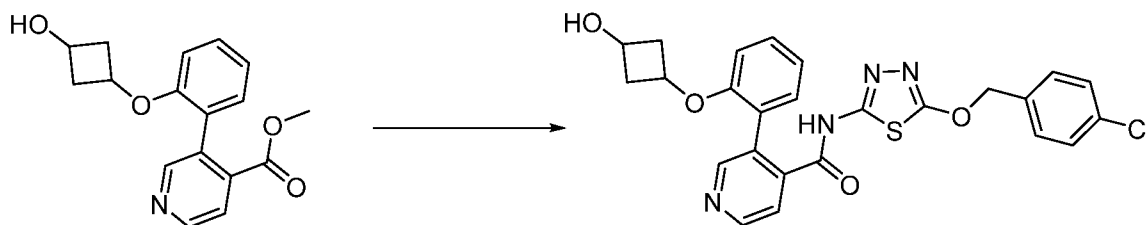
[0553] The title compound was prepared using General Procedure E employing 2-(2-(3-(benzyloxy)cyclobutoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and methyl 3-bromopyridine-4-carboxylate.

Step 5. Preparation of methyl 3-(2-(3-hydroxycyclobutoxy)phenyl)isonicotinate



[0554] To a solution of methyl 3-(2-(3-(benzyloxy)cyclobutoxy)phenyl)isonicotinate (580 mg, 1.5 mmol) in MeOH (150 mL) was added Pd/C (10%, 0.119 g) under nitrogen atmosphere. The mixture stirred at room temperature overnight under hydrogen atmosphere. The mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure to afford the title compound (430 mg, 86% yield) as a light yellow solid.

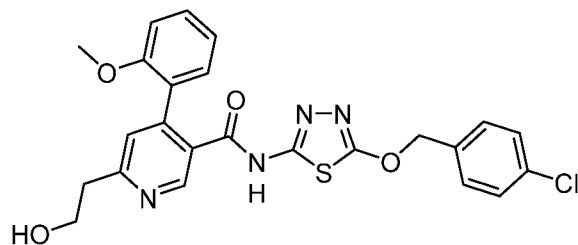
Step 6. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(2-(3-hydroxycyclobutoxy)phenyl)isonicotinamide



[0555] The title compound was prepared using General Procedures F and A. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. ^1H NMR (300 MHz, DMSO- d_6): δ 12.97 (s, 1H), 8.74 (d, 1H), 8.59 (s, 1H), 7.66 (d, 1H), 7.52 - 7.50 (m, 4H), 7.37 - 7.31 (m, 2H), 7.08 - 7.06 (m, 1H), 6.69 - 6.67 (m, 1H), 5.49 (s, 2H), 5.01 (d, 1H), 4.66 - 4.62 (m, 1H), 3.95 - 3.92 (m, 1H), 2.10-2.14 (m, 4H). m/z 509 $[\text{M}+\text{H}^+]$.

Example 166

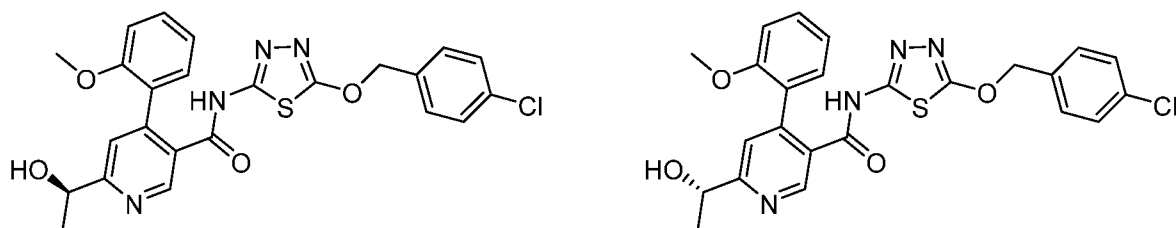
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-(2-hydroxyethyl)-4-(2-methoxyphenyl)nicotinamide



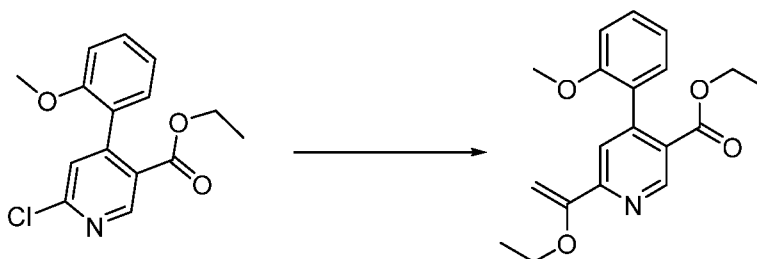
[0556] The title compound was prepared using General Procedures F and A. For General Procedure F ethyl 6-(2-hydroxyethyl)-4-(2-methoxyphenyl)pyridine-3-carboxylate (Example 164, Step 3) was employed. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. ¹H NMR (300 MHz, DMSO-d₆): δ 12.73 (s, 1H), 8.68 (s, 1H), 7.54 - 7.46 (m, 4H), 7.41 - 7.34 (m, 2H), 7.30 (s, 1H), 7.09 (t, 1H), 7.00 (d, 1H), 5.46 (s, 2H), 4.70 (t, 1H), 3.83 - 3.77 (m, 2H), 3.49 (s, 3H), 2.97 (t, 2H). m/z 497 [M+H⁺].

Example 167

Synthesis of (R)-N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-6-(1-hydroxyethyl)-4-(2-methoxyphenyl)pyridine-3-carboxamide and (S)-N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-6-(1-hydroxyethyl)-4-(2-methoxyphenyl)pyridine-3-carboxamide



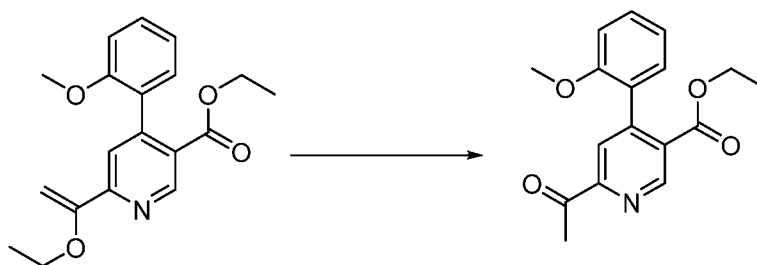
Step 1. Preparation of ethyl 6-(1-ethoxyethenyl)-4-(2-methoxyphenyl)pyridine-3-carboxylate



[0557] To a solution of ethyl 6-chloro-4-(2-methoxyphenyl)pyridine-3-carboxylate (400 mg, 1.4 mmol, Example 105, Step 1) in toluene (4 mL) was added tributyl(1-ethoxyethenyl)stannane (743 mg, 2.1 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (158 mg, 0.14 mmol). The mixture was stirred for 4 hours at 100 °C.

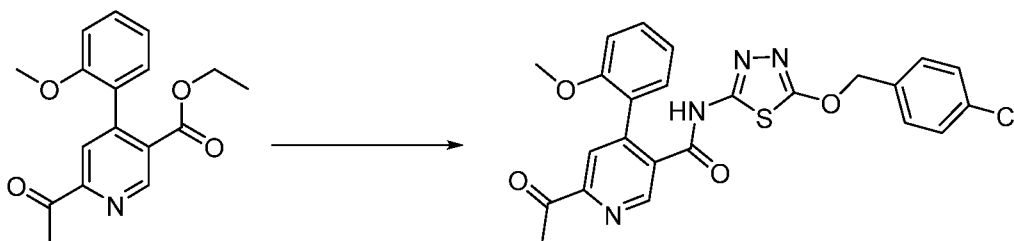
[0558] The mixture was cooled room temperature and diluted with water. The mixture was extracted with EtOAc. The organic layer was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE:EtOAc, 2:1) to afford the title compound (350 mg, yield 73% yield) as a colorless oil.

Step 2. Preparation of ethyl 6-acetyl-4-(2-methoxyphenyl)pyridine-3-carboxylate



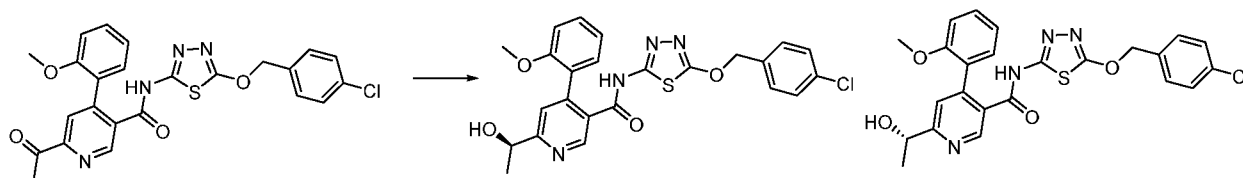
[0559] To a solution of ethyl 6-(1-ethoxyethenyl)-4-(2-methoxyphenyl)pyridine-3-carboxylate (350 mg, 1.1 mmol) in water (3mL) was added HCl in 1,4-dioxane (3 mL). The mixture was stirred for 4 hours at room temperature. The mixture was diluted with water. The mixture was extracted with EtOAc and the organic layer was concentrated under reduced pressure to afford the title compound 410 mg (yield 92% yield) of as an off-white solid.

Step 3. Preparation of 6-acetyl-N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)pyridine-3-carboxamide



[0560] The title compound was prepared using General Procedures F and A. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used.

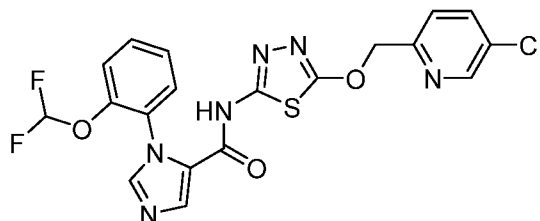
Step 4. Preparation of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-6-(1-hydroxyethyl)-4-(2-methoxyphenyl)pyridine-3-carboxamide



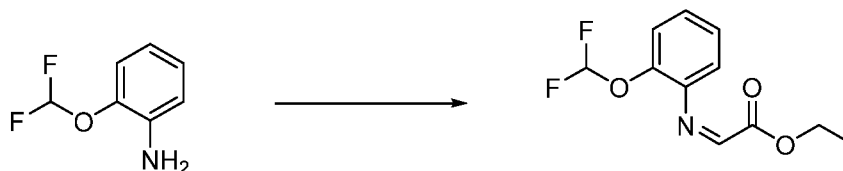
[0561] To a solution of 6-acetyl-N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)pyridine-3-carboxamide (95 mg, 0.19 mmol) in MeOH (1 mL) at 0 °C was added a solution of NaBH₄ (22 mg, 0.58 mmol) in THF (3 mL) under nitrogen atmosphere. The mixture was stirred for 1 hour at 0 °C. The mixture was warmed to rt and NH₄Cl (aq.) was added. The mixture was extracted with EtOAc and the organic layer was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE:EtOAc, 2:1) to afford the title compound as a racemic mixture (54 mg, yield 56%) as a white solid. ¹H NMR (300 MHz, DMSO-d₆): δ 12.76 (s, 1H), 8.70 (s, 1H), 7.35-7.56 (m, 7H), 7.12-7.10 (m, 1H), 6.99 (d, 1H), 5.55-5.48 (m, 3H), 4.84-4.80 (m, 1H), 3.51 (s, 3H), 1.43 (d, 3H). m/z 497 [M+H⁺].

Example 168

Synthesis of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-3-[2-(difluoromethoxy)phenyl]imidazole-4-carboxamide



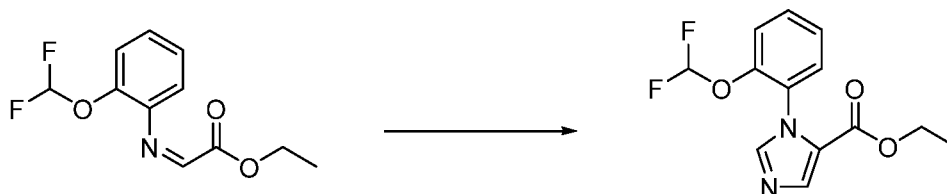
Step 1. Preparation of ethyl 2-[[2-(difluoromethoxy)phenyl]imino]acetate



[0562] To a solution of 2-(difluoromethoxy) aniline (2.0 g, 12.6 mmol) in MeOH (20 mL) was added ethyl glyoxylate (50% in toluene, 3.1 g, 15.1 mmol) at room temperature. The mixture was stirred for 5h at room temperature. The mixture was concentrated under reduced pressure to

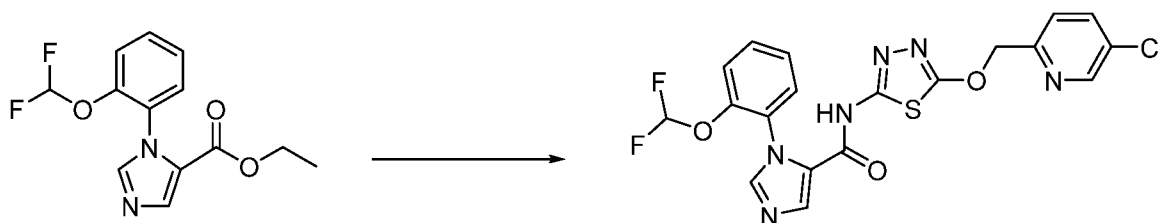
afford the title compound (6 g) as a dark brown oil, which was used in the next step without further purification

Step 2. Preparation of ethyl 3-[2-(difluoromethoxy)phenyl]imidazole-4-carboxylate



[0563] To a solution of ethyl 2-[[2-(difluoromethoxy)phenyl]imino]acetate (6.0 g, 11.1 mmol) in EtOH (20 mL) was added K_2CO_3 (3.1 g, 22.2 mmol) and p-toluenesulfonylmethyl isocyanide (2.2 g, 11.1 mmol) at room temperature. The mixture was stirred for overnight at 80 °C under nitrogen atmosphere. The mixture was cooled room temperature and diluted with water. The mixture was extracted with EtOAc (3 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 11% EtOAc in hexanes to afford the title compound (2.5 g, 66% yield) as a light-yellow oil.

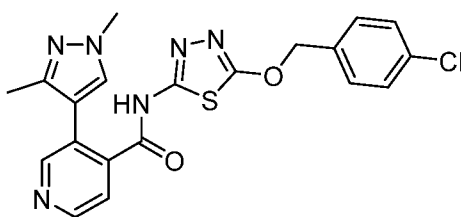
Step 3. Preparation of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-3-[2-(difluoromethoxy)phenyl]imidazole-4-carboxamide



[0564] The title compound was prepared using General Procedures F and A. For General Procedure A, 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C) was used. ^1H NMR (400 MHz, DMSO- d_6): δ 5.53 (s, 2H), 7.07-7.25 (m, 1H), 7.37-7.39 (m, 2H), 7.56 - 7.59 (m, 3H), 8.00 (d, 1H), 8.08 (s, 1H), 8.22 (s, 1H), 8.65 (d, 1H), 12.85 (s, 1H). m/z 479 $[M+H]^+$.

Example 169

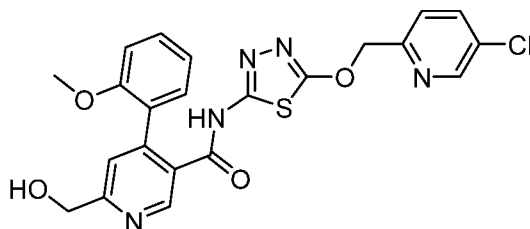
Synthesis of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-3-(1,3-dimethylpyrazol-4-yl)pyridine-4-carboxamide



[0565] The title compound was prepared using General Procedures E, F and A. For General Procedure E, methyl 3-bromopyridine-4-carboxylate and 1,3-dimethylpyrazol-4-ylboronic acid were employed. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. ^1H NMR (300 MHz, DMSO- d_6): δ 12.98 (s, 1H), 8.66 (d, 2H), 7.80 - 7.63 (m, 2H), 7.58 - 7.47 (m, 4H), 5.53 (s, 2H), 3.78 (s, 3H), 2.14 (s, 3H). m/z 441 $[\text{M}+\text{H}^+]$.

Example 170

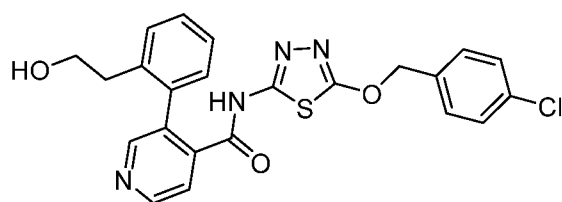
Synthesis of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-6-(hydroxymethyl)-4-(2-methoxyphenyl)pyridine-3-carboxamide



[0566] The title compound was prepared using General Procedure A, employing 6-(hydroxymethyl)-4-(2-methoxyphenyl)pyridine-3-carboxylic acid (Example 105, Step 3) and 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C). ^1H NMR (300 MHz, DMSO- d_6): δ 12.80 (s, 1H), 8.70 (s, 1H), 8.66 (d, 1H), 8.00 (dd, 1H), 7.60 (d, 1H), 7.44 - 7.33 (m, 3H), 7.09 (t, 1H), 6.99 (d, 1H), 5.60 - 5.54 (m, 3H), 4.66 - 4.64 (m, 2H), 3.51 (s, 3H). m/z 484 $[\text{M}+\text{H}^+]$.

Example 171

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(2-(2-hydroxyethyl)phenyl)isonicotinamide

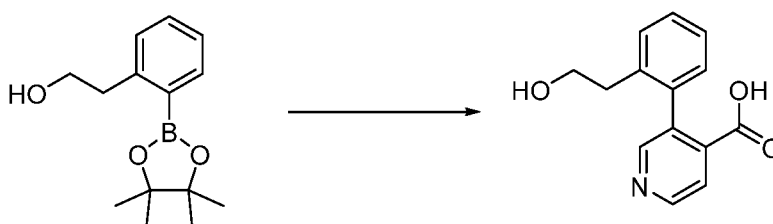


Step 1. Preparation of 2-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethanol



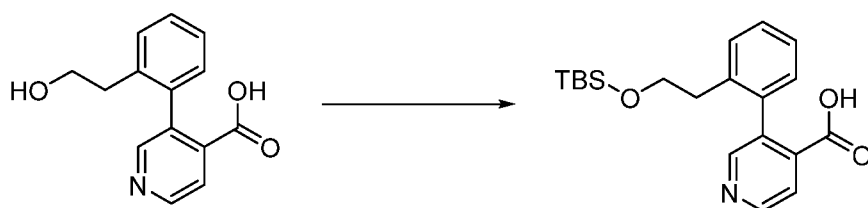
[0567] To a solution of [2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]acetic acid (860 mg, 3.3 mmol) in THF (9 mL) was added $\text{BH}_3\text{-THF}$ (1 M, 3.3 mL, 3.3 mmol) at 0 °C under nitrogen atmosphere. The mixture was stirred for 1 hour at 0 °C. The mixture was warmed to rt and stirred at rt overnight. The mixture was diluted with MeOH and concentrated under reduced pressure. The residue was purified by Prep-TLC (PE:EtOAc, 5:1) to afford the title compound (250 mg, 29% yield) as a yellow solid.

Step 2. Preparation of 3-[2-(2-hydroxyethyl)phenyl]pyridine-4-carboxylic acid



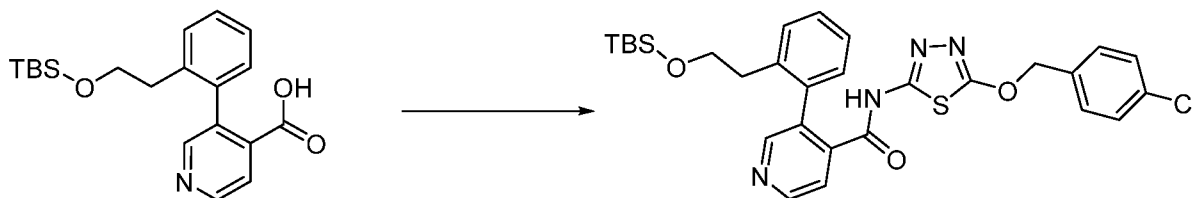
[0568] The title compound was prepared using General Procedures E and F. For General Procedure E, 2-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethanol and methyl 3-bromopyridine-4-carboxylate were employed.

Step 3. Preparation of 3-(2-(2-((tert-butyldimethylsilyl)oxy)ethyl)phenyl)isonicotinic acid



[0569] To a solution of 3-[2-(2-hydroxyethyl)phenyl]pyridine-4-carboxylic acid (180 mg, 0.74 mmol) in THF (2 mL) was added TBSCl (245 mg, 1.6 mmol) and imidazole (151 mg, 2.2 mmol). The mixture was stirred for 4 hours at 50 °C. The mixture was diluted with MeOH concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 20:1) to afford the title compound (160 mg, 58% yield) as a white liquid.

Step 4. Preparation of 3-(2-[2-[(tert-butyldimethylsilyl)oxy]ethyl]phenyl)-N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]pyridine-4-carboxamide



[0570] To a solution of 3-(2-[2-[(tert-butyldimethylsilyl)oxy]ethyl]phenyl)pyridine-4-carboxylic acid (100 mg, 0.28 mmol) in DMF (1 mL) was added 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (74 mg, 0.31 mmol, Intermediate B), EDCI (80 mg, 0.42 mmol) and HOBt (57 mg, 0.42 mmol) at 0 °C. The mixture was stirred for 10 min at 0 °C. Then the mixture was warmed to rt and stirred at rt overnight. The mixture was diluted with water and extracted with EtOAc (3 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 20:1) to afford the title compound (60 mg, 36% yield) as a white liquid.

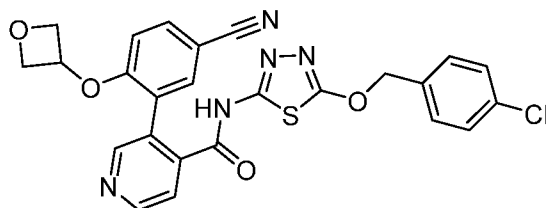
Step 5. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(2-(2-hydroxyethyl)phenyl)isonicotinamide



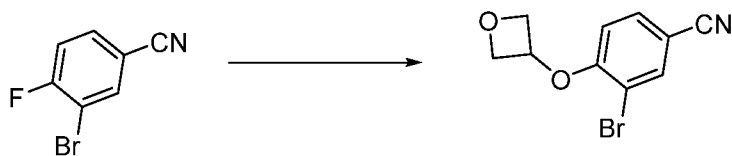
[0571] To a solution of 3-(2-[2-[(tert-butyldimethylsilyl)oxy]ethyl]phenyl)-N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]pyridine-4-carboxamide (55 mg, 0.095 mmol) in THF (1 mL) was added TBAF (25 mg, 0.095 mmol) and CsF (144 mg, 0.95 mmol). The mixture was stirred for overnight at room temperature. The mixture was diluted with water and extracted with EtOAc (5 x). The combined organic layers were concentrated under vacuum. The residue was purified by Prep-TLC (DCM:MeOH, 20:1) to afford the title compound (24 mg, 54% yield) as a white solid. ^1H NMR (300 MHz, DMSO- d_6): δ 8.75 (d, 1H), 8.58 (s, 1H), 7.71 (d, 1H), 7.52 - 7.50 (m, 4H), 7.36 - 7.28 (m, 2H), 7.23 - 7.18 (m, 1H), 7.09 (d, 1H), 5.44 (s, 2H), 3.47 (t, 2H), 2.67 - 2.59 (m, 2H). m/z 467 $[\text{M}+\text{H}^+]$.

Example 172

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(5-cyano-2-(oxetan-3-yloxy)phenyl)isonicotinamide



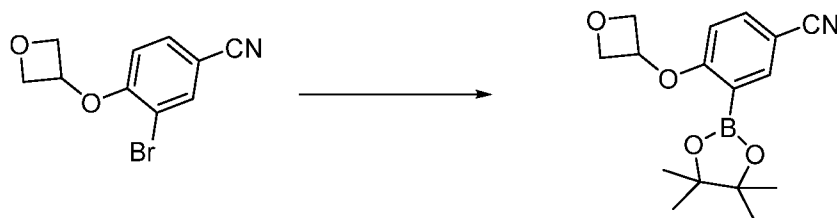
Step 1. Preparation of 3-bromo-4-(oxetan-3-yloxy)benzonitrile



[0572] To a solution of 3-bromo-4-fluorobenzonitrile (5 g, 25.0 mmol) in DMF (50 mL) was added oxetan-3-ol (2.8 g, 37.5 mmol) and K_2CO_3 (6.9 g, 50.0 mmol). The mixture was stirred for 30 min under nitrogen atmosphere at room temperature. The mixture was stirred for overnight at 100 °C under nitrogen atmosphere. The mixture was cooled room temperature and diluted with water. The mixture was extracted with EtOAc (3 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column

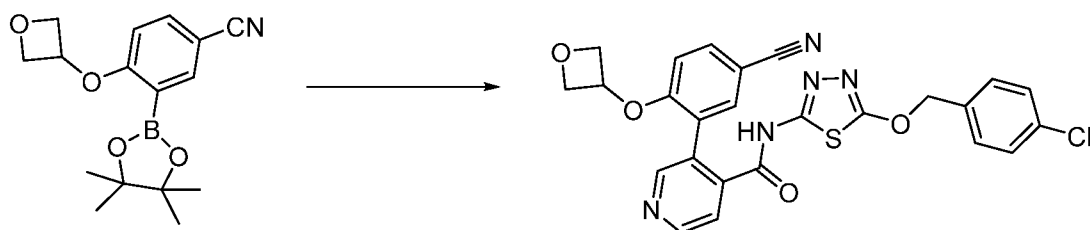
chromatography, eluted with 17% EtOAc in PE to afford the title compound (2.3g, 36% yield) as a dark yellow oil.

Step 2. Preparation of 4-(oxetan-3-yloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile



[0573] To a solution of 3-bromo-4-(oxetan-3-yloxy)benzonitrile (2.3 g, 9.1 mmol) in dioxane (23 mL) was added bis(pinacolato)diboron (3.5 g, 13.6 mmol). The mixture was stirred for 5 min at room temperature under nitrogen atmosphere. Then KOAc (1.8 g, 18.1 mmol) was added in portions at room temperature under nitrogen atmosphere. Then [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.66 g, 0.91 mmol) was added in portions at room temperature under nitrogen atmosphere. The mixture was stirred for overnight at 80 °C under nitrogen atmosphere. The mixture was cooled to room temperature and diluted with water. The mixture was extracted with EtOAc (3 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 17% EtOAc in PE to afford the title compound (2g, 73% yield) as a yellow oil.

Step 3. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-3-(5-cyano-2-(oxetan-3-yloxy)phenyl)isonicotinamide

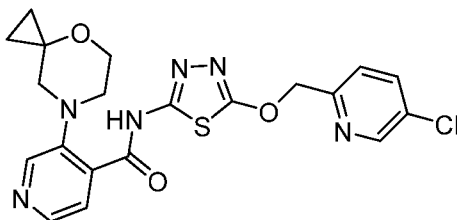


The title compound was prepared using General Procedures E, F and A. For General Procedure E, were employed. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. ¹H NMR (300 MHz, DMSO-d₆): δ 13.09 (s, 1H), 8.81 (d, 1H), 8.67

(s, 1H), 7.94 (s, 1H), 7.85 (d, 1H), 7.76 (d, 1H), 7.54 - 7.46 (m, 4H), 6.72 (d, 1H), 5.47 (s, 2H), 5.12-5.11 (m, 1H), 4.69 (s, 2H), 4.34 (s, 2H). m/z 520 [M+H⁺].

Example 173

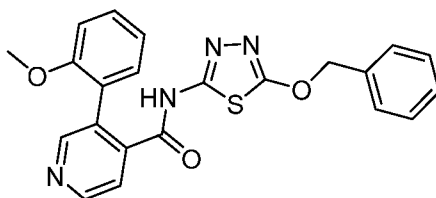
Synthesis of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-3-[4-oxa-7-azaspiro[2.5]octan-7-yl]pyridine-4-carboxamide



[0574] The title compound was prepared using General Procedures C and A. For General Procedures C, 3-fluoropyridine-4-carboxylic acid and 4-oxa-7-azaspiro[2.5]octane were employed. For General Procedures C, MeCN was replaced with NMP and temperature was 120 °C. For General Procedure A, 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C) was used and mixture was stirred at 70°C for 4 h. ¹H NMR (300 MHz, DMSO-d₆): δ 13.85 (s, 1H), 8.76 (s, 1H), 8.67 (d, 1H), 8.52 (d, 1H), 8.04 - 8.00 (m, 1H), 7.71 (d, 1H), 7.65 (d, 1H), 5.59 (s, 2H), 3.84 - 3.81 (m, 2H), 3.20 - 3.16 (m, 2H), 3.09 (s, 2H), 0.75 - 0.71 (m, 2H), 0.56 (t, 2H). m/z 459 [M+H⁺].

Example 174

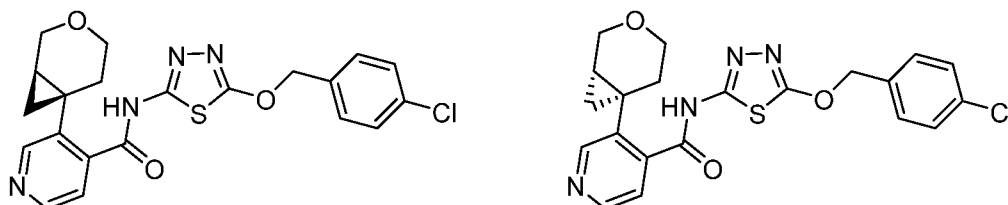
Synthesis of N-(5-(benzyloxy)-1,3,4-thiadiazol-2-yl)-3-(2-methoxyphenyl)isonicotinamide



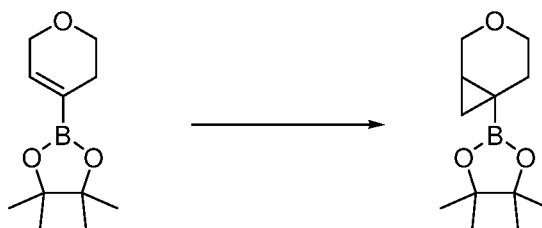
[0575] The title compound was prepared using similar procedures as the synthesis of Example 141, Steps 2 and 3, replacing 1-[4-(hydroxymethyl)phenyl]cyclopropane-1-carbonitrile with benzyl alcohol in Step 2. ¹H NMR (300 MHz, DMSO-d₆): δ 12.86 (s, 1H), 8.71 (d, 1H), 8.61 (s, 1H), 7.63 (d, 1H), 7.51 - 7.50 (m, 2H), 7.48-7.35 (m, 5H), 7.09-6.97 (m, 2H), 5.47 (s, 2H), 3.51 (s, 3H). m/z 419 [M+H⁺].

Example 175

Synthesis of 3-((1R,6S)-3-oxabicyclo[4.1.0]heptan-6-yl)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)isonicotinamide and 3-((1S,6R)-3-oxabicyclo[4.1.0]heptan-6-yl)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)isonicotinamide

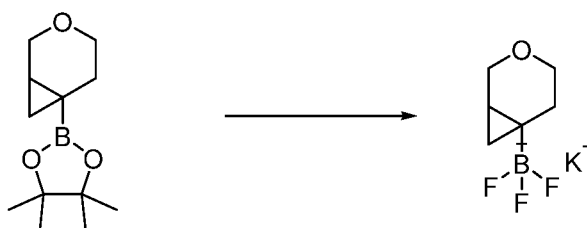


Step 1. Preparation of 2-(3-oxabicyclo[4.1.0]heptan-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



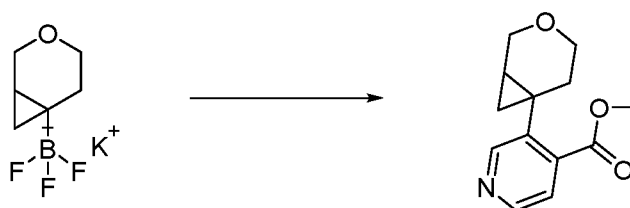
[0576] To a solution of 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1 g, 4.8 mmol) in fluorobenzene (30 mL) was added diethylzinc (2.94 g, 23.8 mmol) and chloriodomethane (8.4 g, 47.6 mmol) at -5 °C. The mixture was stirred at -5 °C for 10 min. Then three subsequent additions of diethylzinc (0.29 g, 2.4 mmol) and chloriodomethane (3.4 g, 19.0 mmol) were added in the same manner. The mixture was stirred overnight at room temperature under nitrogen atmosphere. Then an aq solution of NH₄Cl was added and the mixture was extracted with diethyl ether (3 x). The combined organic layers were concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with 5% EtOAc in hexanes to afford the title compound (450 mg, 42% yield) as a white solid.

Step 2. Preparation of potassium (3-oxabicyclo[4.1.0]heptan-6-yl)trifluoroborate



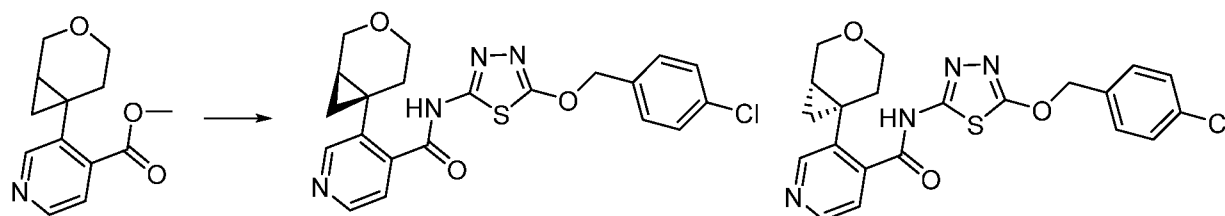
[0577] To a solution of 2-(3-oxabicyclo[4.1.0]heptan-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (400 mg, 1.8 mmol) in MeCN (4 mL) and MeOH (4 mL) was added a solution of KF (415 mg, 7.1 mmol) in water (1.6 mL) at room temperature. The mixture was stirred at rt for 10 min and then a solution of L(+)-Tartaric acid (536 mg, 3.57 mmol) in THF (0.20 mL) was added. The mixture was stirred overnight at room temperature. The mixture was diluted with diethyl ether and the precipitate was collected to afford the title compound (350 mg, 96% yield) as a white solid.

Step 3. Preparation of methyl 3-(3-oxabicyclo[4.1.0]heptan-6-yl)isonicotinate



[0578] To a solution of potassium (3-oxabicyclo[4.1.0]heptan-6-yl)trifluoroborate (200 mg, 0.98 mmol) in toluene (2 mL) and water (0.20 mL) was added methyl 3-bromopyridine-4-carboxylate (254 mg, 1.2 mmol), Cs₂CO₃ (639 mg, 2.0 mmol) and PdCl₂ (17 mg, 0.098 mmol) at room temperature. The mixture was stirred for 15 h at 110 °C under nitrogen atmosphere. The mixture was cooled room temperature and diluted with water. The mixture was extracted with EtOAc (3 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 10:1) to afford the title compound (165 mg, 72% yield) as a white solid.

