

5,6 UNSATURATED BICYCLIC HETEROCYCLES USEFUL AS INHIBITORS OF NOD-LIKE RECEPTOR PROTEIN 3

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/505,807 filed June 2, 2023, the entire contents of which are incorporated by reference herein.

BACKGROUND

[0002] Inflammasomes function as central signaling hubs of the innate immune system. They are multi-protein complexes assembled after activation of intracellular pattern recognition receptors (PRRs) by a variety of pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs). It has been shown that inflammasomes can be formed by nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) and Pyrin and HIN200-domain-containing proteins (Van Opdenbosch N and Lamkanfi M. *Immunity*, 2019 Jun 18;50(6):1352-1364). Inflammasome activation triggers a cascade of events that releases pro-inflammatory cytokines and promotes an inflammatory form of cell death called pyroptosis induced by the activation of Gasdermin. Pyroptosis is a unique form of inflammatory cell death that leads to the release of not only cytokines but also other intracellular components that promote a broader immune response both of the innate and acquired immune system. Thus, inflammasome activation is a major regulator of the inflammatory cascade.

[0003] The (NOD)-like receptor protein 3 (NLRP3) inflammasome is the most well-studied of all the inflammasomes. NLRP3 can be activated by numerous stimuli including environmental crystals, pollutants, host-derived DAMPs and protein aggregates (Tartey S and Kanneganti TD. *Immunology*, 2019 Apr; 156(4):329-338). Danger-associated molecular patterns that engage NLRP3 include uric acid and cholesterol crystals that cause gout and atherosclerosis, amyloid-P fibrils that are neurotoxic in Alzheimer's disease, and asbestos particles that cause mesothelioma (Kelley et al., *Int J Mol Sci*, 2019 Jul 6;20(13)). Additionally, NLRP3 is activated by infectious agents, such as vibrio cholerae, fungal pathogens, such as *Aspergillus fumigatus* and *Candida albicans*, adenoviruses, influenza A virus and SARS-CoV-2 (Tartey and Kanneganti, 2019 (see above); Fung et al. *Emerg Microbes Infect*, 2020 Mar 14;9(1):558-570).

[0004] The NLRP3 activation mechanism in humans remains unclear. It has been suggested that the NLRP3 inflammasome requires regulation at both the transcriptional and the post-transcriptional level (Yang Yet al., *Cell Death Dis*, 2019 Feb 12;10(2): 128). The NOD-like

receptor protein 3 (NLRP3) is a protein-coding gene that encodes a protein consisting of a N-terminal pyrin domain, a nucleotide-binding site domain (NBD), and a leucine-rich repeat (LRR) motif on the C-terminal (Inoue et al., *Immunology*, 2013, 139, 11-18; Sharif et al., *Nature*, 2019 Jun; 570(7761):338-343).

[0005] In response to sterile inflammatory danger signals PAMPs or DAMPs, NLRP3 interacts with the adaptor protein, apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and with the protease caspase-1 to form the NLRP3 inflammasome. Upon activation, procaspase-1 undergoes autoproteolysis and cleaves gasdermin D (Gsdmd) to produce the N-terminal Gsdmd molecule that leads to pore-formation in the plasma membrane and results in a lytic form of cell death called pyroptosis. Alternatively, caspase-1 cleaves the pro-inflammatory cytokines pro-IL-1 β and pro-IL-18 to allow release of its biologically active form (Kelley et al., 2019 - see above). The NLRP3 inflammasome activation results in the release of the inflammatory cytokines IL-1 β (interleukin-1 β) and IL-18 (interleukin-18), which when dysregulated can lead to a number of diseases.

[0006] Dysregulation of the NLRP3 inflammasome or its downstream mediators are associated with numerous immune diseases, inflammatory diseases, auto-immune diseases and auto-inflammatory diseases. Activation of the NLRP3 inflammasome has been linked to the following diseases and disorders: Cryopyrin-associated Periodic Syndromes; sickle cell disease; systemic lupus erythematosus; allodynia; graft versus host disease; hepatic disorders including non-alcoholic steatohepatitis (NASH), chronic liver disease, viral hepatitis, alcoholic steatohepatitis, and alcoholic liver disease; inflammatory bowel diseases including Crohn's disease and ulcerative colitis; inflammatory joint disorders including gout, pseudogout, arthropathy, osteoarthritis, rheumatoid arthritis; additional rheumatic diseases including dermatomyositis, Still's disease, and juvenile idiopathic arthritis. kidney related diseases including hyperoxaluria, lupus nephritis, hypertensive nephropathy, hemodialysis related inflammation, diabetic nephropathy, and diabetic kidney disease and other inflammatory diseases (Miyamae T. *Paediatr Drugs*, 2012 Apr 1, 14(2): 109-17; Szabo G and Petrasek J. *Nat Rev Gastroenterol Hepatol*, 2015 Jul;12(7):387-400; Zhen Y and Zhang H. *Front Immunol*, 2019 Feb 28;10:276; Vande Walle Let al., *Nature*, 2014 Aug 7;512(7512):69-73; Knauf et al., *Kidney Int*, 2013 Nov;84(5):895-901; Krishnan et al., *Br J Pharmacol*, 2016 Feb;l 73(4):752-65); Shahzad et al., *Kidney Int*, 2015 Jan; 87(1):74-84; Jankovic, et al. *J Exp Med*. 2013 Sep 23;210(10):1899-910.). The onset and progression of neuroinflammation-related disorders, such as brain infection, acute injury, multiple sclerosis, amyotrophic lateral sclerosis and additional neurodegenerative diseases such

as Parkinsons and Alzheimer's disease have also been linked to NLRP3 inflammasome activation (Sarkar et al., NPJ Parkinsons Dis, 2017 Oct 17;3:30).

[0007] Cardiovascular and metabolic disorders such as atherosclerosis, type I and type II diabetes and diabetes complications including nephropathy and retinopathy, peripheral artery disease, acute heart failure and hypertension have been associated to NLRP3 (Ridker et al., CANTOS Trial Group. N Engl J Med, 2017 Sep 21;377(12):1119-1131; and Toldo S and Abbate A Nat Rev Cardiol, 2018 Apr;15(4):203-214). NLRP3 associated skin diseases include wound healing and scar formation; inflammatory skin diseases such as acne, atopic dermatitis, hidradenitis suppurativa and psoriasis (Kelly et al., Br J Dermatol, 2015 Dec;173(6)). NLRP3 inflammasome activity has also been linked to respiratory conditions such as asthma, sarcoidosis, acute respiratory distress syndrome, Severe Acute Respiratory Syndrome (SARS) (Nieto-Torres et al., Virology, 2015 Nov;485:330-9)); and ocular diseases including age-related macular degeneration (AMD) and diabetic retinopathy (Doyle et al., Nat Med, 2012 May;18(5):791-8). Cancers linked to NLRP3 include myeloproliferative neoplasms, leukemias, myelodysplastic syndromes, myelofibrosis, lung cancer and colon cancer (Ridker et al., Lancet, 2017 Oct 21;390(10105): 1833-1842; Derangere et al., Cell Death Differ. 2014 Dec;21(12): 1914-24; Basiorka et al., Lancet Haematol, 2018 Sep;5(9): e393-e402, Zhang et al., Hum Immunol, 2018 Jan;79(1):57-62).

[0008] Immune diseases and inflammatory disorders are typically difficult to diagnose or treat efficiently and effectively. Most treatments include treatment of the symptoms, slowing down disease progression, lifestyle changes and surgery.

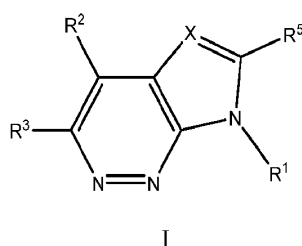
[0009] There remains a need for inhibitors of NLRP3 to provide new treatments for diseases and disorders associated with NLRP3 inflammasome activation and dysregulation. The compounds of structural formula I are useful for the treatment and prevention of diseases, disorders and conditions mediated by formation and propagation of the NLRP3 inflammasome.

[0010] NLRP3 inhibitors are disclosed in the following publications: *Nat.* 2022, 1; *Cell.* 2021, 184, 1; *J. Mol. Biol.* 2021, 433, 167308; *J. Med. Chem.* 2021, 64, 101; *Nat. Chem. Biol.* 2019, 15, 556; *Nat.* 2019, 570, 338; *Nat. Chem. Biol.* 2019, 15, 560; *PLOS Biol.* 2019, 1; *Nat. Med.* 2015, 21, 248; *Cell.* 2014, 156, 1193; *Nat. Immunol.* 2014, 15, 738; *PNAS.* 2007, 104, 8041; *Nat.* 2006, 440, 9; *Immunity.* 2006, 24, 317. Several patent applications describe NLRP3 inhibitors, including WO 2021/239885, WO 2021/209552, WO 2021/209539, WO 2021/193897, WO 2020/018975, WO 2020/037116, WO 2020/021447, WO 2020/010143, WO 2019/079119, WO 2019/0166621, WO 2019/121691, WO 2019/034696, WO 2019/034697, WO 2019/034693, WO

2019/034692, WO 2019/034690, WO 2019/034688, WO 2019/034686, WO 2019/008025, WO 2019/008029, WO 2019/023145, WO 2019/023147, WO 2019/025467, WO 2018/167468, WO 2018/015445, WO 2017/184746, WO 2017/184735, WO 2017/184623, WO 2017/184604, WO 2017/184624, WO 2017/140778, WO 2016/131098, US 11,319,319, US 2020/0361898, WO 2023/032987, WO 2023/032987, WO 2022/230912, WO 2023/275366, WO 2022/237781, WO 2022/036204, WO 2023/288039, WO 2022/204227, WO 2022/229315, WO 2022/184843, WO 2022/184842, WO 2022/063896, WO 2022/063876, WO 2021/219784, WO 2023/032987, WO 2022/166890, WO 2023/028534, WO 2023/028536, WO 2022/238347, WO 2022/253936, WO 2022/253326, WO 2022/135567, WO 2023/278438, and US 11,618,751.

SUMMARY

[0011] The present disclosure relates to novel compounds of structural formula I:



and pharmaceutically acceptable salts, hydrates and solvates thereof.

[0012] The compounds of structural formula I, and embodiments thereof, are inhibitors of NOD-like receptor protein 3 (NLRP3) and may be useful in the treatment and prevention of diseases, disorders and conditions mediated by NLRP3 such as, but not limited to, gout, pseudogout (chondrocalcinosis), cryopyrin-associated periodic syndromes (CAPS), NASH, fibrosis, heart failure, idiopathic pericarditis, atopic dermatitis, inflammatory bowel disease, Alzheimer's Disease, Parkinson's Disease and traumatic brain injury.

The present disclosure also relates to pharmaceutical compositions comprising the compounds of structural formula I, or a pharmaceutically acceptable salt, hydrate or solvate thereof, and a pharmaceutically acceptable carrier.

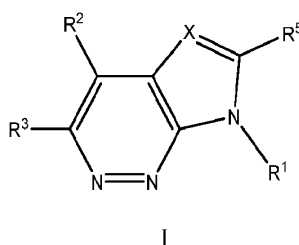
[0013] Also disclosed are methods for the treatment, management, prevention, alleviation, amelioration, suppression or control of disorders, diseases, and conditions that may be responsive to inhibition of the NLRP3 receptor in a subject in need thereof by administering the compounds and pharmaceutical compositions of the present disclosure.

[0014] The present disclosure also relates to the use of compounds of structural formula I for manufacture of a medicament useful in treating diseases, disorders and conditions that may be responsive to the inhibition of the NLRP3 receptor.

[0015] The present disclosure is also concerned with treatment or prevention of these diseases, disorders and conditions by administering the compounds of structural formula I in combination with a therapeutically effective amount of another agent that may be useful to treat the disease, disorder and condition. The disclosure is further concerned with processes for preparing the compounds of structural formula I.

DETAILED DESCRIPTION

[0016] The present disclosure is concerned with novel compounds of structural Formula I:



and pharmaceutically acceptable salts, hydrates and solvates thereof, wherein

X is independently selected from the group:

- (1) =C(R⁴)-, and
- (2) =N-;

R¹ is selected from the group:

- (1) -C₃₋₁₂cycloalkyl,
- (2) -C₃₋₁₂cycloalkenyl,
- (3) -C₂₋₁₁cycloheteroalkyl,
- (4) -C₂₋₁₁cycloheteroalkenyl,
- (5) aryl,
- (6) heteroaryl,
- (7) -C₁₋₆alkyl,
- (8) -C₁₋₆alkyl-OH,
- (9) -C₁₋₆alkyl-C₃₋₁₂cycloalkyl,
- (10) -C₁₋₆alkyl-C₃₋₁₂cycloalkenyl,

- (11) -C₁₋₆alkyl-C₂₋₁₁cycloheteroalkyl,
- (12) -C₁₋₆alkyl-C₂₋₁₁cycloheteroalkenyl,
- (13) -C₁₋₆alkyl-aryl, and
- (14) -C₁₋₆alkyl-heteroaryl,

wherein R¹ is unsubstituted or substituted with one to six substituents selected from R^a;

R² is selected from the group:

- (1) hydrogen,
- (2) CN,
- (3) -CF₃,
- (4) -CHF₂,
- (5) -C₁₋₆alkyl, and
- (6) halogen,

wherein alkyl is unsubstituted or substituted with one to five substituents selected from

R^b;

R³ is selected from the group:

- (1) aryl, and
- (2) heteroaryl,

wherein aryl and heteroaryl are unsubstituted or substituted with one to five substituents

selected from R^c;

R⁴ is selected from the group:

- (1) hydrogen,
- (2) CN,
- (3) -C₁₋₆alkyl,
- (4) -O-C₁₋₆alkyl, and
- (5) halogen,

wherein each alkyl is unsubstituted or substituted with one to five substituents selected

from R^d;

R⁵ is selected from the group:

- (1) hydrogen,
- (2) CN,
- (3) -C₁₋₆alkyl,

(4) -O-C₁₋₆alkyl, and

(5) halogen,

wherein each alkyl is unsubstituted or substituted with one to five substituents selected from R^e;

each R^a is independently selected from the group:

- (1) CN,
- (2) oxo,
- (3) -OH,
- (4) halogen,
- (5) -C₁₋₆alkyl,
- (6) -C₁₋₆alkyl-OH,
- (7) -O-C₁₋₆alkyl,
- (8) -C₃₋₆cycloalkyl,
- (9) -C₂₋₆cycloheteroalkyl,
- (10) aryl,
- (11) heteroaryl,
- (12) -C(O)C₁₋₆alkyl,
- (13) -C(O)C₃₋₆cycloalkyl,
- (14) -C₁₋₆alkyl-aryl,
- (15) -C₁₋₆alkyl-heteroaryl,
- (16) -C₁₋₆alkyl-C₃₋₆cycloalkyl,
- (17) -C₁₋₆alkyl-C₂₋₆cycloheteroalkyl,
- (18) -(CH₂)_p-O-C₁₋₆alkyl,
- (19) -(CH₂)_p-O-C₃₋₆cycloalkyl,
- (20) -(CH₂)_p-O-C₂₋₆cycloheteroalkyl,
- (21) -(CH₂)_p-O-aryl,
- (22) -(CH₂)_p-O-heteroaryl,
- (23) -(CH₂)_p-S(O)_rR^f, and
- (24) -N(R^g)₂.

wherein each R^a is unsubstituted or substituted with one to six substituents selected from halogen, CF₃, OH, C₁₋₆alkyl, and -OC₁₋₆alkyl;

each R^b is independently selected from the group:

- (1) CF₃,
- (2) halogen,
- (3) -C₁₋₆alkyl, and
- (4) -C₃₋₆cycloalkyl;

each R^c is independently selected from the group:

- (1) CN,
- (2) -OH,
- (3) oxo,
- (4) halogen,
- (5) -C₁₋₆alkyl,
- (6) -O-C₁₋₆alkyl,
- (7) -C₃₋₆cycloalkyl,
- (8) -C₂₋₆cycloheteroalkyl,
- (9) aryl,
- (10) heteroaryl,
- (11) -C₁₋₆alkyl-aryl,
- (12) -C₁₋₆alkyl-heteroaryl,
- (13) -C₁₋₆alkyl-C₃₋₆cycloalkyl,
- (14) -C₁₋₆alkyl-C₂₋₆cycloheteroalkyl,
- (15) -(CH₂)_q-O-C₁₋₆alkyl,
- (16) -(CH₂)_q-O-C₃₋₆cycloalkyl,
- (17) -(CH₂)_q-O-C₂₋₆cycloheteroalkyl,
- (18) -(CH₂)_q-O-aryl,
- (19) -(CH₂)_q-O-heteroaryl,
- (20) -OC₁₋₆alkyl-C₃₋₆cycloalkyl,
- (21) -OC₁₋₆alkyl-C₂₋₆cycloheteroalkyl,
- (22) -OC₁₋₆alkyl-aryl,

(23) $-\text{OC}_{1-6}\text{alkyl-heteroaryl}$,

(24) $-(\text{CH}_2)_q-\text{S}(\text{O})_r\text{R}^h$,

(25) $-\text{N}(\text{R}^i)_2$,

(26) $-\text{C}(\text{O})\text{R}^j$, and

(27) $-\text{C}(\text{O})\text{NR}^i$,

wherein each R^c is unsubstituted or substituted with one to six substituents selected from halogen, CF_3 , CF_2H , OCF_3 , CN , CH_2CF_3 , CF_2CH_3 , $-\text{C}_{1-6}\text{alkyl}$, and $-\text{OC}_{1-6}\text{alkyl}$;

each R^d is independently selected from the group:

- (1) hydrogen,
- (2) OH
- (3) halogen, and
- (4) $-\text{C}_{1-6}\text{alkyl}$;

each R^e is independently selected from the group:

- (1) hydrogen,
- (2) OH,
- (3) halogen, and
- (4) $-\text{C}_{1-6}\text{alkyl}$;

each R^f is independently selected from the group:

- (1) hydrogen,
- (2) $-\text{C}_{1-6}\text{alkyl}$,
- (3) $-\text{C}_{3-6}\text{cycloalkyl}$, and
- (4) $-\text{C}_{2-6}\text{cycloheteroalkyl}$;

each R^g is independently selected from the group:

- (1) hydrogen,
- (2) $-\text{C}_{1-6}\text{alkyl}$,
- (3) $-\text{C}_{3-6}\text{cycloalkyl}$,
- (4) $-\text{C}_{2-6}\text{cycloheteroalkyl}$,
- (5) aryl,
- (6) heteroaryl,
- (7) $-\text{C}(\text{O})\text{C}_{1-6}\text{alkyl}$, and

(8) $-S(O)_rR^f$,

wherein alkyl can be unsubstituted or substituted with one to three substituents selected from: CF_3 , halogen, OH and $-OC_1-6alkyl$;

each R^h is independently selected from the group:

- (1) hydrogen,
- (2) $-C_1-6alkyl$,
- (3) $-C_3-6cycloalkyl$, and
- (4) $-C_2-6cycloheteroalkyl$;

each R^i is independently selected from the group:

- (1) hydrogen,
- (2) $-C_1-6alkyl$,
- (3) $-C_3-6cycloalkyl$, and
- (4) $-C_2-6cycloheteroalkyl$;

each R^j is independently selected from the group:

- (1) OH,
- (2) $-C_1-6alkyl$,
- (3) $-C_3-6cycloalkyl$, and
- (4) $-C_2-6cycloheteroalkyl$,

wherein alkyl can be unsubstituted or substituted with one to three substituents selected from: CF_3 , halogen, OH and $-OC_1-6alkyl$;

p is 0, 1, 2, 3, 4, 5 or 6;

q is 0, 1, 2, 3, 4, 5 or 6; and

r is 1 or 2.

[0017] The disclosure has numerous embodiments, which are summarized below. The disclosure includes the compounds as shown, and also includes individual diastereoisomers, enantiomers, and epimers of the compounds, and mixtures of diastereoisomers and/or enantiomers thereof including racemic mixtures.

[0018] In another embodiment of this invention, X is independently selected from the group: $=C(R^4)-$ and $=N-$. In a class of this embodiment, X is $=C(R^4)-$. In another class of this embodiment, X is $=N-$.

[0019] In one embodiment, R¹ is selected from the group: -C₃₋₁₂cycloalkyl, -C₃₋₁₂cycloalkenyl, -C₂₋₁₁cycloheteroalkyl, -C₂₋₁₁cycloheteroalkenyl, aryl, heteroaryl, -C₁₋₆alkyl, -C₁₋₆alkyl-OH, -C₁₋₆alkyl-C₃₋₁₂cycloalkyl, -C₁₋₆alkyl-C₃₋₁₂cycloalkenyl, -C₁₋₆alkyl-C₂₋₁₁cycloheteroalkyl, -C₁₋₆alkyl-C₂₋₁₁cycloheteroalkenyl, -C₁₋₆alkyl-aryl, and -C₁₋₆alkyl-heteroaryl, wherein R¹ is unsubstituted or substituted with one to six substituents selected from R^a.

[0020] In another embodiment, R¹ is selected from the group: -C₃₋₁₂cycloalkyl, -C₂₋₁₁cycloheteroalkyl, aryl, heteroaryl, -C₁₋₆alkyl, -C₁₋₆alkyl-OH, -C₁₋₆alkyl-C₃₋₁₂cycloalkyl, -C₁₋₆alkyl-C₂₋₁₁cycloheteroalkyl, -C₁₋₆alkyl-aryl, and -C₁₋₆alkyl-heteroaryl, wherein R¹ is unsubstituted or substituted with one to six substituents selected from R^a.

[0021] In another embodiment, R¹ is selected from the group: -C₃₋₁₂cycloalkyl, -C₂₋₁₁cycloheteroalkyl, aryl, heteroaryl, -C₁₋₆alkyl, -C₁₋₆alkyl-OH, -C₁₋₆alkyl-C₃₋₁₂cycloalkyl, and -C₁₋₆alkyl-C₂₋₁₁cycloheteroalkyl, wherein R¹ is unsubstituted or substituted with one to six substituents selected from R^a.

[0022] In another embodiment, R¹ is selected from the group: -C₃₋₁₂cycloalkyl, -C₂₋₁₁cycloheteroalkyl, heteroaryl, -C₁₋₆alkyl, -C₁₋₆alkyl-OH, -C₁₋₆alkyl-C₃₋₁₂cycloalkyl, and -C₁₋₆alkyl-C₂₋₁₁cycloheteroalkyl, wherein R¹ is unsubstituted or substituted with one to six substituents selected from R^a.

[0023] In another embodiment, R¹ is selected from the group: -C₃₋₁₂cycloalkyl, -C₂₋₁₁cycloheteroalkyl, heteroaryl, -C₁₋₆alkyl-OH, -C₁₋₆alkyl-C₃₋₁₂cycloalkyl, and -C₁₋₆alkyl-C₂₋₁₁cycloheteroalkyl, wherein R¹ is unsubstituted or substituted with one to six substituents selected from R^a.

[0024] In another embodiment, R¹ is selected from the group: -C₃₋₁₂cycloalkyl, -C₂₋₁₁cycloheteroalkyl, -C₁₋₆alkyl-C₃₋₁₂cycloalkyl, and -C₁₋₆alkyl-C₂₋₁₁cycloheteroalkyl, wherein R¹ is unsubstituted or substituted with one to six substituents selected from R^a.

[0025] In another embodiment, R¹ is selected from the group: -C₃₋₁₂cycloalkyl, and -C₂₋₁₁cycloheteroalkyl, wherein R¹ is unsubstituted or substituted with one to six substituents selected from R^a. In a class of this embodiment, R¹ is selected from the group: bicyclo[3.1.1]heptane, piperidine, 8-azabicyclo[3.2.1]octane, and octahydroindolizine, wherein R¹ is unsubstituted or substituted with one to six substituents selected from R^a.

[0026] In another embodiment, R^1 is $-C_{3-12}$ cycloalkyl, wherein R^1 is unsubstituted or substituted with one to six substituents selected from R^a . In a class of this embodiment, R^1 is bicyclo[3.1.1]heptane, wherein bicyclo[3.1.1]heptane is unsubstituted or substituted with one to six substituents selected from R^a .

[0027] In another embodiment, R^1 is C_{2-11} cycloheteroalkyl, wherein cycloheteroalkyl is unsubstituted or substituted with one to six substituents selected from R^a . In a class of this embodiment, R^1 is piperidine, wherein piperidine is unsubstituted or substituted with one to six substituents selected from R^a . In another class of this embodiment, R^1 is selected from the group: piperidine, 8-azabicyclo[3.2.1]octane, and octahydroindolizine, wherein R^1 is unsubstituted or substituted with one to six substituents selected from R^a .

[0028] In another embodiment, R^2 is selected from the group: hydrogen, CN, $-CF_3$, $-CHF_2$, $-C_{1-6}$ alkyl, and halogen, wherein R^2 is unsubstituted or substituted with one to five substituents selected from R^b . In a class of this embodiment, R^2 is selected from the group: hydrogen, and $-C_{1-6}$ alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents selected from R^b . In a subclass of this class, R^2 is hydrogen or $-CH_3$, wherein $-CH_3$ is unsubstituted or substituted with one to three substituents selected from R^b . In another class of this embodiment, R^2 is $-C_{1-6}$ alkyl, wherein R^2 is unsubstituted or substituted with one to five substituents selected from R^b . In a subclass of this class, R^2 is $-CH_3$, wherein R^2 is unsubstituted or substituted with one to three substituents selected from R^b . In another class of this embodiment, R^2 is hydrogen.

[0029] In another embodiment of the present invention, R^3 is selected from the group: aryl and heteroaryl, wherein R^3 is unsubstituted or substituted with one to five substituents selected from R^c . In a class of this embodiment, R^3 is selected from the group: phenyl, benzothiophene and indane, wherein R^3 is unsubstituted or substituted with one to five substituents selected from R^c .

[0030] In another embodiment, R^3 is heteroaryl, wherein heteroaryl is unsubstituted or substituted with one to five substituents selected from R^c . In a class of this embodiment, R^3 is benzothiophene, wherein R^3 is unsubstituted or substituted with one to five substituents selected from R^c .

