

1-AMINO-4-PHENYLPHthalAZINE DERIVATIVES USEFUL FOR THE TREATMENT OF NEURODEGENERATIVE DISEASES

FIELD OF THE INVENTION

[0001] This invention relates to 1-amino-4-phenylphthalazine derivatives which are inhibitors of the NLRP3 inflammasome, to pharmaceutical compositions which contain them, and to their use to treat diseases, disorders, and conditions associated with NLRP3, including neurodegenerative diseases, such as Parkinson's disease.

BACKGROUND OF THE INVENTION

[0002] More than 1% of the world's population suffers from neurodegenerative diseases, including Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS) and prion disease, all of which lack effective therapies. The incidence of neurodegenerative diseases is expected to double in the coming decades, especially affecting countries with an aging population. *See* I. Fernández-Cruz and E. Reynaud, "Proteasome Subunits Involved in Neurodegenerative Diseases," *Arch Med Res* 52(1):1-14 (2021).

[0003] One of the pathological hallmarks of neurodegenerative diseases is the aggregation of certain proteins into oligomers or fibrils. These conformational changes result in neurotoxicity, leading to inflammation and neurodegeneration. Although the clinical presentation of these diseases are heterogeneous, they often share common underlying mechanisms and pathophysiologies. *See* B. N. Dugger and D. W. Dickson, "Pathology of Neurodegenerative Diseases," *Cold Spring Harbor Perspect Biol* 9(7):a028035 (2017). Indeed, systemic activation of the innate immune system, which is the first line of host defense against pathogens and tissue injury, and subsequent neuroinflammation play a key role in the onset and the progression of these diseases. *See* S. Amor, F. Puentes, D. Baker, et al., "Inflammation in neurodegenerative diseases," *Immunology* 129(2):154-69 (2010). Neuroinflammation is a physiological response to exogenous and endogenous insults that target the central nervous system (CNS) and represents a protective response in the brain. However, excessive inflammatory responses are detrimental to the CNS. *See* L. I. Labzin, M. T. Heneka and E. Latz, "Innate Immunity and Neurodegeneration," *Annu Rev Med* 69:437-449 (2018).

[0004] Microglia, which are myeloid cells of the CNS, play a major role during innate immune responses in the CNS. They express pattern recognition receptors (PRRs) which enable the host to recognize pathogen-associated molecular patterns (PAMPS) and host- or

environment-derived danger-associated molecular patterns (DAMPs). *See* R. M. Ransohoff, M. A. Brown, “Innate immunity in the central nervous system,” *J Clin Invest* 122(4):1164-71 (2012). PRRs include Toll-like receptors, C-type lectin receptors, RIG-1 like receptors, and nucleotide-binding oligomerization domain-like receptors (NLRs). *See* P. Broz and V. M. Dixit, “Inflammasomes: mechanism of assembly, regulation and signaling,” *Nat Rev Immunol* 16(7):407-20 (2016). Engagement of PRRs activates a variety of inflammatory signaling pathways to eliminate infection and repair damaged tissue. The ongoing inflammation found in a variety of neurodegenerative diseases can be maintained by the key innate immune sensor for danger signals, the inflammasomes. There are several different inflammasomes, all defined by the PRRs they contain. Among the PRRs from the NLR family, the NLRs – NLRP1, NLRP3, NLRC4 –and two other PRRs – Pyrin and AIM2 – are known to form inflammasomes. *See* D. Zheng, T. Liwinski and E. Elinav, “Inflammasome activation and regulation: toward a better understanding of complex mechanisms,” *Cell Discov* 6:36 (2020).

[0005] The NLRP3 (nucleotide-binding domain (NOD)-, leucine-rich repeats-containing domain (LRR), and pyrin domain-containing 3) inflammasome has been the subject of intense interest in the past decade. *See* N. Kelley, D. Jeltema, Y. Duan, et al., “The NLRP3 Inflammasome: An Overview of Mechanisms of Activation and Regulation,” *Int J Mol Sci* 20(13):3328 (2019). The NLRP3 inflammasome consists of three main components: a pattern recognition receptor (PRR) protein, NLRP3; an apoptosis-associated speck-like protein (ASC) containing a caspase activation and recruitment domain (CARD), which functions as a central adaptor protein; and an inflammatory caspase, caspase-1. *See* Kelley et al. (2019). NLRP3 is comprised of three domains: an amino-terminal pyrin domain (PYD); a central NACHT domain, having ATPase activity that is vital for NLRP3 self-association and oligomerization; and a carboxy-terminal LLR domain. *See* Broz and Dixit (2016).

[0006] The activation of NLRP3 inflammasome involves a two-step process. A first “priming” signal is generated by the detection of PAMPs or DAMPs via TLRs. This priming signal results in NF- κ B-dependent transcriptional upregulation of NLRP3 and pro-IL-1, but also controls post-translational modifications of NLRP3. *See* J. Yang, Z. Liu and T. S. Xiao, “Post-translational regulation of inflammasomes,” *Cell Mol Immunol* 14(1):65-79 (2017). The initial trigger is followed by a second “activation” signal (β -amyloid, α -synuclein and other proteinaceous insults, ATP, crystals, nucleic acids, toxins) that induces conformational change of the various inflammasome components to subsequently assemble and nucleate the

oligomerization of monomeric NLRP3, leading to the formation and activation of the NLRP3 inflammasome. *See* A. Lu, V. G Magupalli, J. Ruan, et al., “Unified polymerization mechanism for the assembly of ASC-dependent inflammasomes,” *Cell* 156(6):1193-1206 (2014). This large multimeric protein acts via caspase-1 dependent proteolytic cleavage of several proteins, including pro-interleukin (pro-IL)-18 and pro-IL-1 β to their mature inflammatory cytokines, IL-18 and IL-1 β . *See* Kelley et al. (2019). Caspase-1 can also cleave gasdermin D (GSDMD), which facilitates GSDMD's insertion into cellular membranes to form pores, thus initiating a specific kind of cell death called pyroptosis that releases the soluble intracellular fraction which fuels the inflammatory response. *See* S. L. Fink and B. T Cookson, “Caspase-1-dependent pore formation during pyroptosis leads to osmotic lysis of infected host macrophages,” *Cell Microbiol* 8(11):1812-25 (2006).

[0007] Besides this “canonical” NLRP3 inflammasome activation pathway, a “noncanonical” NLRP3 activation pathway has been described in the literature. The noncanonical pathway involves the activation of caspase-4/5 (or its mouse ortholog caspase-11) by cytosolic LPS, the induction of pyroptosis through the cleavage of GSDMD, and the release of high mobility group box 1 protein (HMGB1), resulting in the production of IL-1 β . *See* M. Lamkanfi and V. M. Dixit, “Mechanisms and functions of inflammasomes,” *Cell* 157(5):1013-22 (2014); F. Shi, Y. Yang, M. Kouadir M, et al., “Inhibition of phagocytosis and lysosomal acidification suppresses neurotoxic prion peptide-induced NALP3 inflammasome activation in BV2 microglia,” *J Neuroimmunol* 260(1-2):121-5 (2013). In both pathways, the activation of NLRP3 inflammasome results in the generation of the biologically active form of pro-inflammatory cytokines IL-1 β and IL-18 that initiate inflammatory signaling cascades, contributing to neuroinflammation, neuronal injury and cell death. *See* S. M Allan, P. J. Tyrrell and N. J. Rothwell, “Interleukin-1 and neuronal injury,” *Nat Rev Immunol*, 5(8):629-40 (2005); A. Alboni, D. Cervia, S. Sugama, et al., “Interleukin 18 in the CNS,” *J Neuroinflammation*, 7:9 (2010).

[0008] Heterozygous gain of function mutations in the NLRP3 gene have been associated with the development of an autoinflammatory condition called cryopyrin-associated periodic syndromes (CAPS). *See* L. M. Booshehri and H. M. Hoffman, “CAPS and NLRP3,” *J Clin Immunol* 39(3):277-286 (2019). This is a rare inherited autoinflammatory disorder characterized by systemic, cutaneous, musculoskeletal and central nervous system inflammation, and is estimated to affect about 1 to 3 individuals per million people worldwide. *See* L. Cuisset, I. Jeru, B. Dumont, et al., “Mutations in the autoinflammatory

cryopyrin-associated periodic syndrome gene: epidemiological study and lessons from eight years of genetic analysis in France,” *Ann Rheum Dis* 70(3):495-9 (2011); Erratum in: *Ann Rheum Dis* 71(7):1264 (2012). Clinicians classify CAPS disorders based on the severity of symptoms. The most severe form of CAPS is known as neonatal-onset multisystem inflammatory disease (NOMID/CINCA). An intermediate form of CAPS is called Muckle-Wells syndrome (MWS). The familial cold autoinflammatory syndrome (FCAS) is a milder form of CAPS, which is triggered by low temperatures. See Booshehri and Hoffman (2019). Current anti-IL-1 therapies (anakinra, rilonacept, canakinumab) have proven successful in treating CAPS, but clinical experience over the last decade has shown that some CAPS patients are less responsive over time and require higher or more frequent dosing or switching of therapies. See R. Caorsi, L. Lepore, F. Zulian, et al., “The schedule of administration of canakinumab in cryopyrin associated periodic syndrome is driven by the phenotype severity rather than the age,” *Arthritis Res Ther* 15(1):R33 (2013); S. Urien, C. Bardin, B. Bader-Meunier, et al., “Anakinra pharmacokinetics in children and adolescents with systemic-onset juvenile idiopathic arthritis and autoinflammatory syndromes,” *BMC Pharmacol Toxicol* 14:40 (2013).

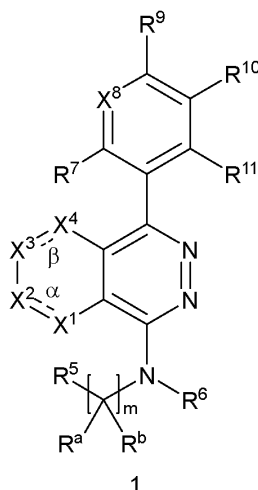
[0009] Several small molecule inhibitors have recently been reported that block the NLRP3 inflammasome pathways. These include the prototype NLRP3 inhibitor MCC-950. See R. C. Coll, J. R. Hill, C. J. Day, et al., “MCC950 directly targets the NLRP3 ATP-hydrolysis motif for inflammasome inhibition,” *Nat Chem Biol* 15(6):556-559 (2019); R. C. Coll, A. A. Robertson, J. J. Chae, et al., “A small-molecule inhibitor of the NLRP3 inflammasome for the treatment of inflammatory diseases,” *Nat Med* 21(3):248-55 (2015). Other NLRP3 inhibitors include Bay 11-7082, CY-09, oridonin, tranilast, INF-39, glyburide and JC-124. See W. Jiang, M. Li, F. He, et al., “Inhibition of NLRP3 inflammasome attenuates spinal cord injury-induced lung injury in mice,” *J Cell Physiol* 234(5):6012-6022 (2019). MCC-950 has been used in many studies as a pharmacological tool to demonstrate NLRP3 inflammasome as a viable drug target to development therapeutics for human diseases. See S. E. Corcoran, R. Halai and M. A. Cooper, “Pharmacological Inhibition of the Nod-Like Receptor Family Pyrin Domain Containing 3 Inflammasome with MCC950,” *Pharmacol Rev* 73(3):968-1000 (2021).

[0010] Inhibitors of the NLRP3 inflammasome pathways are expected to be useful for treating neurodegenerative diseases, including Parkinson's disease, and for treating CAPS disorders associated with heterozygous gain of function mutations in the NLRP3 gene.

SUMMARY OF THE INVENTION

[0011] This invention provides 1-amino-4-phenylphthalazine derivatives and pharmaceutically acceptable salts thereof. This invention also provides pharmaceutical compositions that contain the 1-amino-4-phenylphthalazine derivatives and provides for their use to treat diseases, disorders and conditions associated with NLRP3, including Parkinson's disease and other neurodegenerative disorders.

[0012] One aspect of the invention provides a compound of Formula 1:



or a pharmaceutically acceptable salt thereof in which:

α is a single bond and β is a single bond; and

- (i) X^1 is CH_2 , $\text{CH}(\text{CH}_3)$, or X^{C} ;
 X^2 is O and X^3 is CH_2 or X^{C} , or
 X^2 is CH_2 or X^{C} and X^3 is O; and
 X^4 is a bond, CH_2 , CH_2CH_2 , or X^{C} ;

wherein X^{C} is selected from C_{3-6} cycloalkylidene and C_{3-5}

oxacycloalkylidene, each substituted with 0 to 4 substituents

independently selected from halo, and wherein one, and no more

than one, of X^1 , X^2 , X^3 and X^4 is X^{C} ; or

- (ii) X^1 is $\text{C}(\text{HR}^1)$;
 X^2 is O;
 X^3 is $\text{C}(\text{HR}^3)$; and
 X^4 is CH_2 ;

wherein R^1 and R^3 taken together represent a C_{1-3} alkanediyl bridging the carbon atoms to which R^1 and R^2 are attached; or

- (iii) X^1 is CH_2 ;
 X^2 is $\text{C}(\text{HR}^2)$;
 X^3 is O;
and X^4 is $\text{C}(\text{HR}^4)$;
wherein R^2 and R^4 taken together represent a C_{1-3} alkanediyl bridging the carbon atoms to which R^2 and R^4 are attached; or
- (iv) X^1 is $\text{C}(\text{HR}^1)$;
 X^2 is O and X^3 is CH_2 , or
 X^2 is CH_2 and X^3 is O; and
 X^4 is $\text{C}(\text{HR}^4)$;
wherein R^1 and R^4 taken together represent a C_{1-3} alkanediyl; or
- (v) X^1 is $\text{C}(\text{HR}^1)$;
 X^2 is CH_2 ;
 X^3 is $\text{C}(\text{HR}^3)$; and
 X^4 is CH_2 ;
wherein R^1 and R^3 taken together represent a C_{1-2} alkanediyloxy or O bridging the carbon atoms to which R^1 and R^3 are attached; or
- (vi) X^1 is $\text{C}(\text{HR}^1)$;
 X^2 is CH_2 ;
 X^3 is CH_2 ; and
 X^4 is $\text{C}(\text{HR}^4)$;
wherein R^1 and R^4 taken together represent a C_{1-2} alkanediyloxy or O bridging the carbon atoms to which R^1 and R^4 are attached;

m is selected from 0, 1 and 2;

each R^a and R^b is independently selected from hydrogen and C_{1-4} alkyl, or R^a and R^b , together with a carbon atom to which both R^a and R^b are attached, form a C_{3-6} cycloalkylidene, provided if m is 2, then no more than one R^a and R^b , together with the carbon atom to which R^a and R^b are attached, form a C_{3-6} cycloalkylidene;

R^5 is selected from:

- (a) C_{3-8} cycloalkyl, which is substituted with 0 to 5 substituents independently selected from:
 - (i) halo, hydroxy, cyano and oxo;

- (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
 - (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;
- (b) C₃₋₈ heterocyclyl in which up to 3 carbon ring atoms are each independently substituted with 0 to 2 substituents independently selected from:
- (i) halo, hydroxy, cyano and oxo;
 - (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
 - (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;

and in which a nitrogen ring atom, if present, is unsubstituted or substituted with a substituent selected from:

- (i) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;
- (ii) C₃₋₈ cycloalkyl-(CH₂)_n, which C₃₋₈ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl, C₁₋₄ alkoxy and oxo; and
- (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl and C₁₋₄ alkoxy;

wherein the C₃₋₈ heterocyclyl has only one ring heteroatom, the ring heteroatom selected from nitrogen, oxygen, and sulfur; and

n is selected from 0 and 1;

provided:

- if m is 0, X¹ is C(HR¹), X² is CH₂, X³ is CH₂, X⁴ is C(HR⁴), X⁸ is CH, α and β are both single bonds, R¹ and R⁴ taken together represent an ethan-1,2-diyl bridging the carbon atoms to which R¹ and R⁴ are attached, R⁶, R¹⁰ and R¹¹ are each hydrogen, R⁷ is hydroxy, and R⁹ is cyano, methyl or cyclopropyl, then R⁵ is not 1-methylpiperidin-3-yl; and
- if m is 0, X¹ is C(HR¹), X² is CH₂, X³ is CH₂, X⁴ is C(HR⁴), X⁸ is CH, α and β are both single bonds, R¹ and R⁴ taken together represent a methan-1,1-diyl or O bridging the carbon atoms to which R¹ and R⁴ are

attached, R⁶, R¹⁰ and R¹¹ are each hydrogen, R⁷ is hydroxy, and R⁹ is cyano, methyl or cyclopropyl, then R⁵ is not 1-methylpiperidin-3-yl;

- (c) phenyl, which is substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl and C₁₋₄ alkoxy, provided at least one of the substituents is hydroxy;

R⁶ is selected from hydrogen and C₁₋₄ alkyl;

X⁸ is selected from N and CR⁸;

R⁷, R⁸ and R¹¹ are each independently selected from:

- (i) hydrogen, halo, hydroxy and cyano;
- (ii) C₁₋₄ alkyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo; and
- (iii) C₃₋₈ cycloalkyl which is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl and C₁₋₄ alkoxy; and

R⁹ and R¹⁰ are each independently selected from:

- (i) hydrogen, halo, hydroxy and cyano;
- (ii) C₁₋₄ alkyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo; and
- (iii) C₃₋₈ cycloalkyl which is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl and C₁₋₄ alkoxy; or

R⁹ and R¹⁰ form an ethan-1,2-dioxy moiety bridging the carbon atoms to which they are attached.

[0013] Another aspect of the invention provides a compound which is selected from the group of compounds described in the examples and their pharmaceutically acceptable salts.

[0014] A further aspect of the invention provides a compound or pharmaceutically acceptable salt as defined in the preceding paragraphs for use as a medicament.

[0015] An additional aspect of the invention provides a pharmaceutical composition which includes a compound of Formula 1 or a pharmaceutically acceptable salt thereof, or any one of the compounds or pharmaceutically acceptable salts defined in the preceding paragraphs; and a pharmaceutically acceptable excipient.

[0016] Another aspect of the invention provides a compound of Formula 1 or a pharmaceutically acceptable salt thereof, or any one of the compounds or pharmaceutically acceptable salts defined in the preceding paragraphs, for treatment of a disease, disorder or condition associated with NLRP3, including a disease, disorder or condition associated with a

heterozygous gain of function mutation in the NLRP3 gene such as cryopyrin-associated periodic syndrome (CAPS).

[0017] A further aspect of the invention provides a use of a compound of Formula 1 or a pharmaceutically acceptable salt thereof, or any one of the compounds or pharmaceutically acceptable salts defined in the preceding paragraphs, for the manufacture of a medicament for the treatment of a disease, disorder or condition associated with NLRP3, including a disease, disorder or condition associated with a heterozygous gain of function mutation in the NLRP3 gene such as cryopyrin-associated periodic syndrome (CAPS).

[0018] An additional aspect of the invention provides a method for treating a disease, disorder or condition associated with NLRP3, including a disease, disorder or condition associated with a heterozygous gain of function mutation in the NLRP3 gene such as cryopyrin-associated periodic syndrome (CAPS), the method comprising administering to the subject an effective amount of a compound of Formula 1 or a pharmaceutically acceptable salt thereof, or any one of the compounds or pharmaceutically acceptable salts defined in the preceding paragraphs.

[0019] Another aspect of the invention provides a method for treating a cryopyrin-associated periodic syndrome (CAPS), including neonatal-onset multisystem inflammatory disease (NOMID/CINCA), Muckle-Wells syndrome (MWS), and familial cold autoinflammatory syndrome (FCAS), the method comprising administering to the subject an effective amount of a compound of Formula 1 or a pharmaceutically acceptable salt thereof, or any one of the compounds or pharmaceutically acceptable salts defined in the preceding paragraphs.

[0020] A further aspect of the invention provides a method for treating a disease, disorder or condition in a subject, the method comprising administering to the subject an effective amount of a compound of Formula 1 or a pharmaceutically acceptable salt thereof, or any one of the compounds or pharmaceutically acceptable salts defined in the preceding paragraphs, wherein the disease, disorder or condition is a neurodegenerative disease, disorder or condition.

[0021] An additional aspect of the invention provides a method for treating a disease, disorder or condition in a subject, the method comprising administering to the subject an effective amount of a compound of Formula 1 or a pharmaceutically acceptable salt thereof, or any one of the compounds or pharmaceutically acceptable salts defined in the preceding

paragraphs, wherein the disease, disorder or condition is selected from Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis and prion disease.

[0022] Another aspect of the invention provides an effective amount of a compound of Formula 1 or a pharmaceutically acceptable salt thereof, or any one of the compounds or pharmaceutically acceptable salts defined in the preceding paragraphs; and at least one additional pharmacologically active agent.

DETAILED DESCRIPTION OF THE INVENTION

[0023] Unless otherwise indicated, this disclosure uses definitions provided below.

[0024] “Substituted,” when used in connection with a chemical substituent or moiety (e.g., a C₁₋₆ alkyl group), means that one or more hydrogen atoms of the substituent or moiety have been replaced with one or more non-hydrogen atoms or groups, provided valence requirements are met and a chemically stable compound results from the substitution.

[0025] “About” or “approximately,” when used in connection with a measurable numerical variable, refers to the indicated value of the variable and to all values of the variable that are within the experimental error of the indicated value or within ± 10 percent of the indicated value, whichever is greater.

[0026] “Alkyl” refers to straight chain and branched saturated hydrocarbon groups, generally having a specified number of carbon atoms (e.g., C₁₋₄ alkyl refers to an alkyl group having 1 to 4 (i.e., 1, 2, 3 or 4) carbon atoms, C₁₋₆ alkyl refers to an alkyl group having 1 to 6 carbon atoms, and so on). Examples of alkyl groups include methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *s*-butyl, *i*-butyl, *t*-butyl, pent-1-yl, pent-2-yl, pent-3-yl, 3-methylbut-1-yl, 3-methylbut-2-yl, 2-methylbut-2-yl, 2,2,2-trimethyleth-1-yl, *n*-hexyl, and the like.

[0027] “Alkanediyl” refers to divalent alkyl groups, where alkyl is defined above, and generally having a specified number of carbon atoms (e.g., C₁₋₄ alkanediyl refers to an alkanediyl group having 1 to 4 (i.e., 1, 2, 3 or 4) carbon atoms, C₁₋₆ alkanediyl refers to an alkanediyl group having 1 to 6 carbon atoms, and so on). Examples of alkanediyl groups include methylene, ethane-1,1-diyl, ethane-1,2-diyl, propane-1,3-diyl, propane-1,2-diyl, propane-1,1-diyl, propane-2,2-diyl, butane-1,4-diyl, butane-1,3-diyl, butane-1,2-diyl, butane-1,1-diyl, isobutane-1,3-diyl, isobutane-1,1-diyl, isobutane-1,2-diyl, and the like.

[0028] “Alkenyl” refers to straight chain and branched hydrocarbon groups having one or more carbon-carbon double bonds, and generally having a specified number of carbon atoms. Examples of alkenyl groups include ethenyl, 1-propen-1-yl, 1-propen-2-yl, 2-propen-1-yl, 1-

buten-1-yl, 1-buten-2-yl, 3-buten-1-yl, 3-buten-2-yl, 2-buten-1-yl, 2-buten-2-yl, 2-methyl-1-propen-1-yl, 2-methyl-2-propen-1-yl, 1,3-butadien-1-yl, 1,3-butadien-2-yl, and the like.

[0029] “Alkynyl” refers to straight chain or branched hydrocarbon groups having one or more triple carbon-carbon bonds, and generally having a specified number of carbon atoms. Examples of alkynyl groups include ethynyl, 1-propyn-1-yl, 2-propyn-1-yl, 1-butyne-1-yl, 3-butyne-1-yl, 3-butyne-2-yl, 2-butyne-1-yl, and the like.

[0030] “Alkoxy” refers to straight chain and branched saturated hydrocarbon groups attached through an oxygen atom, generally having a specified number of carbon atoms (e.g., C₁₋₄ alkoxy refers to an alkoxy group having 1 to 4 (i.e., 1, 2, 3 or 4) carbon atoms, C₁₋₆ alkoxy refers to an alkoxy group having 1 to 6 carbon atoms, and so on). Examples of alkoxy groups include methoxy, ethoxy, *n*-propoxy, *i*-propoxy, *n*-butoxy, *s*-butoxy, *i*-butoxy, *t*-butoxy, pent-1-yloxy, pent-2-yloxy, pent-3-yloxy, 3-methylbut-1-yloxy, 3-methylbut-2-yloxy, 2-methylbut-2-yloxy, 2,2,2-trimethyleth-1-yloxy, *n*-hexoxy, and the like.

[0031] “Alkanediyl” refers to divalent alkoxy groups, where alkoxy is defined above, and generally having a specified number of carbon atoms (e.g., C₁₋₃ alkanediyl refers to an alkanediyl group having 1 to 3 (i.e., 1, 2 or 3) carbon atoms, C₁₋₂ alkanediyl refers to an alkanediyl group having 1 or 2 carbon atoms, and so on). Examples of alkanediyl groups include methane-1,1-diyl, ethane-1,2-diyl, ethane-1,1-diyl, propane-1,3-diyl, propane-1,2-diyl, propane-1,1-diyl, propane-2,2-diyl, and the like.

[0032] “Alkylcarbonyl” and “alkylsulfonyl” refer to an alkyl group, as defined above, which is attached, respectively, through a carbonyl (C(O)) group or a sulfonyl (SO₂) group, and generally having a specified number of carbon atoms, including the carbon atom of the carbonyl group. For example, C₁₋₄ alkylcarbonyl refers to an alkylcarbonyl group having 1 to 4 (i.e., 1, 2, 3 or 4) carbon atoms, including the carbonyl moiety, C₁₋₆ alkylsulfonyl refers to an alkylsulfonyl group having 1 to 6 carbon atoms, and so on. Examples of alkylcarbonyl groups include carbonyl (formyl), methylcarbonyl (acetyl), ethylcarbonyl, *i*-propylcarbonyl, *n*-propylcarbonyl, and the like. Examples of alkylsulfonyl groups include methylsulfonyl, ethylsulfonyl, *i*-propylsulfonyl, *n*-propylsulfonyl, and the like.

[0033] “Halo,” “halogen” and “halogeno” may be used interchangeably and refer to fluoro, chloro, bromo, and iodo.

[0034] “Haloalkyl,” “haloalkenyl,” and “haloalkynyl,” refer, respectively, to alkyl, alkenyl, and alkynyl groups substituted with one or more halogen atoms, where alkyl, alkenyl, and alkynyl are defined above, and generally having a specified number of carbon atoms.

Examples of haloalkyl groups include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 1-fluoroethyl, 1,1-difluoroethyl, 1-chloroethyl, 1,1-dichloroethyl, 1-fluoro-1-methylethyl, 1-chloro-1-methylethyl, and the like.

[0035] “Cycloalkyl” refers to saturated monocyclic and bicyclic hydrocarbon groups, generally having a specified number of carbon atoms that comprise the ring or rings (e.g., C₃₋₈ cycloalkyl refers to a cycloalkyl group having 3 to 8 carbon atoms as ring members). Bicyclic hydrocarbon groups may include isolated rings (two rings sharing no carbon atoms), spiro rings (two rings sharing one carbon atom), fused rings (two rings sharing two carbon atoms and the bond between the two common carbon atoms), and bridged rings (two rings sharing two carbon atoms, but not a common bond). The cycloalkyl group may be attached through any ring atom unless such attachment would violate valence requirements, and where indicated, may optionally include one or more non-hydrogen substituents unless such substitution would violate valence requirements.

[0036] Examples of monocyclic cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. Examples of fused bicyclic cycloalkyl groups include bicyclo[2.1.0]pentanyl (i.e., bicyclo[2.1.0]pentan-1-yl, bicyclo[2.1.0]pentan-2-yl, and bicyclo[2.1.0]pentan-5-yl), bicyclo[3.1.0]hexanyl, bicyclo[3.2.0]heptanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.3.0]octanyl, bicyclo[4.2.0]octanyl, bicyclo[4.3.0]nonanyl, bicyclo[4.4.0]decanyl, and the like. Examples of bridged cycloalkyl groups include bicyclo[2.1.1]hexanyl, bicyclo[2.2.1]heptanyl, bicyclo[3.1.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[3.2.1]octanyl, bicyclo[4.1.1]octanyl, bicyclo[3.3.1]nonanyl, bicyclo[4.2.1]nonanyl, bicyclo[3.3.2]decanyl, bicyclo[4.2.2]decanyl, bicyclo[4.3.1]decanyl, bicyclo[3.3.3]undecanyl, bicyclo[4.3.2]undecanyl, bicyclo[4.3.3]dodecanyl, and the like. Examples of spiro cycloalkyl groups include spiro[3.3]heptanyl, spiro[2.4]heptanyl, spiro[3.4]octanyl, spiro[2.5]octanyl, spiro[3.5]nonanyl, and the like. Examples of isolated bicyclic cycloalkyl groups include those derived from bi(cyclobutane), cyclobutanecyclopentane, bi(cyclopentane), cyclobutanecyclohexane, cyclopentanecyclohexane, bi(cyclohexane), etc.

[0037] “Cycloalkanediyl” refers to divalent cycloalkyl groups, where cycloalkyl is defined above, and generally having a specified number of carbon atoms (e.g., C₃₋₅ cycloalkanediyl refers to a cycloalkanediyl group having 3 to 5 (i.e., 3, 4 or 5) carbon atoms, C₃₋₆ cycloalkanediyl refers to a cycloalkanediyl group having 3 to 6 carbon atoms, and so on).

Examples of cycloalkanediyl groups include cyclopropane-1,1-diyl, cyclopropane-1,2-diyl, cyclobutane-1,1-diyl, cyclobutane-1,2-diyl, and the like.

[0038] “Cycloalkylidene” refers to a divalent monocyclic cycloalkyl group, where cycloalkyl is defined above, which is attached through a single carbon atom of the group, and generally having a specified number of carbon atoms that comprise the ring (e.g., C₃₋₆ cycloalkylidene refers to a cycloalkylidene group having 3 to 6 carbon atoms as ring members). Examples include cyclopropylidene, cyclobutylidene, cyclopentylidene, and cyclohexylidene.

[0039] “Oxacycloalkylidene” refers to a divalent cycloalkyl group, as defined above, in which one of carbon atom is replaced with an oxygen atom, and which is attached through a single carbon atom of the group, and generally having a specified number of carbon atoms that comprise the ring (e.g., C₃₋₅ oxacycloalkylidene refers to a cycloalkylidene group having 3 to 5 carbon atoms and one oxygen atom as ring members). Examples include 2-oxacyclobutylidene, 3-oxacyclobutylidene, 2-oxacyclopentylidene, 3-oxacyclopentylidene, 2-oxacyclohexylidene, 3-oxacyclohexylidene and 4-oxacyclohexylidene.

[0040] “Cycloalkenyl” refers to partially unsaturated monocyclic and bicyclic hydrocarbon groups, generally having a specified number of carbon atoms that comprise the ring or rings. As with cycloalkyl groups, the bicyclic cycloalkenyl groups may include isolated, spiro, fused, or bridged rings. Similarly, the cycloalkenyl group may be attached through any ring atom, and where indicated, may optionally include one or more non-hydrogen substituents unless such attachment or substitution would violate valence requirements. Examples of cycloalkenyl groups include the partially unsaturated analogs of the cycloalkyl groups described above, such as cyclobutenyl (i.e., cyclobuten-1-yl and cyclobuten-3-yl), cyclopentenyl, cyclohexenyl, bicyclo[2.2.1]hept-2-enyl, and the like.

[0041] “Aryl” refers to fully unsaturated monocyclic aromatic hydrocarbons and to polycyclic hydrocarbons having at least one aromatic ring, both monocyclic and polycyclic aryl groups generally having a specified number of carbon atoms that comprise their ring members (e.g., C₆₋₁₄ aryl refers to an aryl group having 6 to 14 carbon atoms as ring members). The group may be attached through any ring atom, and where indicated, may optionally include one or more non-hydrogen substituents unless such attachment or substitution would violate valence requirements. Examples of aryl groups include phenyl, biphenyl, cyclobutabenzenyl, indenyl, naphthalenyl, benzocycloheptanyl, biphenylenyl, fluorenyl, groups derived from cycloheptatriene cation, and the like.

[0042] “Arylene” refers to divalent aryl groups, where aryl is defined above. Examples of arylene groups include *o*-phenylene (i.e., benzene-1,2-diyl).

[0043] “Heterocycle” and “heterocyclyl” may be used interchangeably and refer to saturated or partially unsaturated monocyclic or bicyclic groups having ring atoms composed of carbon atoms and one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur. Both the monocyclic and bicyclic groups generally have a specified number of carbon atoms in their ring or rings (e.g., C₂₋₆ heterocyclyl refers to a heterocyclyl group having 2 to 6 carbon atoms and, e.g., 1 to 4 heteroatoms, as ring members). As with bicyclic cycloalkyl groups, bicyclic heterocyclyl groups may include isolated rings, spiro rings, fused rings, and bridged rings. The heterocyclyl group may be attached through any ring atom, and where indicated, may optionally include one or more non-hydrogen substituents unless such attachment or substitution would violate valence requirements or result in a chemically unstable compound. Examples of heterocyclyl groups include oxiranyl, thiiranyl, aziridinyl (e.g., aziridin-1-yl and aziridin-2-yl), oxetanyl, thietanyl, azetidiny, tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, 1,4-dioxanyl, 1,4-oxathianyl, morpholinyl, 1,4-dithianyl, piperazinyl, 1,4-azathianyl, oxepanyl, thiepanyl, azepanyl, 1,4-dioxepanyl, 1,4-oxathiepanyl, 1,4-oxaazepanyl, 1,4-dithiepanyl, 1,4-thiazepanyl, 1,4-diazepanyl, 3,4-dihydro-2*H*-pyranyl, 3,6-dihydro-2*H*-pyranyl, 2*H*-pyranyl, 1,2-dihydropyridinyl, 1,2,3,4-tetrahydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,6-dihydropyrimidinyl, 1,2,3,4-tetrahydropyrimidinyl, and 1,2-dihydropyrazolo[1,5-*c*][1,2,4]triazinyl.

[0044] “Heterocycle-diyl” refers to heterocyclyl groups which are attached through two ring atoms of the group, where heterocyclyl is defined above. They generally have a specified number of carbon atoms in their ring or rings (e.g., C₂₋₆ heterocycle-diyl refers to a heterocycle-diyl group having 2 to 6 carbon atoms and, e.g., 1 to 4 heteroatoms, as ring members). Examples of heterocycle-diyl groups include the multivalent analogs of the heterocycle groups described above, such as morpholine-3,4-diyl, pyrrolidine-1,2-diyl, 1-pyrrolidinyl-2-ylidene, 1-pyridinyl-2-ylidene, 1-(4*H*)-pyrazolyl-5-ylidene, 1-(3*H*)-imidazolyl-2-ylidene, 3-oxazolyl-2-ylidene, 1-piperidinyl-2-ylidene, 1-piperazinyl-6-ylidene, and the like.

[0045] “Heteroaromatic” and “heteroaryl” may be used interchangeably and refer to unsaturated monocyclic aromatic groups and to polycyclic groups having at least one aromatic ring, each of the groups having ring atoms composed of carbon atoms and one or

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

[0046] Examples of heteroaryl groups also include bicyclic groups such as benzofuranyl, isobenzofuranyl, benzothienyl, benzo[*c*]thienyl, 1*H*-indolyl, 3*H*-indolyl, isoindolyl, 1*H*-isoindolyl, indolinyl, isoindolinyl, benzimidazolyl, 1*H*-indazolyl, 2*H*-indazolyl, benzotriazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, 1*H*-pyrrolo[2,3-*c*]pyridinyl, 1*H*-pyrrolo[3,2-*c*]pyridinyl, 1*H*-pyrrolo[3,2-*b*]pyridinyl, 3*H*-imidazo[4,5-*b*]pyridinyl, 3*H*-imidazo[4,5-*c*]pyridinyl, 1*H*-pyrazolo[4,3-*b*]pyridinyl, 1*H*-pyrazolo[4,3-*c*]pyridinyl, 1*H*-pyrazolo[3,4-*c*]pyridinyl, 1*H*-pyrazolo[3,4-*b*]pyridinyl, 7*H*-purinyl, indolizinyl, imidazo[1,2-*a*]pyridinyl, imidazo[1,5-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, pyrrolo[1,2-*b*]pyridazinyl, imidazo[1,2-*c*]pyrimidinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, 1,6-naphthyridinyl, 1,7-naphthyridinyl, 1,8-naphthyridinyl, 1,5-naphthyridinyl, 2,6-naphthyridinyl, 2,7-naphthyridinyl, pyrido[3,2-*d*]pyrimidinyl, pyrido[4,3-*d*]pyrimidinyl, pyrido[3,4-*d*]pyrimidinyl, pyrido[2,3-*d*]pyrimidinyl, pyrido[2,3-*b*]pyrazinyl, pyrido[3,4-*b*]pyrazinyl, pyrimido[5,4-*d*]pyrimidinyl, pyrazino[2,3-*b*]pyrazinyl, pyrimido[4,5-*d*]pyrimidinyl, 1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazinyl, 2,3-dihydrobenzo[*b*][1,4]dioxinyl, 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazinyl, 2,3-dihydro-1*H*-benzo[*d*]imidazolyl, benzo[*d*]thiazolyl, 2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, [1,2,4]triazolo[1,5-*a*]pyridinyl, 2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridinyl, tetrazolo[1,5-*a*]pyridinyl, 7*H*-pyrrolo[2,3-*d*]pyrimidinyl, pyrazolo[1,5-*a*]pyrimidinyl, imidazo[1,2-*a*]pyrimidinyl, 4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidinyl, 2,3,6,7-tetrahydro-1*H*-purinyl, 5*H*-pyrrolo[2,3-*b*]pyrazinyl,

imidazo[1,2-*a*]pyrazinyl, imidazo[1,2-*b*]pyridazinyl, and 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazinyl.

[0047] “Heteroarylene” refers to heteroaryl groups which are attached through two ring atoms of the group, where heteroaryl is defined above. They generally have a specified number of carbon atoms in their ring or rings (e.g., C₃₋₅ heteroarylene refers to a heteroarylene group having 3 to 5 carbon atoms and, e.g., 1 to 4 heteroatoms, as ring members). Examples of heteroarylene groups include the multivalent analogs of the heteroaryl groups described above, such as pyridine-2,3-diyl, pyridine-3,4-diyl, pyrazole-4,5-diyl, pyrazole-3,4-diyl, and the like.

[0048] “Oxo” refers to a double bonded oxygen (=O).