Step 4. Preparation of 3-((1R,6S)-3-oxabicyclo[4.1.0]heptan-6-yl)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)isonicotinamide and 3-((1S,6R)-3-oxabicyclo[4.1.0]heptan-6-yl)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)isonicotinamide

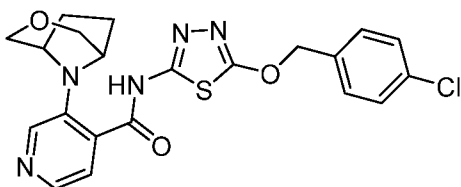


[0579] The title compound as a racemic mixture was prepared using General Procedures F and A. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. ¹H NMR (400 MHz, DMSO-d₆): δ 12.98 (s, 1H), 8.67 (s, 1H), 8.58 (d, 1H), 7.57 (d,

2H), 7.53 - 7.46 (m, 3H), 5.52 (s, 2H), 3.82 (d, 1H), 3.62 (d, 1H), 3.51 - 3.49 (m, 1H), 3.18 - 3.15 (m, 1H), 2.03 - 2 (m, 1H), 1.82 - 1.74 (m, 1H), 1.23 - 1.15 (m, 1H), 1.02 (d, 1H), 0.77 (d, 1H).
m/z 443 [M+H⁺].

Example 176

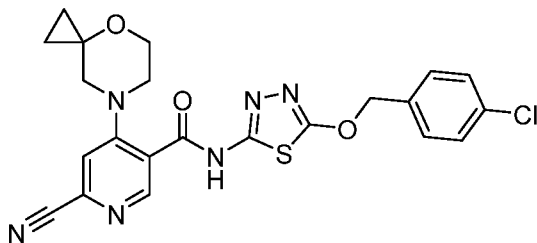
Synthesis of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-3-[3-oxa-8-azabicyclo[3.2.1]octan-8-yl]pyridine-4-carboxamide



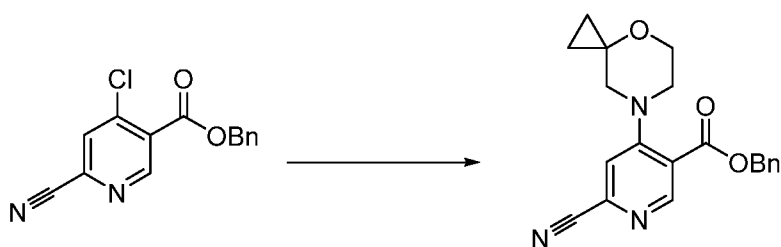
[0580] The title compound was prepared using General Procedures C and A. For General Procedures C, 3-fluoropyridine-4-carboxylic acid and 3-oxa-8-azabicyclo[3.2.1]octane were employed. For General Procedures C, MeCN was replaced with NMP and temperature was 150 °C. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. ¹H NMR (300 MHz, DMSO-d₆): δ 12.88 (s, 1H), 8.42 (s, 1H), 8.20 (d, 1H), 7.57 - 7.48 (m, 4H), 7.40 (d, 1H), 5.50 (s, 2H), 3.83 (s, 2H), 3.67 (d, 2H), 3.51 - 3.48 (m, 2H), 1.90 - 1.83 (m, 4H). m/z 458 [M+H⁺].

Example 177

Synthesis of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-6-cyano-4-[4-oxa-7-azaspiro[2.5]octan-7-yl]pyridine-3-carboxamide

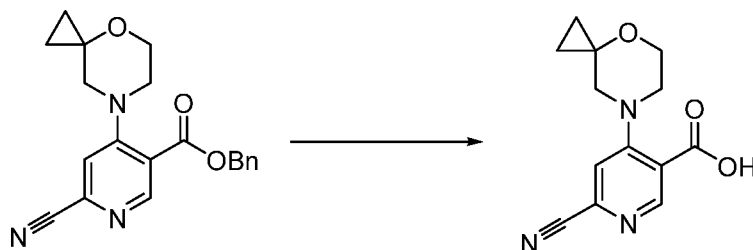


Step 1. Preparation of benzyl 6-cyano-4-[4-oxa-7-azaspiro[2.5]octan-7-yl]pyridine-3-carboxylate



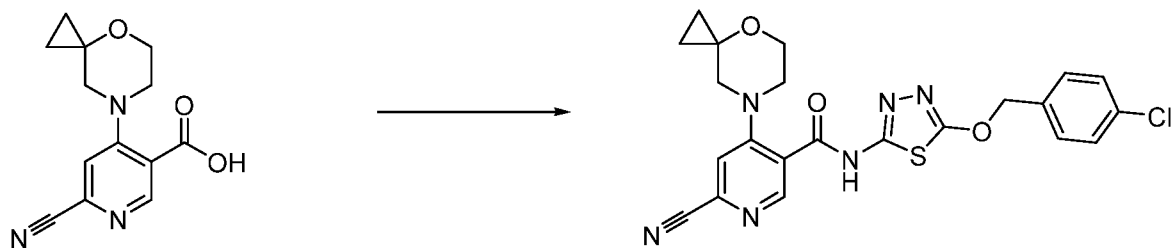
[0581] To a solution of benzyl 4-chloro-6-cyanopyridine-3-carboxylate (400 mg, 1.47 mmol) in MeCN (5 mL) was added 4-oxa-7-azaspiro[2.5]octane hydrochloride (241 mg, 1.6 mmol), TEA (594 mg, 5.9 mmol). The mixture was stirred for 4 hr at room temperature. The mixture was diluted with water and extracted with EtOAc (2 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (hexane:EtOAc, 5:1) to afford the title compound (360 mg, 65% yield) as an off-white solid.

Step 2. Preparation of 6-cyano-4-[4-oxa-7-azaspiro[2.5]octan-7-yl]pyridine-3-carboxylic acid



[0582] To a solution of benzyl 6-cyano-4-[4-oxa-7-azaspiro[2.5]octan-7-yl]pyridine-3-carboxylate (340 mg, 0.97 mmol) in THF (20 mL) was added Pd/C (10%, 34 mg) under nitrogen. The mixture was stirred at room temperature for 2h under hydrogen atmosphere. The mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 5:1) to afford the title compound (105 mg, 40% yield) as a light yellow solid.

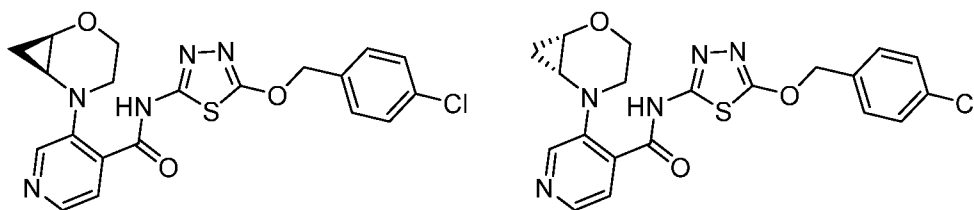
Step 3. Preparation of N-[5-[(4-chlorophenyl)methoxy]-1,3,4-thiadiazol-2-yl]-6-cyano-4-[4-oxa-7-azaspiro[2.5]octan-7-yl]pyridine-3-carboxamide



[0583] The title compound was prepared using General Procedure A employing 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) and 6-cyano-4-[4-oxa-7-azaspiro[2.5]octan-7-yl]pyridine-3-carboxylic acid. ¹H NMR (300 MHz, DMSO-d₆): δ 9.11 (s, 1H), 7.44 - 7.37 (m, 5H), 5.47 (s, 2H), 4.01 - 3.98 (t, 2H), 3.24 (t, 2H), 3.15 (s, 2H), 1.02 (t, 2H), 0.65 (t, 2H). m/z 483 [M+H⁺].

Example 178

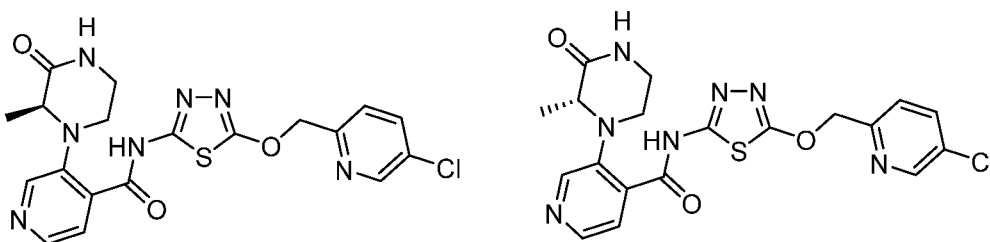
Synthesis of 3-((1R,6S)-2-oxa-5-azabicyclo[4.1.0]heptan-5-yl)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)isonicotinamide and 3-((1S,6R)-2-oxa-5-azabicyclo[4.1.0]heptan-5-yl)-N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)isonicotinamide



[0584] The title compound as a racemic mixture was prepared using similar procedure as Example 144, replacing (3R,5R)-3,5-dimethylmorpholine hydrochloride with 2-oxa-5-azabicyclo[4.1.0]heptane in step 2. ¹H NMR (300 MHz, DMSO-d₆): δ 12.99 (s, 1H), 8.50 (s, 1H), 8.08 (d, 1H), 7.56 - 7.47 (m, 4H), 7.32 (d, 1H), 5.49 (s, 2H), 3.78 - 3.68 (m, 3H), 3.20 - 3.11 (m, 2H), 2.57 - 2.53 (m, 1H), 0.70 - 0.54 (m, 2H). m/z 444 [M+H⁺].

Example 179

Synthesis of (S)-N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-3-(2-methyl-3-oxopiperazin-1-yl)isonicotinamide and (R)-N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-3-(2-methyl-3-oxopiperazin-1-yl)isonicotinamide

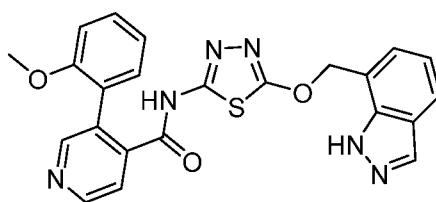


[0585] The title compound as a racemic mixture was prepared using similar procedure as Example 144, replacing (3R,5R)-3,5-dimethylmorpholine hydrochloride with 3-methylpiperazin-

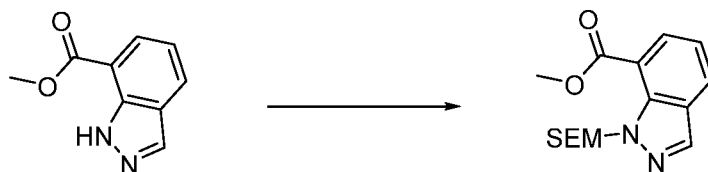
2-one in step 2 and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) with 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C) in step 3. ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 13.50 (s, 1H), 8.75 (s, 1H), 8.66 (d, 1H), 8.50 (d, 1H), 8.03 - 7.98 (m, 2H), 7.66 - 7.62 (m, 2H), 5.57 (s, 2H), 3.95 (t, 1H), 3.33 - 3.26 (m, 4H), 1.11 (d, 3H). m/z 460 $[\text{M}+\text{H}^+]$.

Example 180

Synthesis of N-[5-(3H-1,3-benzodiazol-4-ylmethoxy)-1,3,4-thiadiazol-2-yl]-3-(2-methoxyphenyl)pyridine-4-carboxamide

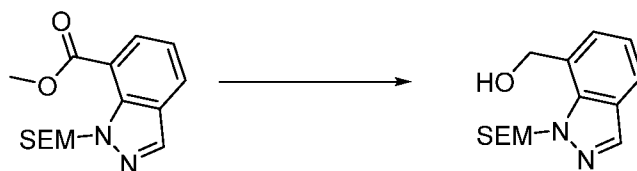


Step 1. Preparation of methyl 3-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole-4-carboxylate



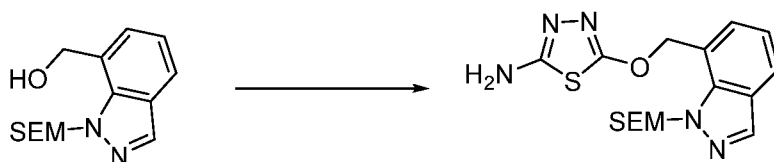
[0586] To a solution of methyl 3H-1,3-benzodiazole-4-carboxylate (5000 mg, 28.4 mmol) in DMF (50 mL) was added NaH (60% dispersion in oil, 1.36 g, 34.1 mmol) at 0 °C under nitrogen atmosphere. The mixture was stirred at 0 °C for 30 min. Then, 2-(trimethylsilyl)ethoxymethyl chloride (7098 mg, 42.5 mmol) was added. The mixture was warmed to room temperature and stirred at room temperature for 1 h. The mixture was diluted with water and extracted with EtOAc. The organic layer was washed with water (3 x), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 9% EtOAc in PE to afford the title compound (5500 mg, 63% yield) as a yellow oil.

Step 2. Preparation of (3-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-4-yl)methanol



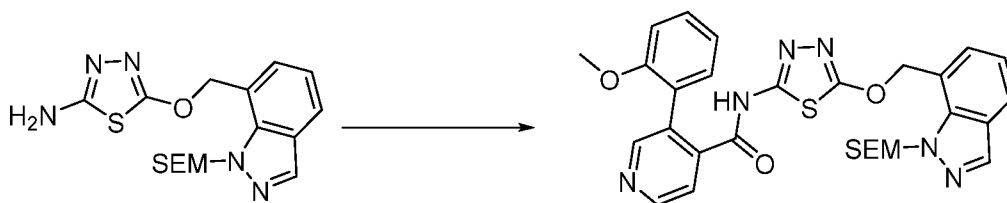
[0587] To a solution of methyl 3-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole-4-carboxylate (5500 mg, 17.9 mmol) in THF (50 mL) at 0 °C was added LiAlH₄ (1022 mg, 26.9 mmol) in portions under nitrogen atmosphere. The mixture was warmed to rt and stirred for 1 h at rt under nitrogen atmosphere. The mixture was diluted with NaHCO₃ (aq.) and extracted with DCM (3 x). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 17% EtOAc in PE to afford the title compound (3400 mg, 68% yield) as a light-yellow oil.

Step 3. Preparation of 5-[(3-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-4-yl)methoxy]-1,3,4-thiadiazol-2-amine



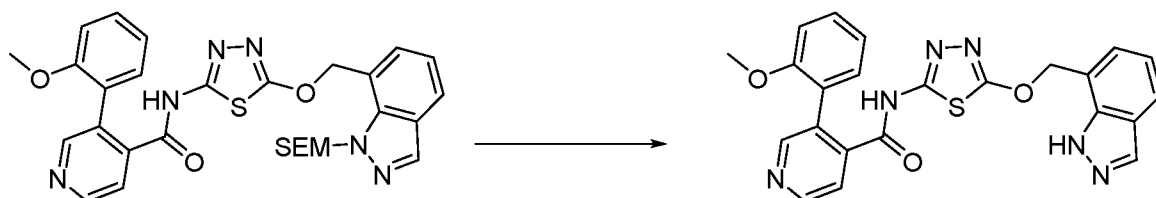
[0588] The title compound was prepared using similar procedures as the synthesis of Intermediate C, replacing (5-chloropyridin-2-yl)methanol with (3-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-4-yl)methanol in Step 1.

Step 4. Preparation of 3-(2-methoxyphenyl)-N-[5-[(3-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-4-yl)methoxy]-1,3,4-thiadiazol-2-yl]pyridine-4-carboxamide



[0589] The title compound was prepared using General Procedure A employing 3-(2-methoxyphenyl)pyridine-4-carboxylic acid (Intermediate H) and 5-[(3-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-4-yl)methoxy]-1,3,4-thiadiazol-2-amine.

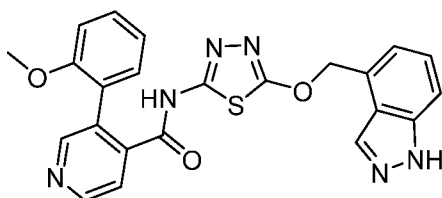
Step 5. Preparation of N-[5-(3H-1,3-benzodiazol-4-ylmethoxy)-1,3,4-thiadiazol-2-yl]-3-(2-methoxyphenyl)pyridine-4-carboxamide



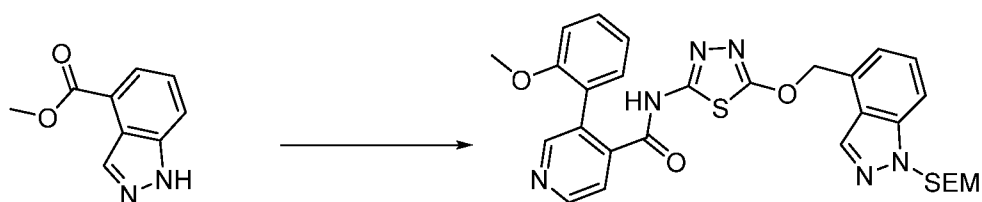
[0590] To a solution of 3-(2-methoxyphenyl)-N-[5-[(3-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-4-yl)methoxy]-1,3,4-thiadiazol-2-yl]pyridine-4-carboxamide (200 mg, 0.34 mmol) in THF (2 mL) was added TBAF (444 mg, 1.7 mmol), CsF (516 mg, 3.4 mmol) at room temperature. The mixture was stirred overnight at 70 °C. The mixture was cooled room temperature and diluted with water. The mixture was extracted with EtOAc (2 x). The combined organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 20:1) to afford the title compound (14 mg, 9% yield) as a white solid. ¹H NMR (300 MHz, DMSO-d₆): δ 13.34 (s, 1H), 12.83 (s, 1H), 8.71 (d, 1H), 8.60 (s, 1H), 8.14 (s, 1H), 7.82 – 7.79 (m, 1H), 7.63 (d, 1H), 7.48 (d, 1H), 7.40-7.35 (m, 2H), 7.16-6.97 (m, 3H), 5.76 (s, 2H), 3.52 (s, 3H). m/z 459 [M+H⁺].

Example 181

Synthesis of N-[5-(1H-indazol-4-ylmethoxy)-1,3,4-thiadiazol-2-yl]-3-(2-methoxyphenyl)pyridine-4-carboxamide



Step 1. Preparation of 3-(2-methoxyphenyl)-N-[5-[(1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-4-yl)methoxy]-1,3,4-thiadiazol-2-yl]pyridine-4-carboxamide



[0591] The title compound was prepared using similar procedure as Example 180, Steps 1-4, replacing methyl 3H-1,3-benzodiazole-4-carboxylate with methyl 1H-indazole-4-carboxylate in Step 1.

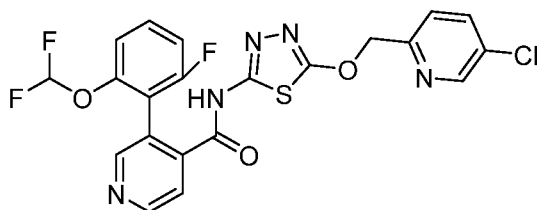
Step 2. Preparation of N-[5-(1H-indazol-4-ylmethoxy)-1,3,4-thiadiazol-2-yl]-3-(2-methoxyphenyl)pyridine-4-carboxamide



[0592] To a solution of 3-(2-methoxyphenyl)-N-[5-[(1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-4-yl)methoxy]-1,3,4-thiadiazol-2-yl]pyridine-4-carboxamide (140 mg, 0.24 mmol) in THF (1.4 mL) was added CsF (722 mg, 4.8 mmol) and TBAF (1 M in THF, 1.2 mL, 1.2 mmol). The mixture was stirred for 2 hr at 70 °C. The mixture was cooled room temperature and diluted with water. The mixture was extracted with EtOAc. The organic layer was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 15:1) to afford the title compound (42 mg, 38% yield) as a yellow solid. ¹H NMR (300 MHz, DMSO-*d*₆): δ 13.22 (s, 1H), 12.86 (s, 1H), 8.71 (d, 1H), 8.61 (s, 1H), 8.20 (s, 1H), 7.63 (d, 1H), 7.58 - 7.56 (m, 1H), 7.40 - 7.35 (m, 3H), 7.23 (d, 1H), 7.09 - 7.07 (m, 1H), 7.00 - 6.98 (m, 1H), 5.81 (s, 2H), 3.51 (s, 3H). *m/z* 459 [M+H⁺].

Example 182

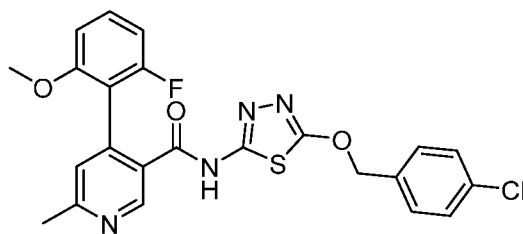
Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-3-(2-(difluoromethoxy)-6-fluorophenyl)isonicotinamide



[0593] The title compound was prepared using General Procedure A employing 3-(2-(difluoromethoxy)-6-fluorophenyl)isonicotinic acid (Example 109, Step 4) and 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C). ^1H NMR (300 MHz, DMSO- d_6): δ 8.80 (d, 1H), 8.65-8.62 (m, 2H), 8.01-8.00 (m, 1H), 7.89-7.86 (m, 1H), 7.66-7.58 (m, 2H), 7.40-6.91 (m, 3H), 5.53 (s, 3H). m/z 508 $[\text{M}+\text{H}^+]$.

Example 183

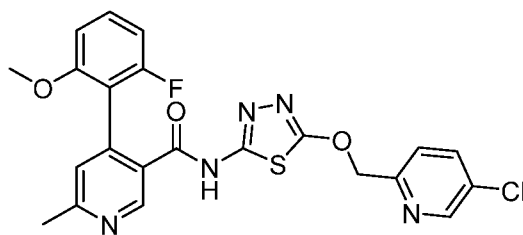
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-(2-fluoro-6-methoxyphenyl)-6-methylnicotinamide



[0594] The title compound was prepared using General Procedures E, F and A. For General Procedure E, methyl 4-chloro-6-methylpyridine-3-carboxylate and 2-fluoro-6-methoxyphenylboronic acid were employed. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. ^1H NMR (300 MHz, DMSO- d_6): δ 2.56 (s, 3H), 3.57 (s, 3H), 5.46 (s, 2H), 6.86 - 6.94 (m, 2H), 7.32 - 7.48 (m, 2H), 7.43 - 7.54 (m, 4H), 8.78 (s, 1H), 12.86 (s, 1H). m/z 485 $[\text{M}+\text{H}^+]$.

Example 184

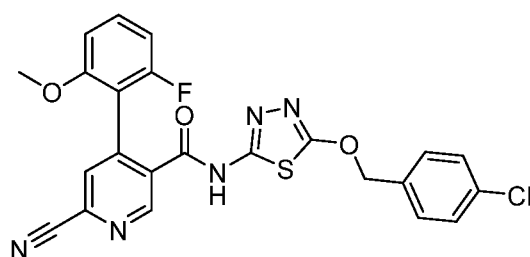
Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-fluoro-6-methoxyphenyl)-6-methylnicotinamide



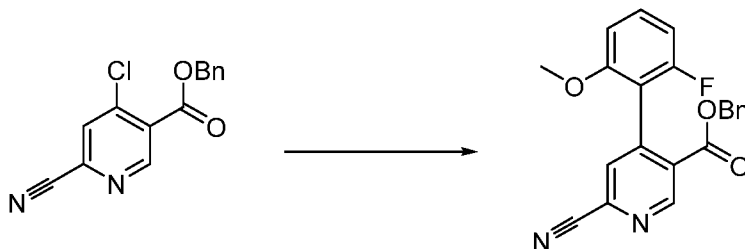
[0595] The title compound was prepared using General Procedures E, F and A. For General Procedure E, methyl 4-chloro-6-methylpyridine-3-carboxylate and 2-fluoro-6-methoxyphenylboronic acid were employed. For General Procedure A, 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C) was used. ^1H NMR (300 MHz, DMSO- d_6): δ 2.57 (s, 3H), 3.58 (s, 3H), 5.76 (s, 2H), 6.87 - 6.95 (m, 2H), 7.33 (s, 1H), 7.36 - 7.44 (m, 1H), 7.59 - 7.61 (m, 1H), 8.00 (d, 1H), 8.65 (s, 1H), 8.80 (s, 1H), 12.90 (s, 1H). m/z 486 $[\text{M}+\text{H}^+]$.

Example 185

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-4-(2-fluoro-6-methoxyphenyl)nicotinamide

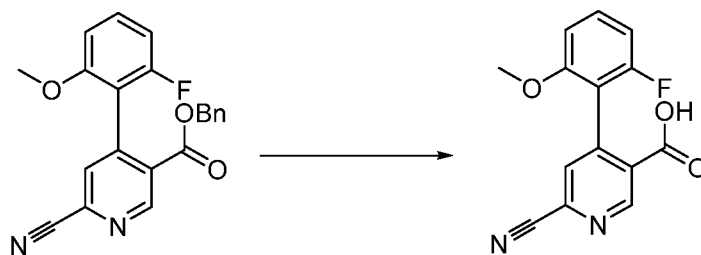


Step 1. Preparation of benzyl 6-cyano-4-(2-fluoro-6-methoxyphenyl)pyridine-3-carboxylate



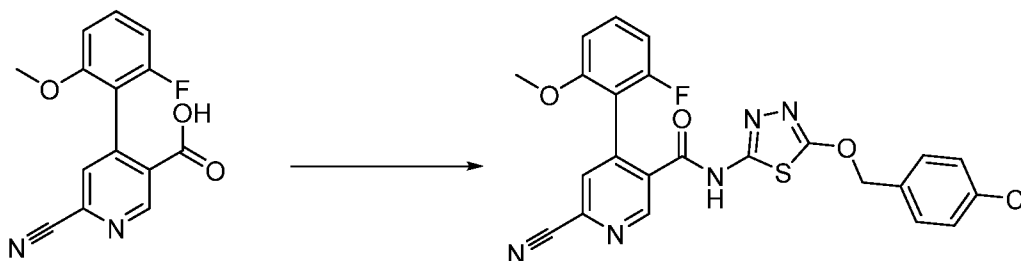
[0596] The title compound was prepared using General Procedure E employing benzyl 4-chloro-6-cyanopyridine-3-carboxylate (Example 92, Step 2) and 2-fluoro-6-methoxyphenylboronic acid.

Step 2. Preparation of 6-cyano-4-(2-fluoro-6-methoxyphenyl)pyridine-3-carboxylic acid



[0597] To a solution of benzyl 6-cyano-4-(2-fluoro-6-methoxyphenyl)pyridine-3-carboxylate (610 mg, 1.7 mmol) in THF (20 mL) was added Pd/C (10%, 120 mg) under nitrogen atmosphere. The mixture was stirred at rt for 4 h under hydrogen atmosphere. The mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to afford the title compound (580 mg), which was used in the next step without further purification.

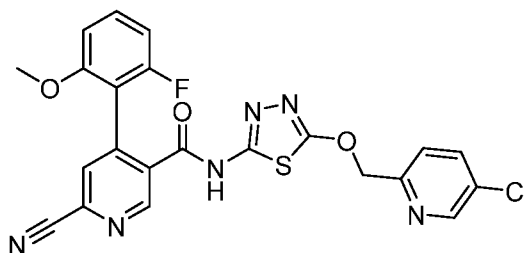
Step 3. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-4-(2-fluoro-6-methoxyphenyl)nicotinamide



[0598] The title compound was prepared using General Procedure A employing 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) and 6-cyano-4-(2-fluoro-6-methoxyphenyl)pyridine-3-carboxylic acid. ^1H NMR (300 MHz, DMSO- d_6): δ 13.2 (s, 1H), 9.08 (s, 1H), 8.24 (s, 1H), 7.54 - 7.43 (m, 5H), 7.01 - 6.92 (m, 2H), 5.48 (s, 2H), 3.60 (s, 3H). m/z 496 $[\text{M}+\text{H}^+]$.

Example 186

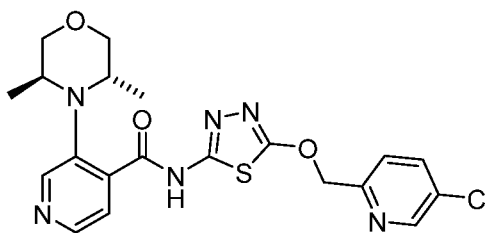
Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-6-cyano-4-(2-fluoro-6-methoxyphenyl)nicotinamide



[0599] The title compound was prepared using General Procedure A employing 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C) and 6-cyano-4-(2-fluoro-6-methoxyphenyl)pyridine-3-carboxylic acid (Example 185, Step 2). ¹H NMR (300 MHz, DMSO-d₆): δ 13.23 (s, 1H), 9.09 (s, 1H), 8.65 (s, 1H), 8.24 (s, 1H), 8.00 (d, 1H), 7.62 - 7.59 (m, 1H), 7.47 (t, 1H), 7.00 - 6.92 (m, 2H), 5.55 (s, 2H), 3.60 (s, 3H). m/z 497 [M+H⁺].

Example 187

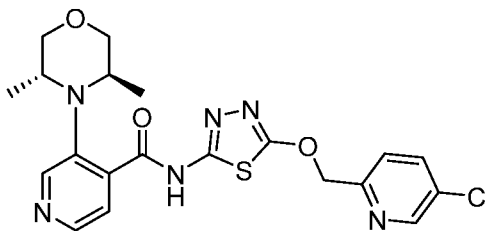
Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-3-((3S,5S)-3,5-dimethylmorpholino)isonicotinamide



[0600] The title compound was prepared using similar procedures as the synthesis of Example 144, replacing (3R,5R)-3,5-dimethylmorpholine hydrochloride with (3S,5S)-3,5-dimethylmorpholine hydrochloride in Step 2; replacing 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) with 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C) in Step 4. ¹H NMR (300 MHz, DMSO-d₆): δ 14.26 (s, 1H), 8.74 (s, 1H), 8.67 (d, 1H), 8.60 (d, 1H), 8.01 (dd, 1H), 7.89 (d, 1H), 7.64 (d, 1H), 5.58 (s, 2H), 3.94 - 3.70 (m, 4H), 3.27 - 3.23 (m, 2H), 1.12 - 0.96 (m, 3H), 0.94 - 0.80 (m, 3H). m/z 461 [M+H⁺].

Example 188

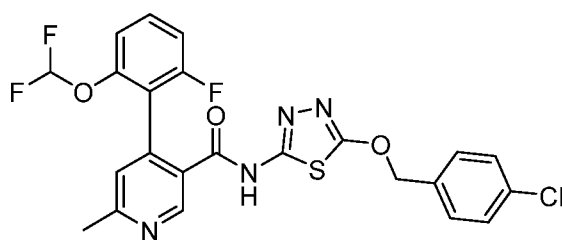
Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-3-((3R,5R)-3,5-dimethylmorpholino)isonicotinamide



[0601] The title compound was prepared using similar procedures as the synthesis of Example 144, replacing 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) with 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C) in Step 4. ^1H NMR (300 MHz, DMSO- d_6): δ 14.27 (s, 1H), 8.74 (s, 1H), 8.67 (d, 1H), 8.61 (d, 1H), 8.01 (dd, 1H), 7.89 (d, 1H), 7.64 (d, 1H), 5.58 (s, 2H), 3.95 - 3.72 (m, 4H), 3.32 - 3.24 (m, 2H), 1.12 - 0.96 (m, 3H), 0.94 - 0.80 (m, 3H). m/z 461 $[\text{M}+\text{H}^+]$.

Example 189

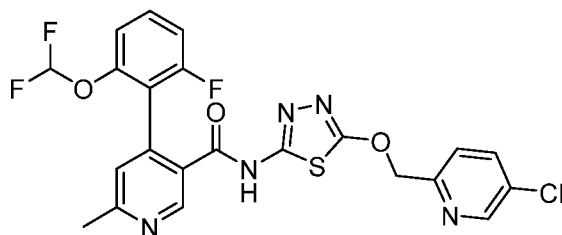
Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-(2-(difluoromethoxy)-6-fluorophenyl)-6-methylnicotinamide



[0602] The title compound was prepared using General Procedures E, F and A. For General Procedure E, ethyl 4-bromo-6-methylpyridine-3-carboxylate and 2-[2-(difluoromethoxy)-6-fluorophenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane were employed. For General Procedure A, 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) was used. ^1H NMR (300 MHz, DMSO- d_6): δ 13.02 (s, 1H), 8.93 (s, 1H), 7.68 - 7.47 (m, 5H), 7.47 - 6.79 (m, 4H), 5.46 (s, 2H), 2.58 (s, 3H). m/z 521 $[\text{M}+\text{H}^+]$.

Example 190

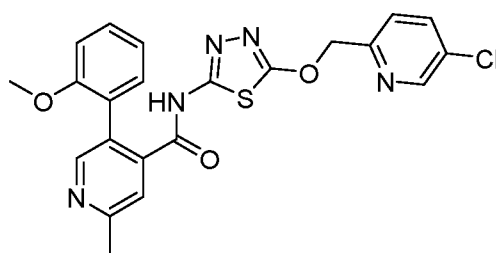
Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-(difluoromethoxy)-6-fluorophenyl)-6-methylnicotinamide



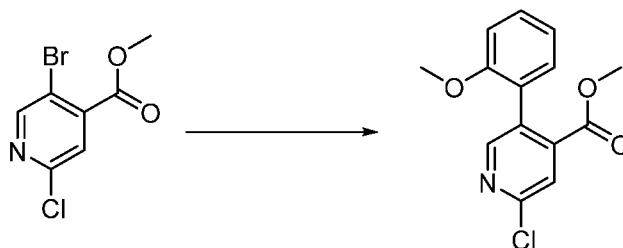
[0603] The title compound was prepared using General Procedures E, F and A. For General Procedure E, ethyl 4-bromo-6-methylpyridine-3-carboxylate and 2-[2-(difluoromethoxy)-6-fluorophenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane were employed. For General Procedure A, 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C) was used. ¹H NMR (300 MHz, DMSO-*d*₆): δ 13.03 (s, 1H), 8.98 (s, 1H), 8.65 (d, 1H), 8.00 (dd, 1H), 7.68 - 7.50 (m, 2H), 7.50 - 6.83 (m, 4H), 5.53 (s, 2H), 2.58 (s, 3H). *m/z* 522 [M+H⁺].

Example 191

Synthesis of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-5-(2-methoxyphenyl)-2-methylpyridine-4-carboxamide

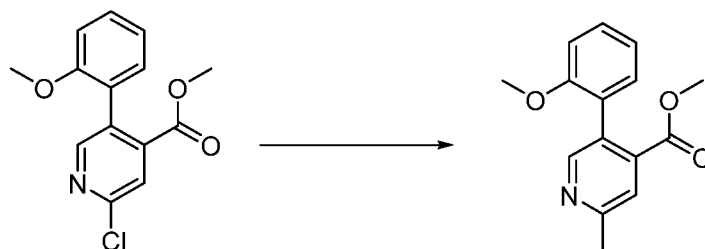


Step 1. Preparation of methyl 2-chloro-5-(2-methoxyphenyl)pyridine-4-carboxylate



[0604] The title compound was prepared using General procedure E employing 5-bromo-2-chloropyridine-4-carboxylate and 2-methoxyphenylboronic acid.

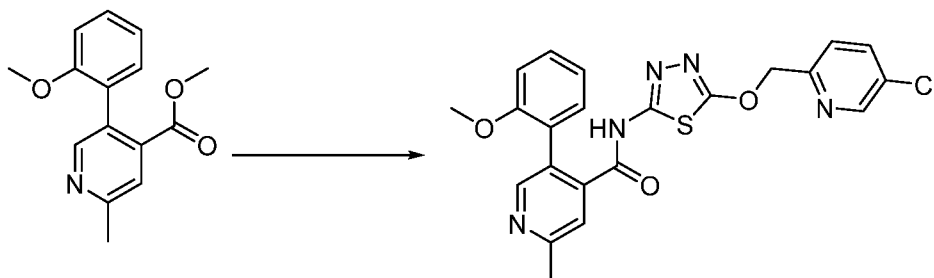
Step 2. Preparation of methyl 5-(2-methoxyphenyl)-2-methylpyridine-4-carboxylate



[0605] To a solution of methyl 2-chloro-5-(2-methoxyphenyl)pyridine-4-carboxylate (1.0 g, 3.6 mmol), in dioxane (30 mL) was added methylboronic acid (1.1 g, 18.0 mmol), K₂CO₃ (1.0 g,

7.2 mmol) and Pd(dtbpf)Cl₂ (235 mg, 0.36 mmol). The mixture was stirred overnight at 120°C under nitrogen atmosphere. The mixture was diluted with water and extracted with EtOAc (2 x). The combined organic layers were concentrated under reduced pressure and the residue. The residue was purified using silica gel chromatography (eluent: 25% EtOAc in PE) to afford the title compound (720 mg, 78% yield) as a white solid.