[0031] In another embodiment, R^3 is aryl, wherein aryl is unsubstituted or substituted with one to five substituents selected from R^c . In a class of this embodiment, R^3 is phenyl or indane, wherein R^3 is unsubstituted or substituted with one to five substituents selected from R^c . In

another class of this embodiment, R³ is phenyl, unsubstituted or substituted with one to five substituents selected from R^c. In another class of this embodiment, R³ is indane, unsubstituted or substituted with one to five substituents selected from R^c.

[0032] In another embodiment of this invention, R⁴ is selected from the group: hydrogen, CN, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and halogen, wherein each alkyl is unsubstituted or substituted with one to five substituents selected from R^d.

[0033] In another embodiment of this invention, R⁴ is hydrogen or -C₁₋₆alkyl, wherein each alkyl is unsubstituted or substituted with one to five substituents selected from R^d.

[0034] In another embodiment of this invention, R⁴ is -C₁₋₆alkyl, wherein each alkyl is unsubstituted or substituted with one to five substituents selected from R^d.

[0035] In another embodiment of this invention, R⁴ is hydrogen.

[0036] In another embodiment of this invention, R⁵ is selected from the group: hydrogen, CN, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and halogen, wherein each alkyl is unsubstituted or substituted with one to five substituents selected from R^e.

[0037] In another embodiment of this invention, R⁵ is selected from the group: hydrogen, CN, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and halogen, wherein each alkyl is unsubstituted or substituted with one to five substituents selected from R^e.

[0038] In another embodiment of this invention, R⁵ is hydrogen or -C₁₋₆alkyl, wherein each alkyl is unsubstituted or substituted with one to five substituents selected from R^e. In a class of this embodiment, R⁵ is hydrogen or -CH₃.

[0039] In another embodiment of this invention, R⁵ is -C₁₋₆alkyl, wherein each alkyl is unsubstituted or substituted with one to five substituents selected from R^e. In a class of this embodiment, R⁵ is -CH₃.

[0040] In another embodiment of this invention, R⁵ is hydrogen.

[0041] In another embodiment, each R^a is independently selected from the group: CN, oxo, -OH, halogen, -C₁₋₆alkyl, -C₁₋₆alkyl-OH, -O-C₁₋₆alkyl, -C₃₋₆cycloalkyl, -C₂₋₆cycloheteroalkyl, aryl, heteroaryl, -C(O)C₁₋₆alkyl, -C(O)C₃₋₆cycloalkyl, -C₁₋₆alkyl-aryl, -C₁₋₆alkyl-heteroaryl, -C₁₋₆alkyl-C₃₋₆cycloalkyl, -C₁₋₆alkyl-C₂₋₆cycloheteroalkyl, -(CH₂)_p-O-C₁₋₆alkyl, -(CH₂)_p-O-C₃₋₆cycloalkyl, -(CH₂)_p-O-C₂₋₆cycloheteroalkyl, -(CH₂)_p-O-aryl, -(CH₂)_p-O-heteroaryl, -(CH₂)_p-S(O)_rR^f, and -N(R^g)₂, wherein each R^a is unsubstituted or

substituted with one to six substituents selected from halogen, CF₃, OH, C₁₋₆alkyl, and -OC₁₋₆alkyl.

[0042] In another embodiment, each R^a is independently selected from the group: CN, oxo, -OH, halogen, -C₁₋₆alkyl, -C₁₋₆alkyl-OH, -O-C₁₋₆alkyl, -C₃₋₆cycloalkyl, -C₂₋₆cycloheteroalkyl, aryl, heteroaryl, -C₁₋₆alkyl-aryl, -C₁₋₆alkyl-heteroaryl, -C₁₋₆alkyl-C₃₋₆cycloalkyl, -C₁₋₆alkyl-C₂₋₆cycloheteroalkyl, -(CH₂)_p-S(O)_rR^f, and -N(R^g)₂, wherein each R^a is unsubstituted or substituted with one to six substituents selected from halogen, CF₃, OH, C₁₋₆alkyl, and -OC₁₋₆alkyl.

[0043] In another embodiment, each R^a is independently selected from the group: CN, oxo, -OH, halogen, -C₁₋₆alkyl, -C₁₋₆alkyl-OH, -O-C₁₋₆alkyl, -C₃₋₆cycloalkyl, -C₂₋₆cycloheteroalkyl, -C₁₋₆alkyl-C₃₋₆cycloalkyl, -C₁₋₆alkyl-C₂₋₆cycloheteroalkyl, -(CH₂)_p-S(O)_rR^f, and -N(R^g)₂, wherein each CH₂, alkyl, cycloalkyl and cycloheteroalkyl is independently unsubstituted or substituted with one to six substituents selected from halogen, CF₃, OH, C₁₋₆alkyl, and -OC₁₋₆alkyl.

[0044] In another embodiment, each R^a is independently selected from the group: CN, oxo, -OH, halogen, -C₁₋₆alkyl, -C₁₋₆alkyl-OH, -O-C₁₋₆alkyl, -C₃₋₆cycloalkyl, -C₂₋₆cycloheteroalkyl, aryl, heteroaryl, -C₁₋₆alkyl-C₃₋₆cycloalkyl, -C₁₋₆alkyl-C₂₋₆cycloheteroalkyl, -(CH₂)_p-S(O)_rR^f, and -N(R^g)₂, wherein each CH₂, alkyl, cycloalkyl and cycloheteroalkyl is independently unsubstituted or substituted with one to six substituents selected from halogen, CF₃, OH, C₁₋₆alkyl, and -OC₁₋₆alkyl.

[0045] In another embodiment, each R^a is independently selected from the group: CN, oxo, -OH, halogen, -C₁₋₆alkyl, -C₁₋₆alkyl-OH, -O-C₁₋₆alkyl, -C₃₋₆cycloalkyl, -C₂₋₆cycloheteroalkyl, aryl, heteroaryl, -C₁₋₆alkyl-C₃₋₆cycloalkyl, and -C₁₋₆alkyl-C₂₋₆cycloheteroalkyl, wherein each CH₂, alkyl, cycloalkyl and cycloheteroalkyl is independently unsubstituted or substituted with one to six substituents selected from halogen, CF₃, OH, C₁₋₆alkyl, and -OC₁₋₆alkyl.

[0046] In another embodiment, each R^a is independently selected from the group: CN, oxo, -OH, halogen, -C₁₋₆alkyl, -C₁₋₆alkyl-OH, -O-C₁₋₆alkyl, -C₃₋₆cycloalkyl, -C₁₋₆alkyl-C₃₋₆cycloalkyl, -(CH₂)_p-S(O)_rR^f and -N(R^g)₂, wherein each CH₂, alkyl, and cycloalkyl is

independently unsubstituted or substituted with one to six substituents selected from halogen, CF₃, OH, C₁₋₆alkyl, and -OC₁₋₆alkyl.

[0047] In another embodiment, each R^a is independently selected from the group: CN, oxo, -OH, halogen, -C₁₋₆alkyl, -C₁₋₆alkyl-OH, -O-C₁₋₆alkyl, -C₃₋₆cycloalkyl, and -C₁₋₆alkyl-C₃₋₆cycloalkyl, wherein each CH₂, alkyl, and cycloalkyl is independently unsubstituted or substituted with one to six substituents selected from halogen, CF₃, OH, C₁₋₆alkyl, and -OC₁₋₆alkyl.

[0048] In another embodiment, each R^a is independently selected from the group: -OH, -C₁₋₆alkyl, and -C₃₋₆cycloalkyl, wherein each alkyl, and cycloalkyl is independently unsubstituted or substituted with one to six substituents selected from halogen, CF₃, OH, C₁₋₆alkyl, and -OC₁₋₆alkyl. In a class of this embodiment, each R^a is independently selected from the group: -OH, -CH₃, -CD₃, -CH₂CH₃, -CH(CH₃)₂, and cyclobutyl. In another class of this embodiment, each R^a is independently selected from the group: -OH, -CH₃, -CH₂CH₃, -CH(CH₃)₂, and cyclobutyl. In another class of this embodiment, each R^a is independently selected from the group: -OH, -CH₃, -CD₃, -CH₂CH₃, and -CH(CH₃)₂. In another class of this embodiment, each R^a is independently selected from the group: -OH, -CH₃, -CH₂CH₃, and -CH(CH₃)₂.

[0049] In another embodiment, each R^a is -OH or -C₁₋₆alkyl, wherein each alkyl is unsubstituted or substituted with one to six substituents selected from halogen, CF₃, OH, C₁₋₆alkyl, and -OC₁₋₆alkyl. In a class of this embodiment, each R^a is independently selected from the group: -OH, -CH₃ and -CH₂CH₃.

[0050] In another embodiment, each R^a is -OH.

[0051] In another embodiment, each R^a is -C₁₋₆alkyl, wherein each alkyl is unsubstituted or substituted with one to six substituents selected from halogen, CF₃, OH, C₁₋₆alkyl, and -OC₁₋₆alkyl. In a class of this embodiment, each R^a is -CH₃ or -CH₂CH₃.

[0052] In another embodiment of this invention, each R^b is independently selected from the group: CF₃, halogen, -C₁₋₆alkyl, and -C₃₋₆cycloalkyl. In a class of this embodiment, each R^b is independently selected from the group: CF₃, halogen, and -C₁₋₆alkyl. In another class of this embodiment, each R^b is CF₃. In another class of this embodiment, each R^b is halogen. In another class of this embodiment, each R^b is -C₁₋₆alkyl.

[0053] In another embodiment of this invention, each R^c is independently selected from the group: CN, -OH, oxo, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -C₃₋₆cycloalkyl, -C₂₋₆cycloheteroalkyl, aryl, heteroaryl, -C₁₋₆alkyl-aryl, -C₁₋₆alkyl-heteroaryl, -C₁₋₆alkyl-C₃₋₆cycloalkyl, -C₁₋₆alkyl-C₂₋₆cycloheteroalkyl, -(CH₂)_q-O-C₁₋₆alkyl, -(CH₂)_q-O-C₃₋₆cycloalkyl, -(CH₂)_q-O-C₂₋₆cycloheteroalkyl, -(CH₂)_q-O-aryl, -(CH₂)_q-O-heteroaryl, -OC₁₋₆alkyl-C₃₋₆cycloalkyl, -OC₁₋₆alkyl-C₂₋₆cycloheteroalkyl, -OC₁₋₆alkyl-aryl, -OC₁₋₆alkyl-heteroaryl, -(CH₂)_q-S(O)_rR^h, -N(Rⁱ)₂, -C(O)R^j, and -C(O)NRⁱ, wherein each R^c is unsubstituted or substituted with one to six substituents selected from halogen, CF₃, CF₂H, OCF₃, CN, CH₂CF₃, CF₂CH₃, -C₁₋₆alkyl, and -OC₁₋₆alkyl.

[0054] In another embodiment, each R^c is independently selected from the group: CN, -OH, oxo, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -C₃₋₆cycloalkyl, -C₂₋₆cycloheteroalkyl, aryl, heteroaryl, -(CH₂)_q-S(O)_rR^h, -N(Rⁱ)₂, -C(O)R^j, and -C(O)NRⁱ, wherein each R^c is unsubstituted or substituted with one to six substituents selected from halogen, CF₃, CF₂H, OCF₃, CN, CH₂CF₃, CF₂CH₃, -C₁₋₆alkyl, and -OC₁₋₆alkyl.

[0055] In another embodiment, each R^c is independently selected from the group: CN, -OH, oxo, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -(CH₂)_q-S(O)_rR^h, -N(Rⁱ)₂, -C(O)R^j, and -C(O)NRⁱ, wherein each alkyl is unsubstituted or substituted with one to six substituents selected from halogen, CF₃, CF₂H, OCF₃, CN, CH₂CF₃, CF₂CH₃, -C₁₋₆alkyl, and -OC₁₋₆alkyl.

[0056] In another embodiment, each R^c is independently selected from the group: CN, -OH, oxo, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -C₃₋₆cycloalkyl, and -N(Rⁱ)₂, wherein each R^c is unsubstituted or substituted with one to six substituents selected from halogen, CF₃, CF₂H, OCF₃, CN, CH₂CF₃, CF₂CH₃, -C₁₋₆alkyl, and -OC₁₋₆alkyl. In a class of this embodiment, each R^c is independently selected from the group: -OH, Cl, F, -CH₃, -CF₃, -OCHF₂, cyclopropyl and NH₂. In another class of this embodiment, each R^c is independently selected from the group: -OH, Cl, -CH₃, -CF₃, and -OCHF₂.

[0057] In another embodiment, each R^c is independently selected from the group: -OH, halogen, -C₁₋₆alkyl, -C₃₋₆cycloalkyl, and -N(Rⁱ)₂, wherein each R^c is unsubstituted or substituted with one to six substituents selected from halogen, CF₃, CF₂H, OCF₃, CN, CH₂CF₃, CF₂CH₃, -C₁₋₆alkyl, and -OC₁₋₆alkyl. In a class of this embodiment, each R^c is independently

selected from the group: -OH, Cl, F, -CH₃, -CF₃, -OCHF₂, cyclopropyl and NH₂. In another class of this embodiment, each R^c is independently selected from the group: -OH, Cl, -CH₃, -CF₃, and -OCHF₂.

[0058] In another embodiment, each R^c is independently selected from the group: -OH, halogen, -C₁₋₆alkyl and -O-C₁₋₆alkyl, wherein each alkyl is unsubstituted or substituted with one to six substituents selected from halogen, CF₃, CF₂H, OCF₃, CN, CH₂CF₃, CF₂CH₃, -C₁₋₆alkyl, and -OC₁₋₆alkyl. In a class of this embodiment, each R^c is independently selected from the group: -OH, Cl, F, -CH₃, -CF₃, and -OCHF₂. In another class of this embodiment, each R^c is independently selected from the group: -OH, Cl, -CH₃, -CF₃, and -OCHF₂.

[0059] In another embodiment, each R^c is independently selected from the group: -OH and -C₁₋₆alkyl, wherein each alkyl is unsubstituted or substituted with one to six substituents selected from halogen, CF₃, CF₂H, OCF₃, CN, CH₂CF₃, CF₂CH₃, -C₁₋₆alkyl, and -OC₁₋₆alkyl. In a class of this embodiment, each R^c is independently selected from the group: -OH, -CH₃, and -CF₃.

[0060] In another embodiment, each R^c is independently selected from the group: -OH.

[0061] In another embodiment, each R^c is independently selected from the group: -C₁₋₆alkyl, wherein each alkyl is unsubstituted or substituted with one to six substituents selected from halogen, CF₃, CF₂H, OCF₃, CN, CH₂CF₃, CF₂CH₃, -C₁₋₆alkyl, and -OC₁₋₆alkyl. In a class of this embodiment, each R^c is independently selected from the group: -OH, -CH₃, and -CF₃.

[0062] In another embodiment of this invention, each R^d is independently selected from the group: hydrogen, OH, halogen, and -C₁₋₆alkyl. In another embodiment of this invention, each R^d is independently selected from the group: hydrogen, halogen, and -C₁₋₆alkyl. In another embodiment of this invention, each R^d is independently selected from the group: hydrogen, and -C₁₋₆alkyl. In a class of this embodiment, each R^d is -C₁₋₆alkyl. In another class of this embodiment, each R^d is hydrogen.

[0063] In another embodiment of this invention, each R^e is independently selected from the group: hydrogen, OH, halogen, and -C₁₋₆alkyl. In another embodiment of this invention, each R^e is independently selected from the group: hydrogen, halogen, and -C₁₋₆alkyl. In another embodiment of this invention, each R^e is independently selected from the group: hydrogen, and -

C₁₋₆alkyl. In a class of this embodiment, each R^e is -C₁₋₆alkyl. In another class of this embodiment, each R^e is hydrogen.

[0064] In another embodiment, each R^f is independently selected from the group: hydrogen, -C₁₋₆alkyl, -C₃₋₆cycloalkyl, and -C₂₋₆cycloheteroalkyl. In another embodiment, each R^f is independently selected from the group: hydrogen, and -C₁₋₆alkyl. In a class of this embodiment, each R^f is independently selected from the group: hydrogen, and CH₃. In another embodiment, each R^f is -C₁₋₆alkyl. In a class of this embodiment, each R^f is CH₃. In another embodiment, each R^f is hydrogen.

[0065] In another embodiment of this invention, each R^g is independently selected from the group: hydrogen, -C₁₋₆alkyl, -C₃₋₆cycloalkyl, -C₂₋₆cycloheteroalkyl, aryl, heteroaryl, -C(O)C₁₋₆alkyl, and -S(O)_rR^f, wherein alkyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl can be unsubstituted or substituted with one to three substituents selected from: CF₃, halogen, OH and -OC₁₋₆alkyl. In a class of this embodiment, each R^g is independently selected from the group: hydrogen, -C₁₋₆alkyl, -C₃₋₆cycloalkyl, -C₂₋₆cycloheteroalkyl, -C(O)C₁₋₆alkyl, and -S(O)_rR^f, wherein alkyl, cycloalkyl and cycloheteroalkyl can be unsubstituted or substituted with one to three substituents selected from: CF₃, halogen, OH and -OC₁₋₆alkyl.

[0066] In another embodiment, each R^g is independently selected from the group: hydrogen, -C₁₋₆alkyl, -C(O)C₁₋₆alkyl, and -S(O)_rR^f, wherein alkyl can be unsubstituted or substituted with one to three substituents selected from: CF₃, halogen, OH and -OC₁₋₆alkyl. In another embodiment, each R^g is hydrogen or -C₁₋₆alkyl, wherein alkyl can be unsubstituted or substituted with one to three substituents selected from: CF₃, halogen, OH and -OC₁₋₆alkyl. In a class of this embodiment, each R^g is -C₁₋₆alkyl, wherein alkyl can be unsubstituted or substituted with one to three substituents selected from: CF₃, halogen, OH and -OC₁₋₆alkyl. In another class of this embodiment, each R^g is hydrogen.

[0067] In another embodiment of this invention, each R^h is independently selected from the group: hydrogen, -C₁₋₆alkyl, -C₃₋₆cycloalkyl, and -C₂₋₆cycloheteroalkyl. In another embodiment, each R^h is independently selected from the group: hydrogen and -C₁₋₆alkyl. In a class of this embodiment, each R^h is independently selected from the group: hydrogen and CH₃.

In another embodiment, each R^h is -C₁₋₆alkyl. In a class of this embodiment, each R^h is CH₃. In another embodiment, each R^h is hydrogen.

[0068] In another embodiment of this invention, each R^i is independently selected from the group: hydrogen, -C₁₋₆alkyl, -C₃₋₆cycloalkyl, and -C₂₋₆cycloheteroalkyl. In another embodiment, each R^i is independently selected from the group: hydrogen and -C₁₋₆alkyl. In a class of this embodiment, each R^i is independently selected from the group: hydrogen, and CH₃. In another embodiment, each R^i is -C₁₋₆alkyl. In a class of this embodiment, each R^i is CH₃. In another embodiment, each R^i is hydrogen.

[0069] In another embodiment of this invention, each R^j is independently selected from the group: OH, -C₁₋₆alkyl, -C₃₋₆cycloalkyl, and -C₂₋₆cycloheteroalkyl, wherein alkyl, cycloalkyl and cycloheteroalkyl can be unsubstituted or substituted with one to three substituents selected from: CF₃, halogen, OH and -OC₁₋₆alkyl. In another embodiment of this invention, each R^j is independently selected from the group: OH, -C₁₋₆alkyl, -C₃₋₆cycloalkyl, and -C₂₋₆cycloheteroalkyl. In another embodiment, each R^j is independently selected from the group: OH and -C₁₋₆alkyl. In a class of this embodiment, each R^j is independently selected from the group: OH and CH₃. In another embodiment, each R^j is -C₁₋₆alkyl. In a class of this embodiment, each R^j is CH₃. In another embodiment, each R^j is OH.

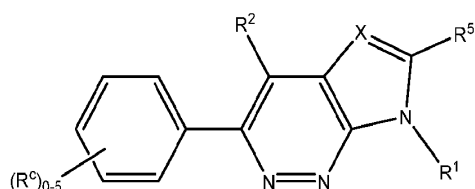
[0070] In another embodiment, p is 0, 1, 2, 3, 4, 5 or 6. In another embodiment, p is 0, 1, 2, 3, 4, or 5. In another embodiment, p is 1, 2, 3, 4, 5 or 6. In another embodiment, p is 1, 2, 3, 4 or 5. In another embodiment, p is 0, 1, 2, 3, or 4. In another embodiment, p is 1, 2, 3, or 4. In another embodiment, p is 0, 1, 2, or 3. In another embodiment, p is 1, 2, or 3. In another embodiment, p is 0, 1 or 2. In another embodiment, p is 1 or 2. In another embodiment, p is 0. In another embodiment, p is 1. In another embodiment, p is 2. In another embodiment, p is 3. In another embodiment, p is 4. In another embodiment, p is 5. In another embodiment, p is 6.

[0071] In another embodiment, q is 0, 1, 2, 3, 4, 5 or 6. In another embodiment, q is 0, 1, 2, 3, 4, or 5. In another embodiment, q is 1, 2, 3, 4, 5 or 6. In another embodiment, q is 1, 2, 3, 4 or 5. In another embodiment, q is 0, 1, 2, 3, or 4. In another embodiment, q is 1, 2, 3, or 4. In another embodiment, q is 0, 1, 2, or 3. In another embodiment, q is 1, 2, or 3. In another embodiment, q is 0, 1 or 2. In another embodiment, q is 1 or 2. In another embodiment, q is 0. In another

embodiment, q is 1. In another embodiment, q is 2. In another embodiment, q is 3. In another embodiment, q is 4. In another embodiment, q is 5. In another embodiment, q is 6.

[0072] In another embodiment, r is 1 or 2. In another embodiment, r is 1. In another embodiment, r is 2.

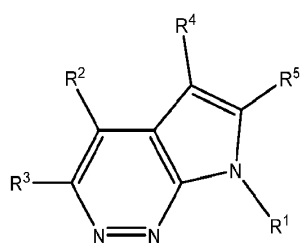
[0073] In another embodiment, the disclosure relates to compounds of structural formula Ia:



Ia

or a pharmaceutically acceptable salt, hydrate or solvate thereof.

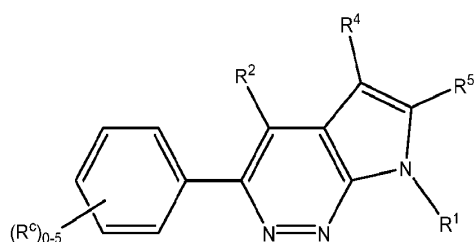
[0074] In another embodiment, the disclosure relates to compounds of structural formula Ib:



Ib

or a pharmaceutically acceptable salt, hydrate or solvate thereof.

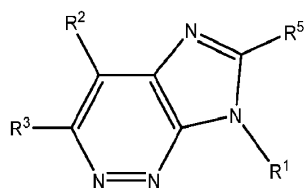
[0075] In another embodiment, the disclosure relates to compounds of structural formula Ic:



Ic

or a pharmaceutically acceptable salt, hydrate or solvate thereof.

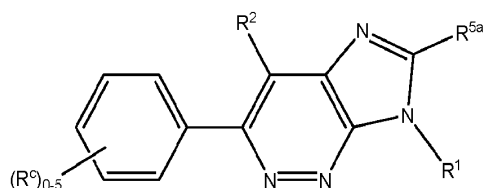
[0076] In another embodiment, the disclosure relates to compounds of structural formula Id:



Id

or a pharmaceutically acceptable salt, hydrate or solvate thereof.

[0077] In another embodiment, the disclosure relates to compounds of structural formula i.e.,



Ic

or a pharmaceutically acceptable salt, hydrate or solvate thereof.

[0078] The compound of structural formula I, includes the compounds of structural formulas Ia, Ib, Ic, Id, and i.e., and pharmaceutically acceptable salts, hydrates and solvates thereof.

[0079] In another embodiment, the disclosure relates to compounds of structural formula I wherein:

X is =C(R⁴)- or =N-;

R¹ is selected from the group:

- (1) -C₃₋₁₂cycloalkyl,
- (2) -C₂₋₁₁cycloheteroalkyl,
- (3) heteroaryl,
- (4) -C₁₋₆alkyl-OH,
- (5) -C₁₋₆alkyl-C₃₋₁₂cycloalkyl, and
- (6) -C₁₋₆alkyl-C₂₋₁₁cycloheteroalkyl,

wherein R¹ is unsubstituted or substituted with one to six substituents selected from R^a;

R² is selected from the group: hydrogen, and -C₁₋₆alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents selected from R^b;

R³ is heteroaryl, wherein heteroaryl is unsubstituted or substituted with one to five substituents selected from R^c;

R^4 is hydrogen or $-C_{1-6}$ alkyl, wherein each alkyl is unsubstituted or substituted with one to five substituents selected from R^d ; and

R^5 is hydrogen or $-C_{1-6}$ alkyl, wherein each alkyl is unsubstituted or substituted with one to five substituents selected from R^e ;

and the other substituents are as defined above;

or pharmaceutically acceptable salts, hydrates and solvates thereof.

[0080] In another embodiment, the disclosure relates to compounds of structural formula I wherein:

X is $=C(R^4)-$ or $=N-$;

R^1 is C_{2-11} cycloheteroalkyl, wherein cycloheteroalkyl is unsubstituted or substituted with one to six substituents selected from R^a ;

R^2 is selected from the group: hydrogen, and $-C_{1-6}$ alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents selected from R^b ;

R^3 is aryl, wherein aryl is unsubstituted or substituted with one to five substituents selected from R^c ;

R^4 is hydrogen; and

R^5 is hydrogen;

and the other substituents are as defined above;

or pharmaceutically acceptable salts, hydrates and solvates thereof.