[0049] “Leaving group” refers to any group that leaves a molecule during a fragmentation process, including substitution reactions, elimination reactions, and addition-elimination reactions. Leaving groups may be nucleofugal, in which the group leaves with a pair of electrons that formerly served as the bond between the leaving group and the molecule, or may be electrofugal, in which the group leaves without the pair of electrons. The ability of a nucleofugal leaving group to leave depends on its base strength, with the strongest bases being the poorest leaving groups. Common nucleofugal leaving groups include nitrogen (e.g., from diazonium salts); sulfonates, including alkylsulfonates (e.g., mesylate), fluoroalkylsulfonates (e.g., triflate, hexaflate, nonaflate, and tresylate), and arylsulfonates (e.g., tosylate, brosylate, closylate, and nosylate). Others include carbonates, halide ions, carboxylate anions, phenolate ions, and alkoxides. Some stronger bases, such as NH₂⁻ and OH⁻ can be made better leaving groups by treatment with an acid. Common electrofugal leaving groups include the proton, CO₂, and metals.

[0050] “Opposite enantiomer” refers to a molecule that is a non-superimposable mirror image of a reference molecule, which may be obtained by inverting all the stereogenic centers of the reference molecule. For example, if the reference molecule has *S* absolute stereochemical configuration, then the opposite enantiomer has *R* absolute stereochemical configuration. Likewise, if the reference molecule has *S,S* absolute stereochemical configuration, then the opposite enantiomer has *R,R* stereochemical configuration, and so on.

[0051] “Stereoisomer” and “stereoisomers” of a compound with given stereochemical configuration refer to the opposite enantiomer of the compound and to any diastereoisomers, including geometrical isomers (*Z/E*) of the compound. For example, if a compound has *S,R,Z* stereochemical configuration, its stereoisomers would include its opposite enantiomer having

R,S,Z configuration, and its diastereomers having *S,S,Z* configuration, *R,R,Z* configuration, *S,R,E* configuration, *R,S,E* configuration, *S,S,E* configuration, and *R,R,E* configuration. If the stereochemical configuration of a compound is not specified, then “stereoisomer” refers to any one of the possible stereochemical configurations of the compound.

[0052] “Substantially pure stereoisomer” and variants thereof refer to a sample containing a compound having a specific stereochemical configuration and which comprises at least about 95% of the sample.

[0053] “Pure stereoisomer” and variants thereof refer to a sample containing a compound having a specific stereochemical configuration and which comprises at least about 99.5% of the sample.

[0054] “Subject” refers to a mammal, including a human.

[0055] “Pharmaceutically acceptable” substances refer to those substances which are suitable for administration to subjects.

[0056] “Treating” refers to reversing, alleviating, inhibiting the progress of, or preventing a disease, disorder or condition to which such term applies, or to reversing, alleviating, inhibiting the progress of, or preventing one or more symptoms of such disease, disorder or condition.

[0057] “Treatment” refers to the act of “treating,” as defined immediately above.

[0058] “Drug,” “drug substance,” “active pharmaceutical ingredient,” and the like, refer to a compound (e.g., compounds of Formula 1, including subgeneric compounds and compounds specifically named in the specification) that may be used for treating a subject in need of treatment.

[0059] “Effective amount” of a drug, “therapeutically effective amount” of a drug, and the like, refer to the quantity of the drug that may be used for treating a subject and may depend on the weight and age of the subject and the route of administration, among other things.

[0060] “Excipient” refers to any diluent or vehicle for a drug.

[0061] “Pharmaceutical composition” refers to the combination of one or more drug substances and one or more excipients.

[0062] “Drug product,” “pharmaceutical dosage form,” “dosage form,” “final dosage form” and the like, refer to a pharmaceutical composition suitable for treating a subject in need of treatment and generally may be in the form of tablets, capsules, sachets containing powder or granules, liquid solutions or suspensions, patches, films, and the like.

[0063] “Condition associated with NLRP3” and similar phrases relate to a disease, disorder or condition in a subject for which inhibition of the NLRP3 inflammasome pathway may provide a therapeutic or prophylactic benefit.

[0064] The following abbreviations may be used in the specification: Ac (acetyl); Ac₂O (acetic anhydride); ACN (acetonitrile); AIBN (azo-bis-isobutyronitrile); AmPhos (bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II)); API (active pharmaceutical ingredient); aq (aqueous); BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl); Boc (*tert*-butoxycarbonyl); BrettPhos (2-(dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl); BrettPhos-Pd-G3 ([2-(di-cyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl]-2-(2'-amino-1,1'-biphenyl)]palladium(II)methanesulfonate); Cbz (carbobenzyloxy); DAST (*N,N*-diethyl-*S,S,S*-trifluoro- λ^4 -sulfanamine); dba (dibenzylideneacetone); DBU (1,8-diazabicyclo[5.4.0]undec-7-ene); DCC (1,3-dicyclohexylcarbodiimide); DCE (1,1-dichloroethane); DCM (dichloromethane); DEA (diethylamine); DIAD (diisopropyl azodicarboxylate); DIPEA (*N,N*-diisopropylethylamine, Hünig's Base); DMA (*N,N*-dimethylacetamide); DMAP (4-dimethylaminopyridine); DME (1,2-dimethoxyethane); DMF (*N,N*-dimethylformamide); DMP (Dess-Martin periodinane); DMSO (dimethylsulfoxide); dppf (1,1'-bis(diphenylphosphino)ferrocene); DTT (dithiothreitol); EC₅₀ (effective concentration at half maximal response); EDA (ethoxylated dodecyl alcohol, Brj®35); EDC (*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide); EDTA (ethylenediaminetetraacetic acid); ee (enantiomeric excess); ELS (evaporative light scattering); eq (equivalents); Et (ethyl); Et₃N (triethylamine); EtOAc (ethyl acetate); EtOH (ethanol); FA (formic acid); HATU (2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate(V)); HEPES (4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid); HOAc (acetic acid); HOBt (1*H*-benzo[*d*][1,2,3]triazol-1-ol); IC₅₀ (concentration at 50% inhibition); IPA (isopropanol); IPAc (isopropyl acetate); IPE (isopropylether); LDA (lithium diisopropylamide); LiHMDS (lithium bis(trimethylsilyl)amide); mCPBA (*m*-chloroperoxybenzoic acid); Me (methyl); MeOH (methanol); MOMO (methoxymethoxy); MTBE (methyl *tert*-butyl ether); mp (melting point); NaOt-Bu (sodium tertiary butoxide); NMM (*N*-methylmorpholine); NMP 1-methylpyrrolidin-2-one); OTBS (*tert*-butyldimethylsilyl ether); OTf (triflate); PE (petroleum ether); Ph (phenyl); pEC₅₀ (-log₁₀(EC₅₀), where EC₅₀ is given in molar (M) units); pIC₅₀ (-log₁₀(IC₅₀), where IC₅₀ is given in molar (M) units); Pr (propyl); *c*-Pr (cyclopropyl), *i*-Pr (isopropyl); PTFE (polytetrafluoroethylene); PyBOP ((benzotriazol-1-

xyloxy)tripyrrolidinophosphonium hexafluorophosphate); PyBroP® (bromotripyrrolidinophosphonium hexafluorophosphate); PCy₃ (tricyclohexylphosphine); R-BINAP ((*R*)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl); RT (room temperature, approximately 20°C to 25°C); SFC (supercritical fluid chromatography); T3P (2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide); TBAF (*N,N,N*-tributylbutan-1-aminium fluoride); TBSOTf (*tert*-butyldimethylsilyl trifluoromethanesulfonate); TCEP (*tris*(2-carboxyethyl)phosphine); TFA (trifluoroacetic acid); TFAA (2,2,2-trifluoroacetic anhydride); THF (tetrahydrofuran); TMEDA (*N,N,N,N*-tetramethylethane-1,2-diamine); TMS (trimethylsilyl); TMSOTf (trimethylsilyl trifluoromethanesulfonate); Tris buffer (2-amino-2-hydroxymethyl-propane-1,3-diol buffer); XPhos (2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl); and Xphos Pd G2 (chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II)).

[0065] As described, below, this disclosure concerns compounds of Formula 1 and their pharmaceutically acceptable salts. This disclosure also concerns materials and methods for preparing compounds of Formula 1, pharmaceutical compositions which contain them, and the use of compounds of Formula 1 and their pharmaceutically acceptable salts (optionally in combination with other pharmacologically active agents) for treating diseases, disorders or conditions of the CNS, including neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and other diseases, disorders or conditions associated with NLRP3.

[0066] The compounds of Formula 1, and pharmaceutically acceptable salts thereof, include those in which:

- (1) α is a single bond and β is a single bond; and
 - (i) X¹ is CH₂, CH(CH₃), or X^C;
 X² is O and X³ is CH₂ or X^C, or
 X² is CH₂ or X^C and X³ is O; and
 X⁴ is a bond, CH₂, CH₂CH₂, or X^C;
 wherein X^C is selected from C₃₋₆ cycloalkylidene and C₃₋₅ oxacycloalkylidene, each substituted with 0 to 4 substituents independently selected from halo, and wherein one, and no more than one, of X¹, X², X³ and X⁴ is X^C; or
 - (ii) X¹ is C(HR¹);
 X² is O;
 X³ is C(HR³); and

X^4 is CH_2 ;

wherein R^1 and R^3 taken together represent a C_{1-3} alkanediyl bridging the carbon atoms to which R^1 and R^2 are attached; or

(iii) X^1 is CH_2 ;

X^2 is $\text{C}(\text{HR}^2)$;

X^3 is O;

and X^4 is $\text{C}(\text{HR}^4)$;

wherein R^2 and R^4 taken together represent a C_{1-3} alkanediyl bridging the carbon atoms to which R^2 and R^4 are attached; or

(iv) X^1 is $\text{C}(\text{HR}^1)$;

X^2 is O and X^3 is CH_2 , or

X^2 is CH_2 and X^3 is O; and

X^4 is $\text{C}(\text{HR}^4)$;

wherein R^1 and R^4 taken together represent a C_{1-3} alkanediyl; or

(v) X^1 is $\text{C}(\text{HR}^1)$;

X^2 is CH_2 ;

X^3 is $\text{C}(\text{HR}^3)$; and

X^4 is CH_2 ;

wherein R^1 and R^3 taken together represent a C_{1-2} alkanediyloxy or O bridging the carbon atoms to which R^1 and R^3 are attached; or

(vi) X^1 is $\text{C}(\text{HR}^1)$;

X^2 is CH_2 ;

X^3 is CH_2 ; and

X^4 is $\text{C}(\text{HR}^4)$;

wherein R^1 and R^4 taken together represent a C_{1-2} alkanediyloxy or O bridging the carbon atoms to which R^1 and R^4 are attached;

m is selected from 0, 1 and 2;

each R^a and R^b is independently selected from hydrogen and C_{1-4} alkyl, or R^a and R^b , together with a carbon atom to which both R^a and R^b are attached, form a C_{3-6} cycloalkylidene, provided if m is 2, then no more than one R^a and R^b , together with the carbon atom to which R^a and R^b are attached, form a C_{3-6} cycloalkylidene;

R^5 is selected from:

- (a) C₃₋₈ cycloalkyl, which is substituted with 0 to 5 substituents independently selected from:
- (i) halo, hydroxy, cyano and oxo;
 - (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
 - (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;

- (b) C₃₋₈ heterocyclyl in which up to 3 carbon ring atoms are each independently substituted with 0 to 2 substituents independently selected from:

- (i) halo, hydroxy, cyano and oxo;
- (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
- (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;

and in which a nitrogen ring atom, if present, is unsubstituted or substituted with a substituent selected from:

- (i) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;
- (ii) C₃₋₈ cycloalkyl-(CH₂)_n, which C₃₋₈ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl, C₁₋₄ alkoxy and oxo; and
- (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl and C₁₋₄ alkoxy;

wherein the C₃₋₈ heterocyclyl has only one ring heteroatom, the ring heteroatom selected from nitrogen, oxygen, and sulfur; and
n is selected from 0 and 1;

provided:

if m is 0, X¹ is C(HR¹), X² is CH₂, X³ is CH₂, X⁴ is C(HR⁴), X⁸ is CH, α and β are both single bonds, R¹ and R⁴ taken together represent an ethan-1,2-diyl bridging the carbon atoms to which R¹ and R⁴ are attached, R⁶, R¹⁰ and R¹¹ are each hydrogen, R⁷ is hydroxy, and R⁹ is cyano, methyl or cyclopropyl, then R⁵ is not 1-methylpiperidin-3-yl; and
if m is 0, X¹ is C(HR¹), X² is CH₂, X³ is CH₂, X⁴ is C(HR⁴), X⁸ is CH, α and β are both single bonds, R¹ and R⁴ taken together represent a methan-1,1-diyl or O bridging the carbon atoms to which R¹ and R⁴ are attached, R⁶, R¹⁰ and R¹¹ are each hydrogen, R⁷ is hydroxy, and R⁹ is cyano, methyl or cyclopropyl, then R⁵ is not 1-methylpiperidin-3-yl;

(c) phenyl, which is substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl and C₁₋₄ alkoxy, provided at least one of the substituents is hydroxy;

R⁶ is selected from hydrogen and C₁₋₄ alkyl;

X⁸ is selected from N and CR⁸;

R⁷, R⁸ and R¹¹ are each independently selected from:

- (i) hydrogen, halo, hydroxy and cyano;
- (ii) C₁₋₄ alkyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo; and
- (iii) C₃₋₈ cycloalkyl which is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl and C₁₋₄ alkoxy; and

R⁹ and R¹⁰ are each independently selected from:

- (i) hydrogen, halo, hydroxy and cyano;
- (ii) C₁₋₄ alkyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo; and
- (iii) C₃₋₈ cycloalkyl which is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl and C₁₋₄ alkoxy; or

R⁹ and R¹⁰ form an ethan-1,2-dioxy moiety bridging the carbon atoms to which they are attached.

[0067] In addition to embodiment (1) above, the compounds of Formula 1 include those in which:

- (61) α is a single bond and β is a single bond; and
- (i) X^1 is CH_2 , $\text{CH}(\text{CH}_3)$, or X^C ;
 X^2 is O and X^3 is CH_2 or X^C , or
 X^2 is CH_2 or X^C and X^3 is O; and
 X^4 is a bond, CH_2 , CH_2CH_2 , or X^C ;
 wherein X^C is selected from C_{3-6} cycloalkylidene and C_{3-5} oxacycloalkylidene, each substituted with 0 to 4 substituents independently selected from halo, and wherein one, and no more than one, of X^1 , X^2 , X^3 and X^4 is X^C ; or
- (ii) X^1 is $\text{C}(\text{HR}^1)$;
 X^2 is O;
 X^3 is $\text{C}(\text{HR}^3)$; and
 X^4 is CH_2 ;
 wherein R^1 and R^3 taken together represent a C_{1-3} alkanediyl bridging the carbon atoms to which R^1 and R^2 are attached; or
- (iii) X^1 is CH_2 ;
 X^2 is $\text{C}(\text{HR}^2)$;
 X^3 is O;
 and X^4 is $\text{C}(\text{HR}^4)$;
 wherein R^2 and R^4 taken together represent a C_{1-3} alkanediyl bridging the carbon atoms to which R^2 and R^4 are attached; or
- (iv) X^1 is $\text{C}(\text{HR}^1)$;
 X^2 is O and X^3 is CH_2 , or
 X^2 is CH_2 and X^3 is O; and
 X^4 is $\text{C}(\text{HR}^4)$;
 wherein R^1 and R^4 taken together represent a C_{1-3} alkanediyl; or
- (v) X^1 is $\text{C}(\text{HR}^1)$;
 X^2 is CH_2 ;
 X^3 is $\text{C}(\text{HR}^3)$; and
 X^4 is CH_2 ;

wherein R¹ and R³ taken together represent a C₁₋₂ alkanediyloxy or O bridging the carbon atoms to which R¹ and R³ are attached; or

(vi) X¹ is C(HR¹);

X² is CH₂;

X³ is CH₂; and

X⁴ is C(HR⁴);

wherein R¹ and R⁴ taken together represent a C₁₋₂ alkanediyloxy or O bridging the carbon atoms to which R¹ and R⁴ are attached.

[0068] In addition to embodiment (61) in the preceding paragraph, the compounds of Formula 1 include those in which:

(62) X¹ is CH₂, CH(CH₃), or X^C;

X² is O and X³ is CH₂ or X^C, or

X² is CH₂ or X^C and X³ is O; and

X⁴ is a bond, CH₂, CH₂CH₂, or X^C;

wherein X^C is selected from C₃₋₆ cycloalkylidene and C₃₋₅ oxacycloalkylidene, each substituted with 0 to 4 substituents independently selected from halo, and wherein one, and no more than one, of X¹, X², X³ and X⁴ is X^C.

[0069] In addition to embodiment (62) in the preceding paragraph, the compounds of Formula 1 include those in which:

(63) X^C is selected from C₃₋₄ cycloalkylidene and C₃₋₅ oxacycloalkylidene, each substituted with 0 to 4 substituents independently selected from halo;

(64) X^C is C₃₋₄ cycloalkylidene, which is substituted with 0 to 4 substituents independently selected from halo;

(65) X^C is cyclopropylidene, which is substituted with 0 to 4 substituents independently selected from halo;

(66) X^C is cyclobutylidene, which is substituted with 0 to 4 substituents independently selected from halo;

(67) X^C is C₃₋₅ oxacycloalkylidene, which is substituted with 0 to 4 substituents independently selected from halo;

(68) X^C is oxacyclobutylidene, which is substituted with 0 to 4 substituents independently selected from halo;

(69) X^C is 3-oxacyclobutylidene, which is substituted with 0 to 4 substituents independently selected from halo;

- (70) X^C is oxacyclopentylidene, which is substituted with 0 to 4 substituents independently selected from halo;
- (71) X^C is 3-oxacyclopentylidene, which is substituted with 0 to 4 substituents independently selected from halo;
- (72) X^C is oxacyclohexylidene, which is substituted with 0 to 4 substituents independently selected from halo; or
- (73) X^C is 4-oxacyclohexylidene, which is substituted with 0 to 4 substituents independently selected from halo.

[0070] In addition to embodiments (62) to (73) in the preceding paragraph, the compounds of Formula 1 include those in which:

- (74) X^1 is CH_2 or X^C ;
 X^2 is O and X^3 is CH_2 or X^C , or
 X^2 is CH_2 or X^C and X^3 is O; and
 X^4 is CH_2 or X^C ;
- (75) X^1 is CH_2 or X^C ;
 X^2 is O and X^3 is CH_2 or X^C , or
 X^2 is CH_2 or X^C and X^3 is O; and
 X^4 is a bond;
- (76) X^1 is CH_2 or X^C ;
 X^2 is O and X^3 is CH_2 or X^C ; and
 X^4 is a bond;
- (77) X^1 is X^C ;
 X^2 is O and X^3 is CH_2 , or
 X^2 is CH_2 and X^3 is O; and
 X^4 is a bond;
- (78) X^1 is X^C ;
 X^2 is O and X^3 is CH_2 ; and
 X^4 is a bond;
- (79) X^1 is CH_2 or X^C ;
 X^2 is O and X^3 is CH_2 or X^C , or
 X^2 is CH_2 or X^C and X^3 is O; and
 X^4 is CH_2CH_2 ; or
- (80) X^1 is X^C ;

X^2 is O and X^3 is CH_2 , or
 X^2 is CH_2 and X^3 is O; and
 X^4 is CH_2CH_2 .

[0071] In addition to embodiments (62) to (80) in the preceding paragraphs, the compounds of Formula 1 include those in which:

- (81) X^C is substituted with 0 to 3 substituents independently selected from halo;
- (82) X^C is substituted with 0 to 2 substituents independently selected from halo;
- (83) X^C is substituted with 0 to 1 substituents independently selected from halo; or
- (84) X^C is unsubstituted.

[0072] In addition to embodiments (62) to (80) above, the compounds of Formula 1 include those in which:

- (85) X^C is substituted with 0 to 4 fluoro;
- (86) X^C is substituted with 0 to 3 fluoro;
- (87) X^C is substituted with 0 to 2 fluoro; or
- (88) X^C is substituted with 0 to 1 fluoro.

[0073] In addition to embodiment (61) above, the compounds of Formula 1 include those in which X^1 is $\text{C}(\text{HR}^1)$, X^2 is O, X^3 is $\text{C}(\text{HR}^3)$ and X^4 is CH_2 , wherein R^1 and R^3 taken together represent:

- (89) a C_{1-3} alkanediyl bridging the carbon atoms to which R^1 and R^3 are attached;
- (90) a C_{1-2} alkanediyl bridging the carbon atoms to which R^1 and R^3 are attached;
- (91) methane-1,1-diyl bridging the carbon atoms to which R^1 and R^3 are attached; or
- (92) ethane-1,2-diyl bridging the carbon atoms to which R^1 and R^3 are attached.

[0074] In addition to embodiment (61) above, the compounds of Formula 1 include those in which X^1 is CH_2 , X^2 is $\text{C}(\text{HR}^2)$, X^3 is O and X^4 is $\text{C}(\text{HR}^4)$, wherein R^2 and R^4 taken together represent:

- (93) a C_{1-3} alkanediyl bridging the carbon atoms to which R^2 and R^4 are attached;
- (94) a C_{1-2} alkanediyl bridging the carbon atoms to which R^2 and R^4 are attached;
- (95) methane-1,1-diyl bridging the carbon atoms to which R^2 and R^4 are attached; or
- (96) ethane-1,2-diyl bridging the carbon atoms to which R^2 and R^4 are attached.

[0075] In addition to embodiment (61) above, the compounds of Formula 1 include those in which:

- (97) X^1 is $\text{C}(\text{HR}^1)$;
 X^2 is O and X^3 is CH_2 , or

- X^2 is CH_2 and X^3 is O; and
 X^4 is $\text{C}(\text{HR}^4)$;
 wherein R^1 and R^4 taken together represent a C_{1-3} alkanediyl;
- (98) X^1 is $\text{C}(\text{HR}^1)$;
 X^2 is O;
 X^3 is CH_2 , and
 X^4 is $\text{C}(\text{HR}^4)$;
 wherein R^1 and R^4 taken together represent a C_{1-3} alkanediyl; or
- (99) X^1 is $\text{C}(\text{HR}^1)$;
 X^2 is CH_2 ;
 X^3 is O; and
 X^4 is $\text{C}(\text{HR}^4)$;
 wherein R^1 and R^4 taken together represent a C_{1-3} alkanediyl.

[0076] In addition to embodiments (97) to (99) in the preceding paragraph, the compounds of Formula 1 include those in which R^1 and R^4 taken together represent:

- (100) a C_{1-2} alkanediyl bridging the carbon atoms to which R^1 and R^4 are attached;
 (101) methane-1,1-diyl bridging the carbon atoms to which R^1 and R^4 are attached; or
 (102) ethane-1,2-diyl bridging the carbon atoms to which R^1 and R^4 are attached.

[0077] In addition to embodiment (61) above, the compounds of Formula 1 include those in which:

- (103) X^1 is $\text{C}(\text{HR}^1)$;
 X^2 is CH_2 ;
 X^3 is $\text{C}(\text{HR}^3)$; and
 X^4 is CH_2 ;
 wherein R^1 and R^3 taken together represent a C_{1-2} alkanediyloxy or O bridging the carbon atoms to which R^1 and R^3 are attached.

[0078] In addition to embodiment (103) in the preceding paragraph, the compounds of Formula 1 include those in which R^1 and R^3 taken together represent:

- (104) a C_{1-2} alkanediyloxy bridging the carbon atoms to which R^1 and R^3 are attached;
 (105) methane-1,1-diyl bridging the carbon atoms to which R^1 and R^3 are attached;
 (106) ethane-1,2-diyl bridging the carbon atoms to which R^1 and R^3 are attached; or
 (107) O.

[0079] In addition to embodiment (61) above, the compounds of Formula 1 include those in which:

(108) X^1 is $C(HR^1)$;

X^2 is CH_2 ;

X^3 is CH_2 ; and

X^4 is $C(HR^4)$;

wherein R^1 and R^4 taken together represent a C_{1-2} alkanediyoxy or O bridging the carbon atoms to which R^1 and R^4 are attached.

[0080] In addition to embodiment (108) in the preceding paragraph, the compounds of Formula 1 include those in which R^1 and R^4 taken together represent:

(109) a C_{1-2} alkanediyoxy bridging the carbon atoms to which R^1 and R^4 are attached;

(110) methane-1,1-diyoxy bridging the carbon atoms to which R^1 and R^4 are attached;

(111) ethane-1,2-diyoxy bridging the carbon atoms to which R^1 and R^4 are attached; or

(112) O.

[0081] In addition to any one of embodiments (1) to (112) above, the compounds of Formula 1 include those in which m is:

(116) 0; or

(117) 1 or 2.

[0082] In addition to embodiment (117) in the preceding paragraph, the compounds of Formula 1 include those in which:

(118) each R^a and R^b is independently selected from hydrogen and C_{1-4} alkyl;

(119) each R^a and R^b is independently selected from hydrogen and C_{1-3} alkyl;

(120) each R^a and R^b is independently selected from hydrogen and methyl;

(121) each R^a is methyl and each R^b is hydrogen;

(122) each R^a is methyl and each R^b is methyl;

(123) each R^a is hydrogen and each R^b is hydrogen;

(124) each R^a and R^b is independently selected from hydrogen and C_{1-4} alkyl, or R^a and R^b , together with a carbon atom to which both R^a and R^b are attached, form a cyclopropylidene or cyclobutylidene, provided if m is 2, then no more than one R^a and R^b , together with the carbon atom to which R^a and R^b are attached, form a cyclopropylidene or cyclobutylidene;

(125) each R^a and R^b is independently selected from hydrogen and C_{1-4} alkyl, or R^a and R^b , together with a carbon atom to which both R^a and R^b are attached, form a

cyclopropylidene, provided if m is 2, then no more than one R^a and R^b, together with the carbon atom to which R^a and R^b are attached, form a cyclopropylidene;

(126) each R^a and R^b is independently selected from hydrogen and C₁₋₃ alkyl, or R^a and R^b, together with a carbon atom to which both R^a and R^b are attached, form a cyclopropylidene, provided if m is 2, then no more than one R^a and R^b, together with the carbon atom to which R^a and R^b are attached, form a cyclopropylidene.

(127) each R^a and R^b is independently selected from hydrogen and methyl, or R^a and R^b, together with a carbon atom to which both R^a and R^b are attached, form a cyclopropylidene, provided if m is 2, then no more than one R^a and R^b, together with the carbon atom to which R^a and R^b are attached, form a cyclopropylidene; or

(128) each R^a and R^b is hydrogen, or R^a and R^b, together with a carbon atom to which both R^a and R^b are attached, form a cyclopropylidene, provided if m is 2, then no more than one R^a and R^b, together with the carbon atom to which R^a and R^b are attached, form a cyclopropylidene.

[0083] In addition to any one of embodiments (1) to (128) above, the compounds of Formula 1 include those in which R⁵ is:

(129) C₃₋₈ cycloalkyl, which is substituted with 0 to 5 substituents independently selected from:

- (i) halo, hydroxy, cyano and oxo;
- (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
- (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;

(130) C₄₋₇ cycloalkyl, which is substituted with 0 to 5 substituents independently selected from:

- (i) halo, hydroxy, cyano and oxo;
- (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
- (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;

(131) a cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptan-1-yl and spiro[3.3]heptan-2-yl, each substituted with 0 to 5 substituents independently selected from:

- (i) halo, hydroxy, cyano and oxo;
 - (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
 - (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;
- (132) a cycloalkyl selected from cyclobutyl, cyclohexyl, bicyclo[2.2.1]heptan-1-yl and spiro[3.3]heptan-2-yl, each substituted with 0 to 5 substituents independently selected from:
- (i) halo, hydroxy, cyano and oxo;
 - (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
 - (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;
- (133) a cycloalkyl selected from cyclobutyl, cyclohexyl and bicyclo[2.2.1]heptan-1-yl, each substituted with 0 to 5 substituents independently selected from:
- (i) halo, hydroxy, cyano and oxo;
 - (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
 - (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;
- (134) a cycloalkyl which is cyclobutyl substituted with 0 to 5 substituents independently selected from:
- (i) halo, hydroxy, cyano and oxo;
 - (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
 - (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;
- (135) a cycloalkyl which is cyclohexyl substituted with 0 to 5 substituents independently selected from:
- (i) halo, hydroxy, cyano and oxo;
 - (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
 - (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo; or

(136) a cycloalkyl which is bicyclo[2.2.1]heptan-1-yl substituted with 0 to 5 substituents independently selected from:

- (i) halo, hydroxy, cyano and oxo;
- (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
- (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo.

[0084] In addition to any one of embodiments (129) to (136) in the preceding paragraph, the compounds of Formula 1 include those in which the R⁵ cycloalkyl is substituted with 0 to 5 substituents independently selected from:

- (137)
 - (i) halo, hydroxy and oxo;
 - (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
 - (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;
- (138)
 - (i) halo and hydroxy;
 - (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
 - (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;
- (139)
 - (i) hydroxy and fluoro;
 - (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
 - (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;
- (140)
 - (i) hydroxy;
 - (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
 - (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;
- (141)
 - (i) halo, hydroxy, cyano and oxo;
 - (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₃ alkyl; and

- (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;
- (142) (i) halo, hydroxy, cyano and oxo;
- (ii) amino, which is substituted with 0 to 2 substituents independently selected from methyl; and
- (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;
- (143) (i) halo, hydroxy, cyano and oxo;
- (ii) amino, which is unsubstituted; and
- (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;
- (144) (i) halo, hydroxy, cyano and oxo;
- (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
- (iii) C₁₋₃ alkyl, C₁₋₃ alkylcarbonyl and C₁₋₃ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;
- (145) (i) halo, hydroxy, cyano and oxo;
- (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
- (iii) methyl, methylcarbonyl, ethylcarbonyl, methoxy and ethoxy, each substituted with 0 to 3 substituents independently selected from halo;
- (146) (i) halo, hydroxy, cyano and oxo;
- (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
- (iii) methyl and methoxy, each substituted with 0 to 3 substituents independently selected from halo;
- (147) (i) hydroxy;
- (ii) amino, which is substituted with 0 to 2 substituents independently selected from methyl; and
- (iii) methyl and methoxy, each substituted with 0 to 3 substituents independently selected from halo;
- (148) (i) hydroxy;

- (ii) amino, which is substituted with 0 to 2 substituents independently selected from methyl; and
 - (iii) methyl and methoxy, each substituted with 0 to 3 substituents independently selected from fluoro; or
- (149) hydroxy, dimethylamino, methyl, trifluoromethyl and methoxy.

[0085] In addition to any one of embodiments (129) to (149) in the preceding paragraphs, the compounds of Formula 1 include those in which the R⁵ cycloalkyl is:

- (150) substituted with 0 to 4 substituents;
- (151) substituted with 0 to 3 substituents;
- (152) substituted with 0 to 2 substituents;
- (153) substituted with 0 to 1 substituents; or
- (154) is unsubstituted.

[0086] In addition to any one of embodiments (1) to (128) above, the compounds of Formula 1 include those in which R⁵ is:

- (155) C₃₋₈ heterocyclyl in which up to 3 carbon ring atoms are each independently substituted with 0 to 2 substituents independently selected from:
- (i) halo, hydroxy, cyano and oxo;
 - (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
 - (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;

and in which a nitrogen ring atom, if present, is unsubstituted or substituted with a substituent selected from:

- (i) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;
- (ii) C₃₋₈ cycloalkyl-(CH₂)_n, which C₃₋₈ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl, C₁₋₄ alkoxy and oxo; and
- (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl and C₁₋₄ alkoxy;

(156) C₃₋₈ heterocyclyl in which the ring heteroatom is selected from nitrogen and oxygen and up to 3 carbon ring atoms are each independently substituted with 0 to 2 substituents independently selected from:

- (i) halo, hydroxy, cyano and oxo;
- (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
- (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;

and in which a nitrogen ring atom, if present, is unsubstituted or substituted with a substituent selected from:

- (i) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;
- (ii) C₃₋₈ cycloalkyl-(CH₂)_n, which C₃₋₈ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl, C₁₋₄ alkoxy and oxo; and
- (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl and C₁₋₄ alkoxy;

(157) C₃₋₈ heterocyclyl in which the ring heteroatom is nitrogen and up to 3 carbon ring atoms are each independently substituted with 0 to 2 substituents independently selected from:

- (i) halo, hydroxy, cyano and oxo;
- (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
- (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;

and in which the nitrogen ring atom is unsubstituted or substituted with a substituent selected from:

- (i) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;
- (ii) C₃₋₈ cycloalkyl-(CH₂)_n, which C₃₋₈ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl, C₁₋₄ alkoxy and oxo; and

- (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl and C₁₋₄ alkoxy;

(158) a heterocyclyl selected from azetidiny, piperidiny, 1-azabicyclo[2.2.1]heptany, quinuclidiny, pyrrolidiny, 3-azabicyclo[3.1.0]hexan-1-yl and 2-oxabicyclo[2.2.1]heptan-4-yl in which up to 3 carbon ring atoms of the R⁵ heterocyclyl are each independently substituted with 0 to 2 substituents independently selected from:

- (i) halo, hydroxy, cyano and oxo;
- (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
- (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;

and in which a nitrogen ring atom of the R⁵ heterocyclyl, if present, is unsubstituted or substituted with a substituent selected from:

- (i) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;
- (ii) C₃₋₈ cycloalkyl-(CH₂)_n, which C₃₋₈ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl, C₁₋₄ alkoxy and oxo; and
- (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl and C₁₋₄ alkoxy; or

(159) a heterocyclyl selected from azetidin-1-yl, piperidin-2-yl, piperidin-3-yl, 1-azabicyclo[2.2.1]heptan-3-yl, quinuclidine-3-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, 3-azabicyclo[3.1.0]hexan-1-yl and 2-oxabicyclo[2.2.1]heptan-4-yl in which up to 3 carbon ring atoms of the R⁵ heterocyclyl are each independently substituted with 0 to 2 substituents independently selected from:

- (i) halo, hydroxy, cyano and oxo;
- (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
- (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;

and in which a nitrogen ring atom of the R⁵ heterocyclyl, if present, is unsubstituted or substituted with a substituent selected from:

- (i) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;
- (ii) C₃₋₈ cycloalkyl-(CH₂)_n, which C₃₋₈ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl, C₁₋₄ alkoxy and oxo; and
- (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl and C₁₋₄ alkoxy.

[0087] In addition to any one of embodiments (155) to (159) in the preceding paragraph, the compounds of Formula 1 include those in which up to 3 carbon ring atoms of the R⁵ heterocyclyl are each independently substituted with 0 to 2 substituents independently selected from:

- (160)
 - (i) halo, hydroxy and oxo;
 - (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
 - (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;
- (161)
 - (i) halo and oxo;
 - (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
 - (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;
- (162)
 - (i) halo;
 - (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
 - (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;
- (163)
 - (i) halo, hydroxy, cyano and oxo;
 - (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₃ alkyl; and

- (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;
- (164) (i) halo, hydroxy, cyano and oxo;
(ii) amino, which is substituted with 0 to 2 substituents independently selected from methyl; and
(iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;
- (165) (i) halo, hydroxy, cyano and oxo;
(ii) amino, which is unsubstituted; and
(iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;
- (166) (i) halo, hydroxy, cyano and oxo;
(ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
(iii) C₁₋₃ alkyl, C₁₋₃ alkylcarbonyl and C₁₋₃ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;
- (167) (i) halo, hydroxy, cyano and oxo;
(ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
(iii) methyl, methylcarbonyl, ethylcarbonyl, methoxy and ethoxy, each substituted with 0 to 3 substituents independently selected from halo;
- (168) (i) halo, hydroxy, cyano and oxo;
(ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
(iii) methyl and methoxy, each substituted with 0 to 3 substituents independently selected from halo;
- (169) (i) halo and oxo;
(ii) amino, which is substituted with 0 to 2 substituents independently selected from methyl; and
(iii) methyl and methoxy, each substituted with 0 to 3 substituents independently selected from halo;
- (170) (i) halo and oxo;

- (ii) amino, which is substituted with 0 to 2 substituents independently selected from methyl; and
 - (iii) methyl and methoxy, each substituted with 0 to 3 substituents independently selected from fluoro;
- (171) halo, oxo, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy and isopropoxy;
- (172) halo, oxo, methyl, ethyl, propyl and isopropyl; or
- (173) fluoro, oxo, methyl, ethyl, propyl and isopropyl.
- [0088]** In addition to any one of embodiments (155) to (173) in the preceding paragraphs, the compounds of Formula 1 include those in which:
- (174) up to 2 carbon ring atoms of the R^5 heterocyclyl are each substituted;
 - (175) up to 1 carbon ring atoms of the R^5 heterocyclyl is substituted; or
 - (176) none of the carbon ring atoms of the R^5 heterocyclyl is substituted.
- [0089]** In addition to any one of embodiments (155) to (176) in the preceding paragraphs, the compounds of Formula 1 include those in which R^5 is C_{3-8} heterocyclyl in which a nitrogen ring atom, if present, is unsubstituted or substituted with a substituent selected from:
- (177) (i) C_{1-3} alkyl, C_{1-3} alkylcarbonyl and C_{1-3} alkylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;
 - (ii) C_{3-8} cycloalkyl- $(CH_2)_n$, which C_{3-8} cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from halo, C_{1-4} alkyl, C_{1-4} alkylcarbonyl, C_{1-4} alkoxy and oxo; and
 - (iii) phenyl- $(CH_2)_n$ and pyridinyl- $(CH_2)_n$, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C_{1-4} alkyl and C_{1-4} alkoxy;
- (178) (i) C_{1-3} alkyl, methylcarbonyl, ethylcarbonyl, methylsulfonyl and ethylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;
- (ii) C_{3-8} cycloalkyl- $(CH_2)_n$, which C_{3-8} cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from halo, C_{1-4} alkyl, C_{1-4} alkylcarbonyl, C_{1-4} alkoxy and oxo; and
 - (iii) phenyl- $(CH_2)_n$ and pyridinyl- $(CH_2)_n$, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C_{1-4} alkyl and C_{1-4} alkoxy;

- (179) (i) methyl, ethyl, isopropyl, methylcarbonyl and methylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;
- (ii) C₃₋₈ cycloalkyl-(CH₂)_n, which C₃₋₈ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl, C₁₋₄ alkoxy and oxo; and
- (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl and C₁₋₄ alkoxy;
- (180) (i) methyl, ethyl, isopropyl, methylcarbonyl, methylsulfonyl, each substituted with 0 to 3 substituents selected from fluoro;
- (ii) C₃₋₈ cycloalkyl-(CH₂)_n, which C₃₋₈ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl, C₁₋₄ alkoxy and oxo; and
- (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl and C₁₋₄ alkoxy;
- (181) (i) methyl, ethyl, isopropyl, methylcarbonyl, methylsulfonyl, each unsubstituted;
- (ii) C₃₋₈ cycloalkyl-(CH₂)_n, which C₃₋₈ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl, C₁₋₄ alkoxy and oxo; and
- (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl and C₁₋₄ alkoxy;
- (182) (i) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;
- (ii) C₃₋₅ cycloalkyl-(CH₂)_n, which C₃₋₅ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl, C₁₋₄ alkoxy and oxo; and
- (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl and C₁₋₄ alkoxy;

- (183) (i) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;
- (ii) C₃₋₅ cycloalkyl-(CH₂)_n, which C₃₋₅ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from halo, C₁₋₃ alkyl, C₁₋₃ alkylcarbonyl, C₁₋₃ alkoxy and oxo; and
- (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl and C₁₋₄ alkoxy;
- (184) (i) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;
- (ii) C₃₋₅ cycloalkyl-(CH₂)_n, which C₃₋₅ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from halo, C₁₋₃ alkyl and C₁₋₃ alkoxy; and
- (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl and C₁₋₄ alkoxy;
- (185) (i) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;
- (ii) C₃₋₅ cycloalkyl-(CH₂)_n, which C₃₋₅ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from C₁₋₃ alkyl and C₁₋₃ alkoxy; and
- (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl and C₁₋₄ alkoxy;
- (186) (i) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;
- (ii) C₃₋₅ cycloalkyl-(CH₂)_n, which C₃₋₅ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from halo, methyl and methoxy; and
- (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl and C₁₋₄ alkoxy;
- (187) (i) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;

- (ii) C₃₋₅ cycloalkyl-(CH₂)_n, which C₃₋₅ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from fluoro, methyl and methoxy; and
 - (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl and C₁₋₄ alkoxy;
- (188)
- (i) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;
 - (ii) C₃₋₅ cycloalkyl-(CH₂)_n, which C₃₋₅ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from methyl and methoxy; and
 - (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl and C₁₋₄ alkoxy;
- (189)
- (i) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;
 - (ii) C₃₋₅ cycloalkyl-(CH₂)_n, which C₃₋₅ cycloalkyl moiety is unsubstituted; and
 - (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl and C₁₋₄ alkoxy;
- (190)
- (i) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;
 - (ii) C₃₋₈ cycloalkyl-(CH₂)_n, which C₃₋₈ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl, C₁₋₄ alkoxy and oxo; and
 - (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₃ alkyl and C₁₋₃ alkoxy;
- (191)
- (i) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;
 - (ii) C₃₋₈ cycloalkyl-(CH₂)_n, which C₃₋₈ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl, C₁₋₄ alkoxy and oxo; and

- (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, methyl and methoxy;
- (192) (i) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;
- (ii) C₃₋₈ cycloalkyl-(CH₂)_n, which C₃₋₈ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl, C₁₋₄ alkoxy and oxo; and
- (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from halo, hydroxy, methyl and methoxy;
- (193) (i) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;
- (ii) C₃₋₈ cycloalkyl-(CH₂)_n, which C₃₋₈ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl, C₁₋₄ alkoxy and oxo; and
- (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from fluoro, chloro, hydroxy, methyl and methoxy;
- (194) (i) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;
- (ii) C₃₋₈ cycloalkyl-(CH₂)_n, which C₃₋₈ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl, C₁₋₄ alkoxy and oxo; and
- (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from fluoro, hydroxy, methyl and methoxy;
- (195) (i) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;
- (ii) C₃₋₈ cycloalkyl-(CH₂)_n, which C₃₋₈ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl, C₁₋₄ alkoxy and oxo; and

- (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are unsubstituted;
- (196) (i) methyl, ethyl, isopropyl, methylcarbonyl, methylsulfonyl, each substituted with 0 to 3 substituents selected from fluoro;
- (ii) C₃₋₅ cycloalkyl-(CH₂)_n, which C₃₋₅ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from fluoro, methyl and methoxy; and
- (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from fluoro, hydroxy, methyl and methoxy;
- (197) (i) methyl, ethyl, isopropyl, methylcarbonyl, methylsulfonyl, each substituted with 0 to 3 substituents selected from fluoro;
- (ii) C₃₋₅ cycloalkyl-(CH₂)_n, which C₃₋₅ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from methyl and methoxy; and
- (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from fluoro, hydroxy, methyl and methoxy; or
- (198) (i) methyl, ethyl, isopropyl, methylcarbonyl, methylsulfonyl, each substituted with 0 to 3 substituents selected from fluoro;
- (ii) C₃₋₅ cycloalkyl-(CH₂)_n, which C₃₋₅ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from methyl and methoxy; and
- (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are unsubstituted.