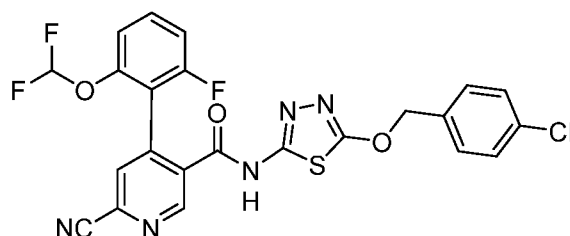
Step 3. Preparation of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-5-(2-methoxyphenyl)-2-methylpyridine-4-carboxamide



[0606] The title compound was prepared using F and A employing in General procedure F methyl 5-(2-methoxyphenyl)-2-methylpyridine-4-carboxylate and 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (Intermediate B) in General procedures A. ¹H NMR (300 MHz, DMSO-d₆): δ 2.57 (s, 3H), 3.50 (s, 3H), 5.54 (s, 2H), 6.97 (d, 1H), 7.05 (t, 1H), 7.33-7.38 (m, 2H), 7.52 (s, 1H), 7.61 (d, 1H), 8.00 (dd, 1H), 8.45 (s, 1H), 8.65 (s, 1H), 12.80 (s, 1H) ppm. m/z 468 [M+H⁺].

Example 192

Synthesis of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-4-(2-(difluoromethoxy)-6-fluorophenyl)nicotinamide

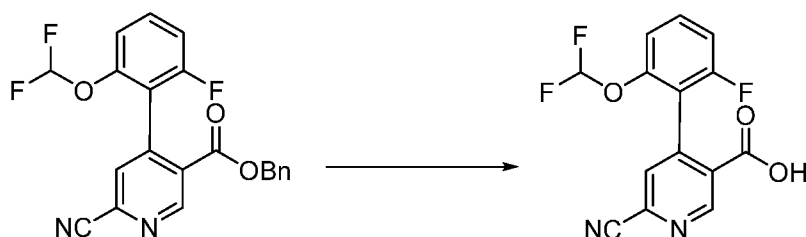


Step 1. Preparation of benzyl 6-cyano-4-[2-(difluoromethoxy)-6-fluorophenyl]pyridine-3-carboxylate



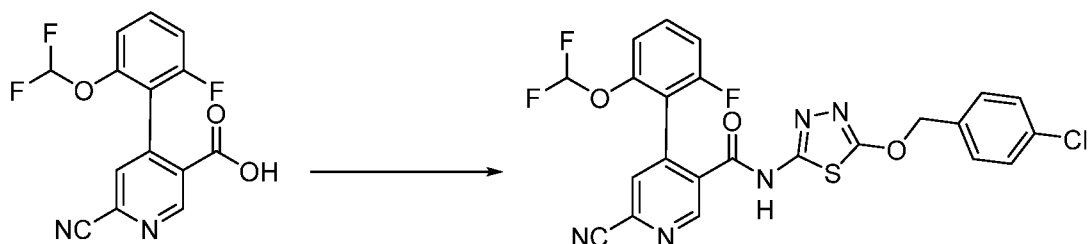
[0607] The title compound was prepared using General Procedure E replacing [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)·CH₂Cl₂.

Step 2. Preparation of 6-cyano-4-[2-(difluoromethoxy)-6-fluorophenyl]pyridine-3-carboxylic acid



[0608] To a solution of benzyl 6-cyano-4-[2-(difluoromethoxy)-6-fluorophenyl]pyridine-3-carboxylate (540 mg, 1.4 mmol) in THF (50 mL) was added 10% Pd/C (54 mg). The mixture was stirred for 40 mins at room temperature. The mixture was diluted with THF and filtered. The solids were washed with THF (2x). The mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH, 20:1) to afford 6-cyano-4-[2-(difluoromethoxy)-6-fluorophenyl]pyridine-3-carboxylic acid (270 mg, yield 63% yield) as a white solid.

Step 3. Preparation of N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-6-cyano-4-(2-(difluoromethoxy)-6-fluorophenyl)nicotinamide

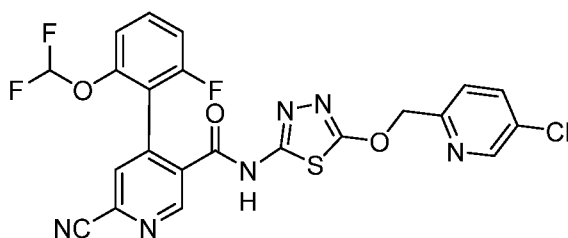


[0609] To a solution of 6-cyano-4-[2-(difluoromethoxy)-6-fluorophenyl]pyridine-3-carboxylic acid (100 mg, 0.32 mmol) in DMF (1.0 mL) was added HOBt (66 mg, 0.49 mmol), EDCI (93

mg, 0.49 mmol), 5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-amine (78 mg, 0.32 mmol, Intermediate B). The mixture was stirred overnight at room temperature. The mixture was diluted with water and filtered. The solids were washed with EtOAc. The solid was purified by trituration with MeCN to afford the title compound (99 mg, 56% yield) as a light pink solid. ¹H NMR (300 MHz, DMSO-d₆): δ 13.42 (s, 1H), 9.20 (s, 1H), 8.32 (s, 1H), 7.63-7.46 (m, 5H), 7.40-6.92 (m, 3H), 5.48 (s, 2H) ppm. m/z 532 [M+H⁺].

Example 193

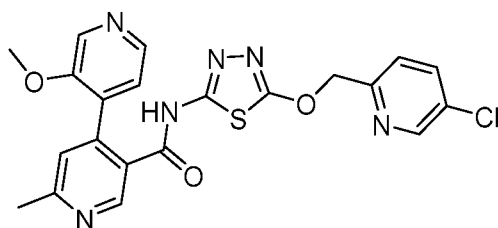
Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-6-cyano-4-(2-(difluoromethoxy)-6-fluorophenyl) nicotinamide



[0610] To a solution of 6-cyano-4-[2-(difluoromethoxy)-6-fluorophenyl]pyridine-3-carboxylic acid (120.00 mg, 0.389 mmol, Example 192, Step 2) in DCM (1.2 mL) was added pyridine (154 mg, 1.9 mmol). The mixture was cooled to 0 °C. Then a solution of oxalyl chloride (54 mg, 0.43 mmol) in DCM (0.5 mL) dropwise at 0 °C over 2 mins. The mixture was stirred for 30 mins at 0 °C. Then 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (94 mg, 0.39 mmol, Intermediate C), was added in portions at 0 °C over 5 min. The mixture was stirred for 1 h at 0 °C. The mixture was warmed to rt and water was added. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were concentrated under reduced pressure. The residue was purified by trituration with MeOH to afford the title compound (29 mg, 14% yield as a white solid. ¹H NMR (300 MHz, DMSO-d₆): δ 13.39 (s, 1H), 9.21 (s, 1H), 8.65 (s, 1H), 8.32 (s, 1H), 8.00 (d, 1H), 7.64 - 7.56 (m, 2H), 7.41 - 6.92 (m, 3H), 5.55 (s, 2H). m/z 533 [M+H⁺].

Example 194

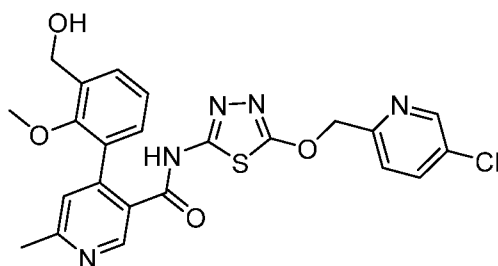
Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-3'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide



[0611] The title compound was prepared using General Procedures E, F and A. For General Procedure E, methyl 4-chloro-6-methylpyridine-3-carboxylate and 3-methoxypyridin-4-ylboronic acid were employed. For General Procedure A, 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C) was used. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ : 12.94 (s, 1H), 8.78 (s, 1H), 8.66 (d, $J = 2.4$ Hz, 1H), 8.39 – 8.31 (m, 2H), 8.01 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.61 (d, $J = 8.4$ Hz, 1H), 7.41 – 7.35 (m, 2H), 5.55 (s, 2H), 3.64 (s, 3H), 2.59 (s, 3H). m/z 469.0 $[\text{M}+\text{H}^+]$.

Example 195

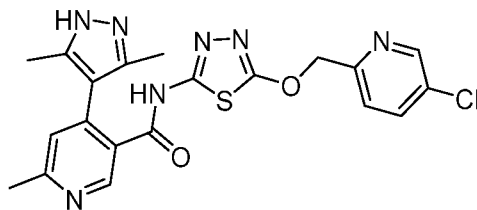
Synthesis of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-[3-(hydroxymethyl)-2-methoxyphenyl]-6-methylpyridine-3-carboxamide



[0612] The title compound was prepared using General Procedures E, F and A. For General Procedure E, methyl 4-chloro-6-methylpyridine-3-carboxylate and 3-(hydroxymethyl)-2-methoxyphenylboronic acid were employed. For General Procedure A, 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C) was used. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ : 12.87 (s, 1H), 8.75 (s, 1H), 8.66 (d, $J = 2.4$ Hz, 1H), 8.04 – 7.97 (m, 1H), 7.61 (d, $J = 8.4$ Hz, 1H), 7.51 – 7.44 (m, 1H), 7.37 (s, 1H), 7.21 (d, $J = 4.8$ Hz, 2H), 5.55 (s, 2H), 5.19 – 5.12 (m, 1H), 4.50 (d, $J = 5.6$ Hz, 2H), 3.27 (s, 3H), 2.59 (s, 3H). m/z 498.0 $[\text{M}+\text{H}^+]$.

Example 196

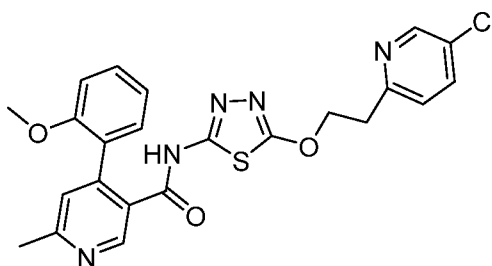
Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(3,5-dimethyl-1H-pyrazol-4-yl)-6-methylnicotinamide



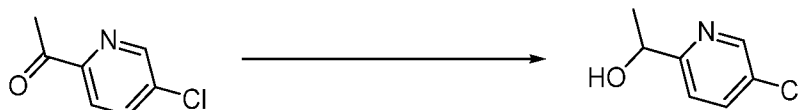
[0613] The title compound was prepared using General Procedures E, F and A. For General Procedure E, 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole and methyl 4-chloropyridine-3-carboxylate were employed. For General Procedure A, 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C) was used. ¹HNMR (400 MHz, DMSO-*d*₆): δ 12.51 (s, 1H), 8.72 – 8.64 (m, 2H), 8.01 (s, 1H), 7.62 (s, 1H), 7.20 (s, 1H), 5.55 (s, 2H), 2.55 (s, 3H), 2.03 (s, 6H). m/z 456.1 [M+H⁺].

Example 197

Synthesis of N-(5-(2-(5-chloropyridin-2-yl)ethoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)-6-methylnicotinamide



Step-1: Synthesis of 1-(5-chloropyridin-2-yl)ethan-1-ol



[0614] To a solution of 1-(5-chloropyridin-2-yl)ethanone (3.0 g, 19.2 mmol) in MeOH (10 mL) was added NaBH₄ (763 mg, 20.1 mmol) in portions at 0 °C. The mixture was stirred at room temperature for 2 hours. The reaction mixture was then quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford the title compound (2.5 g, crude) as a yellow oil.

Step-2: Synthesis of O-(2-(5-chloropyridin-2-yl)ethyl) S-methyl carbonodithioate



[0615] To a solution of 1-(5-chloropyridin-2-yl)ethanol (2.28 g, 14.4 mmol) in THF (10 mL) was added NaH (0.69 g, 28.9 mmol) in portions at 0 °C and stirred at 0 °C for 30 min. Then CS₂ (1.65 g, 21.7 mmol) was added to the above mixture at 0 °C and stirred at 0 °C for 20 min, then MeI (3.08 g, 21.7 mmol) was added to the mixture at 0~5 °C under nitrogen. The mixture was stirred at room temperature for 1 hour under nitrogen. The reaction mixture was then quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~40% ethyl acetate in petroleum ether to afford the title compound (2.64 g, 74%) (crude) as a colorless oil.

Step-3: Synthesis of O-(2-(5-chloropyridin-2-yl)ethyl) hydrazinecarbothioate



[0616] To a solution of 1-(5-chloropyridin-2-yl)ethyl sulfanylmethanethioate (1 g, 4.27 mmol) in MeOH (10 mL) was added N₂H₄·H₂O (250 mg, 4.27 mmol) at room temperature. The mixture was stirred at room temperature for 2 hours. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford the title compound (980 mg, crude) as red oil.

Step-4: Synthesis of 5-(2-(5-chloropyridin-2-yl)ethoxy)-1,3,4-thiadiazol-2-amine



[0617] To a solution of ([1-(5-chloropyridin-2-yl)ethoxy]methanethioyl)amino)amine (1 g, 4.40 mmol) in MeOH (10 mL) were added BrCN (513 mg, 4.84 mmol) and TEA (890 mg, 8.80 mmol). The mixture was stirred at room temperature for 30 min. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~50% ethyl acetate in petroleum ether to afford the title compound (749 mg, 67%) as a red solid.

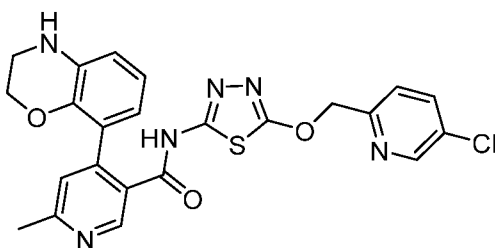
Step-5: Synthesis of N-(5-(2-(5-chloropyridin-2-yl)ethoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)-6-methylnicotinamide



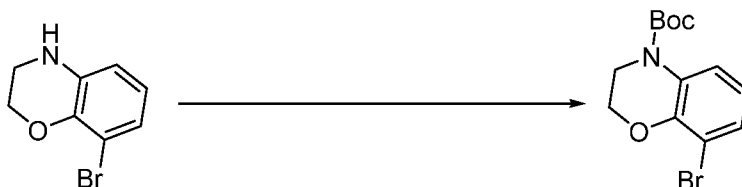
[0618] To a solution of 5-(2-(5-chloropyridin-2-yl)ethoxy)-1,3,4-thiadiazol-2-amine (670 mg, 2.60 mmol) in DMF (5 mL) were added DIEA (1.02 g, 7.81 mmol), HATU (1.48 g, 3.90 mmol) and 4-(2-methoxyphenyl)-6-methylpyridine-3-carboxylic acid (Example 113, Step 2, 635 mg, 2.60 mmol). The mixture was stirred at room temperature for 12 h. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~10% methanol in dichloromethane and further purified by prep-HPLC (column, C18 silica gel; mobile phase, water (10 mM NH_4HCO_3 +0.1% $\text{NH}_3\cdot\text{H}_2\text{O}$) and ACN) to afford the title compound (121 mg, 14%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 12.71 (s, 1H), 8.65 (s, 1H), 8.36 – 8.35 (m, 1H), 7.85 – 7.82 (m, 1H), 7.49 – 7.47 (m, 1H), 7.41 – 7.33 (m, 2H), 7.30 (s, 1H), 7.09 – 7.07 (m, 1H), 7.05 – 6.96 (m, 1H), 4.65 (d, J = 6.4 Hz, 2H), 3.49 (s, 3H), 3.13 (d, J = 6.4 Hz, 2H), 2.50 (s, 3H). m/z 482.1 $[\text{M}+\text{H}^+]$.

Example 198

Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)-6-methylnicotinamide

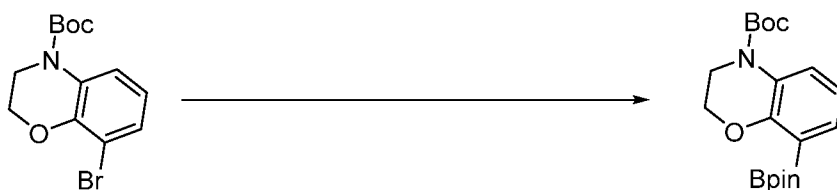


Step-1: Synthesis of tert-butyl 8-bromo-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate



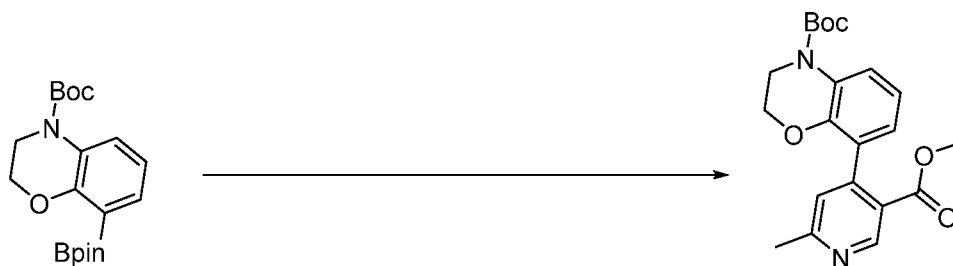
[0619] To a stirred mixture of 8-bromo-3,4-dihydro-2H-benzo[b][1,4]oxazine (500.0 mg, 2.33 mmol) in 1,4-dioxane (10.0 mL) were added TEA (709.0 mg, 7.00 mmol), Boc₂O (152.9 mg, 0.70 mmol) and DMAP (57.0 mg, 0.46 mmol). The resulting mixture was stirred for overnight at 50 °C before concentrated under vacuum. The residue was purified by flash column chromatography with 0~12% ethyl acetate in petroleum ether to afford the title compound (549 mg, 74%) as a colorless oil.

Step-2: Synthesis of tert-butyl 8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate



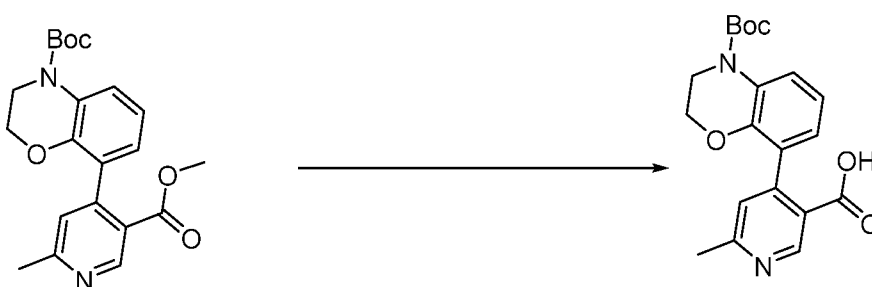
[0620] To a stirred solution of tert-butyl 8-bromo-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate (540.0 mg, 2.30 mmol) in 1,4-dioxane (10.0 mL) were added (B₂pin)₂ (1063.2 mg, 5.76 mmol), KOAc (615.3 mg, 6.92 mmol) and Pd(dppf)Cl₂ (153 mg, 0.23 mmol) under nitrogen. The resulting mixture was stirred for overnight at 80 °C under N₂. The resulting mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with 0~12% ethyl acetate in petroleum ether to afford the title compound (410 mg, 76%) as a colorless oil.

Step-3: Synthesis of tert-butyl 8-(5-(methoxycarbonyl)-2-methylpyridin-4-yl)-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate



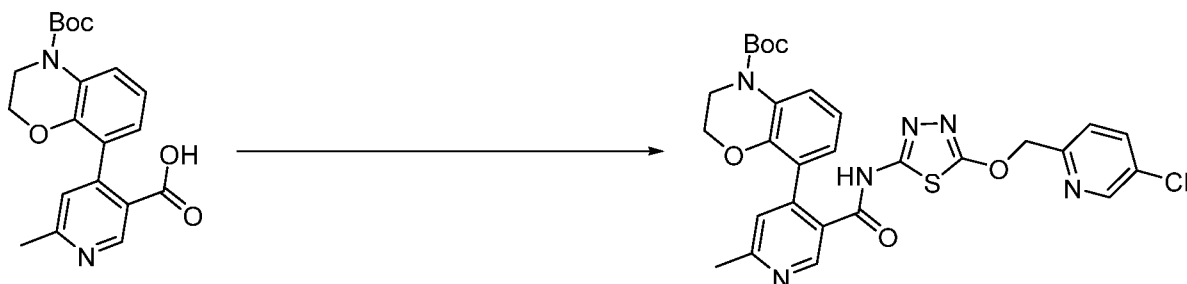
[0621] To a degassed mixture of tert-butyl 8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate (390 mg, 1.66 mmol) in 1,4-dioxane (5.0 mL) and H₂O (1.0 mL) were added K₂CO₃ (690 mg, 4.99 mmol), methyl 4-chloro-6-methylnicotinate (463 mg, 2.49 mmol) and Pd(dppf)Cl₂ (121 mg, 0.16 mmol) under nitrogen atmosphere. The resulting mixture was stirred for 4 h at 80 °C under N₂. The resulting mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with 0~37% ethyl acetate in petroleum ether to afford the title compound (260 mg, 40%) as a yellow solid.

Step-4: Synthesis of 4-(4-(tert-butoxycarbonyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)-6-methylnicotinic acid



[0622] To a stirred solution of tert-butyl 8-(5-(methoxycarbonyl)-2-methylpyridin-4-yl)-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate (235 mg, 0.61 mmol) in MeOH (3.0 mL) were added NaOH (48.9 mg, 1.22 mmol) and H₂O (3.0 mL). The resulting mixture was stirred at 50 °C for 2 h. The reaction mixture was acidified to pH ~6 with HCl (1 N) and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford the title compound (224 mg, 98%) as an orange solid.

Step-5: Synthesis of tert-butyl 8-(5-((5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)carbamoyl)-2-methylpyridin-4-yl)-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate



[0623] To a stirred mixture of 4-(4-(tert-butoxycarbonyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)-6-methylnicotinic acid (200 mg, 0.54 mmol) in DMF (4.0 mL) were added HATU (410 mg, 1.08 mmol). The resulting mixture was stirred for 5 min at room temperature. To the above mixture were added 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C, 196 mg, 0.81 mmol) and DIEA (209 mg, 1.62 mmol). The resulting mixture was stirred for additional 2 h at room temperature. The resulting mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and filtered. The filtrate was collected and concentrated under vacuum. The residue was purified by flash column chromatography with 0~12% ethyl acetate in petroleum ether to afford the title compound (239 mg, 74%) as a yellow oil.

Step-6: Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)-6-methylnicotinamide

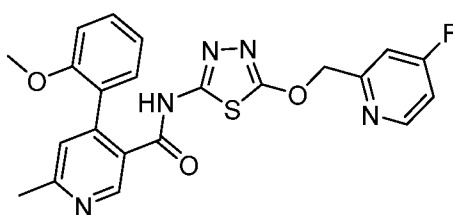


[0624] To a mixture of tert-butyl 8-(5-((5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)carbamoyl)-2-methylpyridin-4-yl)-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate (210 mg, 0.35 mmol) in DCM (4.0 mL) was added TFA (4.0 mL) dropwise at 0 °C. The resulting mixture was stirred for 1 h at room temperature before concentrated under vacuum. The residue was basified to pH 7 with saturated NaHCO₃ aqueous solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and filtered.

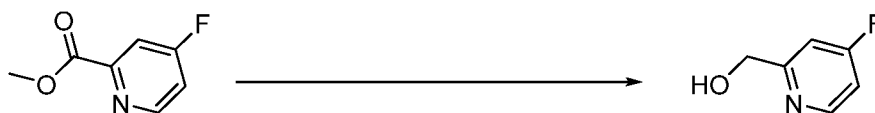
The filtrate was collected and concentrated under vacuum. The crude product was purified by Prep-HPLC (column, C18 silica gel; mobile phase, water (10 mM $\text{NH}_4\text{HCO}_3 + 0.1\% \text{NH}_3 \cdot \text{H}_2\text{O}$) and ACN) to afford the title compound (17.9 mg, 10%) as a white solid. ^1H NMR (400 MHz, CD_3OD): δ 8.64 (s, 1H), 8.59 (d, $J = 2.0$ Hz, 1H), 7.94 – 7.92 (m, 1H), 7.62 (d, $J = 8.4$ Hz, 1H), 7.36 (s, 1H), 6.86 – 6.82 (m, 1H), 6.72 – 6.68 (m, 2H), 5.56 (s, 2H), 3.97 – 3.95 (m, 2H), 3.21 – 3.19 (m, 2H), 2.64 (s, 3H). m/z 495.1 $[\text{M} + \text{H}^+]$.

Example 199

Synthesis of N-(5-((4-fluoropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)-6-methylnicotinamide



Step-1: Synthesis of (4-fluoropyridin-2-yl)methanol



[0625] To a solution of methyl 4-fluoropyridine-2-carboxylate (500 mg, 3.22 mmol) in MeOH (15 mL) was added NaBH_4 (245 mg, 6.44 mmol) in portions at 0°C and stirred at room temperature for 4 h. The reaction mixture was then quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford the title compound (420 mg, 84%) as a yellow solid.

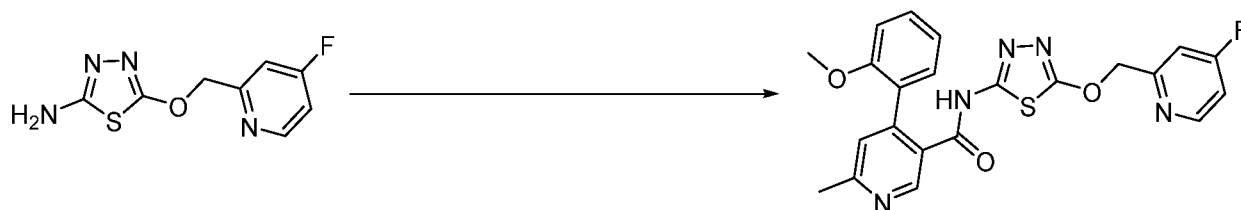
Step-2: Synthesis of 5-((4-fluoropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine



[0626] To a solution of NaH (175 mg, 4.36 mmol, 60%) in THF (20 mL) was added (4-fluoropyridin-2-yl)methanol (370 mg, 2.91 mmol) in portions at $0\sim 5^\circ\text{C}$ and stirred at 5°C for 1 h. Then 5-bromo-1,3,4-thiadiazol-2-amine (629 mg, 3.49 mmol) was added to the mixture in

small portions at 5 °C and stirred at 5 °C for 5 h. The reaction mixture was then quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~50% ethyl acetate in petroleum ether to afford (198 mg, 54%) as a white solid.

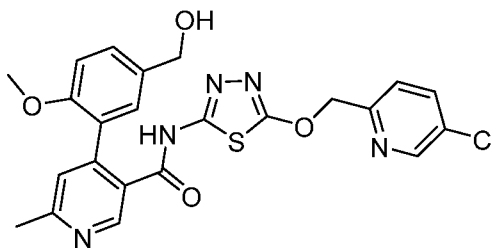
Step-3: Synthesis of N-(5-((4-fluoropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)-6-methylnicotinamide



[0627] To a solution of 4-(2-methoxyphenyl)-6-methylpyridine-3-carboxylic acid (Example 113, Step 2, 122 mg, 0.502 mmol) in DMF (5 mL) were added DIEA (195 mg, 1.51 mmol), HATU (382 mg, 1.00 mmol) and 5-((4-fluoropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (170 mg, 0.752 mmol). The mixture was stirred at room temperature for 16 h. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~10% methanol in dichloromethane and further purified by prep-HPLC (column, C18 silica gel; mobile phase, water (0.1% FA) and ACN) to afford the title compound (3.9 mg, 0.03%) as a white solid. ¹H NMR (400 MHz, CD₃OD): δ 8.67 (s, 1H), 8.60 (s, 1H), 7.48 – 7.36 (m, 4H), 7.24 (s, 1H), 7.11 (s, 1H), 6.99 (s, 1H), 5.59 (s, 2H), 3.62 (s, 3H), 2.66 (s, 3H). m/z 452.1 [M+H⁺].

Example 200

Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(5-(hydroxymethyl)-2-methoxyphenyl)-6-methylnicotinamide



Step-1: Synthesis of methyl 4-(5-(hydroxymethyl)-2-methoxyphenyl)-6-methylnicotinate



[0628] To a solution of methyl 4-chloro-6-methylpyridine-3-carboxylate (500 mg, 2.69 mmol) in dioxane (25 mL) and H₂O (5 mL) were added 5-(hydroxymethyl)-2-methoxyphenylboronic acid (735 mg, 4.04 mmol), K₂CO₃ (1.12 g, 8.08 mmol) and Pd(dppf)Cl₂ (197 mg, 0.269 mmol) under nitrogen. The resulting solution was stirred at 80 °C for 8 hours under nitrogen. The aqueous solution was concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~70% ethyl acetate in petroleum ether to afford the title compound (370 mg, 74%) as a white solid.

Step-2: Synthesis of methyl 4-(2-methoxy-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)-6-methylnicotinate



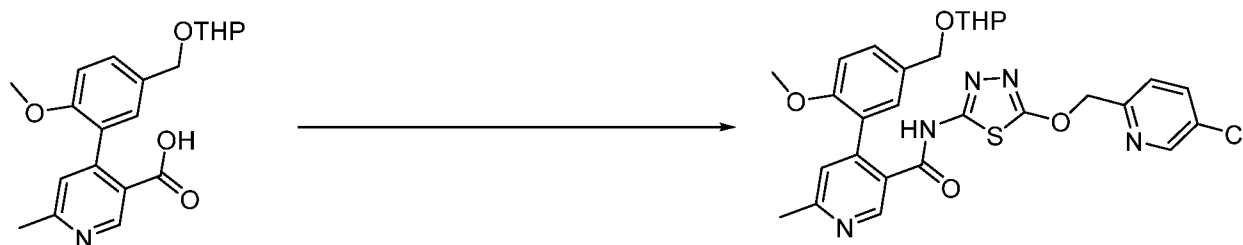
[0629] To a solution of methyl 4-[5-(hydroxymethyl)-2-methoxyphenyl]-6-methylpyridine-3-carboxylate (250 mg, 0.870 mmol) in THF (5 mL) were added DHP (147 mg, 1.74 mmol) and TsOH (75 mg, 0.435 mmol). The resulting mixture was stirred at room temperature for 16 h. The aqueous solution was quenched with saturated NaHCO₃ aqueous solution and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum to afford the title compound (230 mg, crude) as an off-yellow solid.

Step-3: Synthesis of 4-(2-methoxy-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)-6-methylnicotinic acid



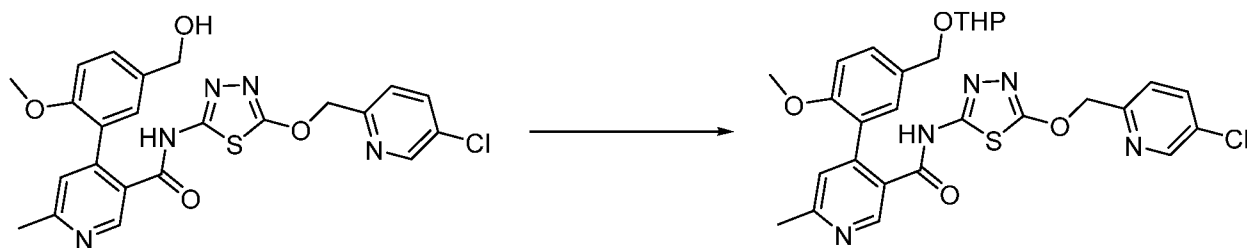
[0630] To a solution of 4-(2-methoxy-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)-6-methylnicotinate (200 mg, 0.563 mmol) in MeOH (10 mL) and H₂O (5 mL) was added NaOH (45 mg, 1.12 mmol). The mixture was stirred at 50 °C for 2 hours. The aqueous solution was neutralized with HCl (1 N) to pH ~6. The aqueous solution was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum to afford the title compound (131 mg, crude) as a white solid.

Step-4: Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxy-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)-6-methylnicotinamide



[0631] To a mixture of 4-[2-methoxy-5-[(oxan-2-yl)oxy)methyl]phenyl]-6-methylpyridine-3-carboxylic acid (120 mg, 0.336 mmol) in DMF (2 mL) were added DIEA (130 mg, 1.00 mmol), HATU (191 mg, 0.504 mmol) and 5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-amine (Intermediate C, 123 mg, 0.504 mmol). The mixture was stirred at room temperature for 2 h. The residue was purified by flash chromatography on silica gel with 0~10% methanol in dichloromethane to afford the title compound (25 mg, 21%) as a white solid.

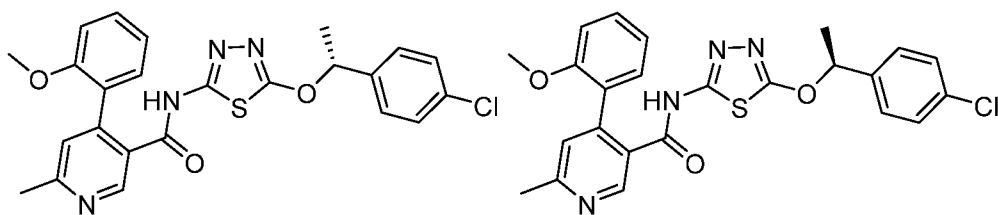
Step-5: Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(5-(hydroxymethyl)-2-methoxyphenyl)-6-methylnicotinamide



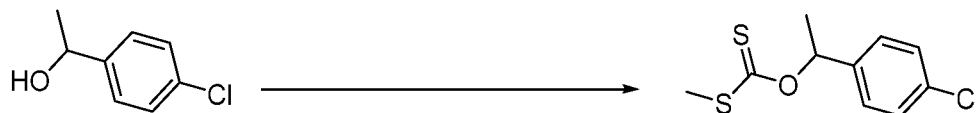
[0632] To a mixture of *N*-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-[2-methoxy-5-[(oxan-2-yloxy)methyl]phenyl]-6-methylpyridine-3-carboxamide (25 mg, 0.043 mmol) in CH_2Cl_2 (5 mL) were added TFA (1 mL). The mixture was stirred at room temperature for 2 h before concentrated under vacuum. The residue was purified by prep-HPLC (column, C18 silica gel; mobile phase, water (0.1% FA) and ACN) to afford the title compound (10.2 mg, 41%) as a white solid. ^1H NMR (400 MHz, CD_3OD): δ 8.66 (s, 1H), 8.59 (s, 1H), 7.94 – 7.93 (m, 1H), 7.62 (s, 1H), 7.45 – 7.40 (m, 3H), 7.00 – 6.93 (m, 1H), 5.57 (s, 2H), 4.64 (s, 2H), 3.61 (s, 3H), 2.66 (s, 3H). m/z 498.1 $[\text{M}+\text{H}^+]$.