[0081] Another embodiment, the disclosure relates to compounds of structural formula I wherein:

X is $=N-$;

R^1 is C_{2-11} cycloheteroalkyl, wherein cycloheteroalkyl is unsubstituted or substituted with one to six substituents selected from R^a ;

R^2 is selected from the group: hydrogen, and $-C_{1-6}$ alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents selected from R^b ;

R^3 is aryl, wherein aryl is unsubstituted or substituted with one to five substituents selected from R^c ;

R^4 is hydrogen; and

R^5 is hydrogen;

and the other substituents are as defined above;

or pharmaceutically acceptable salts, hydrates and solvates thereof.

[0082] Illustrative, but non-limiting, examples of compounds of the disclosure that are useful as inhibitors of the NLRP3 are the following compounds:

- (1) (*R*)-2-(7-(1-ethylpiperidin-3-yl)-7*H*-pyrrolo[2,3-*c*]pyridazin-3-yl)-3-methyl-5-(trifluoromethyl)phenol;
- (2) (*R*)-2-(7-(1-ethylpiperidin-3-yl)-4-methyl-7*H*-pyrrolo[2,3-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol;
- (3) (*R*)-2-(7-(1-ethylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-3-methyl-5-(trifluoromethyl)phenol;
- (4) (*R*)-3-methyl-2-(7-(1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol;
- (5) (*S*)-3-methyl-2-(7-(1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol;
- (6) (*R*)-2-(4-methyl-7-(piperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol;
- (7) (3*S*,4*R*)-3-(3-(2-hydroxy-4-(trifluoromethyl)phenyl)-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-7-yl)piperidin-4-ol;
- (8) (*R*)-2-(7-(1-ethylpiperidin-3-yl)-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol;
- (9) (*R*)-2-(7-(1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol;
- (10) (*S*)-2-(7-(1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol;
- (11) (*R*)-3-(2-(difluoromethoxy)-4-(trifluoromethyl)phenyl)-7-(1-ethylpiperidin-3-yl)-4-methyl-7*H*-imidazo[4,5-*c*]pyridazine;
- (12) (*R*)-2-(4-methyl-7-(1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol;
- (13) (3*S*,4*R*)-3-(3-(2-hydroxy-4-(trifluoro-methyl)phenyl)-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-7-yl)-1-methylpiperidin-4-ol; and
- (14) (3*S*,4*R*)-1-ethyl-3-(3-(2-hydroxy-4-(trifluoro-methyl)phenyl)-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-7-yl)piperidin-4-ol;
- (15) (*R*)-5-chloro-2-(4-methyl-7-(piperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)phenol;

- (16) (R)-2-(4,6-dimethyl-7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol;
- (17) (R)-5-(4-methyl-7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)benzo[*b*]thiophen-4-ol;
- (18) (R)-5-(4-methyl-7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)-2,3-dihydro-1H-inden-4-ol;
- (19) (R)-5-chloro-2-(4-methyl-7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)phenol; and
- (20) (R)-5-chloro-2-(7-(1-ethylpiperidin-3-yl)-4-methyl-7H-imidazo[4,5-c]pyridazin-3-yl)phenol;

or a pharmaceutically acceptable salt thereof.

[0083] Additional illustrative, but non-limiting, examples of compounds of the disclosure that are useful as inhibitors of the NLRP3 are the following compounds:

- (1) (R)-2-(7-(1-ethylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)-3-methyl-5-(trifluoromethyl)phenol;
- (2) (R)-2-(4-methyl-7-(piperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol;
- (3) (R)-2-(7-(1-ethylpiperidin-3-yl)-4-methyl-7H-imidazo[4,5-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol; and
- (4) (R)-2-(4-methyl-7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol;

or a pharmaceutically acceptable salt, hydrate or solvate thereof.

[0084] Although the specific stereochemistries described above are preferred, other stereoisomers, including diastereoisomers, enantiomers, epimers, and mixtures of these may also have utility in treating NLRP3 mediated diseases.

[0085] Synthetic methods for making the compounds are disclosed in the Examples shown below. Where synthetic details are not provided in the examples, the compounds are readily made by a person of ordinary skill in the art of medicinal chemistry or synthetic organic chemistry by applying the synthetic information provided herein. Where a stereochemical center is not defined, the structure represents a mixture of stereoisomers at that center. For such compounds, the individual stereoisomers, including enantiomers, diastereoisomers, and mixtures of these are also compounds of the disclosure.

DEFINITIONS

[0086] “Ac” is acetyl, which is $\text{CH}_3\text{C}(=\text{O})-$.

[0087] “Alkyl” means saturated carbon chains which may be linear or branched or combinations thereof, unless the carbon chain is defined otherwise. Other groups having the prefix „alk“, such as alkoxy and alkanoyl, also may be linear or branched, or combinations thereof, unless the carbon chain is defined otherwise. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, and the like. In one embodiment, alkyl is methyl or ethyl. In another embodiment, alkyl is methyl. In another embodiment, alkyl is ethyl.

[0088] “Alkenyl” means carbon chains which contain at least one carbon-carbon double bond, and which may be linear or branched, or combinations thereof, unless otherwise defined. Examples of alkenyl include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, and the like.

[0089] “Alkynyl” means carbon chains which contain at least one carbon-carbon triple bond, and which may be linear or branched, or combinations thereof, unless otherwise defined. Examples of alkynyl include ethynyl, propargyl, 3-methyl-1-pentyne, 2-heptyne and the like.

[0090] “Cycloalkyl” means a saturated monocyclic, bicyclic, spirocyclic, fused or bridged carbocyclic ring, having a specified number of carbon atoms. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like. In one embodiment, cycloalkyl is $\text{-C}_3\text{-}_{12}\text{cycloalkyl}$.

[0091] “Cycloalkenyl” means a monocyclic, bicyclic, spirocyclic, fused or bridged carbocyclic ring, having a specified number of carbon atoms with at least one double bond. Examples of cycloalkenyl include cyclopropene, cyclobutene, cyclopentene, cyclohexene, cycloheptene, and the like.

[0092] “Cycloheteroalkyl” means a monocyclic, bicyclic, spirocyclic, fused or bridged ring or ring system having a specified number of carbon atoms and containing at least one saturated ring wherein at least one ring heteroatom selected from N, NH, S (including SO and SO_2) and O, or with at least one partially unsaturated ring wherein at least one ring heteroatom selected from N, NH, S (including SO and SO_2) and O. The cycloheteroalkyl ring may be substituted on the ring carbons and/or the ring nitrogen or sulfur. The cycloheteroalkyl ring may be fused to an aryl or heteroaryl ring. Examples of cycloheteroalkyl include tetrahydrofuranyl, pyrrolidinyl, tetrahydrothiophenyl, azetidyl, piperazinyl, piperidinyl, morpholinyl, oxetanyl and

tetrahydropyranyl. In one embodiment, cycloheteroalkyl is C₂₋₁₁cycloheteroalkyl. In another embodiment, C₂₋₁₁cycloheteroalkyl is piperidine.

[0093] “Cycloheteroalkenyl” means a monocyclic, bicyclic, spirocyclic, fused, or bridged ring or ring system having a specified number of carbon atoms and containing at least one double bond and at least one heteroatom selected from N, NH, S (including SO and SO₂) and O.

Examples of cycloheteroalkenyl include dihydropyran and dihydrofuran, and the like.

[0094] “Aryl” means a monocyclic, bicyclic or tricyclic carbocyclic aromatic ring or ring system containing 6-14 carbon atoms, wherein at least one of the rings is aromatic. Examples of aryl include phenyl, indane and naphthalene. In one embodiment, aryl is phenyl. In another embodiment, aryl is indane.

[0095] “Heteroaryl” means a monocyclic, bicyclic or tricyclic ring or ring system containing 5-14 ring atoms and containing at least one ring heteroatom selected from N, NH, S (including SO and SO₂) and O, wherein at least one of the heteroatom containing rings is aromatic. Examples of heteroaryl include pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl, oxazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, triazinyl, thienyl, pyrimidyl, pyridazinyl, pyrazinyl, benzisoxazolyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl, quinolyl, indolyl, isoquinolyl, quinazolinyl, dibenzofuranyl, and the like. In one embodiment, heteroaryl is benzothiophene.

[0096] “Halogen” includes fluorine, chlorine, bromine and iodine. In one embodiment, halogen is fluorine, chlorine or bromine. In another embodiment, halogen is fluorine or chlorine. In another embodiment, halogen is chlorine or bromine. In another embodiment, halogen is fluorine or bromine. In another embodiment, halogen is fluorine. In another embodiment, halogen is chlorine. In another embodiment, halogen is bromine.

[0097] “Me” represents methyl.

[0098] “Oxo” represents =O.

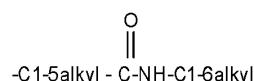
[0099] “Saturated” means containing only single bonds.

[0100] “Unsaturated” means containing at least one double or triple bond. In one embodiment, unsaturated means containing at least one double bond. In another embodiment, unsaturated means containing at least one triple bond.

[0101] When any variable (e.g., R¹, R^a, etc.) occurs more than one time in any constituent or in structural formula I, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such

combinations result in stable compounds. A squiggly line across a bond in a substituent variable represents the point of attachment.

[0102] Under nomenclature used throughout this disclosure, the point of attachment is described first, followed by the terminal portion of the designated side chain. For example, a C₁-5 alkylcarbonylamino C₁-6 alkyl substituent is equivalent to:



[0103] In choosing compounds of the present disclosure, one of ordinary skill in the art will recognize that the various substituents, i.e., R¹, R², etc., are to be chosen in conformity with well-known principles of chemical structure connectivity and stability.

[0104] The term "substituted" shall be deemed to include multiple degrees of substitution by a named substituent. Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally. By independently substituted, it is meant that the (two or more) substituents can be the same or different.

[0105] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, salts and/or dosage forms which are, using sound medical judgment, and following all applicable government regulations, safe and suitable for administration to a human being or an animal.

[0106] Compounds of structural formula I may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present disclosure is meant to encompass all such isomeric forms of the compounds of structural formula I.

[0107] The independent syntheses of optical isomers and diastereoisomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the X-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration or sufficient heavy atoms to make an absolute assignment.

[0108] If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well-known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound

to form a diastereoisomeric mixture, followed by separation of the individual diastereoisomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diastereomeric derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art.

[0109] Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

[0110] Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

[0111] Tautomers are defined as compounds that undergo rapid proton shifts from one atom of the compound to another atom of the compound. Some of the compounds described herein may exist as tautomers with different points of attachment of hydrogen. Such an example may be a ketone and its enol form known as keto-enol tautomers. The individual tautomers as well as mixture thereof are encompassed with compounds of structural formula I.

[0112] In the compounds of structural formula I, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominately found in nature. The present disclosure is meant to include all suitable isotopic variations of the compounds of structural formula I. For example, different isotopic forms of hydrogen (H) include protium (^1H), deuterium (^2H or D), and tritium (^3H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Tritium is radioactive and may therefore provide for a radiolabeled compound, useful as a tracer in metabolic or kinetic studies. Isotopically-enriched compounds within structural formula I, can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

[0113] Furthermore, some of the crystalline forms for compounds of the present disclosure may exist as polymorphs and as such are intended to be included in the present disclosure. In addition,

some of the compounds of the present disclosure may form solvates with water or common organic solvents. Such solvates are encompassed within the scope of this disclosure.

[0114] It is generally preferable to administer compounds of the present disclosure as enantiomerically pure formulations. Racemic mixtures can be separated into their individual enantiomers by any of a number of conventional methods. These include chiral chromatography, derivatization with a chiral auxiliary followed by separation by chromatography or crystallization, and fractional crystallization of diastereomeric salts.

Salts

[0115] It will be understood that, as used herein, references to the compounds of the present disclosure are meant to also include the pharmaceutically acceptable salts, and also salts that are not pharmaceutically acceptable when they are used as precursors to the free compounds or their pharmaceutically acceptable salts or in other synthetic manipulations.

[0116] The compounds of the present disclosure may be administered in the form of a pharmaceutically acceptable salt. The term "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts of basic compounds encompassed within the term "pharmaceutically acceptable salt" refer to non-toxic salts of the compounds of this disclosure which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts of basic compounds of the present disclosure include, but are not limited to, the following: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, formic, fumarate, gluceptate, gluconate, glutamate, glycolylars-anilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate, diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, trifluoroacetate and valerate. Where the compounds of the disclosure carry an acidic moiety, suitable pharmaceutically acceptable salts thereof include, but are not limited to, salts derived from inorganic bases including aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, mangamous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium,

magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, cyclic amines, and basic ion-exchange resins, 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.

[0117] Also, in the case of a carboxylic acid (-COOH) or alcohol group being present in the compounds of the present disclosure, pharmaceutically acceptable esters of carboxylic acid derivatives, such as methyl, ethyl, or pivaloyloxymethyl, or acyl derivatives of alcohols, such as *O*-acetyl, *O*-pivaloyl, *O*-benzoyl, and *O*-aminoacyl, can be employed. Included are those esters and acyl groups known in the art for modifying the solubility or hydrolysis characteristics for use as sustained-release or prodrug formulations.

[0118] The term “prodrug” means compounds that are rapidly transformed, for example, by hydrolysis in blood, *in vivo* to the parent compound, e.g., conversion of a prodrug of structural formula I to a compound of structural formula I, or to a salt thereof; a thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference. This disclosure includes prodrugs of the compounds of structural formula I. Solvates, and in particular, the hydrates of the compounds of structural formula I are also included in the present disclosure as well.

Utilities

[0119] The compounds of structural formula I are potent inhibitors of Nod-Like Receptor Protein 3 (NLRP3). The compounds of structural formula I, and pharmaceutically acceptable salts, hydrates and solvates thereof, may be efficacious in the treatment of diseases, disorders and conditions that are mediated by the inhibition of Nod-Like Receptor Protein 3 (NLRP3).

[0120] The present disclosure relates to the treatment or prevention of a disease, disorder or condition mediated by NLRP3 such as inflammation, an auto-immune disease, a cancer, an infection, a disease or disorder of the central nervous system, a metabolic disease, a cardiovascular disease, a fibrotic disease or fibrosis, a respiratory disease, a kidney disease, a

liver disease, an ophthalmic or ocular disease, a skin disease, a lymphatic disease, a rheumatic disease, graft versus host disease, allodynia, or an NLRP3-related disease in a subject that has been determined to carry a germline or somatic non-silent mutation in NLRP3.

[0121] The disease, disorder or condition mediated by NLRP3 includes but is not limited to: gout, pseudogout, osteoarthritis, familial cold autoinflammatory syndrome, Muckle-Wells syndrome, neonatal onset multisystem inflammatory disease, diabetes, NASH, sepsis, age related macular degeneration, diabetic retinopathy, liver fibrosis, kidney fibrosis, atherosclerosis, heart failure, peripheral artery disease, myeloproliferative neoplasm, leukemia, myelodysplastic syndrome, myelofibrosis, lung cancer, colon cancer, Parkinson's disease, Alzheimer's disease, traumatic brain injury, spinal cord injury, amyotrophic lateral sclerosis, multiple sclerosis, atopic dermatitis, hidradenitis suppurativa, pericarditis, myocarditis, preeclampsia, dermatomyositis, Still's disease, juvenile idiopathic arthritis, age related macular degeneration, diabetic retinopathy, acute kidney disease, a chronic kidney disease, or a rare kidney disease. Diseases, disorders or conditions mediated by Nod-Like Receptor Protein 3 (NLRP3)), also include, but are not limited to, gout, pseudogout, CAPS, NASH, fibrosis, osteoarthritis, atherosclerosis, heart failure, idiopathic pericarditis, myocarditis, atopic dermatitis, hidradenitis suppurativa, inflammatory bowel disease, cancer, Alzheimer's Disease, Parkinson's Disease and traumatic brain injury.

[0122] In one embodiment, the condition, disease or disorder is an inflammatory joint disease such as gout, pseudogout, or osteoarthritis.

[0123] In another embodiment, the cryopyrin-associated autoinflammatory syndrome is familial cold autoinflammatory syndrome, Muckle-Wells syndrome, or neonatal onset multisystem inflammatory disease.

[0124] In another embodiment, the metabolic disease is diabetes.

[0125] In another embodiment, the liver disease is NASH.

[0126] In another embodiment, the infection is sepsis.

[0127] In another embodiment, the ophthalmic or ocular disease is age related macular degeneration or diabetic retinopathy.

[0128] In another embodiment, the fibrotic disease is liver fibrosis or kidney fibrosis.

[0129] In some embodiments, the cardiovascular disease is atherosclerosis, heart failure or peripheral artery disease.

[0130] In another embodiment, the cancer is myeloproliferative neoplasm, leukemia, myelodysplastic syndrome, myelofibrosis, lung cancer or colon cancer.

[0131] In another embodiment, the condition, disease or disorder of the central nervous system is Parkinson's disease, Alzheimer's disease, traumatic brain injury, spinal cord injury, amyotrophic lateral sclerosis, or multiple sclerosis.

[0132] In another embodiment, the skin disease is atopic dermatitis or hidradenitis suppurativa (HS).

[0133] In another embodiment, the inflammatory disease is pericarditis or myocarditis.

[0134] In another embodiment, the inflammatory disease is preeclampsia.

[0135] In another embodiment, the rheumatic disease is dermatomyositis, Still's disease, or juvenile idiopathic arthritis.

[0136] In another embodiment, the ocular disease is age related macular degeneration, or diabetic retinopathy.

[0137] In another embodiment, the kidney disease is an acute kidney disease, a chronic kidney disease, or a rare kidney disease.

[0138] One or more of these conditions or diseases may be treated, managed, prevented, reduced, alleviated, ameliorated or controlled by the administration of a therapeutically effective amount of a compound of structural formula I, or a pharmaceutically acceptable salt thereof, to a patient in need of treatment.

[0139] The compounds of structural formula I may also be used for the manufacture of a medicament which may be useful for treating, preventing, managing, alleviating, ameliorating or controlling one or more of these conditions, diseases or disorders, including but not limited to: gout, pseudogout, osteoarthritis, familial cold autoinflammatory syndrome, Muckle-Wells syndrome, neonatal onset multisystem inflammatory disease, diabetes, NASH, sepsis, age related macular degeneration, diabetic retinopathy, liver fibrosis, kidney fibrosis, atherosclerosis, heart failure, peripheral artery disease, myeloproliferative neoplasm, leukemia, myelodysplastic syndrome, myelofibrosis, lung cancer, colon cancer, Parkinson's disease, Alzheimer's disease, traumatic brain injury, spinal cord injury, amyotrophic lateral sclerosis, multiple sclerosis, atopic dermatitis, hidradenitis suppurativa, pericarditis, myocarditis, preeclampsia, dermatomyositis, Still's disease, juvenile idiopathic arthritis, age related macular degeneration, diabetic retinopathy, acute kidney disease, a chronic kidney disease, or a rare kidney disease. The compounds of structural formula I may also be used for the manufacture of a medicament which may be useful for treating, preventing, managing, alleviating, ameliorating or controlling one or more of these conditions, diseases or disorders, including but not limited to: gout, pseudogout, CAPS, NASH, fibrosis, osteoarthritis, atherosclerosis, heart failure, idiopathic pericarditis,

myocarditis, atopic dermatitis, hidradenitis suppurativa, inflammatory bowel disease, cancer, Alzheimer's Disease, Parkinson's Disease and traumatic brain injury.

[0140] Preferred uses of the compounds may be for the treatment of one or more of the following diseases by administering a therapeutically effective amount to a patient in need of treatment. The compounds may be used for manufacturing a medicament for the treatment of one or more of these diseases:

- 1) gout,
- 2) pseudogout,
- 3) cryopyrin-associated periodic syndromes,
- 4) non-alcoholic steatohepatitis,
- 5) fibrosis,
- 6) osteoarthritis,
- 7) atherosclerosis,
- 8) atopic dermatitis,
- 9) hidradenitis suppurativa,
- 10) Alzheimer's Disease, and
- 11) Parkinson's Disease.

[0141] Treatment of a disease, disorder or condition mediated by NLPR3 or the NLPR3 inflammasome pathway refers to the administration of the compounds of structural formula I to a subject with the disease, disorder or condition.

[0142] One outcome of treatment may be reducing the disease, disorder or condition mediated by NLPR3 or the NLPR3 inflammasome pathway. Another outcome of treatment may be alleviating the disease, disorder or condition mediated by NLPR3 or the NLPR3 inflammasome pathway. Another outcome of treatment may be ameliorating the disease, disorder or condition mediated by NLPR3 or the NLPR3 inflammasome pathway. Another outcome of treatment may be suppressing the disease, disorder or condition mediated by mediated by NLPR3 or the NLPR3 inflammasome pathway. Another outcome of treatment may be managing the disease, disorder or condition mediated by NLPR3 or the NLPR3 inflammasome pathway. Another outcome of treatment may be preventing the disease, disorder or condition mediated by NLPR3 or the NLPR3 inflammasome pathway.

[0143] Prevention of the disease, disorder or condition mediated by NLPR3 or the NLPR3 inflammasome pathway refers to the administration of the compounds of structural formula I to a subject at risk of the disease, disorder or condition. One outcome of prevention may be reducing

the disease, disorder or condition mediated by NLPR3 or the NLPR3 inflammasome pathway in a subject at risk of the disease, disorder or condition. Another outcome of prevention may be suppressing the disease, disorder or condition mediated by NLPR3 or the NLPR3 inflammasome pathway in a subject at risk of the disease, disorder or condition. Another outcome of prevention may be ameliorating the disease, disorder or condition mediated by NLPR3 or the NLPR3 inflammasome pathway in a subject at risk of the disease, disorder or condition. Another outcome of prevention may be alleviating the disease, disorder or condition mediated by NLPR3 or the NLPR3 inflammasome pathway in a subject at risk of the disease, disorder or condition. Another outcome of prevention may be managing the disease, disorder or condition mediated by NLPR3 or the NLPR3 inflammasome pathway in a subject at risk of the disease, disorder or condition.

[0144] The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of structural formula I or a prodrug of a compound of structural formula I to the individual or mammal in need of treatment.

[0145] The administration of the compound of structural formula I in order to practice the present methods of therapy is carried out by administering an effective amount of the compound of structural formula I to the mammal in need of such treatment or prophylaxis. The need for a prophylactic administration according to the methods of the present disclosure is determined via the use of well known risk factors. The effective amount of an individual compound is determined, in the final analysis, by the physician or veterinarian in charge of the case, but depends on factors such as the exact disease to be treated, the severity of the disease and other diseases or conditions from which the patient suffers, the chosen route of administration other drugs and treatments which the patient may concomitantly require, and other factors in the physician's judgment.

[0146] The usefulness of the present compounds in these diseases or disorders may be demonstrated in animal disease models that have been reported in the literature.

Administration and Dose Ranges

[0147] Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dose of a compound of structural formula I. For example, oral, intravenous, infusion, subcutaneous, transcutaneous, intramuscular, intradermal, transmucosal, intramucosal, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions,

capsules, creams, ointments, aerosols, and the like. Preferably compounds of structural formula I are administered orally.

[0148] In the treatment or prevention of disorders, diseases and/ or conditions which require inhibition of NLRP3 a suitable dosage level will generally be about 0.0001 to 500 mg per kg patient body weight per day which can be administered in single or multiple doses. In one embodiment, a suitable dosage level may be about 0.001 to 500 mg per kg patient body weight per day. In another embodiment, a suitable dosage level may be about 0.001 to about 250 mg/kg per day. In another embodiment, a suitable dosage level may be about 0.01 to about 250 mg/kg per day. In another embodiment, a suitable dosage level may be about 0.1 to about 100 mg/kg per day. In another embodiment, a suitable dosage level may be about 0.05 to 100 mg/kg per day. In another embodiment, a suitable dosage level may be about 0.1 to 50 mg/kg per day. In another embodiment, a suitable dosage level may be about 0.05 to 0.5 mg/kg per day. In another embodiment, a suitable dosage level may be about 0.5 to 5 mg/kg per day. In another embodiment, a suitable dosage level may be about 5 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01 to 1000 mg of the active ingredient, particularly 0.01, 0.025, 0.05, 0.075, 0.1, 0.25, 0.5, 0.75, 1.0, 2.5, 5.0, 7.5, 10.0, 15.0, 20.0, 25.0, 30.0, 40.0, 50.0, 60.0, 70.0, 75.0, 80.0, 90.0, 100.0, 110.0, 120.0, 125.0, 130.0, 140.0, 150.0, 160.0, 170.0, 175.0, 180.0, 190.0, 200.0, 210.0, 220.0, 225.0, 230.0, 240.0, 250.0, 260.0, 270.0, 275.0, 280.0, 290.0, 300.0, 310.0, 320.0, 325.0, 330.0, 340.0, 350.0, 360.0, 370.0, 375.0, 380.0, 390.0, 400.0, 410.0, 420.0, 425.0, 430.0, 440.0, 450.0, 460.0, 470.0, 475.0, 480.0, 490.0, 500.0, 510.0, 520.0, 525.0, 530.0, 540.0, 550.0, 560.0, 570.0, 575.0, 580.0, 590.0, 600.0, 610.0, 620.0, 625.0, 630.0, 640.0, 650.0, 660.0, 670.0, 675.0, 680.0, 690.0, 750.0, 800.0, 810.0, 820.0, 825.0, 830.0, 840.0, 850.0, 860.0, 870.0, 875.0, 880.0, 890.0, 900.0, 910.0, 920.0, 925.0, 930.0, 940.0, 950.0, 960.0, 970.0, 975.0, 980.0, 990.0, and 1000.0 mg of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 8 times per day; preferably, 1 to 4 times a day; more preferably once or twice per day, even more preferably once a day. This dosage regimen may be adjusted to provide the optimal therapeutic response.

[0149] It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate

of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

[0150] The compounds of structural formula I may be used in pharmaceutical compositions comprising (a) the compound(s) or pharmaceutically acceptable salts thereof, and (b) a pharmaceutically acceptable carrier. The compounds of structural formula I may be used in pharmaceutical compositions in which the compound of structural formula I or a pharmaceutically acceptable salt thereof is the only active ingredient. The compounds of structural formula I may also be used in pharmaceutical compositions that include one or more other active pharmaceutical ingredients.