[0090] In addition to any one of embodiments (155) to (198) in the preceding paragraphs, the compounds of Formula 1 include those in which:

- (199) R⁵ is C₃₋₈ heterocyclyl and n is 0; or
- (200) R⁵ is C₃₋₈ heterocyclyl and n is 1.

[0091] In addition to any one of embodiments (1) to (128) above, the compounds of Formula 1 include those in which R⁵ is phenyl, which is:

- (201) substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl and C₁₋₄ alkoxy, provided at least one of the substituents is hydroxy;
- (202) substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₃ alkyl and C₁₋₃ alkoxy, provided at least one of the substituents is hydroxy;

(203) substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, methyl and methoxy, provided at least one of the substituents is hydroxy;

(204) substituted with 0 to 2 substituents independently selected from halo, hydroxy, cyano, methyl and methoxy, provided at least one of the substituents is hydroxy;

(205) unsubstituted or substituted with hydroxy; or

(206) unsubstituted.

[0092] In addition to any one of embodiments (1) to (206) in the preceding paragraphs, the compounds of Formula 1 include those in which R^6 is selected from:

(207) hydrogen and C_{1-3} alkyl;

(208) hydrogen and methyl;

(209) methyl; or

(210) hydrogen.

[0093] In addition to any one of embodiments (1) to (210) in the preceding paragraphs, the compounds of Formula 1 include those in which:

(211) X^8 is CR^8 .

[0094] In addition to any one of embodiments (1) to (211) in the preceding paragraphs, the compounds of Formula 1 include those in which R^7 , R^8 and R^{11} are each independently selected from:

(212) (i) hydrogen, halo and hydroxy;

(ii) C_{1-4} alkyl and C_{1-4} alkoxy, each substituted with 0 to 3 substituents independently selected from halo; and

(iii) C_{3-8} cycloalkyl which is substituted with 0 to 3 substituents independently selected from halo, C_{1-4} alkyl and C_{1-4} alkoxy;

(213) (i) hydrogen, halo and hydroxy; and

(ii) C_{1-4} alkyl and C_{1-4} alkoxy, each substituted with 0 to 3 substituents independently selected from halo;

(214) (i) hydrogen, halo and hydroxy; and

(ii) C_{1-3} alkyl and C_{1-3} alkoxy, each substituted with 0 to 3 substituents independently selected from halo;

(215) (i) hydrogen, halo and hydroxy; and

(ii) methyl and methoxy, each substituted with 0 to 3 substituents independently selected from halo; or

(216) (i) hydrogen, halo and hydroxy; and

- (ii) methyl and methoxy, each substituted with 0 to 3 fluoro.

[0095] In addition to any one of embodiments (1) to (211) above, the compounds of Formula 1 include those in which R⁷ and R⁸ are both hydrogen, and R¹¹ is selected from:

- (217) (i) hydrogen, halo and hydroxy; and
 - (ii) C₁₋₃ alkyl and C₁₋₃ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;
- (218) (i) hydrogen, halo and hydroxy; and
 - (ii) methyl and methoxy, each substituted with 0 to 3 substituents independently selected from halo; or
- (219) (i) hydrogen, halo and hydroxy; and
 - (ii) methyl and methoxy, each substituted with 0 to 3 fluoro.

[0096] In addition to any one of embodiments (1) to (219) in the preceding paragraphs, the compounds of Formula 1 include those in which R⁹ and R¹⁰ are each independently selected from:

- (220) (i) hydrogen, halo, hydroxy and cyano;
 - (ii) C₁₋₄ alkyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo; and
 - (iii) C₃₋₈ cycloalkyl which is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl and C₁₋₄ alkoxy;
- (221) (i) hydrogen, halo, hydroxy and cyano;
 - (ii) C₁₋₄ alkyl and C₁₋₃ alkoxy, each substituted with 0 to 3 substituents independently selected from halo; and
 - (iii) C₃₋₈ cycloalkyl which is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl and C₁₋₄ alkoxy;
- (222) (i) hydrogen, halo, hydroxy and cyano;
 - (ii) C₁₋₄ alkyl and methoxy, each substituted with 0 to 3 substituents independently selected from halo; and
 - (iii) C₃₋₈ cycloalkyl which is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl and C₁₋₄ alkoxy;
- (223) (i) hydrogen, halo, hydroxy and cyano;
 - (ii) C₁₋₄ alkyl and methoxy, each substituted with 0 to 3 fluoro; and
 - (iii) C₃₋₈ cycloalkyl which is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl and C₁₋₄ alkoxy;

- (224) (i) hydrogen, halo, hydroxy and cyano;
(ii) C₁₋₄ alkyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo; and
(iii) C₃₋₅ cycloalkyl which is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl and C₁₋₄ alkoxy;
- (225) (i) hydrogen, halo, hydroxy and cyano;
(ii) C₁₋₄ alkyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo; and
(iii) C₃₋₅ cycloalkyl which is substituted with 0 to 3 substituents independently selected from C₁₋₄ alkyl and C₁₋₄ alkoxy;
- (226) (i) hydrogen, halo, hydroxy and cyano;
(ii) C₁₋₄ alkyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo; and
(iii) C₃₋₅ cycloalkyl which is substituted with 0 to 3 substituents independently selected from C₁₋₃ alkyl and C₁₋₃ alkoxy;
- (227) (i) hydrogen, halo, hydroxy and cyano;
(ii) C₁₋₄ alkyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo; and
(iii) C₃₋₅ cycloalkyl which is substituted with 0 to 3 substituents independently selected from methyl and methoxy;
- (228) (i) hydrogen, halo, hydroxy and cyano;
(ii) C₁₋₄ alkyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo; and
(iii) cyclopropyl and cyclobutyl, each substituted with 0 to 3 substituents independently selected from methyl and methoxy;
- (229) (i) hydrogen, halo, hydroxy and cyano;
(ii) C₁₋₄ alkyl and C₁₋₃ alkoxy, each substituted with 0 to 3 substituents independently selected from halo; and
(iii) C₃₋₅ cycloalkyl which is substituted with 0 to 3 substituents independently selected from C₁₋₃ alkyl and C₁₋₃ alkoxy;
- (230) (i) hydrogen, halo, hydroxy and cyano;
(ii) C₁₋₄ alkyl and C₁₋₃ alkoxy, each substituted with 0 to 3 fluoro; and

- (iii) C₃₋₅ cycloalkyl which is substituted with 0 to 3 substituents independently selected from C₁₋₃ alkyl and C₁₋₃ alkoxy; or
- (231) (i) hydrogen, halo, hydroxy and cyano;
- (ii) C₁₋₄ alkyl and C₁₋₃ alkoxy, each substituted with 0 to 3 fluoro; and
- (iii) C₃₋₅ cycloalkyl which is substituted with 0 to 3 substituents independently selected from methyl and methoxy.

[0097] Compounds of Formula 1 include embodiments (1) through (231) described in the preceding paragraphs and compounds specifically named in the examples, may exist as salts, complexes, solvates, hydrates, and liquid crystals. Likewise, compounds of Formula 1 that are salts may exist as complexes, solvates, hydrates, and liquid crystals.

[0098] Compounds of Formula 1 may form pharmaceutically acceptable complexes, salts, solvates and hydrates. These salts include acid addition salts (including di-acids) and base salts. Pharmaceutically acceptable acid addition salts include salts derived from inorganic acids such as hydrochloric acid, nitric acid, phosphoric acid, sulfuric acid, hydrobromic acid, hydroiodic acid, hydrofluoric acid, and phosphorous acids, as well nontoxic salts derived from organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanolic acids, hydroxy alkanolic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts include acetate, adipate, aspartate, benzoate, besylate, bicarbonate, carbonate, bisulfate, sulfate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulfate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate, hydrogen phosphate, dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinofoate salts.

[0099] Pharmaceutically acceptable base salts include salts derived from bases, including metal cations, such as an alkali or alkaline earth metal cation, as well as amines. Examples of suitable metal cations include sodium, potassium, magnesium, calcium, zinc, and aluminum. Examples of suitable amines include arginine, *N,N'*-dibenzylethylenediamine, chloroprocaine, choline, diethylamine, diethanolamine, dicyclohexylamine, ethylenediamine, glycine, lysine, *N*-methylglucamine, olamine, 2-amino-2-hydroxymethyl-propane-1,3-diol, and procaine. For a discussion of useful acid addition and base salts, see S. M. Berge et al., *J. Pharm. Sci.*

(1977) 66:1-19; see also Stahl and Wermuth, *Handbook of Pharmaceutical Salts: Properties, Selection, and Use* (2002).

[0100] Pharmaceutically acceptable salts may be prepared using various methods. For example, a compound of Formula 1 may be reacted with an appropriate acid or base to give the desired salt. Alternatively, a precursor of the compound of Formula 1 may be reacted with an acid or base to remove an acid- or base-labile protecting group or to open a lactone or lactam group of the precursor. Additionally, a salt of the compound of Formula 1 may be converted to another salt (or free form) through treatment with an appropriate acid or base or through contact with an ion exchange resin. Following reaction, the salt may be isolated by filtration if it precipitates from solution, or by evaporation to recover the salt. The degree of ionization of the salt may vary from completely ionized to almost non-ionized.

[0101] Compounds of Formula 1 may exist in a continuum of solid states ranging from fully amorphous to fully crystalline. The term “amorphous” refers to a state in which the material lacks long range order at the molecular level and, depending upon temperature, may exhibit the physical properties of a solid or a liquid. Typically, such materials do not give distinctive X-ray diffraction patterns and, while exhibiting the properties of a solid, are more formally described as a liquid. Upon heating, a change from solid to liquid properties occurs which is characterized by a change of state, typically second order (“glass transition”). The term “crystalline” refers to a solid phase in which the material has a regular ordered internal structure at the molecular level and gives a distinctive X-ray diffraction pattern with defined peaks. Such materials when heated sufficiently will also exhibit the properties of a liquid, but the change from solid to liquid is characterized by a phase change, typically first order (“melting point”).

[0102] Compounds of Formula 1 may also exist in unsolvated and solvated forms. The term “solvate” describes a molecular complex comprising the compound and one or more pharmaceutically acceptable solvent molecules (e.g., ethanol). The term “hydrate” is a solvate in which the solvent is water. Pharmaceutically acceptable solvates include those in which the solvent may be isotopically substituted (e.g., D₂O, acetone-*d*₆, DMSO-*d*₆).

[0103] A currently accepted classification system for solvates and hydrates of organic compounds is one that distinguishes between isolated site, channel, and metal-ion coordinated solvates and hydrates. See, e.g., K. R. Morris (H. G. Brittain ed.) *Polymorphism in Pharmaceutical Solids* (1995). Isolated site solvates and hydrates are ones in which the solvent (e.g., water) molecules are isolated from direct contact with each other by intervening

molecules of the organic compound. In channel solvates, the solvent molecules lie in lattice channels where they are next to other solvent molecules. In metal-ion coordinated solvates, the solvent molecules are bonded to the metal ion.

[0104] When the solvent or water is tightly bound, the complex will have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly bound, as in channel solvates and in hygroscopic compounds, the water or solvent content will depend on humidity and drying conditions. In such cases, non-stoichiometry will typically be observed.

[0105] Compounds of Formula 1 may also exist as multi-component complexes (other than salts and solvates) in which the compound (drug) and at least one other component are present in stoichiometric or non-stoichiometric amounts. Complexes of this type include clathrates (drug-host inclusion complexes) and co-crystals. The latter are typically defined as crystalline complexes of neutral molecular constituents which are bound together through non-covalent interactions but could also be a complex of a neutral molecule with a salt. Co-crystals may be prepared by melt crystallization, by recrystallization from solvents, or by physically grinding the components together. See, e.g., O. Almarsson and M. J. Zaworotko, *Chem. Commun.* (2004) 17:1889-1896. For a general review of multi-component complexes, see J. K. Halebian, *J. Pharm. Sci.* (1975) 64(8):1269-88.

[0106] When subjected to suitable conditions, compounds of Formula 1 may exist in a mesomorphic state (mesophase or liquid crystal). The mesomorphic state lies between the true crystalline state and the true liquid state (either melt or solution). Mesomorphism arising as the result of a change in temperature is described as “thermotropic” and mesomorphism resulting from the addition of a second component, such as water or another solvent, is described as “lyotropic.” Compounds that have the potential to form lyotropic mesophases are described as “amphiphilic” and include molecules which possess a polar ionic moiety (e.g., $\text{-COO}^-\text{Na}^+$, $\text{-COO}^-\text{K}^+$, $\text{-SO}_3^-\text{Na}^+$) or polar non-ionic moiety (such as $\text{-N}^+\text{N}^+(\text{CH}_3)_3$). See, e.g., N. H. Hartshorne and A. Stuart, *Crystals and the Polarizing Microscope* (4th ed, 1970).

[0107] Each compound of Formula 1 may exist as polymorphs, stereoisomers, tautomers, or some combination thereof, may be isotopically-labeled, may result from the administration of a prodrug, or form a metabolite following administration.

[0108] “Prodrugs” refer to compounds having little or no pharmacological activity that can, when metabolized *in vivo*, undergo conversion to compounds having desired pharmacological activity. Prodrugs may be prepared by replacing appropriate functionalities present in

pharmacologically active compounds with “pro-moieties” as described, for example, in H. Bundgaard, *Design of Prodrugs* (1985). Examples of prodrugs include ester, ether or amide derivatives of compounds of Formula 1 having carboxylic acid, hydroxy, or amino functional groups, respectively. For further discussions of prodrugs, see e.g., T. Higuchi and V. Stella “Pro-drugs as Novel Delivery Systems,” *ACS Symposium Series* 14 (1975) and E. B. Roche ed., *Bioreversible Carriers in Drug Design* (1987).

[0109] “Metabolites” refer to compounds formed *in vivo* upon administration of pharmacologically active compounds. Examples include hydroxymethyl, hydroxy, secondary amino, primary amino, phenol, and carboxylic acid derivatives of compounds of Formula 1 having methyl, alkoxy, tertiary amino, secondary amino, phenyl, and amide groups, respectively.

[0110] Compounds of Formula 1 may exist as stereoisomers that result from the presence of one or more stereogenic centers, one or more double bonds, or both. The stereoisomers may be pure, substantially pure, or mixtures. Such stereoisomers may also result from acid addition or base salts in which the counter-ion is optically active, for example, when the counter-ion is D-lactate or L-lysine.

[0111] Compounds of Formula 1 may exist as tautomers, which are isomers resulting from tautomerization. Tautomeric isomerism includes, for example, imine-enamine, keto-enol, oxime-nitroso, and amide-imidic acid tautomerism.

[0112] Compounds of Formula 1 may exhibit more than one type of isomerism.

[0113] Geometrical (*cis/trans*) isomers may be separated by conventional techniques such as chromatography and fractional crystallization.

[0114] Conventional techniques for preparing or isolating a compound having a specific stereochemical configuration include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high-pressure liquid chromatography (HPLC). Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of Formula 1 contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting diastereomeric mixture may be separated by chromatography, fractional crystallization, etc., and the appropriate diastereoisomer converted to the compound having the requisite stereochemical configuration. For a further discussion of techniques for separating stereoisomers, see E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds* (1994).

[0115] Compounds of Formula 1 may possess isotopic variations, in which at least one atom is replaced by an atom having the same atomic number, but an atomic mass different from the atomic mass usually found in nature. Isotopes suitable for inclusion in compounds of Formula 1 include, for example, isotopes of hydrogen, such as ^2H and ^3H ; isotopes of carbon, such as ^{11}C , ^{13}C and ^{14}C ; isotopes of nitrogen, such as ^{13}N and ^{15}N ; isotopes of oxygen, such as ^{15}O , ^{17}O and ^{18}O ; isotopes of sulfur, such as ^{35}S ; isotopes of fluorine, such as ^{18}F ; isotopes of chlorine, such as ^{36}Cl , and isotopes of iodine, such as ^{123}I and ^{125}I . Use of isotopic variations (e.g., deuterium, ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements. Additionally, certain isotopic variations of the disclosed compounds may incorporate a radioactive isotope (e.g., tritium, ^3H , or ^{14}C), which may be useful in drug and/or substrate tissue distribution studies. Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , may be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds may be prepared by processes analogous to those described elsewhere in the disclosure using an appropriate isotopically-labeled reagent in place of a non-labeled reagent.

[0116] The compounds of Formula 1 may be prepared using the techniques described below. Some of the methods and examples may omit details of common reactions, including oxidations, reductions, and so on, separation techniques (extraction, evaporation, precipitation, chromatography, filtration, trituration, crystallization, and the like), and analytical procedures, which are known to persons of ordinary skill in the art of organic chemistry. The details of such reactions and techniques can be found in several treatises, including Richard Larock, *Comprehensive Organic Transformations* (1999), and the multi-volume series edited by Michael B. Smith and others, *Compendium of Organic Synthetic Methods* (1974 *et seq.*). Starting materials and reagents may be obtained from commercial sources or may be prepared using literature methods. Some of the reaction schemes may omit minor products resulting from chemical transformations (e.g., an alcohol from the hydrolysis of an ester, CO_2 from the decarboxylation of a di-acid, etc.). In addition, in some instances, reaction intermediates may be used in subsequent steps without isolation or purification (i.e., *in situ*).

[0117] In the methods and examples below, certain compounds may be prepared using protecting groups, which prevent undesirable chemical reaction at otherwise reactive sites. Protecting groups may also be used to enhance solubility or otherwise modify physical

properties of a compound. For a discussion of protecting group strategies, a description of materials and methods for installing and removing protecting groups, and a compilation of useful protecting groups for common functional groups, including amines, carboxylic acids, alcohols, ketones, aldehydes, and so on, see T. W. Greene and P. G. Wuts, *Protecting Groups in Organic Chemistry* (1999) and P. Kocienski, *Protective Groups* (2000).

[0118] Generally, the chemical transformations described throughout the specification may be carried out using substantially stoichiometric amounts of reactants, though certain reactions may benefit from using an excess of one or more of the reactants. Additionally, many of the reactions disclosed throughout the specification may be carried out at about room temperature (RT) and ambient pressure, but depending on reaction kinetics, yields, and so on, some reactions may be run at elevated pressures or employ higher temperatures (e.g., reflux conditions) or lower temperatures (e.g., -78°C to 0°C). Any reference in the disclosure and claims to a stoichiometric range, a temperature range, a pH range, etc., whether expressly using the word “range,” also includes the indicated endpoints.

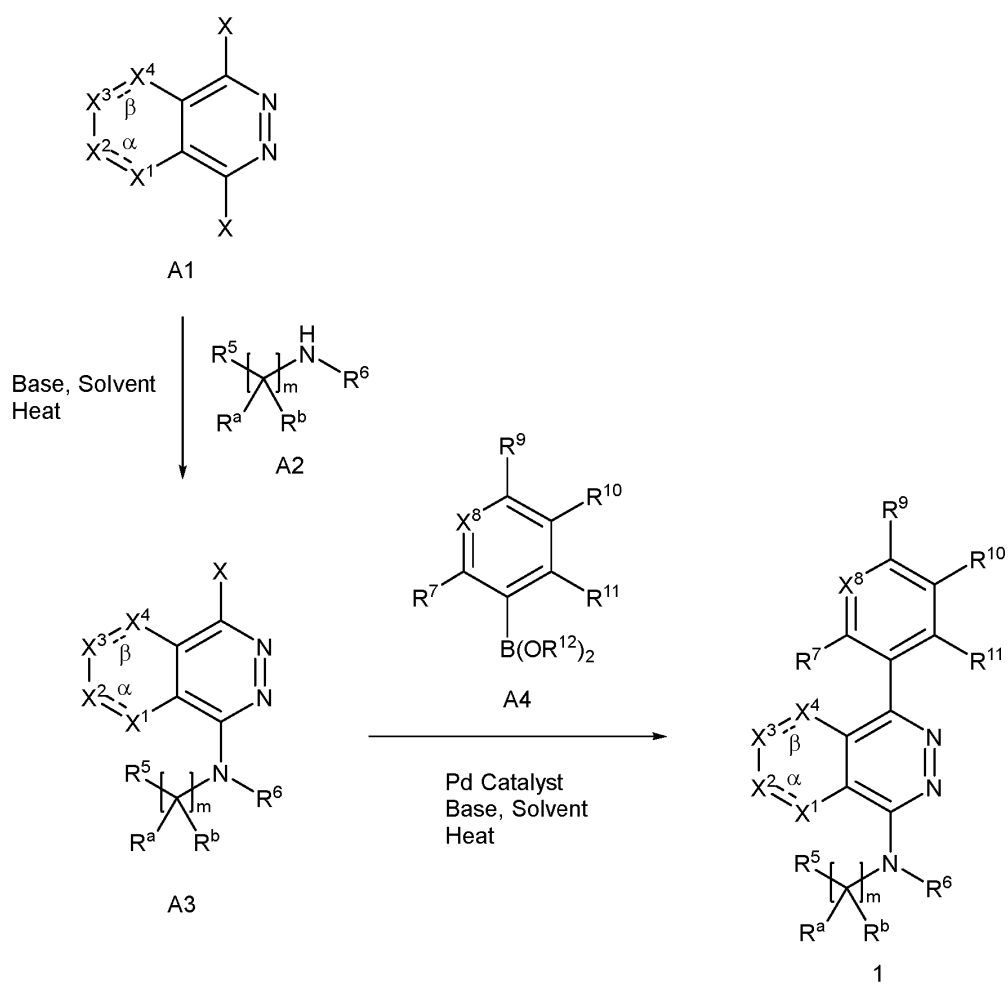
[0119] Many of the chemical transformations may also employ one or more compatible solvents, which may influence the reaction rate and yield. Depending on the nature of the reactants, the one or more solvents may be polar protic solvents (including water), polar aprotic solvents, non-polar solvents, or some combination. Representative solvents include saturated aliphatic hydrocarbons (e.g., *n*-pentane, *n*-hexane, *n*-heptane, *n*-octane, cyclohexane, methylcyclohexane); aromatic hydrocarbons (e.g., benzene, toluene, xylenes); halogenated hydrocarbons (e.g., methylene chloride, chloroform, carbon tetrachloride); aliphatic alcohols (e.g., methanol, ethanol, propan-1-ol, propan-2-ol, butan-1-ol, 2-methylpropan-1-ol, butan-2-ol, 2-methylpropan-2-ol, pentan-1-ol, 3-methylbutan-1-ol, hexan-1-ol, 2-methoxy-ethanol, 2-ethoxy-ethanol, 2-butoxy-ethanol, 2-(2-methoxy-ethoxy)-ethanol, 2-(2-ethoxy-ethoxy)-ethanol, 2-(2-butoxy-ethoxy)-ethanol); ethers (e.g., diethyl ether, di-isopropyl ether, dibutyl ether, 1,2-dimethoxy-ethane, 1,2-diethoxy-ethane, 1-methoxy-2-(2-methoxy-ethoxy)-ethane, 1-ethoxy-2-(2-ethoxy-ethoxy)-ethane, tetrahydrofuran, 1,4-dioxane); ketones (e.g., acetone, methyl ethyl ketone); esters (methyl acetate, ethyl acetate); nitrogen-containing solvents (e.g., formamide, *N,N*-dimethylformamide, acetonitrile, *N*-methylpyrrolidone, pyridine, quinoline, nitrobenzene); sulfur-containing solvents (e.g., carbon disulfide, dimethyl sulfoxide, tetrahydro-thiophene-1,1,-dioxide); and phosphorus-containing solvents (e.g., hexamethylphosphoric triamide).

[0120] In the schemes, below, substituent identifiers (e.g., α , β , m, R^5 , R^6 , R^7 , R^9 , R^{10} , R^{11} , R^a , R^b , X^1 , X^2 , X^3 , X^4 and X^8) are as defined above for Formula 1. As mentioned earlier, some of the starting materials and intermediates may include protecting groups, which are removed prior to the final product. In such cases, the substituent identifier refers to moieties defined in Formula 1 and to those moieties with appropriate protecting groups. For example, a starting material or intermediate in the synthetic methods may include a potentially reactive (secondary) amine. In such cases, the amine would include the moiety with or without, say, a Boc or Cbz group attached to the amine.

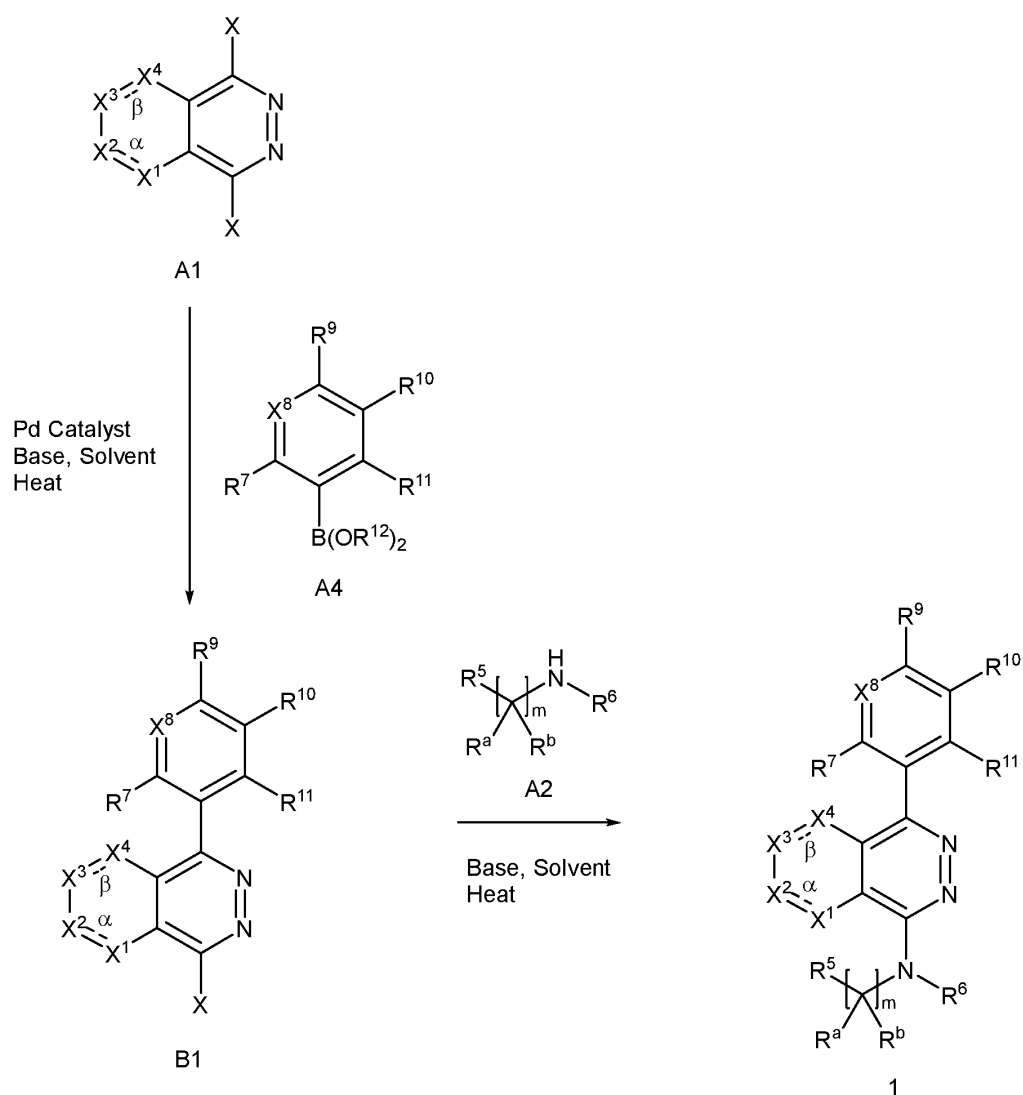
[0121] Schemes A and B show general methods for preparing compounds of Formula 1. In accordance with Scheme A, a 1,4-dihalophthalazine derivative or analog (A1 in which, e.g., X is Cl) is reacted with an amine (A2) in the presence of a base (e.g., DIPEA, K_2CO_3 , etc.) and solvent (e.g., ACN, DMSO, NMP, etc.) at elevated temperature (e.g., 80°C to 150°C) to give a halophthalazine amine (A3). The amine (A3) is subsequently reacted with a diboronic acid or ester (A4 in which, e.g., each R^{12} is H or C_{1-4} alkyl) in the presence of a palladium catalyst (e.g., $Pd(PPh_3)_4$, $Pd(dppf)Cl_2$, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, AmPhos $PdCl_2$, XPhos $PdCl_2$, etc.), base (e.g., Na_2CO_3 , K_2CO_3 , Cs_2CO_3 , KF, etc.) and one or more solvents (e.g., 1,4-dioxane, DMF, ACN, EtOH, H_2O , etc.) at elevated temperature (e.g., 50-110°C) to give the compound of Formula 1, directly or indirectly, e.g., after removal of protecting groups, further elaboration of functional groups, separation of stereoisomers or regioisomers, etc.

[0122] Alternatively, as shown in Scheme B, the 1,4-dihalophthalazine derivative or analog (A1) may be first reacted with the diboronic acid or ester (A4) in the presence of a palladium catalyst, base and solvent as noted for Scheme A. The resulting aromatic-substituted halophthalazine (B1) is then reacted with the amine (A2) in the presence of a base and solvent at elevated temperature, as described for Scheme A, to give the compound of Formula 1, either directly or after removal of protecting groups, further elaboration of functional groups, separation of stereoisomers or regioisomers, etc.

[0123] The methods depicted in the schemes may be varied as desired. For example, protecting groups may be added or removed and products may be further elaborated via, for example, alkylation, acylation, hydrolysis, oxidation, reduction, amidation, sulfonation, alkylation, and the like to give the desired final product. Furthermore, any intermediate or final product which comprises mixture of stereoisomers may be optionally purified by chiral column chromatography (e.g., supercritical fluid chromatography) or by derivatization with optically-pure reagents as described above to give a desired stereoisomer.



Scheme A



Scheme B

[0124] Compounds of Formula 1, which include compounds named above, and their pharmaceutically acceptable complexes, salts, solvates and hydrates, should be assessed for their biopharmaceutical properties, such as solubility and solution stability across pH, permeability, and the like, to select an appropriate dosage form and route of administration. Compounds that are intended for pharmaceutical use may be administered as crystalline or amorphous products, and may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, evaporative drying, microwave drying, or radio frequency drying.

[0125] Compounds of Formula 1 may be administered alone or in combination with one another or with one or more pharmacologically active compounds which are different than the compounds of Formula 1. Generally, one or more of these compounds are administered as a pharmaceutical composition (a formulation) in association with one or more pharmaceutically acceptable excipients. The choice of excipients depends on the mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form, among other things. Useful pharmaceutical compositions and methods for their preparation may be found, for example, in A. R. Gennaro (ed.), *Remington: The Science and Practice of Pharmacy* (20th ed., 2000).

[0126] Compounds of Formula 1 may be administered orally. Oral administration may involve swallowing in which case the compound enters the bloodstream via the gastrointestinal tract. Alternatively, or additionally, oral administration may involve mucosal administration (e.g., buccal, sublingual, supralingual administration) such that the compound enters the bloodstream through the oral mucosa.

[0127] Formulations suitable for oral administration include solid, semi-solid and liquid systems such as tablets; soft or hard capsules containing multi- or nano-particulates, liquids, or powders; lozenges which may be liquid-filled; chews; gels; fast dispersing dosage forms; films; ovules; sprays; and buccal or mucoadhesive patches. Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules (made, e.g., from gelatin or hydroxypropylmethylcellulose) and typically comprise a carrier (e.g., water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil) and one or more emulsifying agents, suspending agents or both. Liquid formulations may also be prepared by the reconstitution of a solid (e.g., from a sachet).

[0128] Compounds of Formula 1 may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Liang and Chen, *Expert Opinion in Therapeutic Patents* (2001) 11(6):981-986.

[0129] For tablet dosage forms, depending on dose, the active pharmaceutical ingredient (API) may comprise from about 1 wt% to about 80 wt% of the dosage form or more typically from about 5 wt% to about 60 wt% of the dosage form. In addition to the API, tablets may include one or more disintegrants, binders, diluents, surfactants, glidants, lubricants, anti-oxidants, colorants, flavoring agents, preservatives, and taste-masking agents. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium

carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, C₁₋₆ alkyl-substituted hydroxypropylcellulose, starch, pregelatinized starch, and sodium alginate. Generally, the disintegrant will comprise from about 1 wt% to about 25 wt% or from about 5 wt% to about 20 wt% of the dosage form.

[0130] Binders are generally used to impart cohesive qualities to a tablet formulation.

Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinized starch, hydroxypropylcellulose and hydroxypropylmethylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

[0131] Tablets may also include surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from about 0.2 wt% to about 5 wt% of the tablet, and glidants may comprise from about 0.2 wt% to about 1 wt% of the tablet.

[0132] Tablets may also contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulfate. Lubricants may comprise from about 0.25 wt% to about 10 wt% or from about 0.5 wt% to about 3 wt% of the tablet.

[0133] Tablet blends may be compressed directly or by roller compaction to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tableting. If desired, prior to blending one or more of the components may be sized by screening or milling or both. The final dosage form may comprise one or more layers and may be coated, uncoated, or encapsulated. Exemplary tablets may contain up to about 80 wt% of API, from about 10 wt% to about 90 wt% of binder, from about 0 wt% to about 85 wt% of diluent, from about 2 wt% to about 10 wt% of disintegrant, and from about 0.25 wt% to about 10 wt% of lubricant. For a discussion of blending, granulation, milling, screening, tableting, coating, as well as a description of alternative techniques for preparing drug products, see A. R. Gennaro (ed.), *Remington: The Science and Practice of Pharmacy* (20th ed., 2000); H. A. Lieberman et al. (ed.), *Pharmaceutical Dosage Forms: Tablets, Vol. 1-3* (2d ed., 1990); and D. K. Parikh & C. K. Parikh, *Handbook of Pharmaceutical Granulation Technology, Vol. 81* (1997).

[0134] Consumable oral films for human or veterinary use are pliable water-soluble or water-swellaable thin film dosage forms which may be rapidly dissolving or mucoadhesive. In addition to the API, a typical film includes one or more film-forming polymers, binders, solvents, humectants, plasticizers, stabilizers or emulsifiers, viscosity-modifying agents, and solvents. Other film ingredients may include anti-oxidants, colorants, flavorants and flavor enhancers, preservatives, salivary stimulating agents, cooling agents, co-solvents (including oils), emollients, bulking agents, anti-foaming agents, surfactants, and taste-masking agents. Some components of the formulation may perform more than one function.

[0135] In addition to dosing requirements, the amount of API in the film may depend on its solubility. If water soluble, the API would typically comprise from about 1 wt% to about 80 wt% of the non-solvent components (solutes) in the film or from about 20 wt% to about 50 wt% of the solutes in the film. A less soluble API may comprise a greater proportion of the composition, typically up to about 88 wt% of the non-solvent components in the film.