Example 201 and 202

Synthesis of *N*-[5-[(1*R*)-1-(4-chlorophenyl)ethoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide (Example 201) and *N*-[5-[(1*S*)-1-(4-chlorophenyl)ethoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide (Example 202)



Step-1: Synthesis of [1-(4-chlorophenyl)ethoxy](methylsulfonyl)methanethione



[0633] To a solution of NaH (153 mg, 6.38 mmol) in THF (2 mL) was added a solution of methyl 1-(4-chlorophenyl)ethanol (500 mg, 3.19 mmol) in THF (5 mL) dropwise at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 30 mins under nitrogen atmosphere, then CS_2 (364 mg, 4.78 mmol) and MeI (679 mg, 4.78 mmol) were sequentially added dropwise at 0 °C. The resulting solution was stirred at 0 °C for additional 1 hour under nitrogen atmosphere.

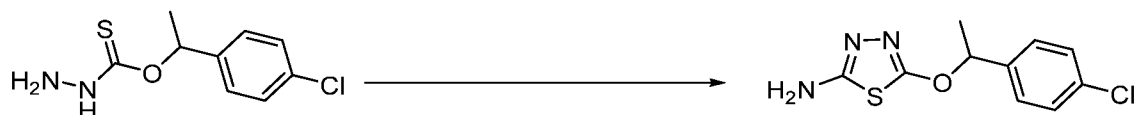
The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography with 0~50% ethyl acetate in petroleum ether to afford the title compound (403 mg, 46%) as a yellow oil.

Step-2: Synthesis of ([1-(4-chlorophenyl)ethoxy]methanethioyl)amino)amine



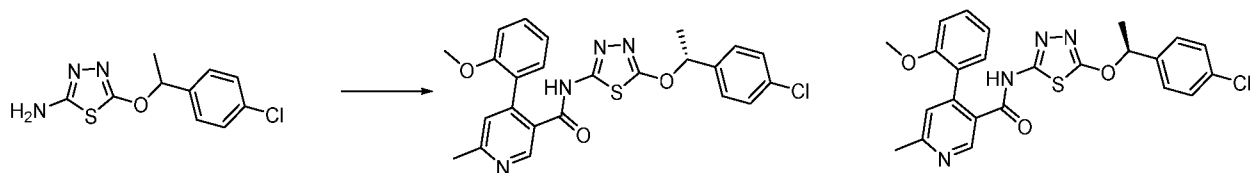
[0634] To a solution of [1-(4-chlorophenyl)ethoxy](methylsulfanyl)methanethione (380 mg, 1.54 mmol) in MeOH (5 mL) was added $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ (84.8 mg, 1.69 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 0.5 h. The resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure to afford the title compound (356 mg, crude) as a yellow oil.

Step-3: Synthesis of methyl 5-[1-(4-chlorophenyl)ethoxy]-1,3,4-thiadiazol-2-amine



[0635] To a solution of methyl ([1-(4-chlorophenyl)ethoxy]methanethioyl)amino)amine (356 mg, 1.54 mmol) and Et_3N (298 mg, 2.95 mmol) in MeOH (5 mL) was added cyanic bromide (179 mg, 1.69 mmol) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C. The resulting mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure to afford the title compound (377 mg, 86%) as a pink solid.

Step-4: Synthesis of *N*-[5-[(1*R*)-1-(4-chlorophenyl)ethoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide and *N*-[5-[(1*S*)-1-(4-chlorophenyl)ethoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide



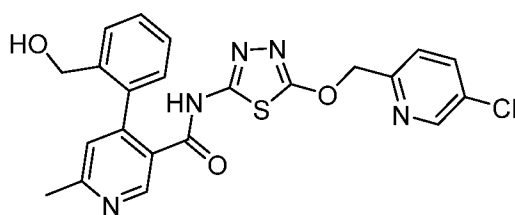
[0636] To a solution of 4-(2-methoxyphenyl)-6-methylpyridine-3-carboxylic acid (Example 113, Step 2, 326 mg, 1.34 mmol) in DMF (3 mL) were added HATU (765 mg, 2.01 mmol), DIEA (520 mg, 4.02 mmol) and 5-[1-(4-chlorophenyl)ethoxy]-1,3,4-thiadiazol-2-amine (343 mg, 1.34 mmol) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at 50 °C for 16 hours under nitrogen atmosphere. The mixture was purified by reverse phase flash column chromatography with 5~40% acetonitrile in water to afford *N*-[5-[1-(4-chlorophenyl)ethoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide (213 mg, 32%) as a white solid. The racemic product was separated by prep-chiral-HPLC (Column: CHIRALPAK IG, mobile Phase A: Hex(0.5% 2M NH₃-MeOH), Mobile Phase B: EtOH:DCM=1:1) to afford *N*-[5-[(1*S*)-1-(4-chlorophenyl)ethoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide (72.1 mg) as a white solid with shorter retention time and *N*-[5-[(1*R*)-1-(4-chlorophenyl)ethoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide (70.2 mg) as a white solid with longer retention time.

[0637] *N*-[5-[(1*R*)-1-(4-chlorophenyl)ethoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide. ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.68 (s, 1H), 8.64 (s, 1H), 7.53 – 7.42 (m, 4H), 7.42 – 7.35 (m, 1H), 7.33 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.28 (s, 1H), 7.06 (dd, *J* = 8.0, 6.8 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.00 (q, *J* = 6.4 Hz, 1H), 3.47 (s, 3H), 2.56 (s, 3H), 1.64 (d, *J* = 6.4 Hz, 3H). *m/z* 481.0 [M+H⁺].

[0638] *N*-[5-[(1*S*)-1-(4-chlorophenyl)ethoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide. ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.68 (s, 1H), 8.63 (s, 1H), 7.53 – 7.42 (m, 4H), 7.39 (td, *J* = 8.0, 2.0 Hz, 1H), 7.34 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.29 (s, 1H), 7.07 (td, *J* = 7.4, 1.2 Hz, 1H), 6.97 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.01 (q, *J* = 6.4 Hz, 1H), 3.47 (s, 3H), 2.56 (s, 3H), 1.64 (d, *J* = 6.4 Hz, 3H). *m/z* 481.1 [M+H⁺].

Example 203

Synthesis of *N*-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-[2-(hydroxymethyl)phenyl]-6-methylpyridine-3-carboxamide

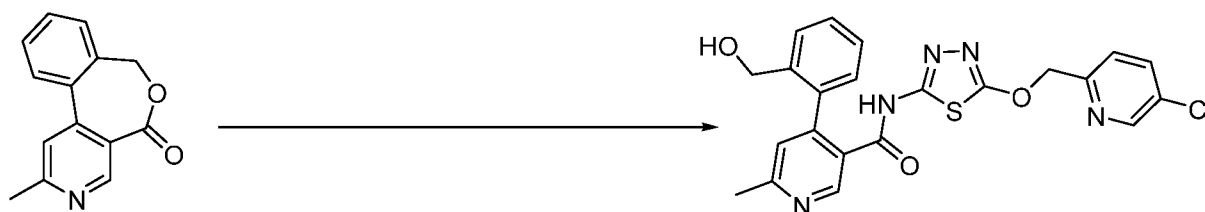


Step-1: Synthesis of 2-methylbenzo[5,6]oxepino[3,4-c]pyridin-5(7H)-one



[0639] To a degassed solution of methyl 4-chloro-6-methylpyridine-3-carboxylate (1.0 g, 5.38 mmol) and [2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (1.26 g, 5.38 mmol) in dioxane (10 mL) and H₂O (1 mL) were added Pd(dppf)Cl₂ (390 mg, 0.533 mmol) and K₂CO₃ (2.23 g, 16.1 mmol) under nitrogen atmosphere. The resulting mixture was stirred at 80 °C for 2 h under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with 0~20% MeOH in DCM to afford the title compound (563 mg, 32%) as a brown solid.

Step-2: Synthesis of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-[2-(hydroxymethyl)phenyl]-6-methylpyridine-3-carboxamide

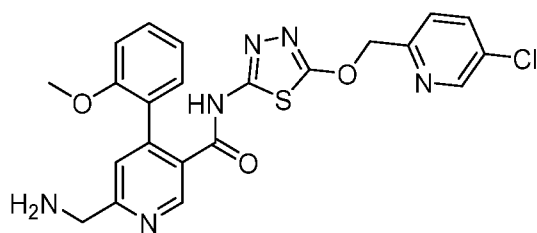


[0640] To a degassed solution of 5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-amine (Intermediate C, 116 mg, 0.48 mmol) in THF (10 mL) was added AlMe₃ (2 M in hexane) (2 mL) dropwise at 0 °C under nitrogen. The resulting mixture was stirred at room temperature for 30 min. To the above solution was added 2-methylbenzo[5,6]oxepino[3,4-c]pyridin-5(7H)-one (90.0 mg, 0.400 mmol) in THF (5 mL) dropwise at 0 °C under nitrogen. The resulting solution was stirred at 60 °C for overnight under nitrogen. The reaction mixture was quenched by the addition of H₂O and extracted with chloroform. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue

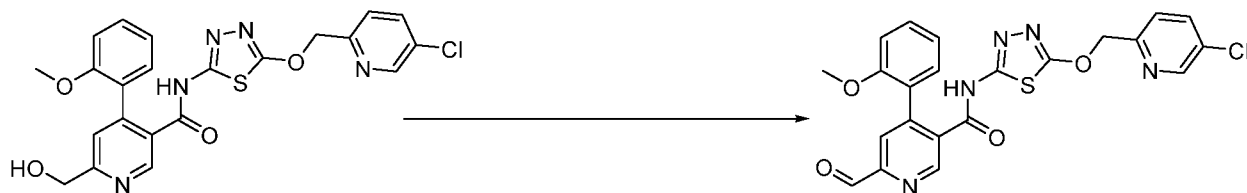
was purified by Prep-HPLC (column, C18 silica gel; mobile phase, water (10 mM NH_4HCO_3) and ACN) to afford the title compound (34.0 mg, 71%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.85 (s, 1H), 8.77 (s, 1H), 8.64 (d, $J = 2.4$ Hz, 1H), 8.01 – 7.97 (m, 1H), 7.61 – 7.50 (m, 2H), 7.40 – 7.38 (m, 1H), 7.31 – 7.23 (m, 2H), 7.05 – 7.03 (m, 1H), 5.52 (s, 2H), 4.32 (s, 2H), 2.56 (s, 3H). m/z 468 $[\text{M}+\text{H}^+]$.

Example 204

Synthesis of 6-(aminomethyl)-N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)pyridine-3-carboxamide



Step 1. Synthesis of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-6-formyl-4-(2-methoxyphenyl)pyridine-3-carboxamide



[0641] To a solution of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-6-(hydroxymethyl)-4-(2-methoxyphenyl)pyridine-3-carboxamide (Example 170, 100 mg, 0.207 mmol) in DCM (6.00 mL) were added Dess-Martin's reagent (132 mg, 0.310 mmol). The resulting mixture was stirred at room temperature for 1 hour. The resulting mixture was quenched with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum to afford the title compound (90mg, crude) as a light yellow solid, which was used for the next step without further purification.

Step 2. Synthesis of (E)-N-[5-[(5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]carbonyl)-4-(2-methoxyphenyl)pyridin-2-yl]carboximide acid



[0642] To a solution of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-6-formyl-4-(2-methoxyphenyl)pyridine-3-carboxamide (80 mg, 0.166 mmol) in MeOH (2.00 mL) were added $\text{NH}_2\text{OH}\cdot\text{HCl}$ (23 mg, 0.332 mmol) and NaHCO_3 (14 mg, 0.166 mmol). The resulting mixture was stirred at room temperature for 16 hours. The resulting mixture was quenched with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum to afford the title compound (76 mg, crude) as a light yellow solid. MS (ESI) calc'd for $(\text{C}_{22}\text{H}_{17}\text{ClN}_6\text{O}_4\text{S})$ $[\text{M}+1]^+$, 497.1; found 497.0.

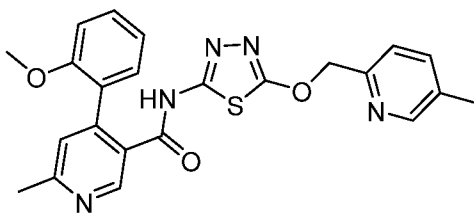
Step 3. Synthesis of 6-(aminomethyl)-N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)nicotinamide



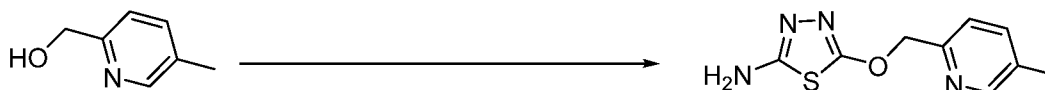
[0643] To a mixture of (E)-N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]carbamoyl-4-(2-methoxyphenyl)pyridin-2-yl]carboximide (76 mg, 0.153 mmol) in methanol (3 mL) were added TFA (322 mg, 2.82 mmol) and Zn (55 mg, 0.841 mmol). The mixture was stirred at room temperature for 4 hours. The resulting mixture was filtered, the filtrate was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (column, C18 silica gel; mobile phase, 15-45% MeCN in water, with both eluents containing 0.1% FA) to afford the title compound as a formate salt (20.2 mg, 29%, white solid). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.95 (s, 1H), 8.84 (s, 1H), 8.66 (d, $J = 2.4$ Hz, 1H), 8.42 (s, 1H), 8.02 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.62 (d, $J = 8.4$ Hz, 1H), 7.57 (s, 1H), 7.49 – 7.40 (m, 1H), 7.37 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.13 (t, $J = 7.6$ Hz, 1H), 7.03 (d, $J = 8.4$ Hz, 1H), 5.56 (s, 2H), 4.33 (s, 2H), 3.53 (s, 3H). m/z 483 $[\text{M}+\text{H}^+]$.

Example 205

Synthesis of 4-(2-methoxyphenyl)-6-methyl-N-(5-((5-methylpyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)nicotinamide



Step-1: Synthesis of 5-((5-methylpyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine



[0644] To a stirred mixture of (5-methylpyridin-2-yl)methanol (500.0 mg, 4.06 mmol) in dry THF (7.0 mL) were added NaH (324.7 mg, 8.12 mmol, 60%) in portions at 5 °C and stirred for 30 min under nitrogen atmosphere. To the above mixture was added 5-bromo-1,3,4-thiadiazol-2-amine (877 mg, 4.87 mmol) in portions at 0~5 °C. The resulting mixture was stirred for additional 4 h at the same temperature. The resulting mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with 0~90% ethyl acetate in petroleum ether to afford the title compound (430 mg, 47%) as a grey solid.

Step-2: Synthesis of 4-(2-methoxyphenyl)-6-methyl-N-(5-((5-methylpyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)nicotinamide

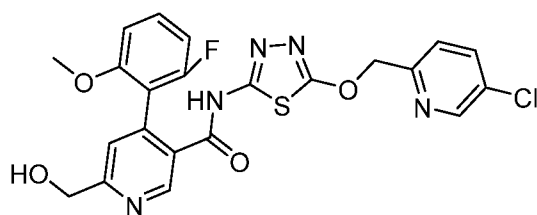


[0645] To a stirred mixture of 4-(2-methoxyphenyl)-6-methylpyridine-3-carboxylic acid (Example 113, Step 2, 240 mg, 0.99 mmol) in DMF (5.0 mL) were added HATU (684 mg, 1.80 mmol). The resulting mixture was stirred for 5 min at room temperature. To the above mixture were added 5-[(5-methylpyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-amine (200 mg, 0.90 mmol) and DIEA (348.8 mg, 2.69 mmol). The resulting mixture was stirred for additional 5 h at room temperature. The resulting mixture was diluted with water and extracted with ethyl acetate. The

combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with 0~8% methanol in ethyl acetate. The product was further purified by washed with methanol and dried under vacuum to afford the title compound (38 mg, 9%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 12.73 (s, 1H), 8.66 (s, 1H), 8.43 (s, 1H), 7.67 (d, $J = 7.2$ Hz, 1H), 7.45 (d, $J = 8.0$ Hz, 1H), 7.41 – 7.34 (m, 2H), 7.30 (s, 1H), 7.09 – 7.05 (m, 1H), 6.98 (d, $J = 8.4$ Hz, 1H), 5.48 (s, 2H), 3.51 (s, 3H), 2.56 (s, 3H), 2.31 (s, 3H). m/z 448.1 $[\text{M}+\text{H}^+]$.

Example 206

Synthesis of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-fluoro-6-methoxyphenyl)-6-(hydroxymethyl)pyridine-3-carboxamide



Step-1: Synthesis of methyl 4-(2-fluoro-6-methoxyphenyl)-6-(hydroxymethyl)pyridine-3-carboxylate



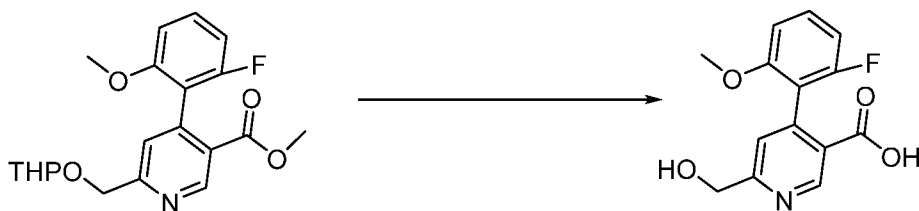
[0646] To a mixture of methyl 4-chloro-6-(hydroxymethyl)pyridine-3-carboxylate (200 mg, 0.992 mmol) and 2-fluoro-6-methoxyphenylboronic acid (169 mg, 0.992 mmol) in dioxane (5 mL) and water (1 mL) were added K_2CO_3 (411 mg, 2.97 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (73 mg, 0.099 mmol). The resulting mixture was stirred at 80 °C for 2 h under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with 0-5% MeOH in DCM to afford the title compound (280 mg, 96%) as a yellow oil.

Step-2: Synthesis of methyl 4-(2-fluoro-6-methoxyphenyl)-6-[(oxan-2-yloxy)methyl]pyridine-3-carboxylate



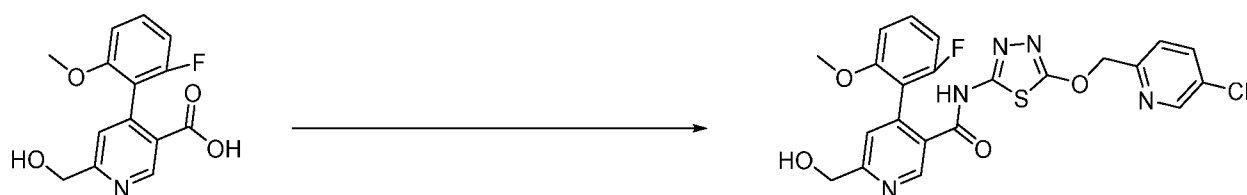
[0647] To a mixture of methyl 4-(2-fluoro-6-methoxyphenyl)-6-(hydroxymethyl)pyridine-3-carboxylate (355 mg, 1.21 mmol) in DCM (5 mL) were added DHP (205 mg, 2.43 mmol) and TsOH (21 mg, 0.122 mmol). The resulting mixture was stirred at 50 °C for 2 hours under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with 0-5% MeOH in CH₂Cl₂ to afford the title compound (300 mg, 65%) as a yellow oil.

Step-3: Synthesis of 4-(2-fluoro-6-methoxyphenyl)-6-[(oxan-2-yloxy)methyl]pyridine-3-carboxylic acid



[0648] To a mixture of methyl 4-(2-fluoro-6-methoxyphenyl)-6-[(oxan-2-yloxy)methyl]pyridine-3-carboxylate (280 mg, 0.746 mmol) in THF (5 mL) and water (5 mL) was added NaOH (120 mg, 2.98 mmol). The resulting mixture was stirred at 50 °C for 4 h. The mixture was acidified with HCl (1 N) to pH 2~3. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with 0-20% acetonitrile in water to afford the title compound (200 mg, 74%) as a green solid.

Step-4: Synthesis of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-fluoro-6-methoxyphenyl)-6-(hydroxymethyl)pyridine-3-carboxamide

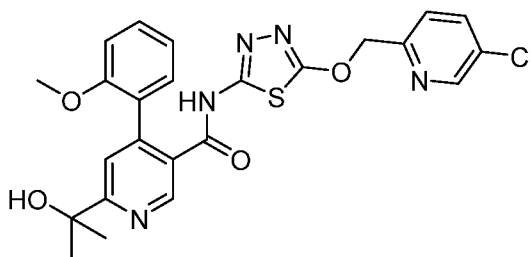


[0649] To a mixture of 4-(2-fluoro-6-methoxyphenyl)-6-(hydroxymethyl)pyridine-3-carboxylic acid (200 mg, 0.721 mmol) and 5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-

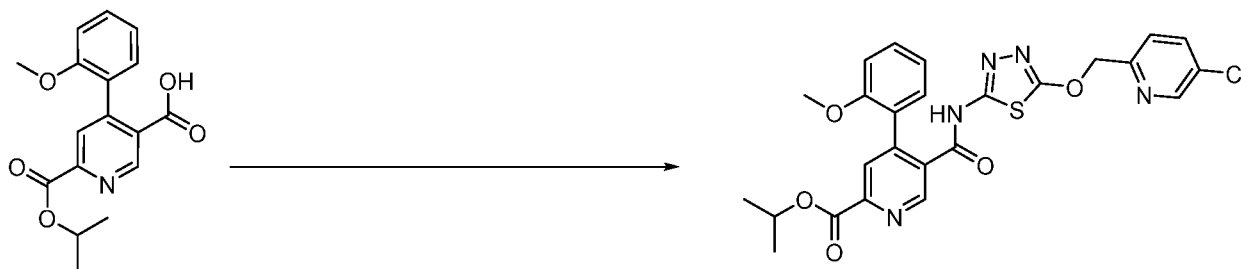
2-amine (Intermediate C, 263 mg, 1.08 mmol) in DMF (10 mL) were added HATU (820 mg, 2.16 mmol) and DIEA (140 mg, 1.08 mmol). The resulting mixture was stirred at room temperature for 2 hours. The residue was purified by reverse phase flash chromatography with 10~40% acetonitrile in water and further purified by prep-HPLC (column, C18 silica gel; mobile phase, water (10 mM $\text{NH}_4\text{HCO}_3 + 0.1\% \text{NH}_3 \cdot \text{H}_2\text{O}$) and ACN) to afford The title compound (77 mg, 21%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 12.82 (s, 1H), 9.00 – 8.89 (m, 1H), 7.77 – 7.69 (m, 1H), 7.98 – 7.89 (m, 1H), 7.81 (s, 1H), 7.49 – 7.31 (m, 2H), 7.01 – 6.91 (m, 2H), 5.71 – 5.601 (m, 1H), 5.61 (s, 2H), 4.81 – 4.75 (m, 2H), 3.59 (s, 3H). m/z 502.0 $[\text{M}+\text{H}^+]$.

Example 207

Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-6-(2-hydroxypropan-2-yl)-4-(2-methoxyphenyl)nicotinamide



Step-1: Synthesis of isopropyl 5-([5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]carbamoyl)-4-(2-methoxyphenyl)pyridine-2-carboxylate



[0650] To a mixture of 6-(isopropoxycarbonyl)-4-(2-methoxyphenyl)pyridine-3-carboxylic acid (Step 3 of Example 102, 2 g, 6.343 mmol), HATU (7.2 g, 19.0 mmol) and DIEA (1.23 g, 9.51 mmol) in DMF (20 mL) was added 5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-amine (Intermediate C, 1.54 g, 6.34 mmol). The resulting mixture was stirred at room temperature for 2 h before concentrated under vacuum. The residue was purified by flash column chromatography with 0-8% MeOH in CH_2Cl_2 to afford the title compound (2.77 g, 81%) as a yellow solid.

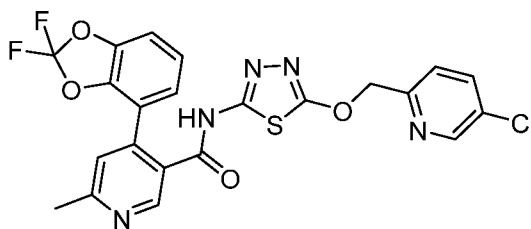
Step-2: Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-6-(2-hydroxypropan-2-yl)-4-(2-methoxyphenyl)nicotinamide



[0651] To a mixture of isopropyl 5-((5-((5-chloropyridin-2-yl) methoxy)-1,3,4-thiadiazol-2-yl)carbamoyl)-4-(2-methoxyphenyl)picolinate (200 mg, 0.35 mmol) in THF (5 mL) was added MeMgBr (3 M, 0.5 mL) at -78 °C under nitrogen. The mixture was stirred at room temperature for 8 hours. The reaction was then quenched by the addition of MeOH and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~10% dichloromethane in methanol and further purified by prep-HPLC (column, C18 silica gel; mobile phase, water (10 mM NH_4HCO_3 +0.1% $\text{NH}_3\cdot\text{H}_2\text{O}$) and ACN) to afford the title compound (20.2 mg, 10%) as an off-white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 12.67 (s, 1H), 8.71 (s, 1H), 8.66 (s, 1H), 8.02 – 7.99 (m, 1H), 7.65 – 7.60 (m, 2H), 7.43 – 7.35 (m, 2H), 7.11 – 7.10 (m, 1H), 7.09 – 6.98 (m, 1H), 5.54 (s, 2H), 5.42 (s, 1H), 3.51 (s, 3H), 1.50 (s, 6H). m/z 512.1 $[\text{M}+\text{H}^+]$.

Example 208

Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-6-methylnicotinamide

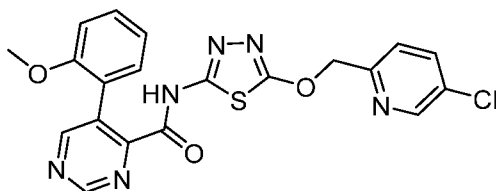


[0652] The title compound was prepared using General Procedure E, F and A. Methyl 4-chloro-6-methylpyridine-3-carboxylate and 2,2-difluoro-3a,7a-dihydro-1,3-benzodioxol-4-ylboronic acid were employed for General Procedure E. For General Procedure A, 5-[(5-chloropyridin-2-yl) methoxy]-1,3,4-thiadiazol-2-amine (Intermediate C) was used. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 13.17 (s, 1H), 8.88 (s, 1H), 8.65 – 8.64 (m, 1H), 8.01 – 7.98 (m, 1H), 7.59 –

7.51 (m, 1H), 7.48 – 7.44 (m, 2H), 7.36 – 7.28 (m, 2H), 5.51 (s, 2H), 2.50 (s, 3H). m/z 518.0 $[M+H]^+$.

Example 209

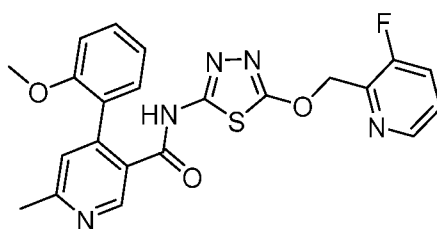
Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-5-(2-methoxyphenyl)pyrimidine-4-carboxamide



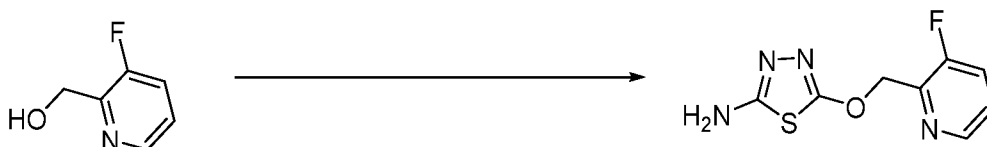
[0653] The title compound was prepared using General Procedure E, F and A. Methyl 5-bromopyrimidine-4-carboxylate and (2-methoxyphenyl)boronic acid were employed for General Procedure E. For General Procedure A, 5-[(5-chloropyridin-2-yl) methoxy]-1,3,4-thiadiazol-2-amine (Intermediate C) was used. ^1H NMR (400 MHz, $DMSO-d_6$): δ 13.07 (s, 1H), 9.33 – 9.34 (m, 1H), 8.98 (s, 1H), 8.66 – 8.65 (m, 1H), 8.02 – 7.99 (m, 1H), 7.62 – 7.60 (m, 1H), 7.45 – 7.41 (m, 2H), 7.11 – 7.03 (m, 2H), 5.56 (s, 2H), 3.55 (s, 3H). m/z 455.0 $[M+H]^+$.

Example 210

Synthesis of N-[5-[(3-fluoropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide



Step-1: Synthesis of 5-((3-fluoropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine



[0654] To a solution of NaH (0.70 g, 17.5 mmol, 60%) in THF (10 mL) was added (3-fluoropyridin-2-yl) methanol (1.50 g, 11.8 mmol) in portions at 0–5 °C and stirred at 5 °C for 1 h

under nitrogen. Then 5-bromo-1,3,4-thiadiazol-2-amine (2.55 g, 14.1 mmol,) was added to the mixture in small portions at 5 °C and stirred at 5 °C for 5 h under nitrogen. The reaction mixture was then quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~50% ethyl acetate in petroleum ether to afford the title compound (1.96 g, 74%) as a white solid.

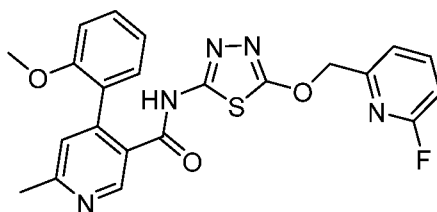
Step-2: Synthesis of N-(5-((3-fluoropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)-6-methylnicotinamide



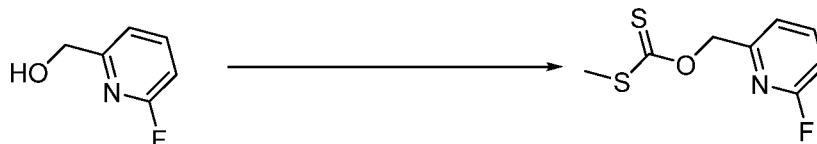
[0655] To a mixture of 5-[(3-fluoropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-amine (280 mg, 1.23 mmol) in DMF (5 mL) were added DIEA (480 mg, 3.71 mmol), HATU (706 mg, 1.85 mmol) and 4-(2-methoxyphenyl)-6-methylpyridine-3-carboxylic acid (Example 113, Step 2, 302 mg, 1.23 mmol). The mixture was stirred at room temperature for 16 h. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~10% dichloromethane in methanol and further purified by prep-HPLC (column, C18 silica gel; mobile phase, water (10 mM NH_4HCO_3 +0.1% $\text{NH}_3\cdot\text{H}_2\text{O}$) and ACN) to afford the title compound (25 mg, 5%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 12.77 (s, 1H), 8.69 (s, 1H), 8.48 – 8.46 (m, 1H), 7.84 – 7.79 (m, 1H), 7.57 – 7.53 (m, 1H), 7.42 – 7.34 (m, 3H), 7.10 – 6.98 (m, 2H), 5.62 (s, 2H), 3.51 (s, 3H), 2.67 (s, 3H). m/z 452.2 $[\text{M}+\text{H}^+]$.

Example 211

Synthesis of N-[5-[(6-fluoropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide

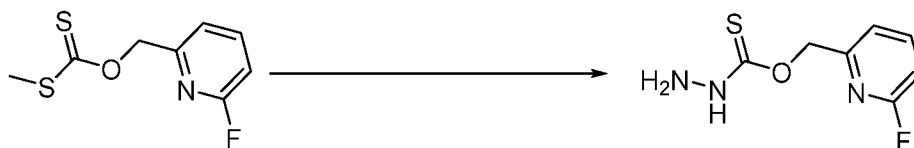


Step-1: Synthesis of [(6-fluoropyridin-2-yl)methoxy](methylsulfanyl)methanethione



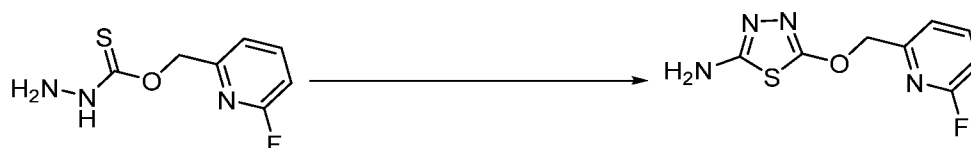
[0656] To a solution of (6-fluoropyridin-2-yl)methanol (500 mg, 3.93 mmol) in THF (3.0 mL) was added NaH (188 mg, 7.86 mmol) slowly at 5 °C under nitrogen atmosphere, the resulting mixture was stirred at 5 °C for 30 min. To the above mixture was added CS₂ (449 mg, 5.90 mmol), the resulting mixture was stirred at 5 °C for 10 min, then to the above mixture was added MeI (837 mg, 5.90 mmol), the resulting mixture was stirred at 5 °C for additional 10 min. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic solution was dried over sodium sulfate, filtered, and concentrated under vacuum to afford the title compound (300 mg, crude) as a yellow oil.

Step-2: Synthesis of [(6-fluoropyridin-2-yl)methoxy](methylsulfanyl)methanethione



[0657] To a solution of [(6-fluoropyridin-2-yl)methoxy](methylsulfanyl)methanethione (300 mg, 1.38 mmol) in MeOH (3.0 mL) was added hydrazine hydrate (80%) (138 mg, 2.76 mmol). The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic solution was dried over sodium sulfate, filtered, and concentrated under vacuum to afford the title compound (280 mg, crude) as a yellow oil.

Step-3: Synthesis of 5-[(6-fluoropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-amine



[0658] To a solution of ([[(6-fluoropyridin-2-yl)methoxy]methanethioyl]amino)amine (280 mg, 1.39 mmol) in MeOH (5.0 mL) was added TEA (211 mg, 2.08 mmol) and cyanogen bromide (221 mg, 2.08 mmol) slowly. The resulting mixture was stirred at room temperature for 30 min under nitrogen atmosphere. The resulting mixture was concentrated under vacuum to afford the title compound (90 mg, crude) as a yellow oil.

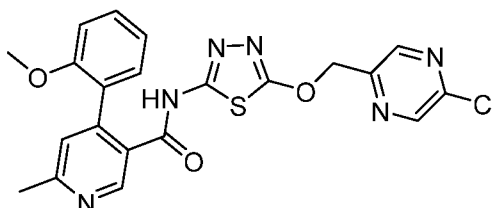
Step-4: Synthesis of N-[5-[(6-fluoropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide



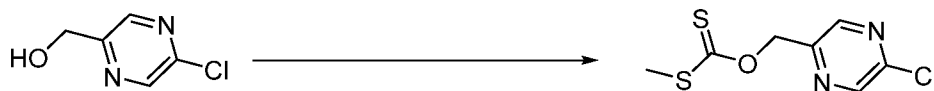
[0659] To a solution of 5-[(6-fluoropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-amine (90 mg, 0.39 mmol) in DMF (3.0 mL) were added 4-(2-methoxyphenyl)-6-methylpyridine-3-carboxylic acid (Example 113, Step 2, 145 mg, 0.59 mmol), DIEA (154 mg, 1.19 mmol), HATU (226 mg, 0.59 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic solution was dried over sodium sulfate, filtered, and concentrated under vacuum. The crude product was purified by Prep-HPLC (column, C18 silica gel; mobile phase, water (10 mM NH_4HCO_3 +0.1% $\text{NH}_3\cdot\text{H}_2\text{O}$) and ACN) to afford the title compound (23.9 mg, 13%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 12.85 (s, 1H), 8.66 (s, 1H), 8.09 – 8.02 (m, 1H), 7.54 – 7.48 (m, 1H), 7.42 – 7.32 (m, 2H), 7.29 (s, 1H), 7.21 – 7.16 (m, 1H), 7.10 – 7.04 (t, $J = 7.6$ Hz, 1H), 7.00 – 6.95 (d, $J = 8.4$ Hz, 1H), 5.50 (s, 2H), 3.51 (s, 3H), 2.56 (s, 3H). m/z 452.1 $[\text{M}+\text{H}^+]$.