[0151] The term "composition," as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present disclosure encompass any composition made by admixing a compound of structural formula I, or a pharmaceutically acceptable salt, hydrate or solvate thereof, and a pharmaceutically acceptable carrier.

[0152] Compounds of structural formula I may be used in combination with other drugs that may also be useful in the treatment or amelioration of the diseases or conditions for which compounds of structural formula I are useful. Such other drugs may be administered, by a route and in an amount commonly used therefore, contemporaneously or sequentially with a compound of structural formula I. In the treatment of patients who suffer from chronic inflammatory conditions, more than one drug may be administered. The compounds of structural formula I may generally be administered to a patient who is already taking one or more other drugs for these conditions. Often the compounds will be administered to a patient who is already being treated with one or more anti-pain compounds when the patient's pain is not adequately responding to treatment.

[0153] The combination therapy also includes therapies in which the compound of structural formula I and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compound of structural formula I and the other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present

disclosure include those that contain one or more other active ingredients, in addition to a compound of structural formula I.

[0154] Examples of other active ingredients that may be administered in combination with a compound of structural formula I, and either administered separately or in the same pharmaceutical composition, include but are not limited to:

- (i) anti-steatotic agents;
- (ii) anti-inflammatory agents;
- (iii) immunooncology agent;
- (iv) lipid-lowering agents;
- (v) cholesterol lowering agents;
- (vi) glucose-lowering agents, including SGLT2 inhibitors;
- (vii) anti-neovascular agents;
- (viii) nonsteroidal anti-inflammatory drugs ("NSAIDs");
- (ix) acetyl-salicylic acid drugs (ASA) including aspirin; paracetamol;
- (x) regenerative therapy treatments;
- (xi) checkpoint inhibitors including anti-PD1 and anti-PDL1 inhibitors;
- (xii) chemotherapy procedures;
- (xiii) radiation therapy;
- (xiv) surgical procedures;
- (xv) urate-lowering therapy;
- (xvi) anabolics and cartilage regenerative therapy;
- (xvii) anti-fibrotics;
- (xviii) JAK inhibitors;
- (xix) TNF-alpha inhibitors;
- (xx) anti-hypertensive agents; and
- (xxi) STING/cGAS antagonists

pharmaceutically acceptable salts thereof.

[0155] In another embodiment, the pharmaceutical composition comprises:

- 1) a compound of Claim 1, or a pharmaceutically acceptable salt thereof;
- 2) one or more compounds, or pharmaceutically acceptable salts thereof, selected

from the group:

- (i) anti-steatotic agents;
- (ii) anti-inflammatory agents;

- (iii) immunooncology agent;
- (iv) lipid-lowering agents;
- (v) cholesterol lowering agents;
- (vi) glucose-lowering agents, including SGLT2 inhibitors;
- (vii) anti-neovascular agents;
- (viii) nonsteroidal anti-inflammatory drugs ("NSAIDs");
- (ix) acetyl-salicylic acid drugs (ASA) including aspirin; paracetamol;
- (x) regenerative therapy treatments;
- (xi) checkpoint inhibitors including anti-PD1 and anti-PDL1 inhibitors;
- (xii) chemotherapy procedures;
- (xiii) radiation therapy;
- (xiv) surgical procedures;
- (xv) urate-lowering therapy;
- (xvi) anabolics and cartilage regenerative therapy;
- (xvii) anti-fibrotics;
- (xviii) JAK inhibitors;
- (xix) TNF-alpha inhibitors;
- (xx) anti-hypertensive agents; and
- (xxi) STING/cGAS antagonists; and

pharmaceutically acceptable salts thereof; and

- (3) a pharmaceutically acceptable carrier.

[0156] Specific compounds of use in combination with a compound of structural formula I include: anti-steatotic agents, including but not limited to, DGAT2 inhibitors.

[0157] Suitable anti-inflammatory agents include, but are not limited to, TNF α inhibitors, JAK inhibitors and NSAIDs.

[0158] Suitable lipid-lowering agents include, but are not limited to statins and PCSK9.

[0159] Suitable immunooncology agents include, but are not limited to, PD-L1 inhibitors and PD-1 inhibitors and STING antagonists.

[0160] Suitable glucose-lowering agents include, but are not limited to, insulin, SGLT2 inhibitors, metformin, GLP1-agonists.

[0161] Suitable anti-neovascular agents include, but are not limited to, anti-VEG-F treatment.

[0162] Suitable NSAIDs or non-steroidal anti-inflammatory drugs include, but are not limited to, aspirin, diclofenac, diflunisal, etodolac, fenoprofin, flurbiprofen, ibuprofen, indomethacin,

ketoprofen, meclofenamic acid, mefenamic acid, meloxicam, naproxen, naproxen sodium, oxaprozin, piroxicam, sulindac, and tolmetin.

[0163] Suitable analgesics include, but are not limited to, acetaminophen and duloxetine.

[0164] The above combinations include combinations of a compound of structural formula I not only with one other active compound, but also with two or more other active compounds. Non-limiting examples include combinations of compounds with two or more active compounds selected from: anti-steatotic agents, anti-inflammatory agents, lipid-lowering agents, anti-fibrosis, immunooncology agents, glucose-lowering agents and anti-neovascular agents, NSAIDs (non-steroidal anti-inflammatory drugs), and an analgesics.

[0165] The present disclosure also provides a method for the treatment or prevention of a NLRP3 mediated disease, disorder or condition, which method comprises administration to a patient in need of such treatment or at risk of developing a NLRP3 mediated disease with a therapeutically effective amount of a NLRP3 inhibitor and an amount of one or more active ingredients, such that together they give effective relief.

[0166] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a NLRP3 inhibitor and one or more active ingredients, together with at least one pharmaceutically acceptable carrier or excipient.

[0167] Thus, according to a further aspect of the present disclosure there is provided the use of a NLRP3 inhibitor and one or more active ingredients for the manufacture of a medicament for the treatment or prevention of an NLRP3-mediated disease, disorder or condition. In a further or alternative aspect of the present disclosure, there is therefore provided a product comprising a NLRP3 inhibitor and one or more active ingredients as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of an NLRP3-mediated disease, disorder or condition. Such a combined preparation may be, for example, in the form of a twin pack.

[0168] It will be appreciated that for the treatment or prevention of cardiometabolic disease, neurodegenerative disease and inflammatory joint diseases, fibrosis, cancer, a compound of structural formula I may be used in conjunction with another pharmaceutical agent effective to treat that disease, disorder or condition.

[0169] The present disclosure also provides a method for the treatment or prevention of chronic inflammatory conditions, which method comprises administration to a patient in need of such treatment an amount of a compound of structural formula I and an amount of another pharmaceutical agent effective to treat that disorder, disease or condition, such that together they give effective relief.

[0170] The present disclosure also provides a method for the treatment or prevention of chronic inflammatory conditions, which method comprises administration to a patient in need of such treatment an amount of a compound of structural formula I and an amount of another pharmaceutical agent useful in treating that particular condition, disorder or disease, such that together they give effective relief.

[0171] The term "therapeutically effective amount" means the amount the compound of structural formula I that will elicit the biological or medical response of a cell, tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disorder being treated. The novel methods of treatment of this disclosure are for disorders known to those skilled in the art. The term "mammal" includes humans, and companion animals such as dogs and cats.

[0172] The weight ratio of the compound of structural formula I to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of structural formula I is combined with an anti-steatotic agent, the weight ratio of the compound of structural formula I generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of structural formula I and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

Methods of Synthesis

[0173] The following reaction schemes and Examples illustrate methods which may be employed for the synthesis of the compounds of structural formula I described in this disclosure. These reaction schemes and Examples are provided to illustrate the disclosure and are not to be construed as limiting the disclosure in any manner. All substituents are as defined above unless indicated otherwise. Several strategies based upon synthetic transformations known in the literature of organic synthesis may be employed for the preparation of the compounds of structural formula I. The scope of the disclosure is defined by the appended claims. Compound names were generated in Chemdraw Version 21.0.0.28.

Instrumentation

[0174] Reverse phase chromatography was carried out on a Waters 150 equipped with a column selected from the following: Phenomenex Synergi C18 (250mm x 30mm x 4 micron),

Phenomenex Luna C18 (250mm x 21mm x 5 micron), Agilent Zorbax Bonus-RP (150mm x 21mm x 5 micron), Waters X-Select CSH C18 (150mm x 19mm x 5 micron). Conditions included either high pH (0-100% acetonitrile/water eluent comprising 0.1% v/v NH₄OH) or low pH (0-100% acetonitrile/water eluent comprising 0.1% v/v TFA or Formic Acid) and are noted for some examples. SFC chiral resolution was carried out on Waters Thar 80 SFC or Berger MG II preparative SFC systems.

[0175] LC/MS determinations were carried out on Waters ACQUITY UPLC equipped with a DAD and QDa MS detectors using the following conditions: Waters ACQUITY UPLC BEH C18 1.7mm 2.1x50mm column using mobile phase containing A: 0.1% TFA in water and B: 0.1% TFA in acetonitrile with a gradient from 10% B to 90% B over 2.0 min and hold at 90% B for 0.4 min at a flow rate of 0.5 mL/min. Proton or ¹H NMR was acquired using a Bruker 500 MHz NEO NMR spectrometer equipped with a 5mm iProbe in accordance with standard analytical techniques, unless specified otherwise, and results of spectral analysis are reported. Chemical shift (δ) values are reported in delta (δ) units, parts per million (ppm). Chemical shifts for ¹H NMR spectra are given relative to signals for residual non-deuterated solvent (CDCl₃ referenced at δ 7.26 ppm; DMSO *d*-6 referenced at δ 2.50 ppm and CD₃OD referenced at δ 3.31 ppm). Multiples are reported by the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt is doublet of triplets, m = multiplet or overlap of nonequivalent resonances. Coupling constants (*J*) are reported in Hertz (Hz).

Chiral Separation Methods: The general preparative conditions of separating diastereomeric or enantiomeric mixtures of compounds using chiral SFC are as follows:

Chiral Column	Stationary Phase	Method
DAICEL CHIRALPAK IC	30% EtOH (0.1% NH ₄ OH)/CO ₂	A
DAICEL CHIRALPAK IH	20% EtOH (0.1% NH ₄ OH)/CO ₂	B
DAICEL CHIRALPAK AD	40% EtOH (0.1% NH ₄ OH)/CO ₂	C
DAICEL CHIRALPAK AD	45% MeOH (0.1% NH ₄ OH)/CO ₂	D

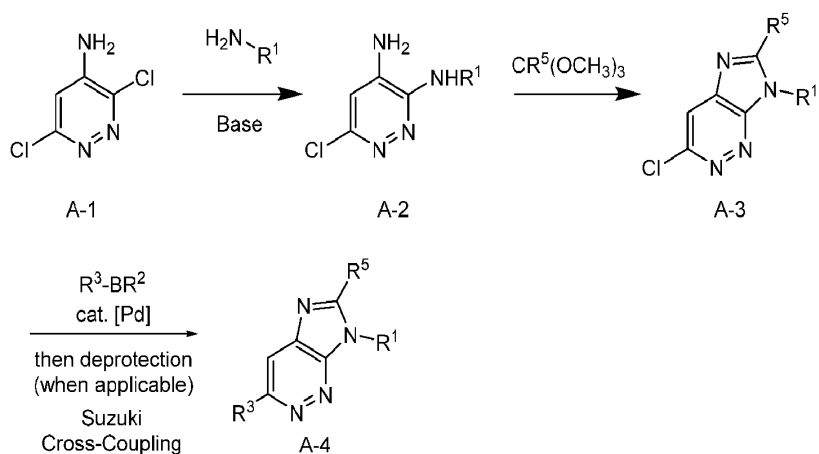
Abbreviations

[0176] “*” in a molecule designates a stereocenter; Ac is acetyl; Ad₂*n*-BuP Pd G2 is Chloro[(di(1-adamantyl)-*N*-butylphosphine)-2-(2-aminobiphenyl)]-palladium(II); OAc is acetate; AcOH is acetic acid; aq. is aqueous; B₂pin₂ is bis(pinacolato)diboron; BPin ester is boronic acid pinacol ester; Boc or boc is *tert*-butoxycarbonyl; br is broad; °C is degrees Celsius; calc'd is

calculated; cat. is catalytic; δ is chemical shift; d is doublet; D is deuterium; DCM is dichloromethane; dd is doublet of doublets; DIPEA is *N,N*-diisopropylethylamine; DMA is dimethylacetamide; DMF is dimethylformamide; DMSO is dimethylsulfoxide; DMSO-*d*₆ is deuterated dimethylsulfoxide; dppf is 1,1'-bis(diphenylphosphino)-ferrocene; dtbpf is bis(di-*tert*-butylphosphino)ferrocene; ESI is electrospray ionization; Et is ethyl; Et₃N is triethylamine; EtOAc is ethyl acetate; EtOH is ethanol; FA is formic acid; g is grams; h is hour(s); HPLC is high-performance liquid chromatography; Hz is hertz; ¹Pr is isopropyl; *J* is coupling constant; L is liter; LC is liquid chromatography; LCMS is liquid chromatography/mass spectrometry; m is multiplet; M is molar; Me is methyl; MeCN is acetonitrile; MeOD-*d*₄ is deuterated methanol; MeOH is methanol; mg is milligrams; MHz is megahertz; min is minutes; mL is milliliter; mM is millimolar; mmol is millimole(s); μ L is microliter; MPLC is medium pressure liquid chromatography; MS is mass spectrometry; *n*-BuOH is *n*-butanol; nM is nanomolar; NMP is *N*-methylpyrrolidone; NMR is Nuclear Magnetic Resonance; PdCl₂(dppf) or Pd(dppf)Cl₂ is [1,1'-bis-(diphenylphosphino)-ferrocene]dichloropalladium(II); PG is protecting group; Ph is phenyl; POCl₃ is phosphorus oxychloride; q is quartet; qd is quartet of doublets; *rac* is racemic mixture; s is singlet; sat. is saturated; SFC is Supercritical Fluid Chromatography; S_NAr is nucleophilic aromatic substitution; t is triplet; *t*-AmOH is *tert*-amyl alcohol; *t*-Bu or ^tBu is *tert*-butyl; *tert* is tertiary; TFA is trifluoroacetic acid; THF is tetrahydrofuran; TLC is thin layer chromatography; tt is triplet of triplets; XPhos Pd G3 is (2-Dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate; UV is ultraviolet; and wt% is weight percent.

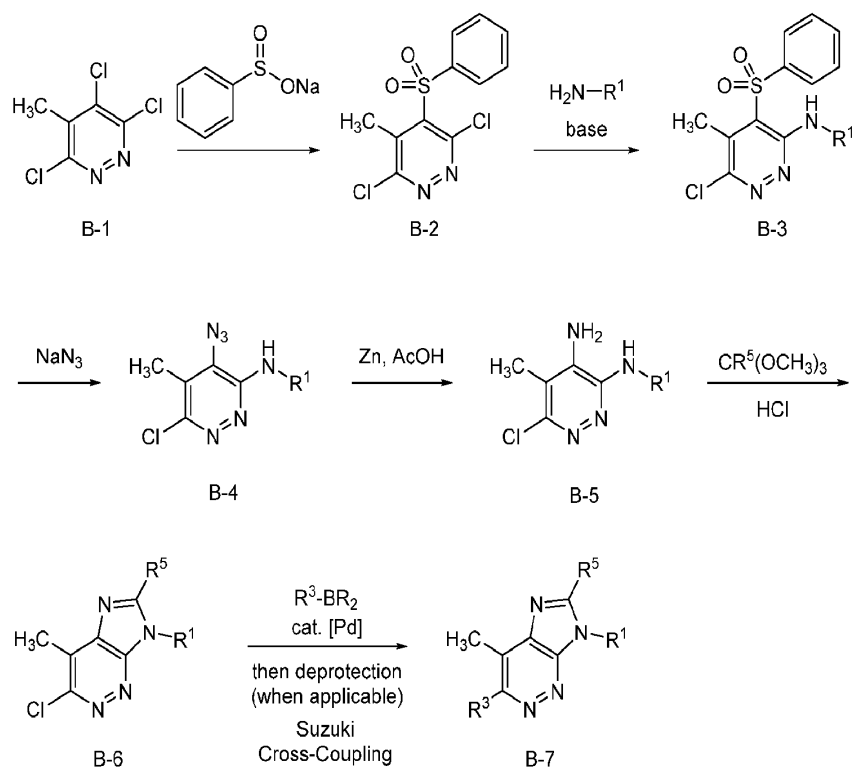
General Schemes

SCHEME A



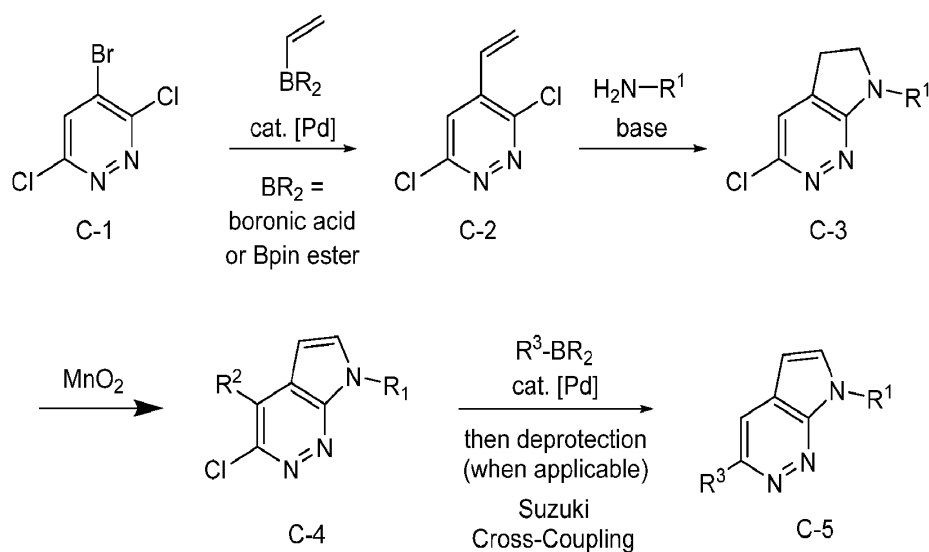
[0177] Scheme A illustrates the synthetic sequence for the preparation of biaryl pyridazine derivatives of the formula A-4. Dihaloaminopyridazine A-1 undergoes regioselective $\text{S}_{\text{N}}\text{Ar}$ with various primary amines to afford diamines such as A-2. Cyclization of diamines A-2 with an appropriate orthoester provides the imidazo-pyridazines of the formula A-3. Cross coupling using an appropriate aryl nucleophile (e.g., aryl boronic acid) and palladium catalyst gives biaryl products which are deprotected *in situ*, when applicable, to afford compounds of the formula A-4.

SCHEME B



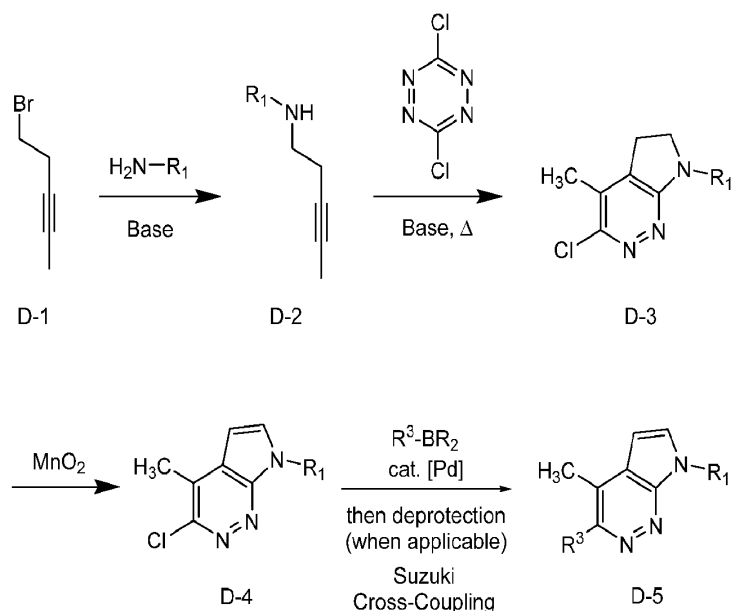
[0178] Scheme B illustrates the synthetic sequence for the preparation of biaryl pyridazine derivatives of the formula B-7. Methyl trihalopyridazine B-1 reacts regioselectively with sodium benzenesulfonate to generate sulfone B-2, which can then be coupled with various primary amines under $\text{S}_{\text{N}}\text{Ar}$ conditions to form aminopyridazines such as B-3. Displacement of the sulfone with sodium azide generates aminoazidopyridazines B-4, which can be reduced to the diaminopyridazines B-5 after treatment with Zn in AcOH . Cyclization of diamines B-5 with an appropriate orthoester provides the imidazopyridazines of the formula B-6. Cross coupling using an appropriate aryl nucleophile (e.g., aryl boronic acid) and palladium catalyst gives biaryl products which are deprotected *in situ* (when applicable) to afford compounds of the formula B-7.

SCHEME C



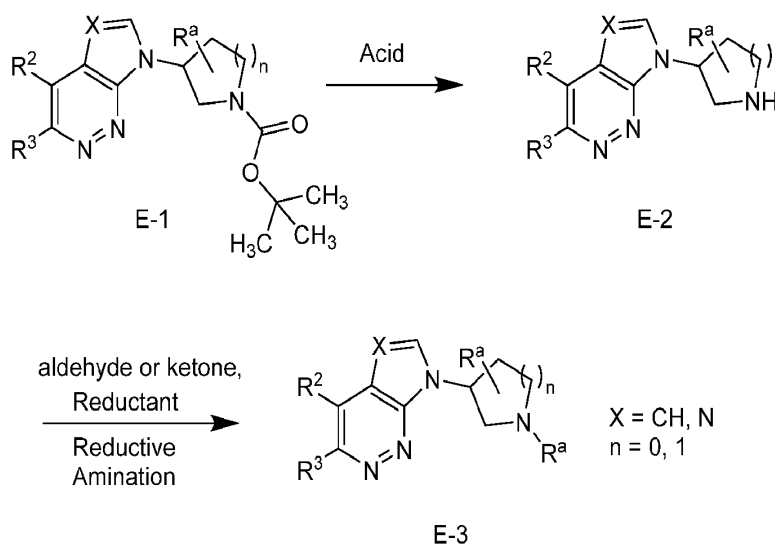
[0179] Scheme C illustrates the synthetic sequence for the preparation of biaryl pyrrolopyridazine derivatives of the formula C-5. Trihalopyridazine C-1 undergoes mono-selective cross coupling with a suitable vinyl boron reagent to afford vinyl derivatives such as C-2. Reaction of vinyl derivatives C-2 with various primary amines in the presence of base (e.g., DIPEA) produces dihydropyrrolopyridazines of the formula C-3. Oxidation with manganese oxide in a suitable solvent (e.g., toluene) at elevated temperature affords the pyrrolopyridazine core represented by C-4. Cross coupling using an appropriate aryl nucleophile (e.g., aryl boronic acid) and palladium catalyst gives biaryl products which are deprotected *in situ*, when applicable, to afford compounds of the formula C-5.

SCHEME D



[0180] Scheme D illustrates the synthetic sequence for the preparation of biaryl pyrrolopyridazine derivatives of the formula D-5. Various primary amines are alkylated with bromopentyne D-1 to generate aminoalkynes of the formula D-2. Reaction of aminoalkynes D-2 with dichlorotetrazine in the presence of a base (e.g., Et₃N) and elevated temperature directly affords pyridazopyrrolidines of the formula D-3 *via* a sequence of S_NAr, hetero Diels-Alder cycloaddition, and retro Diels-Alder. Oxidation with manganese oxide in a suitable solvent (e.g., toluene) at elevated temperature affords the pyrrolopyridazine core represented by D-4. Cross coupling using an appropriate aryl nucleophile (e.g., aryl boronic acid) and palladium catalyst gives biaryl products which are deprotected *in situ*, when applicable, to afford compounds of the formula D-5.

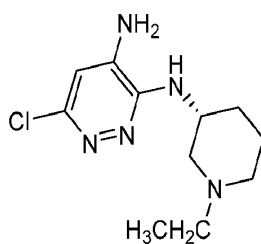
SCHEME E



[0181] Scheme E illustrates the synthetic sequence for the preparation of biaryl pyridazine derivatives of the formula E-3. *N*-Boc cyclic amines E-1 can be deprotected with acid (e.g., TFA or HCl) to afford secondary amines such as E-2. Reductive amination of E-2 with suitable aldehydes or ketones in the presence of a reducing agent (e.g., sodium cyanoborohydride or sodium triacetoxyborohydride) provides the trialkylamines of the formula E-3.

Intermediate 1

(*R*)-6-chloro-*N*³-(1-ethylpiperidin-3-yl)pyridazine-3,4-diamine

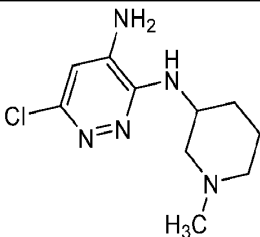


[0182] A suspension of 3,6-dichloropyridazin-4-amine (Ambeed, 800 mg, 4.88 mmol) and (*R*)-1-ethylpiperidin-3-amine (Enamine, 688 mg, 5.37 mmol) in *n*-BuOH (1.63 mL) was treated with DIPEA (1.19 mL, 6.83 mmol). The reaction mixture was heated to 150 °C for 2 days. Then the reaction mixture was cooled to room temperature, filtered, and purified via preparative reverse

phase HPLC (C18 stationary phase, MeCN/water + 0.1% TFA) to afford the title compound.

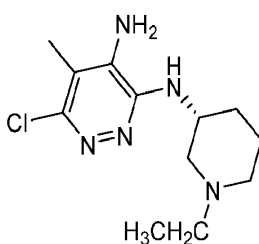
LCMS $[M+H]^+ = 256.2$ (calcd. 256.2).

Table 1. The following intermediate was prepared using a procedure similar to that described for Intermediate 1 using the appropriate starting material.