[0136] The film-forming polymer may be selected from natural polysaccharides, proteins, or synthetic hydrocolloids and typically comprises from about 0.01 wt% to about 99 wt% or from about 30 wt% to about 80 wt% of the film.

[0137] Film dosage forms are typically prepared by evaporative drying of thin aqueous films coated onto a peelable backing support or paper, which may be carried out in a drying oven or tunnel (e.g., in a combined coating-drying apparatus), in lyophilization equipment, or in a vacuum oven.

[0138] Useful solid formulations for oral administration may include immediate release formulations and modified release formulations. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted-, and programmed-release. For a general description of suitable modified release formulations, see US Patent No. 6,106,864. For details of other useful release technologies, such as high energy dispersions and osmotic and coated particles, see Verma et al, *Pharmaceutical Technology On-line* (2001) 25(2):1-14.

[0139] Compounds of Formula 1 may also be administered directly into the blood stream, muscle, or an internal organ of the subject. Suitable techniques for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial, and subcutaneous administration. Suitable devices for parenteral administration include needle injectors, including microneedle injectors, needle-free injectors, and infusion devices.

[0140] Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (e.g., pH of from about 3 to about 9). For some applications, however, compounds of Formula 1 may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water. The preparation of parenteral formulations under sterile conditions (e.g., by lyophilization) may be readily accomplished using standard pharmaceutical techniques.

[0141] The solubility of compounds which are used in the preparation of parenteral solutions may be increased through appropriate formulation techniques, such as the incorporation of solubility-enhancing agents. Formulations for parenteral administration may be formulated to be immediate or modified release. Modified release formulations include delayed, sustained, pulsed, controlled, targeted, and programmed release. Thus, compounds of Formula 1 may be formulated as a suspension, a solid, a semi-solid, or a thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and semi-solids and suspensions comprising drug-loaded poly(DL-lactic-co-glycolic) acid (PLGA) microspheres.

[0142] Compounds of Formula 1 may also be administered topically, intradermally, or transdermally to the skin or mucosa. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibers, bandages and microemulsions. Liposomes may also be used. Typical carriers may include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Topical formulations may also include penetration enhancers. See, e.g., Finnin and Morgan, *J. Pharm. Sci.* 88(10):955-958 (1999).

[0143] Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (e.g. PowderjectTM and BiojectTM) injection. Formulations for topical administration may be formulated to be immediate or modified release as described above.

[0144] Compounds of Formula 1 may also be administered intranasally or by inhalation, typically in the form of a dry powder, an aerosol spray, or nasal drops. An inhaler may be used to administer the dry powder, which comprises the API alone, a powder blend of the API and a diluent, such as lactose, or a mixed component particle that includes the API and a phospholipid, such as phosphatidylcholine. For intranasal use, the powder may include a

bioadhesive agent, e.g., chitosan or cyclodextrin. A pressurized container, pump, sprayer, atomizer, or nebulizer, may be used to generate the aerosol spray from a solution or suspension comprising the API, one or more agents for dispersing, solubilizing, or extending the release of the API (e.g., EtOH with or without water), one or more solvents (e.g., 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane) which serve as a propellant, and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid. An atomizer using electrohydrodynamics may be used to produce a fine mist.

[0145] Prior to use in a dry powder or suspension formulation, the drug product is usually comminuted to a particle size suitable for delivery by inhalation (typically 90% of the particles, based on volume, having a largest dimension less than 5 microns). This may be achieved by any appropriate size reduction method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing, high pressure homogenization, or spray drying.

[0146] Capsules, blisters and cartridges (made, for example, from gelatin or hydroxypropylmethyl cellulose) for use in an inhaler or insufflator may be formulated to contain a powder mixture of the active compound, a suitable powder base such as lactose or starch, and a performance modifier such as L-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or monohydrated. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose, and trehalose.

[0147] A suitable solution formulation for use in an atomizer using electrohydrodynamics to produce a fine mist may contain from about 1 µg to about 20 mg of the API per actuation and the actuation volume may vary from about 1 µL to about 100 µL. A typical formulation may comprise one or more compounds of Formula 1, propylene glycol, sterile water, EtOH, and NaCl. Alternative solvents, which may be used instead of propylene glycol, include glycerol and polyethylene glycol.

[0148] Formulations for inhaled administration, intranasal administration, or both, may be formulated to be immediate or modified release using, for example, PGLA. Suitable flavors, such as menthol and levomenthol, or sweeteners, such as saccharin or sodium saccharin, may be added to formulations intended for inhaled/intranasal administration.

[0149] In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve that delivers a metered amount. Units are typically arranged to administer a metered dose or “puff” containing from about 10 µg to about 1000 µg of the API. The overall daily dose will typically range from about 100 µg to about 10 mg which may be administered in a single dose or, more usually, as divided doses throughout the day.

[0150] The active compounds may be administered rectally or vaginally, e.g., in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate. Formulations for rectal or vaginal administration may be formulated to be immediate or modified release as described above.

[0151] Compounds of Formula 1 may also be administered directly to the eye or ear, typically in the form of drops of a micronized suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, gels, biodegradable implants (e.g. absorbable gel sponges, collagen), non-biodegradable implants (e.g. silicone), wafers, lenses, and particulate or vesicular systems, such as niosomes or liposomes. The formulation may include one or more polymers and a preservative, such as benzalkonium chloride. Typical polymers include cross-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, cellulosic polymers (e.g., hydroxypropylmethylcellulose, hydroxyethylcellulose, methyl cellulose), and heteropolysaccharide polymers (e.g., gelatin gum). Such formulations may also be delivered by iontophoresis. Formulations for ocular or aural administration may be formulated to be immediate or modified release as described above.

[0152] To improve their solubility, dissolution rate, taste-masking, bioavailability, or stability, compounds of Formula 1 may be combined with soluble macromolecular entities, including cyclodextrin and its derivatives and polyethylene glycol-containing polymers. For example, API-cyclodextrin complexes are generally useful for most dosage forms and routes of administration. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the API, the cyclodextrin may be used as an auxiliary additive, i.e. as a carrier, diluent, or solubilizer. Alpha-, beta- and gamma-cyclodextrins are commonly used for these purposes. See, e.g., WO 91/11172, WO 94/02518, and WO 98/55148.

[0153] As noted above, one or more compounds of Formula 1, including compounds specifically named above, and their pharmaceutically active complexes, salts, solvates and hydrates, may be combined with each other or with one or more other active pharmaceutically active compounds to treat various diseases, conditions and disorders. In such cases, the active compounds may be combined in a single dosage form as described above or may be provided in the form of a kit which is suitable for coadministration of the compositions. The kit comprises (1) two or more different pharmaceutical compositions, at least one of which contains a compound of Formula 1; and (2) a device for separately

retaining the two pharmaceutical compositions, such as a divided bottle or a divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets or capsules. The kit is suitable for administering different types of dosage forms (e.g., oral and parenteral) or for administering different pharmaceutical compositions at separate dosing intervals, or for titrating the different pharmaceutical compositions against one another. To assist with patient compliance, the kit typically comprises directions for administration and may be provided with a memory aid.

[0154] For administration to human patients, the total daily dose of the claimed and disclosed compounds is typically in the range of about 0.1 mg to about 3000 mg depending on the route of administration. For example, oral administration may require a total daily dose of from about 1 mg to about 3000 mg, while an intravenous dose may only require a total daily dose of from about 0.1 mg to about 300 mg. The total daily dose may be administered in single or divided doses and, at the physician's discretion, may fall outside of the typical ranges given above. Although these dosages are based on an average human subject having a mass of about 60 kg to about 70 kg, the physician will be able to determine the appropriate dose for a patient (e.g., an infant) whose mass falls outside of this weight range.

[0155] As noted above, the compounds of Formula 1 may be used to treat diseases, disorders, and conditions for which inhibition of the NLRP3 inflammasome pathway is indicated, including diseases, disorders or conditions associated with a heterozygous gain of function mutation in the NLRP3 gene, such as a cryopyrin-associated periodic syndrome (CAPS). These may include neonatal-onset multisystem inflammatory disease (NOMID/CINCA), Muckle-Wells syndrome (MWS), and familial cold autoinflammatory syndrome (FCAS).

[0156] The compounds of Formula 1 may be used to treat neurodegenerative diseases, disorders, and conditions associated with NLRP3. These may include Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, prion disease, Alzheimer's disease, and other forms of dementia (i.e., major or mild neurocognitive disorders) associated with one or more medical conditions, including frontotemporal lobar degeneration, Lewy body disease, vascular disease, traumatic brain injury, substance or medication use, HIV infection, prion disease, Parkinson's disease, and Huntington's disease. The compounds of Formula 1 may also be used to treat major or mild neurocognitive disorders associated with depression, schizophrenia, bipolar disorder, and autism.

[0157] The claimed and disclosed compounds may be combined with one or more other pharmacologically active compounds or therapies to treat one or more disorders, diseases or conditions for which inhibition of the NLRP3 inflammasome pathway is indicated. Such combinations may offer significant therapeutic advantages, including fewer side effects, improved ability to treat underserved patient populations, or synergistic activity. For example, compounds of Formula 1, which include compounds specifically named above, and their pharmaceutically acceptable complexes, salts, solvates and hydrates, may be administered simultaneously, sequentially or separately in combination with one or more compounds or therapies for treating Alzheimer's disease, including beta-secretase inhibitors, gamma-secretase inhibitors, HMG-CoA reductase inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs, such as apazone, aspirin, celecoxib, diclofenac (with and without misoprostol), diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate sodium, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, choline and magnesium salicylates, salsalate, and sulindac), vitamin E, and anti-amyloid antibodies. Specific examples of compounds used to treat Alzheimer's disease include donepezil, rivastigmine, memantine, and galantamine.

[0158] In addition to drugs used to improve cognition, the compounds of Formula 1 may be combined with sedatives, hypnotics, anxiolytics, antipsychotics, tranquilizers, and other medications that are used in the treatment of Alzheimer's disease. For example, the compounds of Formula 1 may be combined with one or more agents for treating depression (antidepressants) and/or schizophrenia (atypical or typical antipsychotics) including amitriptyline, amoxapine, aripiprazole, asenapine, bupropion, chlordiazepoxide, citalopram, chlorpromazine, clozapine, desipramine, desvenlafaxine, doxepin, duloxetine, escitalopram, fluoxetine, fluoxetine, fluphenazine, haloperidol, iloperidone, imipramine, isocarboxazid, lamotrigine, levomilnacipran, lurasidone, mirtazapine, nefazodone, nortriptyline, olanzapine, paliperidone, paroxetine, perphenazine, phenelzine, protriptyline, quetiapine, risperidone, selegiline, sertraline, tranlycypromine, trazodone, trimipramine, venlafaxine, vilazodone, and vortioxetine, and ziprasidone.

[0159] Likewise, the compounds of Formula 1 may be combined with one or more agents for treating anxiety (anxiolytics) including benzodiazepines (alprazolam, chlordiazepoxide, clobazepam, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, prazepam, quazepam, temazepam, and triazolam), antihistamines

(hydroxyzine), non-benzodiazepines (eszopiclone, zaleplon, zolpidem, and zopiclone) and buspirone.

[0160] The compounds of Formula 1 may also be combined with one or more agents for treating epilepsy (antiepileptics or anticonvulsants) including acetazolamide, carbamazepine, clobazam, clonazepam, eslicarbazepine acetate, ethosuximide, gabapentin, lacosamide, lamotrigine, levetiracetam, nitrazepam, oxcarbazepine, perampanel, piracetam, phenobarbital, phenytoin, pregabalin, primidone, retigabine, rufinamide, sodium valproate, stiripentol, tiagabine, topiramate, vigabatrin, and zonisamide.

[0161] BIOLOGICAL ACTIVITY

[0162] The biological activity of the compound of Formula 1 with respect to NLRP3 may be determined using the following *in vitro* methods.

[0163] IL-1 β Assay (reported as IC₅₀)

[0164] Monocytic THP-1 cells (ATCC: TIB-202) are maintained in accordance with the provider's instructions in RPMI media (Life Technologies, Cat # A10491-01); RPMI is supplemented with 10% heat inactivated fetal bovine serum (Hyclone Cat # SH30396.03). The cells are differentiated into macrophages by the addition of 25 ng/mL IFN- γ (PeproTech, Cat # 300-02-100UG) for 24 hours at 37°C/5% CO₂. Media is exchanged with fresh media with no FBS, and the cells are treated with 50 ng/mL LPS (priming step) for 24 hours at 37°C/5% CO₂ (LPS-EK: Invivogen, Cat # tlr1-pek1ps). Media is exchanged with fresh media with no FBS. The cells are plated at 40,000 cells per well in 384-well flat-bottom cell culture plates (Costar 3764) containing compounds (added in 1:1000) in a 1:3.16 serial dilution series in DMSO and are incubated for 30 minutes at 37°C/5% CO₂. The NLRP3 inflammasome is activated with the addition of 2.5 mM ATP (Sigma Cat # A3377) and the cells are incubated for 2 hours at 37°C/5% CO₂. At the end of the incubation period, 40 μ L supernatant is removed, and IL-1 β levels are monitored using an ELISA (Human IL-1 β ELISA, R&D systems, Cat # DY201) in accordance with the manufacturer's instructions.

[0165] Description of the TNF- α Assay (reported as IC₅₀)

[0166] Monocytic THP-1 cells (ATCC: TIB-202) are maintained in accordance with the provider's instructions in RPMI media (Life Technologies, Cat # A10491-01); RPMI is supplemented with 10% heat inactivated fetal bovine serum (Hyclone Cat # SH30396.03). The cells are differentiated into macrophages by the addition of 25 ng/mL IFN- γ for 24 hours at 37°C/5% CO₂. Media is exchanged with fresh media with no FBS. The cells are plated at 40,000 cells per well in 384-well flat-bottom cell culture plates (Costar 3764) containing

compounds (added in 1:1000) in a 1:3.16 serial dilution series in DMSO and are incubated for 30 minutes at 37°C/5% CO₂. The NF-κB pathway is activated with the addition of 50 ng/mL LPS and the cells are incubated for 3 hours at 37°C/5% CO₂. At the end of the incubation period, supernatant (40 μL) is removed, and IL-1β levels are monitored using an ELISA (Human TNF-α ELISA, R&D systems, Cat # DY210) according to the manufacturer's instructions.

[0167] Data Interpretation

[0168] The IC₅₀ values are calculated from a plot of percentage of inhibition versus the inhibitor concentration by a logistics curve fit according to: $Y = [\text{Bottom} + (\text{Top} - \text{Bottom})] / (1 + 10^{[(\text{Log IC}_{50} - X) \cdot \text{Hill Slope}]}$, where Y is the % inhibition at the inhibitor concentration, X, “Bottom” is the lowest inhibition value, i.e. 0 %, “Top” is the maximum inhibition value, i.e. 100 %, and the “Hill Slope” describes the slope of the sigmoidal curve between the “Bottom” and “Top” values. The curve fitting was conducted with internally developed software.

[0169] The following *in vitro* assay may be used to assess the ability of a compound of Formula 1 to enter the CNS through the blood-brain barrier.

[0170] MDCK-MDR1 Assay (reported as Apparent Permeability and Efflux Ratio)

[0171] Madine-Darby Canine Kidney (MDCK) cells transfected with Multidrug resistance protein 1 (MDR1) are maintained in accordance with the provider's instructions in Dulbecco's Modified Eagle media (DMEM, Fisher Scientific Cat# 10569044). DMEM is supplemented with 10% heat inactivated fetal bovine serum (Gibco Cat # 16000-044), Penicillin-Streptomycin (100 units/mL) (Gibco Cat# 15140122) and an inducer of P-gp, colchicine (200 nM) (Sigma Cat# C9754). The cells are seeded onto the apical side of HTS-Transwell-96 Plates (0.4 μm pore size, Corning Cat# 3381) at a density of 6.25×10^3 cells per well with 75 μL and 250 μL of DMEM media in apical and basolateral wells, respectively, and are incubated at 37°C/5% CO₂. Fresh DMEM media is exchanged in the apical and basolateral compartments after 72 hours and cells are allowed to grow into a monolayer for 144 hours before beginning the experimental incubation. Incubations are performed in Hanks' Balanced Salt Solution (HBSS, Fisher Scientific Cat# 14025134) at pH 7.4 with 1% Bovine Serum Albumin (Sigma, Cat# A9418) and 10 mM HEPES (Fisher Scientific, Cat# 15630080). DMEM media is removed and cells are rinsed with warm (37°C) HBSS. HBSS with test compound at 1 μM substrate concentration (0.1% v/v DMSO) is added to either the apical or basolateral compartment (75 μL or 250 μL, respectively) and blank HBSS buffer is

added to the compartment which lacks test compound in singlicate. The cells are incubated for 60 minutes at 37°C/5% CO₂. At the end of the incubation period, 50 µL of sample is removed from each receiver compartment and diluted into 150 µL of acetonitrile (Fisher Scientific, Cat# A996SK4) + 0.1% formic acid (Sigma, Cat# F0507). The samples are centrifuged at 2000 rcf for 10 minutes at 4°C, after which 100 µL of supernatant is transferred to a new microplate and diluted with 100 µL of HPLC grade water (Fisher Scientific, Cat# W64). Samples are analyzed using a triple quadrupole mass spectrometer API-5500QTrap (ABSciex, Serial No. AU23291006) along with associated autosampler and high performance liquid chromatography pump instrumentation optimized for the detection of test articles through a Kinetix 2.1 x 50 mm C18 100 Å column (Phenomenex, Cat# 00B-4605-AN).

[0172] Apparent permeability (P_{app}) values and efflux ratio are calculated using the following equations:

$$P_{app\ A-B} \text{ (nm} \times \text{sec}^{-1}\text{)} = \frac{\text{Conc}_{BL} \times 0.25 \times 10000}{A \times t \times 10} ;$$

$$P_{app\ B-A} \text{ (nm} \times \text{sec}^{-1}\text{)} = \frac{\text{Conc}_{AP} \times 0.075 \times 10000}{A \times t \times 10} ;$$

$$\text{ER} = \frac{P_{app\ B-A}}{P_{app\ A-B}} ;$$

where $P_{app\ A-B}$ is the apparent permeability from the apical well to basolateral well; $P_{app\ B-A}$ is the apparent permeability from the basolateral well to the apical well; Conc_{BL} is the basolateral well concentration; Conc_{AP} is the apical well concentration; A is the well surface area (cm²), which for the above assay is 0.143 cm²; t is the incubation time (seconds), which for the above assay is 3600 seconds; and ER is the P-gp mediated efflux ratio.

EXAMPLES

[0173] The following examples are intended to be illustrative and non-limiting and represent specific embodiments of the present invention.

[0174] ¹H Nuclear magnetic resonance (NMR) spectra were obtained for many of the compounds in the following examples. Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks, including s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). The following abbreviations are used for common solvents:

CDCl₃ (deuteriochloroform), DMSO-*d*₆ (deuterodimethylsulfoxide), CD₃OD (deuteromethanol), CD₃CN (deuteroacetonitrile), and THF-*d*₈ (deuterotetrahydrofuran). The mass spectra (*m/z* for [M+H]⁺) were recorded using electrospray ionization (ESI-MS) or atmospheric pressure chemical ionization (APCI-MS) mass spectrometry.

[0175] Where indicated, intermediate preparations and example compounds are purified by HPLC. Tables 1 to 3 list the column, mobile phases and gradients used for some of the HPLC separations.

[0176] TABLE 1: HPLC Method A

Column	Phenomenex Gemini® C18
Mobile Phase	ACN (0.035% TFA) and water (0.005% TFA)
Gradient	10% to 100% ACN (unless indicated otherwise)

[0177] TABLE 2: HPLC Method B

Column	Xtimate C18; Boston Green ODS; Welch Xtimate C18; Waters Xbridge BEH C18; YMC-Triart Prep C18; Phenomenex Gemini-NX
Mobile Phase	Water (0.225% FA) and ACN
Gradient	15% to 45% ACN gradient over 10 minutes (unless indicated otherwise)

[0178] TABLE 3: HPLC Method C

Column	Phenomenex Gemini® C18; Waters 2525 or 2545; Boston Prime C18; Phenomenex Gemini-NX C18
Mobile Phase	10 mM NH ₄ HCO ₃ in water and ACN (pH=9.5-10) or water (0.05% NH ₃ H ₂ O + 10mM NH ₄ HCO ₃) and ACN
Gradient	55% to 85% ACN (unless indicated otherwise)

[0179] The preparations and examples may employ supercritical fluid chromatography (SFC) to separate enantiomers. Table 4 lists equipment, materials, and conditions for some of the SFC separations.

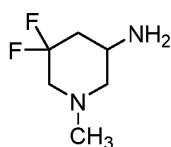
[0180] TABLE 4: SFC Method

Column	OD-H (21 mm x 250 mm) 5 micron or AS-H column with 30% isopropyl alcohol
Mobile Phase	CO ₂ and EtOH + 0.05% DEA (diethyl amine) or CO ₂ and MeOH + 0.05% DEA

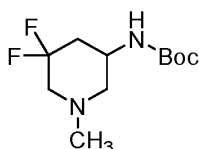
[0181] Besides HPLC, some of the preparations and examples may employ flash chromatography or preparative thin layer chromatography (TLC). Preparative TLC is typically carried out on silica gel 60 F₂₅₄ plates.

[0182] After isolation by chromatography, the solvent may be removed and the product dried in a centrifugal evaporator (e.g., GeneVacTM), rotary evaporator, evacuated flask, etc. Reactions in an inert (e.g., nitrogen) or reactive (e.g., H₂) atmosphere are typically carried out at a pressure of about 1 atmosphere (14.7 psi).

[0183] PREPARATION 1: 5,5-difluoro-1-methylpiperidin-3-amine



[0184] STEP 1: *tert*-butyl (5,5-difluoro-1-methylpiperidin-3-yl)carbamate

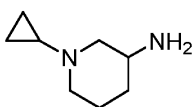


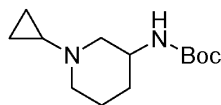
[0185] A mixture of *tert*-butyl (5,5-difluoropiperidin-3-yl)carbamate (500 mg, 2.12 mmol) and aqueous formaldehyde (343.49 mg, 4.23 mmol, 315.12 μ L, 37% purity) in THF (1 mL) was stirred at 25°C for 1 hour. Formic acid (203.34 mg, 4.23 mmol) was added drop-wise and the mixture was stirred at 70°C for 1 hour. The reaction mixture was quenched with NH₃.H₂O (5 mL) and concentrated under reduced pressure. The residue was purified by flash chromatography (ISCO® SepaFlash® 12 g silica gel column) using a gradient of 0 to 20% DCM in MeOH (35 mL/min) to give the title compound (310 mg, crude). ESI-MS m/z [M+H]⁺ 251.1.

[0186] STEP 2: 5,5-difluoro-1-methylpiperidin-3-amine

[0187] A mixture of *tert*-butyl (5,5-difluoro-1-methylpiperidin-3-yl)carbamate (310 mg, 1.24 mmol) and HCl in dioxane (4 M, 5 mL) was stirred at 20°C for 15 hours and then concentrated under reduced pressure. The resulting residue was triturated with EtOAc (15 mL) for 30 minutes and filtered. The filter cake was dried under vacuum to give an HCl salt of the title compound as a colorless oil (240 mg, crude). ESI-MS m/z [M+H]⁺ 151.1

[0188] PREPARATION 2: 1-cyclopropylpiperidin-3-amine

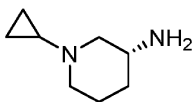
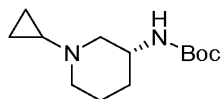


[0189] STEP 1: *tert*-butyl (1-cyclopropylpiperidin-3-yl)carbamate

[0190] To a mixture of *tert*-butyl piperidin-3-ylcarbamate (3 g, 14.98 mmol) in THF (72 mL) and MeOH (8.1 mL) were added molecular sieve 4Å (3 g) and (1-ethoxycyclopropoxy)trimethylsilane (7.83 g, 44.94 mmol, 9.03 mL), followed by acetic acid (10.79 g, 179.75 mmol, 10.28 mL) and NaBH₃CN (2.82 g, 44.94 mmol). The mixture was stirred at 65°C for 16 hours. The resulting suspension was filtered and concentrated. The crude product was diluted with aq NaHCO₃ (50 mL) and extracted with DCM (100 mL x 3). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure and the resulting residue was purified by column chromatography (DCM/MeOH = 1:0 to 10:1). The title compound was obtained as a colorless oil (6.5 g, 90%). ¹H NMR (400 MHz, CD₃Cl) δ ppm 4.92 - 5.27 (m, 1 H), 3.73 (br s, 1 H), 2.49 - 2.81 (m, 4 H), 1.67 (br s, 4 H), 1.55 (br s, 1 H), 1.45 (s, 9 H), 0.47 (br d, *J*=6.27 Hz, 4 H).

[0191] STEP 2: 1-cyclopropylpiperidin-3-amine

[0192] To a mixture of *tert*-butyl (1-cyclopropylpiperidin-3-yl)carbamate (4.9 g, 20.39 mmol) was added HCl in dioxane (4 M, 50.97 mL) in one portion at 25°C under N₂. The mixture was stirred at 25°C for 1 hour. Excess HCl/dioxane was removed under reduced pressure to give a yellow solid, which was triturated with EtOAc (80 mL). The solids were collected by filtration and dried under vacuum to give the dihydrochloride salt of the title compound as a white solid (2.8 g, 64%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.65 - 0.96 (m, 2 H), 1.02 - 1.24 (m, 2 H), 1.45 - 1.69 (m, 1 H), 1.90 (br d, *J*=3.26 Hz, 2 H), 2.03 - 2.20 (m, 1 H), 2.84 - 3.10 (m, 1 H), 2.89 - 3.00 (m, 1 H), 3.40 - 3.52 (m, 1 H), 3.45 (br d, *J*=11.80 Hz, 1 H), 3.61 (br d, *J*=9.03 Hz, 2 H), 8.70 (br s, 3 H), 11.49 (br s, 1 H).

[0193] PREPARATION 3: (*R*)-1-cyclopropylpiperidin-3-amine**[0194]** STEP 1: *tert*-butyl (*R*)-(1-cyclopropylpiperidin-3-yl)carbamate

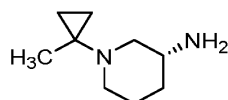
[0195] To *tert*-butyl (*R*)-piperidin-3-ylcarbamate (3 g, 14.98 mmol) in THF (72 mL) and MeOH (8.1 mL) were added molecular sieve 4Å (3 g, 14.98 mmol), (1-

ethoxycyclopropoxy)trimethylsilane (7.83 g, 44.94 mmol, 9.03 mL), acetic acid (10.79 g, 179.75 mmol, 10.28 mL) and NaBH₃CN (2.82 g, 44.94 mmol). The mixture was stirred at 65°C for 16 hours. LC-MS showed the desired product was formed as the major component and TLC (DCM/MeOH = 10:1) showed the reaction was complete (R_f for desired product = 0.43). The suspension was filtered and concentrated. The crude was diluted with aq NaHCO₃ (50 mL) and extracted with DCM (100 mL x 3). The organic layers were combined, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂, DCM/MeOH = 1:0 to 10:1) to give an HCl salt of the title compound as a white solid (3.5 g, 97%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.27 (br s, 2 H), 0.39 (br d, $J=3.51$ Hz, 2 H), 1.04 - 1.20 (m, 1 H), 1.37 (s, 9 H), 1.52 - 1.72 (m, 3 H), 1.87 - 2.12 (m, 2 H), 2.68 - 2.95 (m, 2 H), 3.21 - 3.32 (m, 1 H), 6.51 - 6.79 (m, 1 H); ESI-MS m/z [M+H]⁺ 241.2.

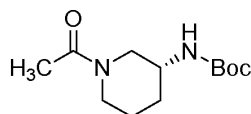
[0196] STEP 2: (*R*)-1-cyclopropylpiperidin-3-amine

[0197] To *tert*-butyl (*R*)-(1-cyclopropylpiperidin-3-yl)carbamate (0.5 g, 2.08 mmol) was added HCl in dioxane (4 M, 10 mL). The mixture was stirred at 25°C for 2 hours. LC-MS showed the starting material was consumed. The reaction mixture was concentrated under reduced pressure to give an HCl salt of the title compound (350 mg, 95.2%) which was used without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.81 (br d, $J=6.48$ Hz, 2 H), 1.04 - 1.24 (m, 2 H), 1.46 - 1.67 (m, 1 H), 1.89 (br s, 2 H), 2.00 - 2.14 (m, 1 H), 2.79 - 3.20 (m, 4 H), 3.54 - 3.71 (m, 1 H), 8.59 (br s, 2 H); ESI-MS m/z [M+H]⁺ 141.1.

[0198] PREPARATION 4: (*R*)-1-(1-methylcyclopropyl)piperidin-3-amine



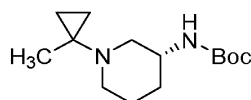
[0199] STEP 1: *tert*-butyl (*R*)-(1-acetylpiperidin-3-yl)carbamate



[0200] To a mixture of *tert*-butyl (*R*)-piperidin-3-ylcarbamate (1 g, 4.99 mmol) and DIPEA (1.94 g, 14.98 mmol, 2.61 mL) in DCM (15 mL) was added Ac₂O (560.71 mg, 5.49 mmol, 514.42 μ L). The mixture was stirred at 20°C for 12 hours. TLC (DCM/MeOH = 10:1) indicated the starting material was totally consumed (R_f = 0.25) and one main new spot had formed (R_f = 0.53). The mixture was washed with H₂O (20 mL) and concentrated *in vacuo*, and the resulting residue was purified by flash chromatography (ISCO® SepaFlash® 24 g

silica gel column) using a gradient of 0 to 3% MeOH in DCM (35 mL/min). The title compound was obtained as a white solid (1 g, 83%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.38 (m, 11 H), 1.59 - 1.83 (m, 2 H), 1.90 - 2.02 (m, 3 H), 2.42 (dd, *J*=12.1, 10.2 Hz, 1 H), 2.89 - 3.09 (m, 1 H), 3.18 - 3.30 (m, 1 H), 3.59 (br t, *J*=13.3 Hz, 1 H), 3.71 - 4.17 (m, 1 H), 6.75 - 7.06 (m, 1 H).

[0201] STEP 2: *tert*-butyl (*R*)-(1-(1-methylcyclopropyl)piperidin-3-yl)carbamate

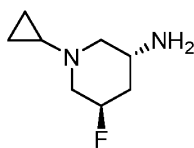


[0202] To a solution of *tert*-butyl (*R*)-(1-acetyl)piperidin-3-yl)carbamate (900 mg, 3.71 mmol) and Ti(*i*-PrO)₄ (2.11 g, 7.43 mmol, 2.19 mL) in THF (15 mL) was added dropwise EtMgBr (3 M, 6.19 mL) at 0°C. The mixture was stirred at 20°C for 12 hours. TLC (EtOAc/MeOH = 20:1) indicated about 40% of starting material remained (*R*_f = 0.68) and one major new spot was detected (*R*_f = 0.66). The reaction mixture was quenched with H₂O (2 mL) and filtered. The filtrate was concentrated *in vacuo* and the resulting residue was purified by flash chromatography (ISCO® SepaFlash® 20 g silica gel column) using a gradient of 0 to 5% MeOH in DCM (35 mL/min). The title compound was obtained as a colorless gum (160 mg, 16.9%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.29 (br s, 2 H), 0.41 (br s, 2 H), 0.97 (s, 3 H), 1.03 - 1.23 (m, 2 H), 1.37 (s, 9 H), 1.48 - 1.74 (m, 2 H), 2.02 - 2.14 (m, 1 H), 2.18 - 2.29 (m, 1 H), 2.59 (br d, *J*=11.3 Hz, 1 H), 2.75 (br d, *J*=6.9 Hz, 1 H), 3.25 (br s, 1 H), 6.60 (br d, *J*=7.1 Hz, 1 H).

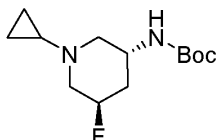
[0203] STEP 3: (*R*)-1-(1-methylcyclopropyl)piperidin-3-amine

[0204] A mixture of *tert*-butyl (*R*)-(1-(1-methylcyclopropyl)piperidin-3-yl)carbamate (160 mg, 629.01 μmol) in HCl/dioxane (4 M, 5 mL) was stirred at 20°C for 12 hours. TLC (EtOAc/MeOH = 20:1) indicated the starting material was consumed completely (*R*_f = 0.66). The mixture was concentrated *in vacuo* to give an HCl salt of the title compound as a yellow solid (120 mg, crude) which was used without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.72 - 0.82 (m, 2 H), 1.31 (s, 5 H), 1.51 - 1.66 (m, 1 H), 1.74 - 2.14 (m, 3 H), 3.06 - 3.33 (m, 3 H), 3.40 - 3.50 (m, 1 H), 3.62 - 3.94 (m, 1 H), 8.53 (br s, 2 H), 11.27 (br s, 1 H).

[0205] PREPARATION 5: (3*R*,5*R*)-1-cyclopropyl-5-fluoropiperidin-3-amine



[0206] STEP 1: *tert*-butyl ((3*R*,5*R*)-1-cyclopropyl-5-fluoropiperidin-3-yl)carbamate

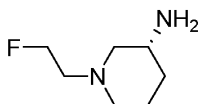


[0207] A solution of *tert*-butyl ((3*R*,5*R*)-5-fluoropiperidin-3-yl)carbamate (0.327 g, 1.50 mmol) in THF (5 mL), MeOH (5 mL) and acetic acid (1.0 mL) was treated with (1-ethoxycyclopropoxy)trimethylsilane (0.523 g, 3.00 mmol), followed by sodium cyanoborohydride (0.283 g, 4.50 mmol). The reaction mixture was stirred at 60°C overnight and then partitioned between EtOAc and saturated aqueous NaHCO₃. The aqueous phase was extracted with EtOAc. The organic layers were combined, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography with ELS detection (ISCO® RediSep Rf Gold® 40 g silica gel column) using a gradient of 0 to 100% EtOAc in heptanes. The product-containing fractions were evaporated to give the title compound as a white solid (0.333 g, 86%). ESI-MS *m/z* [M+H]⁺ 259.0.

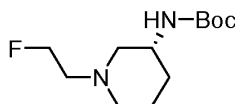
[0208] STEP 2: (3*R*,5*R*)-1-cyclopropyl-5-fluoropiperidin-3-amine

A solution of *tert*-butyl ((3*R*,5*R*)-1-cyclopropyl-5-fluoropiperidin-3-yl)carbamate (0.333 g, 1.29 mmol) in dioxane (6.45 mL) was treated with HCl (4 M in dioxane, 1.61 mL, 6.45 mmol). The reaction mixture was stirred at room temperature over the weekend. A small amount of MeOH was added to ensure the mixture was homogeneous. The reaction mixture was concentrated to dryness *in vacuo* to give the dihydrochloride salt of the title compound (351.5 mg crude, 298 mg theoretical, assumed quantitative and 84% purity) which was used without additional purification. ESI-MS *m/z* [M+H]⁺ 159.2.

[0209] PREPARATION 22: (*R*)-1-(2-fluoroethyl)piperidin-3-amine



[0210] STEP 1: *tert*-butyl (*R*)-(1-(2-fluoroethyl)piperidin-3-yl)carbamate

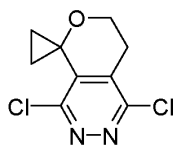


[0211] To a mixture of *tert*-butyl (*R*)-piperidin-3-ylcarbamate (15 g, 74.90 mmol) and 1-bromo-2-fluoroethane (19.02 g, 149.79 mmol) in ACN (80 mL) were added NaI (5.61 g, 37.45 mmol) and K₂CO₃ (51.76 g, 374.48 mmol). The mixture was stirred at 15°C for 12 hours and then diluted with H₂O (150 mL) and extracted with EtOAc (200 mL x 2). The organic layers were combined, washed with brine (200 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (ISCO® SepaFlash® 220 g silica gel column) using a gradient of 0 to 100% EtOAc in PE (85 mL/min). The title compound was obtained as a white solid (14.3 g, 77.5%). ESI-MS *m/z* [M+H]⁺ 247.1.

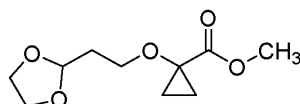
[0212] STEP 2: (*R*)-1-(2-fluoroethyl)piperidin-3-amine

[0213] A mixture of *tert*-butyl (*R*)-(1-(2-fluoroethyl)piperidin-3-yl)carbamate (7 g, 28.42 mmol) in HCl/dioxane (4 M, 20 mL) was stirred at 18°C for 12 hours and then concentrated under reduced pressure to give a dihydrochloride salt of the title compound as a white solid (6.1 g, 98% yield, 100% purity). ELSD-MS *m/z* [M+H]⁺ 147.1.

[0214] PREPARATION 56: 1',4'-dichloro-7',8'-dihydrospiro[cyclopropane-1,5'-pyrano[3,4-*d*]pyridazine]



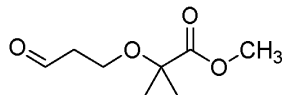
[0215] STEP 1: methyl 1-(2-(1,3-dioxolan-2-yl)ethoxy)cyclopropane-1-carboxylate



[0216] To a solution of NaH (2.07 g, 51.67 mmol, 60% purity) in DMF (100 mL) was added methyl 1-hydroxycyclopropane-1-carboxylate (5 g, 43.06 mmol) at 0°C. The mixture was stirred at 0°C for 0.5 hours. Next, 2-(2-bromoethyl)-1,3-dioxolane (19.49 g, 107.65 mmol, 12.91 mL) was added and the mixture was stirred at 25°C for 16 hours. TLC (PE/EtOAc = 5:1, R_f = 0.3 for desired product) showed one new spot. The reaction mixture was quenched with water (100 mL) and extracted with EtOAc (100 mL). The organic phase was washed with water (150 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated to dryness under reduce pressure. The residue was purified by silica gel column chromatography, using a gradient of 0 to 20% EtOAc in PE. The pure fractions were collected and the solvent was evaporated under vacuum to give the title compound as a

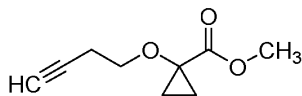
yellow oil (3.5 g). ^1H NMR (400MHz, CDCl_3) δ ppm 4.96 (t, $J=4.8$ Hz, 1H), 3.98 - 3.93 (m, 2H), 3.87 - 3.82 (m, 2H), 3.75 - 3.71 (m, 5H), 1.93 (dt, $J=5.2$, 6.8 Hz, 2H), 1.29 - 1.26 (m, 2H), 1.18 - 1.14 (m, 2H).