Example 212

Synthesis of N-[5-[(5-chloropyrazin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide

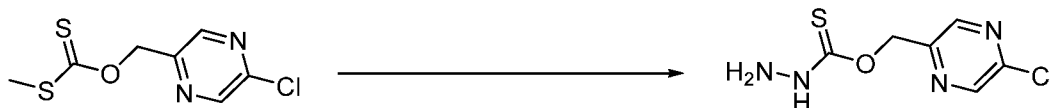


Step-1: Synthesis of [(5-chloropyrazin-2-yl)methoxy](methylsulfanyl)methanethione



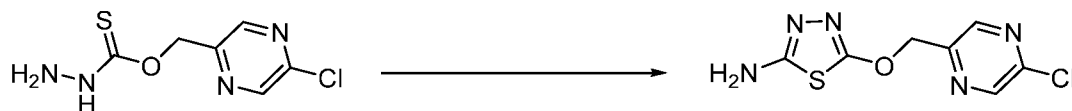
[0660] To a solution of NaH (166.01 mg, 6.91 mmol) in THF (2 mL) was added a solution of (5-chloropyrazin-2-yl)methanol (500 mg, 3.45 mmol) in THF (5 mL) under nitrogen. The resulting solution was stirred at 0 °C for 30 mins under nitrogen atmosphere, then CS₂ (395 mg, 5.18 mmol) and MeI (736 mg, 5.18 mmol) were sequentially added to the above mixture at 0 °C. The resulting solution was stirred at 0 °C for 1 hours under nitrogen atmosphere. The resulting mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography with 0~10% MeOH in dichloromethane to afford the title compound (450mg, 49%) as a light yellow solid.

Step-2: Synthesis of ([[(5-chloropyrazin-2-yl)methoxy]methanethioyl]amino)amine



[0661] To a solution of [(5-chloropyrazin-2-yl)methoxy](methylsulfanyl)methanethione (400 mg, 1.70 mmol) in MeOH (5 mL) was added NH₂NH₂·H₂O (93.8 mg, 1.87 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 0.5 h. The resulting mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford the title compound (380 mg, crude) as a colorless oil.

Step-3: Synthesis of 5-[(5-chloropyrazin-2-yl)methoxy]-1,3,4-thiadiazol-2-amine



[0662] To a solution of ([[(5-chloropyrazin-2-yl)methoxy]methanethioyl]amino)amine (380 mg, 1.73 mmol) and Et₃N (350 mg, 3.47 mmol) in MeOH (5 mL) was added BrCN (202 mg, 1.91 mmol) at 0 °C under nitrogen. The resulting mixture was stirred at 0 °C for 30 min. The resulting mixture was diluted with water and extracted with ethyl acetate. The combined organic

layers were washed with brine, dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under vacuum to afford the title compound (240 mg, crude) as a reddish solid.

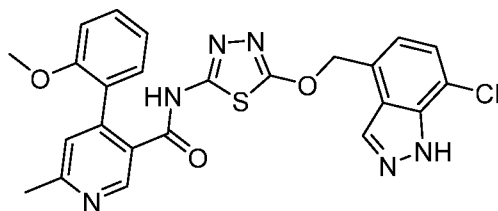
Step-4: Synthesis of N-[5-[(5-chloropyrazin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide



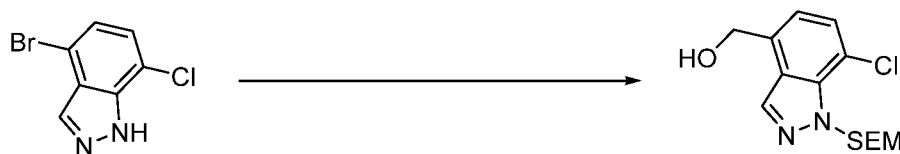
[0663] To a solution of 4-(2-methoxyphenyl)-6-methylpyridine-3-carboxylic acid (Example 113, Step 2, 99.8 mg, 0.410 mmol) in DMF (2 mL) were added HATU (234 mg, 0.616 mmol), DIEA (159 mg, 1.23 mmol) and 5-[(5-chloropyrazin-2-yl)methoxy]-1,3,4-thiadiazol-2-amine (100 mg, 0.410 mmol). The resulting mixture was stirred at 50 °C for 2 hours under nitrogen atmosphere. The residue was purified by flash column chromatography with 5~30% acetonitrile in water to afford the title compound (19 mg, 9.8%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 12.83 (s, 1H), 8.85 (d, $J = 1.2$ Hz, 1H), 8.75 – 8.69 (m, 2H), 7.46 – 7.33 (m, 3H), 7.09 (t, $J = 7.6$ Hz, 1H), 7.00 (d, $J = 8.4$ Hz, 1H), 5.64 (s, 2H), 3.51 (s, 3H), 2.60 (s, 3H). m/z 469.1 $[\text{M}+\text{H}^+]$.

Example 213

Synthesis of N-[5-[(7-chloro-1H-indazol-4-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide

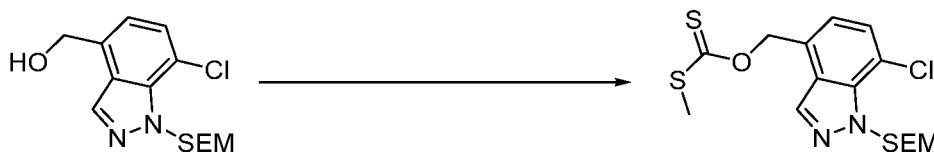


Step-1: Synthesis of 4-bromo-7-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]indazole



[0664] To a solution of 4-bromo-7-chloro-1H-indazole (4 g, 17.2 mmol) in anhydrous DMF (6.0 mL) was added NaH (1.03 g, 25.9 mmol, 60%) in portions at 0°C. The resulting mixture was stirred at 0 °C for 20 min. To the above mixture was added 2-(trimethylsilyl)ethoxymethyl chloride (4.3 g, 25.9 mmol) dropwise at 0 °C. The resulting mixture was stirred at room temperature for 16 h. The resulting mixture was quenched by the addition of water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~20% ethyl acetate in petroleum ether to afford the title compound (6 g, 96%) as a colorless oil.

Step-2: Synthesis of [(7-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-4-yl)methoxy](methylsulfanyl)methanethione



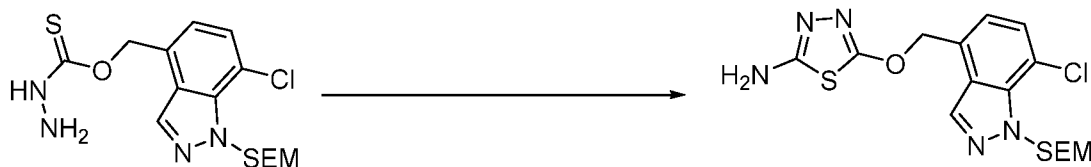
[0665] To a solution of NaH (250 mg, 6.38 mmol, 60%) in THF (6.0 mL) was added (7-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-4-yl)methanol (1.00 g, 3.19 mmol) dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 30 min. To the above mixture was added CS₂ (370 mg, 5 mmol) dropwise at 0°C and stirred at 0 °C for 20min. Then MeI (680 mg, 5 mmol) was added to the above mixture dropwise at 0 °C. The resulting mixture was stirred at room temperature for 1 hour. The resulting mixture was quenched by the addition of water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~30% ethyl acetate in petroleum ether to afford the title compound (820 mg, 64%) as a yellow oil.

Step-3: Synthesis of (((7-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-4-yl)methoxy)methanethioyl)amino)amine



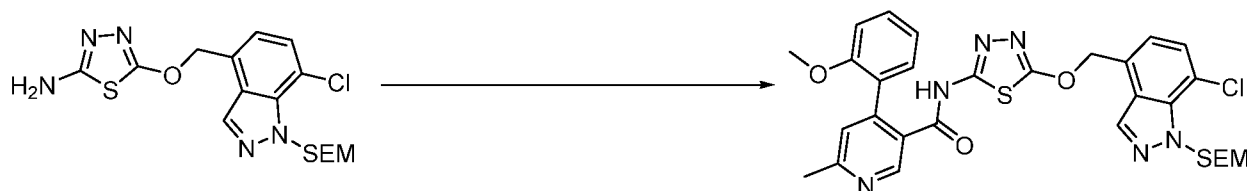
[0666] To a mixture of [(7-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-4-yl)methoxy](methylsulfanyl)methanethione (820 mg, 2.0 mmol) in MeOH (8.0 mL) was added $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (102 mg, 2.0 mmol). The mixture was stirred at 0 °C for 1 hour before concentrated under vacuum. The residue was purified by flash column chromatography with 5-50% acetonitrile in water to afford the title compound (370 mg, 47%) as a yellow solid.

Step-4: Synthesis of 5-[(7-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-4-yl)methoxy]-1,3,4-thiadiazol-2-amine



[0667] To a mixture of ([[(7-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-4-yl)methoxy]methanethioyl]amino)amine (115 mg, 0.30 mmol) and Et_3N (60.1 mg, 0.60 mmol) in MeOH (3 mL) was added BrCN (34.6 mg, 0.33 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 hour. The resulting mixture was quenched with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum to afford the title compound (80 mg, crude) as a yellow solid.

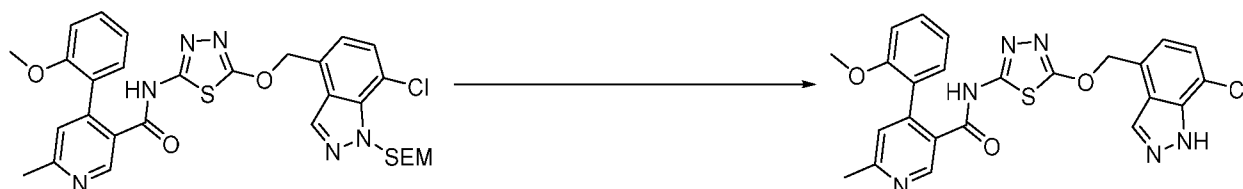
Step-5: Synthesis of N-[5-[(7-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-4-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide



[0668] To a mixture of 4-(2-methoxyphenyl)-6-methylpyridine-3-carboxylic acid (Example 113, Step 2, 71 mg, 0.29 mmol) and HATU (82 mg, 0.21 mmol) in DMF (1 mL) were added DIEA (50 mg, 0.388 mmol). The resulting mixture was stirred at room temperature for 30 min. To the above mixture was added 5-[(7-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-4-yl)methoxy]-1,3,4-thiadiazol-2-amine (80 mg, 0.194 mmol). The mixture was stirred at room temperature for 16 hours under nitrogen atmosphere. The resulting mixture was quenched with water and extracted with ethyl acetate. The organic layers were combined, washed with brine,

dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~5% methanol in dichloromethane to afford the title compound (110 mg, 88%) as a light yellow solid.

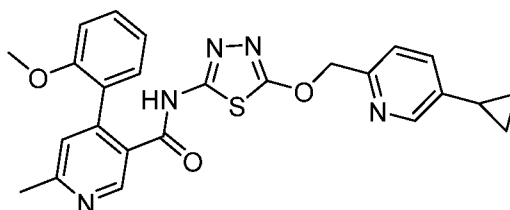
Step-6: Synthesis of N-[5-[(7-chloro-1H-indazol-4-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide



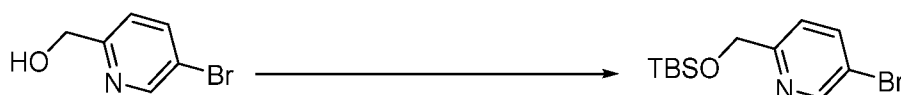
[0669] To a mixture of N-[5-[(7-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-4-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide (100 mg, 0.157 mmol) and TBAF (246 mg, 0.942 mmol) in THF (5 mL) was added CsF (238 mg, 1.56 mmol). The resulting mixture was stirred at 70 °C for 16 hours. The residue was purified by flash chromatography on silica gel with 0~5% methanol in dichloromethane and further purified by prep-HPLC (column, C18 silica gel; mobile phase, water (10 mM NH_4HCO_3) and ACN) to afford the title compound (18 mg, 21%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.75 (s, 1H), 12.73 (s, 1H), 8.65 (s, 1H), 8.33 (s, 1H), 7.48 (d, $J = 7.6$ Hz, 1H), 7.43 – 7.31 (m, 2H), 7.31 – 7.22 (m, 2H), 7.11 – 7.03 (m, 1H), 6.97 (d, $J = 8.0$ Hz, 1H), 5.80 (s, 2H), 3.50 (s, 3H), 2.55 (s, 3H). m/z 507 $[\text{M}+\text{H}^+]$.

Example 214

Synthesis of N-(5-((5-cyclopropylpyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)-6-methylnicotinamide

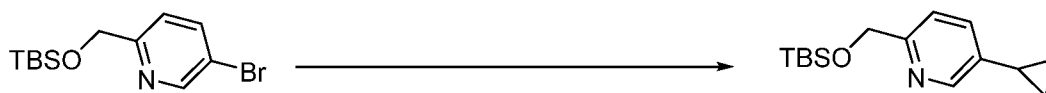


Step-1: Synthesis of 5-bromo-2-(((tert-butyl)dimethylsilyl)oxy)methyl)pyridine



[0670] To a stirred mixture of (5-bromopyridin-2-yl)methanol (3.00 g, 15.9 mmol) in DCM (30 mL) were added imidazole (3.25 g, 47.8 mmol) and t-butyldimethylchlorosilane (3.60 g, 23.9 mmol). The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was quenched with water and extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with 0~12% ethyl acetate in petroleum ether to afford the title compound (4.6 g, 95%) as a colorless oil.

Step-2: Synthesis of 2-(((tert-butyldimethylsilyl)oxy)methyl)-5-cyclopropylpyridine



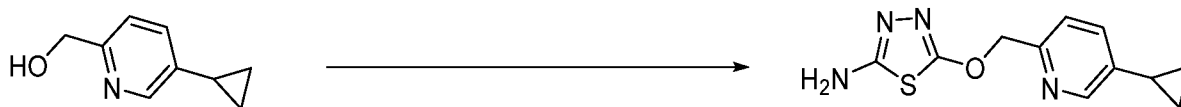
[0671] To a degassed solution of 5-bromo-2-(((tert-butyldimethylsilyl)oxy)methyl)pyridine (1.00 g, 3.30 mmol) in 1,4-dioxane (10 mL) and water (1 mL) were added K_2CO_3 (1.37 g, 9.92 mmol), cyclopropylboronic acid (568 mg, 6.61 mmol) and $Pd(dppf)Cl_2$ (242 mg, 0.33 mmol). The resulting mixture was stirred at 100 °C for 16 h under N_2 before concentrated under vacuum. The residue was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with 0~20% ethyl acetate in petroleum ether to afford the title compound (840 mg, 96%) as a yellow oil.

Step-3: Synthesis of (5-cyclopropylpyridin-2-yl)methanol



[0672] To a stirred mixture of 2-[[[(tert-butyldimethylsilyl)oxy]methyl]-5-cyclopropylpyridine (500 mg, 1.89 mmol) in THF (7.0 mL) was added TBAF (744 mg, 2.84 mmol). The resulting mixture was stirred at room temperature for 1 h. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with 0~10% methanol in DCM to afford the title compound (200 mg, 70%) as a yellow solid.

Step-4: Synthesis of 5-((5-cyclopropylpyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine



[0673] To a stirred mixture of (5-cyclopropylpyridin-2-yl)methanol (180 mg, 1.20 mmol) in THF (5.0 mL) was added NaH (96.7 mg, 2.41 mmol, 60%) at 0~5 °C under nitrogen. The resulting mixture was maintained this temperature and stirred 1 h under nitrogen. 5-Bromo-1,3,4-thiadiazol-2-amine (260.6 mg, 1.44 mmol) was added to the above mixture at 0 °C. The resulting mixture was stirred at 0~5 °C for 3 h. The resulting mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under vacuum. The residue was purified by reverse phase flash chromatography with 5~45% acetonitrile in water to afford the title compound (390 mg, 50%) as a grey solid.

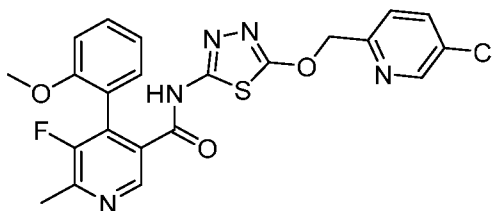
Step-5: Synthesis of N-(5-((5-cyclopropylpyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)-6-methylnicotinamide



[0674] To a stirred mixture of 4-(2-methoxyphenyl)-6-methylpyridine-3-carboxylic acid (Example 113, Step 2, 108 mg, 0.44 mmol) in DMF (4.0 mL) were added HATU (306 mg, 0.80 mmol). The resulting mixture was stirred for 5 min at room temperature. To the above mixture were added 5-((5-cyclopropylpyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (100 mg, 0.40 mmol) and DIEA (156 mg, 1.20 mmol). The resulting mixture was stirred for additional 3 h at room temperature. The resulting mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with 0~10% methanol in ethyl acetate. The product was washed with methanol and dried under vacuum to afford the title compound (31.7 mg, 16%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.74 (s, 1H), 8.66 (s, 1H), 8.41 (s, 1H), 7.52 – 7.49 (m, 1H), 7.43 – 7.39 (m, 3H), 7.29 (s, 1H), 7.09 – 7.05 (m, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 5.47 (s, 2H), 3.50 (s, 3H), 2.56 (s, 3H), 2.01 – 1.94 (m, 1H), 1.08 – 1.02 (m, 2H), 0.80 – 0.76 (m, 2H). *m/z* 472.2 [M+H⁺].

Example 215

Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-5-fluoro-4-(2-methoxyphenyl)-6-methylnicotinamide



Step-1: Synthesis of ethyl 4-chloro-5-fluoro-6-methylnicotinate



[0675] To a solution of ethyl 4,6-dichloro-5-fluoronicotinate (1 g, 4.237 mmol) in dioxane (10 mL) and water (1 mL) were added K_2CO_3 (1.75 g, 12.7 mmol), $Pd(dppf)Cl_2$ (0.35 g, 0.424 mmol) and 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (427 mg, 3.39 mmol) under nitrogen. The mixture was stirred at 80 °C for 5 hours under nitrogen. The reaction mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~30% ethyl acetate in petroleum ether to afford the title compound (990 mg, 60%) as a yellow solid.

Step-2: Synthesis of ethyl 5-fluoro-4-(2-methoxyphenyl)-6-methylnicotinate



[0676] To a solution of ethyl 4-chloro-5-fluoro-6-methylnicotinate (110 mg, 0.507 mmol) in dioxane (5 mL) and water (1 mL) was added K_2CO_3 (220 mg, 1.52 mmol), (2-methoxyphenyl)boronic acid (115 mg, 0.760 mmol) and $Pd(dppf)Cl_2$ (44 mg, 0.051 mmol) under nitrogen. The mixture was stirred at 80 °C for 5 hours under nitrogen. The mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel with

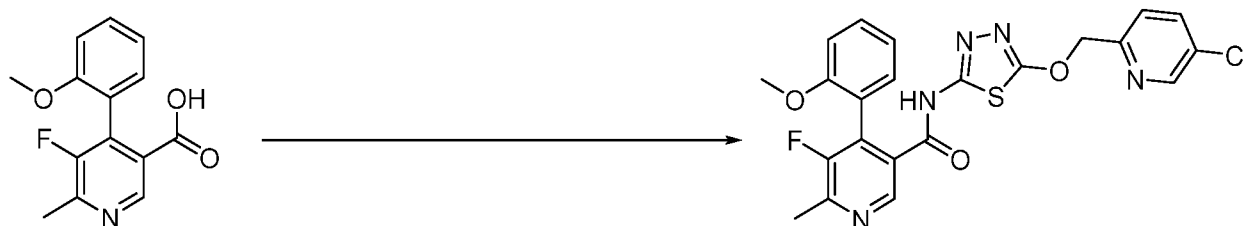
0~20% ethyl acetate in petroleum ether to afford the title compound (80 mg, 73%) as a yellow oil.

Step-3: Synthesis of 5-Fluoro-4-(2-methoxyphenyl)-6-methylnicotinic acid



[0677] To a solution of ethyl 5-fluoro-4-(2-methoxyphenyl)-6-methylnicotinate (80 mg, 0.277 mmol) in MeOH (2 mL) and H₂O (1 mL) was added NaOH (22 mg, 0.55 mmol). The mixture was stirred at 70 °C for 2 hours. The aqueous solution was acidified with HCl (1 N) to pH 5~6. The aqueous solution was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum to afford the title compound (60 mg, crude) as a yellow solid.

Step-4: Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-5-fluoro-4-(2-methoxyphenyl)-6-methylnicotinamide

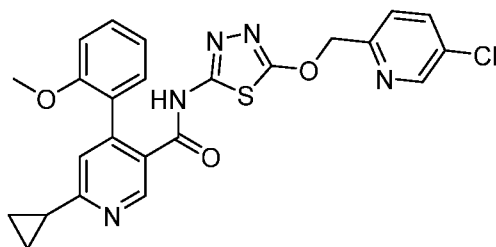


[0678] To a solution of 5-fluoro-4-(2-methoxyphenyl)-6-methylnicotinic acid (60 mg, 0.223 mmol) in DMF (1 mL) was added DIEA (86 mg, 0.669 mmol), HATU (127 mg, 0.334 mmol) and 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C, 54 mg, 0.223 mmol). The mixture was stirred at room temperature for 16 h. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~10% methanol in dichloromethane and further purified by prep-HPLC (column, C18 silica gel; mobile phase, water (0.1% FA) and ACN) to afford the title compound (19 mg, 14.4%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.06 (s, 1H), 8.98 (s, 1H), 8.66 – 8.65 (m, 1H), 8.01 – 7.99 (m, 1H), 7.62 – 7.60

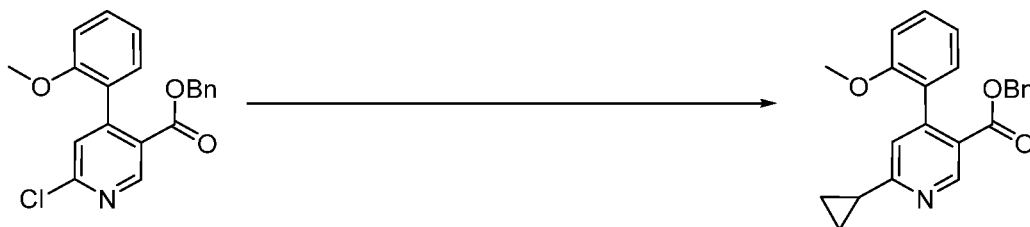
(m, 1H), 7.48 – 7.39 (m, 2H), 7.11 – 7.08 (m, 1H), 7.05 – 7.03 (m, 1H), 5.56 (s, 2H), 3.55 (s, 3H), 2.70-2.40 (m, 3H). m/z 486.2 $[M+H]^+$.

Example 216

Synthesis of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-6-cyclopropyl-4-(2-methoxyphenyl)pyridine-3-carboxamide



Step-1: Synthesis of benzyl 6-cyclopropyl-4-(2-methoxyphenyl)pyridine-3-carboxylate



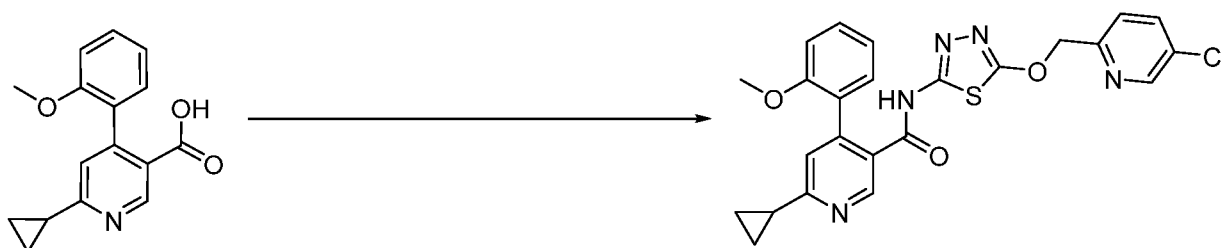
[0679] A degassed mixture of benzyl 6-chloro-4-(2-methoxyphenyl)pyridine-3-carboxylate (200 mg, 0.56 mmol), cyclopropylboronic acid (97.1 mg, 1.13 mmol), $Pd(PPh_3)_4$ (130 mg, 0.11 mmol) and cesium carbonate (368 mg, 1.13 mmol) in dioxane (2.0 mL) and water (0.2 mL) was stirred at 80 °C for 2 h under nitrogen atmosphere. The resulting mixture was quenched with water and the aqueous phase was extracted with ethyl acetate. The combined organic solution was dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with 0~19% acetate ethyl in petroleum ether to afford the title compound (145 mg, 71 %) as a colorless oil.

Step-2: Synthesis of 6-cyclopropyl-4-(2-methoxyphenyl)pyridine-3-carboxylic acid



[0680] A solution of benzyl 6-cyclopropyl-4-(2-methoxyphenyl)pyridine-3-carboxylate (350 mg, 0.97 mmol) and sodium hydroxide (155 mg, 3.89 mmol) in water (3.0 mL) and THF (3.0 mL) was stirred at 70 °C for 16 h. The residue was diluted with water and acidified to pH 4-5 with HCl (2 *N*). The aqueous layer was extracted with ethyl acetate. The combined organic solution was dried over sodium sulfate, filtered, and concentrated under vacuum to afford the title compound (240 mg, crude) as a white solid, which was used for the next step without further purification.

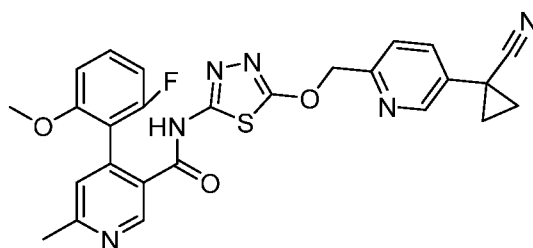
Step-3: Synthesis of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-6-cyclopropyl-4-(2-methoxyphenyl)pyridine-3-carboxamide



[0681] To a solution of 6-cyclopropyl-4-(2-methoxyphenyl)pyridine-3-carboxylic acid (180 mg, 0.66 mmol) in DMF (4.0 mL) were added 5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-amine (Intermediate C, 243 mg, 1.00 mmol), HATU (381 mg, 1.00 mmol) and DIEA (259 mg, 2.00 mmol). The resulting mixture was stirred for 16 h at room temperature. The resulting mixture was quenched with water and the aqueous phase was extracted with ethyl acetate. The combined organic solution was dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by reverse phase flash column chromatography with 5~55% acetonitrile in water and further purified by Prep-HPLC (column, C18 silica gel; mobile phase, water (10 mM $\text{NH}_4\text{HCO}_3 + 0.1\% \text{NH}_3 \cdot \text{H}_2\text{O}$) and ACN) to afford the title compound (113 mg, 39%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6): δ 12.68 (s, 1H), 8.68 – 8.64 (d, $J = 2.4$ Hz, 1H), 8.61 (s, 1H), 8.04 – 7.97 (m, 1H), 7.64 – 7.56 (d, $J = 8.4$ Hz, 1H), 7.44 – 7.30 (m, 3H), 7.12 – 7.04 (t, $J = 5.6$ Hz, 1H), 7.01 – 6.96 (d, $J = 8.4$ Hz, 1H), 5.54 (s, 2H), 3.51 (s, 3H), 2.29 – 2.20 (m, 1H), 1.09 – 0.98 (m, 4H). m/z 494.0 $[\text{M} + \text{H}^+]$.

Example 217

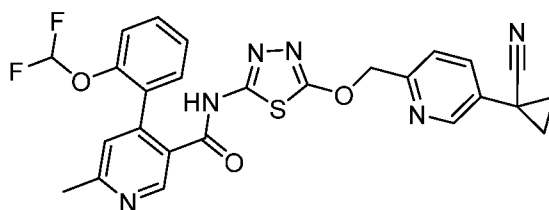
Synthesis of N-(5-((5-(1-cyanocyclopropyl)pyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-fluoro-6-methoxyphenyl)-6-methylnicotinamide



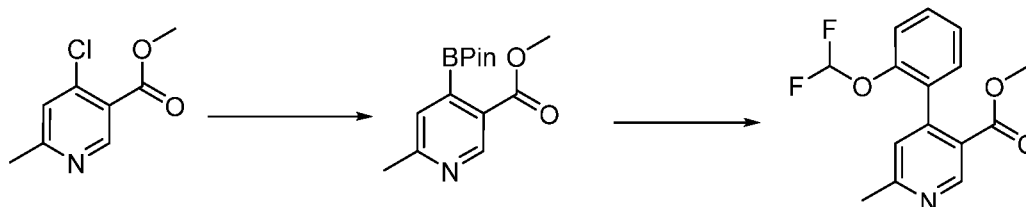
[0682] The title compound was prepared using General Procedures E, F and A. For General Procedure E, methyl 4-chloro-6-methylpyridine-3-carboxylate and 2-fluoro-6-methoxyphenylboronic acid were employed. For General Procedure A, 1-(6-[[5-(5-amino-1,3,4-thiadiazol-2-yl)oxy]methyl]pyridin-3-yl)cyclopropane-1-carbonitrile (Example 220, Step 5) was used. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 12.83 (s, 1H), 8.81 (s, 1H), 8.59 (s, 1H), 7.82 – 7.81 (m, 1H), 7.57 – 7.55 (m, 1H), 7.41 – 7.39 (m, 1H), 7.32 (s, 1H), 6.91 – 6.88 (m, 2H), 5.54 (s, 2H), 3.59 (s, 3H), 2.57 (s, 3H), 1.86 – 1.74 (m, 2H), 1.71 – 1.59 (m, 2H). m/z 517.1 $[\text{M}+\text{H}^+]$.

Example 218

Synthesis of N-(5-[[5-(1-cyanocyclopropyl)pyridin-2-yl]methoxy]-1,3,4-thiadiazol-2-yl)-4-[2-(difluoromethoxy)phenyl]-6-methylpyridine-3-carboxamide



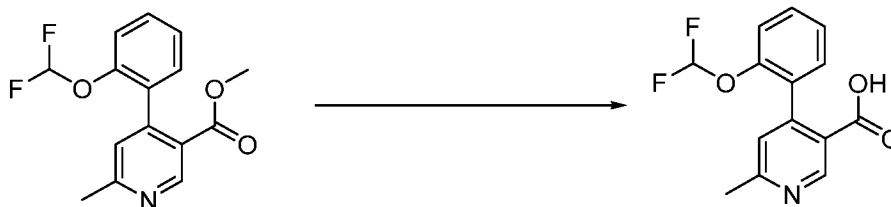
Step-1 & Step-2: Synthesis of methyl 4-(2-(difluoromethoxy)phenyl)-6-methylnicotinate



[0683] To a degassed solution of methyl 4-chloro-6-methylpyridine-3-carboxylate (2.0 g, 10.7 mmol) and B_2Pin_2 (5.45 g, 21.5 mmol) and AcOK (3.17 g, 32.3 mmol) in dioxane (10 mL) was added $\text{Pd}(\text{dppf})\text{Cl}_2$ (2.37 g, 3.23 mmol) under nitrogen. The resulting solution was stirred at 80 $^\circ\text{C}$ for 3 hours under nitrogen atmosphere. Then 1-bromo-2-(difluoromethoxy)benzene (724 mg, 3.24 mmol), K_2CO_3 (1.34 g, 9.74 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (712 mg, 0.974 mmol) and water (1.0 mL)

was added to the above mixture. The resulting mixture was stirred at 80 °C for 16 h under nitrogen. The solids were filtered out and the filtrate was concentrated under vacuum. The residue was purified by reverse phase flash column chromatography with 5%-50% acetonitrile in water to afford the title compound (850 mg, 90%) as a white solid.

Step-3: Synthesis of 4-[2-(difluoromethoxy)phenyl]-6-methylpyridine-3-carboxylic acid



[0684] A mixture of 4-[2-(difluoromethoxy)phenyl]-6-methylpyridine-3-carboxylate (850 mg, 2.89 mmol) and NaOH (463 mg, 11.5 mmol) in H₂O (1.0 mL) and THF (5.0 mL). The resulting solution was stirred at 50 °C for 16 h. The reaction mixture was acidified with HCl (1 N) to pH 1~2, and then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by reverse phase flash column chromatography with 5-50% acetonitrile in water to afford the title compound (290 mg, 32%) as a white solid.

Step-4: Synthesis of *N*-(5-[[5-(1-cyanocyclopropyl)pyridin-2-yl]methoxy]-1,3,4-thiadiazol-2-yl)-4-[2-(difluoromethoxy)phenyl]-6-methylpyridine-3-carboxamide

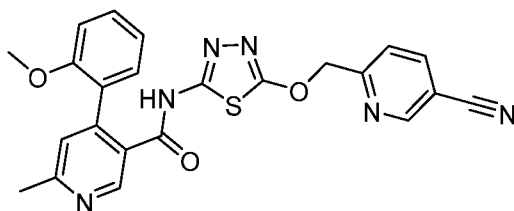


[0685] To a solution of 4-[2-(difluoromethoxy)phenyl]-6-methylpyridine-3-carboxylic acid (100 mg, 0.358 mmol) in DMF (1.5 mL) was added HATU (204 mg, 0.573 mmol), DIEA (138 mg, 1.07 mmol) and 1-(6-[[[(5-amino-1,3,4-thiadiazol-2-yl)oxy]methyl]pyridin-3-yl]cyclopropane-1-carbonitrile (Example 220, Step 5, 97 mg, 0.358 mmol). The resulting mixture was stirred at 50 °C for 16 h. The residue was purified by reverse phase flash column chromatography with 5-30% acetonitrile in water to afford the title compound (29.3 mg, 15%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.95 (s, 1H), 8.83 (s, 1H), 8.59 (d, *J* = 2.4 Hz, 1H), 7.80 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.52 – 7.43 (m, 1H), 7.41 – 7.26 (m,

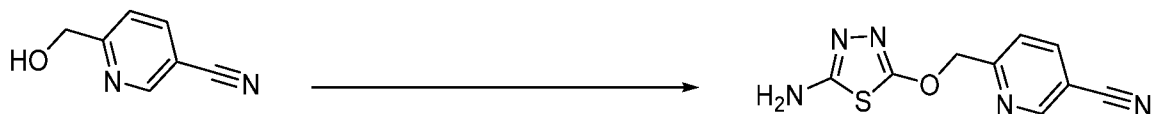
3H), 7.24 – 7.15 (m, 1H), 5.52 (s, 2H), 2.56 (s, 3H), 1.85 – 1.77 (m, 2H), 1.66 – 1.58 (m, 2H).
 m/z 535.1 $[M+H]^+$.