Intermediate	Structure	Name	LCMS $[M+H]^+$
2		(<i>R</i> and <i>S</i>)-6-chloro- <i>N</i> ³ -(1-methylpiperidin-3-yl)pyridazine-3,4-diamine	Calcd. 242.1, Found 242.2

Intermediate 3

(*R*)-6-chloro-*N*³-(1-ethylpiperidin-3-yl)-5-methylpyridazine-3,4-diamine



[0183] Step 1: 3,4,6-trichloro-5-methylpyridazine: A solution of 4-bromo-5-methylpyridazine-3,6-diol (Enamine, 1.20 g, 5.85 mmol) and POCl_3 (10 mL, 107 mmol) was stirred at 100 °C for 2 h. Then the mixture was cooled to room temperature, and slowly added to water. The mixture was diluted with EtOAc, the layers were separated, and the aqueous layer was extracted with EtOAc (x2). The combined organic layers were concentrated, and the resulting crude residue was purified by silica gel chromatography (EtOAc:petroleum ether) to give the title compound. LCMS $[M+H]^+ = 197.1$ (calcd. 196.9).

[0184] Step 2: phenyl 3,6-dichloro-5-methylpyridazine-4-sulfinate: A solution of 3,4,6-trichloro-5-methylpyridazine (6.4 g, 32.4 mmol) in THF (50 mL) and DMSO (10 mL) was treated with sodium benzenesulfinate (5.6 g, 34.0 mmol). The resulting reaction mixture was heated to 40 °C for 48 h. Then the reaction mixture was cooled to room temperature and diluted with water and EtOAc. The layers were separated, and the aqueous layer was extracted with

EtOAc (x3). The combined organic layers were concentrated, and the resulting crude residue was purified by silica gel chromatography (EtOAc:petroleum ether) to give the title compound.

LCMS $[M+H]^+ = 303.1$ (calcd. 303.0).

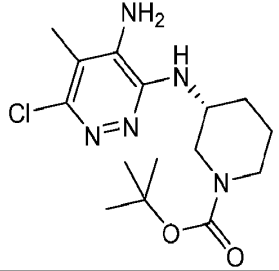
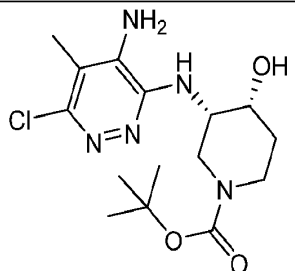
[0185] Step 3: 6-chloro-3-(((*R*)-1-ethylpiperidin-3-yl)amino)-5-methylpyridazin-4-yl benzenesulfinate: A solution of phenyl 3,6-dichloro-5-methylpyridazine-4-sulfinate (1.5 g, 4.95 mmol) in 1,4-dioxane (30 mL) was treated with (*R*)-1-ethylpiperidin-3-amine (Enamine, 952 mg, 7.42 mmol) and K_2CO_3 (3.08 g, 22.3 mmol). The resulting mixture was heated to 100 °C for 12 h. After cooling to room temperature, the reaction mixture was filtered, and purified via preparative reverse phase HPLC (C18 stationary phase, MeCN/water + 0.05% TFA) to afford the title compound. LCMS $[M+H]^+ = 395.1$ (calcd. 395.1).

[0186] Step 4: (*R*)-4-azido-6-chloro-*N*-(1-ethylpiperidin-3-yl)-5-methylpyridazin-3-amine: A solution of 6-chloro-3-(((*R*)-1-ethylpiperidin-3-yl)amino)-5-methylpyridazin-4-yl benzenesulfinate (500 mg, 1.27 mmol) in 1,4-dioxane (8 mL) and DMSO (2 mL) was treated with NaN_3 (494 mg, 7.60 mmol). The resulting mixture was heated to 50 °C for 12 h. After cooling to room temperature, the reaction mixture was filtered and purified via preparative reverse phase HPLC (C18 stationary phase, MeCN/water + 0.05% NH_4OH + 10 mM NH_4HCO_3) to afford the title compound. LCMS $[M+H]^+ = 296.2$ (calcd. 296.1).

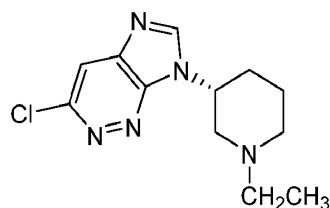
[0187] Step 5: (*R*)-6-chloro-*N*³-(1-ethylpiperidin-3-yl)-5-methylpyridazine-3,4-diamine: A solution of (*R*)-4-azido-6-chloro-*N*-(1-ethylpiperidin-3-yl)-5-methylpyridazin-3-amine (300 mg, 1.01 mmol) in DCM (5 mL) and AcOH (1 mL) was cooled to 0 °C and treated with zinc (133 mg, 2.03 mmol). The resulting mixture was stirred at 0 °C for 2 h, then filtered and concentrated to give the title compound. LCMS $[M+H]^+ = 270.1$ (calcd. 270.1).

Table 2. The following intermediates were prepared using a procedure similar to that described for Intermediate 3 using the appropriate commercially available amine. In Step 4 a modified procedure was used wherein the solvent was pure DMSO and the reaction temperature was 60 °C. The compounds were purified at all component steps with silica gel chromatography instead of reverse phase HPLC.

Intermediate	Structure	Name	LCMS $[M+H]^+$
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4		<i>tert</i> -butyl (<i>R</i>)-3-((4-amino-6-chloro-5-methylpyridazin-3-yl)amino)piperidine-1-carboxylate	Calcd. 342.2, Found 342.2
5		<i>tert</i> -butyl (3 <i>S</i> ,4 <i>R</i>)-3-((4-amino-6-chloro-5-methylpyridazin-3-yl)amino)-4-hydroxypiperidine-1-carboxylate	Calcd. 358.2, Found 358.3

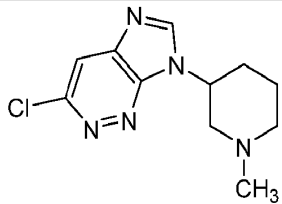
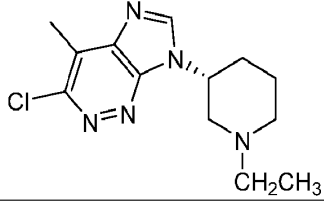
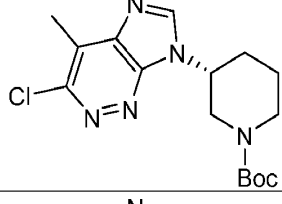
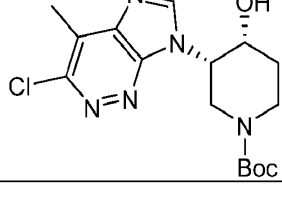
Intermediate 6

(R)-3-chloro-7-(1-ethylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazine

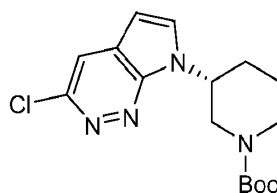
[0188] A suspension of (*R*)-6-chloro-*N*³-(1-ethylpiperidin-3-yl)pyridazine-3,4-diamine (Intermediate 1, 400 mg, 1.56 mmol) in trimethyl orthoformate (4.2 mL) was treated with HCl (4 M in 1,4-dioxane, 380 μ L, 1.52 mmol). The reaction mixture was heated to 100 °C for 2 h. Then the reaction mixture was cooled to room temperature and concentrated. The resulting crude residue was purified by silica gel chromatography (MeOH:DCM) to give the title compound. LCMS $[M+H]^+$ = 266.2 (calcd. 266.1).

Table 3. The following intermediates were prepared using a procedure similar to that described for Intermediate 6 using the appropriate starting material.

Intermediate	Structure	Name	LCMS $[M+H]^+$
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7		(<i>R</i> and <i>S</i>)-3-chloro-7-(1-methylpiperidin-3-yl)-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazine	Calcd. 252.1, Found 252.1
8		(<i>R</i>)-3-chloro-7-(1-ethylpiperidin-3-yl)-4-methyl-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazine	Calcd. 280.1, Found 280.1
9		<i>tert</i> -butyl (<i>R</i>)-3-(3-chloro-4-methyl-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazin-7-yl)piperidine-1-carboxylate	Calcd. 352.2, Found 352.4
10		<i>tert</i> -butyl (3 <i>S</i> ,4 <i>R</i>)-3-(3-chloro-4-methyl-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazin-7-yl)-4-hydroxypiperidine-1-carboxylate	Calcd. 368.1, Found 368.5

Intermediate 11

tert-butyl (*R*)-3-(3-chloro-7*H*-pyrrolo[2,3-*c*]pyridazin-7-yl)piperidine-1-carboxylate

[0189] Step 1: 3,6-dichloro-4-vinylpyridazine: A suspension of 4-bromo-3,6-dichloropyridazine (Combi-Blocks, 3.00 g, 13.2 mmol), potassium vinyltrifluoroborate (1.85 g, 13.8 mmol), and Cs₂CO₃ (12.9 g, 39.5 mmol) in 1,4-dioxane (44 mL) and water (9 mL) was degassed with argon for 10 min. Then Pd(dppf)Cl₂ (482 mg, 0.658 mmol) was added, and the mixture was heated to 50 °C for 1.5 h while stirring under argon. The reaction mixture was then cooled to room temperature and diluted with H₂O and DCM. The layers were separated, and the

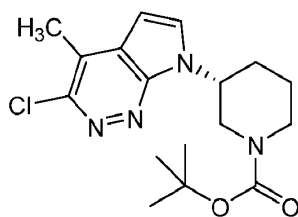
organic phase was dried over Na₂SO₄, filtered, and solvents were removed. The resulting crude residue containing the title compound was used in the next step without further purification.

[0190] Step 2: *tert*-butyl (*R*)-3-(3-chloro-5,6-dihydro-7*H*-pyrrolo[2,3-*c*]pyridazin-7-yl)piperidine-1-carboxylate: A sealed vial was charged with 3,6-dichloro-4-vinylpyridazine (100 mg, 0.571 mmol) and 1,4-dioxane (2.5 mL). Then DIPEA (200 μ L, 1.14 mmol) and *tert*-butyl (*R*)-3-aminopiperidine-1-carboxylate (Pharmablock, 122 μ L, 0.686 mmol) were added. The vial was sealed, and the reaction mixture was heated to 150 °C for 2 h. Then the reaction mixture was cooled to room temperature and concentrated. The resulting crude residue was purified by silica gel chromatography (EtOAc:hexanes) to give the title compound. LCMS [M+H]⁺ = 339.3, (calcd. 339.2).

[0191] Step 3: *tert*-butyl (*R*)-3-(3-chloro-7*H*-pyrrolo[2,3-*c*]pyridazin-7-yl)piperidine-1-carboxylate: A solution of *tert*-butyl (*R*)-3-(3-chloro-5,6-dihydro-7*H*-pyrrolo[2,3-*c*]pyridazin-7-yl)piperidine-1-carboxylate (135 mg, 0.398 mmol) in toluene (8 mL) was treated with MnO₂ (225 mg, 2.59 mmol). The reaction mixture was heated to 125 °C for 2.5 days. Then the reaction mixture was cooled to room temperature, filtered through Celite®, and concentrated. The resulting crude residue was purified by silica gel chromatography (EtOAc:hexanes) to give the title compound. LCMS [M+Na]⁺ = 359.2 (calcd. 359.1).

Intermediate 12

tert-butyl (*R*)-3-(3-chloro-4-methyl-7*H*-pyrrolo[2,3-*c*]pyridazin-7-yl)piperidine-1-carboxylate



[0192] Step 1: *tert*-butyl (*R*)-3-(pent-3-yn-1-ylamino)piperidine-1-carboxylate: A suspension of *tert*-butyl (*R*)-3-aminopiperidine-1-carboxylate (Pharmablock, 1.50 g, 7.48 mmol) and K₂CO₃ (1.41 g, 10.2 mmol) in MeCN (27 mL) was treated with 5-bromopent-2-yne (Enamine, 1.00 g, 6.80 mmol). The mixture was heated to 80 °C for 12 h with stirring. Then the reaction mixture was cooled to room temperature, filtered, and concentrated. The resulting crude residue was

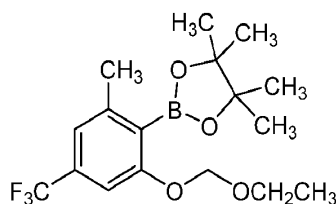
purified by silica gel chromatography (EtOAc:hexanes) to give the title compound. LCMS $[M+H]^+ = 267.2$ (calcd. 267.2).

[0193] Step 2: *tert*-butyl (*R*)-3-(3-chloro-4-methyl-5,6-dihydro-7*H*-pyrrolo[2,3-*c*]pyridazin-7-yl)piperidine-1-carboxylate: A solution of 3,6-dichloro-1,2,4,5-tetrazine (Pharmablock, 75 mg, 0.500 mmol) in THF (2 mL) in a sealed tube was treated with Et₃N (77 μ L, 0.550 mmol) and *tert*-butyl (*R*)-3-(pent-3-yn-1-ylamino)piperidine-1-carboxylate (133 mg, 0.5 mmol). The reaction mixture was heated to 110 °C for 16 h. Then the reaction mixture was cooled to room temperature and diluted with water and EtOAc. The mixture was filtered through Celite®. The layers were separated, and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated. The resulting crude residue was purified by silica gel chromatography (EtOAc:hexanes) to give the title compound. LCMS $[M+H]^+ = 353.2$ (calcd. 353.2).

[0194] Step 3: *tert*-butyl (*R*)-3-(3-chloro-4-methyl-7*H*-pyrrolo[2,3-*c*]pyridazin-7-yl)piperidine-1-carboxylate: A solution of *tert*-butyl (*R*)-3-(3-chloro-4-methyl-5,6-dihydro-7*H*-pyrrolo[2,3-*c*]pyridazin-7-yl)piperidine-1-carboxylate (70 mg, 0.20 mmol) in toluene (4 mL) was treated with MnO₂ (103 mg, 1.19 mmol). The reaction mixture was heated to 125 °C for 2.5 days. Then the reaction mixture was cooled to room temperature, filtered through Celite®, and concentrated. The resulting crude residue was purified by silica gel chromatography (EtOAc:hexanes) to give the title compound. LCMS $[M+Na]^+ = 373.3$ (calcd. 373.1).

Intermediate 13

2-(2-(ethoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)-
4,4,5,5-tetramethyl-1,3,2-dioxaborolane



[0195] Step 1: 3-Methyl-5-(trifluoromethyl)phenol: To a solution of 3-bromo-5-(trifluoromethyl)phenol (Carbosynth, 500 g, 2.07 mol), K₂CO₃ (859 g, 6.22 mol) and Pd(dppf)Cl₂ (75.8 g, 103.7 mmol) in 1,4-dioxane (7.5 L) under N₂ atmosphere, was added portion wise

trimethyl-1,3,5,2,4,6-trioxatriborinane (Aldrich, 1.04 kg, 4.15 mol, 50 wt% in THF). The resulting mixture was stirred for 12 h at 100 °C, followed by cooling to 25 °C. The reaction was then quenched with ice water at 0 °C and diluted with EtOAc. The organic layer was separated, washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The resulting crude residue was purified by silica gel chromatography (EtOAc:petroleum ether) to afford the title compound. LCMS [M-H]⁻ = 175.1 (calcd. 175.0).

[0196] Step 2: 2-Iodo-3-methyl-5-(trifluoromethyl)phenol: NaH (128.5 g, 3.21 mol, 60 wt%) was added at 0 °C to a stirring solution of 3-methyl-5-(trifluoromethyl)phenol (283 g, 1.61 mol) in toluene (1.42 L) under a N₂ atmosphere. The resulting mixture was stirred at 0 °C for 30 min., followed by the portion wise addition of a solution of I₂ (306.1 g, 1.21 mmol) in toluene (5.66 L). The reaction was stirred at 20 °C for 3 h, and then quenched by pouring onto a water/ice bath. The mixture was diluted with EtOAc, and the layers were separated. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, and the solvent was removed under reduced pressure. The resulting crude residue containing the title compound was used in the next step without further purification.

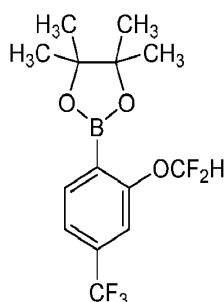
[0197] Step 3: 1-(Ethoxymethoxy)-2-iodo-3-methyl-5-(trifluoromethyl)benzene: Chloromethyl ethyl ether (290 g, 3.07 mol) was added at 0 °C to a stirring solution of 2-iodo-3-methyl-5-(trifluoromethyl)phenol (463 g, 1.53 mol) and Cs₂CO₃ (999 g, 3.07 mmol) in DMF (4.6 L) under a N₂ atmosphere. The resulting mixture was stirred for 8 h at room temperature, then cooled to 0 °C, and quenched by the addition of ice water. The resulting mixture was diluted with EtOAc, and the organic layer was separated, washed with brine, and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure, and the resulting crude residue was purified by silica gel chromatography (EtOAc:petroleum ether) to afford the title compound. ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.55 (s, 1H), 7.18 (s, 1H), 5.42 (s, 2H), 3.75 - 3.65 (m, 2H), 2.50 (s, 3H), 1.21 - 1.10 (m, 3H).

[0198] Step 4: 2-(2-(Ethoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: A mixture of 1-(ethoxymethoxy)-2-iodo-3-methyl-5-(trifluoromethyl)benzene (330 g, 916.4 mmol), B₂pin₂ (469 g, 3.67 mol), Et₃N (556 g, 5.50 mol), Pd(OAc)₂ (10.3 g, 45.8 mmol), and biphenyl-2-yl-dichlorohexylphosphine (32.1 g, 91.6 mmol) in 1,4-dioxane (3.3 L) was placed under a N₂ atmosphere. The resulting solution was stirred for 6 h at 100 °C, and then cooled to 25 °C and quenched with ice water. The resulting mixture was filtered, and the solid residue washed with EtOAc. The organic filtrate layer was separated, washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The resulting crude residue

was purified by silica gel chromatography (EtOAc:petroleum ether), and the desired fractions were concentrated. The resulting solid was dissolved in hexanes and stirred for 5 min at -30°C . The precipitated solids were collected by filtration to afford the title compound. ^1H NMR (300 MHz, CDCl_3) δ 7.13-7.03 (m, 2H), 5.23 (s, 2H), 3.74 (q, $J = 7.1$ Hz, 2H), 2.41 (s, 3H), 1.41 (s, 12H), 1.24 (t, $J = 7.1$ Hz, 3H).

Intermediate 14

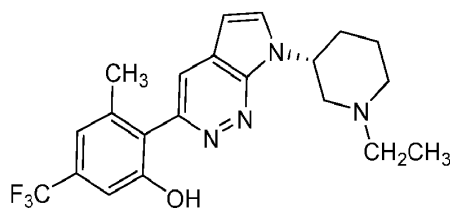
2-(2-(difluoromethoxy)-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



[0199] A solution of 1-bromo-2-(difluoromethoxy)-4-(trifluoromethyl)benzene (Enamine, 200 mg, 0.687 mmol) in toluene (5 mL) was treated with B_2pin_2 (0.262 g, 1.031 mmol), KOAc (0.202 g, 2.062 mmol) and $\text{PdCl}_2(\text{dppf})$ (Aldrich, 0.050 g, 0.069 mmol). The resulting mixture was degassed, and the reaction was stirred at 85°C under N_2 for 13 h. After cooling to room temperature, the reaction mixture was concentrated, and the resulting crude residue was purified by silica gel chromatography (EtOAc:petroleum ether) to give the title compound. ^1H NMR (CDCl_3 , 400 MHz) δ 7.88 (d, $J = 7.6$ Hz, 1H), 7.51 (d, $J = 7.7$ Hz, 1H), 7.41 (s, 1H), 6.56 (t, $J = 58.0$ Hz, 1H), 1.37 (s, 12H).

Example 1

(*R*)-2-(7-(1-ethylpiperidin-3-yl)-7*H*-pyrrolo[2,3-*c*]pyridazin-3-yl)-3-methyl-5-(trifluoromethyl)phenol



[0200] Step 1: *tert*-butyl (*R*)-3-(3-(2-(ethoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)-7*H*-pyrrolo[2,3-*c*]pyridazin-7-yl)piperidine-1-carboxylate: A first vial was charged with *tert*-butyl (*R*)-3-(3-chloro-7*H*-pyrrolo[2,3-*c*]pyridazin-7-yl)piperidine-1-carboxylate (Intermediate 11, 78 mg, 0.232 mmol), 2-(2-(ethoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Intermediate 13, 125 mg, 0.347 mmol), XPhos Pd G3 (16.6 mg, 0.019 mmol), and potassium carbonate (160 mg, 1.16 mmol), then evacuated and backfilled with N₂. In a second vial, a solvent mixture of 1,4-dioxane (1.2 mL) and water (0.3 mL) was sparged with N₂ for 15 min and then added to the first vial. The reaction mixture was heated to 100 °C for 3 h, then cooled to room temperature, and diluted with water and DCM. The layers were separated, and the aqueous layer was extracted with DCM (x3). The combined organic layers were dried over anhydrous MgSO₄, filtered and concentrated. The resulting crude residue was purified by silica gel chromatography (EtOAc:hexanes) to give the title compound. LCMS [M+H]⁺ = 535.2, (calcd. 535.3).

[0201] Step 2: (*R*)-3-methyl-2-(7-(piperidin-3-yl)-7*H*-pyrrolo[2,3-*c*]pyridazin-3-yl)-5-(trifluoro-methyl)phenol, hydrochloride: A solution of *tert*-butyl (*R*)-3-(3-(2-(ethoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)-7*H*-pyrrolo[2,3-*c*]pyridazin-7-yl)piperidine-1-carboxylate (121 mg, 0.226 mmol) in 1,4-dioxane (2.3 mL) was treated with HCl (4 M in 1,4-dioxane, 283 µL, 1.13 mmol). The reaction mixture was heated to 70 °C and stirred for 3 h. Then the reaction mixture was cooled to room temperature, and the precipitated solids were collected by filtration to afford the title compound. LCMS [M+H]⁺ = 377.2, (calcd. 377.2).

[0202] Step 3: (*R*)-2-(7-(1-ethylpiperidin-3-yl)-7*H*-pyrrolo[2,3-*c*]pyridazin-3-yl)-3-methyl-5-(trifluoromethyl)phenol: A solution of (*R*)-3-methyl-2-(7-(piperidin-3-yl)-7*H*-pyrrolo[2,3-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol, hydrochloride (72 mg, 0.174 mmol) and acetaldehyde (20 µL, 0.35 mmol) in DCM (1.7 mL) was treated with sodium triacetoxyborohydride (74 mg, 0.35 mmol). The resulting reaction mixture was stirred for 1 h at 25 °C, then quenched with water and partitioned with 10% MeOH in DCM. The layers were separated, and the aqueous layer was extracted with 10% MeOH in DCM (x2). The combined organic layers

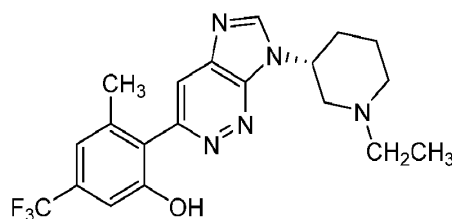
were dried over anhydrous MgSO_4 , filtered, and concentrated. The resulting crude residue was taken up in DMSO, filtered, and purified via preparative reverse phase HPLC (C18 stationary phase, MeCN/water + 0.05% FA) to afford the title compound. LCMS $[\text{M}+\text{H}]^+ = 405.2$, (calcd. 405.2). ^1H NMR (500 MHz, DMSO- d_6) 10.02 (s, 1H), 8.15 (d, $J = 3.1$ Hz, 1H), 7.80 (s, 1H), 7.15 (s, 1H), 7.09 (s, 1H), 6.60 (d, $J = 3.3$ Hz, 1H), 5.10 (br s, 1H), 3.29 – 3.26 (m, 1H), 3.13 (br s, 1H), 2.88 (br s, 1H), 2.61 – 2.54 (m, 2H), 2.21 (s, 1H), 2.09 – 2.02 (m, 2H), 2.05 (s, 3H), 1.86 – 1.81 (m, 1H), 1.72 (br s, 1H), 1.04 (t, $J = 7.1$ Hz, 3H).

Table 4. The following compound was prepared using procedures similar to those described for Example 1 using the appropriate starting materials.

Example	Structure	Name	LCMS $[\text{M}+\text{H}]^+$
2		(<i>R</i>)-2-(7-(1-ethylpiperidin-3-yl)-4-methyl-7 <i>H</i> -pyrrolo[2,3- <i>c</i>]pyridazin-3-yl)-5-(trifluoromethyl)phenol	Calcd. 405.2, Found 405.4

Example 3

(*R*)-2-(7-(1-ethylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-3-methyl-5-(trifluoromethyl)phenol



[0203] Step 1: (*R*)-3-(2-(ethoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)-7-(1-ethylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazine: A vial was charged with (*R*)-3-chloro-7-(1-ethylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazine (Intermediate 6, 100 mg, 0.376 mmol), 2-(2-(ethoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Intermediate 13, 203 mg, 0.564 mmol), XPhos Pd G3 (26 mg, 0.030 mmol), and potassium carbonate (260 mg, 1.88 mmol). The vial was then evacuated and backfilled with nitrogen (3x).

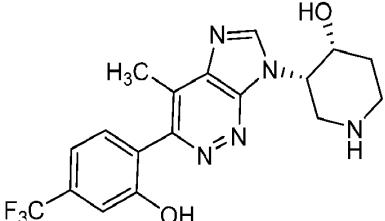
In a second vial, a solvent mixture of 1,4-dioxane (2 mL) and water (0.5 mL) was sparged with nitrogen for 15 min, and then added to the first vial. The reaction was heated to 100 °C for 3 h. Then the reaction mixture was cooled to room temperature and diluted with water and DCM. The layers were separated, and the aqueous layer was extracted with DCM (x3). The combined organic layers were dried over anhydrous MgSO₄, filtered and concentrated. The resulting crude residue was purified by silica gel chromatography (MeOH:DCM) to give the title compound.

LCMS [M+H]⁺ = 464.4, (calcd. 464.2).