[0217] STEP 2: methyl 1-(3-oxopropoxy)cyclopropane-1-carboxylate



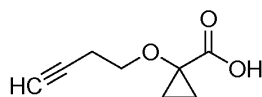
[0218] To a solution of methyl 1-(2-(1,3-dioxolan-2-yl)ethoxy)cyclopropane-1-carboxylate (2 g, 9.25 mmol) in THF (10 mL) was added aq HCl (1 M, 27.75 mL) at 25°C. The mixture was stirred at 25°C for 16 hours. TLC (PE/EtOAc = 5:1, R_f = 0.2 for desired product) showed one new spot. The reaction mixture was adjusted to pH greater than 7 and then extracted with EtOAc (15 mL). The organic phase was washed with water (15 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated to dryness under reduce pressure to give the title compound (crude) as a yellow oil (1.4 g, 88%). ^1H NMR (400MHz, CDCl_3) δ ppm 9.79 (t, $J=1.6$ Hz, 1H), 3.93 (t, $J=6.0$ Hz, 2H), 3.73 (s, 3H), 2.66 (dt, $J=1.6$, 6.0 Hz, 2H), 1.29 (t, $J=3.6$ Hz, 2H), 1.20 - 1.16 (m, 2H).

[0219] STEP 3: methyl 1-(but-3-yn-1-yloxy)cyclopropane-1-carboxylate



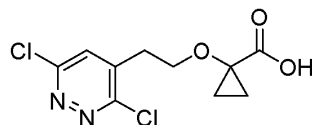
[0220] To a solution of dimethyl (1-diazo-2-oxopropyl)phosphonate (2.68 g, 13.94 mmol) in MeOH (3 mL) was added K_2CO_3 (963.23 mg, 6.97 mmol) at 0°C. The mixture was stirred at 0°C for 0.5 hours. Next, a solution of methyl 1-(3-oxopropoxy)cyclopropane-1-carboxylate (1.2 g, 6.97 mmol) in MeOH (2 mL) was added and the mixture was stirred at 25°C for 2 hours. TLC (PE/EtOAc = 5:1, R_f = 0.6 for desired product) showed one new spot. The mixture was diluted with DCM (15 mL) and the organic phase was washed with water (15 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated to dryness under reduced pressure. The residue was purified by silica gel column chromatography, using a gradient of 0 to 20% EtOAc in PE. The pure fractions were collected and the solvent evaporated under vacuum to give the title compound as a yellow oil (300 mg). ^1H NMR (400 MHz, CDCl_3) δ ppm 3.76 - 3.72 (m, 5H), 2.47 (dt, $J=2.4$, 6.8 Hz, 2H), 1.98 (t, $J=2.4$ Hz, 1H), 1.35 - 1.29 (m, 2H), 1.23 - 1.18 (m, 2H).

[0221] STEP 4: 1-(but-3-yn-1-yloxy)cyclopropane-1-carboxylic acid



[0222] To a solution of methyl 1-(but-3-yn-1-yloxy)cyclopropane-1-carboxylate (100 mg, 594.57 μmol) in MeOH (2 mL) were added LiOH.H₂O (99.80 mg, 2.38 mmol) and H₂O (1 mL) at 25°C. The mixture was stirred at 25°C for 12 hours. TLC (PE/EtOAc = 5:1, R_f = 0.2 for desired product) showed one new spot. The mixture was adjusted to pH < 6 with aq 1 N HCl and then extracted with DCM (5 mL). The organic phase was washed with water (5 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated to dryness under reduced pressure to give the title compound (crude) as a yellow oil (60 mg, 65%). ¹H NMR (400 MHz, CDCl₃) δ ppm 3.75 (t, *J*=6.8 Hz, 2H), 2.48 (dt, *J*=2.4, 6.8 Hz, 2H), 2.01 (t, *J*=2.4 Hz, 1H), 1.43 - 1.38 (m, 2H), 1.32 - 1.27 (m, 2H).

[0223] STEP 5: 1-(2-(3,6-dichloropyridazin-4-yl)ethoxy)cyclopropane-1-carboxylic acid



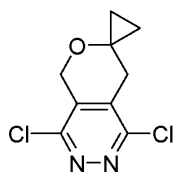
[0224] To a solution of 1-(but-3-yn-1-yloxy)cyclopropane-1-carboxylic acid (60 mg, 389.20 μmol) in toluene (1 mL) was added 3,6-dichloro-1,2,4,5-tetrazine (70.50 mg, 467.04 μmol) at 25°C. The mixture was stirred at 100°C for 2 hours. TLC (PE/EtOAc = 3:1, R_f = 0.2 for desired product) showed one new spot. The mixture was concentrated to dryness under reduce pressure and the residue was purified by silica gel column chromatography, using a gradient of 0 to 40% EtOAc in PE. The pure fractions were collected and the solvent was evaporated under vacuum to give the title compound as a red oil (40 mg). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.85 (s, 1H), 3.97 (t, *J*=5.6 Hz, 2H), 2.99 (t, *J*=5.6 Hz, 2H), 1.45 - 1.39 (m, 2H), 1.22 - 1.15 (m, 2H).

[0225] STEP 6: 1',4'-dichloro-7',8'-dihydrospiro[cyclopropane-1,5'-pyrano[3,4-*d*]pyridazine]

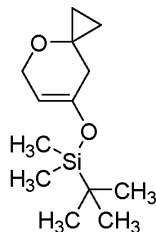
[0226] To a solution of 1-(2-(3,6-dichloropyridazin-4-yl)ethoxy)cyclopropane-1-carboxylic acid (120 mg, 433.05 μmol) in H₂O (5 mL) and acetone (5 mL) were added AgNO₃ (100 mg, 588.67 μmol), ammonium peroxydisulfate (1.6 M, 541.31 μL) and TFA (1 M, 108.26 μL) at 25°C. The mixture was stirred for 2 hours at 50°C. TLC (PE/EtOAc = 3:1, R_f = 0.4 for desired product) showed one new spot. The mixture was cooled to room temperature (25°C), poured into ice-cold saturated aqueous NaHCO₃ (100 mL) and then extracted with EtOAc (80

mL x 2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated to give a brown gum, which was purified by silica gel column chromatography, using a gradient of 0 to 30% PE in EtOAc. The pure fractions were collected and the solvent was evaporated under vacuum to give the title compound as a light-yellow solid (17 mg). ¹H NMR (400 MHz, CDCl₃) δ ppm 4.00 (t, *J*=5.6 Hz, 2H), 2.98 (t, *J*=5.6 Hz, 2H), 2.17 - 2.10 (m, 2H), 1.31 - 1.24 (m, 2H); ESI-MS *m/z* [M+H]⁺ 230.8.

[0227] PREPARATION 57: 1',4'-dichloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine]



[0228] STEP 1: ((4-oxaspiro[2.5]oct-6-en-7-yl)oxy)(*tert*-butyl)dimethylsilane

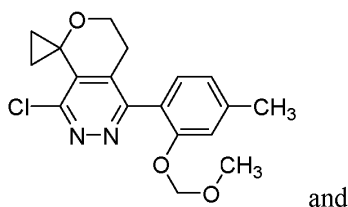


[0229] A mixture of 4-oxaspiro[2.5]octan-7-one (2.1 g, 16.65 mmol), TBSOTf (5.46 g, 20.66 mmol, 4.75 mL) and DIPEA (4.30 g, 33.29 mmol, 5.80 mL) in DCM (30 mL) was degassed and purged with N₂ (3 x) and then stirred at 25°C for 3 hours. TLC (PE/EtOAc = 3:1, stained by I₂) indicated the starting material was consumed and showed one major new spot with lower polarity. The mixture was diluted with water (50 mL) and DCM (100 mL). The aqueous and organic phases were separated. The organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated to give crude product (5.0 g) as a dark brown oil. The crude product was purified by flash chromatography (20 g silica gel column) using a gradient of 0 to 20% EtOAc in PE. The title compound was obtained as a light yellow oil (3.6 g, 90%). ¹H NMR (400 MHz, CDCl₃) δ ppm 4.27-4.81 (m, 1H), 3.70-3.97 (m, 2H), 1.97-2.10 (m, 2H), 0.77 (d, *J*=1.2 Hz, 9H), 0.61-0.71 (m, 2H), 0.27-0.42 (m, 2H), 0.00 (d, *J*=2.8 Hz, 6H).

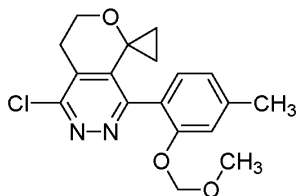
[0230] STEP 2: 1',4'-dichloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine]

[0231] Reactants ((4-oxaspiro[2.5]oct-6-en-7-yl)oxy)(*tert*-butyl)dimethylsilane (1.8 g, 7.49 mmol) and 3,6-dichloro-1,2,4,5-tetrazine (1.36 g, 8.98 mmol) were combined in toluene (40 mL) with stirring at 25°C. The mixture was stirred and heated to 105°C for 2 hours. LC-MS indicated the desired product was obtained. The mixture was concentrated to give a red solid (3.0 g). The product was purified by chromatography (SiO₂ column) using a gradient of 0 to 30% EtOAc in PE. The first batch of product (0.8 g) was combined with second (790 mg) and third batches (820 mg) and further purified by SFC (DAICEL CHIRALPAK® AD-10 μ m, 30 mm x 250 mm column) using a mobile phase of CO₂ and 35% Neu-ACN. The title compound was obtained as a light yellow solid (1.8 g, 69%). ¹H NMR (400 MHz, CDCl₃) δ ppm 4.47-4.86 (m, 2H), 2.86 (s, 2H), 1.00-1.14 (m, 2H), 0.56-0.76 (m, 2H); ESI-MS *m/z* [M+H]⁺ 230.6.

[0232] PREPARATION 58: 4'-chloro-1'-(2-(methoxymethoxy)-4-methylphenyl)-7',8'-dihydrospiro[cyclopropane-1,5'-pyrano[3,4-*d*]pyridazine]



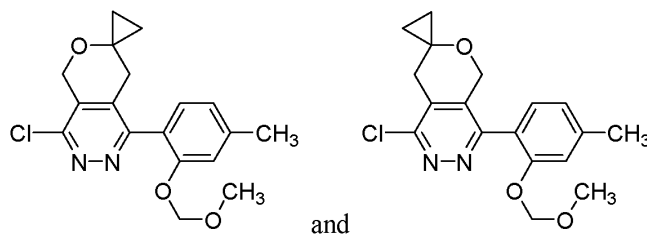
[0233] PREPARATION 59: 1'-chloro-4'-(2-(methoxymethoxy)-4-methylphenyl)-7',8'-dihydrospiro[cyclopropane-1,5'-pyrano[3,4-*d*]pyridazine]



[0234] To a mixture of 1',4'-dichloro-7',8'-dihydrospiro[cyclopropane-1,5'-pyrano[3,4-*d*]pyridazine] (200 mg, 865.51 μ mol) and 2-(2-(methoxymethoxy)-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (312.96 mg, 1.13 mmol) in dioxane (3 mL) and H₂O (0.75 mL) were added Cs₂CO₃ (1.13 g, 3.46 mmol) and Pd(dppf)Cl₂ (70.68 mg, 86.55 μ mol) in one portion. The mixture was stirred at 100°C for 1 hour. LC-MS showed the desired product was obtained. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by flash chromatography (ISCO® SepaFlash® 12 g silica gel column) using a gradient of 0 to 30% EtOAc in PE (25 mL/min). The title compound of Preparation 58 was obtained as a white solid (42 mg, 14% yield, 96.99% purity). ¹H NMR (400 MHz,

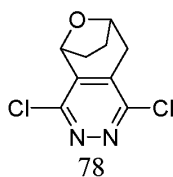
DMSO-*d*₆) δ ppm 1.15 - 1.28 (m, 2 H), 2.05 (br s, 1 H), 2.23 - 2.33 (m, 1 H), 2.42 (s, 3 H), 2.53 (br d, $J=17.73$ Hz, 1 H), 2.92 - 3.08 (m, 1 H), 3.38 (s, 3 H), 3.78 - 4.00 (m, 2 H), 5.11 (br d, $J=4.89$ Hz, 2 H), 6.97 (d, $J=7.70$ Hz, 1 H), 7.07 (s, 1 H), 7.18 (d, $J=7.58$ Hz, 1 H); ESI-MS m/z $[M+H]^+$ 347.0. The title compound of Preparation 59 was obtained as a yellow oil (55 mg, 16% yield, 85% purity). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.88 - 1.06 (m, 4 H), 2.40 (s, 3 H), 2.99 - 3.08 (m, 2 H), 3.38 (s, 3 H), 4.06 (q, $J=6.28$ Hz, 2 H), 5.02 - 5.14 (m, 2 H), 6.87 (d, $J=7.70$ Hz, 1 H), 6.98 - 7.04 (m, 2 H); ESI-MS m/z $[M+H]^+$ 347.0.

[0235] PREPARATION 60 and 61: 4'-chloro-1'-(2-(methoxymethoxy)-4-methylphenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] and 1'-chloro-4'-(2-(methoxymethoxy)-4-methylphenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine]



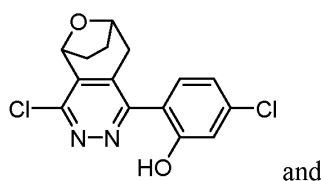
[0236] To a solution of 1',4'-dichloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (500 mg, 2.16 mmol) and 2-(2-(methoxymethoxy)-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (782.41 mg, 2.81 mmol) in dioxane (5 mL) and H₂O (1 mL) were added Cs₂CO₃ (2.82 g, 8.66 mmol) and Pd(dppf)Cl₂·CH₂Cl₂ (176.70 mg, 216.38 μ mol). The mixture was stirred at 80°C for 1 hour under N₂. LC-MS showed the desired product was obtained. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by flash chromatography (ISCO® SepaFlash® 24 g silica gel column) using a gradient of 0 to 30% EtOAc in PE (35 mL/min). A mixture of the title compounds was obtained as a yellow oil (416 mg). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.40 - 0.60 (m, 1 H), 0.65 - 0.77 (m, 1 H), 0.84 - 1.08 (m, 2 H), 2.23 - 2.38 (m, 1 H), 2.43 (s, 3 H), 2.79 - 3.11 (m, 1 H), 3.39 (d, $J=10.0$ Hz, 3 H), 4.28 - 4.52 (m, 1 H), 4.77 (br d, $J=2.3$ Hz, 1 H), 5.11 (d, $J=5.6$ Hz, 2 H), 6.99 (d, $J=7.5$ Hz, 1 H), 7.08 (s, 1 H), 7.23 (d, $J=7.6$ Hz, 1 H).

[0237] PREPARATION 62: 1,4-dichloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine

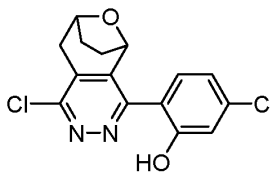


[0238] To a flask charged with toluene (100 mL) were added 8-oxabicyclo[3.2.1]octan-3-one (2500 mg, 19.8 mmol), 4-methylbenzenesulfonic acid monohydrate (38 mg, 0.198 mmol) and pyrrolidine (1.6 mL, 19.8 mmol). The mixture was stirred at room temperature for 0.5 hours. The solvent was removed by rotary evaporation and the mixture was transferred into a flask charged with 3,6-dichloro-1,2,4,5-tetrazine (2991 mg, 19.8 mmol) and toluene (100 mL). The reaction mixture was heated to 120°C and stirred for 0.5 hours. The reaction mixture was concentrated and then purified by flash chromatography (ISCO® SepaFlash® 80 g silica gel column) using an eluent of 100% DCM (24 mL/min) to give the title compound.

[0239] PREPARATION 63: 5-chloro-2-(4-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol

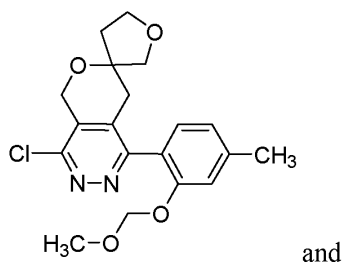


[0240] PREPARATION 64: 5-chloro-2-(1-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)phenol

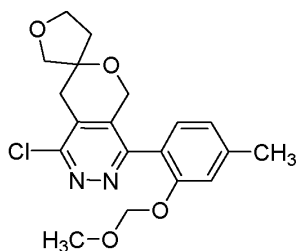


[0241] A mixture of 1,4-dichloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine (1500 mg, 6.5 mmol), Cs₂CO₃ (4.2 g, 13.0 mmol), Pd(dppf)Cl₂.CH₂Cl₂ (530 mg, 0.65 mmol) and (4-chloro-2-hydroxyphenyl)boronic acid (1.12 g, 6.5 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was stirred in a sealed tube on a metal heating block at 100°C for 30 minutes. The reaction mixture was purified by flash chromatography (ISCO® SepaFlash® 40 g silica gel column) using an eluent of 50% EtOAc in heptane (24 mL/min) to give the two title compounds.

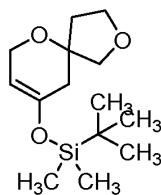
[0242] PREPARATION 65: *rac*-4'-chloro-1'-(2-(methoxymethoxy)-4-methylphenyl)-4,5,5',8'-tetrahydro-2*H*-spiro[furan-3,7'-pyrano[3,4-*d*]pyridazine]



[0243] PREPARATION 66: *rac*-1'-chloro-4'-(2-(methoxymethoxy)-4-methylphenyl)-4,5,5',8'-tetrahydro-2*H*-spiro[furan-3,7'-pyrano[3,4-*d*]pyridazine]

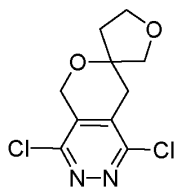


[0244] STEP 1: *tert*-butyl-(2,6-dioxaspiro[4.5]dec-8-en-9-yloxy)dimethylsilane



[0245] To a mixture of 2,6-dioxaspiro[4.5]decan-9-one (1.00 g, 6.40 mmol) and triethylamine (13 mL, 12.8 mmol) in DCM (16 mL) cooled to 0°C was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.5 mL, 6.72 mmol) dropwise. The mixture was stirred at room temperature overnight and then treated with water and extracted with DCM. The organic layers were washed with water and brine, dried over MgSO₄, and concentrated to give the title compound as a tan oil (crude). ESI-MS [M+H]⁺ calc'd for C₁₄H₂₆O₃Si 270.17; found 271.28.

[0246] STEP 2: 1',4'-dichloro-4,5,5',8'-tetrahydro-2*H*-spiro[furan-3,7'-pyrano[3,4-*d*]pyridazine]



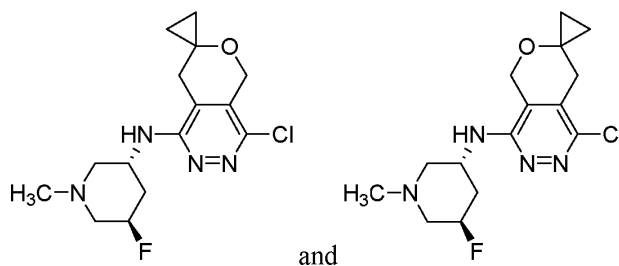
[0247] A mixture of 3,6-dichloro-1,2,4,5-tetrazine (0.83 g, 5.47 mmol) in toluene (8 mL) was cooled to 0°C. A solution of *tert*-butyl-(2,6-dioxaspiro[4.5]dec-8-en-9-

xyloxy)dimethylsilane (1.48 g, 5.47 mmol) in toluene (3 mL) was added dropwise. The mixture was heated at 120°C overnight and then filtered. The filtrate was concentrated and purified by normal phase silica gel column chromatography (40 g) eluting with a gradient of heptane/EtOAc (5:1 to 0:1). The combined fractions were concentrated to give the title compound (0.604 g, 42%). ESI-MS $[M+H]^+$ calc'd for $C_{10}H_{10}Cl_2N_2O_2$ 260.01; found 261.1.

[0248] STEP 3: *rac*-4'-chloro-1'-(2-(methoxymethoxy)-4-methylphenyl)-4,5,5',8'-tetrahydro-2*H*-spiro[furan-3,7'-pyrano[3,4-*d*]pyridazine] and *rac*-1'-chloro-4'-(2-(methoxymethoxy)-4-methylphenyl)-4,5,5',8'-tetrahydro-2*H*-spiro[furan-3,7'-pyrano[3,4-*d*]pyridazine]

[0249] A mixture of 1,4-dichlorospiro[5,8-dihydropyrano[3,4-*d*]pyridazine-7,3'-tetrahydrofuran] (374 mg, 1.43 mmol), Cs_2CO_3 (898 mg, 2.75 mmol), 2-(2-(methoxymethoxy)-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (306 mg, 1.10 mmol), $Pd(dppf)Cl_2$ (90 mg, 0.110 mmol), and 1,4-dioxane (6 mL) and water (1.5 mL) was purged with nitrogen for 5 minutes and then heated at 90°C under nitrogen for 4 hours. The mixture was diluted with water and extracted with EtOAc. The organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by normal phase silica-gel column (80 g) with a gradient of heptane/EtOAc (20% to 70%). The product-containing fractions were concentrated to give the two title compounds. Preparation 65 (123 mg, 29%), ESI-MS $[M+H]^+$ calc'd for $C_{19}H_{21}ClN_2O_4$ 376.12; found 377.3; and Preparation 66 (17 mg, 4%), ESI-MS $[M+H]^+$ calc'd for $C_{19}H_{21}ClN_2O_4$ 376.12; found 377.3.

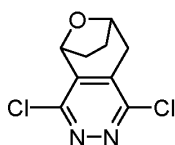
[0250] PREPARATION 68: 4'-chloro-*N*-((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-amine and 1'-chloro-*N*-((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-amine



[0251] To a solution of 1',4'-dichloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (550 mg, 2.38 mmol), (3*R*,5*R*)-5-fluoro-1-methyl-piperidin-3-amine (1.95 g, 9.52 mmol, 2*HCl*) in DMSO (10 mL) were added K_3PO_4 (3.03 g, 14.28 mmol) and BTMPO

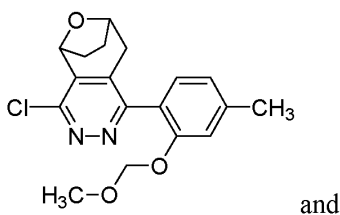
(300.07 mg, 714.04 μmol), CuI (181.32 mg, 952.06 μmol). The mixture was stirred at 120°C for 48 hours under N_2 . LC-MS showed 52% of desired mass was detected. The reaction was filtered and evaporated to dryness. The residue was purified by preparative HPLC (Xtimate C18-10 μm , 40 mm x 150 mm column) using a gradient of 0 to 26% ACN in water (with formic acid) to give a mixture of the title compounds as a black solid (420 mg, crude product). ESI-MS $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{15}\text{H}_{20}\text{ClFN}_4\text{O}$, 326.13; found, 327.1.

[0252] PREPARATION 69: 1,4-dichloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine

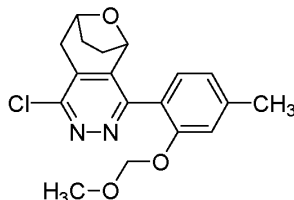


[0253] To a flask containing with 8-oxabicyclo[3.2.1]octan-3-one (2500 mg, 19.8 mmol), *p*-toluenesulfonic acid monohydrate (38 mg, 0.198 mmol) and pyrrolidine (1.6 mL, 19.8 mmol) was added to toluene (100 mL). The mixture was stirred at room temperature for half an hour. The solvent was removed by rotary evaporation and the mixture was then transferred into a flask charged with 3,6-dichloro-1,2,4,5-tetrazine (2991 mg, 19.8 mmol) and toluene (100 mL). The reaction was heated to 120°C and stirred for half an hour. The reaction mixture was concentrated and purified by flash chromatography (ISCO® SepaFlash® 80 g silica gel column) eluting with DCM (24 mL/min) to give the title compound.

[0254] PREPARATION 70: 4-chloro-1-(2-(methoxymethoxy)-4-methylphenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine

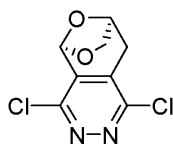


[0255] PREPARATION 71: 1-chloro-4-(2-(methoxymethoxy)-4-methylphenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine



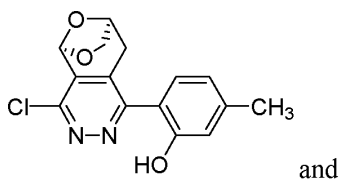
[0256] A mixture of 1,4-dichloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine (600 mg, 2.6 mmol), Cs₂CO₃ (1.69 g, 5.19 mmol), Pd(dppf)Cl₂.CH₂Cl₂ (212 mg, 0.26 mmol), and [2-(methoxymethoxy)-4-methyl-phenyl]boronic acid (0.509 g, 2.6 mmol) in 1,4-dioxane (13.6 mL) and water (3.4 mL) was stirred in a sealed tube on metal heating block at 100°C for 1 hour. The reaction mixture was purified by flash chromatography (ISCO® 40 g SepaFlash® silica gel column) eluting with 50% EtOAc in heptane (24 mL/min) to give the two title compounds.

[0257] PREPARATION 72: (5*R*,8*S*)-1,4-dichloro-5,7,8,9-tetrahydro-5,8-epoxyxepino[3,4-*d*]pyridazine

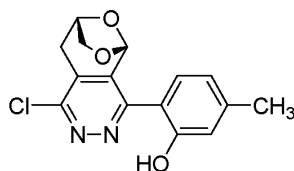


[0258] To a flask containing dihydrolevoglucosenone (2536 mg, 19.8 mmol), *p*-toluenesulfonic acid monohydrate (38 mg, 0.198 mmol) and pyrrolidine (1.6 mL, 19.8 mmol) was added to toluene (100 mL). The mixture was stirred at room temperature for half an hour. The solvent was removed by rotary evaporation and the mixture was transferred to a flask charged with 3,6-dichloro-1,2,4,5-tetrazine (2991 mg, 19.8 mmol) and toluene (100 mL). The reaction was heated to 120°C and stirred for half an hour. The reaction mixture was concentrated and purified by flash chromatography (ISCO® 80 g SepaFlash® silica gel column) eluting with DCM (24 mL/min) to give the title compound.

[0259] PREPARATION: 73: 2-((5*R*,8*S*)-4-chloro-5,7,8,9-tetrahydro-5,8-epoxyxepino[3,4-*d*]pyridazin-1-yl)-5-methylphenol

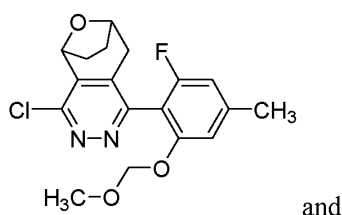


[0260] PREPARATION: 74: 2-((5*R*,8*S*)-1-chloro-5,7,8,9-tetrahydro-5,8-epoxyxepino[3,4-*d*]pyridazin-4-yl)-5-methylphenol

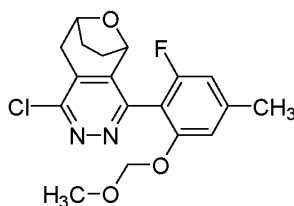


[0261] A mixture of 1,4-dichloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine (900 mg, 3.9 mmol), Cs₂CO₃ (3.1 g, 9.65 mmol), Pd(dppf)Cl₂.CH₂Cl₂ (315 mg, 0.39 mmol), and (2-hydroxy-4-methyl-phenyl)boronic acid (0.587 g, 3.9 mmol) in 1,4-dioxane (13.6 mL) and water (3.4 mL) was stirred in a sealed tube on metal heating block at 100°C for 1 hour. The reaction mixture was purified by flash chromatography (ISCO® 40 g SepaFlash® silica gel column) eluting with 50% EtOAc in heptane (24 mL/min) to give the two title compounds.

[0262] PREPARATION 75: 4-chloro-1-(2-fluoro-6-(methoxymethoxy)-4-methylphenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine

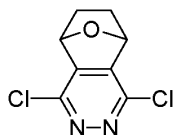


[0263] PREPARATION 76: 1-chloro-4-(2-fluoro-6-(methoxymethoxy)-4-methylphenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine



[0264] A mixture of 1,4-dichloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine (100 mg, 0.43 mmol), XPhos Palladacycle G4 (56 mg, 0.065 mmol), and 2-(2-fluoro-6-(methoxymethoxy)-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.128 g, 0.43 mmol) in THF (2.26 mL) and 0.5M K₃PO₄ (0.56 mL) was stirred in a sealed tube on metal heating block at 100°C for 1 hour. The reaction mixture was purified by flash chromatography (ISCO® 40 g SepaFlash® silica gel column) eluting with 50% EtOAc in heptane (24 mL/min) to give the two title compounds.

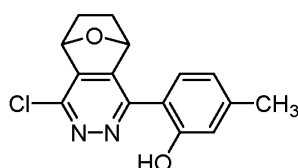
[0265] PREPARATION: 77: 1,4-dichloro-5,6,7,8-tetrahydro-5,8-epoxyphthalazine



[0266] A solution of *rac*-(1*S*,4*R*)-7-oxabicyclo[2.2.1]heptan-2-one (200 mg, 1.78 mmol) in toluene (8.9182 mL) was treated with pyrrolidine (0.15 mL, 1.78 mmol) and *p*-

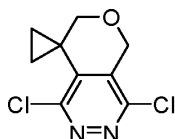
toluenesulfonic acid monohydrate (3.4 mg, 0.0178 mmol) and stirred for 30 minutes at room temperature. Next, 3,6-dichloro-1,2,4,5-tetrazine (296 mg, 1.96 mmol) was added in small portions. The reaction mixture was stirred at 120°C for 2 hours and subsequently concentrated under reduced pressure. The residue was purified by flash column chromatography (ISCO® 24 g RediSep® Gold column) using a gradient of 0-100% EtOAc in heptanes to give the title compound as an off-white solid (25 mg, 6.5%).

[0267] PREPARATION: 78: 2-(4-chloro-5,6,7,8-tetrahydro-5,8-epoxyphthalazin-1-yl)-5-methylphenol

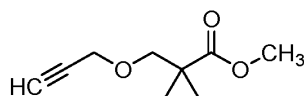


[0268] A mixture of 1,4-dichloro-5,6,7,8-tetrahydro-5,8-epoxyphthalazine (21.6 mg, 0.1 mmol), Cs₂CO₃ (65 mg, 0.2 mmol), Pd(dppf)Cl₂.CH₂Cl₂ (8.1 mg, 0.01 mmol), and (2-hydroxy-4-methyl-phenyl)boronic acid (0.015 g, 0.1 mmol) in 1,4-dioxane (0.5 mL) and water (0.13 mL) was stirred in a sealed tube on metal heating block at 100°C for 1 hour. The reaction mixture was purified by flash chromatography (ISCO® 40 g SepaFlash® silica gel column) eluting with 50% EtOAc in heptane (24 mL/min) to give the title compound.

[0269] PREPARATION 79: 1,4-dichlorospiro[5,7-dihydropyrano[3,4-*d*]pyridazine-8,1'-cyclopropane]



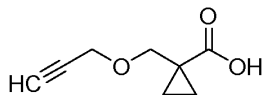
[0270] STEP 1: methyl 1-((prop-2-yn-1-yloxy)methyl)cyclopropane-1-carboxylate



[0271] To a mixture of methyl 1-(hydroxymethyl)cyclopropanecarboxylate (5 g, 38.42 mmol) and 3-bromoprop-1-yne (5.48 g, 46.10 mmol, 3.97 mL) in THF (50 mL) was added NaH (1.84 g, 46.10 mmol, 60% purity) at 0°C. The mixture was stirred at 0°C for 30 minutes and then at 60°C for 5 hours. TLC (PE/EtOAc = 3:1, R_f = 0.6 for desired product) indicated the starting alcohol was consumed completely. The mixture was quenched with H₂O (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by flash

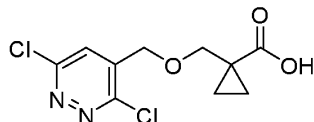
chromatography (ISCO® 40 g SepaFlash® silica gel column) using a gradient of 0 to 20% EtOAc in PE (45 mL/min) to give the title compound as a white solid (3.6 g, 56%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.89 - 0.97 (m, 2 H), 1.25 - 1.32 (m, 2 H), 2.42 (t, *J*=2.32 Hz, 1 H), 3.65 - 3.70 (m, 5 H), 4.19 (d, *J*=2.32 Hz, 2 H).

[0272] STEP 2: 1-((prop-2-yn-1-yloxy)methyl)cyclopropane-1-carboxylic acid



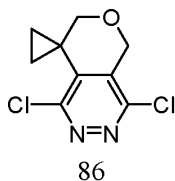
[0273] To a solution of ethyl 1-(prop-2-ynoxymethyl)cyclopropanecarboxylate (10 g, 54.88 mmol) in MeOH (80 mL) were added LiOH·H₂O (9.21 g, 219.52 mmol) and H₂O (40 mL). The mixture was stirred at 25°C for 12 hours. TLC (PE/EtOAc = 3:1, *R*_f = 0.3 for desired product) indicated the starting ester was consumed completely. The reaction mixture was acidified with 2 M HCl to pH=5-6 at 0°C, and extracted with EtOAc (30 x 5 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound as colorless oil (8.4 g, 89 % yield, 90% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.83 - 0.88 (m, 2 H), 1.05 - 1.09 (m, 2 H), 3.38 - 3.44 (m, 1 H), 3.54 (s, 2 H), 4.11 (d, *J*=2.20 Hz, 2 H), 12.16 (br s, 1 H).

[0274] STEP 3: 1-[(3,6-dichloropyridazin-4-yl)methoxymethyl]cyclopropanecarboxylic acid



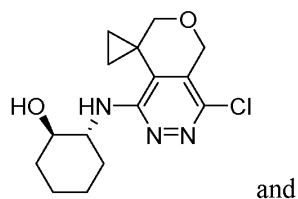
[0275] To a solution of 1-(prop-2-ynoxymethyl)cyclopropanecarboxylic acid (1 g, 6.49 mmol) in toluene (20 mL) was added 3,6-dichloro-1,2,4,5-tetrazine (1.47 g, 9.73 mmol). The mixture was stirred at 120°C for 2 hours. TLC (PE/EtOAc = 1:1, *R*_f = 0.4 for desired product) indicated the starting acid was consumed completely. The mixture was concentrated in vacuum. The residue was purified by flash chromatography (ISCO® 20 g SepaFlash® silica gel column) eluting with a gradient of 0 to 50% EtOAc in PE (40 mL/min) to give the title compound as a red solid (500 mg, 27.8%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.99 - 1.13 (m, 2 H), 1.38 - 1.54 (m, 2 H), 3.77 (s, 2 H), 4.60 (s, 2 H), 7.82 (s, 1 H).

[0276] STEP 4: 1,4-dichlorospiro[5,7-dihydropyrano[3,4-*d*]pyridazine-8,1'-cyclopropane]

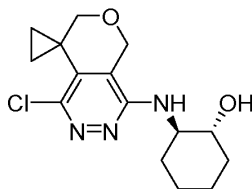


[0277] To a solution of 1-[(3,6-dichloropyridazin-4-yl)methoxymethyl]cyclopropanecarboxylic acid (2 g, 7.22 mmol) in ACN (80 mL) and H₂O (80 mL) was added silver nitrate (4.11 g, 24.19 mmol) at 25°C. Sulfuric acid (1 M, 21.65 mL) and peroxydisulfuric acid, ammonia salt (1.6 M, 13.53 mL) were added. The mixture was stirred at 70°C for 2 hours. LC-MS showed desired mass was detected. The mixture was cooled to room temperature, poured into ice-cold saturated aqueous NaHCO₃ (50 mL), filtered and then extracted with DCM (50 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by flash chromatography (ISCO® 20 g SepaFlash® silica gel column) using a gradient of 0 10% EtOAc in PE (45 mL/min) to give the title compound as a white solid (290 mg, 17.4%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.90 - 1.00 (m, 2 H), 2.16 - 2.24 (m, 2 H), 3.63 (s, 2 H), 4.82 (s, 2 H).

[0278] PREPARATION 80: (1*R*,2*R*)-2-((1'-chloro-5'*H*,7'*H*-spiro[cyclopropane-1,8'-pyrano[3,4-*d*]pyridazin]-1'-yl)amino)cyclohexan-1-ol



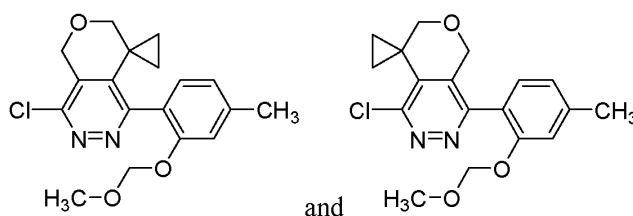
[0279] PREPARATION 81: (1*R*,2*R*)-2-((1'-chloro-5'*H*,7'*H*-spiro[cyclopropane-1,8'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclohexan-1-ol



[0280] Starting materials 1',4'-dichloro-5'*H*,7'*H*-spiro[cyclopropane-1,8'-pyrano[3,4-*d*]pyridazine] (200 mg, 865.51 μmol), (1*R*,2*R*)-2-aminocyclohexan-1-ol (249.21 mg, 2.16 mmol) and NaI (389.20 mg, 2.60 mmol) were taken up in NMP (5 mL) into a microwave tube. The sealed tube was heated at 180°C for 3 hours in a microwave reactor. LC-MS showed the desired mass was detected. The mixture was purified by preparative HPLC (Boston Green ODS-5 μm, 30 mm x 150 mm column) using a gradient of 21 to 61% ACN in water (with formic acid). The crude product was purified by flash chromatography (ISCO® 10 g SepaFlash® silica gel column) using a gradient of 0 to 10% EtOAc in PE (30 mL/min).

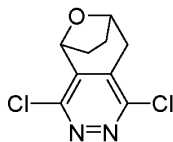
The title compound of Preparation 80 was obtained as a yellow solid (70 mg). ^1H NMR (400 MHz, CDCl_3) δ ppm 0.88 - 0.97 (m, 2 H), 1.16 - 1.58 (m, 4 H), 1.65 - 1.87 (m, 4 H), 2.06 - 2.25 (m, 2 H), 3.37 - 3.47 (m, 1 H), 3.59 (q, $J=11.78$ Hz, 2 H), 3.97 - 4.12 (m, 1 H), 4.20 - 4.31 (m, 1 H), 4.72 - 4.76 (m, 2 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ 310.1. The title compound of Preparation 81 was obtained as a yellow solid (70 mg). ^1H NMR (400 MHz, CDCl_3) δ ppm 0.74 - 0.92 (m, 2 H), 1.21 - 1.51 (m, 4 H), 1.70 - 1.81 (m, 2H), 2.01 - 2.19 (m, 4H), 3.48 - 3.53 (m, 2H), 3.56 - 3.68 (m, 1 H), 3.94 - 4.10 (m, 1 H), 4.33 (br d, $J=5.26$ Hz, 1 H), 4.53 - 4.76 (m, 2 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ 310.1.