Example 219

Synthesis of N-(5-((5-cyanopyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)-6-methylnicotinamide



Step-1: Synthesis of 6-(((5-amino-1,3,4-thiadiazol-2-yl)oxy)methyl)nicotinonitrile



[0686] To a stirred mixture of 6-(hydroxymethyl)nicotinonitrile (500 mg, 3.72 mmol) in THF (5.0 mL) was added NaH (298 mg, 7.45 mmol, 60%) in portions at 0~5 °C. The resulting mixture was stirred at the same temperature for 1 h under nitrogen atmosphere. To the above mixture was added 5-bromo-1,3,4-thiadiazol-2-amine (805 mg, 4.47 mmol) in portions at 0 °C. The resulting mixture was stirred for additional 4 h at 0~5 °C. The reaction was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by reverse phase flash chromatography with 5~35% acetonitrile in water to afford the title compound (130 mg, 14%) as an orange solid.

Step-2: Synthesis of N-(5-((5-cyanopyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)-6-methylnicotinamide

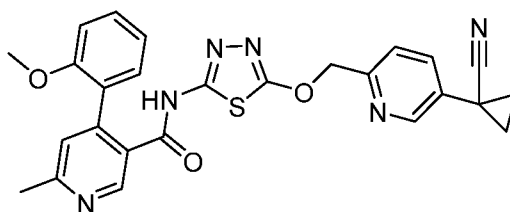


[0687] To a stirred mixture of 4-(2-methoxyphenyl)-6-methylpyridine-3-carboxylic acid (Example 113, Step 2, 187 mg, 0.77 mmol) in DMF (4.0 mL) were added HATU (391 mg, 1.02

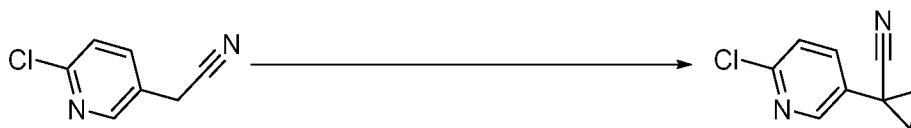
mmol). The resulting mixture was stirred for 5 min at room temperature. To the above mixture were added 6-(((5-amino-1,3,4-thiadiazol-2-yl)oxy)methyl)nicotinonitrile (120 mg, 0.51 mmol) and DIEA (199 mg, 1.54 mmol). The resulting mixture was stirred at room temperature for 16 h. The resulting mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography with 20~90% ethyl acetate in petroleum ether. The product was washed with MeOH and dried under vacuum to afford the title compound (60 mg, 24%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 12.77 (s, 1H), 9.04 (s, 1H), 8.65 (s, 1H), 8.38 – 8.36 (m, 1H), 7.72 (d, $J = 8.0$ Hz, 1H), 7.41 – 7.34 (m, 2H), 7.30 (s, 1H), 7.09 – 7.05 (m, 1H), 6.98 (d, $J = 8.0$ Hz, 1H), 5.64 (s, 2H), 3.50 (s, 3H), 3.15 (s, 3H). m/z 459.1 $[\text{M}+\text{H}^+]$.

Example 220

Synthesis of N-(5-[[5-(1-cyanocyclopropyl)pyridin-2-yl]methoxy]-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide

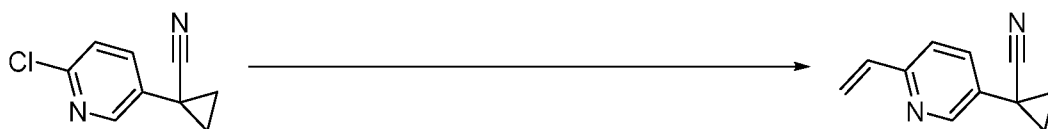


Step-1: Synthesis of 1-(6-chloropyridin-3-yl)cyclopropane-1-carbonitrile



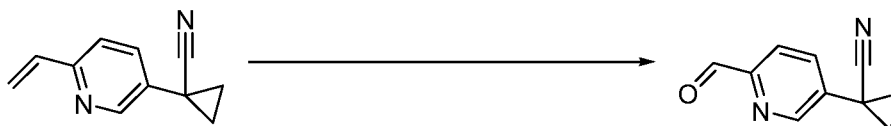
[0688] To a solution of NaOH (100 g) in H_2O (100 mL) were added 2-(6-chloropyridin-3-yl)acetonitrile (20 g, 131.079 mmol) and dibromoethane (27 g, 142 mmol). The mixture was stirred at 50 °C for 16 hours. The resulting mixture was extracted with ethyl acetate. The combined organic layers was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~50% ethyl acetate in petroleum ether to afford the title compound (18 g, 77%) as a yellow solid.

Step-2: Synthesis of 1-(6-vinylpyridin-3-yl)cyclopropane-1-carbonitrile



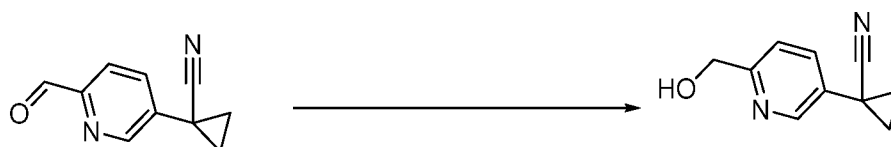
[0689] To a solution of ethenyltrifluoro-lambda4-borane potassium (11.5 g, 0.084 mmol) in dioxane (100 mL) and H₂O (20 mL) were added 1-(6-chloropyridin-3-yl)cyclopropane-1-carbonitrile (10 g, 55 mmol), K₂CO₃ (23.2 g, 0.168 mmol) and Pd(dppf)Cl₂ (4.1 g, 5.4 mmol). The resulting mixture was stirred at 80 °C for 12 hours under nitrogen. The resulting mixture was extracted with ethyl acetate. The combined organic layers was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~50% ethyl acetate in petroleum ether to afford the title compound (6.84 g, 72%) as a yellow solid.

Step-3: Synthesis of 1-(6-formylpyridin-3-yl)cyclopropane-1-carbonitrile



[0690] To a solution of 1-(6-ethenylpyridin-3-yl)cyclopropane-1-carbonitrile (6.84 g, 40.1 mmol) in THF (120 mL) and H₂O (40 mL) were added OsO₄ (1.02 g, 4.01 mmol) and NaIO₄ (34.5 g, 160 mmol). The resulting mixture was stirred at room temperature for 16 h. The resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~50% ethyl acetate in petroleum ether to afford the title compound (2.11 g, 40%) as a yellow solid.

Step-4: Synthesis of 1-(6-(hydroxymethyl)pyridin-3-yl)cyclopropane-1-carbonitrile



[0691] To a solution of 1-(6-formylpyridin-3-yl)cyclopropane-1-carbonitrile (2.12 g, 12.2 mmol) in MeOH (20 mL) was added NaBH₄ (0.46 g, 12.254 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h. The reaction was then quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over

anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford the title compound (1.11 g, 70%) as a yellow solid.

Step-5: Synthesis of 1-(6-(((5-amino-1,3,4-thiadiazol-2-yl)oxy)methyl)pyridin-3-yl)cyclopropane-1-carbonitrile



[0692] To a solution of NaH (0.73 g, 17.5 mmol, 60%) in THF (10 mL) was added 1-[6-(hydroxymethyl)pyridin-3-yl]cyclopropane-1-carbonitrile (2.11 g, 12.1 mmol) in portions at 0~5 °C and stirred at 5 °C for 1 h. Then 5-bromo-1,3,4-thiadiazol-2-amine (2.62 g, 14.5 mmol,) was added to the mixture in small portions at 5 °C and stirred at 5 °C for 5 h. The reaction mixture was then quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~10% methanol in dichloromethane to afford the title compound (1.11 g, 33%) as a white solid.

Step-6: Synthesis of N-(5-((5-(1-cyanocyclopropyl)pyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-4-(2-methoxyphenyl)-6-methylnicotinamide

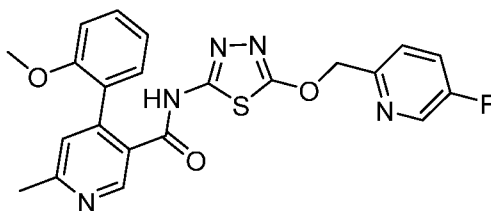


[0693] To a solution 1-(6-[[5-(5-amino-1,3,4-thiadiazol-2-yl)oxy]methyl]pyridin-3-yl)cyclopropane-1-carbonitrile (Example 220, Step 5, 200 mg, 0.732 mmol) in DMF (10 mL) were added HATU (418 mg, 1.09 mmol), DIEA (283 mg, 2.19 mmol) and 4-(2-methoxyphenyl)-6-methylpyridine-3-carboxylic acid (Example 113, Step 2, 178 mg, 0.732 mmol). The mixture was stirred at room temperature for 2 hours. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~10% methanol in dichloromethane. The product was further purified by washed with methanol and dried under vacuum to afford the title compound (50 mg, 13%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.75 (s, 1H), 8.66 (s, 1H), 8.59 (s,

1H), 7.83 – 7.80 (m, 1H), 7.58 – 7.56 (m, 1H), 7.41 – 7.30 (m, 3H), 7.09 – 7.05 (m, 1H), 6.99 – 6.97 (m, 1H), 5.54 (s, 2H), 3.57 (s, 3H), 2.67 (s, 3H), 1.84 – 1.80 (m, 2H), 1.64 – 1.61 (m, 2H). m/z 499.2 [M+H⁺].

Example 221

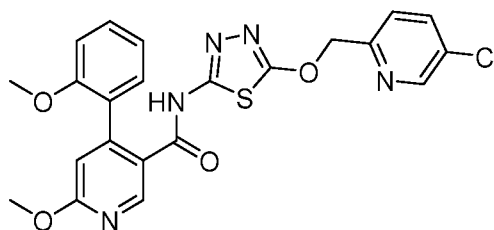
Synthesis of N-[5-[(5-fluoropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-4-(2-methoxyphenyl)-6-methylpyridine-3-carboxamide



[0694] The title compound was prepared using procedures from Example 219. For Step 1, (5-fluoropyridin-2-yl)methanol was used. For Step 2, -(2-methoxyphenyl)-6-methylpyridine-3-carboxylic acid (Example 113, Step 2) was used. ¹H NMR (400 MHz, CD₃OD): δ 8.66 (s, 1H), 8.50 (t, *J* = 1.8 Hz, 1H), 7.73 – 7.66 (m, 2H), 7.47 – 7.36 (m, 3H), 7.11 (td, *J* = 7.6, 1.2 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 5.56 (s, 2H), 3.62 (s, 3H), 2.66 (s, 3H). m/z 452.1 [M+H⁺].

Example 222

Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-6-methoxy-4-(2-methoxyphenyl)nicotinamide

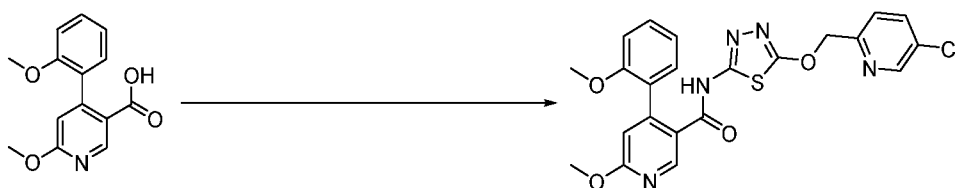


Step 1. Synthesis of 6-methoxy-4-(2-methoxyphenyl)nicotinic acid



[0695] To a solution of benzyl 6-chloro-4-(2-methoxyphenyl)nicotinate (1.0 g, 2.82 mmol) in MeOH (10.0 mL) was added NaOMe (763.4 mg, 14.1 mmol). The resulting mixture was stirred at 70 °C for 16 h. The resulting mixture was concentrated under vacuum. The residue was dissolved in tetrahydrofuran (5 mL) and H₂O (5 mL) and added NaOH (565 mg, 14.1 mmol) at room temperature. The resulting mixture was stirred for additional 2 h at room temperature. The reaction mixture was diluted with water and acidified to pH ~3 with HCl (1 N), the mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with 0~60% acetonitrile in water to afford the title compound (880 mg, 82%) as an off-white solid.

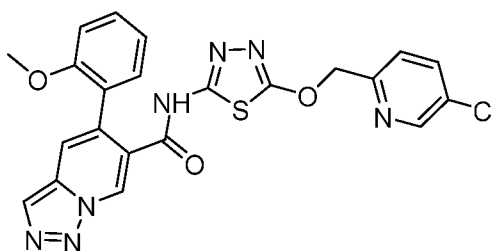
Step 2. Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-6-methoxy-4-(2-methoxyphenyl)nicotinamide



[0696] The title compound was prepared using General Procedures A employing 6-methoxy-4-(2-methoxyphenyl)nicotinic acid and 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C). ¹H NMR (400 MHz, DMSO-d₆): δ 12.67 (s, 1H), 8.65 (d, J = 2.4 Hz, 1H), 8.45 (s, 1H), 8.01 – 7.99 (m, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.41 – 7.33 (m, 2H), 7.07 – 7.04 (m, 1H), 6.98 – 6.96 (d, J = 0.8 Hz, 1H), 6.80 (s, 1H), 5.54 (s, 2H), 3.95 (s, 3H), 3.51 (s, 3H). m/z 484.0 [M+H⁺].

Example 223

Synthesis of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-5-(2-methoxyphenyl)-[1,2,3]triazolo[1,5-a]pyridine-6-carboxamide



Step-1: Synthesis of ethyl 4-chloro-6-methanehydrazonoylpyridine-3-carboxylate



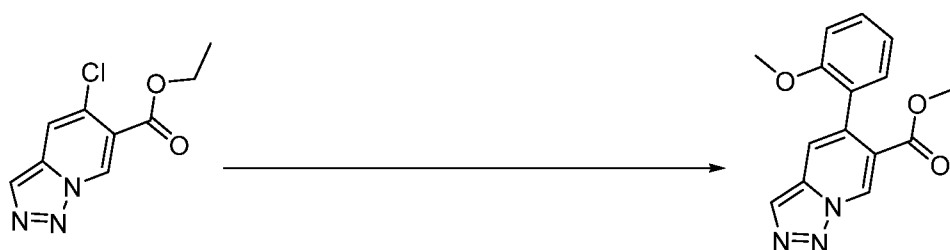
[0697] To a solution of ethyl 4-chloro-6-formylpyridine-3-carboxylate (600 mg, 2.80 mmol) in EtOH (10 mL) were added $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (421 mg, 8.42 mmol). The resulting mixture was stirred for 1h at room temperature under nitrogen atmosphere. The resulting mixture was quenched with water and extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under vacuum to afford the title compound (450 mg, 37%) as a yellow solid.

Step-2: Synthesis of ethyl 5-chloro-[1,2,3]triazolo[1,5-a]pyridine-6-carboxylate



[0698] To a stirred solution of ethyl 4-chloro-6-methanehydrazonoylpyridine-3-carboxylate (450 mg, 1.97 mmol) in DCM (5 mL) was added $\text{PhI}(\text{OAc})_2$ (700 mg, 2.17 mmol) in portions. The resulting mixture was stirred at room temperature for overnight. The reaction mixture was quenched with saturated NaHCO_3 aqueous solution and extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography with 0-45% ethyl acetate in petroleum ether to afford the title compound (310 mg, 69%) as a yellow solid.

Step-3: Synthesis of ethyl 5-(2-methoxyphenyl)-[1,2,3]triazolo[1,5-a]pyridine-6-carboxylate



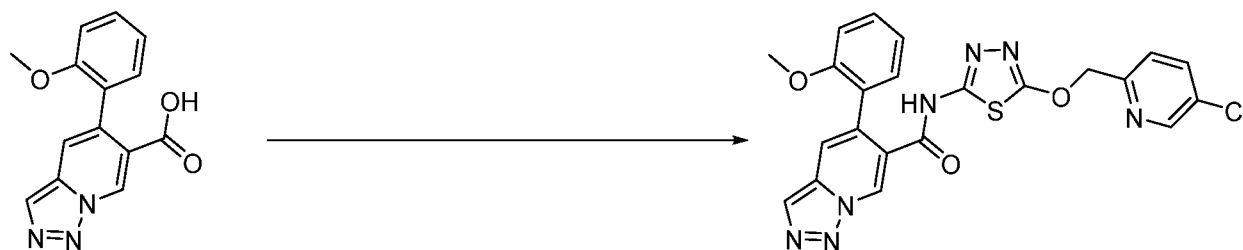
[0699] To a mixture of ethyl 5-chloro-[1,2,3]triazolo[1,5-a]pyridine-6-carboxylate (150 mg, 0.665 mmol) and 2-methoxyphenylboronic acid (151 mg, 0.997 mmol) in dioxane (2 mL) and H₂O (0.40 mL) were added K₂CO₃ (275 mg, 1.994 mmol) and Pd(PPh₃)₄ (76 mg, 0.066 mmol) under nitrogen atmosphere. The resulting mixture was stirred at 80 °C for 2 h under nitrogen atmosphere. After filtered, the filtrate was collected and concentrated under vacuum. The residue was purified by reverse phase flash column chromatography with 5~30% acetonitrile in water to afford the title compound (100 mg, 51%) as a white solid.

Step-4: Synthesis of 5-(2-methoxyphenyl)-[1,2,3]triazolo[1,5-a]pyridine-6-carboxylic acid



[0700] To a mixture of ethyl 5-(2-methoxyphenyl)-[1,2,3]triazolo[1,5-a]pyridine-6-carboxylate (100 mg, 0.336 mmol) in THF (1.0 mL) and H₂O (1.0 mL) was added NaOH (54 mg, 1.34 mmol). The resulting mixture was stirred at 80 °C for 2 h. The aqueous solution was acidified with HCl (1 N) to pH 1~2. The residue was purified by reverse phase flash column chromatography with 5~40% acetonitrile in water to afford the title compound (54 mg, 59%) as a pink solid.

Step-5: Synthesis of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-5-(2-methoxyphenyl)-[1,2,3]triazolo[1,5-a]pyridine-6-carboxamide

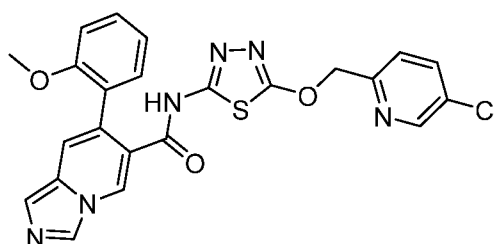


[0701] To a mixture of 5-(2-methoxyphenyl)-[1,2,3]triazolo[1,5-a]pyridine-6-carboxylic acid (20 mg, 0.074 mmol), TCFH (27 mg, 0.097 mmol) and NMI (21 mg, 0.260 mmol) in MeCN (1.00 mL) was added 5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-amine (Intermediate C, 23 mg, 0.097 mmol) under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 1 h under nitrogen atmosphere. The residue was purified by reverse phase flash

column chromatography with 5~60% acetonitrile in water to afford the title compound (7.2 mg, 20%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 13.01 (s, 1H), 9.50 (s, 1H), 8.66 (d, J = 2.4 Hz, 1H), 8.29 (s, 1H), 8.05 – 7.98 (m, 1H), 7.94 (s, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.46 – 7.36 (m, 2H), 7.13 – 7.05 (m, 1H), 6.98 (d, J = 8.0 Hz, 1H), 5.56 (s, 2H), 3.51 (s, 3H). m/z 494.0 $[\text{M}+\text{H}^+]$.

Example 224

Synthesis of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-7-(2-methoxyphenyl)imidazo[1,5-a]pyridine-6-carboxamide

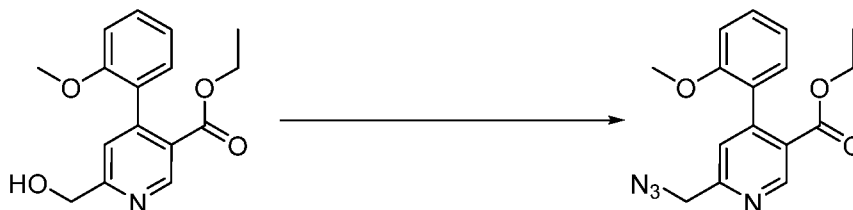


Step-1: Synthesis of ethyl 6-(hydroxymethyl)-4-(2-methoxyphenyl)pyridine-3-carboxylate



[0702] To a stirred mixture of ethyl 4-chloro-6-(hydroxymethyl)pyridine-3-carboxylate (2.0 g, 9.27 mmol), 2-methoxyphenylboronic acid (1.7 g, 11.1 mmol) and K_2CO_3 (2.56 g, 18.5 mmol) in dioxane (20 mL) and H_2O (4.0 mL) was added $\text{Pd}(\text{dppf})\text{Cl}_2$ (680 mg, 0.928 mmol) under nitrogen. The resulting mixture was stirred at 80 °C for 2 hours under nitrogen atmosphere. The residue was purified by reverse phase flash column chromatography with 5~50% acetonitrile in water to afford the title compound (2.19 g, 70%) as a light yellow oil.

Step-2: Synthesis of ethyl 6-(azidomethyl)-4-(2-methoxyphenyl)pyridine-3-carboxylate



[0703] To a mixture of ethyl 6-(hydroxymethyl)-4-(2-methoxyphenyl)pyridine-3-carboxylate (1.5 g, 5.22 mmol) in THF (10 mL) were added DPPA (1.7 g, 6.26 mmol) and DBU (955 mg, 6.26 mmol) sequentially at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for overnight under nitrogen atmosphere. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by reverse phase flash column chromatography with 5~40% acetonitrile in water to afford the title compound (1.2 g, 74%) as a yellow oil.

Step-3: Synthesis of ethyl 6-(aminomethyl)-4-(2-methoxyphenyl)pyridine-3-carboxylate



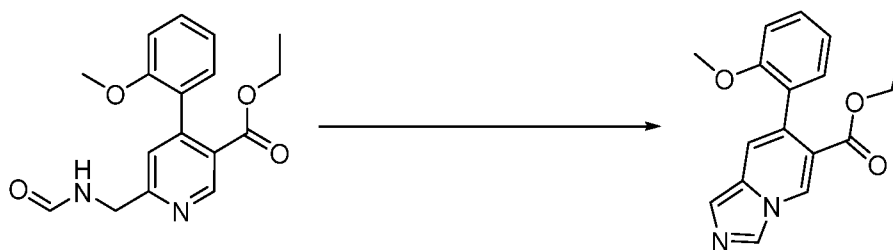
[0704] To a mixture of ethyl 6-(azidomethyl)-4-(2-methoxyphenyl)pyridine-3-carboxylate (1.2g, 3.84 mmol) in ethanol (10 mL) were added Pd/C (150 mg, 1.41 mmol) under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature under hydrogen atmosphere. The suspension was filtered. The filtrate was collected and concentrated under vacuum to afford the title compound (1.2 g, crude) as a yellow oil.

Step-4: Synthesis of ethyl 6-(formamidomethyl)-4-(2-methoxyphenyl)pyridine-3-carboxylate



[0705] To a mixture of ethyl 6-(aminomethyl)-4-(2-methoxyphenyl)pyridine-3-carboxylate (300 mg, 1.04 mmol) in THF (4 mL) was added acetyl formate (184 mg, 2.09 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 1 h. The resulting mixture was concentrated under reduced pressure to afford the title compound (290 mg, 88%) as a yellow solid.

Step-5: Synthesis of ethyl 7-(2-methoxyphenyl)imidazo[1,5-a]pyridine-6-carboxylate



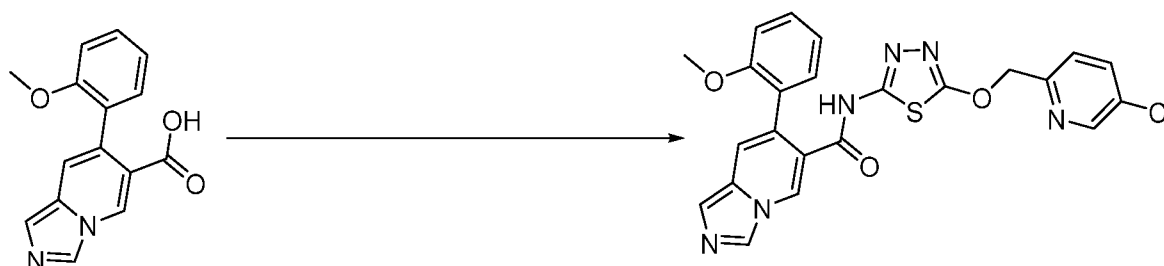
[0706] To a mixture of ethyl 6-(formamidomethyl)-4-(2-methoxyphenyl)pyridine-3-carboxylate (270 mg, 0.859 mmol) in Toluene (5 mL) was added POCl_3 (263 mg, 1.71 mmol). The resulting mixture was stirred at 100 °C for 2 hours before concentrated under vacuum. The residue was basified with $\text{NH}_3\cdot\text{H}_2\text{O}$ to pH 9~10 and purified by reverse phase flash column chromatography with 5~50% acetonitrile in water to afford the title compound (113 mg, 44%) as a yellow oil.

Step-6: Synthesis of 7-(2-methoxyphenyl)imidazo[1,5-a]pyridine-6-carboxylic acid



[0707] To a mixture of ethyl 7-(2-methoxyphenyl)imidazo[1,5-a]pyridine-6-carboxylate (113 mg, 0.381 mmol) in THF (1.0 mL) and H_2O (1.0 mL) was added NaOH (61 mg, 1.52 mmol). The resulting mixture was stirred at 80 °C for overnight. The aqueous solution was acidified with HCl (1 N) to pH 1~2. The residue was purified by reverse phase flash column chromatography with 5~30% acetonitrile in water to afford the title compound (77 mg, 75%) as a white solid.

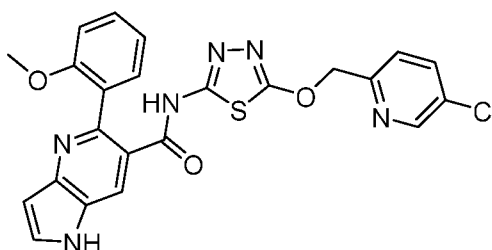
Step-7: Synthesis of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-7-(2-methoxyphenyl)imidazo[1,5-a]pyridine-6-carboxamide



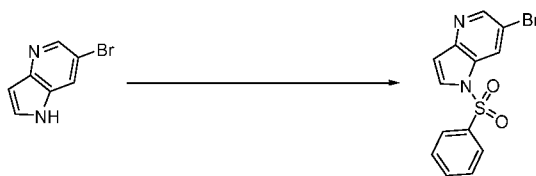
[0708] To a mixture of 7-(2-methoxyphenyl)imidazo[1,5-a]pyridine-6-carboxylic acid (60 mg, 0.224 mmol), TCFH (82 mg, 0.291 mmol), NMI (64 mg, 0.783 mmol) in MeCN (1 mL) was added 5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-amine (70 mg, 0.291 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 2 h under nitrogen atmosphere. The residue was purified by reverse phase flash column chromatography with 5~60% acetonitrile in water to afford the title compound (37.5 mg, 21%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.76 (s, 1H), 8.83 (s, 1H), 8.66 (d, *J* = 2.4 Hz, 1H), 8.53 (s, 1H), 8.05 – 7.98 (m, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.52 (s, 1H), 7.46 (s, 1H), 7.41 – 7.29 (m, 2H), 7.08 – 7.00 (m, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 5.55 (s, 2H), 3.49 (s, 3H). *m/z* 493.0 [M+H⁺].

Example 225

Synthesis of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-5-(2-methoxyphenyl)-1H-pyrrolo[3,2-b]pyridine-6-carboxamide

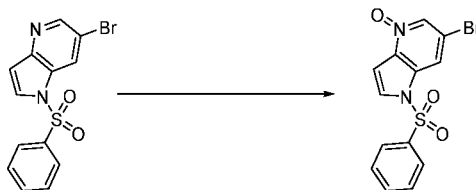


Step-1: Synthesis of 1-(benzenesulfonyl)-6-bromopyrrolo[3,2-b]pyridine



[0709] To a solution of NaH (550 mg, 22.8 mmol) in THF (30 mL) was added 6-bromo-1H-pyrrolo[3,2-b]pyridine (3.0 g, 15.2 mmol) in small portions at 0 °C. The resulting mixture was stirred at 0 °C for 15 minutes. A solution of benzenesulfonyl chloride (4.0 g, 22.8 mmol) in THF (24 mL) was then added to the above mixture dropwise at 0 °C. The resulting mixture was then stirred at room temperature for 1 hour. The resulting mixture was quenched with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum to afford the title compound (5 g, crude) as a yellow solid.

Step-2: Synthesis of 1-(benzenesulfonyl)-6-bromo-4lambda5-pyrrolo[3,2-b]pyridin-4-one



[0710] To a solution of 1-(benzenesulfonyl)-6-bromopyrrolo[3,2-b]pyridine (5.0 g, 14.8 mmol) in DCM (70 mL) was added mCPBA (3.3 g, 19.3 mmol) at 0°C. The resulting mixture was stirred at room temperature for 16 hours. The solution was washed with saturated aqueous NaHCO₃ (20 mL x 3) and extracted with ethyl acetate. The organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~15% methanol in dichloromethane to afford the title compound (3.5 g, 67%) as an off-white solid.

Step-3: Synthesis of 1-(benzenesulfonyl)-6-bromo-5-chloropyrrolo[3,2-b]pyridine



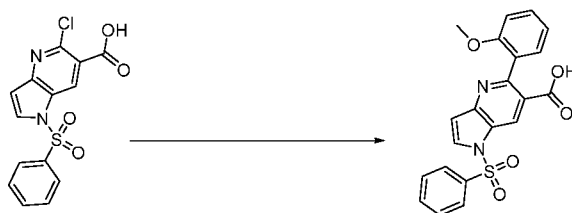
[0711] To a mixture of 1-(benzenesulfonyl)-6-bromo-4lambda5-pyrrolo[3,2-b]pyridin-4-one (3.50 g, 9.9 mmol) in toluene (20 mL) was added phosphorus oxychloride (5.0 mL). The mixture was stirred at 80 °C for 3 before concentrated under vacuum. The residue was quenched with water and extracted with ethyl acetate. The organic layers were separated, washed with saturated aqueous NaHCO₃ brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~5% methanol in dichloromethane to afford the title compound (1.8 g, 49%) as a white solid.

Step-4: Synthesis of 1-(benzenesulfonyl)-5-chloropyrrolo[3,2-b]pyridine-6-carboxylic acid



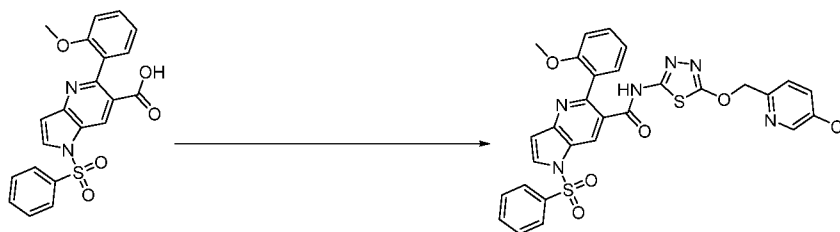
[0712] To a mixture of 1-(benzenesulfonyl)-6-bromo-5-chloropyrrolo[3,2-b]pyridine (1.2 g, 3.23 mmol) and oxalic acid hydrate (435 mg, 4.84 mmol) in DMF (5 mL) were added acetic anhydride (494 mg, 4.84 mmol), DIEA (626 mg, 4.84 mmol) and Pd(OAc)₂ (72.5 mg, 0.323 mmol). The mixture was stirred at 80 °C for 2 hours under nitrogen atmosphere. The residue was purified by reverse phase flash chromatography with 5~50% acetonitrile in water to afford the title compound (800 mg, 73%) as a yellow solid.

Step-5: Synthesis of 1-(benzenesulfonyl)-5-(2-methoxyphenyl)pyrrolo[3,2-b]pyridine-6-carboxylic acid



[0713] To a mixture of 1-(benzenesulfonyl)-5-chloropyrrolo[3,2-b]pyridine-6-carboxylic acid (800 mg, 2.37 mmol) and 2-methoxyphenylboronic acid (541 mg, 3.56 mmol) in dioxane (10 mL) and H₂O (2.0 mL) were added K₂CO₃ (985 mg, 7.12 mmol) and Pd(PPh₃)₄ (274 mg, 0.238 mmol). The mixture was stirred at 80 °C for 2 hours under nitrogen atmosphere. The resulting mixture was extracted with ethyl acetate. The aqueous solution was acidified to pH 2 with citric acid and then concentrated. The residue was purified by reverse phase flash chromatography with 5~50% acetonitrile in water to afford the title compound (40 mg, 64%) as a yellow solid.

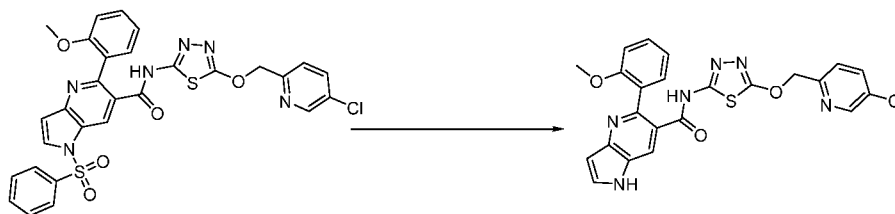
Step-6: Synthesis of 1-(benzenesulfonyl)-N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-5-(2-methoxyphenyl)pyrrolo[3,2-b]pyridine-6-carboxamide



[0714] To a solution of 1-(benzenesulfonyl)-5-(2-methoxyphenyl)pyrrolo[3,2-b]pyridine-6-carboxylic acid (40 mg, 0.098 mmol) and 5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-amine (Intermediate C, 30.9 mg, 0.127 mmol) in MeCN (0.50 mL) and DMF (0.50 mL) were added TCFH (35.7 mg, 0.127 mmol) and NMI (40.2 mg, 0.490 mmol). The resulting mixture was stirred at room temperature for 1 hour under nitrogen atmosphere. The resulting mixture was

quenched with water and the aqueous phase was extracted with ethyl acetate. The combined organic solution was dried over sodium sulfate, filtered, and concentrated under vacuum to afford the title compound (40 mg, crude) as a yellow solid.

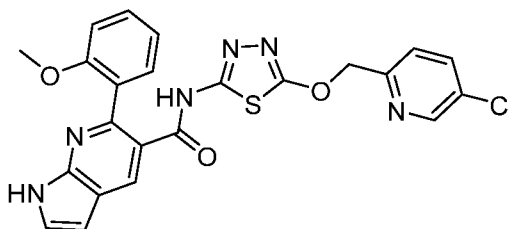
Step-7: Synthesis of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-5-(2-methoxyphenyl)-1H-pyrrolo[3,2-b]pyridine-6-carboxamide



[0715] To a mixture of 1-(benzenesulfonyl)-N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-5-(2-methoxyphenyl)pyrrolo[3,2-b]pyridine-6-carboxamide (40.00 mg, 0.063 mmol) in MeOH (1.00 mL) was added NaOH (2 M, 1mL). The resulting mixture was stirred at 50 °C for 30 minutes. The residue was acidified to pH 2 with citric acid. The residue was purified by reverse phase flash chromatography with 5~50% acetonitrile in water to afford the title compound (9.3 mg, 29%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.55 (s, 1H), 11.70 (s, 1H), 8.66 (d, *J* = 2.4 Hz, 1H), 8.07 (s, 1H), 8.05 – 7.98 (m, 1H), 7.84 (t, *J* = 2.8 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.56 – 7.49 (m, 1H), 7.37 – 7.29 (m, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.66 (d, *J* = 3.2 Hz, 1H), 5.54 (s, 2H), 3.49 (s, 3H). *m/z* 493.0 [M+H⁺].