[0204] Step 2: (*R*)-2-(7-(1-ethylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-3-methyl-5-(trifluoromethyl)phenol: A solution of (*R*)-3-(2-(ethoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)-7-(1-ethylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazine (30 mg, 0.065 mmol) in 1,4-dioxane (0.65 mL) was treated with HCl (4 M in 1,4-dioxane, 81 μL, 0.324 mmol). The reaction mixture was heated to 70 °C and stirred for 3 h. Then the reaction mixture was cooled to room temperature and concentrated. The resulting crude residue was taken up in DMSO, filtered, and purified via preparative reverse phase HPLC (C18 stationary phase, MeCN/water + 0.05% FA) to afford the title compound. LCMS [M+H]⁺ = 406.4, (calcd. 406.2). ¹H NMR (500 MHz, MeOD-*d*₄) δ 8.94 (s, 1H), 7.92 (s, 1H), 7.09 (s, 1H), 7.05 (s, 1H), 5.07 – 4.97 (m, 1H), 3.30 – 3.22 (m, 1H), 2.89 – 2.75 (m, 2H), 2.56 – 2.47 (m, 2H), 2.38 – 2.15 (m, 3H), 2.09 (s, 3H), 1.93 – 1.72 (m, 2H), 1.10 (t, *J* = 7.2 Hz, 3H).

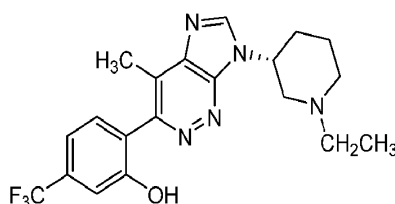
Table 5. The following compounds were prepared using procedures similar to those described for Example 3 using the appropriate starting materials.

Example	Structure	Name	LCMS [M+H] ⁺
4		(<i>R</i> and <i>S</i>)-3-methyl-2-(7-(1-methylpiperidin-3-yl)-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazin-3-yl)-5-(trifluoromethyl)phenol	Calcd. 392.2, Found 392.1
5		(<i>R</i>)-2-(4-methyl-7-(piperidin-3-yl)-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazin-3-yl)-5-(trifluoromethyl)phenol	Calcd. 378.2, Found 378.2

6		(3 <i>S</i> ,4 <i>R</i>)-3-(3-(2-hydroxy-4-(trifluoromethyl)phenyl)-4-methyl-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazin-7-yl)piperidin-4-ol	Calcd. 394.1, Found 394.2
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Example 7

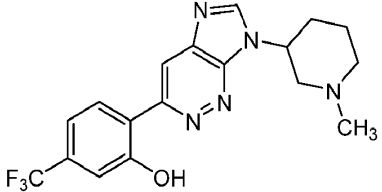
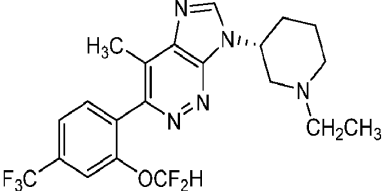
(*R*)-2-(7-(1-ethylpiperidin-3-yl)-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol



[0205] A solution of (*R*)-3-chloro-7-(1-ethylpiperidin-3-yl)-4-methyl-7*H*-imidazo[4,5-*c*]pyridazine (Intermediate 8, 40 mg, 0.143 mmol) in 1,4-dioxane (3 mL) and water (0.8 mL) was treated with (2-hydroxy-4-(trifluoromethyl)phenyl)boronic acid (Combi-Blocks, 35.3 mg, 0.172 mmol), K₂CO₃ (59.3 mg, 0.429 mmol) and PdCl₂(dppf) (10.5 mg, 0.014 mmol). The mixture was degassed with argon and then heated to 100 °C for 12 h. After cooling to room temperature, the reaction mixture was filtered and concentrated. The resulting crude residue was purified via preparative reverse phase HPLC (C18 stationary phase, MeCN/water + 0.05% TFA) to afford the title compound. LCMS [M+H]⁺ = 406.2, (calcd. 406.2). ¹H NMR (400 MHz, MeOD-*d*₄) δ 8.82 (s, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 7.2 Hz, 1H), 7.27 (s, 1H), 5.17 (br s, 1H), 4.07 (br d, *J* = 10.8 Hz, 1H), 3.79 - 3.62 (m, 2H), 3.36 (br s, 2H), 3.14 (br t, *J* = 12.4 Hz, 1H), 2.61 (br s, 1H), 2.56 (s, 3H), 2.46 (br s, 1H), 2.32 (br d, *J* = 14.7 Hz, 1H), 2.16 - 2.00 (m, 1H), 1.41 (br t, *J* = 7.2 Hz, 3H).

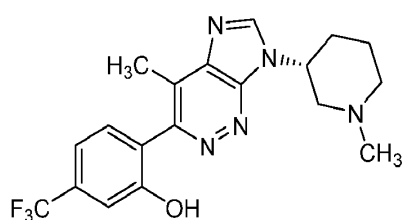
Table 6. The following compounds were prepared using a procedure similar to that described for Example 7 using the appropriate starting materials.

Example	Structure	Name	LCMS [M+H] ⁺
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8		(<i>R</i> and <i>S</i>)-2-(7-(1-methylpiperidin-3-yl)-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazin-3-yl)-5-(trifluoromethyl)phenol	Calcd. 378.2, Found 378.1
9		(<i>R</i>)-3-(2-(difluoromethoxy)-4-(trifluoromethyl)phenyl)-7-(1-ethylpiperidin-3-yl)-4-methyl-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazine	Calcd. 456.2, Found 456.2

Example 10

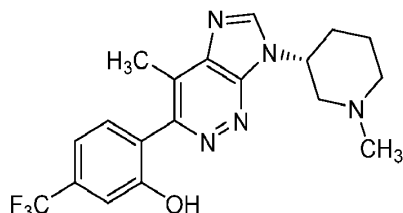
(*R*)-2-(4-methyl-7-(1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol



[0206] A mixture of (*R*)-2-(4-methyl-7-(piperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol (Example 5, 20 mg, 0.053 mmol) in MeOH (0.27 mL) and THF (0.27 mL) was treated with formaldehyde (37% in water, 24 μ L, 0.318 mmol) and sodium triacetoxyborohydride (34 mg, 0.159 mmol). The reaction mixture was stirred at 25 °C for 1 h. Then the reaction was quenched with 4 drops of AcOH, and concentrated. The resulting crude residue was taken up in DMSO, filtered, and purified via preparative reverse phase HPLC (C18 stationary phase, MeCN/water + 0.1% TFA) to afford the title compound. LCMS $[M+H]^+$ = 392.3 (calcd. 392.2). ^1H NMR (500 MHz, MeOD-*d*₄) δ 8.88 (s, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.24 (s, 1H), 5.10 – 5.00 (m, 1H), 3.40 – 3.28 (m, 2H), 3.08 – 2.88 (m, 2H), 2.51 (s, 3H), 2.51 (s, 3H), 2.36 – 2.21 (m, 2H), 2.04 – 1.83 (m, 2H).

Example 10 (Alternate Synthesis)

(*R*)-2-(4-methyl-7-(1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol



[0207] Step 1: 3,4,6-trichloro-5-methylpyridazine: A solution of 4-bromo-5-methylpyridazine-3,6-diol (Enamine, 1.20 g, 5.85 mmol) and POCl₃ (10 mL, 107 mmol) was stirred at 100 °C for 2 h. Then the mixture was cooled to room temperature, and slowly added to water. The mixture was diluted with EtOAc, the layers were separated, and the aqueous layer was extracted with EtOAc (x2). The combined organic layers were concentrated, and the resulting crude residue was purified by silica gel chromatography (EtOAc:petroleum ether) to give the title compound. LCMS [M+H]⁺ = 197.1 (calcd. 196.9).

[0208] Step 2: phenyl 3,6-dichloro-5-methylpyridazine-4-sulfinate: A solution of 3,4,6-trichloro-5-methylpyridazine (6.4 g, 32.4 mmol) in THF (50 mL) and DMSO (10 mL) was treated with sodium benzenesulfinate (5.6 g, 34.0 mmol). The resulting reaction mixture was heated to 40 °C for 48 h. Then the reaction mixture was cooled to room temperature and diluted with water and EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were concentrated, and the resulting crude residue was purified by silica gel chromatography (EtOAc:petroleum ether) to give the title compound. LCMS [M+H]⁺ = 303.1 (calcd. 303.0).

[0209] Step 3: *tert*-butyl (*R*)-3-((6-chloro-5-methyl-4-(phenylsulfonyl)pyridazin-3-yl)amino)piperidine-1-carboxylate: Two 40 mL scintillation vials were set up in duplicate. In each vial, a solution of phenyl 3,6-dichloro-5-methylpyridazine-4-sulfinate (750 mg, 2.47 mmol) in 1,4-dioxane (15 mL) was treated with *tert*-butyl (*R*)-3-aminopiperidine-1-carboxylate (Aldrich, 743 mg, 3.71 mmol) and K₂CO₃ (1.54 g, 11.1 mmol). The resulting mixtures were heated to 100 °C for 5 h. After cooling to room temperature, the reaction mixtures were combined, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by silica

gel chromatography ([25% EtOH in EtOAc]:hexanes) to afford the title compound. LCMS $[M+Na]^+ = 489.4$ (calcd. 489.1).

[0210] Step 4: *tert*-butyl (*R*)-3-((4-azido-6-chloro-5-methylpyridazin-3-yl)amino)piperidine-1-carboxylate: A solution of *tert*-butyl (*R*)-3-((6-chloro-5-methyl-4-(phenylsulfonyl)pyridazin-3-yl)amino)piperidine-1-carboxylate (1.50 g, 3.21 mmol) in DMSO (23 mL) was treated with NaN₃ (1.25 g, 19.3 mmol). The resulting mixture was heated to 60 °C for 5 h. After cooling to room temperature, the reaction mixture was quenched with water and extracted with EtOAc (3x). The combined organic layers were washed with water (2x) and brine, dried over anhydrous MgSO₄, filtered and concentrated *in vacuo*. The resulting crude residue was purified by silica gel chromatography (MeOH:DCM) to afford the title compound. LCMS $[M+H]^+ = 368.2$ (calcd. 368.2).

[0211] Step 5: *tert*-butyl (*R*)-3-((4-amino-6-chloro-5-methylpyridazin-3-yl)amino)piperidine-1-carboxylate: A solution of *tert*-butyl (*R*)-3-((4-azido-6-chloro-5-methylpyridazin-3-yl)amino)piperidine-1-carboxylate (686 mg, 1.87 mmol) in DCM (9.1 mL) and AcOH (1.8 mL) was cooled to 0 °C and treated with zinc (244 mg, 3.73 mmol). The resulting mixture was stirred at 0 °C for 2 h, then filtered and concentrated *in vacuo* to give the title compound. LCMS $[M+H]^+ = 342.2$ (calcd. 342.2).

[0212] Step 6: *tert*-butyl (*R*)-3-(3-chloro-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-7-yl)piperidine-1-carboxylate: A solution of *tert*-butyl (*R*)-3-((4-amino-6-chloro-5-methylpyridazin-3-yl)amino)piperidine-1-carboxylate (1.10 g, 3.22 mmol) in trimethyl orthoformate (21.5 mL) was treated with HCl (4 M in 1,4-dioxane, 40 µL, 0.161 mmol). The reaction mixture was heated to 100 °C for 2 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The resulting crude residue was purified by silica gel chromatography (MeOH:DCM) to give the title compound. LCMS $[M+H]^+ = 352.4$ (calcd. 352.2).

[0213] Step 7: *tert*-butyl (*R*)-3-(3-(2-hydroxy-4-(trifluoromethyl)phenyl)-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-7-yl)piperidine-1-carboxylate: A vial was charged with *tert*-butyl (*R*)-3-(3-chloro-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-7-yl)piperidine-1-carboxylate (700 mg, 1.99 mmol), (2-hydroxy-4-(trifluoromethyl)phenyl)boronic acid (Combi-Blocks, 615 mg, 2.98 mmol), XPhos Pd G3 (135 mg, 0.159 mmol), and potassium carbonate (1.38 g, 9.95 mmol). The vial was then evacuated and backfilled with nitrogen (3x). In a second vial, a solvent mixture of 1,4-dioxane (10.6 mL) and water (2.7 mL) was sparged with nitrogen for 15 min, and then added to the first vial. The reaction was heated to 100 °C for 3 h. Then the reaction mixture was cooled to room temperature and diluted with water and DCM. The layers were separated, and the aqueous

layer was extracted with DCM (x3). The combined organic layers were dried over anhydrous MgSO_4 , filtered and concentrated *in vacuo*. The resulting crude residue was purified by silica gel chromatography (MeOH:DCM) to give the title compound. LCMS $[\text{M}+\text{H}]^+ = 478.4$, (calcd. 478.2).

[0214] Step 8: (*R*)-2-(4-methyl-7-(piperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoro-methyl)phenol: A solution of *tert*-butyl (*R*)-3-(3-(2-hydroxy-4-(trifluoro-methyl)phenyl)-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-7-yl)piperidine-1-carboxylate (503 mg, 1.05 mmol) in DCM (10.5 mL) was treated with HCl (4 M in 1,4-dioxane, 1.32 mL, 5.27 mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was then diluted with MeOH, then loaded onto a Biotage Isolute® SCX-2 ion exchange column, eluting first with MeOH and second with 7 M ammonia in MeOH. The 7 M ammonia layer was concentrated *in vacuo* to afford the title compound. LCMS $[\text{M}+\text{H}]^+ = 378.2$, (calcd. 378.2).

[0215] Step 9: (*R*)-2-(4-methyl-7-(1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol: A mixture of (*R*)-2-(4-methyl-7-(piperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol (20 mg, 0.053 mmol) in MeOH (0.27 mL) and THF (0.27 mL) was treated with formaldehyde (37% in water, 24 μL , 0.318 mmol) and sodium triacetoxyborohydride (34 mg, 0.159 mmol). The reaction mixture was stirred at 25 °C for 1 h. Then the reaction was quenched with 4 drops of AcOH, and concentrated. The resulting crude residue was taken up in DMSO, filtered, and purified via preparative reverse phase HPLC (C18 stationary phase, MeCN/water + 0.1% TFA) to afford the title compound. LCMS $[\text{M}+\text{H}]^+ = 392.3$ (calcd. 392.2). ^1H NMR (500 MHz, $\text{MeOD}-d_4$) δ 8.88 (s, 1H), 7.48 (d, $J = 7.8$ Hz, 1H), 7.29 (d, $J = 8.0$ Hz, 1H), 7.24 (s, 1H), 5.10 – 5.00 (m, 1H), 3.40 – 3.28 (m, 2H), 3.08 – 2.88 (m, 2H), 2.51 (s, 3H), 2.51 (s, 3H), 2.36 – 2.21 (m, 2H), 2.04 – 1.83 (m, 2H).

Table 7. The following compounds were prepared using a procedure similar to that described for Example 10 using the appropriate starting materials and aldehydes.

Example	Structure	Name	LCMS $[\text{M}+\text{H}]^+$
11		(3 <i>S</i> ,4 <i>R</i>)-3-(3-(2-hydroxy-4-(trifluoromethyl)phenyl)-4-methyl-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazin-7-yl)-1-methylpiperidin-4-ol	Calcd. 408.2, Found 408.2

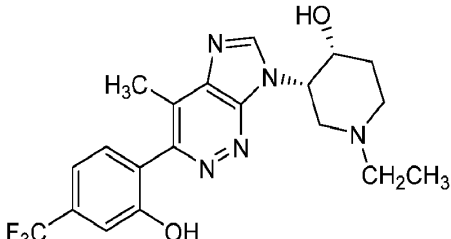
12		(3 <i>S</i> ,4 <i>R</i>)-1-ethyl-3-(3-(2-hydroxy-4-(trifluoromethyl)phenyl)-4-methyl-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazin-7-yl)piperidin-4-ol	Calcd. 422.2, Found 422.2
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Table 8. The following intermediate was prepared using a procedure similar to that described for Intermediate 3 using the appropriate commercially available amine.

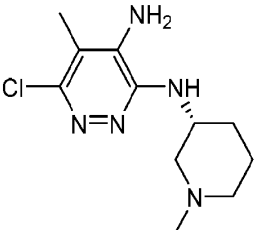
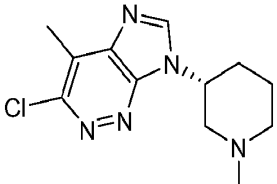
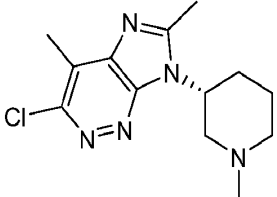
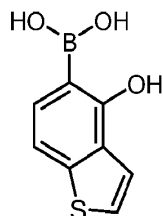
Intermediate	Structure	Name	LCMS [M+H] ⁺
15		(<i>R</i>)-6-chloro-5-methyl- <i>N</i> ³ -(1-methylpiperidin-3-yl)pyridazine-3,4-diamine	Calcd. 256.1, Found 256.1

Table 9. The following intermediates were prepared using a procedure similar to that described for Intermediate 6 using the appropriate starting materials.

Intermediate	Structure	Name	LCMS [M+H] ⁺
16		(<i>R</i>)-3-chloro-4-methyl-7-(1-methylpiperidin-3-yl)-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazine	Calcd. 266.1, Found 266.1
17		(<i>R</i>)-3-chloro-4,6-dimethyl-7-(1-methylpiperidin-3-yl)-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazine	Calcd. 280.1, Found 280.1

Intermediate 18

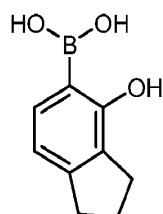
(4-hydroxybenzo[*b*]thiophen-5-yl)boronic acid

[0216] Step 1: 5,5-dibromo-6,7-dihydrobenzo[*b*]thiophen-4(5*H*)-one: A solution of CuBr₂ (5.87 g, 26.3 mmol) in EtOAc (30 mL) was stirred at 80 °C for 10 min. Then a solution of 6,7-dihydrobenzo[*b*]thiophen-4(5*H*)-one (Combi-Blocks, 1.00 g, 6.57 mmol) in CHCl₃ (30 mL) was added dropwise, and the resulting mixture was stirred for 12 h at 80 °C. The reaction mixture was then cooled to room temperature, diluted with EtOAc, and filtered over Al₂O₃. The filtrate was washed with saturated aqueous NaHCO₃ solution, dried over anhydrous Na₂SO₄, filtered and concentrated. The resulting crude residue was purified by silica gel chromatography (EtOAc:petroleum ether) to afford the title compound. LCMS [M+H]⁺ = 310.9, (calcd. 310.9).

[0217] Step 2: 5-bromobenzo[*b*]thiophen-4-ol: Li₂CO₃ (2.26 g, 30.6 mmol) was added to a solution of 5,5-dibromo-6,7-dihydrobenzo[*b*]thiophen-4(5*H*)-one (1.58 g, 5.10 mmol) in DMF (30 mL). The resulting mixture was stirred for 12 h at 100 °C. Then the reaction mixture was cooled to room temperature, filtered and concentrated under reduced pressure. The resulting crude residue was purified by silica gel chromatography (EtOAc:petroleum ether) to afford the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.51 (d, *J* = 5.5 Hz, 1H), 7.40 (s, 1H), 7.39 (d, *J* = 1.7 Hz, 1H), 7.36 - 7.32 (m, 1H), 5.87 (s, 1H).

[0218] Step 3: (4-hydroxybenzo[*b*]thiophen-5-yl)boronic acid: A mixture of 5-bromobenzo[*b*]thiophen-4-ol (400 mg, 1.75 mmol), B₂(OH)₄ (313 mg, 3.49 mmol), and chloro[(di(1-adamantyl)-*n*-butylphosphine)-2-(2-aminobiphenyl)]palladium(II) (117 mg, 0.175 mmol) in MeOH (5 mL) under N₂ atmosphere was stirred for 12 h at room temperature. The reaction mixture was then filtered and concentrated under reduced pressure. The resulting crude residue was purified by MPLC (C18 stationary phase, MeCN/water + 0.5% TFA) to afford the title compound. LCMS [M+H]⁺ = 194.5, (calcd. 195.0).

Intermediate 19

(4-hydroxy-2,3-dihydro-1*H*-inden-5-yl)boronic acid

[0219] Step 1: 5-bromo-2,3-dihydro-1*H*-inden-4-ol: Diisopropylamine (9.1 mg, 0.090 mmol) was added to a solution of 2,3-dihydro-1*H*-inden-4-ol (Combi-Blocks, 1.00 g, 7.45 mmol) in DCM (50 mL), and the resulting mixture was cooled to 0 °C. To this solution was added 1-bromopyrrolidine-2,5-dione (1.33 g, 7.45 mmol) in small portions. The reaction mixture was warmed to room temperature and stirred for 12 h. Then the reaction mixture was washed with water and brine, and the organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated. The resulting crude residue was purified by silica gel chromatography (EtOAc:petroleum ether) to afford the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.15 (d, *J* = 8.0 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 5.43 - 5.32 (m, 1H), 2.83 (dt, *J* = 17.3, 7.6 Hz, 4H), 2.10 - 1.97 ppm (m, 2H).

[0220] Step 2: (4-hydroxy-2,3-dihydro-1*H*-inden-5-yl)boronic acid: A mixture of 5-bromo-2,3-dihydro-1*H*-inden-4-ol (50 mg, 0.235 mmol), B₂(OH)₄ (42.1 mg, 0.469 mmol) and chloro[(di(1-adamantyl)-*n*-butylphosphine)-2-(2-aminobiphenyl)]palladium(II) (15.7 mg, 0.023 mmol) in MeOH (2 mL) under N₂ atmosphere was cooled to 0 °C. Then DIPEA (0.123 mL, 0.704 mmol) was added dropwise, and the reaction mixture was then warmed to room temperature and stirred for 12 h. The reaction mixture was then filtered and concentrated under reduced pressure. The resulting crude residue was purified via preparative reverse phase HPLC (C18 stationary phase, MeCN/water + 0.1% TFA) to afford the title compound. LCMS [M+H]⁺ = 179.2, (calcd. 179.1).

Table 10. The following compound was prepared using procedures similar to those described for Example 3 using the appropriate starting materials.

Example	Structure	Name	LCMS [M+H] ⁺
13		(<i>R</i>)-5-chloro-2-(4-methyl-7-(piperidin-3-yl)-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazin-3-yl)phenol	Calcd. 344.1, Found 344.3

Table 11. The following compounds were prepared using a procedure similar to that described for Example 7 using the appropriate starting materials.

Example	Structure	Name	LCMS [M+H] ⁺
14		(<i>R</i>)-2-(4,6-dimethyl-7-(1-methylpiperidin-3-yl)-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazin-3-yl)-5-(trifluoromethyl)phenol	Calcd. 406.2, Found 406.2
15		(<i>R</i>)-5-(4-methyl-7-(1-methylpiperidin-3-yl)-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazin-3-yl)benzo[<i>b</i>]thiophen-4-ol	Calcd. 380.2, Found 380.1
16		(<i>R</i>)-5-(4-methyl-7-(1-methylpiperidin-3-yl)-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazin-3-yl)-2,3-dihydro-1 <i>H</i> -inden-4-ol	Calcd. 364.2, Found 364.1

Table 12. The following compounds were prepared using a procedure similar to that described for Example 10 using the appropriate starting materials and aldehydes.

Example	Structure	Name	LCMS [M+H] ⁺
17		(R)-5-chloro-2-(4-methyl-7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)phenol	Calcd. 358.1, Found 358.4
18		(R)-5-chloro-2-(7-(1-ethylpiperidin-3-yl)-4-methyl-7H-imidazo[4,5-c]pyridazin-3-yl)phenol	Calcd. 372.2, Found 372.4

Table 13. The following intermediates were prepared using a procedure similar to that described for Intermediate 3 using the appropriate commercially available amines.

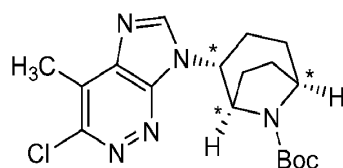
Intermediate	Structure	Name	LCMS [M+H] ⁺
20		<i>tert</i> -butyl (1 <i>R</i> ,2 <i>R</i> ,5 <i>R</i> and 1 <i>S</i> ,2 <i>S</i> ,5 <i>S</i>)-2-((4-amino-6-chloro-5-methylpyridazin-3-yl)amino)-8-azabicyclo[3.2.1]octan-8-ylcarboxylate	Calcd. 368.2, Found 368.1
21		<i>tert</i> -butyl (5-((4-amino-6-chloro-5-methylpyridazin-3-yl)amino)bicyclo[3.1.1]heptan-1-yl)carbamate	Calcd. 368.2, Found 368.0
22		6-chloro-5-methyl- <i>N</i> ³ -(((8 <i>R</i> ,8 <i>aS</i> and 8 <i>S</i> ,8 <i>aR</i>)-octahydroindolizin-8-yl)pyridazine-3,4-diamine	Calcd. 282.1, Found 282.0

Table 14. The following intermediates were prepared using a procedure similar to that described for Intermediate 6 using the appropriate starting materials.

Intermediate	Structure	Name	LCMS [M+H] ⁺
23		<i>tert</i> -butyl (1 <i>R</i> ,2 <i>R</i> ,5 <i>R</i> and 1 <i>S</i> ,2 <i>S</i> ,5 <i>S</i>)-2-(3-chloro-4-methyl-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate	Calcd. 378.2, Found 378.1
24		<i>tert</i> -butyl (5-(3-chloro-4-methyl-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazin-7-yl)bicyclo[3.1.1]heptan-1-yl)carbamate	Calcd. 378.2, Found 378.0
25		3-chloro-4-methyl-7-((8 <i>R</i> ,8 <i>aS</i> and 8 <i>S</i> ,8 <i>aR</i>)-octahydroindolizin-8-yl)-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazine	Calcd. 292.1, Found 292.2

Intermediate 23 (Alternate Synthesis)

tert-butyl (1*R*,2*R*,5*R* and 1*S*,2*S*,5*S*)-2-(3-chloro-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate



[0221] Step 1: 3,4,6-trichloro-5-methylpyridazine: A solution of 4-bromo-5-methylpyridazine-3,6-diol (Enamine, 1.20 g, 5.85 mmol) and POCl₃ (10 mL, 107 mmol) was stirred at 100 °C for 2 h. Then the mixture was cooled to room temperature, and slowly added to water. The mixture was diluted with EtOAc, the layers were separated, and the aqueous layer was extracted with EtOAc (x2). The combined organic layers were concentrated, and the resulting crude residue was

purified by silica gel chromatography (EtOAc:petroleum ether) to give the title compound.