[0281] PREPARATION 82: 4'-chloro-1'-(2-(methoxymethoxy)-4-methylphenyl)-5'*H*,7'*H*-spiro[cyclopropane-1,8'-pyrano[3,4-*d*]pyridazine] and 1'-chloro-4'-(2-(methoxymethoxy)-4-methylphenyl)-5'*H*,7'*H*-spiro[cyclopropane-1,8'-pyrano[3,4-*d*]pyridazine]

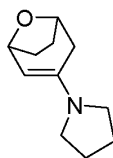


[0282] To a mixture of 1',4'-dichloro-5'*H*,7'*H*-spiro[cyclopropane-1,8'-pyrano[3,4-*d*]pyridazine] (310 mg, 1.34 mmol) in dioxane (4 mL) and water (1 mL) were added 2-(2-(methoxymethoxy)-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (373.15 mg, 1.34 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (219.11 mg, 268.31 μmol) and Cs_2CO_3 (1.75 g, 5.37 mmol). The mixture was stirred at 100°C for 1 hour under N_2 . LC-MS showed desired mass was detected. The mixture was quenched with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated in vacuum. The residue was purified by flash chromatography (ISCO® 10 g SepaFlash® silica gel column) using a gradient of 0 to 10% EtOAc in PE (30 mL/min) to give a mixture of the two title compounds as a yellow solid (280 mg).

[0283] PREPARATION 83: 1,4-dichloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine



[0284] STEP 1: 1-(8-oxabicyclo[3.2.1]oct-2-en-3-yl)pyrrolidine

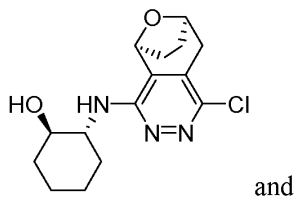


[0285] To a solution of 8-oxabicyclo[3.2.1]octan-3-one (21 g, 166.45 mmol) in toluene (800 mL) were added TsOH (2.86 g, 16.63 mmol) and pyrrolidine (23.69 g, 332.93 mmol, 27.80 mL). The mixture was stirred at 80°C for 0.5 hours and then heated at reflux in a Dean-Stark apparatus for 0.5 hours to remove water. TLC (PE/EtOAc = 3:1) indicated the starting material was consumed completely and one new spot had formed. The reaction mixture was concentrated under reduced pressure to give the title compound as a red solid (28 g, crude).

[0286] STEP 2: 1,4-dichloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine

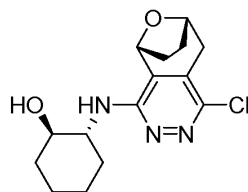
[0287] To a solution of 1-(8-oxabicyclo[3.2.1]oct-2-en-3-yl)pyrrolidine (28.0 g, crude) in toluene (800 mL) was added 3,6-dichloro-1,2,4,5-tetrazine (35.30 g, 234.30 mmol). The mixture was stirred at 120°C for 1.5 hours. TLC (PE/EtOAc = 3:1) indicated the starting material was consumed completely and desired product had formed. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by flash chromatography (ISCO® 330 g SepaFlash® silica gel column) using a gradient of 0 to 25% EtOAc in PE (80 mL/min) to give crude product (36 g). The crude product was recrystallized from EtOAc (600 mL) and PE (2400 mL) to give the title compound as a white solid (21 g, 78% yield, 100% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.54 - 1.80 (m, 1 H), 1.94 - 2.06 (m, 1 H), 2.15 - 2.33 (m, 2 H), 2.41 (d, *J*=18.51 Hz, 1 H), 3.10 (m, 1 H), 4.74 - 4.91 (m, 1 H), 5.17 (d, *J*=6.25 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ 230.0.

[0288] PREPARATION 84: (1*R*,2*R*)-2-(((5*S*,8*R*)-1-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol



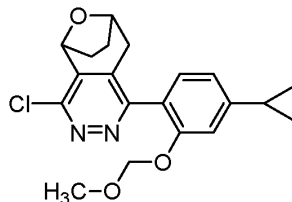
and

[0289] PREPARATION 85: (1*R*,2*R*)-2-(((5*R*,8*S*)-1-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol



[0290] Starting materials 1,4-dichloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine (1 g, 4.33 mmol), (1*R*,2*R*)-2-aminocyclohexanol (1.25 g, 10.82 mmol), DIPEA (5.59 g, 43.28 mmol, 7.54 mL) and NaI (1.95 g, 12.98 mmol) were taken up in NMP (8 mL) into a microwave tube. The sealed tube was heated at 180°C for 3 hours in a microwave reactor. LC-MS showed starting material was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by flash chromatography (ISCO® 40 g SepaFlash® silica gel column) using a gradient of 0 to 10% MeOH/DCM (35 mL/min) to give a mixture of stereoisomers as a colorless oil (1.2 g, crude with NMP). The stereoisomers were separated by chiral SFC (DAICEL CHIRALPAK® AD-10 μ m, 30 mm x 250 mm column) using a mobile phase of CO₂ and 40% iPrOH (with 0.1% NH₃OH). The title compound of Preparation 84 was obtained as a white solid (180 mg, 13.4%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.21 - 1.27 (m, 3 H), 1.62 - 1.72 (m, 3 H), 1.89 - 2.20 (m, 6 H), 2.90 (m, 1 H), 3.41 - 3.54 (m, 2 H), 3.79 - 3.90 (m, 1 H), 4.55 (d, *J*=5.00 Hz, 1 H), 4.74 (br t, *J*=5.82 Hz, 1 H), 5.18 (d, *J*=6.13 Hz, 1 H), 6.05 (d, *J*=7.50 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ 309.12. The title compound of Preparation 85 was obtained as a white solid (130 mg, 9.22%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.29 (br d, *J*=8.50 Hz, 3 H), 1.64 - 1.79 (m, 3 H), 1.83 - 2.22 (m, 6 H), 2.96 (m, 1 H), 3.47 - 3.59 (m, 2 H), 3.84 - 3.98 (m, 1 H), 4.69 - 4.83 (m, 2 H), 5.23 (d, *J*=6.25 Hz, 1 H), 6.15 (br d, *J*=7.63 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ 309.12.

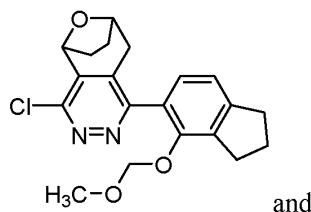
[0291] PREPARATION 86: 4-chloro-1-(4-cyclopropyl-2-(methoxymethoxy)phenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine



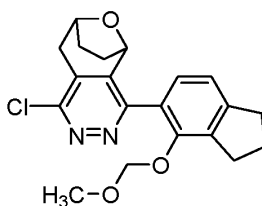
[0292] A mixture of 1,4-dichloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine (1.5 g, 6.49 mmol), 2-(4-cyclopropyl-2-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.97 g, 6.49 mmol), Cs₂CO₃ (8.46 g, 25.97 mmol), Pd(dppf)Cl₂·CH₂Cl₂ (1.06

g, 1.30 mmol) and H₂O (5 mL) in dioxane (20 mL) was degassed and purged with N₂ (3 x) and then stirred at 100°C for 1 hour under N₂ atmosphere. LC-MS showed starting material was consumed completely and one main peak with desired mass was detected. The residue was diluted with H₂O (100 mL) and extracted with EtOAc 80 mL (80 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by preparative HPLC (Xtimate C18-10 µm, 40 mm x 150 mm column) using a gradient of 28 to 68% ACN in water (with NH₃H₂O+NH₄HCO₃) over 36 minutes to give the title compound as a white solid (1.3 g, crude). The crude product was further purified by SFC (REGIS (S,S) WHELK-O® 1-5 µm, 30 mm x 250 mm column) using a mobile phase of CO₂ and 45% EtOH (with 0.1% NH₃OH) to give the title compound as a white solid (600 mg, 24.8%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.67 - 0.81 (m, 2 H), 0.96 - 1.10 (m, 3 H), 1.51 - 1.71 (m, 1 H), 1.90 - 2.25 (m, 5 H), 3.17 - 3.24 (m, 3 H), 4.62 - 4.78 (m, 1 H), 5.07 - 5.26 (m, 3 H), 6.72 - 6.88 (m, 1 H), 6.92 - 7.02 (m, 1 H), 7.11 - 7.24 (m, 1 H); ESI-MS *m/z* [M+H]⁺ 372.9.

[0293] PREPARATION 87: 4-chloro-1-(4-(methoxymethoxy)-2,3-dihydro-1*H*-inden-5-yl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine

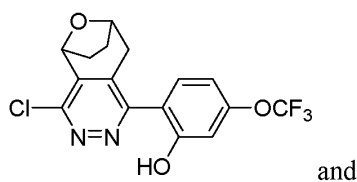


[0294] PREPARATION 88: 1-chloro-4-(4-(methoxymethoxy)-2,3-dihydro-1*H*-inden-5-yl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine



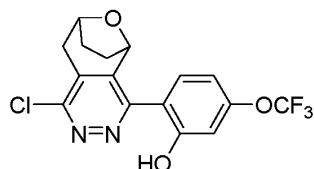
[0295] The title compounds were synthesized like Preparation 86.

[0296] PREPARATION 89: 2-(4-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethoxy)phenol



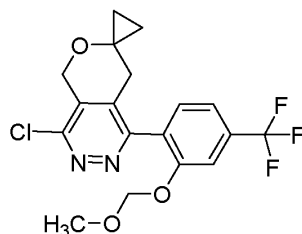
and

[0297] PREPARATION 90: 2-(1-chloro-6,7,8,9-tetrahydro-5H-5,8-epoxycyclohepta[d]pyridazin-4-yl)-5-(trifluoromethoxy)phenol



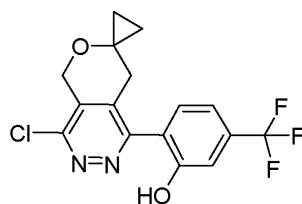
[0298] The title compounds were synthesized like Preparation 86.

[0299] PREPARATION 91: 4'-chloro-1'-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-d]pyridazine]



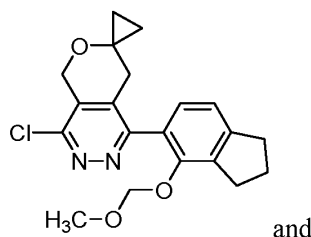
[0300] To a 20 mL vial were added 1',4'-dichloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-d]pyridazine] (300 mg, 1.30 mmol), 2-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (431 mg, 1.30 mmol), Pd(dppf)Cl₂.CH₂Cl₂ (106 mg, 0.130 mmol), and tripotassium tris(hydrogen phosphate) (554 mg, 2.60 mmol) in 1,4-dioxane (9.2784 mL) and water (2.3196 mL) under nitrogen. The reaction was heated to 80°C and allowed to stir overnight. The reaction mixture was allowed to cool to room temperature and was extracted with EtOAc (2 x 20 mL) and water (20 mL). The organics were dried with MgSO₄ and filtered. The solution was concentrated, dissolved in toluene (2 mL) and purified by flash chromatography, using a gradient of 0 to 50% EtOAc in heptane, to give the title compound as the first eluting compound (120 mg, 23.1%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.46 – 0.53 (m, 2 H), 0.90 - 1.05 (m, 2 H), 2.29 (m, 1 H), 2.95 (m, 1 H), 3.38 (s, 3 H), 4.75 (m, 2 H), 5.15 (br s, 2 H), 7.38 - 7.48 (m, 2 H), 7.51 (s, 1 H); ESI-MS m/z [M+H]⁺ calc'd for C₁₈H₁₆ClF₃N₂O₃ 400.08; found 401.0.

[0301] PREPARATION 92: 2-(4'-chloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-d]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol

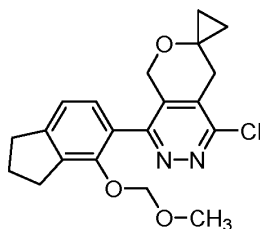


[0302] To a 20 mL vial were added 1',4'-dichloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-d]pyridazine] (220 mg, 0.952 mmol), (2-hydroxy-4-(trifluoromethyl)phenyl)boronic acid (196 mg, 0.952 mmol), Pd(dppf)Cl₂.CH₂Cl₂ (78 mg, 0.0952 mmol), and tripotassium tris(hydrogen phosphate) (406 mg, 1.90 mmol) in 1,4-dioxane (6.8041 mL) and water (1.701 mL) under nitrogen. The reaction was heated to 80°C and allowed to stir overnight. The reaction mixture was allowed to cool to room temperature and was extracted with EtOAc (2 x 20 mL) and water (20 mL). The organics were dried with MgSO₄ and filtered. The solution was concentrated with silica gel and purified by flash chromatography, using a gradient of 0 to 50% EtOAc in heptane, to give the title compound as the first eluting compound (71 mg, 20.9%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.43 - 0.61 (m, 2 H), 0.78 - 0.91 (m, 2 H), 2.66 (s, 2 H), 4.74 (s, 2 H), 7.18 - 7.36 (m, 2 H), 7.51 (d, *J*=8.03 Hz, 1 H), 10.73 (s, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₁₆H₁₂ClF₃N₂O₂ 356.05; found 357.0.

[0303] PREPARATION 93: 4'-chloro-1'-(4-(methoxymethoxy)-2,3-dihydro-1*H*-inden-5-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine]

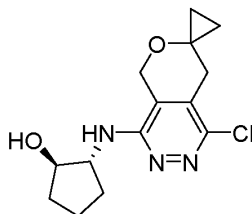


[0304] PREPARATION 94: 1'-chloro-4'-(4-(methoxymethoxy)-2,3-dihydro-1*H*-inden-5-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine]



[0305] A microwave vial was charged with 1',4'-dichloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (178 mg 0.769 mmol), 2-(4-(methoxymethoxy)-2,3-dihydro-1*H*-inden-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (234 mg, 0.789 mmol), tripotassium phosphate (328 mg, 1.54 mmol) and Pd(dppf)Cl₂.CH₂Cl₂ (31.4 mg, 0.038 mmol) in 1,4-dioxane/H₂O (4:1) (15.4 mL, 0.05 M). The vial was capped and a stream of nitrogen was bubbled through the solution for 15 minutes. The reaction mixture was heated to 100°C in a microwave reactor and stirred for 3 hours. The reaction was quenched with saturated aq NH₄Cl and the mixture extracted with DCM. The organic phase was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (ISCO® 120g SepaFlash® silica gel column) using a gradient of 0 to 50% EtOAc in heptane (40 mL/min). The title compound of Preparation 93 was obtained as pale-yellow oil (97.6 mg, 34%). ESI-MS *m/z* [M+H]⁺ calc'd for C₂₀H₂₁ClN₂O₃ 372.1; found 373.1. The title compound of Preparation 94 was obtained as a white solid (77.9 mg, 27%). ESI-MS *m/z* [M+H]⁺ calc'd for C₂₀H₂₁ClN₂O₃ 372.1; found 373.1.

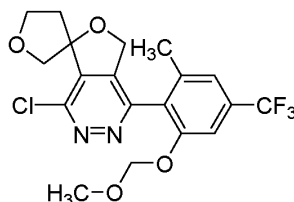
[0306] PREPARATION 95: (1*R*,2*R*)-2-((1'-chloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclopentan-1-ol



[0307] A mixture of 1',4'-dichloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (2.00 g, 8.66 mmol), (1*R*,2*R*)-aminocyclopentan-1-ol (2.19 g, 21.6 mmol), NaI (6.49 g, 43.3 mmol), and DIPEA (15 mL, 86.6 mmol) in NMP (28.853 mL) was stirred in a microwave reactor on high absorbance for 1 hour at 180°C. The reaction mixture was diluted with H₂O (200 mL) to furnish a brown solution. The crude product was extracted with EtOAc (2 x 200 mL). The organic extracts were combined, dried over Na₂SO₄, filtered, rinsed with EtOAc, and concentrated via rotary evaporation to provide the crude product as a brown oil (7.25 g). The crude material was dissolved in toluene (10 mL), concentrated via rotary evaporation, reconstituted in toluene (8 mL) and purified via medium pressure chromatography (RediSep® Rf Gold 330 g silica gel column) using a gradient of 0 to 100% EtOAc in heptane. The early fractions were combined, concentrated via rotary evaporation, and dried *in vacuo* to provide the title compound as an orange oil (crude). The oil was

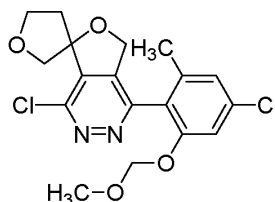
dissolved in iPrOAc (5 mL) at reflux and cooled to room temperature. The resulting solid was filtered, rinsed with iPrOAc (3 x 1 mL), and dried *in vacuo* to provide the title compound as an ivory solid (115.6 mg, 4.5%). The filtrate and the mixed fractions were combined and purified via medium pressure chromatography using a gradient of 1 to 100% EtOAc in heptane. The early fractions were combined, concentrated via rotary evaporation, and dried *in vacuo* to provide a second crop of the title compound (340.0 mg, 13.3%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.54 - 0.72 (m, 2 H), 0.75 - 0.93 (m, 2 H), 1.40 - 1.55 (m, 2 H), 1.57 - 1.74 (m, 2 H), 1.86 (ddt, *J*=12.58, 8.31, 6.37, 6.37 Hz, 1 H), 2.11 (dtd, *J*=12.99, 7.69, 7.69, 5.52 Hz, 1 H), 2.67 (s, 2 H), 4.00 (dt, *J*=10.42, 5.33 Hz, 1 H), 4.09 (quin, *J*=6.40 Hz, 1 H), 4.37 - 4.52 (m, 2 H), 4.80 - 4.87 (m, 1 H), 6.01 (d, *J*=6.27 Hz, 1 H); ESI-MS [*M*+*H*]⁺ calc'd for C₁₄H₁₈ClN₃O₂, 295.11; found, 296.1.

[0308] PREPARATION 96: 4'-chloro-1'-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazine]



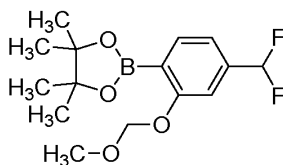
[0309] The title compound was synthesized like Preparation 86.

[0310] PREPARATION 97: 4'-chloro-1'-(4-chloro-2-(methoxymethoxy)-6-methylphenyl)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazine]

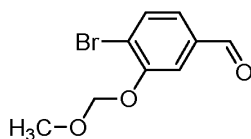


[0311] The title compound was synthesized like Preparation 86.

[0312] PREPARATION 98: 2-(4-(difluoromethyl)-2-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

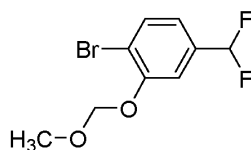


[0313] STEP 1: 4-bromo-3-(methoxymethoxy)benzaldehyde



[0314] To a solution of 4-bromo-3-hydroxy-benzaldehyde (5 g, 24.87 mmol) in THF (80 mL) was added NaH (1.09 g, 27.36 mmol, 60% purity) at 20°C. After stirring for 15 minutes, bromo (methoxy)methane (3.11 g, 24.87 mmol, 2.03 mL) was added to the reaction at 20°C. The mixture was stirred at 20°C for 2 hours. TLC (PE/EtOAc = 5:1) indicated the starting material was consumed completely and one new spot had formed. The reaction solution was diluted in aq NH₄Cl (100 mL), stirred for 15 minutes, and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound as a colorless oil (6.1 g, 90% yield, 90% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 3.54 (s, 3 H), 5.34 (s, 2 H), 7.40 (dd, *J*=8.07, 1.31 Hz, 1 H), 7.64 (d, *J*=1.25 Hz, 1 H), 7.74 (d, *J*=8.13 Hz, 1 H), 9.95 (s, 1 H).

[0315] STEP 2: 1-bromo-4-(difluoromethyl)-2-(methoxymethoxy)benzene



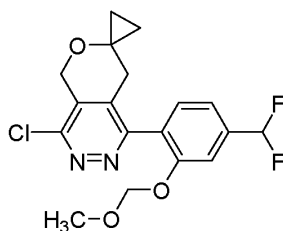
[0316] To a solution of 4-bromo-3-(methoxymethoxy)benzaldehyde (6.1 g, 24.89 mmol) in DCM (30.5 mL) was added DAST (6.82 g, 42.31 mmol, 5.59 mL) at 0°C. The mixture was stirred at 20°C for 12 hours. TLC (PE/EtOAc = 5:1) indicated starting material was consumed completely and two new spots had formed. The reaction mixture was diluted with NH₄Cl (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (50 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (ISCO® 120 g SepaFlash® silica gel column) using a gradient of 0 to 3% EtOAc in PE (70 mL/min). The title compound was obtained as a colorless oil (6.1 g, 91% yield, 90% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 3.53 (s, 3 H), 5.28 (s, 2 H), 6.38 - 6.77 (m, 1 H), 7.04 (d, *J*=7.88 Hz, 1 H), 7.29 (s, 1 H), 7.63 (d, *J*=8.25 Hz, 1 H).

[0317] STEP 3: 2-(4-(difluoromethyl)-2-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

[0318] A mixture of 1-bromo-4-(difluoromethyl)-2-(methoxymethoxy)benzene (700 mg, 2.62 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-

dioxaborolane (865.26 mg, 3.41 mmol), Pd(dppf)Cl₂ (191.79 mg, 262.11 μmol) and KOAc (514.46 mg, 5.24 mmol) in dioxane (18 mL) was degassed and stirred at 100°C for 2 hours. TLC (PE/EtOAc = 10:1) indicated the limiting reactant was consumed completely and two new spots had formed. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (ISCO® 12 g SepaFlash® silica gel column) using a gradient of 0 to 2% EtOAc in PE (30 mL/min) to give the title compound as a colorless oil (400 mg, 43.7% yield, 90% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.36 (s, 12 H), 3.52 (s, 3 H), 5.23 (s, 2 H), 6.43 - 6.78 (m, 1 H), 7.11 - 7.19 (m, 2 H), 7.76 (d, *J*=7.50 Hz, 1 H).

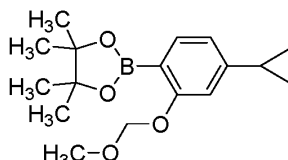
[0319] PREPARATION 99: 4'-chloro-1'-(4-(difluoromethyl)-2-(methoxymethoxy)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine]



[0320] A mixture of 1',4'-dichloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (173 mg, 748.66 μmol), 2-(4-(difluoromethyl)-2-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (235.18 mg, 748.66 μmol), Pd(dppf)Cl₂ (109.56 mg, 149.73 μmol), Cs₂CO₃ (975.72 mg, 2.99 mmol) in dioxane (3.5 mL) and H₂O (0.9 mL) was degassed and purged with N₂ (3 x) and then stirred at 80°C for 12 hours under N₂ atmosphere. TLC (PE/EtOAc = 3:1) indicated the starting material was consumed completely and two new spots had formed. The reaction mixture was diluted with H₂O (5 mL) and extracted with DCM (5 mL x 3). The combined organic layers were washed with brine (5 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (ISCO® 4 g SepaFlash® silica gel column) using a gradient 0 to 10% EtOAc in PE (30 mL/min), followed by SFC (DAICEL CHIRALPAK® IK-10 μm, 50 mm x 250 mm column) using a mobile phase of CO₂ and 15% MeOH (with 0.1% NH₃OH). The title compound was obtained as a white solid (12 mg, 19% yield, 95% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.36 - 0.65 (m, 2 H), 0.96 (br d, *J*=18.76 Hz, 2 H), 2.28 (br d, *J*=16.88 Hz, 1 H), 2.96 (br d, *J*=17.01 Hz, 1 H), 3.37 (s, 3 H), 4.75 (br d,

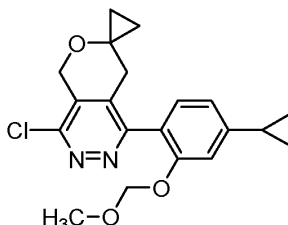
$J=16.13$ Hz, 2 H), 5.14 (br d, $J=5.13$ Hz, 2 H), 6.52 - 6.83 (m, 1 H), 7.29 (br d, $J=7.88$ Hz, 1 H), 7.40 (s, 1 H).

[0321] PREPARATION 100: 2-(4-cyclopropyl-2-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



[0322] To a mixture of 1-cyclopropyl-3-(methoxymethoxy)benzene (2 g, 11.22 mmol) and TMEDA (2.74 g, 23.57 mmol, 3.56 mL) in THF (20 mL) was added *n*-BuLi (2.5M in *n*-hexane) (2.5 M, 9.43 mL) in one portion at 0°C under N₂. The mixture was stirred at 10°C for 1 hour, then cooled to -78°C, and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.59 g, 24.69 mmol, 5.04 mL) was added. The mixture was stirred at 10°C for 12 hours. TLC (PE/EtOAc =10:1) indicated starting material was consumed completely and three new spots had formed. The reaction mixture was quenched by addition aq NH₄Cl (100 mL) and extracted with EtOAc (100 mL x 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (ISCO® 12 g SepaFlash® silica gel column) using a gradient of 0 to 5% EtOAc in PE (40 mL/min). The product was further purified by preparative HPLC (Welch Ultimate XB-CN-10 μm, 50 mm x 250 mm) using a gradient of 1 to 17% of EtOH in hexane. The title compound was obtained as a colorless oil (1.48 g, 39% yield, 90% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.66 - 0.77 (m, 2 H), 0.93 - 1.03 (m, 2 H), 1.34 (s, 12 H), 1.84 - 1.92 (m, 1 H), 3.53 (s, 3 H), 5.19 (s, 2 H), 6.70 (dd, $J=7.63$, 1.38 Hz, 1 H), 6.77 (d, $J=1.25$ Hz, 1 H), 7.60 (d, $J=7.63$ Hz, 1 H).

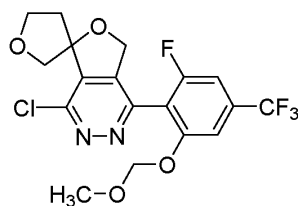
[0323] PREPARATION 101: 4'-chloro-1'-(4-cyclopropyl-2-(methoxymethoxy)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine]



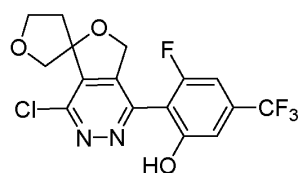
[0324] To a solution of 1',4'-dichloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (500 mg, 2.16 mmol) and 2-(4-cyclopropyl-2-(methoxymethoxy)phenyl)-

4,4,5,5-tetramethyl-1,3,2-dioxaborolane (658.19 mg, 2.16 mmol) in dioxane (4 mL) and H₂O (1 mL) was added Cs₂CO₃ (2.82 g, 8.66 mmol) followed by Pd(dppf)Cl₂ (316.65 mg, 432.75 μmol). The mixture was stirred at 100°C for 12 hours under N₂. LC-MS showed the starting material was consumed completely and a new peak was detected. The reaction mixture was diluted with H₂O (30 mL) and extracted with EtOAc (30 mL x 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (ISCO® 4 g SepaFlash® silica gel column) using a gradient of 0 to 20% EtOAc in PE (30 mL/min) to give crude product (350 mg). The product was purified by SFC (DAICEL CHIRALPAK® AD-H-5 μm, 30 mm x 250 mm column) using a mobile phase of CO₂ and 30% EtOH (with 0.1% NH₃OH). The title compound was obtained as a yellow solid (109 mg, 13.1% yield, 96.7% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.41 - 0.58 (m, 2 H), 0.76 (br d, *J*=1.4 Hz, 2 H), 0.91 - 1.10 (m, 4 H), 1.59 - 1.76 (m, 1 H), 1.88 - 1.99 (m, 1 H), 2.90 - 3.10 (m, 1 H), 3.36 (br s, 3 H), 4.74 (br d, *J*=1.8 Hz, 2 H), 5.09 (br s, 2 H), 6.81 (br d, *J*=7.6 Hz, 1 H), 6.99 (br s, 1 H), 7.21 (br d, *J*=7.6 Hz, 1 H).

[0325] PREPARATION 102: 4'-chloro-1'-(2-fluoro-6-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-4,5-dihydro-2*H*,7*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazine]



[0326] STEP 1: 2-(4'-chloro-4,5-dihydro-2*H*,7*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-3-fluoro-5-(trifluoromethyl)phenol



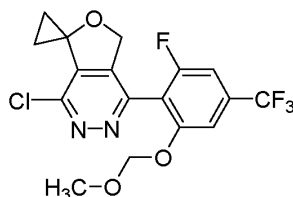
[0327] A mixture of 1',4'-dichloro-4,5-dihydro-2*H*,7*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazine] (200 mg, 0.809 mmol), 3-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol (248 mg, 0.809 mmol), Pd(dppf)Cl₂.CH₂Cl₂ (66 mg, 0.0809 mmol), and tripotassium tris(hydrogen phosphate) (345 mg, 1.62 mmol) in 1,4-dioxane (6 mL) and water (1.5 mL) was purged with nitrogen for 5 minutes and then heated at 100°C for 40 minutes. The mixture was treated with water and was extracted with EtOAc. The organics

were washed with brine, dried over MgSO_4 , and concentrated. The residue was purified by silica column eluting with heptane/EtOAc (9:1 to 0:1). The combined fractions were concentrated to give the title compound (222 mg, 70%). ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{16}\text{H}_{11}\text{ClF}_4\text{N}_2\text{O}_3$ 390.0; found 391.2.

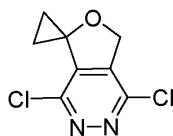
[0328] STEP 2: 4'-chloro-1'-(2-fluoro-6-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazine]

[0329] A solution of 2-(4'-chloro-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-3-fluoro-5-(trifluoromethyl)phenol (222 mg, 0.568 mmol) in THF (8 mL) was cooled to 0°C. Sodium hydride (34 mg, 0.852 mmol) was added, and after 30 minutes, bromomethyl methyl ether (0.070 mL, 0.852 mmol) was added. The mixture was stirred at room temperature for 10 minutes and then treated with saturated NH_4Cl and extracted with EtOAc. The organic layers were combined, washed with brine, dried over MgSO_4 , and concentrated to give the crude product, which was used without purification. ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{18}\text{H}_{15}\text{ClF}_4\text{N}_2\text{O}_4$ 434.1; found 435.0.

[0330] PREPARATION 103: 4'-chloro-1'-(2-fluoro-6-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-7'*H*-spiro[cyclopropane-1,5'-furo[3,4-*d*]pyridazine]



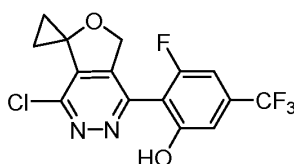
[0331] STEP 1: 1',4'-dichloro-7'*H*-spiro[cyclopropane-1,5'-furo[3,4-*d*]pyridazine]



[0332] A mixture of 4-oxaspiro[2.4]heptan-6-one (1000 mg, 8.92 mmol), *p*-toluenesulfonic acid monohydrate (17 mg, 0.0892 mmol), and pyrrolidine (0.74 mL, 8.92 mmol) in toluene (20 mL) was stirred at room temperature overnight. The mixture was concentrated *in vacuo* and the resulting residue was dissolved in toluene (8 mL) and was added to a solution of 3,6-dichloro-1,2,4,5-tetrazine (1178 mg, 7.80 mmol) in toluene (18 mL) at 0°C. The mixture was heated at 80°C under nitrogen for 1 hour. The mixture was then treated with water and was

extracted with EtOAc. Combined organic layers were washed with brine, dried over MgSO₄, and concentrated. The residue was purified by silica gel column (40 g) eluting with heptane/EtOAc gradient (9:1 to 0:1). The combined fractions were concentrated to give the title compound (0.885 g, 45.7%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.24 - 1.42 (m, 2 H), 1.54 - 1.72 (m, 2 H), 5.23 (s, 2 H); ESI-MS m/z [M+H]⁺ calc'd for C₈H₆Cl₂N₂O 216.0; found 217.0.

[0333] STEP 2: 2-(4'-chloro-7'*H*-spiro[cyclopropane-1,5'-furo[3,4-*d*]pyridazin]-1'-yl)-3-fluoro-5-(trifluoromethyl)phenol

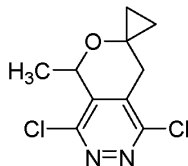


[0334] A mixture of 1',4'-dichloro-7'*H*-spiro[cyclopropane-1,5'-furo[3,4-*d*]pyridazine] (250 mg, 1.15 mmol), 3-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenol (353 mg, 1.15 mmol), Pd(dppf)Cl₂.CH₂Cl₂ (94 mg, 0.115 mmol), and tripotassium tris(hydrogen phosphate) (491 mg, 2.30 mmol) in 1,4-dioxane (10 mL) and water (2.5 mL) was purged with nitrogen for 5 minutes and then heated at 100°C under nitrogen for 35 minutes. The mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated. The residue was purified by silica gel column (40 g) eluting with a heptane/EtOAc gradient (4:1 to 0:1). The combined fractions were concentrated to give the title compound (0.112 g, 26.9%). ESI-MS m/z [M+H]⁺ calc'd for C₁₅H₉ClF₄N₂O₂ 360.0; found 361.1.

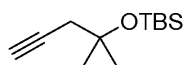
[0335] STEP 3: 4'-chloro-1'-(2-fluoro-6-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-7'*H*-spiro[cyclopropane-1,5'-furo[3,4-*d*]pyridazine]

[0336] A solution of 2-(4'-chloro-7'*H*-spiro[cyclopropane-1,5'-furo[3,4-*d*]pyridazin]-1'-yl)-3-fluoro-5-(trifluoromethyl)phenol (112 mg, 0.311 mmol) in THF (8 mL) was cooled to 0°C. Sodium hydride (19 mg, 0.466 mmol) was added. After stirring 30 minutes, bromomethyl methyl ether (0.038 mL, 0.466 mmol) was added. The mixture was stirred at room temperature for 10 minutes and then treated with saturated NH₄Cl and extracted with EtOAc. The organic extracts were washed with brine, dried over MgSO₄, and concentrated to give the title compound, which was used without purification. ESI-MS m/z [M+H]⁺ calc'd for C₁₇H₁₃ClF₄N₂O₃ 404.1; found 404.9.

[0337] PREPARATION 104: 1',4'-dichloro-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine]

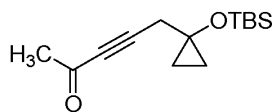


[0338] STEP 1: *tert*-butyldimethyl(1-(prop-2-yn-1-yl)cyclopropoxy)silane



[0339] To a solution of 2-(1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)acetaldehyde (11.5 g, 53.64 mmol) in MeOH (90 mL) were added 1-diazo-1-dimethoxyphosphoryl-propan-2-one (20.61 g, 107.29 mmol) and K₂CO₃ (7.41 g, 53.64 mmol). The mixture was stirred at 0°C for 10 hours. TLC (PE/EtOAc = 10:1) indicated the starting material was consumed completely and one new spot had formed. The reaction mixture was quenched with aq NH₄Cl (200 mL) and extracted with DCM (200 mL x 3). The combined organic phase was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (ISCO® 330 g SepaFlash® silica gel column) using a gradient of 0 to 1% EtOAc in PE (100 mL/min) to give the title compound as a colorless oil (5.3 g, 44% yield, 95% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.10 - 0.14 (m, 6 H), 0.69 - 0.72 (m, 2 H), 0.73 (br s, 2 H), 0.86 (s, 9 H), 1.95 (t, *J*=2.44 Hz, 1 H), 2.59 (d, *J*=2.50 Hz, 2 H).

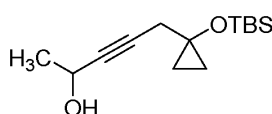
[0340] STEP 2: 5-(1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)pent-3-yn-2-one



[0341] A 50-mL flame-dried flask was charged with *tert*-butyldimethyl(1-(prop-2-yn-1-yl)cyclopropoxy)silane (15.7 g, 74.62 mmol) and THF (40 mL). The solution was cooled to -78°C and *n*-BuLi (2.5 M in hexane, 32.83 mL) was added dropwise. The solution was stirred at -78°C for 30 minutes before dropwise addition of *N*-methoxy-*N*-methyl-acetamide (8.46 g, 82.09 mmol, 8.73 mL). The reaction was warmed to 0°C and stirred for additional 3 hours. TLC (PE/EtOAc = 20:1) indicated the starting material was consumed completely and one

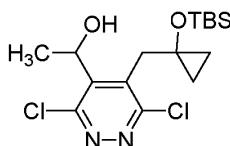
new spot had formed. The reaction mixture was poured into saturated aq NH_4Cl (100 mL) in an ice bath. The phases were separated and the aqueous layer was extracted with EtOAc (100 mL x 3). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (ISCO® 220 g SepaFlash® silica gel column) using a gradient of 0-4% EtOAc in PE (100 mL/min) to give the title compound as a colorless oil (15.24 g, 80.89% yield, 90% purity). ^1H NMR (400 MHz, CDCl_3) δ ppm 0.14 (s, 6 H), 0.68 (s, 2 H), 0.80 (s, 2 H), 0.87 (s, 9 H), 2.33 (s, 3 H), 2.73 (s, 2 H).

[0342] STEP 3: 5-(1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)pent-3-yn-2-ol



[0343] To a solution of 5-(1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)pent-3-yn-2-one (15.24 g, 60.37 mmol) and trichlorocerium (19.35 g, 78.49 mmol, 4.93 mL) in MeOH (50 mL) at 25°C was added NaBH_4 (3.05 g, 80.62 mmol). The reaction mixture was stirred for 0.5 hours. TLC (PE/EtOAc = 20:1) indicated the starting material was consumed completely and one new spot had formed. The mixture was poured into saturated aqueous NH_4Cl (100 mL) in an ice bath. The phases were separated and the aqueous layer was extracted with EtOAc (100 x 3 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (ISCO® 80 g SepaFlash® silica gel column) using a gradient of 0 to 5% EtOAc in PE (75 mL/min) to give the title compound as a colorless oil (12.8 g, 85.3% yield, 90% purity). ^1H NMR (400 MHz, CDCl_3) δ ppm 0.12 (s, 6 H), 0.62 - 0.69 (m, 2 H), 0.70 - 0.76 (m, 2 H), 0.86 (s, 9 H), 1.42 (d, $J=6.50$ Hz, 3 H), 2.60 (s, 2 H), 4.50 (q, $J=6.50$ Hz, 1 H).

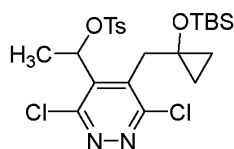
[0344] STEP 4: 1-(5-(1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)methyl)-3,6-dichloropyridazin-4-yl)ethan-1-ol



[0345] A mixture of 5-(1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)pent-3-yn-2-ol (6.6 g, 25.94 mmol) and 3,6-dichloro-1,2,4,5-tetrazine (5.09 g, 33.72 mmol) in toluene (30 mL) was

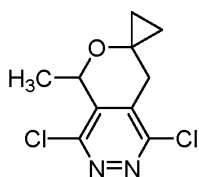
degassed and purged with N₂ (3 x) and then stirred at 100°C for 48 hours under N₂ atmosphere. TLC (PE/EtOAc = 20:1) indicated the starting material remained and two new spots had formed. The mixture was filtered. The filtrate was evaporated under vacuum to give a residue, which was purified by flash chromatography (ISCO® 120 g SepaFlash® silica gel column) using a gradient of 0 to 10% EtOAc in PE (75 mL/min). The title compound was obtained as a brown oil (1.81 g, 18.6% yield, 90% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm - 0.13 (s, 3 H), -0.01 (s, 3 H), 0.56 - 0.66 (m, 1 H), 0.74 (s, 9 H), 0.83 (dt, *J*=11.16, 6.61 Hz, 1 H), 0.88 - 0.98 (m, 1 H), 1.13 - 1.21 (m, 1 H), 1.57 (d, *J*=6.75 Hz, 3 H), 2.80 (d, *J*=13.38 Hz, 1 H), 4.24 - 4.33 (m, 2 H), 5.44 (q, *J*=6.55 Hz, 1 H).