Example 226

Synthesis of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-6-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridine-5-carboxamide



Step-1: Synthesis of 1-(benzenesulfonyl)-5-bromo-6-chloropyrrolo[2,3-b]pyridine



[0716] To a solution of NaH (54.4 mg, 2.26 mmol) in THF (3.0 mL) was added 5-bromo-6-chloro-1H-pyrrolo[2,3-b]pyridine (350 mg, 1.51 mmol) in small portions at 0 °C. The resulting mixture was stirred at 0 °C for 15 minutes. A solution of benzenesulfonyl chloride (400 mg, 2.26 mmol) in THF (3.0 mL) was then added to the above mixture dropwise at 0 °C. The resulting mixture was then stirred at room temperature for 1 hour under nitrogen. The resulting mixture was quenched with water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with 0~20% ethyl acetate in petroleum ether to afford the title compound (500 mg, 88%) as a white solid.

Step-2: Synthesis of 1-(benzenesulfonyl)-6-chloropyrrolo[2,3-b]pyridine-5-carboxylic acid



[0717] To a mixture of 1-(benzenesulfonyl)-5-bromo-6-chloropyrrolo[2,3-b]pyridine (450 mg, 1.21 mmol) in DMF (3.0 mL) were added acetic anhydride (165 mg, 1.81 mmol), DIEA (234 mg, 1.81 mmol) XantPhos (70.1 mg, 1.21 mmol) and Pd(OAc)₂ (27.2 mg, 1.21 mmol). The mixture was stirred at 80 °C for 2 hours under nitrogen atmosphere. The residue was purified by reverse phase flash chromatography with 5~70% acetonitrile in water to afford the title compound (120 mg, 29%) as a white solid.

Step-3: Synthesis of 1-(benzenesulfonyl)-6-(2-methoxyphenyl)pyrrolo[2,3-b]pyridine-5-carboxylic acid



[0718] To a mixture of 1-(benzenesulfonyl)-6-chloropyrrolo[2,3-b]pyridine-5-carboxylic acid (120.0 mg, 0.356 mmol) and 2-methoxyphenylboronic acid (81.2 mg, 0.535 mmol) in dioxane (2.00 mL) and H₂O (0.40 mL) were added K₂CO₃ (147.7 mg, 1.069 mmol) and Pd(PPh₃)₄ (41.2 mg, 0.036 mmol). The mixture was stirred at 80 °C for 2 hours under nitrogen atmosphere. The resulting mixture was extracted with ethyl acetate. The aqueous solution was acidified to pH 2

with citric acid and then concentrated. The residue was purified by reverse phase flash chromatography with 5~50% acetonitrile in water to afford the title compound (40 mg, 27%) as a yellow solid.

Step-4: Synthesis of 1-(benzenesulfonyl)-N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-6-(2-methoxyphenyl)pyrrolo[2,3-b]pyridine-5-carboxamide



[0719] To a solution of 1-(benzenesulfonyl)-6-(2-methoxyphenyl)pyrrolo[2,3-b]pyridine-5-carboxylic acid (30 mg, 0.073 mmol) and 5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-amine (Intermediate C, 23 mg, 0.095 mmol) in MeCN (0.50 mL) and DMF (0.50 mL) were added TCFH (26.8 mg, 0.095 mmol) and NMI (30.2 mg, 0.367 mmol). The resulting mixture was stirred for 1 hour at room temperature under nitrogen atmosphere. The resulting mixture was quenched with water and the aqueous phase was extracted with ethyl acetate. The combined organic solution was dried over sodium sulfate, filtered, and concentrated under vacuum to afford the title compound (30 mg, 641%) as a yellow solid.

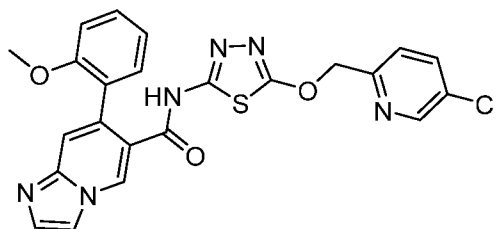
Step-5: Synthesis of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-6-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridine-5-carboxamide



[0720] To a solution of 1-(benzenesulfonyl)-N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-6-(2-methoxyphenyl)pyrrolo[2,3-b]pyridine-5-carboxamide (30 mg, 0.047 mmol) in MeOH (1.0 mL) was added NaOH (2 M, 0.75 mL). The resulting mixture was stirred at 50 °C for 30 minutes. The residue was acidified to pH 2 with citric acid. The residue was purified by reverse phase flash chromatography with 5~50% acetonitrile in water to afford the title compound (8.8 mg, 37%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.72 (s, 1H), 8.64 (d, *J* = 2.4 Hz, 1H), 8.40 – 8.31 (m, 1H), 8.07 – 7.91 (m, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.51 (s, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.33 – 7.23 (m, 1H), 7.01 – 6.93 (m, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.53 (d, *J* = 3.2 Hz, 1H), 5.45 (s, 2H), 3.48 (s, 3H). *m/z* 493.1 [M+H⁺].

Example 227

Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-7-(2-methoxyphenyl)imidazo[1,2-a]pyridine-6-carboxamide



Step-1: Synthesis of ethyl 6-chloro-4-(2-methoxyphenyl)nicotinate



[0721] To a degassed solution of ethyl 4,6-dichloronicotinate (5.0 g, 22.8 mmol) in dioxane (50 mL) and H₂O (10 mL) were added K₂CO₃ (9.4 g, 68.4 mmol) and Pd(dtbpf)Cl₂ (1.48 g, 2.28 mmol) at room temperature under nitrogen. The mixture was stirred at 80 °C for 5 hours under nitrogen before concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~50% ethyl acetate in petroleum ether to afford the title compound (3.34 g, 50%) as a yellow oil.

Step-2: Synthesis of ethyl 6-((diphenylmethylene)amino)-4-(2-methoxyphenyl)nicotinate



[0722] To a degassed solution of ethyl 6-chloro-4-(2-methoxyphenyl)nicotinate (1.0 g, 3.4 mmol) in toluene (10 mL) were added diphenylmethanimine (1.24 g, 3.4 mmol), t-BuONa (500 mg, 5.1 mmol), BINAP (656 mg, 0.68 mmol) and Pd₂(dba)₃ (356 mg, 0.34 mmol) under nitrogen. The mixture was stirred at 100 °C for 5 hours under nitrogen. The mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~50% ethyl acetate in petroleum ether to afford the title compound (550 mg, 36%) as a yellow solid.

Step-3: Synthesis of ethyl 6-amino-4-(2-methoxyphenyl)nicotinate



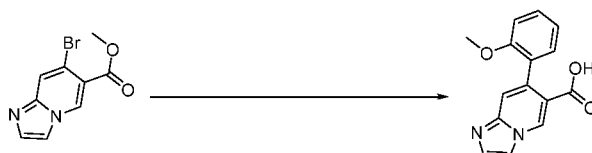
[0723] To a solution of ethyl 6-((diphenylmethylene)amino)-4-(2-methoxyphenyl)nicotinate (550 mg, 1.26 mmol) in MeOH (2 mL) was added $\text{H}_2\text{NOH}\cdot\text{HCl}$ (175 mg, 2.52 mmol) and KOAc (371 mg, 3.78 mmol). The mixture was stirred at room temperature for 2 hours. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford the title compound (400 mg, 45%) as a yellow solid.

Step-4: Synthesis of methyl 7-bromoimidazo[1,2-a]pyridine-6-carboxylate



[0724] To a solution of ethyl 6-amino-4-(2-methoxyphenyl)nicotinate (400 mg, 1.46 mmol) in EtOH (2.0 mL) was added NaHCO_3 (234 mg, 2.92 mmol) and 2-chloroacetaldehyde (497 mg, 6.5 mmol). The mixture was stirred at 80 °C for overnight. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~50% ethyl acetate in petroleum ether to afford the title compound (307 mg, 76%) as a yellow oil.

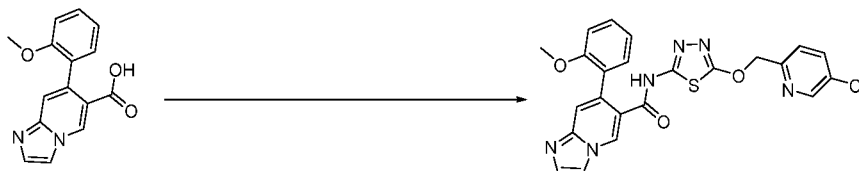
Step-5: Synthesis of 7-(2-methoxyphenyl)imidazo[1,2-a]pyridine-6-carboxylic acid



[0725] To a solution of methyl 7-bromoimidazo[1,2-a]pyridine-6-carboxylate (307 mg, 1.2 mmol) in EtOH (2.0 mL) and water (1.0 mL) was added NaOH (96 mg, 2.4 mmol). The mixture was stirred at room temperature for overnight. The aqueous solution was acidified with HCl (1 N) to PH~5. The mixture was diluted with water and extracted with ethyl acetate. The combined

organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford the title compound (245 mg, crude) as a yellow solid.

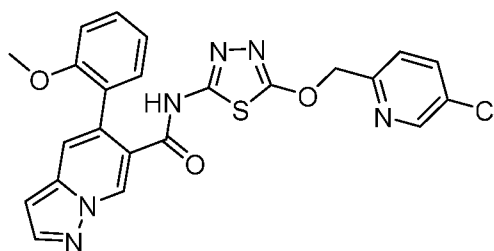
Step-6: Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-7-(2-methoxyphenyl)imidazo[1,2-a]pyridine-6-carboxamide



[0726] To a solution of 7-(2-methoxyphenyl)imidazo[1,2-a]pyridine-6-carboxylic acid (245 mg, 0.91 mmol) in DMF (2.0 mL) was added DIEA (354 mg, 2.73 mmol), HATU (520 mg, 1.35 mmol) and 5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-amine (Intermediate C, 431 mg, 0.91 mmol). The mixture was stirred at 50 °C for 12 hours. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~10% methanol in dichloromethane and further purified by prep-HPLC (column, C18 silica gel; mobile phase, water (10 mM NH_4HCO_3 +0.1% $\text{NH}_3\cdot\text{H}_2\text{O}$) and ACN) to afford the title compound (1.3 mg, 1%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 12.77 (s, 1H), 9.03 (s, 1H), 8.66 – 8.62 (m, 1H), 8.08 – 8.00 (m, 2H), 7.71 – 7.61 (m, 2H), 7.49 – 7.34 (m, 3H), 7.08 – 6.95 (m, 2H), 5.55 (s, 2H), 3.51 (s, 3H). m/z 493.0 $[\text{M}+\text{H}^+]$.

Example 228

Synthesis of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-5-(2-methoxyphenyl)pyrazolo[1,5-a]pyridine-6-carboxamide



Step-1: Synthesis of ethyl 4-(2-methoxyphenyl)pyridine-3-carboxylate



[0727] A degassed mixture of ethyl 4-chloropyridine-3-carboxylate hydrochloride (1.0 g, 4.50 mmol), 2-methoxyphenylboronic acid (1.37 g, 9.01 mmol), Pd(PPh₃)₄ (0.52 g, 0.45 mmol) and Potassium carbonate (1.24 g, 9.01 mmol) in dioxane (40.0 mL) and Water (8.0 mL) was stirred at 80 °C for 2 h under nitrogen atmosphere. The reaction mixture was quenched with water and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with acetate ethyl in petroleum ether (0~30%) to afford the title compound (900 mg, 77%) as a yellow oil.

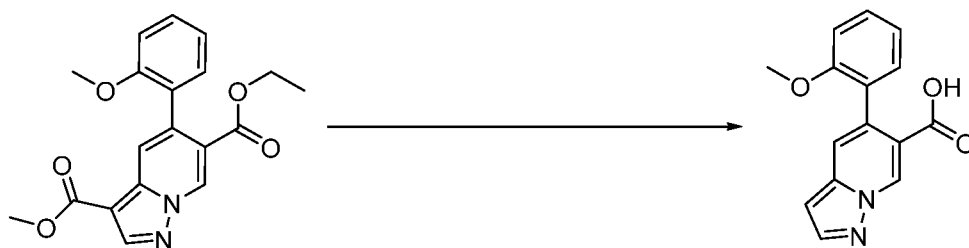
Step-2: Synthesis of 6-ethyl 3-methyl 5-(2-methoxyphenyl)pyrazolo[1,5-a]pyridine-3,6-dicarboxylate



[0728] To a mixture of ethyl 4-(2-methoxyphenyl)pyridine-3-carboxylate (900 mg, 3.61 mmol) in DCM (20 mL) amino 2,4,6-trimethylbenzenesulfonate (1.16 g, 5.42 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 18 h under nitrogen atmosphere before concentrated under vacuum. The resulting mixture was washed with 100 mL of Et₂O to afford 1-amino-3-(ethoxycarbonyl)-4-(2-methoxyphenyl)pyridin-1-ium (1.3.0 g, crude) as a yellow solid. To a mixture of 1-amino-3-(methoxycarbonyl)-4-(2-methoxyphenyl)pyridin-1-ium (1.30 g, 5.014 mmol) and Potassium carbonate (2.08 g, 15.0 mmol) in DMF (20 mL) was added propiolic acid methyl ester (0.63 g, 7.49 mmol) and stirred at room temperature for 18 h under nitrogen atmosphere. The reaction mixture was quenched with water and the aqueous layer was extracted with ethyl acetate. The combined organic solution was dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography,

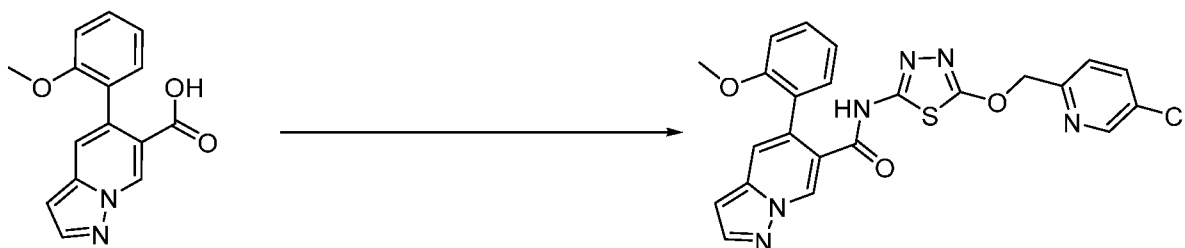
eluted with acetate ethyl in petroleum ether (0~ 35 %) to afford the title compound (200 mg, 38%) as a yellow solid.

Step-3: Synthesis of 5-(2-methoxyphenyl)pyrazolo[1,5-a]pyridine-6-carboxylic acid



[0729] A mixture of 6-ethyl 3-methyl 5-(2-methoxyphenyl)pyrazolo[1,5-a]pyridine-3,6-dicarboxylate (200 mg) in concentrated HCl (3.0 mL) was stirred at 100 °C for 2 h. The reaction mixture was diluted with water and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography with 5~33% acetonitrile in water to afford the title compound (55 mg, 27%) as a white solid.

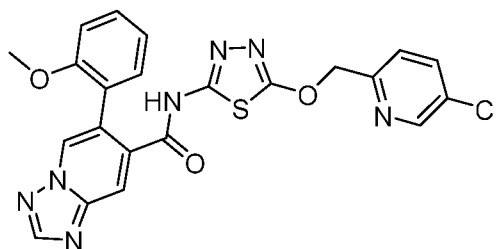
Step-4: Synthesis of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-5-(2-methoxyphenyl)pyrazolo[1,5-a]pyridine-6-carboxamide



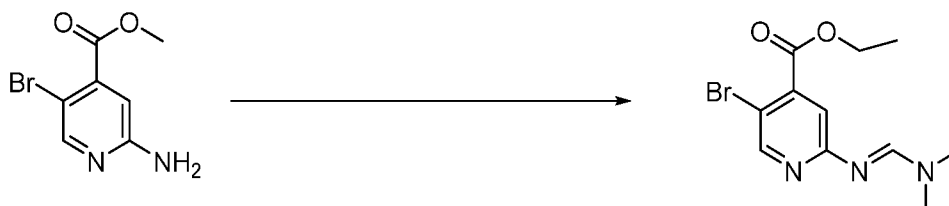
[0730] A mixture of 5-(2-methoxyphenyl)pyrazolo[1,5-a]pyridine-6-carboxylic acid (55.0 mg, 0.20 mmol), 5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-amine (Intermediate C, 59.7 mg, 0.24 mmol), TCFH (63.2 mg, 0.22 mmol), NMI (35.3 mg, 0.43 mmol) in DMF (1.0 mL) was stirred at room temperature for 2 h. The crude mixture was purified by Prep-HPLC (column, C18 silica gel; mobile phase, water (10 mM NH₄HCO₃) and ACN) to afford the title compound (36.5 mg, 36%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 12.80 (s, 1H), 9.07 (s, 1H), 8.66 (d, *J* = 2.4 Hz, 1H), 8.17 (d, *J* = 2.4 Hz, 1H), 8.01 (d, *J* = 2.4 Hz, 1H), 7.65 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.42 – 7.33 (m, 2H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.73 (d, *J* = 2.4 Hz, 1H), 5.55 (s, 2H), 3.51 (s, 3H). *m/z* 493.1 [M+H⁺].

Example 229

Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-6-(2-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyridine-7-carboxamide

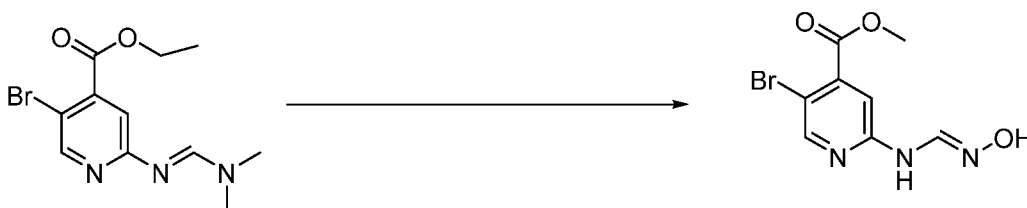


Step-1: Synthesis of ethyl (E)-5-bromo-2-(((dimethylamino)methylene)amino)isonicotinate



[0731] A mixture of methyl 2-amino-5-bromoisonicotinate (1.3 g, 5.65 mmol) in DMF-DMA (5.0 mL) and isopropanol (5.0 mL) was stirred at 80 °C for 8 hours. The mixture was concentrated under vacuum to afford the title compound (1.6 g, crude) as an off-white solid.

Step-2: Synthesis of methyl (E)-5-bromo-2-(N'-hydroxyformimidamido)isonicotinate



[0732] To a mixture of ethyl (E)-5-bromo-2-(((dimethylamino)methylene)amino)isonicotinate (1.6 g, 5.33 mmol) in isopropanol (10 mL) was added hydroxylamine hydrochloride (783 mg, 11.1 mmol). The mixture was stirred at 50 °C for 8 hours before concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~10% methanol in dichloromethane to afford the title compound (760 mg, 47%) as a yellow solid.

Step-3: Synthesis of methyl 6-bromo-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylate



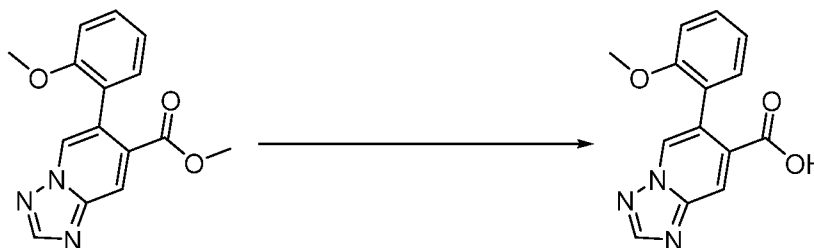
[0733] A mixture of methyl (E)-5-bromo-2-(N'-hydroxyformimidamido)isonicotinate (760 mg, 2.78 mmol) in trifluoromethanesulfonic anhydride (10 mL) and THF (10 mL) was stirred at 40 °C for 4 hours. The mixture was concentrated under vacuum and purified by flash chromatography on silica gel with 0~10% methanol in dichloromethane to afford the title compound (588 mg, 77%) as a yellow solid.

Step-4: Synthesis of methyl 6-(2-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylate



[0734] To a solution of methyl 6-bromo-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylate (588 mg, 2.30 mmol) in dioxane (10 mL) and H₂O (1 mL) were added 2-methoxyphenylboronic acid (445 mg, 2.92 mmol), K₂CO₃ (955 mg, 6.92 mmol) and Pd(dppf)Cl₂ (189 mg, 0.232 mmol) under nitrogen. The resulting solution was stirred at 80 °C for 8 hours under nitrogen before concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~50% ethyl acetate in petroleum ether to afford the title compound (483 mg, 82%) as a white solid.

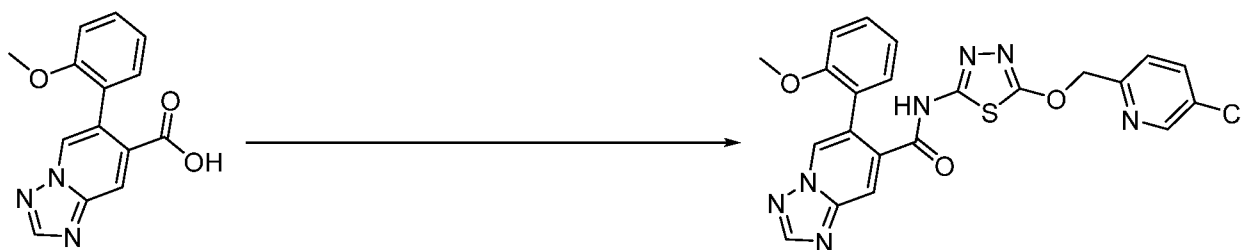
Step-5: 6-(2-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylic acid



[0735] To a solution of methyl 6-(2-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylate (483 mg, 1.70 mmol) in MeOH (5 mL) and H₂O (2.5 mL) was added NaOH (136 mg, 3.4 mmol). The mixture was stirred at 70 °C for 2 hours. The aqueous solution was acidified

with HCl (1 *N*) to pH 5~6. The aqueous solution was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum to afford the title compound (236 mg, 48%) as an off-white solid.

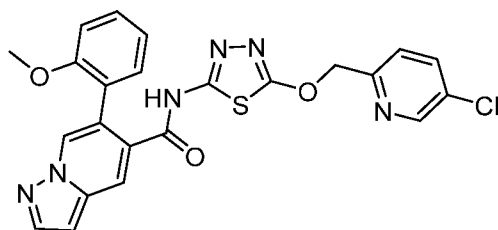
Step-6: Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-6-(2-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyridine-7-carboxamide



[0736] To a solution of 6-(2-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylic acid (236 mg, 0.874 mmol) in DMF (5.0 mL) were added DIEA (329 mg, 2.55 mmol), HATU (484 mg, 1.27 mmol) and 5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-amine (Intermediate C, 310 mg, 1.27 mmol). The mixture was stirred at room temperature for 3 hours. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~10% methanol in dichloromethane and further purified by prep-HPLC (column, C18 silica gel; mobile phase, water (0.1% FA) and ACN) to afford the title compound (29.8 mg, 12%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.77 (s, 1H), 8.95 (s, 1H), 8.66 – 8.65 (m, 2H), 8.19 (s, 1H), 8.02 – 8.01 (m, 1H), 7.61 (s, 1H), 7.46 – 7.34 (m, 2H), 7.06 (s, 1H), 6.99 (s, 1H), 5.54 (s, 2H), 3.52 (s, 3H). *m/z* 494.1 [M+H⁺].

Example 230

Synthesis of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-6-(2-methoxyphenyl)pyrazolo[1,5-a]pyridine-5-carboxamide



Step-1: Synthesis of methyl 3-(2-methoxyphenyl)pyridine-4-carboxylate



[0737] A mixture of methyl 3-bromopyridine-4-carboxylate (1.00 g, 4.62 mmol), 2-methoxyphenylboronic acid (1.41 g, 9.25 mmol), Pd(dppf)Cl₂ (0.34 g, 0.463 mmol) and Potassium carbonate (1.28 g, 9.25 mmol) in dioxane (15 mL) and water (3.0 mL) was stirred at 80 °C for 2 h under nitrogen atmosphere. The reaction mixture was quenched with water and the aqueous layer was extracted with ethyl acetate. The combined organic solution was dried over sodium sulfate, filtered, and concentrated under vacuum. The solution was purified by silica gel column chromatography, eluted with acetate ethyl in petroleum ether (0~42%) to afford the title compound (1.0 g, 88%) as a yellow solid.

Step-2: Synthesis of 3,5-dimethyl 6-(2-methoxyphenyl)pyrazolo[1,5-a]pyridine-3,5-dicarboxylate



[0738] A mixture of methyl 3-(2-methoxyphenyl)pyridine-4-carboxylate (500 mg, 2.05 mmol), amino 2,4,6-trimethylbenzenesulfonate (663 mg, 3.08 mmol) in DCM (10 mL) was stirred at room temperature for 18 h under nitrogen atmosphere. The resulting mixture was concentrated under vacuum and the residue was washed with 100 mL of Et₂O to afford 1-amino-4-(methoxycarbonyl)-3-(2-methoxyphenyl)pyridin-1-ium (510 mg, crude) as a yellow solid. To a

mixture of 1-amino-4-(methoxycarbonyl)-3-(2-methoxyphenyl)pyridin-1-ium (510 mg, 1.96 mmol) and potassium carbonate (815 mg, 5.90 mmol) in DMF (15 mL) was added propionic acid methyl ester (248 mg, 2.95 mmol) and stirred at room temperature for 18 h under nitrogen atmosphere. The reaction mixture was quenched with water and the aqueous layer was extracted with ethyl acetate. The combined organic solution was dried over sodium sulfate, filtered, and concentrated under vacuum. The solution was purified by silica gel column chromatography, eluted with acetate ethyl in petroleum ether (0~24%) to afford the title compound (160 mg, 23%) as a yellow solid.

Step-3: Synthesis of 6-(2-methoxyphenyl)pyrazolo[1,5-a]pyridine-5-carboxylic acid



[0739] A mixture of 3,5-dimethyl 6-(2-methoxyphenyl)pyrazolo[1,5-a]pyridine-3,5-dicarboxylate (110 mg) in concentrated HCl (3.0 mL) was stirred at 100 °C for 2 h. The resulting mixture was diluted with water and extracted with ethyl acetate. The combined organic solution was dried over sodium sulfate, filtered, and concentrated under vacuum. the resulting solution was purified by reverse phase flash column chromatography with 5~39% acetonitrile in water to afford the title compound (50 mg, 57%) as a white solid.

Step-4: Synthesis of N-[5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-yl]-6-(2-methoxyphenyl)pyrazolo[1,5-a]pyridine-5-carboxamide

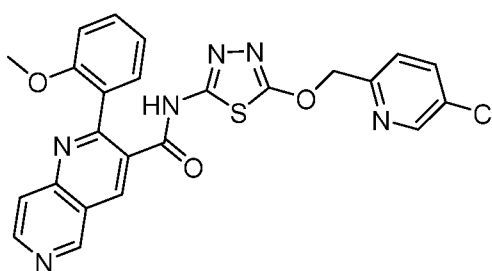


[0740] A mixture of 6-(2-methoxyphenyl)pyrazolo[1,5-a]pyridine-5-carboxylic acid (50.0 mg, 0.18 mmol), 5-[(5-chloropyridin-2-yl)methoxy]-1,3,4-thiadiazol-2-amine (Intermediate C, 54.2 mg, 0.22 mmol), TCFH (57.5 mg, 0.20 mmol) NMI (42 mg, 0.52 mmol) in DMF (1.0 mL) was

stirred at room temperature for 2 h. The mixture was purified by Prep-HPLC (column, C18 silica gel; mobile phase, water (10 mM NH_4HCO_3 +0.1% $\text{NH}_3\cdot\text{H}_2\text{O}$) and ACN) to afford the title compound (35.9 mg, 38%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 12.82 (s, 1H), 8.69 – 8.62 (m, 2H), 8.14 (d, $J = 2.4$ Hz, 1H), 8.10 (s, 1H), 8.01 (dd, $J = 2.4$ Hz, 1H), 7.61 (d, $J = 8.4$ Hz, 1H), 7.47 (d, $J = 6.4$ Hz, 1H), 7.40 – 7.32 (m, 1H), 7.05 (t, $J = 7.6$ Hz, 1H), 6.96 (d, $J = 8.4$ Hz, 1H), 6.87 (d, $J = 2.4$ Hz, 1H), 5.55 (s, 2H), 3.51 (s, 3H). m/z 493.0 $[\text{M}+\text{H}^+]$.

Example 231

Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-2-(2-methoxyphenyl)-1,6-naphthyridine-3-carboxamide

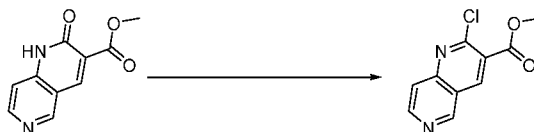


Step-1: Synthesis of methyl 2-oxo-1,2-dihydro-1,6-naphthyridine-3-carboxylate



[0741] To a stirred solution of 4-aminonicotinaldehyde (4.0 g, 32.7 mmol) in MeOH (30.0 mL) were added diethyl malonate (14.2 g, 88.4 mmol), AcOH (196 mg, 3.27 mmol) and piperidine (7.5 g, 88.4 mmol) at room temperature. The resulting mixture was stirred at 60 °C for 18 h under N_2 . The resulting mixture was concentrated under vacuum. The precipitated solids were washed with ethyl ether and collected by filtration. The resulting solid was dried under vacuum to afford the title compound (5.2 g, 77%) as a yellow solid.

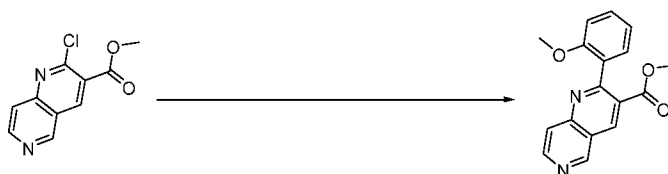
Step-2: Synthesis of methyl 2-chloro-1,6-naphthyridine-3-carboxylate



[0742] To a stirred solution of methyl 2-oxo-1,2-dihydro-1,6-naphthyridine-3-carboxylate (3.0 g) in POCl_3 (200 mL) was stirred at 130 °C for 48 h under N_2 . The mixture was allowed to cool

down to room temperature. The resulting mixture was concentrated under vacuum. The residue was dissolved in ice water. The residue was basified to pH 9 with saturated Na_2CO_3 (aq.). The resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography with 5~45% ethyl acetate in petroleum ether to afford the title compound (292 mg, 10%) as a yellow solid.

Step-3: Synthesis of methyl 2-(2-methoxyphenyl)-1,6-naphthyridine-3-carboxylate



[0743] To a stirred solution of methyl 2-chloro-1,6-naphthyridine-3-carboxylate (270 mg, 1.21 mmol) in 1,4-dioxane (5.0 mL) and H_2O (1.0 mL) were added (2-methoxyphenyl)boronic acid (221 mg, 1.45 mmol), K_2CO_3 (502 mg, 3.63 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (88.7 mg, 0.12 mmol). The resulting mixture was stirred for 2 h at 80 °C under N_2 . The resulting mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure to afford methyl 2-(2-methoxyphenyl)-1,6-naphthyridine-3-carboxylate (300 mg, crude) as a brown solid.

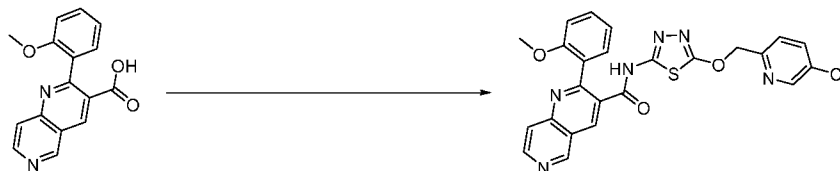
Step-4: Synthesis of 2-(2-methoxyphenyl)-1,6-naphthyridine-3-carboxylic acid



[0744] To a stirred solution of methyl 2-(2-methoxyphenyl)-1,6-naphthyridine-3-carboxylate (270 mg, 0.91 mmol) in EtOH (4.0 mL) were added H_2O (4.0 mL) and NaOH (183 mg, 4.58 mmol). The resulting mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The aqueous solution was acidified to pH 7 with HCl (1 N). The resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 . After filtration, the filtrate

was concentrated under reduced pressure to afford the title compound (200 mg, crude) as a light yellow solid.

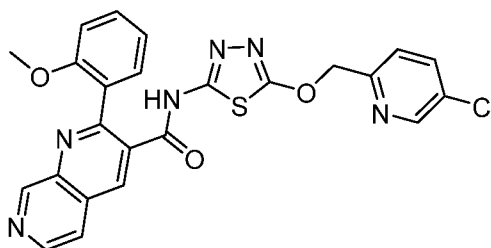
Step-5: Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-2-(2-methoxyphenyl)-1,6-naphthyridine-3-carboxamide



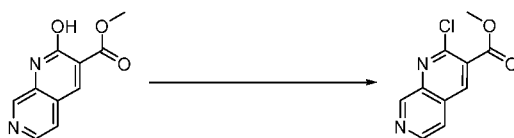
[0745] To a stirred solution of 2-(2-methoxyphenyl)-1,6-naphthyridine-3-carboxylic acid (100 mg, 0.35 mmol) in acetonitrile (3.0 mL) were added TCFH (110.1 mg, 0.39 mmol), 5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-amine (Intermediate C, 103 mg, 0.42 mmol) and NMI (61.5 mg, 0.74 mmol). The resulting mixture was stirred for 1.5 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with 0~60% acetonitrile in water and further purified by Prep-HPLC (column, C18 silica gel; mobile phase, water (10 mM NH_4HCO_3) and ACN) to afford the title compound (35mg, 19%) as an off-white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 13.05 (s, 1H), 9.53 (s, 1H), 8.93 (s, 1H), 8.86 (d, $J = 6.0$ Hz, 1H), 8.67 (d, $J = 2.0$ Hz, 1H), 8.03 – 7.99 (m, 2H), 7.68 – 7.62 (m, 2H), 7.49 – 7.45 (m, 1H), 7.16 – 7.12 (m, 1H), 7.02 (d, $J = 8.4$ Hz, 1H), 5.57 (s, 2H), 3.53 (s, 3H). m/z 505.0 $[\text{M}+\text{H}^+]$.

Example 232

Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-2-(2-methoxyphenyl)-1,7-naphthyridine-3-carboxamide



Step-1: Synthesis of methyl 2-chloro-1,7-naphthyridine-3-carboxylate



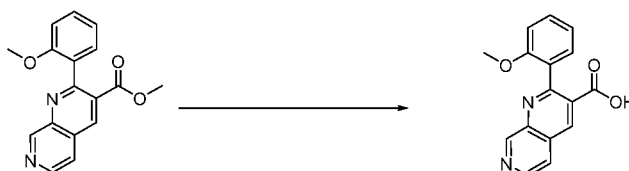
[0746] A solution of methyl 2-hydroxy-1,7-naphthyridine-3-carboxylate (500 mg, 2.45 mmol) in POCl_3 (5.0 mL) was stirred at 120 °C for 5 hours. The reaction mixture was concentrated under vacuum. The aqueous solution was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~50% ethyl acetate in petroleum ether to afford the title compound (500 mg, 92%) as a yellow solid.