LCMS $[M+H]^+ = 197.1$ (calcd. 196.9).

[0222] Step 2: phenyl 3,6-dichloro-5-methylpyridazine-4-sulfinate: A solution of 3,4,6-trichloro-5-methylpyridazine (6.4 g, 32.4 mmol) in THF (50 mL) and DMSO (10 mL) was treated with sodium benzenesulfinate (5.6 g, 34.0 mmol). The resulting reaction mixture was heated to 40 °C for 48 h. Then the reaction mixture was cooled to room temperature and diluted with water and EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were concentrated, and the resulting crude residue was purified by silica gel chromatography (EtOAc:petroleum ether) to give the title compound.

LCMS $[M+H]^+ = 303.1$ (calcd. 303.0).

[0223] Step 3: *tert*-butyl (1*R*,2*R*,5*R* and 1*S*,2*S*,5*S*)-2-((6-chloro-5-methyl-4-(phenylsulfonyl)pyridazin-3-yl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate: A solution of phenyl 3,6-dichloro-5-methylpyridazine-4-sulfinate (580 mg, 1.91 mmol) in 1,4-dioxane (10 mL) was treated with *tert*-butyl (1*R*,2*R*,5*R* and 1*S*,2*S*,5*S*)-2-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (Combi-Blocks, 433 mg, 1.91 mmol) and Na₂CO₃ (608 mg, 5.74 mmol). The resulting mixture was heated to 100 °C for 12 h. After cooling to room temperature, the reaction mixture was quenched with water and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The resulting crude residue was purified by silica gel chromatography (EtOAc:petroleum ether) to afford the title compound. LCMS $[M+H]^+ = 493.1$ (calcd. 493.2).

[0224] Step 4: *tert*-butyl (1*R*,2*R*,5*R* and 1*S*,2*S*,5*S*)-2-((4-azido-6-chloro-5-methylpyridazin-3-yl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate: A solution of *tert*-butyl (1*R*,2*R*,5*R* and 1*S*,2*S*,5*S*)-2-((6-chloro-5-methyl-4-(phenylsulfonyl)pyridazin-3-yl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (800 mg, 1.62 mmol) in DMF (12 mL) was treated with NaN₃ (844 mg, 13.0 mmol). The resulting mixture was heated to 50 °C for 12 h. After cooling to 0 °C, the reaction mixture was quenched with water and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The resulting crude residue was purified by silica gel chromatography (EtOAc:petroleum ether) to afford the title compound. LCMS $[M+H]^+ = 394.1$ (calcd. 394.2).

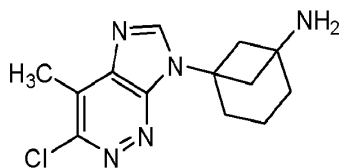
[0225] Step 5: *tert*-butyl (1*R*,2*R*,5*R* and 1*S*,2*S*,5*S*)-2-((4-amino-6-chloro-5-methylpyridazin-3-yl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate: A solution of *tert*-butyl (1*R*,2*R*,5*R* and 1*S*,2*S*,5*S*)-2-((4-azido-6-chloro-5-methylpyridazin-3-yl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (480 mg, 1.22 mmol) in DCM (5 mL) and AcOH (1 mL) was cooled to 0 °C and

treated with zinc (159 mg, 2.44 mmol). The resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with DCM, then filtered and washed with brine (2x). The resulting organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to give the title compound. LCMS [M+H]⁺ = 368.1 (calcd. 368.2).

[0226] Step 6: : *tert*-butyl (1*R*,2*R*,5*R* and 1*S*,2*S*,5*S*)-2-(3-chloro-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate: A solution of *tert*-butyl (1*R*,2*R*,5*R* and 1*S*,2*S*,5*S*)-2-((4-amino-6-chloro-5-methylpyridazin-3-yl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (240 mg, 0.652 mmol) in trimethyl orthoformate (0.3 mL) was treated with HCl (4 M in 1,4-dioxane, 8.2 µL, 0.033 mmol). The reaction mixture was heated to 100 °C for 30 min. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The resulting crude residue was purified by silica gel chromatography (EtOAc:petroleum ether) to give the title compound. LCMS [M+H]⁺ = 378.1 (calcd. 378.2).

Intermediate 26

5-(3-chloro-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-7-yl)bicyclo[3.1.1]heptan-1-amine



[0227] A solution of *tert*-butyl (5-(3-chloro-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-7-yl)bicyclo[3.1.1]-heptan-1-yl)carbamate (Intermediate 24, 40 mg, 0.106 mmol) in DCM (1 mL) was treated with TFA (36 mg, 0.318 mmol). The resulting mixture was stirred at 20°C for 1 h. Then the reaction mixture was concentrated *in vacuo*, and the resulting crude residue was purified via preparative reverse phase HPLC (C18 stationary phase, MeCN/water + 0.1% TFA) to give the title compound. LCMS [M+H]⁺ = 278.0, (calcd. 278.1).

Table 15. The following compound was prepared using procedures similar to those described for Example 3 using the appropriate starting materials.

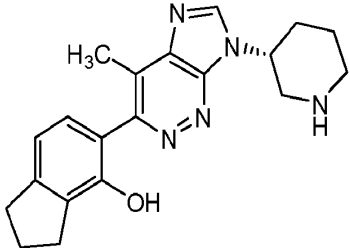
Example	Structure	Name	LCMS [M+H] ⁺
19		(<i>R</i>)-5-(4-methyl-7-(piperidin-3-yl)-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazin-3-yl)-2,3-dihydro-1 <i>H</i> -inden-4-ol	Calcd. 350.2, Found 350.3

Table 16. The following compounds were prepared using a procedure similar to that described for Example 7 using the appropriate starting materials.

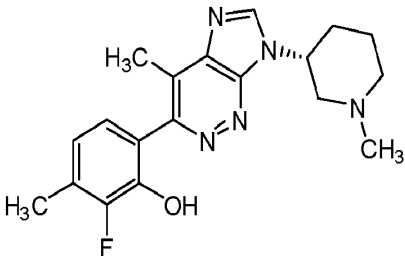
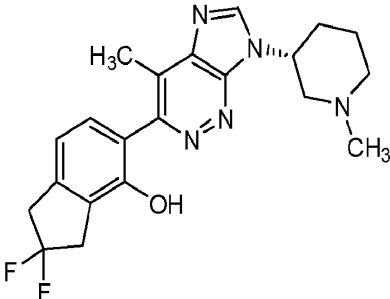
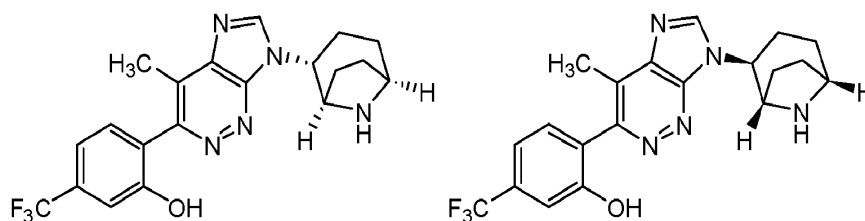
Example	Structure	Name	LCMS [M+H] ⁺
20		(<i>R</i>)-2-fluoro-3-methyl-6-(4-methyl-7-(1-methylpiperidin-3-yl)-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazin-3-yl)phenol	Calcd. 356.2, Found 356.4
21		(<i>R</i>)-2,2-difluoro-5-(4-methyl-7-(1-methylpiperidin-3-yl)-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazin-3-yl)-2,3-dihydro-1 <i>H</i> -inden-4-ol	Calcd. 400.2, Found 400.3

Table 17. The following compounds were prepared using a procedure similar to that described for Example 10 using the appropriate starting materials and ketones. DCM was used as the solvent in place of a mixture of THF and MeOH. For Example 22, the reaction temperature was increased to 50 °C.

Example	Structure	Name	LCMS [M+H] ⁺
22		(<i>R</i>)-2-(7-(1-isopropylpiperidin-3-yl)-4-methyl-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazin-3-yl)-5-(trifluoromethyl)phenol	Calcd. 420.2, Found 420.2
23		(<i>R</i>)-2-(7-(1-cyclobutylpiperidin-3-yl)-4-methyl-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazin-3-yl)-5-(trifluoromethyl)phenol	Calcd. 432.2, Found 432.2

Examples 24 and 25

2-(7-((1*R*,2*R*,5*S*)-8-azabicyclo[3.2.1]octan-2-yl)-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol, and
2-(7-((1*S*,2*S*,5*R*)-8-azabicyclo[3.2.1]octan-2-yl)-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol

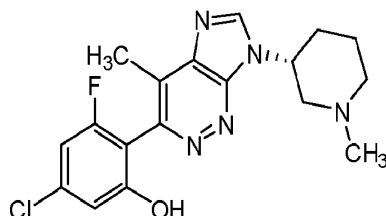


[0228] Step 1: *tert*-butyl (1*R*,2*R*,5*R* and 1*S*,2*S*,5*S*)-2-(3-(2-hydroxy-4-(trifluoromethyl)phenyl)-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate: A solution of *tert*-butyl (1*R*,2*R*,5*R* and 1*S*,2*S*,5*S*)-2-(3-chloro-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (Intermediate 23, 40 mg, 0.106 mmol) and (2-hydroxy-4-(trifluoromethyl)phenyl)boronic acid (Combi-Blocks, 26 mg, 0.127 mmol) in *t*-AmOH (1 mL) and water (0.2 mL) was treated with cesium carbonate (103 mg, 0.318 mmol) and Ad₂*n*-BuP Pd G2 (7.1 mg, 0.011 mmol). The reaction mixture was heated to 100 °C for 3 h, then cooled to room temperature and diluted with water and EtOAc. The layers were separated, and the aqueous

layer was extracted with EtOAc (2x). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The resulting crude residue was purified by preparative TLC (EtOAc:petroleum ether) to give the title compound. LCMS [M+H]⁺ = 504.1, (calcd. 504.2).

[0229] Step 2: 2-(7-((1*R*,2*R*,5*S*)-8-azabicyclo[3.2.1]octan-2-yl)-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol and 2-(7-((1*S*,2*S*,5*R*)-8-azabicyclo[3.2.1]octan-2-yl)-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol: A solution of *tert*-butyl (1*R*,2*R*,5*R* and 1*S*,2*S*,5*S*)-2-(3-(2-hydroxy-4-(trifluoromethyl)phenyl)-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (45 mg, 0.089 mmol) in DCM (1 mL) was treated with TFA (51 mg, 0.447 mmol). The resulting mixture was stirred at 20°C for 1 h. Then the reaction mixture was directly concentrated *in vacuo*, and the resulting crude residue was purified via preparative reverse phase HPLC (C18 stationary phase, MeCN/water + 0.1% TFA). The resulting racemic mixture was separated by chiral method A to provide 2-(7-((1*R*,2*R*,5*S*)-8-azabicyclo[3.2.1]octan-2-yl)-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol (Example 24) as the faster eluting isomer, and 2-(7-((1*S*,2*S*,5*R*)-8-azabicyclo[3.2.1]octan-2-yl)-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol (Example 25) as the slower eluting isomer. Example 24: LCMS [M+H]⁺ = 404.1, (calcd. 404.2). ¹H NMR (400 MHz, MeOD-*d*₄) δ 8.90 (s, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.31 (d, *J* = 7.7 Hz, 1H), 7.26 (s, 1H), 5.13 (br d, *J* = 10.8 Hz, 1H), 4.22 (br d, *J* = 5.2 Hz, 1H), 3.79 (br s, 1H), 2.64 (qd, *J* = 12.7, 5.9 Hz, 1H), 2.54 (s, 3H), 2.27 (br d, *J* = 12.3 Hz, 1H), 2.09 – 1.78 (m, 6H). Example 25: LCMS [M+H]⁺ = 404.1, (calcd. 404.2). ¹H NMR (400 MHz, MeOD-*d*₄) δ 8.91 (s, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.26 (s, 1H), 5.16 (br d, *J* = 11.4 Hz, 1H), 4.30 (br d, *J* = 5.7 Hz, 1H), 3.88 (br s, 1H), 2.67 (qd, *J* = 12.7, 6.0 Hz, 1H), 2.54 (s, 3H), 2.29 (br d, *J* = 13.4 Hz, 1H), 2.14 – 1.83 (m, 6H).

Example 26

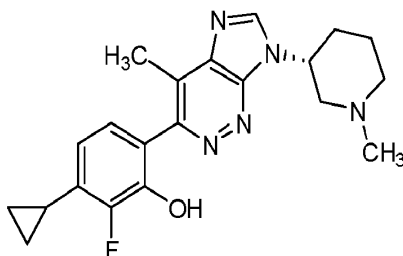
5-chloro-3-fluoro-2-(4-methyl-7-((*R*)-1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)phenol

[0230] Step 1: 3-(4-chloro-2-fluoro-6-methoxyphenyl)-4-methyl-7-((*R*)-1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazine: A mixture of (*R*)-3-chloro-4-methyl-7-(1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazine (Intermediate 16, 80 mg, 0.300 mmol), (4-chloro-2-fluoro-6-methoxyphenyl)boronic acid (Ambeed, 49 mg, 0.240 mmol), K₂CO₃ (124 mg, 0.900 mmol) and PdCl₂(dppf) (22 mg, 0.030 mmol) under nitrogen was treated with 1,4-dioxane (1.25 mL) and water (0.25 mL). The resulting mixture was heated to 100 °C for 12 h. After cooling to room temperature, the reaction mixture was directly purified via preparative reverse phase HPLC (C18 stationary phase, MeCN/water + 0.1% TFA) to give the title compound. LCMS [M+H]⁺ = 390.1, (calcd. 390.1).

[0231] Step 2: 5-chloro-3-fluoro-2-(4-methyl-7-((*R*)-1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)phenol: A solution of 3-(4-chloro-2-fluoro-6-methoxyphenyl)-4-methyl-7-((*R*)-1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazine (10 mg, 0.026 mmol) in DCM (1 mL) was cooled to 0 °C and treated with BBr₃ (1 M in heptanes, 0.128 mL, 0.128 mmol). The resulting mixture was stirred for 16 h, then slowly warmed to room temperature. Then the reaction was cooled to 0 °C, quenched with MeOH, and concentrated. The resulting crude residue was purified via preparative reverse phase HPLC (C18 stationary phase, MeCN/water + 0.05% FA) to give the title compound. LCMS [M+H]⁺ = 376.2, (calcd. 376.1). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.86 (s, 1H), 8.46 (d, *J* = 3.1 Hz, 1H), 6.75 – 6.59 (m, 1H), 4.99 – 4.78 (m, 1H), 2.71 – 2.62 (m, 2H), 2.35 (s, 3H), 2.26 (s, 3H), 2.21 – 2.11 (m, 2H), 1.83 – 1.62 (m, 2H), 1.27 – 1.20 (m, 1H), 0.83 (dt, *J* = 21.3, 6.6 Hz, 1H).

Example 27

(*R*)-3-cyclopropyl-2-fluoro-6-(4-methyl-7-(1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)phenol



[0232] Step 1: (*R*)-3-(4-chloro-3-fluoro-2-methoxyphenyl)-4-methyl-7-(1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazine: A mixture of (*R*)-3-chloro-4-methyl-7-(1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazine (Intermediate 16, 100 mg, 0.376 mmol), 2-(4-chloro-3-fluoro-2-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (AOB Chem, 108 mg, 0.376 mmol), K₂CO₃ (156 mg, 1.13 mmol) and PdCl₂(dppf) (28 mg, 0.038 mmol) under nitrogen was treated with 1,4-dioxane (3.1 mL) and water (0.63 mL). The resulting mixture was heated to 100 °C for 12 h. Then the reaction mixture was cooled to room temperature, and directly concentrated *in vacuo*. The resulting crude residue was dissolved in DMSO, filtered, and purified via preparative reverse phase HPLC (C18 stationary phase, MeCN/water + 0.1% TFA). The desired fractions were collected, and then diluted with EtOAc, water, and saturated aqueous NaHCO₃. The layers were separated, and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo* to give the title compound. LCMS [M+H]⁺ = 390.2, (calcd. 390.1).

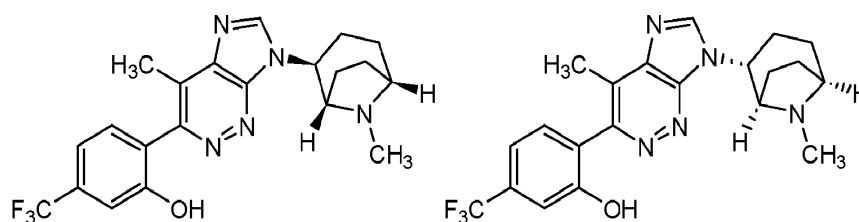
[0233] Step 2: (*R*)-3-(4-cyclopropyl-3-fluoro-2-methoxyphenyl)-4-methyl-7-(1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazine: A mixture of (*R*)-3-(4-chloro-3-fluoro-2-methoxyphenyl)-4-methyl-7-(1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazine (33 mg, 0.085 mmol) and PdCl₂(dppf) (6.2 mg, 0.0085 mmol) in 1,4-dioxane (0.85 mL) under nitrogen was treated with cyclopropylzinc(II) bromide (0.5 M in THF, 0.51 mL, 0.254 mmol). The resulting mixture was heated to 70 °C for 3 h. After cooling to room temperature, the reaction mixture was quenched with saturated aqueous NH₄Cl and extracted with EtOAc (4x). The combined organic layers were dried over anhydrous MgSO₄, filtered and concentrated *in vacuo*. The resulting crude residue was then purified via preparative reverse phase HPLC (C18

stationary phase, MeCN/water + 0.1% TFA) to give the title compound. LCMS $[M+H]^+ = 396.3$, (calcd. 396.2).

[0234] Step 3: (*R*)-3-cyclopropyl-2-fluoro-6-(4-methyl-7-(1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)phenol: A solution of (*R*)-3-(4-cyclopropyl-3-fluoro-2-methoxyphenyl)-4-methyl-7-(1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazine (15 mg, 0.038 mmol) in DCM (1.5 mL) was cooled to 0 °C and treated with BBr₃ (1 M in heptanes, 0.190 mL, 0.190 mmol). The resulting mixture was stirred for 16 h, then slowly warmed to room temperature. After cooling to 0 °C, the reaction was quenched with the dropwise addition of MeOH and concentrated *in vacuo*. The resulting crude residue was purified via preparative reverse phase HPLC (C18 stationary phase, MeCN/water + 0.05% FA) to give the title compound. LCMS $[M+H]^+ = 382.3$, (calcd. 382.2). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.88 (s, 1H), 8.47 (d, *J* = 5.5 Hz, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 6.53 (s, 1H), 4.88 (d, *J* = 9.6 Hz, 1H), 3.06 – 3.00 (m, 1H), 2.72 – 2.62 (m, 2H), 2.39 (s, 3H), 2.27 (s, 3H), 2.23 – 2.06 (m, 3H), 1.83 – 1.64 (m, 2H), 1.02 (d, *J* = 8.4 Hz, 2H), 0.89 – 0.79 (m, 1H), 0.78 (d, *J* = 5.2 Hz, 2H).

Examples 28 and 29

2-(4-methyl-7-((1*S*,2*S*,5*R*)-8-methyl-8-azabicyclo[3.2.1]octan-2-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol, and
2-(4-methyl-7-((1*R*,2*R*,5*S*)-8-methyl-8-azabicyclo[3.2.1]octan-2-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol



[0235] Step 1: *tert*-butyl (1*R*,2*R*,5*R* and 1*S*,2*S*,5*S*)-2-(3-(2-hydroxy-4-(trifluoromethyl)phenyl)-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate: A solution of *tert*-butyl (1*R*,2*R*,5*R* and 1*S*,2*S*,5*S*)-2-(3-chloro-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (Intermediate 23, 40 mg, 0.106 mmol) and (2-hydroxy-4-(trifluoromethyl)phenyl)boronic acid (Combi-Blocks, 26 mg, 0.127 mmol) in *t*-AmOH (1 mL) and water (0.2 mL) was treated with cesium carbonate (103 mg, 0.318 mmol) and Ad₂*n*-BuP Pd

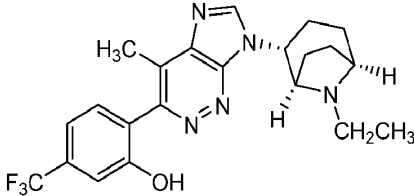
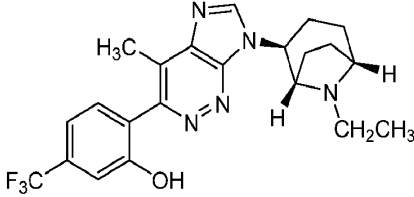
G2 (7.1 mg, 0.011 mmol). The reaction mixture was heated to 100 °C for 3 h, then cooled to room temperature and diluted with water and EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The resulting crude residue was then purified by preparative TLC (EtOAc:petroleum ether) to give the title compound. LCMS [M+H]⁺ = 504.1, (calcd. 504.2).

[0236] Step 2: 2-(7-((1*R*,2*R*,5*S* and 1*S*,2*S*,5*R*)-8-azabicyclo[3.2.1]octan-2-yl)-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol: A solution of *tert*-butyl (1*R*,2*R*,5*R* and 1*S*,2*S*,5*S*)-2-(3-(2-hydroxy-4-(trifluoromethyl)phenyl)-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-7-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (35 mg, 0.070 mmol) in DCM (0.7 mL) was treated with TFA (40 mg, 0.348 mmol). The reaction mixture was stirred at 20 °C for 1 h. Then the reaction mixture was washed with saturated aqueous NaHCO₃, and concentrated *in vacuo* to give the title compound, which was used in the next step without further purification. LCMS [M+H]⁺ = 404.2, (calcd. 404.2).

[0237] Step 3: 2-(4-methyl-7-((1*R*,2*R*,5*S*)-8-methyl-8-azabicyclo[3.2.1]octan-2-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol, and 2-(4-methyl-7-((1*S*,2*S*,5*R*)-8-methyl-8-azabicyclo[3.2.1]octan-2-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol: A solution of 2-(7-((1*R*,2*R*,5*S* and 1*S*,2*S*,5*R*)-8-azabicyclo[3.2.1]octan-2-yl)-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol (28 mg, 0.069 mmol) and formaldehyde (17 mg, 0.21 mmol) in MeOH (1 mL) was cooled to 0 °C, and sodium cyanoborohydride (22 mg, 0.347 mmol) was added. The resulting reaction mixture was warmed to 25 °C and stirred for 30 min. Then the reaction mixture was directly concentrated *in vacuo*, and the resulting crude residue was purified via preparative reverse phase HPLC (C18 stationary phase, MeCN/water + 0.1% TFA). The resulting racemic mixture was separated by chiral method B to provide 2-(4-methyl-7-((1*S*,2*S*,5*R*)-8-methyl-8-azabicyclo[3.2.1]octan-2-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol (Example 28) as the faster eluting isomer, and 2-(4-methyl-7-((1*R*,2*R*,5*S*)-8-methyl-8-azabicyclo[3.2.1]octan-2-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol (Example 29) as the slower eluting isomer. Example 28: LCMS [M+H]⁺ = 418.1, (calcd. 418.2). ¹H NMR (400 MHz, MeOD-*d*₄) δ 8.90 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.24 (s, 1H), 5.20 – 5.10 (m, 1H), 3.98 (br d, *J* = 2.9 Hz, 1H), 3.48 (br s, 1H), 2.57 – 2.49 (m, 7H), 2.33 – 2.16 (m, 2H), 2.11 – 1.96 (m, 2H), 1.95 – 1.80 (m, 3H). Example 29: LCMS [M+H]⁺ = 418.1, (calcd. 418.2). ¹H NMR (400 MHz, MeOD-*d*₄) δ 8.89 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 1H), 7.24 (s, 1H), 5.19 – 5.05 (m,

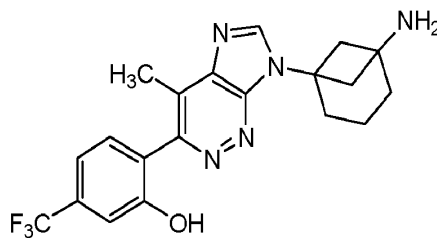
1H), 3.92 (br d, $J = 4.4$ Hz, 1H), 3.40 (br s, 1H), 2.51 (d, $J = 16.6$ Hz, 7H), 2.27 – 2.13 (m, 2H), 2.09 – 1.96 (m, 2H), 1.92 – 1.80 (m, 3H).

Table 18. Following procedures similar to those described for Examples 28 and 29, the following compounds were prepared using the appropriate starting materials. Racemic products were separated using chiral SFC methods specified in the table; for pairs of enantiomers, the faster eluting isomer is listed first.