[0346] STEP 5: 1-(5-((1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)methyl)-3,6-dichloropyridazin-4-yl)ethyl 4-methylbenzenesulfonate



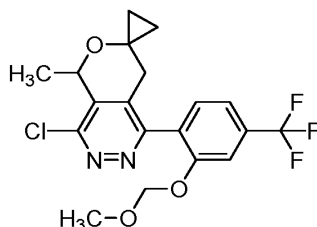
[0347] To a solution of 1-(5-((1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)methyl)-3,6-dichloropyridazin-4-yl)ethanol (5.4 g, 14.31 mmol) in acetone (80 mL) were added K₂CO₃ (5.93 g, 42.93 mmol) and toluenesulfonyl chloride (5.46 g, 28.62 mmol). The mixture was stirred at 70°C for 18 hours. TLC (PE/EtOAc = 5:1) indicated the starting material remained and two new spots had formed. The mixture was filtered. The filtrate was evaporated under vacuum, and the resulting residue was purified by flash chromatography (ISCO® 40 g SepaFlash® silica gel column) using a gradient of 0 to 10% EtOAc in PE (55 mL/min) to give the title compound as a colorless oil (4.54 g, 59.7% yield, 90% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.01 - 0.09 (m, 6 H), 0.36 - 0.49 (m, 1 H), 0.56 (br d, *J*=9.26 Hz, 1 H), 0.71 (s, 9 H), 0.82 - 0.94 (m, 2 H), 1.85 (d, *J*=6.88 Hz, 3 H), 2.39 (s, 3 H), 3.06 (br d, *J*=14.51 Hz, 1 H), 3.67 - 3.78 (m, 1 H), 6.15 (q, *J*=6.75 Hz, 1 H), 7.19 (m, *J*=8.13 Hz, 2 H), 7.56 (m, *J*=8.25 Hz, 2 H).

[0348] STEP 6: 1',4'-dichloro-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine]



[0349] To a solution of 1-(5-((1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)methyl)-3,6-dichloropyridazin-4-yl)ethyl 4-methylbenzenesulfonate (4.45 g, 8.37 mmol) in THF (250 mL) was added TBAF (1 M, 20.93 mL). The mixture was stirred at -20°C for 3 hours. TLC (PE/EtOAc = 20:1) indicated the starting material was consumed completely and one new spot had formed. The reaction was quenched with aqueous NH₄Cl (10 mL) and extracted with DCM (10 mL x 3). The combined organic phase was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (ISCO® 12 g SepaFlash® silica gel column) using a gradient of 0 to 8% EtOAc in PE (35 mL/min) to give the title compound as a yellow oil (1.06 g, 51.5% yield, 95% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.49 (dd, *J*=10.26, 6.75 Hz, 1 H), 0.79 (dt, *J*=10.32, 6.22 Hz, 1 H), 0.87 - 0.95 (m, 1 H), 1.10 - 1.18 (m, 1 H), 1.65 (d, *J*=6.63 Hz, 3 H), 2.67 - 2.75 (m, 1 H), 2.96 - 3.02 (m, 1 H), 4.92 (q, *J*=6.63 Hz, 1 H).

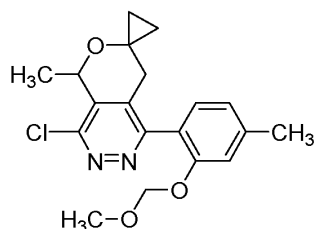
[0350] PREPARATION 105: 4'-chloro-1'-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine]



[0351] A mixture of 1',4'-dichloro-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (150 mg, 611.98 μmol), 2-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (203.25 mg, 611.98 μmol), Pd(dppf)Cl₂ (89.56 mg, 122.40 μmol), and Cs₂CO₃ (797.58 mg, 2.45 mmol) in dioxane (3 mL) and H₂O (0.75 mL) was degassed and purged with N₂ (3 x) and then stirred at 100°C for 2 hours under N₂ atmosphere. TLC (PE/EtOAc = 3:1) indicated the starting material was consumed completely and one new spot had formed. The reaction mixture was diluted with

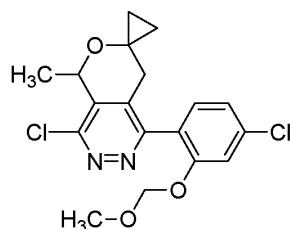
H₂O (5 mL) and extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (5 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (ISCO® 4 g SepaFlash® silica gel column) using a gradient of 0 to 25% EtOAc in PE (30 mL/min) to give the title compound as a colorless oil (119 mg, 44.5% yield, 95% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.16 - 0.41 (m, 1 H), 0.62 (dt, *J*=10.29, 6.24 Hz, 1 H), 0.77 - 0.94 (m, 1 H), 1.00 - 1.13 (m, 1 H), 1.21 - 1.31 (m, 1 H), 1.71 (br d, *J*=6.38 Hz, 3 H), 2.59 (br s, 1 H), 3.12 - 3.29 (m, 1 H), 3.39 (br s, 3 H), 4.99 (br s, 1 H), 5.09 - 5.22 (m, 2 H), 7.39 - 7.54 (m, 3 H)

[0352] PREPARATION 106: 4'-chloro-1'-(2-(methoxymethoxy)-4-methylphenyl)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine]



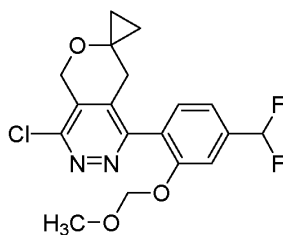
[0353] A mixture of 1',4'-dichloro-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (100 mg, 407.99 μmol), 2-(2-(methoxymethoxy)-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (113.48 mg, 407.99 μmol), Pd(dppf)Cl₂ (59.71 mg, 81.60 μmol), and Cs₂CO₃ (531.72 mg, 1.63 mmol) in dioxane (2 mL) and H₂O (0.5 mL) was degassed and purged with N₂ (3 x) and then stirred at 100°C for 2 hours. LC-MS showed the starting material was consumed completely, and about 67% of desired compound was detected. The reaction mixture was diluted with H₂O (30 mL) and extracted with EtOAc (30 mL x 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (ISCO® 4 g SepaFlash® silica gel column) using a gradient of 0 to 20% EtOAc in PE (30 mL/min) to give the title compound as a colorless oil (110 mg). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.17 - 0.41 (m, 1 H), 0.61 (dt, *J*=10.2, 6.1 Hz, 1 H), 0.74 - 0.93 (m, 1 H), 0.99 - 1.11 (m, 1 H), 1.71 (d, *J*=6.5 Hz, 3 H), 2.42 (s, 3 H), 2.52 - 2.77 (m, 1 H), 3.36 (s, 3 H), 4.95 - 5.04 (m, 1 H), 5.06 - 5.12 (m, 2 H), 6.97 (d, *J*=7.6 Hz, 1 H), 7.06 (s, 1 H), 7.20 - 7.26 (m, 1 H)

[0354] PREPARATION 107: 4'-chloro-1'-(4-chloro-2-(methoxymethoxy)phenyl)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine]



[0355] A mixture of 1',4'-dichloro-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (100 mg, 407.99 μ mol), 2-[4-chloro-2-(methoxymethoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (121.81 mg, 407.99 μ mol), Cs_2CO_3 (531.72 mg, 1.63 mmol), and $\text{Pd}(\text{dppf})\text{Cl}_2$ (59.71 mg, 81.60 μ mol) in dioxane (2 mL) and H_2O (0.5 mL) was degassed and purged with N_2 (3 x) and then stirred at 100°C for 2 hours. TLC (PE/EtOAc = 3:1) indicated the starting material was consumed completely and three new spots had formed. The reaction mixture was diluted with H_2O (4 mL) and extracted with EtOAc (4 mL x 3). The combined organic layers were washed with brine (4 mL x 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (ISCO® 4 g SepaFlash® silica gel column) using a gradient of 0 to 12% EtOAc in PE (25 mL/min) to give the title compound as a yellow oil (70 mg, 41% yield, 90% purity). ^1H NMR (400 MHz, CDCl_3) δ ppm 0.14 - 0.43 (m, 1 H), 0.62 (dt, $J=10.13, 6.32$ Hz, 1 H), 0.74 - 0.91 (m, 1 H), 1.06 (dd, $J=11.32, 5.69$ Hz, 1 H), 1.70 (d, $J=6.50$ Hz, 3 H), 2.48 - 2.68 (m, 1 H), 3.38 (br s, 3 H), 4.88 - 5.04 (m, 1 H), 5.10 (br s, 2 H), 7.12 - 7.16 (m, 1 H), 7.28 (d, $J=1.75$ Hz, 1 H)

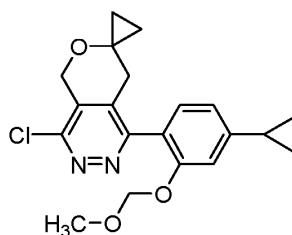
[0356] PREPARATION 108: 4'-chloro-1'-(4-(difluoromethyl)-2-(methoxymethoxy)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine]



[0357] A mixture of 1',4'-dichloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (660 mg, 2.86 mmol), 2-[4-(difluoromethyl)-2-(methoxymethoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (897.22 mg, 2.86 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (417.98 mg, 571.23 μ mol), and Cs_2CO_3 (3.72 g, 11.42 mmol) in dioxane (18 mL) and H_2O (4.5 mL) was

degassed and purged with N₂ (3 x) and then stirred at 80°C for 12 hours. TLC (PE/EtOAc = 3:1) indicated the starting material was consumed completely and two new spots had formed. The reaction mixture was diluted with H₂O (20 mL) and extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (ISCO® 12 g SepaFlash® silica gel column) using a gradient of 0 to 10% EtOAc in PE (40 mL/min). A mixture of the desired compound with its regioisomer (455 mg, mixture) was obtained as white solid. The mixture was purified by SFC (DAICEL CHIRALPAK® IK-10 µm, 50 mm x 250 mm column) using a mobile phase of CO₂ and 15% MeOH (with 0.1% NH₃OH). The title compound (retention time: 4.189 min) was obtained as a white solid (131 mg, 50.9% yield, 99% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.36 - 0.65 (m, 2 H), 0.96 (br d, *J*=18.76 Hz, 2 H), 2.28 (br d, *J*=16.88 Hz, 1 H), 2.96 (br d, *J*=17.01 Hz, 1 H), 3.37 (s, 3 H), 4.75 (br d, *J*=16.13 Hz, 2 H), 5.14 (br d, *J*=5.13 Hz, 2 H), 6.52 - 6.83 (m, 1 H), 7.29 (br d, *J*=7.88 Hz, 1 H), 7.40 (s, 1 H). The regioisomer 1'-chloro-4'-(4-(difluoromethyl)-2-(methoxymethoxy)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (retention time: 4.496 min) was obtained as a white solid (138 mg, 52.5% yield, 97% purity). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.71 (br s, 2 H), 0.86 (br s, 2 H), 2.94 (s, 2 H), 3.27 - 3.30 (m, 3 H), 4.19 - 4.59 (m, 2 H), 5.24 (br s, 2 H), 6.94 - 7.29 (m, 1 H), 7.37 (d, *J*=7.75 Hz, 1 H), 7.44 - 7.56 (m, 2 H).

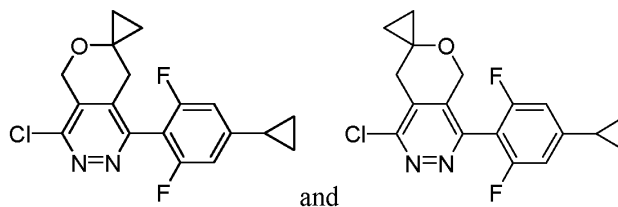
[0358] PREPARATION 109: 1'-chloro-1'-(4-cyclopropyl-2-(methoxymethoxy)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine]



[0359] To a solution of 1',4'-dichloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (500 mg, 2.16 mmol) and 2-(4-cyclopropyl-2-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (658.19 mg, 2.16 mmol) in dioxane (4 mL) and H₂O (1 mL) was added Cs₂CO₃ (2.82 g, 8.66 mmol) followed by Pd(dppf)Cl₂ (316.65 mg, 432.75 µmol). The mixture was stirred at 100°C for 12 hours under N₂. LC-MS showed the starting material was consumed completely and about 42% of desired compound was detected. The

reaction mixture was diluted with H₂O (30 mL) and extracted with EtOAc (30 mL x 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (ISCO® 4 g SepaFlash® silica gel column) using a gradient of 0 to 20% EtOAc in PE (30 mL/min). A mixture of the title compound and its regioisomer was obtained as a white solid (total 350 mg) which was purified by SFC (DAICEL CHIRALPAK® AD-H-5 µm, 30 mm x 250 mm column) using a mobile phase of CO₂ and 30% EtOH (with 0.1% NH₃OH). The title compound (retention time: 6.793 min) was obtained as a yellow solid (109 mg, 13.1% yield, 96.7% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.41 - 0.58 (m, 2 H), 0.76 (br d, *J*=1.4 Hz, 2 H), 0.91 - 1.10 (m, 4 H), 1.59 - 1.76 (m, 1 H), 1.88 - 1.99 (m, 1 H), 2.90 - 3.10 (m, 1 H), 3.36 (br s, 3 H), 4.74 (br d, *J*=1.8 Hz, 2 H), 5.09 (br s, 2 H), 6.81 (br d, *J*=7.6 Hz, 1 H), 6.99 (br s, 1 H), 7.21 (br d, *J*=7.6 Hz, 1 H). Regioisomer 1'-chloro-4'-(4-cyclopropyl-2-(methoxymethoxy)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (retention time: 7.772 min) was obtained as red solid (90 mg, 10% yield, 91% purity). ¹H NMR (400 MHz, CDCl₃) δ = 7.21 (d, *J*=7.8 Hz, 1H), 6.98 (s, 1H), 6.85 - 6.79 (m, 1H), 5.10 (s, 2H), 4.73 - 4.28 (m, 2H), 3.38 (s, 3H), 2.90 (br s, 2H), 2.02 (s, 1H), 1.99 - 1.90 (m, 1H), 1.06 - 1.00 (m, 2H), 0.99 - 0.93 (m, 2H), 0.79 - 0.73 (m, 2H), 0.71 - 0.65 (m, 2H).

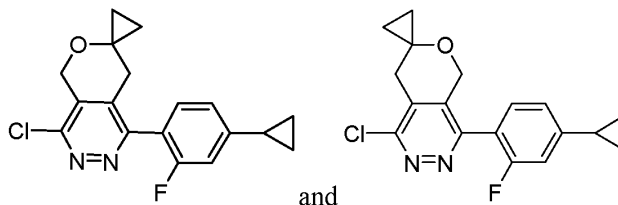
[0360] PREPARATION 110: 4'-chloro-1'-(4-cyclopropyl-2,6-difluorophenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] and 1'-chloro-4'-(4-cyclopropyl-2,6-difluorophenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine]



[0361] To a 20 mL vial were added 1',4'-dichloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (500 mg, 2.16 mmol), 2-(4-cyclopropyl-2,6-difluoro-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.61 g, 2.16 mmol), Xantphos Palladacycle G3 (205 mg, 0.216 mmol), and tripotassium tris(hydrogen phosphate) (1.38 g, 6.49 mmol) in 1,4-dioxane (10 mL) and water (2.5 mL). The vial was flushed with nitrogen and the reaction mixture was heated to 90°C with stirring overnight. The reaction mixture was allowed to cool to room temperature and then extracted with EtOAc (2 x 20 mL) and brine (20 mL). The organics were dried with MgSO₄ and filtered. The solution was concentrated and purified via flash chromatography, using a gradient of 0 to 50% EtOAc in heptane, to give a mixture of

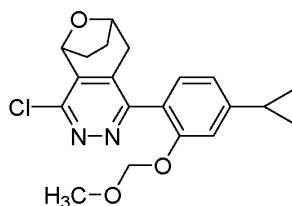
the title compounds (54 mg, 0.0774 mmol, 3.58%). ESI-MS m/z $[M+H]^+$ calc'd for $C_{18}H_{15}ClF_2N_2O$ 348.1; found 349.1.

[0362] PREPARATION 111: 4'-chloro-1'-(4-cyclopropyl-2-fluorophenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] and 1'-chloro-4'-(4-cyclopropyl-2-fluorophenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine]



[0363] To a 20 mL vial fitted with a stir bar were added 1',4'-dichloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (500 mg, 2.16 mmol), 2-(4-cyclopropyl-2-fluoro-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (567 mg, 2.16 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (177 mg, 0.216 mmol), and tripotassium tris(hydrogen phosphate) (0.92 g, 4.33 mmol) in 1,4-dioxane (10 mL) and water (2.5 mL). The vial was flushed with nitrogen and the reaction mixture was heated to 80°C with stirring overnight. The reaction mixture was allowed to cool to room temperature and extracted with EtOAc (2 x 10 mL) and brine (10 mL). The organics were dried with $MgSO_4$ and filtered. The solution was concentrated and purified via flash chromatography, using a gradient of 0 to 50% EtOAc in heptane, to give a mixture of the title compounds (338 mg, 0.511 mmol, 23.61%). ESI-MS m/z $[M+H]^+$ calc'd for $C_{18}H_{16}ClFN_2O$ 330.1; found 331.1.

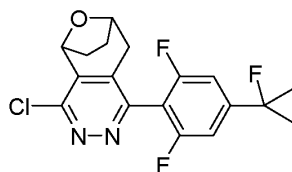
[0364] PREPARATION 112: 4-chloro-1-(2-(methoxymethoxy)-4-methylphenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine



[0365] A mixture of 1,4-dichloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine (460 mg, 2.0 mmol), Cs_2CO_3 (1.3 g, 4.0 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (146 mg, 0.2 mmol), and 2-(4-cyclopropyl-2-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.61 g, 2.0 mmol) in THF (10.4 mL) and 0.5 M K_3PO_4 (2.6 mL) was stirred in a sealed tube on metal heating block at 100°C for 30 minutes. The reaction mixture was purified by flash

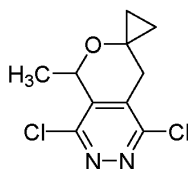
chromatography (ISCO® 40 g SepaFlash® silica gel column) using 33% EtOAc in heptane (24 mL/min) to give the title compound.

[0366] PREPARATION 113: 4-chloro-1-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-6,7,8,9-tetrahydro-5H-5,8-epoxycyclohepta[d]pyridazine

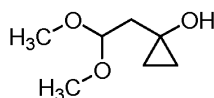


[0367] A mixture of 1,4-dichloro-6,7,8,9-tetrahydro-5H-5,8-epoxycyclohepta[d]pyridazine (231 mg, 1.00 mmol), 2-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (298 mg, 1.00 mmol), Xantphos Palladacycle G4 (96 mg, 0.100 mmol), tripotassium phosphate (637 mg, 3.00 mmol), toluene (10 mL) and water (2.5 mL) was evacuated and back-filled with nitrogen (3 x) and then heated to 60°C and stirred for 4 hours. The mixture was diluted with saturated NH₄Cl (50 mL) and extracted with DCM (50 mL x 3). The organic layers were washed with brine (50 mL), dried over Na₂SO₄, and concentrated to give a mixture of regioisomers, which were separated by flash chromatography (ISCO® 80 g x 2 stacked silica columns) using heptane/dioxane (4:1). The first eluting isomer was assigned as the title compound (75 mg, 20.45%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.10 - 1.18 (m, 2 H), 1.48 - 1.66 (m, 3 H), 2.02 - 2.28 (m, 4 H), 2.95 - 3.06 (m, 1 H), 4.70 - 4.79 (m, 1 H), 5.23 - 5.32 (m, 1 H), 6.84 - 6.97 (m, 2 H).

[0368] PREPARATION 114: 1',4'-dichloro-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-d]pyridazine]



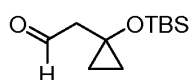
[0369] STEP 1: 1-(2,2-dimethoxyethyl)cyclopropan-1-ol



[0370] To a solution of methyl 3,3-dimethoxypropanoate (60 g, 404.98 mmol, 57.42 mL) in THF (800 mL) was added a solution of tetraisopropoxytitanium (23.02 g, 81.00 mmol, 23.90 mL) at 0°C, followed by dropwise addition of bromo(ethyl)magnesium (3 M in Et₂O, 337.48 mL) at 0°C over a 1-hour period. The reaction mixture was stirred at 0°C for 2 hours. TLC

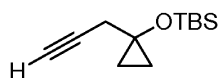
(PE/EtOAc = 5:1) indicated the starting material was consumed completely and two new spots had formed. The reaction mixture was diluted with THF (500 mL) and quenched with aq NH₄Cl (2000 mL). The resulting white precipitate was filtered off and the filtrate was extracted with EtOAc (1000 mL x 3). The combined organic phase was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (ISCO® 330 g SepaFlash® silica gel column) using a gradient of 0 to 15% EtOAc in PE (100 mL/min) to give the title compound as a yellow oil (30 g, 51% yield, 90% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.42 - 0.48 (m, 2 H), 0.74 - 0.80 (m, 2 H), 1.88 (d, *J*=5.75 Hz, 2 H), 3.39 (s, 6 H), 4.68 (t, *J*=5.75 Hz, 1 H).

[0371] STEP 2: 2-(1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)acetaldehyde



[0372] A mixture of 1-(2,2-dimethoxyethyl)cyclopropanol (15 g, 102.61 mmol), 2,6-dimethylpyridine (54.97 g, 513.05 mmol, 59.75 mL), TBSOTf (29.84 g, 112.87 mmol, 25.92 mL) and TMSOTf (34.21 g, 153.92 mmol, 27.81 mL) in DCM (100 mL) was degassed and purged with N₂ (3 x) and then stirred at 25°C for 10 hours under N₂ atmosphere. TLC (PE/EtOAc = 10:1) indicated the starting material was consumed completely and two new spots had formed. The reaction mixture was quenched with aq NH₄Cl (100 mL) and extracted with DCM (100 mL x 3). The combined organic phase was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (ISCO® 330 g SepaFlash® silica gel column) using a gradient of 0 to 5% EtOAc in PE (100 mL/min). The title compound was obtained as a yellow oil (12 g, 49% yield, 90% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.09 (s, 6 H), 0.58 - 0.64 (m, 2 H), 0.83 (s, 9 H), 0.84 - 0.86 (m, 2 H), 2.46 (d, *J*=2.75 Hz, 2 H), 9.94 (t, *J*=2.81 Hz, 1 H).

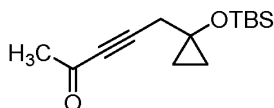
[0373] STEP 3: *tert*-butyl-dimethyl-(1-prop-2-ynylcyclopropoxy)silane



[0374] To a solution of 2-(1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)acetaldehyde (11.5 g, 53.64 mmol) in MeOH (90 mL) were added 1-diazo-1-dimethoxyphosphoryl-propan-2-one (20.61 g, 107.29 mmol) and K₂CO₃ (7.41 g, 53.64 mmol). The mixture was stirred at 0°C for 10 hours. TLC (PE/EtOAc = 10:1) indicated the starting material was consumed completely and one new spot had formed. The reaction mixture was quenched with aq NH₄Cl (200 mL) and extracted with DCM (200 mL x 3). The combined organic phase was dried over

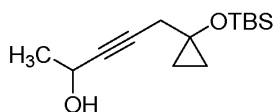
anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (ISCO® 330 g SepaFlash® silica gel column) using a gradient of 0 to 1% EtOAc in PE (100 mL/min). The title compound was obtained as a colorless oil (5.3 g, 44% yield, 95% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.10 - 0.14 (m, 6 H), 0.69 - 0.72 (m, 2 H), 0.73 (br s, 2 H), 0.86 (s, 9 H), 1.95 (t, *J*=2.44 Hz, 1 H), 2.59 (d, *J*=2.50 Hz, 2 H).

[0375] STEP 4: 5-(1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)pent-3-yn-2-one



[0376] A 50-mL flame-dried flask was charged with *tert*-butyl-dimethyl-(1-prop-2-ynylcyclopropoxy)silane (15.7 g, 74.62 mmol) and THF (40 mL). The solution was cooled to -78°C and *n*-BuLi (2.5 M in hexane, 32.83 mL) was added dropwise. The solution was stirred at -78°C for 30 minutes, followed by dropwise addition of *N*-methoxy-*N*-methyl-acetamide (8.46 g, 82.09 mmol, 8.73 mL). The reaction mixture was warmed to 0°C and stirred for 3 hours. TLC (PE/EtOAc = 20:1) indicated the starting material was consumed completely and one new spot had formed. The reaction mixture was poured into saturated aq NH₄Cl (100 mL) in an ice bath and the phases were separated. The aqueous layer was extracted with EtOAc (100 mL x 3) and the combined organic extracts were washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (ISCO® 220 g SepaFlash® silica gel column) using a gradient of 0 to 4% EtOAc in PE (100 mL/min). The title compound was obtained as a colorless oil (15.24 g, 80.89% yield, 90% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.14 (s, 6 H), 0.68 (s, 2 H), 0.80 (s, 2 H), 0.87 (s, 9 H), 2.33 (s, 3 H), 2.73 (s, 2 H).

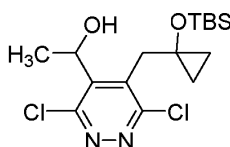
[0377] STEP 5: 5-(1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)pent-3-yn-2-ol



[0378] To a solution of 5-(1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)pent-3-yn-2-one (15.24 g, 60.37 mmol) and trichlorocerium (19.35 g, 78.49 mmol, 4.93 mL) in MeOH (50 mL) at 25°C was added NaBH₄ (3.05 g, 80.62 mmol). The reaction mixture was stirred for 0.5 hours. TLC (PE/EtOAc = 20:1) indicated starting material was consumed completely and one new spot had formed. The mixture was poured into saturated aq NH₄Cl (100 mL) in an ice bath and the phases were separated. The aqueous layer was extracted with EtOAc (100 x 3 mL) and the combined organic extracts were washed with brine (100 mL), dried over

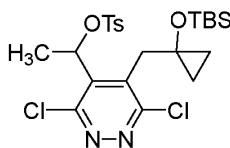
Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (ISCO® 80 g SepaFlash® silica gel column) using a gradient of 0 to 5% EtOAc in PE (75 mL/min). The title compound was obtained as a colorless oil (12.8 g, 85.3% yield, 90% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.12 (s, 6 H), 0.62 - 0.69 (m, 2 H), 0.70 - 0.76 (m, 2 H), 0.86 (s, 9 H), 1.42 (d, *J*=6.50 Hz, 3 H), 2.60 (s, 2 H), 4.50 (q, *J*=6.50 Hz, 1 H).

[0379] STEP 6: 1-(5-((1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)methyl)-3,6-dichloropyridazin-4-yl)ethan-1-ol



[0380] A mixture of 5-(1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)pent-3-yn-2-ol (6.6 g, 25.94 mmol) and 3,6-dichloro-1,2,4,5-tetrazine (5.09 g, 33.72 mmol) in toluene (30 mL) was degassed and purged with N₂ (3 x) and then stirred at 100°C for 48 hours under N₂ atmosphere. TLC (PE/EtOAc = 20:1) indicated some starting material remained and two new spots had formed. The mixture was filtered. The filtrate was evaporated under vacuum and the residue was purified by flash chromatography (ISCO® 120 g SepaFlash® silica gel column) using a gradient of 0 to 10% EtOAc in PE (75 mL/min). The title compound was obtained as a brown oil (1.81 g, 18.6% yield, 90% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm -0.13 (s, 3 H), -0.01 (s, 3 H), 0.56 - 0.66 (m, 1 H), 0.74 (s, 9 H), 0.83 (dt, *J*=11.16, 6.61 Hz, 1 H), 0.88 - 0.98 (m, 1 H), 1.13 - 1.21 (m, 1 H), 1.57 (d, *J*=6.75 Hz, 3 H), 2.80 (d, *J*=13.38 Hz, 1 H), 4.24 - 4.33 (m, 2 H), 5.44 (q, *J*=6.55 Hz, 1 H).

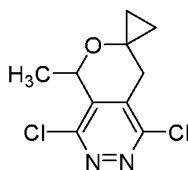
[0381] STEP 7: 1-(5-((1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)methyl)-3,6-dichloropyridazin-4-yl)ethyl 4-methylbenzenesulfonate



[0382] To a solution of 1-(5-((1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)methyl)-3,6-dichloropyridazin-4-yl)ethan-1-ol (5.4 g, 14.31 mmol) in acetone (80 mL) was added K₂CO₃ (5.93 g, 42.93 mmol) and TsCl (5.46 g, 28.62 mmol). The mixture was stirred at 70°C for 18 hours. TLC (PE/EtOAc = 5:1) indicated some starting material remained and two new spots had formed. The mixture was filtered. The filtrate was evaporated under vacuum to give a

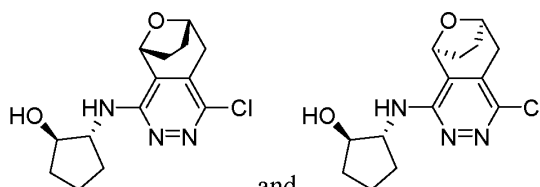
residue, which was purified by flash chromatography (ISCO® 40 g SepaFlash® silica gel column) using a gradient of 0 to 10% EtOAc in PE (55 mL/min). The title compound was obtained as a colorless oil (4.54 g, 59.7% yield, 90% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.01 - 0.09 (m, 6 H), 0.36 - 0.49 (m, 1 H), 0.56 (br d, *J*=9.26 Hz, 1 H), 0.71 (s, 9 H), 0.82 - 0.94 (m, 2 H), 1.85 (d, *J*=6.88 Hz, 3 H), 2.39 (s, 3 H), 3.06 (br d, *J*=14.51 Hz, 1 H), 3.67 - 3.78 (m, 1 H), 6.15 (q, *J*=6.75 Hz, 1 H), 7.19 (m, *J*=8.13 Hz, 2 H), 7.56 (m, *J*=8.25 Hz, 2 H).

[0383] STEP 8: 1',4'-dichloro-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine]



[0384] To a solution of 1-(5-((1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)methyl)-3,6-dichloropyridazin-4-yl)ethyl 4-methylbenzenesulfonate (4.45 g, 8.37 mmol) in THF (250 mL) was added TBAF (1 M, 20.93 mL). The mixture was stirred at -20°C for 3 hours. TLC (PE/EtOAc = 20:1) indicated the starting material was consumed completely and one new spot had formed. The reaction mixture was quenched with aq NH₄Cl (10 mL) and extracted with DCM (10 mL x 3). The combined organic phase was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (ISCO® 12 g SepaFlash® silica gel column) using a gradient of 0 to 8% EtOAc in PE (35 mL/min). The title compound was obtained as a yellow oil (1.06 g, 51.5% yield, 95% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.49 (dd, *J*=10.26, 6.75 Hz, 1 H), 0.79 (dt, *J*=10.32, 6.22 Hz, 1 H), 0.87 - 0.95 (m, 1 H), 1.10 - 1.18 (m, 1 H), 1.65 (d, *J*=6.63 Hz, 3 H), 2.67 - 2.75 (m, 1 H), 2.96 - 3.02 (m, 1 H), 4.92 (q, *J*=6.63 Hz, 1 H).

[0385] PREPARATION 115 and PREPARATION 116: (1*R*,2*R*)-2-(((5*R*,8*S*)-1-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclopentan-1-ol and (1*R*,2*R*)-2-(((5*S*,8*R*)-1-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclopentan-1-ol

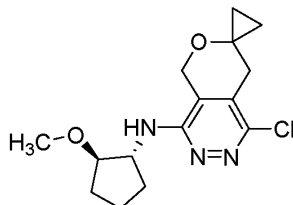


and

115

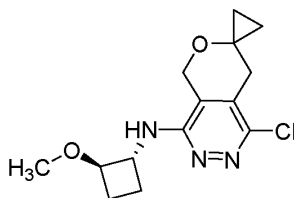
[0386] The title compounds were synthesized like Preparations 84 and 85.

[0387] PREPARATION 117: 1'-chloro-*N*-((1*R*,2*R*)-2-methoxycyclopentyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-amine



[0388] A mixture of 1',4'-dichloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (0.20 g, 0.844 mmol), (1*R*,2*R*)-2-methoxycyclopentyl-1-amine hydrochloride (0.32 g, 2.11 mmol), sodium iodide (0.63 g, 4.22 mmol), and DIPEA (1.5 mL, 8.44 mmol) in NMP (3 mL) was stirred in a microwave reactor on high absorbance for 1 hour at 180°C. The reaction mixture was transferred to a 100 mL separatory funnel and the layers were separated. The bottom layer was diluted with H₂O (20 mL) to furnish a brown solution. The crude product was extracted with EtOAc (2 x 20 mL). The organic extracts were combined, dried over Na₂SO₄, filtered, rinsed with EtOAc, and concentrated via rotary evaporation to provide the crude product as a brown oil (0.864 g). The crude material was dissolved in toluene (3 mL), concentrated via rotary evaporation, reconstituted in toluene (3 mL) and purified via medium pressure chromatography (RediSep[®] Rf Gold 80 g silica gel column) using a gradient of 0 to 100% EtOAc in heptane. The early fractions were combined, concentrated via rotary evaporation, and dried *in vacuo* to provide the title compound as an oil (29.3 mg, 11.2%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.57 - 0.69 (m, 2 H), 0.91 - 1.02 (m, 2 H), 1.43 - 1.53 (m, 1 H), 1.65 - 1.79 (m, 2 H), 1.80 - 1.90 (m, 1 H), 1.90 - 2.00 (m, 1 H), 2.40 (td, *J*=13.55, 8.03 Hz, 1 H), 2.67 - 2.80 (m, 2 H), 3.46 (s, 3 H), 3.68 - 3.82 (m, 2 H), 4.33 - 4.50 (m, 2 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₁₅H₂₀ClN₃O₂ 309.12; found 310.1.

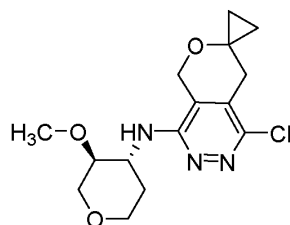
[0389] PREPARATION 118: 1'-chloro-*N*-((1*R*,2*R*)-2-methoxycyclobutyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-amine



[0390] To a 20 mL microwave vial was added 1',4'-dichloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (330 mg, 1.43 mmol), DIPEA (2.5

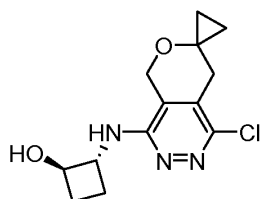
mL, 14.3 mmol), and (1*R*,2*R*)-2-methoxycyclobutanamine (361 mg, 3.57 mmol) in NMP (7.5 mL) was heated in a Biotage microwave reactor at 180°C for 1 hour. The reaction mixture was extracted with EtOAc (2 x 50 mL) and brine (50 mL). The organics were combined, dried with MgSO₄, and concentrated under reduced pressure to give an oil. The crude product was purified via flash chromatography, using a gradient of 0 to 100% EtOAc in heptane, to give the title compound as the first eluting peak (33 mg, 7.8%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.54 - 0.66 (m, 2 H), 0.94 - 1.02 (m, 2 H), 1.45 (br t, *J*=9.79 Hz, 1 H), 1.67 (tdd, *J*=10.85, 10.85, 9.29, 8.41 Hz, 1 H), 2.08 - 2.22 (m, 1 H), 2.31 - 2.43 (m, 1 H), 2.67 - 2.78 (m, 2 H), 3.34 (s, 3 H), 3.84 (q, *J*=7.36 Hz, 1 H), 4.45 (d, *J*=1.51 Hz, 2 H), 4.50 - 4.63 (m, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₁₄H₁₈ClN₃O₂ 295.1; found 296.1.

[0391] PREPARATION 119: 1'-chloro-*N*-((3*S*,4*R*)-3-methoxytetrahydro-2*H*-pyran-4-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-amine



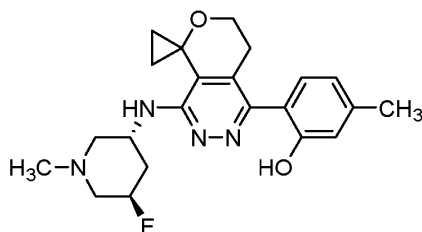
[0392] To a 20 mL microwave vial fitted with a stir bar were added (3*S*,4*R*)-3-methoxytetrahydro-2*H*-pyran-4-amine (710 mg, 5.41 mmol), 1',4'-dichloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (500 mg, 2.16 mmol), DIPEA (3.8 mL, 21.6 mmol), and sodium iodide (1622 mg, 10.8 mmol) in NMP (11 mL). The reaction mixture was stirred in a Biotage microwave reactor at 180°C for 1 hour and then extracted with EtOAc (2 x 50 mL) and brine (50 mL). The organics were separated and dried with MgSO₄. The solution was filtered, concentrated under reduced pressure, and purified by flash chromatography, using a gradient of 20 to 80% EtOAc in heptane, to give the title compound as the first eluting peak (21 mg, 2.98%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.57 - 0.68 (m, 2 H), 0.97 - 0.99 (m, 2 H), 1.53 - 1.56 (m, 1 H), 2.58 - 2.81 (m, 3 H), 3.26 - 3.46 (m, 5 H), 3.55 (td, *J*=11.60, 2.29 Hz, 1 H), 3.88 (dt, *J*=11.74, 3.58 Hz, 1 H), 4.08 - 4.26 (m, 2 H), 4.38 - 4.49 (m, 2 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₁₅H₂₀ClN₃O₃ 325.1; found 326.1.