Step-2: Synthesis of methyl 2-(2-methoxyphenyl)-1,7-naphthyridine-3-carboxylate



[0747] To a solution of ethyl methyl 2-chloro-1,7-naphthyridine-3-carboxylate (500 mg, 2.3 mmol) in dioxane (5.0 mL) and water (1.0 mL) were added K_2CO_3 (932 mg, 6.75 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (180 mg, 0.23 mmol) under nitrogen. The mixture was stirred at 80 °C for 5 hours before concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~50% ethyl acetate in petroleum ether to the title compound (218 mg, 78%) as a yellow oil.

Step-3: Synthesis of 2-(2-methoxyphenyl)-1,7-naphthyridine-3-carboxylic acid



[0748] To a solution of methyl 2-(2-methoxyphenyl)-1,7-naphthyridine-3-carboxylate (518 mg, 1.76 mmol) in MeOH (2.0 mL) and H_2O (2.0 mL) was added NaOH (137 mg, 3.52 mmol). The mixture was stirred at room temperature for 2 hours. The aqueous solution was acidified with HCl (1 N) to PH~5. The mixture extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford the title compound (341 mg, crude) as a yellow solid.

Step-4: Synthesis of N-(5-((5-chloropyridin-2-yl)methoxy)-1,3,4-thiadiazol-2-yl)-2-(2-methoxyphenyl)-1,7-naphthyridine-3-carboxamide



[0749] To a solution of 2-(2-methoxyphenyl)-1,7-naphthyridine-3-carboxylic acid (341 mg, 1.21 mmol) in DMF (2.0 mL) were added DIEA (471 mg, 3.63 mmol), HATU (684 mg, 1.8 mmol) and 4-(2-methoxyphenyl)-6-methylpyridine-3-carboxylic acid (294 mg, 1.21 mmol). The mixture was stirred at room temperature for 12 hours. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with 0~10% methanol in dichloromethane and further purified by prep-HPLC (column, C18 silica gel; mobile phase, water (0.1% FA) and ACN) to afford the title compound (6.4 mg, 0.18%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.09 (s, 1H), 9.49 (s, 1H), 8.80 (s, 1H), 8.74 – 8.73 (m, 1H), 8.67 – 8.66 (m, 1H), 8.07 – 8.01 (m, 2H), 7.70 – 7.62 (m, 2H), 7.49 – 7.44 (m, 1H), 7.16 – 7.13 (m, 1H), 7.03 – 7.01 (m, 1H), 5.57 (s, 2H), 3.53 (s, 3H). *m/z* 505.1 [M+H⁺].

Biological Examples

Example 1

[0750] The ability of the compounds of Formula (I) to inhibit ATPase activity of Pol theta (1-899) was determined using the assay described below.

[0751] Pol Theta ATPase activity was determined by measuring the rate of ATP turn over in a NADH oxidation-coupled enzymatic assay. 10-point dilution series of compounds were used in a 384 well format for the inhibition assays. Pol theta (1-899) (10 nM) in assay buffer (20 mM Tris HCl (pH 7.80), 80 mM KCl, 10 mM MgCl₂, 1 mM DTT, 0.01% BSA, 0.01% Tween, 5% glycerol) was transferred to the test wells (20 μL), except the low control wells (20 μL of assay buffer was added to the low control wells). The plate was then incubated at room temperature for 15 min. An equal volume (20 μL) of 100 μM ATP, 300 nM dT₅₀ (single-stranded DNA (ssDNA) containing 50 thymine bases), 300 μM NADH, 6 mM PEP, 10 U/mL lactate dehydrogenase and 20 U/mL pyruvate kinase in assay buffer was added to all the test wells. The

plate was then centrifuged at 1000 rpm for 1 min. The reaction was monitored for 30 min by measuring absorbance ($\lambda = 340$ nm) in a Tecan Spark multimode plate reader every minute. The high control (DMSO with enzyme) with low absorbance intensity represents no inhibition of ATPase reaction while the low control (DMSO with buffer) with high absorbance intensity represents full inhibition of ATPase activity. Slope of the reaction progress curves were used to calculate the rate of ATP hydrolysis. The rates were used to determine the percent inhibition using a four-parameter inhibition model to generate IC₅₀, Hill slope and max inhibition.

[0752] The IC₅₀ of the compounds in Table 1 above are disclosed in Table 2 below:

IC₅₀: 10 μ M $\geq$ (+) > 1 μ M ; 1 μ M $\geq$ (++) > 500 nM;
500 nM $\geq$ (+++) > 200 nM; 200 nM $\geq$ (++++)

Cpd #	ATPase NADH coupling:Standard Screening:hPolQ IC50 (μ M)	Cpd #	ATPase NADH coupling:Standard Screening:hPolQ IC50 (μ M)
1	+	113	++++
2	++	114	++++
3	+	115	++++
4	++	116	++++
5	+++	117	++++
6	+++	118	+++
7	+++	119	++++
8	+	120	++++
9	+++	121	++++
10	++	122	++++
11	+	123	++++
12	+++	124	++++
13	+++	125	++++
14	++++	126	++++
15	+	127	++++
16	+	128	++
17	++	129	+++
18	++	130	++++
19	+	131	++++
20	+	132	++++
21	+	133	++
22	+	134	++++
23	+	135	++++
24	+	136	++++

Cpd #	ATPase NADH coupling:Standard Screening:hPolQ IC50 (uM)	Cpd #	ATPase NADH coupling:Standard Screening:hPolQ IC50 (uM)
25	+	137	++++
26	+++	138	++++
27	+++	139	++++
28	+	140	++++
29	+	141	++++
30	++++	142	++++
31	++++	143	++++
32	+++	144	++++
33	++	145	++++
34	+	146	++++
35	++++	147	++++
36	+	148	++++
37	+	149	++++
38	+	150	+++
39	+	151	++++
40	+++	152	++++
41	+	153	++++
42	++++	154	++++
43	+++	155	++++
44	++++	156	++++
45	++	157	++++
46	+++	158	++++
47	+++	159	++++
48	+++	160	++++
49	++	161	++++
50	++++	162	++++
51	+	163	++++
52	+++	164	++++
53	++	165	++++
54	++	166	++++
55	+	167	+++
56	+	168	++++
57	++	169	++++
58	++	170	++++
59	+++	171	++++
60	++++	172	++++
61	++	173	+++
62	++++	174	++++
63	+	175	++++
64	++	176	++++

Cpd #	ATPase NADH coupling:Standard Screening:hPolQ IC50 (uM)	Cpd #	ATPase NADH coupling:Standard Screening:hPolQ IC50 (uM)
65	+	177	++++
66	+	178	++++
67	+	179	++++
68	+	180	++++
69	+	181	++++
70	++	182	++++
71	++++	183	++++
72	+++	184	++++
73	+	185	++++
74	++	186	++++
75	++	187	++++
76	++++	188	++++
77	++++	189	++++
78	+	190	++++
79	++	191	+++
80	+++	192	++++
81	++++	193	++++
82	++++	194	++++
83	++	195	++++
84	+	196	++++
85	++++	197	+++
86	++++	198	++++
87	++	199	+++
88	++++	200	++++
89	++++	201	++
90	++	202	++++
91	+++	203	++++
92	++++	204	+
93	++++	205	++++
94	+	206	++++
95	++++	207	+
96	++++	208	++++
97	++++	209	++++
98	++	210	++++
99	++++	211	++++
100	++++	212	++++
101	++++	213	++++
102	++++	214	++++
103	++++	215	++++
104	++++	216	++++

Cpd #	ATPase NADH coupling:Standard Screening:hPolQ IC50 (uM)	Cpd #	ATPase NADH coupling:Standard Screening:hPolQ IC50 (uM)
105	++++	217	++++
106	++++	218	++++
107	++++	219	++++
108	++++	220	++++
109	++++	221	++++
110	++++	222	++++
111	++++	223	++++
112	++++	224	++++

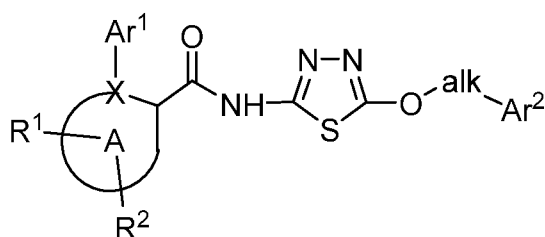
[0753] Certain examples resulted in mixtures of compounds with at least one stereocenter (e.g., Examples 167, 175, 178, and 179). The data above reports the activity measured when testing a mixture of the stereocenters.

[0754] Particular embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Upon reading the foregoing, description, variations of the disclosed embodiments may become apparent to individuals working in the art, and it is expected that those skilled artisans may employ such variations as appropriate. Accordingly, it is intended that the invention be practiced otherwise than as specifically described herein, and that the invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

[0755] All publications, patent applications, accession numbers, and other references cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference.

What is Claimed:

1. A compound of Formula (I):



(I)

wherein:

X is -N- or -C-;

alk is alkylene;

ring A is phenyl or a five to ten membered heteroaryl ring containing, inclusive of X, one to four heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ar¹ is phenyl, heteroaryl, heterocyclyl, bicyclic heterocyclyl, bridged heterocyclyl, or spiroheterocyclyl, wherein each of the aforementioned ring is substituted with R^a, R^b, and/or R^c, wherein R^a and R^b are independently selected from hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, cycloalkyloxy, acyl, acylamino, monoalkylamino, dialkylamino, alkylsulfonyl, cyano, and hydroxy; or R^a and R^b, when on adjacent ring vertices, combine to form a C₃₋₆ cycloalkyl, or R^a and R^b, when on the same ring vertex, combine to form oxo, and R^c is selected from hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, heterocyclylalkyl, heterocyclyloxy, aminocarbonyl;

Ar² is phenyl, heteroaryl, or cycloalkyl, wherein said phenyl and heteroaryl are substituted with R^d, R^e and/or R^f, wherein R^d and R^e are independently selected from hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, and cyano and R^f is selected from hydrogen, alkyl, cycloalkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, cyano, cyanomethyl, aminocarbonylmethyl, heteroaryl, and heterocyclyl, wherein said heteroaryl and heterocyclyl of R^f are unsubstituted or substituted with one, two, or three substituents independently selected from alkyl, halo, haloalkyl, and hydroxy;

R¹ is hydrogen, alkyl, halo, haloalkyl, haloalkoxy, alkoxy, hydroxy, cyano, cyanoalkyl, carboxy, alkoxycarbonyl, acylamino, aminocarbonyl; optionally substituted heteroaryl,

hydroxyalkyl, cycloalkyl, hydroxyalkynyl, alkoxyalkyl, aminoalkyl, aminocarbonylalkyl, sulfonylalkyl, aminosulfonylalkyl, optionally substituted heteroaralkyl, or optionally substituted heterocyclalkyl; and

R^2 is hydrogen, alkyl, halo, haloalkyl, haloalkoxy, or cyano; or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein:

X is -N- or -C-;

alk is alkylene;

ring A is phenyl or a five or six membered heteroaryl ring containing, inclusive of X, one to three heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ar^1 is phenyl, heteroaryl, heterocycl, bicyclic heterocycl, bridged heterocycl, or spiroheterocycl, wherein each of the aforementioned ring is substituted with R^a , R^b , and/or R^c , wherein R^a and R^b are independently selected from hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, cycloalkyloxy, acyl, acylamino, monoalkylamino, dialkylamino, alkylsulfonyl, cyano, and hydroxy, and R^c is selected from hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, heterocyclalkyl, and aminocarbonyl;

Ar^2 is phenyl, heteroaryl, or cycloalkyl, wherein said phenyl and heteroaryl are substituted with R^d , R^e and/or R^f , wherein R^d and R^e are independently selected from hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, and cyano and R^f is selected from hydrogen, alkyl, cycloalkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, cyano, cyanomethyl, aminocarbonylmethyl, heteroaryl, and heterocycl, wherein said heteroaryl and heterocycl of R^f are unsubstituted or substituted with one, two, or three substituents independently selected from alkyl, halo, haloalkyl, and hydroxy;

R^1 is hydrogen, alkyl, halo, haloalkyl, haloalkoxy, alkoxy, hydroxy, cyano, cyanoalkyl, carboxy, alkoxy carbonyl, acylamino, aminocarbonyl; optionally substituted heteroaryl, hydroxyalkyl, hydroxyalkynyl, alkoxyalkyl, aminoalkyl, aminocarbonylalkyl, sulfonylalkyl, aminosulfonylalkyl, optionally substituted heteroaralkyl, or optionally substituted heterocyclalkyl; and

R^2 is hydrogen, alkyl, halo, haloalkyl, haloalkoxy, or cyano; or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, wherein:

X is -N- or -C-;

alk is alkylene;

ring A is phenyl or a five or six membered heteroaryl ring containing, inclusive of X, one to three heteroatoms independently selected from nitrogen, oxygen, or sulfur;

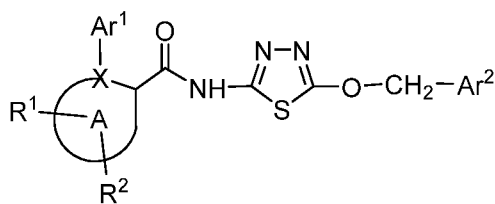
Ar¹ is phenyl, heteroaryl, heterocyclyl, bicyclic heterocyclyl, bridged heterocyclyl, or spiroheterocyclyl, wherein each of the aforementioned ring is substituted with R^a, R^b, and/or R^c, wherein R^a and R^b are independently selected from hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, cycloalkyloxy, acyl, acylamino, monoalkylamino, dialkylamino, alkylsulfonyl, cyano, and hydroxy, and R^c is selected from hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, heterocyclylalkyl, and aminocarbonyl;

Ar² is phenyl, heteroaryl, or cycloalkyl, wherein said phenyl and heteroaryl are substituted with R^d, R^e and/or R^f, wherein R^d and R^e are independently selected from hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, and cyano and R^f is selected from hydrogen, alkyl, cycloalkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, cyano, cyanomethyl, aminocarbonylmethyl, heteroaryl, and heterocyclyl, wherein said heteroaryl and heterocyclyl of R^f are unsubstituted or substituted with one, two, or three substituents independently selected from alkyl, halo, haloalkyl, and hydroxy;

R¹ is hydrogen, alkyl, halo, haloalkyl, haloalkoxy, alkoxy, hydroxy, cyano, carboxy, alkoxycarbonyl, acylamino, aminocarbonyl; optionally substituted heteroaryl, hydroxyalkyl, hydroxyalkynyl, alkoxyalkyl, aminoalkyl, aminocarbonylalkyl, sulfonylalkyl, aminosulfonylalkyl, optionally substituted heteroaralkyl, or optionally substituted heterocyclylalkyl; and

R² is hydrogen, alkyl, halo, haloalkyl, haloalkoxy, or cyano; or
a pharmaceutically acceptable salt thereof.

4. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof wherein the compound has a structure of formula (Ia):



(Ia)

5. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof wherein ring A is phenyl, pyridinyl, pyridazinyl, pyrimidinyl, imidazolyl, pyrazolyl, triazolyl, imidazo[1,2-a]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, imidazo[1,5-a]pyridinyl, pyrrolo[2,3-b]pyridinyl, pyrrolo[3,2-b]pyridinyl, pyrazolo[1,5-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, 1,6-naphthyridinyl, or 1,7-naphthyridinyl.

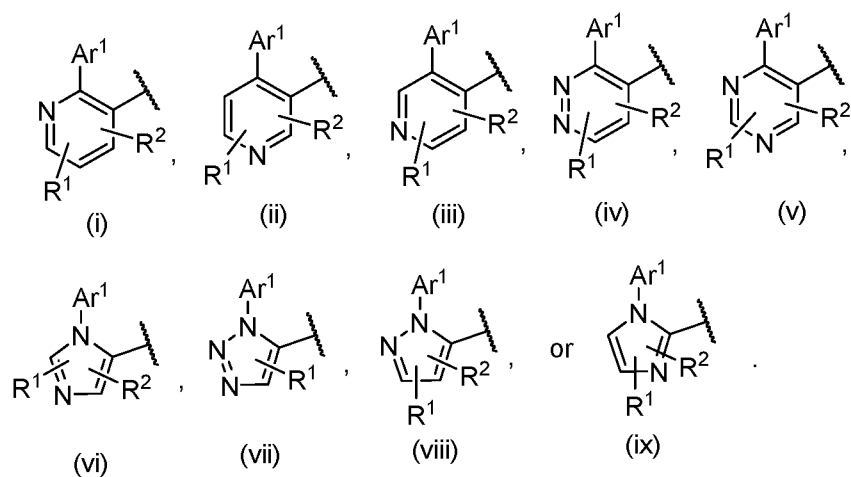
6. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof wherein ring A is a nine or ten membered heteroaryl ring.

7. The compound of claim 6, or a pharmaceutically acceptable salt thereof wherein ring A is imidazo[1,2-a]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, imidazo[1,5-a]pyridinyl, pyrrolo[2,3-b]pyridinyl, pyrrolo[3,2-b]pyridinyl, pyrazolo[1,5-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, 1,6-naphthyridinyl, or 1,7-naphthyridinyl.

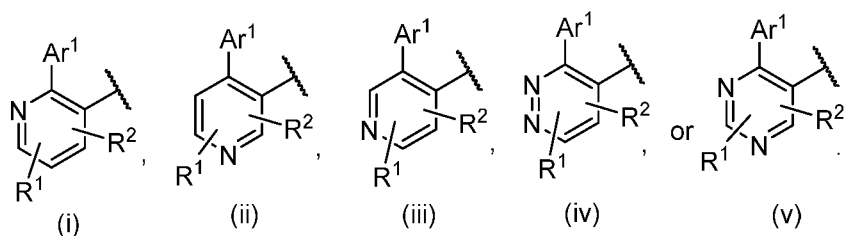
8. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof wherein ring A is a five or six membered heteroaryl ring.

9. The compound of claim 8, or a pharmaceutically acceptable salt thereof wherein ring A is pyridinyl, pyridazinyl, pyrimidinyl, imidazolyl, pyrazolyl, or triazolyl.

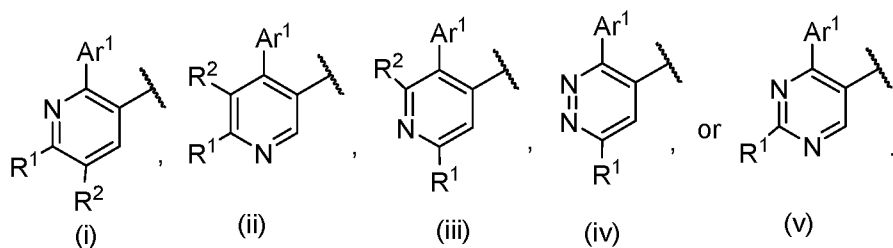
10. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof wherein ring A is:



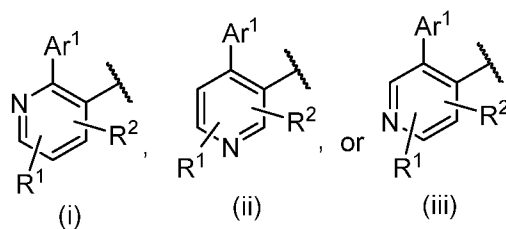
11. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof wherein ring A is:



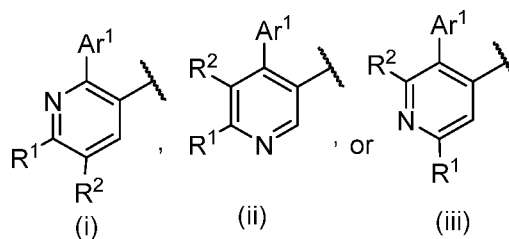
12. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof wherein ring A is:



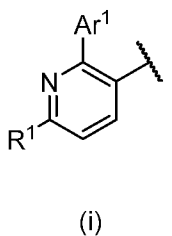
13. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof wherein ring A is:



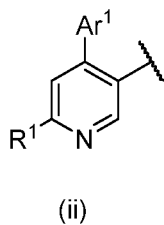
14. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof wherein ring A is:



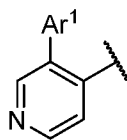
15. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof wherein ring A is:



16. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof wherein ring A is:

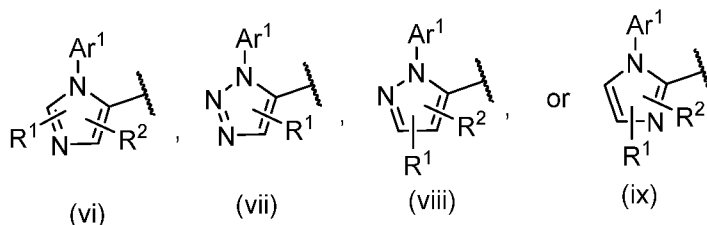


17. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof wherein ring A is:



(iii)

18. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof wherein ring A is:



19. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof wherein ring A is phenyl.

20. The compound of any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof wherein Ar¹ is heterocyclyl substituted with R^a, R^b, and/or R^c.

21. The compound of claim 20, or a pharmaceutically acceptable salt thereof wherein Ar¹ is piperidinyl, piperazinyl, morpholinyl, homomorpholinyl, 2-oxopiperazinyl, 2-oxohomopiperazinyl, tetrahydropyranyl, 3,6-dihydro-2H-pyranyl, 2-oxo-1,2-dihydropyridinyl, thiomorpholinyl, or 1,1-dioxothiomorpholinyl substituted with R^a, R^b, and/or R^c.

22. The compound of claim 20, or a pharmaceutically acceptable salt thereof wherein Ar¹ is piperidin-1-yl, piperazin-1-yl, morpholin-4-yl, homomorpholin-4-yl, 3-oxopiperazin-1-yl, 3-oxohomopiperazin-1-yl, 5-oxohomopiperazin-1-yl, tetrahydropyran-4-yl, 3,6-dihydro-2H-pyran-4-yl, 6-oxo-1,6-dihydropyridin-3-yl, 6-oxo-1,6-dihydropyridin-4-yl, thiomorpholin-4-yl, or 1,1-dioxothiomorpholin-4-yl substituted with R^a, R^b, and/or R^c.

23. The compound of claim 20, or a pharmaceutically acceptable salt thereof wherein Ar¹ is morpholin-4-yl substituted with R^a, R^b, and/or R^c.

24. The compound of any one of claims 20 to 23, or a pharmaceutically acceptable salt thereof wherein R^a is hydrogen or alkyl, R^b is hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, acyl, alkylsulfonyl, cyano, or hydroxy, and R^c is selected from alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, heterocyclalkyl, and aminocarbonyl.

25. The compound of any one of claims 20 to 23, or a pharmaceutically acceptable salt thereof wherein R^a and R^b , when on adjacent ring vertices, combine to form a cyclopropyl or cyclobutyl ring, and R^c is hydrogen.

26. The compound of any one of claims 20 to 23, or a pharmaceutically acceptable salt thereof wherein Ar^1 is substituted with R^b and/or R^c wherein R^b is hydrogen, methyl, fluoro, cyano, methylsulfonyl, or methylcarbonyl and R^c is hydrogen, methyl, ethyl, fluoro, difluoromethyl, trifluoromethyl, trifluoroethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, hydroxy, 2-hydroxyethyl, 2-methoxyethyl, 2-aminoethyl, 2-morpholin-1-ylethyl, $-CONH_2$, methylaminocarbonyl, or dimethylaminocarbonyl.

27. The compound of claim 20, or a pharmaceutically acceptable salt thereof wherein Ar^1 is morpholin-4-yl, homomorpholin-4-yl, 2-methylmorpholin-4-yl, 3-methylmorpholin-4-yl, 3R-methylmorpholin-4-yl, 3S-methylmorpholin-4-yl, 3-oxopiperazin-1-yl, 4-methyl-3-oxopiperazin-1-yl, 2-methyl-3-oxopiperazin-1-yl, 6-methyl-3-oxopiperazin-1-yl, 5-methyl-3-oxopiperazin-1-yl, 3-oxohomopiperazin-1-yl, 5-oxohomopiperazin-1-yl, 4-dimethylaminocarbonylpiperazin-1-yl, tetrahydropyran-4-yl, 3,6-dihydro-2H-pyran-4-yl, 4-(2-hydroxyethyl)-3-oxopiperazin-1-yl, 6-oxo-1,6-dihydropyridin-4-yl, 6-oxo-1,6-dihydropyridin-3-yl, 1-methyl-6-oxo-1,6-dihydropyridin-3-yl, 4-(2-morpholin-4-ylethyl)-3-oxopiperazin-1-yl, 4-methylcarbonylpiperazin-1-yl, 4-methylsulfonylpiperazin-1-yl, 1,1-dioxothiomorpholin-4-yl, or 4,4-difluoropiperidin-1-yl.

28. The compound of any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof wherein Ar^1 is bicyclic heterocycl substituted with R^a , R^b , and/or R^c .

29. The compound of claim 28, or a pharmaceutically acceptable salt thereof wherein Ar¹ is 6-oxohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl or 2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl, each ring substituted with R^a, R^b, and/or R^c.

30. The compound of claim 28, or a pharmaceutically acceptable salt thereof wherein Ar¹ is selected from the group consisting of 6-oxohexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl 3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl, benzo[d][1,3]dioxol-4-yl, (3,4-dihydro-2H-1,4-benzoxazin-8-yl), [5H,6H,7H-pyrazolo[1,5-a]pyrimidin-4-yl] and 2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl, each ring substituted with R^a, R^b, and/or R^c.

31. The compound of any one of claims 28 to 30, or a pharmaceutically acceptable salt thereof wherein R^a is hydrogen, R^b is hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, acyl, alkylsulfonyl, cyano, or hydroxy, and R^c is selected from alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, heterocyclalkyl, and aminocarbonyl.

32. The compound of any one of claims 28 to 30, or a pharmaceutically acceptable salt thereof wherein Ar¹ is substituted with R^b and/or R^c wherein R^b is hydrogen, methyl, fluoro, cyano, methylsulfonyl, or methylcarbonyl and R^c is hydrogen, methyl, ethyl, fluoro, difluoromethyl, trifluoromethyl, trifluoroethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, hydroxy, 2-hydroxyethyl, 2-methoxyethyl, 2-aminoethyl, 2-morpholin-1-ylethyl, -CONH₂, methylaminocarbonyl, or dimethylaminocarbonyl.

33. The compound of any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof wherein Ar¹ is spiroheterocyclalkyl substituted with R^a, R^b, and/or R^c.

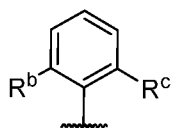
34. The compound of claim 33, or a pharmaceutically acceptable salt thereof wherein Ar¹ is 4-oxa-7-azaspiro[2.5]octan-7-yl substituted with R^a, R^b, and/or R^c.

35. The compound of claim 33 or 34, or a pharmaceutically acceptable salt thereof wherein Ar¹ is substituted with R^b and/or R^c wherein R^b is hydrogen, methyl, fluoro, cyano, methylsulfonyl, or methylcarbonyl and R^c is hydrogen, methyl, ethyl, fluoro, difluoromethyl, trifluoromethyl, trifluoroethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy,

trifluoroethoxy, hydroxy, 2-hydroxyethyl, 2-methoxyethyl, 2-aminoethyl, 2-morpholin-1-ylethyl, -CONH₂, methylaminocarbonyl, or dimethylaminocarbonyl.

36. The compound of any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof wherein Ar¹ is phenyl substituted with R^a, R^b, and/or R^c.

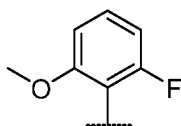
37. The compound of claim 36, or a pharmaceutically acceptable salt thereof, wherein Ar¹ is



38. The compound of claim 36 or claim 37, or a pharmaceutically acceptable salt thereof wherein R^a is hydrogen or alkyl, R^b is hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, acyl, alkylsulfonyl, cyano, or hydroxy, and R^c is selected from alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, heterocyclalkyl, and aminocarbonyl.

39. The compound of any one of claims 36 to 38, or a pharmaceutically acceptable salt thereof wherein Ar¹ is substituted with R^b and/or R^c wherein R^b is hydrogen, methyl, fluoro, cyano, methylsulfonyl, or methylcarbonyl and R^c is hydrogen, methyl, ethyl, fluoro, difluoromethyl, trifluoromethyl, trifluoroethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, hydroxy, 2-hydroxyethyl, 2-methoxyethyl, 2-aminoethyl, 2-morpholin-1-ylethyl, -CONH₂, methylaminocarbonyl, or dimethylaminocarbonyl.

40. The compound of claim 36, or a pharmaceutically acceptable salt thereof, wherein Ar¹ is



41. The compound of claim 36, or a pharmaceutically acceptable salt thereof wherein Ar¹ is phenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,4-dimethoxyphenyl, 2-chlorophenyl, 2-cyanophenyl, or 2-cyclopropyl-oxyphenyl.

42. The compound of claim 36, or a pharmaceutically acceptable salt thereof wherein Ar¹ is 2-methoxyphenyl.

43. The compound of claim 36, or a pharmaceutically acceptable salt thereof wherein Ar¹ is 3-methoxyphenyl.

44. The compound of claim 36, or a pharmaceutically acceptable salt thereof wherein Ar¹ is 2,4-dimethoxyphenyl.

45. The compound of any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof wherein Ar¹ is heteroaryl substituted with R^a, R^b, and/or R^c.

46. The compound of claim 45, or a pharmaceutically acceptable salt thereof wherein Ar¹ is benzo[c][1,2,5]thiadiazolyl, benzo[d]oxazolyl, 1*H*-indazolyl, substituted with R^a, R^b, and/or R^c where R^a is hydrogen or alkyl, R^b is hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, acyl, alkylsulfonyl, cyano, or hydroxy, and R^c is selected from hydrogen alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, heterocyclalkyl, and aminocarbonyl.

47. The compound of claim 45, or a pharmaceutically acceptable salt thereof wherein Ar¹ is pyridinyl, pyrimidinyl, pyrazolyl, pyrrolyl, imidazolyl, or triazolyl substituted with R^a, R^b, and/or R^c where R^a is hydrogen or alkyl, R^b is hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, acyl, alkylsulfonyl, cyano, or hydroxy, and R^c is selected from alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, heterocyclalkyl, and aminocarbonyl.

48. The compound of any one of claims 45 to 47, or a pharmaceutically acceptable salt thereof wherein Ar¹ is substituted with R^b and/or R^c wherein R^b is hydrogen, methyl, fluoro, cyano, methylsulfonyl, or methylcarbonyl and R^c is hydrogen, methyl, ethyl, fluoro, difluoromethyl, trifluoromethyl, trifluoroethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, hydroxy, 2-hydroxyethyl, 2-methoxyethyl, 2-aminoethyl, 2-morpholin-1-ylethyl, -CONH₂, methylaminocarbonyl, or dimethylaminocarbonyl.

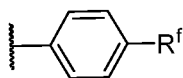
49. The compound of any one of claims 1 to 48, or a pharmaceutically acceptable salt thereof wherein Ar^2 is phenyl substituted with R^d , R^e and/or R^f .

50. The compound of claim 49, or a pharmaceutically acceptable salt thereof wherein R^d is hydrogen, R^e is hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, or cyano and R^f is selected from hydrogen, alkyl, cycloalkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, cyano, cyanomethyl, aminocarbonylmethyl, heteroaryl, and heterocyclyl, wherein said heteroaryl and heterocyclyl of R^f are unsubstituted or substituted with one, two, or three substituents independently selected from alkyl, halo, haloalkyl, and hydroxy.

51. The compound of claim 49, or a pharmaceutically acceptable salt thereof wherein R^f is cycloalkyl optionally substituted with cyano.

52. The compound of claim 49, or a pharmaceutically acceptable salt thereof wherein Ar^2 is phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-methoxyphenyl, 2-chloro-4-fluorophenyl, 4-cyanophenyl, 4-bromophenyl, 4-oxetan-3-ylphenyl, 4-chloro-3-methoxyphenyl, 4-cyclopropylphenyl, or 4-oxazol-2-ylphenyl.

53. The compound of any one of claims 49 to 51, or a pharmaceutically acceptable salt thereof wherein Ar^2 is



54. The compound of claim 49, or a pharmaceutically acceptable salt thereof wherein Ar^2 is 4-fluorophenyl.

55. The compound of claim 49, or a pharmaceutically acceptable salt thereof wherein Ar^2 is 4-chlorophenyl.

56. The compound of any one of claims 1 to 48, or a pharmaceutically acceptable salt thereof wherein Ar^2 is heteroaryl substituted with R^d , R^e and/or R^f .

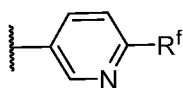
57. The compound of claim 56, or a pharmaceutically acceptable salt thereof wherein R^d is hydrogen, R^e is hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, or cyano and

R^f is selected from hydrogen, alkyl, cycloalkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, cyano, cyanomethyl, aminocarbonylmethyl, heteroaryl, and heterocyclyl, wherein said heteroaryl and heterocyclyl of R^f are unsubstituted or substituted with one, two, or three substituents independently selected from alkyl, halo, haloalkyl, and hydroxy.

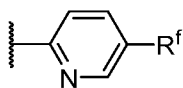
58. The compound of claim 56, or a pharmaceutically acceptable salt thereof wherein R^f is cycloalkyl optionally substituted with cyano.

59. The compound of any one of claims 56 to 58, or a pharmaceutically acceptable salt thereof wherein Ar^2 is heteroaryl selected from pyridinyl or pyrimidinyl.

60. The compound of any one of claims 56 to 58, or a pharmaceutically acceptable salt thereof wherein Ar^2 is



61. The compound of any one of claims 56 to 58, or a pharmaceutically acceptable salt thereof wherein Ar^2 is



62. The compound of any one of claims 1 to 48, or a pharmaceutically acceptable salt thereof wherein Ar^2 is cycloalkyl.

63. The compound of any one of claims 1 to 62, or a pharmaceutically acceptable salt thereof wherein R^1 is hydrogen, cyano, $-CONH_2$, methylaminocarbonyl, dimethylaminocarbonyl, imidazol-2-yl, methoxy, hydroxy, bromo, carboxy, or fluoro.

64. The compound of any one of claims 1 to 62, or a pharmaceutically acceptable salt thereof wherein R^1 is hydroxyalkyl, alkoxyalkyl, aminoalkyl, aminocarbonylalkyl, sulfonylalkyl, aminosulfonylalkyl, optionally substituted heteroaralkyl, or optionally substituted heterocyclalkyl.

65. The compound of any one of claims 1 to 64, or a pharmaceutically acceptable salt thereof wherein R^2 is hydrogen, cyano, or fluoro.

66. A pharmaceutical composition comprising a compound of any one of claims 1 to 64 and at least one pharmaceutically acceptable excipient.

67. A method for treating a disease characterized by overexpression of Polθ in a patient comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1 to 64 or a pharmaceutical composition of claim 66.

68. The method of claim 67, wherein the patient is in recognized need of such treatment and the disease is a cancer.

69. A method of treating a homologous recombinant (HR) deficient cancer in a patient comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1 to 64 or a pharmaceutical composition of claim 66.

70. The method of claim 69, wherein the patient is in recognized need of such treatment.

71. A method for treating a cancer in a patient, wherein the cancer is characterized by a reduction or absence of BRCA gene expression, the absence of the BRAC gene, or reduced function of BRCA protein, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 64 or a pharmaceutical composition of claim 44.

72. The method of any one of claims 67 to 71, wherein the cancer is lymphoma, soft tissue, rhabdoid, multiple myeloma, uterus, gastric, peripheral nervous system, rhabdomyosarcoma, bone, colorectal, mesothelioma, breast, ovarian, lung, fibroblast, central nervous system, urinary tract, upper aerodigestive, leukemia, kidney, skin, esophagus, and pancreas.