Example	Structure	Name	LCMS [M+H] ⁺	Chiral Method
30		2-(7-((1 <i>R</i> ,2 <i>R</i> ,5 <i>S</i>)-8-ethyl-8-aza-bicyclo[3.2.1]octan-2-yl)-4-methyl-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazin-3-yl)-5-(trifluoromethyl)phenol	Calcd. 432.1, Found 432.2	C
31		2-(7-((1 <i>S</i> ,2 <i>S</i> ,5 <i>R</i>)-8-ethyl-8-aza-bicyclo[3.2.1]octan-2-yl)-4-methyl-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazin-3-yl)-5-(trifluoromethyl)phenol	Calcd. 432.1, Found 432.2	C

Example 32

2-(7-(5-aminobicyclo[3.1.1]heptan-1-yl)-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol



[0238] A solution of 5-(3-chloro-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-7-yl)bicyclo[3.1.1]heptan-1-amine (Intermediate 26, 12 mg, 0.042 mmol) and (2-hydroxy-4-(trifluoromethyl)phenyl)boronic acid (Combi-Blocks, 9.8 mg, 0.043 mmol) in *t*-AmOH (0.5 mL)

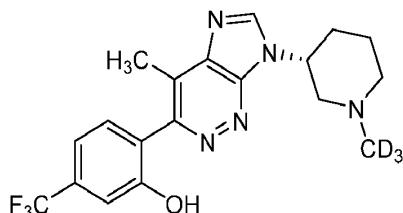
and water (0.1 mL) was treated with cesium carbonate (42 mg, 0.130 mmol) and Ad₂n-BuP Pd G2 (2.9 mg, 0.0043 mmol). The reaction mixture was heated to 100 °C for 2 h under nitrogen, then cooled to room temperature and extracted with EtOAc (2x). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The resulting crude residue was purified via preparative reverse phase HPLC (C18 stationary phase, MeCN/water + 0.05% NH₄OH + 10 mM NH₄HCO₃) to give the title compound. LCMS [M+H]⁺ = 404.1, (calcd. 404.2). ¹H NMR (400 MHz, MeOD-*d*₄) δ 8.64 (s, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.30 (d, *J* = 7.4 Hz, 1H), 7.24 (s, 1H), 2.76 – 2.66 (m, 2H), 2.57 – 2.46 (m, 5H), 2.40 – 2.32 (m, 2H), 2.15 – 2.04 (m, 2H), 1.99 – 1.86 (m, 2H).

Table 19. Following procedures similar to those described for Example 32, the following compounds were prepared using the appropriate intermediates. Racemic products were separated using chiral SFC methods specified in the table; for pairs of enantiomers, the faster eluting isomer is listed first.

Example	Structure	Name	LCMS [M+H] ⁺	Chiral Method
33		2-(4-methyl-7-((8 <i>S</i> ,8 <i>aR</i>)-octahydroindolizin-8-yl)-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazin-3-yl)-5-(trifluoromethyl)phenol	Calcd. 418.2, Found 418.2	D
34		2-(4-methyl-7-((8 <i>R</i> ,8 <i>aS</i>)-octahydroindolizin-8-yl)-7 <i>H</i> -imidazo[4,5- <i>c</i>]pyridazin-3-yl)-5-(trifluoromethyl)phenol	Calcd. 418.2, Found 418.2	D

Example 35

(*R*)-2-(4-methyl-7-(1-(methyl-*d*₃)piperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol



[0239] A solution of (*R*)-2-(4-methyl-7-(piperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol (Example 5, 40 mg, 0.106 mmol) in MeOD-*d*₄ (0.21 mL) was cooled to 0 °C and treated with deuterated formaldehyde (20 wt% in D₂O, 85 µL, 0.530 mmol) and NaBD₄ (13.3 mg, 0.318 mmol). The resulting mixture was slowly warmed to 25 °C and stirred for 12 h. The reaction mixture was then directly concentrated *in vacuo*, and the resulting crude residue was purified via preparative reverse phase HPLC (C18 stationary phase, MeCN/water + 0.1% TFA). The fractions containing the title compound were combined, treated with saturated aqueous NaHCO₃ to neutralize the pH, and then extracted with EtOAc (3x). The combined organic layers were dried over anhydrous MgSO₄, filtered and concentrated to afford the title compound. LCMS [M+H]⁺ = 395.3, (calcd. 395.2). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.88 (s, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.26 (s, 1H), 4.87 (t, *J* = 9.6 Hz, 1H), 3.59 – 3.51 (m, 2H), 2.69 (br s, 1H), 2.38 (s, 3H), 2.26 – 2.03 (m, 3H), 1.76 (br s, 1H), 1.69 (d, *J* = 10.2 Hz, 1H).

EXAMPLE OF A PHARMACEUTICAL COMPOSITION

[0240] As a specific embodiment of an oral pharmaceutical composition, a 100 mg potency tablet is composed of 100 mg of any one of the Examples, 268 mg microcrystalline cellulose, 20 mg of croscarmellose sodium, and 4 mg of magnesium stearate. The active, microcrystalline cellulose, and croscarmellose are blended first. The mixture is then lubricated by magnesium stearate and pressed into tablets.

BIOLOGICAL ASSAY

[0241] Activation of the canonical NLRP3 inflammasome requires two steps, priming and activation. A priming signal such as a pathogen activated molecular patterns (PAMPs) or danger-activated molecular patterns (DAMPs) are recognized by Toll-like receptors leads to nuclear

factor kappa B (NF- κ B)-mediated signaling. This in turn, up-regulates transcription of inflammasome-related components, including inactive NLRP3 and proIL-1 β (Bauernfeind et al., J. Immunol. 2009, 183, 787 - 791; Franchi et al., Nat. Immunol. 2012, 13, 325 - 332; Franchi et al., J. Immunol. 2014, 193, 4214 - 4222). The second step is activation which induces oligomerization of NLRP3 and subsequent assembly of NLRP3, apoptosis-associated speck-like protein containing a CARD (ASC), and procaspase-1 into an inflammasome complex. This triggers the transformation of procaspase-1 to caspase-1, and the production and secretion of mature IL-1 β and IL-18 (Kim et al., J. Inflamm. 2015, 12, 41; Ozaki et al., J. Inflamm. Res. 2015, 8, 15 - 27; Rabeony et al., Eur. J. Immunol. 2015, 45, 2847). During inflammasome complex assembly, the oligomerization of NLRP3 triggers the nucleation of ASC and an event commonly referred to as “ASC SPECK” formation as it is identified in the cell as a discrete puncta within the cell after staining and visualization of ASC using common immunocytochemical methods.

[0242] The ability of compounds to inhibit NLRP3 inflammasome activation was determined *in vitro* by monitoring formation of the ASC-SPECK in human monocytic THP-1 cells after stimulation. THP-1 cells (ATCC catalog #TIB-202) were maintained in complete growth media containing Roswell Park Memorial Institute RPMI (ATCC catalog #30-2001), 10% heat inactivated fetal bovine serum, 1X penicillin/streptomycin and 0.05mM 2-mercaptoethanol. At the start of the assay, undifferentiated THP-1 cells were plated at a density of 20,000 cells per well in a 384-well plate (Poly-D-lysine coated Cell Carrier Ultra microplate, Perkin Elmer catalog #6057500) in complete growth media supplemented with 10 ng/ml phorbol 12-myristate 13-acetate (PMA; Sigma catalog #P8139), and then incubated overnight. The next day, media was replaced with assay media [RPMI (Gibco catalog #11875-093), 0.01% bovine serum albumin (BSA)]. Compounds were serially diluted in DMSO and then added to wells one hour prior to the addition of 12.5 μ g/ml Gramicidin (Enzo Lifescience, catalog #ALX-350-233-M005). All incubations were carried out at 37°C (5% CO₂/95% air). Following a 3-hour treatment with gramicidin, cells are fixed with 4% paraformaldehyde and stored at 4°C until immunofluorescence staining.

[0243] Immunofluorescence staining: Anti-ASC antibody (MBL catalog #D086-3) was desalted and labeled with Alexa 488 antibody labeling kit (Thermo catalog #A20181) prior to use as described below. After fixation, the following steps were carried out at room temperature. Cells were first permeabilized with 0.3% Triton X-100 in phosphate-buffered saline (PBS) for 15 minutes and then incubated in blocking buffer containing 5% goat serum, 0.3% tween-20 and

0.03% sodium azide in PBS for 1 hour. Cells were stained with a mixture of ASC-Alexa 488 antibody (diluted 1:200 in blocking buffer) and nuclear stain DRAQ5 (1:5000 in blocking buffer, Thermo catalog #62251) in blocking buffer for 1 hour. Following a wash with 0.3% Tween-20 in PBS, plates were imaged with an Opera Phenix High Content Screening System. The number of DRAQ5 positive cells containing ASC SPECKS were quantified in each well.

[0244] Data analysis: EC₅₀ values were calculated by standard curve-fitting analysis using an internally developed program in TIBCO Spotfire software.

[0245] The compounds of the present invention inhibit NLRP3 inflammasome activation in the above Biological Assay and have EC₅₀ values of less than 5 micromolar. Specific EC₅₀ values of the compounds of Examples 1-35 in the above Biological Assay are listed in Table I.

Table I. EC₅₀ values (nM) for Examples that inhibit NLRP3 inflammasome activation in the above Biological Assay

Example	EC ₅₀ (nM)
1	19
2	35
3	21
4	91
5	143
6	550
7	13
8	1000
9	699
10	25
11	147
12	103
13	320
14	567
15	61
16	23
17	28
18	29

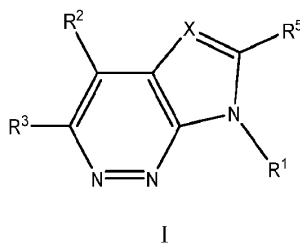
19	53
20	84
21	996
22	20
23	112
24	130
25	1013
26	81
27	1533
28	1409
29	26
30	9
31	889
32	47
33	1356
34	87
35	29

[0246] The scope of the claims should not be limited by the preferred embodiments set forth in the examples but should be given the broadest interpretation consistent with the description as a whole.

[0247] While the disclosure has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the scope of the disclosure. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in responsiveness of the mammal being treated for any of the indications with the compounds of structural formula I indicated above. The specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present disclosure.

WHAT IS CLAIMED IS:

1. A compound of structural formula I:



or a pharmaceutically acceptable salt thereof, wherein

X is independently selected from the group:

- (1) =C(R⁴)-, and
- (2) =N-;

R¹ is selected from the group:

- (1) -C₃₋₁₂cycloalkyl,
- (2) -C₃₋₁₂cycloalkenyl,
- (3) -C₂₋₁₁cycloheteroalkyl,
- (4) -C₂₋₁₁cycloheteroalkenyl,
- (5) aryl,
- (6) heteroaryl,
- (7) -C₁₋₆alkyl,
- (8) -C₁₋₆alkyl-OH,
- (9) -C₁₋₆alkyl-C₃₋₁₂cycloalkyl,
- (10) -C₁₋₆alkyl-C₃₋₁₂cycloalkenyl,
- (11) -C₁₋₆alkyl-C₂₋₁₁cycloheteroalkyl,
- (12) -C₁₋₆alkyl-C₂₋₁₁cycloheteroalkenyl,
- (13) -C₁₋₆alkyl-aryl, and
- (14) -C₁₋₆alkyl-heteroaryl,

wherein R¹ is unsubstituted or substituted with one to six substituents selected from R^a;

R^2 is selected from the group:

- (1) hydrogen,
- (2) CN,
- (3) $-CF_3$,
- (4) $-CHF_2$,
- (5) $-C_{1-6}$ alkyl, and
- (6) halogen,

wherein alkyl is unsubstituted or substituted with one to five substituents selected from

R^b ;

R^3 is selected from the group:

- (1) aryl, and
- (2) heteroaryl,

wherein aryl and heteroaryl are unsubstituted or substituted with one to five substituents

selected from R^c ;

R^4 is selected from the group:

- (1) hydrogen,
- (2) CN,
- (3) $-C_{1-6}$ alkyl,
- (4) $-O-C_{1-6}$ alkyl, and
- (5) halogen,

wherein each alkyl is unsubstituted or substituted with one to five substituents selected

from R^d ;

R^5 is selected from the group:

- (1) hydrogen,
- (2) CN,
- (3) $-C_{1-6}$ alkyl,
- (4) $-O-C_{1-6}$ alkyl, and
- (5) halogen,

wherein each alkyl is unsubstituted or substituted with one to five substituents selected from R^e;

each R^a is independently selected from the group:

- (1) CN,
- (2) oxo,
- (3) -OH,
- (4) halogen,
- (5) -C₁₋₆alkyl,
- (6) -C₁₋₆alkyl-OH,
- (7) -O-C₁₋₆alkyl,
- (8) -C₃₋₆cycloalkyl,
- (9) -C₂₋₆cycloheteroalkyl,
- (10) aryl,
- (11) heteroaryl,
- (12) -C(O)C₁₋₆alkyl,
- (13) -C(O)C₃₋₆cycloalkyl,
- (14) -C₁₋₆alkyl-aryl,
- (15) -C₁₋₆alkyl-heteroaryl,
- (16) -C₁₋₆alkyl-C₃₋₆cycloalkyl,
- (17) -C₁₋₆alkyl-C₂₋₆cycloheteroalkyl,
- (18) -(CH₂)_p-O-C₁₋₆alkyl,
- (19) -(CH₂)_p-O-C₃₋₆cycloalkyl,
- (20) -(CH₂)_p-O-C₂₋₆cycloheteroalkyl,
- (21) -(CH₂)_p-O-aryl,
- (22) -(CH₂)_p-O-heteroaryl,
- (23) -(CH₂)_p-S(O)_rR^f, and
- (24) -N(R^g)₂,

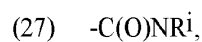
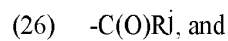
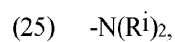
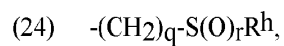
wherein each R^a is unsubstituted or substituted with one to six substituents selected from halogen, CF₃, OH, C₁₋₆alkyl, and -OC₁₋₆alkyl;

each R^b is independently selected from the group:

- (1) CF₃,
- (2) halogen,
- (3) -C₁₋₆alkyl, and
- (4) -C₃₋₆cycloalkyl;

each R^c is independently selected from the group:

- (1) CN,
- (2) -OH,
- (3) oxo,
- (4) halogen,
- (5) -C₁₋₆alkyl,
- (6) -O-C₁₋₆alkyl,
- (7) -C₃₋₆cycloalkyl,
- (8) -C₂₋₆cycloheteroalkyl,
- (9) aryl,
- (10) heteroaryl,
- (11) -C₁₋₆alkyl-aryl,
- (12) -C₁₋₆alkyl-heteroaryl,
- (13) -C₁₋₆alkyl-C₃₋₆cycloalkyl,
- (14) -C₁₋₆alkyl-C₂₋₆cycloheteroalkyl,
- (15) -(CH₂)_q-O-C₁₋₆alkyl,
- (16) -(CH₂)_q-O-C₃₋₆cycloalkyl,
- (17) -(CH₂)_q-O-C₂₋₆cycloheteroalkyl,
- (18) -(CH₂)_q-O-aryl,
- (19) -(CH₂)_q-O-heteroaryl,
- (20) -OC₁₋₆alkyl-C₃₋₆cycloalkyl,
- (21) -OC₁₋₆alkyl-C₂₋₆cycloheteroalkyl,
- (22) -OC₁₋₆alkyl-aryl,
- (23) -OC₁₋₆alkyl-heteroaryl,



wherein each R^c is unsubstituted or substituted with one to six substituents selected from halogen, CF_3 , CF_2H , OCF_3 , CN , CH_2CF_3 , CF_2CH_3 , $-\text{C}_{1-6}\text{alkyl}$, and $-\text{OC}_{1-6}\text{alkyl}$;

each R^d is independently selected from the group:

- (1) hydrogen,
- (2) OH
- (3) halogen, and
- (4) $-\text{C}_{1-6}\text{alkyl}$;

each R^e is independently selected from the group:

- (1) hydrogen,
- (2) OH,
- (3) halogen, and
- (4) $-\text{C}_{1-6}\text{alkyl}$;

each R^f is independently selected from the group:

- (1) hydrogen,
- (2) $-\text{C}_{1-6}\text{alkyl}$,
- (3) $-\text{C}_{3-6}\text{cycloalkyl}$, and
- (4) $-\text{C}_{2-6}\text{cycloheteroalkyl}$;

each R^g is independently selected from the group:

- (1) hydrogen,
- (2) $-\text{C}_{1-6}\text{alkyl}$,
- (3) $-\text{C}_{3-6}\text{cycloalkyl}$,
- (4) $-\text{C}_{2-6}\text{cycloheteroalkyl}$,
- (5) aryl,

- (6) heteroaryl,
- (7) $-C(O)C_{1-6}alkyl$, and
- (8) $-S(O)_rR^f$,

wherein alkyl can be unsubstituted or substituted with one to three substituents selected from: CF_3 , halogen, OH and $-OC_{1-6}alkyl$;

each R^h is independently selected from the group:

- (1) hydrogen,
- (2) $-C_{1-6}alkyl$,
- (3) $-C_{3-6}cycloalkyl$, and
- (4) $-C_{2-6}cycloheteroalkyl$;

each R^i is independently selected from the group:

- (1) hydrogen,
- (2) $-C_{1-6}alkyl$,
- (3) $-C_{3-6}cycloalkyl$, and
- (4) $-C_{2-6}cycloheteroalkyl$;

each R^j is independently selected from the group:

- (1) OH,
- (2) $-C_{1-6}alkyl$,
- (3) $-C_{3-6}cycloalkyl$, and
- (4) $-C_{2-6}cycloheteroalkyl$,

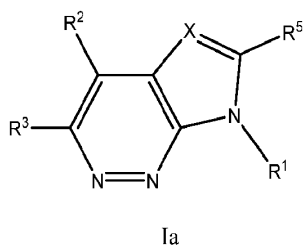
wherein alkyl can be unsubstituted or substituted with one to three substituents selected from: CF_3 , halogen, OH and $-OC_{1-6}alkyl$;

p is 0, 1, 2, 3, 4, 5 or 6;

q is 0, 1, 2, 3, 4, 5 or 6; and

r is 1 or 2.

2. The compound according to Claim 1 of structural formula Ia:



or a pharmaceutically acceptable salt thereof.

3. The compound according to Claim 1 wherein

X is $=C(R^4)-$;

or a pharmaceutically acceptable salt thereof.

4. The compound according to Claim 1 wherein

X is $=N-$;

or a pharmaceutically acceptable salt thereof.

5. The compound according to Claim 1 wherein

R^1 is selected from the group:

- (1) $-C_{3-12}$ cycloalkyl,
- (2) $-C_{2-11}$ cycloheteroalkyl,
- (3) heteroaryl,
- (4) $-C_{1-6}$ alkyl-OH,
- (5) $-C_{1-6}$ alkyl- $-C_{3-12}$ cycloalkyl, and
- (6) $-C_{1-6}$ alkyl- $-C_{2-11}$ cycloheteroalkyl,

wherein R^1 is unsubstituted or substituted with one to six substituents selected from R^a ;

or a pharmaceutically acceptable salt thereof.

6. The compound according to Claim 1 wherein

R^1 is C₂₋₁₁cycloheteroalkyl, wherein cycloheteroalkyl is unsubstituted or substituted with one to six substituents selected from R^a;

or a pharmaceutically acceptable salt thereof.

7. The compound according to Claim 1 wherein

R^2 is selected from the group: hydrogen, and -C₁₋₆alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents selected from R^b;

or a pharmaceutically acceptable salt thereof.

8. The compound according to Claim 1 wherein

R^3 is heteroaryl, wherein heteroaryl is unsubstituted or substituted with one to five substituents selected from R^c;

or a pharmaceutically acceptable salt thereof.

9. The compound according to Claim 1 wherein

R^3 is aryl, wherein aryl is unsubstituted or substituted with one to five substituents selected from R^c;

or a pharmaceutically acceptable salt thereof.

10. The compound according to Claim 1 wherein

R^4 is hydrogen or -C₁₋₆alkyl, wherein each alkyl is unsubstituted or substituted with one to five substituents selected from R^d; and

R^5 is hydrogen or -C₁₋₆alkyl, wherein each alkyl is unsubstituted or substituted with one to five substituents selected from R^e;

or a pharmaceutically acceptable salt thereof.

11. The compound according to Claim 1 wherein

R^4 is hydrogen; and

R^5 is hydrogen;

or a pharmaceutically acceptable salt thereof.

12. The compound according to Claim 1 wherein

R^1 is selected from the group:

- (1) -C₃₋₁₂cycloalkyl,
- (2) -C₂₋₁₁cycloheteroalkyl,
- (3) heteroaryl,
- (4) -C₁₋₆alkyl-OH,
- (5) -C₁₋₆alkyl-C₃₋₁₂cycloalkyl, and
- (6) -C₁₋₆alkyl-C₂₋₁₁cycloheteroalkyl,

wherein R^1 is unsubstituted or substituted with one to six substituents selected from R^a;

R^2 is selected from the group: hydrogen, and -C₁₋₆alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents selected from R^b;

R^3 is heteroaryl, wherein heteroaryl is unsubstituted or substituted with one to five substituents selected from R^c ;

R^4 is hydrogen or $-C_{1-6}$ alkyl, wherein each alkyl is unsubstituted or substituted with one to five substituents selected from R^d ; and

R^5 is hydrogen or $-C_{1-6}$ alkyl, wherein each alkyl is unsubstituted or substituted with one to five substituents selected from R^e ;

or a pharmaceutically acceptable salt thereof.

13. The compound according to Claim 1 wherein

R^1 is C_{2-11} cycloheteroalkyl, wherein cycloheteroalkyl is unsubstituted or substituted with one to six substituents selected from R^a ;

R^2 is selected from the group: hydrogen, and $-C_{1-6}$ alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents selected from R^b ;

R^3 is aryl, wherein aryl is unsubstituted or substituted with one to five substituents selected from R^c ;

R^4 is hydrogen; and

R^5 is hydrogen;

or a pharmaceutically acceptable salt thereof.

14. The compound according to Claim 1 selected from:

- (1) *(R)*-2-(7-(1-ethylpiperidin-3-yl)-7*H*-pyrrolo[2,3-*c*]pyridazin-3-yl)-3-methyl-5-(trifluoromethyl)phenol;

- (2) (R)-2-(7-(1-ethylpiperidin-3-yl)-4-methyl-7H-pyrrolo[2,3-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol;
- (3) (R)-2-(7-(1-ethylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)-3-methyl-5-(trifluoromethyl)phenol;
- (4) (R)-3-methyl-2-(7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol;
- (5) (S)-3-methyl-2-(7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol;
- (6) (R)-2-(4-methyl-7-(piperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol;
- (7) (3S,4R)-3-(3-(2-hydroxy-4-(trifluoromethyl)phenyl)-4-methyl-7H-imidazo[4,5-c]pyridazin-7-yl)piperidin-4-ol;
- (8) (R)-2-(7-(1-ethylpiperidin-3-yl)-4-methyl-7H-imidazo[4,5-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol;
- (9) (R)-2-(7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol;
- (10) (S)-2-(7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol;
- (11) (R)-3-(2-(difluoromethoxy)-4-(trifluoromethyl)phenyl)-7-(1-ethylpiperidin-3-yl)-4-methyl-7H-imidazo[4,5-c]pyridazine;
- (12) (R)-2-(4-methyl-7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol;
- (13) (3S,4R)-3-(3-(2-hydroxy-4-(trifluoro-methyl)phenyl)-4-methyl-7H-imidazo[4,5-c]pyridazin-7-yl)-1-methylpiperidin-4-ol; and
- (14) (3S,4R)-1-ethyl-3-(3-(2-hydroxy-4-(trifluoro-methyl)phenyl)-4-methyl-7H-imidazo[4,5-c]pyridazin-7-yl)piperidin-4-ol;
- (15) (R)-5-chloro-2-(4-methyl-7-(piperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)phenol;
- (16) (R)-2-(4,6-dimethyl-7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol;
- (17) (R)-5-(4-methyl-7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)benzo[b]thiophen-4-ol;
- (18) (R)-5-(4-methyl-7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)-2,3-dihydro-1H-inden-4-ol;

- (19) (R)-5-chloro-2-(4-methyl-7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)phenol; and
- (20) (R)-5-chloro-2-(7-(1-ethylpiperidin-3-yl)-4-methyl-7H-imidazo[4,5-c]pyridazin-3-yl)phenol;

or a pharmaceutically acceptable salt thereof.

15. The compound according to Claim 1 selected from:

- (1) (R)-2-(7-(1-ethylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)-3-methyl-5-(trifluoromethyl)phenol;
- (2) (R)-2-(4-methyl-7-(piperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol;
- (3) (R)-2-(7-(1-ethylpiperidin-3-yl)-4-methyl-7H-imidazo[4,5-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol; and
- (4) (R)-2-(4-methyl-7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol;

or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising a compound of Claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

17. The use of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament useful for the treatment of a disorder, condition, or disease that is responsive to the inhibition of NLRP3 in a mammal in need thereof.

18. The use of a compound of Claim 1, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment, prevention or control of an inflammatory disorder, a fibrotic disorder, a cardiovascular disorder, a metabolic disorder or a neurodegenerative disorder.

19. The use of Claim 18 wherein the disorder is an inflammatory disorder.

20. The use of Claim 19 wherein the inflammatory disorder is selected from: an auto-immune disorder, an auto-inflammatory disorder, an inflammatory joint disorder, an inflammatory skin disorder, and a neuroinflammatory disorder.
21. The use of Claim 17 wherein the disorder is selected from: atherosclerosis, non-alcoholic steatohepatitis, Alzheimer's disease and Parkinson's disease.
22. A compound according to Claim 1, or a pharmaceutically acceptable salt thereof, for use in therapy.
23. A method of treating or preventing a disorder, condition or disease that is responsive to the inhibition of NLRP3 in a patient in need thereof comprising administration of a therapeutically effective amount of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.
24. The method of Claim 23 wherein the disorder is selected from: an inflammatory disorder, a fibrotic disorder, a cardiovascular disorder, a metabolic disorder and a neurodegenerative disorder.
25. The method of Claim 24 wherein the disorder is an inflammatory disorder.
26. The method of Claim 25 wherein the inflammatory disorder is selected from: an auto-immune disorder, an auto-inflammatory disorder, an inflammatory joint disorder, an inflammatory skin disorder, and a neuroinflammatory disorder.
27. The method of Claim 25 wherein the disorder is selected from: atherosclerosis, non-alcoholic steatohepatitis, Alzheimer's disease and Parkinson's disease.