[0393] PREPARATION 120: (1*R*,2*R*)-2-((1'-chloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclobutan-1-ol

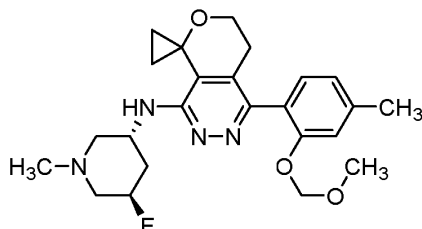


[0394] To a 20 mL microwave vial were added 1',4'-dichloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-d]pyridazine] (600 mg, 2.60 mmol), DIPEA (4.5 mL, 26.0 mmol), (1*R*,2*R*)-2-aminocyclobutan-1-ol (566 mg, 6.49 mmol), and sodium iodide (1946 mg, 13.0 mmol) in NMP (10 mL). The reaction mixture was heated in a Biotage microwave reactor at 180°C for 1 hour and then extracted with EtOAc (2 x 50 mL) and brine (50 mL). The organics were separated, dried with MgSO₄, filtered and concentrated under reduced pressure. The resulting oil was purified by flash chromatography, eluting with a gradient of 0 to 100% EtOAc in heptane, to give the title compound as the first eluting peak (91 mg, 11%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.59 - 0.66 (m, 2 H), 0.90 - 1.03 (m, 2 H), 1.46 - 1.63 (m, 1 H), 1.71 - 1.85 (m, 1 H), 2.14 - 2.28 (m, 2 H), 2.73 - 2.74 (s, 2 H), 3.52 - 3.65 (m, 1 H), 3.90 - 4.06 (m, 2 H), 4.43 - 4.44 (s, 2 H), 4.78 (br s, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₁₃H₁₆ClN₃O₂ 281.1; found 282.0.

[0395] EXAMPLE 233: 2-(4'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-7',8'-dihydrospiro[cyclopropane-1,5'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol



[0396] STEP 1: *N*-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)-1'-(2-(methoxymethoxy)-4-methylphenyl)-7',8'-dihydrospiro[cyclopropane-1,5'-pyrano[3,4-*d*]pyridazin]-4'-amine



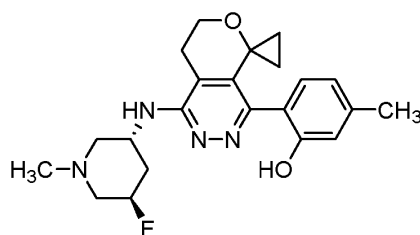
[0397] To a mixture of 4'-chloro-1'-(2-(methoxymethoxy)-4-methylphenyl)-7',8'-dihydrospiro[cyclopropane-1,5'-pyrano[3,4-*d*]pyridazine] (60 mg, 173.01 μmol) and (3*R*,5*R*)-

5-fluoro-1-methylpiperidin-3-amine (141.94 mg, 692.03 μmol , 2 HCl) in toluene (1 mL) were added Cs_2CO_3 (225.48 mg, 692.03 μmol), BINAP (21.55 mg, 34.60 μmol) and $\text{Pd}(\text{OAc})_2$ (3.88 mg, 17.30 μmol) in one portion under N_2 . The mixture was stirred at 100°C for 12 hours. LC-MS showed the desired product was obtained. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (ISCO® SepaFlash® 4 g silica gel column) using a gradient of 0 to 5% MeOH in DCM (20 mL/min). The title compound was obtained as a yellow oil (74.3 mg, 75.5% yield, 77.8% purity). ESI-MS m/z $[\text{M}+\text{H}]^+$ 443.1.

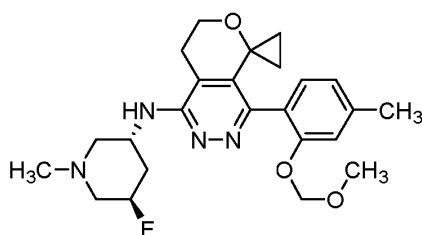
[0398] STEP 2: 2-(4'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-7',8'-dihydrospiro[cyclopropane-1,5'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylpheno

[0399] A mixture of *N*-((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)-1'-(2-(methoxymethoxy)-4-methylphenyl)-7',8'-dihydrospiro[cyclopropane-1,5'-pyrano[3,4-*d*]pyridazin]-4'-amine (65 mg, 146.88 μmol) in DCM (3 mL) and TFA (0.6 mL) was stirred at 28°C for 2 hours. LC-MS showed the desired product was obtained. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by preparative HPLC (Boston Prime C18-5 μm , 30 mm x 150 mm column) using a gradient of 5 to 30% ACN in water (with FA). A formic acid salt of the title compound was obtained as a yellow solid (20.6 mg, 29.3% yield, 98.4% purity). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 0.98 - 1.12 (m, 2 H), 1.69 - 1.84 (m, 2 H), 1.85 - 2.11 (m, 2 H), 2.27 (d, $J=6.82$ Hz, 7 H), 2.44 - 2.49 (m, 1 H), 2.53 - 2.60 (m, 3 H), 2.65 - 2.77 (m, 1 H), 3.78 (t, $J=5.72$ Hz, 2 H), 4.32 (d, $J=7.70$ Hz, 1 H), 4.48 (br s, 1 H), 4.72 - 4.95 (m, 1 H), 6.71 (d, $J=7.70$ Hz, 1 H), 6.74 (s, 1 H), 7.03 (d, $J=7.48$ Hz, 1 H), 9.57 (br s, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ 399.1.

[0400] EXAMPLE 234: 2-(1'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-7',8'-dihydrospiro[cyclopropane-1,5'-pyrano[3,4-*d*]pyridazin]-4'-yl)-5-methylphenol



[0401] STEP 1: *N*-((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)-4'-(2-(methoxymethoxy)-4-methylphenyl)-7',8'-dihydrospiro[cyclopropane-1,5'-pyrano[3,4-*d*]pyridazin]-1'-amine

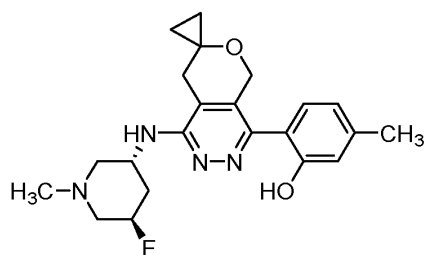


[0402] To a mixture of 1'-chloro-4'-(2-(methoxymethoxy)-4-methylphenyl)-7',8'-dihydrospiro[cyclopropane-1,5'-pyrano[3,4-*d*]pyridazine] (76 mg, 219.14 μ mol) and (3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-amine (179.78 mg, 876.57 μ mol, 2 HCl) in toluene (1 mL) were added Cs_2CO_3 (285.60 mg, 876.57 μ mol), BINAP (27.29 mg, 43.83 μ mol) and $\text{Pd}(\text{OAc})_2$ (4.92 mg, 21.91 μ mol) in one portion under N_2 . The mixture was stirred at 100°C for 12 hours. LC-MS showed the desired product was obtained. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by flash chromatography (ISCO® SepaFlash® 4 g silica gel column) using a gradient of 0 to 5% MeOH in DCM gradient (20 mL/min). The title compound was obtained as a yellow oil (59.4 mg, 61.3%). ESI-MS m/z $[\text{M}+\text{H}]^+$ 443.3.

[0403] STEP 2: 2-(1'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-7',8'-dihydrospiro[cyclopropane-1,5'-pyrano[3,4-*d*]pyridazin]-4'-yl)-5-methylphenol

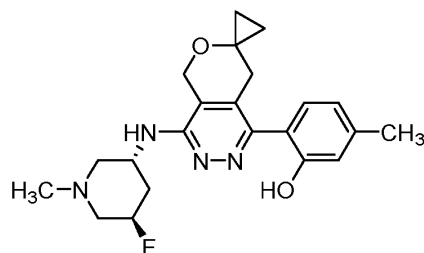
[0404] A mixture of *N*-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)-4'-(2-(methoxymethoxy)-4-methylphenyl)-7',8'-dihydrospiro[cyclopropane-1,5'-pyrano[3,4-*d*]pyridazin]-1'-amine (59 mg, 133.33 μ mol) in DCM (3 mL) and TFA (0.6 mL) was stirred at 28°C for 2 hours. LC-MS showed the desired product was obtained. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by preparative HPLC (Boston Prime C18-5 μ m, 30 mm x 150 mm column) using a gradient of 5 to 30% ACN in water (with FA). A formic acid salt of the title compound was obtained as a white solid (10 mg, 18% yield, 97.7% purity). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 0.59 - 1.03 (m, 4 H), 1.67 - 1.88 (m, 1 H), 1.96 (br t, $J=9.90$ Hz, 1 H), 2.02 - 2.18 (m, 2 H), 2.24 (d, $J=18.93$ Hz, 6 H), 2.53 - 2.60 (m, 2 H), 2.80 - 3.02 (m, 2 H), 3.92 (br t, $J=5.83$ Hz, 2 H), 4.55 (br s, 1 H), 4.84 - 5.06 (m, 1 H), 5.68 (d, $J=8.14$ Hz, 1 H), 6.62 (d, $J=7.48$ Hz, 1 H), 6.66 (s, 1 H), 6.84 (br d, $J=6.38$ Hz, 1 H), 9.34 (br s, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ 399.1.

[0405] EXAMPLE 235: 2-(1'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)-5-methylphenol

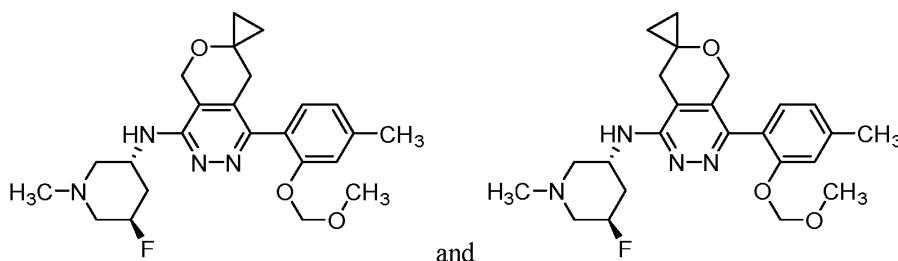


and

[0406] EXAMPLE 236: 2-(4'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol



[0407] STEP 1: *N*-((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)-1'-(2-(methoxymethoxy)-4-methylphenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-amine and *N*-((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)-4'-(2-(methoxymethoxy)-4-methylphenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-amine



and

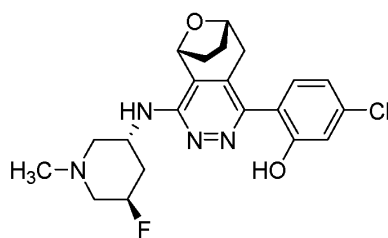
[0408] A mixture of 4'-chloro-1'-(2-(methoxymethoxy)-4-methylphenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] and 1'-chloro-4'-(2-(methoxymethoxy)-4-methylphenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (170 mg), (3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-amine (402.15 mg, 1.96 mmol, 2 HCl), Pd(OAc)₂ (22.01 mg, 98.04 μmol), BINAP (122.09 mg, 196.07 μmol) and Cs₂CO₃ (958.27 mg, 2.94 mmol) in toluene (10 mL) was stirred at 100°C for 12 hours. LC-MS showed the starting material was consumed and the desired product was obtained. The reaction mixture was concentrated under reduced pressure to give crude product, which was purified by flash chromatography (ISCO® SepaFlash® 20 g silica gel column) using a gradient of 0 to 3% MeOH in DCM (35 mL/min). A mixture of the title compounds was

obtained as a brown oil (171 mg, 95% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.44 (s, 1 H), 0.66 (s, 1 H), 0.82 - 1.01 (m, 2 H), 2.20 - 2.82 (m, 2 H), 2.36 - 2.47 (m, 5 H), 3.07 (s, 1 H), 3.41(d, *J*=9.7 Hz, 3 H), 4.53 (br d, *J*=4.8 Hz, 1 H), 4.75 - 4.99 (m, 2 H), 5.10 (br d, *J*=7.0 Hz, 2 H), 5.32 (s, 2 H), 6.94 (d, *J*=7.7 Hz, 1 H), 7.04 (d, *J*=3.5 Hz, 1 H), 7.23 (d, *J*=7.3 Hz, 1 H).

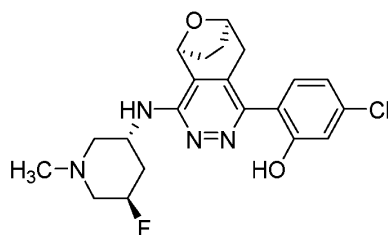
[0409] STEP 2: 2-(1'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)-5-methylphenol and 2-(4'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol

[0410] To a mixture of *N*-((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)-1'-(2-(methoxymethoxy)-4-methylphenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-amine and *N*-((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)-4'-(2-(methoxymethoxy)-4-methylphenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-amine (171 mg) in DCM (15 mL) was added TFA (4.62 g, 40.52 mmol, 3 mL) at 20°C. The reaction mixture was stirred at 20°C for 12 hours. LC-MS showed the starting material was converted to the desired product. The reaction mixture was concentrated under reduced pressure to give crude product, which was purified by preparative HPLC (Method C) to give a mixture of two isomers (63 mg), which was further purified by SFC (DAICEL CHIRALPAK® IG-10 μm, 30 mm x 250 mm column) using a mobile phase of CO₂ and 60% EtOH (with 0.1% NH₃H₂O). The title compound of Example 235 was obtained as a white solid (18.2 mg, 100% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.68 - 0.78 (m, 2 H), 1.06 - 1.14 (m, 2 H), 1.69 - 1.86 (m, 2 H), 2.22 - 2.33 (m, 1 H), 2.36 - 2.38 (m, 3 H), 2.42 (br s, 3 H), 2.48 - 2.64 (m, 4 H), 2.65 - 2.85 (m, 1 H), 2.96 - 3.23 (m, 1 H), 4.67 - 4.97 (m, 5 H), 6.74 (d, *J*=8.1 Hz, 1 H), 6.96 (s, 1 H), 7.05 (d, *J*=7.9 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ 399.1. The title compound of Example 236 was obtained as a white solid (15.8 mg, 100% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.48 - 0.59 (m, 2 H), 0.88 (s, 1 H), 0.91 - 0.98 (m, 2 H), 1.70 - 1.90 (m, 1 H), 2.31 - 2.38 (m, 4 H), 2.38 - 2.48 (m, 2 H), 2.48 - 2.62 (m, 2 H), 2.70 (br s, 1 H), 2.96 (s, 2 H), 3.08 (br s, 1 H), 4.54 (br s, 3 H), 4.80 (br s, 2 H), 6.75 (d, *J*=8.1 Hz, 1 H), 6.95 (s, 1 H), 7.30 (br s, 1 H); ESI-MS *m/z* [M+H]⁺ 399.1.

[0411] EXAMPLE 237: 5-chloro-2-((5*R*,8*S*)-4-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol

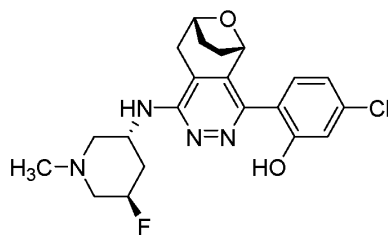


[0412] EXAMPLE 238: 5-chloro-2-((5*S*,8*R*)-4-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol

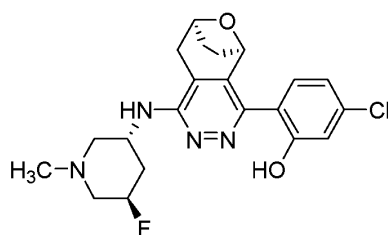


[0413] A mixture of 5-chloro-2-(4-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol (160 mg, 0.50 mmol), Cs₂CO₃ (484 mg, 1.49 mmol), Pd₂(dba)₃ (45 mg, 0.0495 mmol), R-BINAP (62 mg, 0.0990 mmol) and (3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-amine (112 mg, 0.545 mmol, 2 HCl) in toluene (5 mL) was stirred in a sealed tube on a metal heating block at 100°C for 16 hours. The reaction mixture was concentrated under vacuum to give a crude product mixture, which was purified by preparative HPLC (Method A) using a gradient of 10 to 30% ACN (0.035% TFA) in water (0.005% TFA). A TFA salt of the title compound of Example 237 was obtained as a colorless oil (5.5 mg, 2.1%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.69 - 1.82 (m, 1 H), 1.98 - 2.18 (m, 2 H), 2.23 - 2.32 (m, 2 H), 2.36 (d, *J*=18.34 Hz, 1 H), 2.54 - 2.66 (m, 1 H), 2.99 (s, 3 H), 3.01 - 3.10 (m, 1 H), 3.11 - 3.19 (m, 1 H), 3.32 - 3.45 (m, 1 H), 3.76 - 3.89 (m, 2 H), 4.74 - 4.82 (m, 2 H), 5.31 (br d, *J*=6.60 Hz, 2 H), 7.03 - 7.13 (m, 2 H), 7.33 (d, *J*=8.25 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ 419.2. A TFA salt of the title compound of Example 238 was obtained as a pink oil (9.5 mg, 3.6%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.72 - 1.81 (m, 1 H), 2.05 - 2.12 (m, 1 H), 2.11 - 2.32 (m, 3 H), 2.33 - 2.40 (m, 1 H), 2.50 - 2.65 (m, 1 H), 3.00 (s, 3 H), 3.03 - 3.11 (m, 1 H), 3.12 - 3.19 (m, 1 H), 3.35 - 3.47 (m, 1 H), 3.76 - 3.87 (m, 2 H), 4.75 - 4.81 (m, 2 H), 5.20 - 5.39 (m, 2 H), 7.04 - 7.10 (m, 2 H), 7.34 (d, *J*=8.07 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ 419.2.

[0414] EXAMPLE 239: 5-chloro-2-((5*S*,8*R*)-1-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)phenol

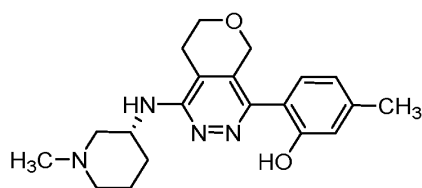


[0415] EXAMPLE 240: 5-chloro-2-(((5*R*,8*S*)-1-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)phenol



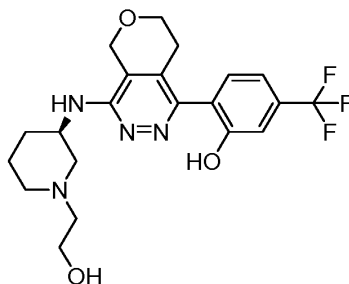
[0416] A mixture of 5-chloro-2-(1-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)phenol (160 mg, 0.50 mmol), Cs₂CO₃ (484 mg, 1.49 mmol), Pd₂(dba)₃ (45 mg, 0.0495 mmol), R-BINAP (62 mg, 0.0990 mmol) and (3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-amine (112 mg, 0.545 mmol, 2 HCl) in toluene (5 mL) was stirred in a sealed tube on a metal heating block at 100°C for 16 hours. The reaction mixture was concentrated under vacuum to give a crude product mixture, which was purified by preparative HPLC (Method A) using a gradient of 10 to 30% ACN (0.035% TFA) in water (0.005% TFA). A TFA salt of the title compound of Example 239 was obtained as a pink oil (19 mg, 7.2%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.78 - 1.92 (m, 1 H), 2.00 - 2.18 (m, 3 H), 2.22 - 2.33 (m, 1 H), 2.47 - 2.61 (m, 2 H), 2.99 (s, 3 H), 3.04 - 3.19 (m, 2 H), 3.34 - 3.48 (m, 1 H), 3.73 - 3.90 (m, 2 H), 4.72 - 4.86 (m, 1 H), 4.86 - 4.91 (m, 2 H), 5.18 - 5.38 (m, 1 H), 7.06 - 7.14 (m, 2 H), 7.34 - 7.38 (m, 1 H); ESI-MS *m/z* [M+H]⁺ 419.2. A TFA salt of the title compound of Example 240 was obtained as a pink oil (16 mg, 6.0%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.79 - 1.89 (m, 1 H), 1.94 - 2.21 (m, 3 H), 2.21 - 2.36 (m, 1 H), 2.45 - 2.61 (m, 2 H), 2.99 (s, 3 H), 3.00 - 3.17 (m, 2 H), 3.32 - 3.47 (m, 1 H), 3.76 - 3.86 (m, 2 H), 4.74 - 4.87 (m, 3 H), 5.21 - 5.39 (m, 1 H), 7.06 - 7.17 (m, 2 H), 7.30 - 7.39 (m, 1 H); ESI-MS *m/z* [M+H]⁺ 419.2.

[0417] EXAMPLE 241: (*R*)-5-methyl-2-(1-((1-methylpiperidin-3-yl)amino)-7,8-dihydro-5*H*-pyrano[3,4-*d*]pyridazin-4-yl)phenol

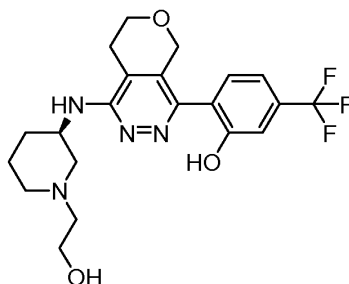


[0418] A mixture of 1-chloro-4-(2-(methoxymethoxy)-4-methylphenyl)-7,8-dihydro-5H-pyrano[3,4-d]pyridazine (60 mg, 0.187 mmol), (*R*)-1-methylpiperidin-3-amine (26 mg, 0.224 mmol), Pd₂(dba)₃ (17 mg, 0.0187 mmol), R-BINAP (23 mg, 0.0374 mmol), and Cs₂CO₃ (183 mg, 0.561 mmol) in toluene (4.8 mL) was purged with nitrogen for 5 minutes, then heated at 100°C under nitrogen overnight. The mixture was treated with water, extracted with EtOAc, washed with brine, dried over MgSO₄, and concentrated. The resulting residue was dissolved in dioxane (2 mL). Hydrogen chloride in dioxane (0.19 mL, 0.748 mmol) was added. The mixture was stirred at room temperature for 4 hours and then purified by preparative HPLC (Phenomenex Gemini C18, 5 μm, 30 mm ID x 150 mm column) using a gradient of 10 to 100% ACN (0.035% TFA) in water (0.05% TFA) with a slow ramp from 10-60% ACN. Fractions containing product were evaporated to afford the title compound as a clear oil (9.3 mg, 11%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.70 - 2.01 (m, 2 H), 2.08 - 2.27 (m, 2 H), 2.37 (s, 3 H), 2.77 (br s, 2 H), 2.86 - 3.02 (m, 5 H), 3.56 (br d, *J*=14.31 Hz, 1 H), 3.76 - 3.86 (m, 1 H), 4.04 - 4.12 (m, 2 H), 4.40 - 4.54 (m, 1 H), 4.56 - 4.62 (m, 2 H), 6.85 - 6.92 (m, 2 H), 7.17 - 7.23 (m, 1 H); ESI-MS [*M*+H]⁺ calc'd for C₂₀H₂₆N₄O₂, 354.21; found, 355.4.

[0419] EXAMPLE 242: (*R*)-2-(4-((1-(2-hydroxyethyl)piperidin-3-yl)amino)-7,8-dihydro-5H-pyrano[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol

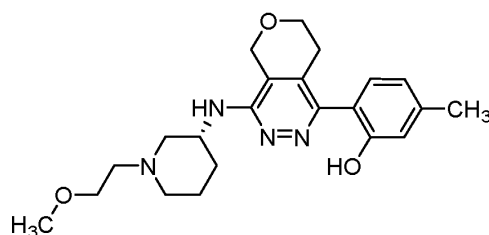


[0420] EXAMPLE 243: (*R*)-2-(1-((1-(2-hydroxyethyl)piperidin-3-yl)amino)-7,8-dihydro-5H-pyrano[3,4-d]pyridazin-4-yl)-5-(trifluoromethyl)phenol



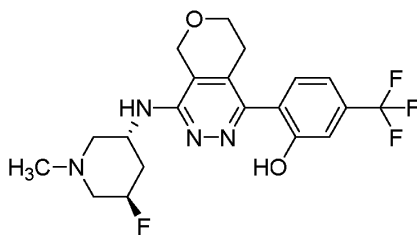
[0421] To a mixture of (*R*)-2-(3-((1-chloro-7,8-dihydro-5H-pyrano[3,4-*d*]pyridazin-4-yl)amino)piperidin-1-yl)ethan-1-ol and (*R*)-2-(3-((4-chloro-7,8-dihydro-5H-pyrano[3,4-*d*]pyridazin-1-yl)amino)piperidin-1-yl)ethan-1-ol (in total 170 mg, 0.54 mmol) in THF (2 mL) were added (2-hydroxy-4-(trifluoromethyl)phenyl)boronic acid (224 mg, 1.08 mmol), $K_3PO_4 \cdot H_2O$ (0.5 M, 4 mL), and Xphos Pd G4 (92 mg, 0.108 mmol). The mixture was degassed and purged with N_2 (3 x) and then stirred at 60°C for 12 hours under N_2 atmosphere. LC-MS showed two peaks with desired MS. The reaction mixture was evaporated and then partitioned between DCM/ H_2O (5 mL/1 mL). The layers were separated and the aqueous phase was extracted with DCM (4 mL x 2). The combined organic layers were collected, dried and concentrated to give a residue, which was purified by preparative HPLC (C18-1, 5 μ m, 30 mm ID x 150 mm) using a gradient of 10 to 50% ACN in water (with NH_4OH) over 9 minutes. The title compound of Example 242 was obtained as a white solid (27 mg, 24%). 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.40 (d, $J=7.70$ Hz, 1 H), 7.18 - 7.26 (m, 2 H), 5.64 (d, $J=7.92$ Hz, 1 H), 4.46 (s, 2 H), 4.21 - 4.40 (m, 2 H), 3.76 (t, $J=5.39$ Hz, 2 H), 3.49 (br t, $J=6.16$ Hz, 2 H), 2.97 - 3.07 (m, 1 H), 2.70 - 2.80 (m, 1 H), 2.36 - 2.45 (m, 4 H), 1.93 - 2.06 (m, 2 H), 1.83 - 1.91 (m, 1 H), 1.63 - 1.74 (m, 1 H), 1.47 - 1.56 (m, 1 H), 1.33 - 1.43 (m, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{21}H_{25}F_3N_4O_3$, 438.19; found 439.1. The title compound of Example 243 was obtained as a white solid (30 mg, 26%). 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.37 (d, $J=7.70$ Hz, 1 H), 7.18 - 7.26 (m, 2 H), 5.84 (d, $J=8.14$ Hz, 1 H), 4.20 - 4.47 (m, 4 H), 3.92 (t, $J=5.61$ Hz, 2 H), 3.50 (br t, $J=6.16$ Hz, 2 H), 2.96 - 3.04 (m, 1 H), 2.68 - 2.78 (m, 1 H), 2.48 (br s, 4 H), 2.06 (br t, $J=10.01$ Hz, 2 H), 1.81 - 1.91 (m, 1 H), 1.68 (br s, 1 H), 1.55 (br s, 2 H); $[M+H]^+$ calc'd for $C_{21}H_{25}F_3N_4O_3$, 438.19; found 439.1.

[0422] EXAMPLE 244: (*R*)-2-(4-((1-(2-methoxyethyl)piperidin-3-yl)amino)-7,8-dihydro-5H-pyrano[3,4-*d*]pyridazin-1-yl)-5-methylphenol



[0423] A mixture of 4-chloro-1-[2-(methoxymethoxy)-4-methyl-phenyl]-7,8-dihydro-5H-pyrano[3,4-*d*]pyridazine (61 mg, 0.190 mmol), (*R*)-1-(2-methoxyethyl)piperidin-3-amine dihydrochloride (44 mg, 0.190 mmol), Pd₂(dba)₃ (17 mg, 0.0190 mmol), R-BINAP (24 mg, 0.0380 mmol), and Cs₂CO₃ (248 mg, 0.761 mmol) in toluene (6 mL) was purged with nitrogen for 5 minutes and then heated at 120°C overnight. The mixture was treated with water and extracted with EtOAc. The extracted layers were washed with brine, dried over MgSO₄, and concentrated. The resulting residue was dissolved in dioxane (2 mL). Hydrogen chloride in dioxane (0.38 mL, 0.761 mmol) was added. The mixture was stirred at room temperature for 3 hours and purified by preparative HPLC (Phenomenex Gemini C18, 5 μm, 30 mm ID x 150 mm column) using a gradient of 10 to 100% ACN (containing 0.079% ammonium bicarbonate) in water (containing 0.079% ammonium) with a slow ramp from 10 to 60% ACN. Fractions containing product were evaporated to afford the title compound as a clear oil (0.8 mg, 0.71%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.51 - 1.72 (m, 2 H), 1.73 - 1.96 (m, 2 H), 2.32 (s, 5 H), 2.54 - 2.70 (m, 5 H), 2.96 - 3.05 (m, 1 H), 3.34 (s, 3 H), 3.52 - 3.58 (m, 2 H), 3.81 - 3.88 (m, 2 H), 4.37 - 4.45 (m, 1 H), 4.54 - 4.59 (m, 2 H), 6.72 - 6.79 (m, 2 H), 7.06 - 7.11 (m, 1 H); ESI-MS [M+H]⁺ calc'd for C₂₂H₃₀N₄O₃ 398.23; found 399.1.

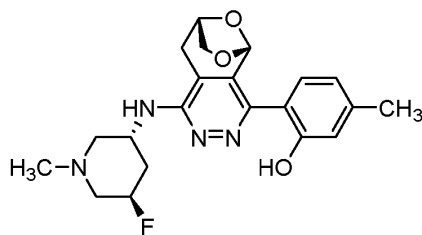
[0424] EXAMPLE 245: 2-(4-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-7,8-dihydro-5H-pyrano[3,4-*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol



[0425] A mixture of 1-chloro-*N*-((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)-7,8-dihydro-5H-pyrano[3,4-*d*]pyridazin-4-amine (50 mg, 166.25 μmol), (2-hydroxy-4-(trifluoromethyl)phenyl)boronic acid (51.35 mg, 249.37 μmol), Pd(dppf)Cl₂.CH₂Cl₂ (13.58 mg, 16.62 μmol), and Cs₂CO₃ (216.66 mg, 664.98 μmol) in a mixture of dioxane (2 mL) and H₂O (0.5 mL) was degassed and purged with N₂ (3 x) and then stirred at 100°C for 2 hours

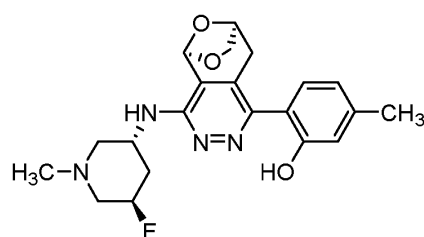
under N₂ atmosphere. LC-MS showed 56% desired mass was detected. The reaction mixture was evaporated and partitioned between DCM/H₂O (5 mL/1 mL). The layers were separated and the aqueous phase was extracted with DCM (4 mL x 2). The combined organic layers were collected, dried, and concentrated to give a residue which was purified by preparative HPLC (Xtimate C18, 5 μ m, 30 mm ID x 150 mm column) using a gradient of 0 to 30% ACN in water (with FA) over 25 minutes. A formic acid salt of the title compound was obtained as a white solid (37.9 mg, 52% yield, 98% purity). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.56 - 1.82 (m, 1 H), 1.86 - 1.98 (m, 1 H), 2.03 - 2.28 (m, 5 H), 2.36 - 2.46 (m, 2 H), 2.84 - 2.95 (m, 1 H), 2.96 - 3.05 (m, 1 H), 3.78 (br t, *J*=5.44 Hz, 2 H), 4.39 - 4.65 (m, 3 H), 4.81 - 5.09 (m, 1 H), 5.63 - 5.85 (m, 1 H), 7.17 - 7.26 (m, 2 H), 7.33 - 7.51 (m, 1 H); ESI-MS [M+H]⁺ calc'd for C₂₀H₂₂F₄N₄O₂ 426.17; found 427.2.

[0426] EXAMPLE 246: 2-((5*R*,8*S*)-1-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5,7,8,9-tetrahydro-5,8-epoxyoxepino[3,4-*d*]pyridazin-4-yl)-5-methylphenol



[0427] A mixture of 2-((5*R*,8*S*)-1-chloro-5,7,8,9-tetrahydro-5,8-epoxyoxepino[3,4-*d*]pyridazin-4-yl)-5-methylphenol (40 mg, 0.131 mmol), Cs₂CO₃ (128 mg, 0.4 mmol), Pd₂(dba)₃ (12 mg, 0.0131 mmol), R-BINAP (16 mg, 0.0263 mmol), and (3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-amine dihydrochloride (54 mg, 0.263 mmol) in toluene (5 mL) was stirred in a sealed tube on metal heating block at 100°C for 16 hours. The reaction mixture was then concentrated under vacuum to give a crude product mixture which was purified by preparative HPLC (Phenomenex Gemini® C18 column) using a 10 to 100% gradient of ACN in water (10 mM NH₄HCO₃, pH=9.5-10). The title compound was obtained as a yellow oil (14 mg, 27%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.64 - 1.84 (m, 1 H), 2.09 - 2.22 (m, 2 H), 2.23 (s, 3 H), 2.28 (s, 3 H), 2.30 - 2.44 (m, 2 H), 2.84 - 3.00 (m, 2 H), 3.05 - 3.14 (m, 1 H), 3.57 - 3.67 (m, 1 H), 3.84 - 3.90 (m, 1 H), 4.56 - 4.65 (m, 1 H), 4.81 - 4.94 (m, 2 H), 5.80 (s, 1 H), 6.63 - 6.72 (m, 2 H), 7.09 - 7.16 (m, 1 H); ESI-MS [M+H]⁺ calc'd for C₂₁H₂₅FN₄O₃ 400.19; found 401.2.

[0428] EXAMPLE 247: 2-((5*R*,8*S*)-4-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5,7,8,9-tetrahydro-5,8-epoxyoxepino[3,4-*d*]pyridazin-1-yl)-5-methylphenol

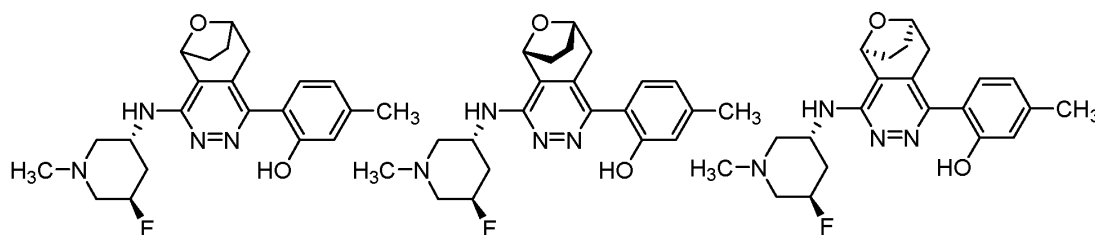


[0429] A mixture of 2-((5*R*,8*S*)-4-chloro-5,7,8,9-tetrahydro-5,8-epoxyoxepino[3,4-*d*]pyridazin-1-yl)-5-methylphenol (40 mg, 0.131 mmol), Cs₂CO₃ (128 mg, 0.4 mmol), Pd₂(dba)₃ (12 mg, 0.0131 mmol), R-BINAP (16 mg, 0.0263 mmol), and (3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-amine dihydrochloride (54 mg, 0.263 mmol) in toluene (5 mL) was stirred in a sealed tube on metal heating block at 100°C for 16 hours. The reaction mixture was then concentrated under vacuum to give a crude product mixture which was purified by preparative HPLC (Phenomenex Gemini® C18 column) using a 10 to 100% gradient of ACN in water (10 mM NH₄HCO₃, pH=9.5-10). The title compound was obtained as an orange oil (3.0 mg, 6%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.84 (s, 2 H), 2.04 - 2.11 (m, 1 H), 2.21 - 2.22 (m, 3 H), 2.23 (s, 3 H), 2.29 (dd, *J*=18.07, 0.75 Hz, 2 H), 2.78 - 2.88 (m, 1 H), 2.93 - 3.09 (m, 2 H), 3.51 - 3.57 (m, 1 H), 3.85 - 3.92 (m, 1 H), 4.58 - 4.68 (m, 1 H), 4.77 - 4.92 (m, 2 H), 6.22 (s, 1 H), 6.61 - 6.64 (m, 1 H), 6.65 - 6.69 (m, 1 H), 6.95 - 7.00 (m, 1 H); ESI-MS [*M*+*H*]⁺ calc'd for C₂₁H₂₅FN₄O₃ 400.19; found 401.2.

[0430] EXAMPLE 248: 2-(4-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-methylphenol

[0431] EXAMPLE 249: 2-((5*R*,8*S*)-4-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-methylphenol

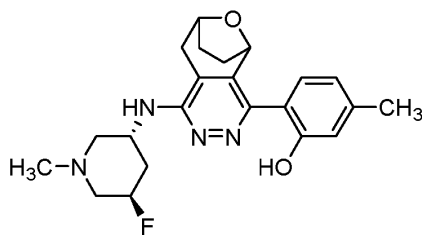
[0432] EXAMPLE 250: 2-((5*S*,8*R*)-4-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-methylphenol



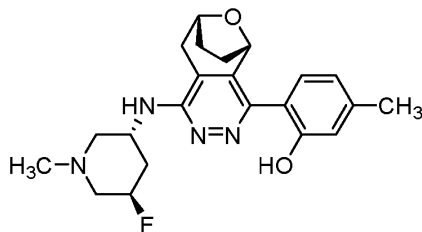
[0433] A mixture of 4-chloro-1-(2-(methoxymethoxy)-4-methylphenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine (300 mg, 0.865 mmol), Cs₂CO₃ (846 mg, 2.6 mmol), Pd₂(dba)₃ (79 mg, 0.0865 mmol), R-BINAP (108 mg, 0.173 mmol), and (3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-amine dihydrochloride (266 mg, 1.298 mmol) in toluene (5 mL) was

stirred in a sealed tube on metal heating block at 100°C for 16 hours. The reaction mixture was added to solution of TFA (2 mL) in DCM (10 mL), stirred for 1 hour at 60°C, and then concentrated under vacuum to give a crude product mixture. The product mixture was purified by preparative HPLC (Phenomenex Gemini® C18 column) using a 10 to 30% gradient of ACN (0.035% TFA) in water (0.005% TFA) to give the title compound of Example 248 as a mixture of diastereomers. The diastereomers were separated by preparative SFC (Waters, ChiralTech IC, 5 µm, 21 mm ID x 150 mm column) using a gradient of 40 to 50% MeOH (with 0.1% NH₄OH) in CO₂. The first product was the title compound of Example 249, which was obtained as a yellow semi-solid (31 mg, 9.0%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.62 - 1.74 (m, 1 H), 1.74 - 1.90 (m, 1 H), 1.96 - 2.05 (m, 1 H), 2.11 - 2.28 (m, 5 H), 2.30 (s, 3 H), 2.32 (s, 3 H), 2.33 - 2.48 (m, 1 H), 2.88 - 2.97 (m, 1 H), 2.98 - 3.05 (m, 1 H), 3.10 - 3.20 (m, 1 H), 4.66 - 4.78 (m, 2 H), 4.90 - 5.02 (m, 1 H), 5.15 (d, *J*=5.77 Hz, 1 H), 6.70 - 6.76 (m, 2 H), 7.04 (d, *J*=7.53 Hz, 1 H); ESI-MS [M+H]⁺ calc'd for C₂₂H₂₇FN₄O₂ 398.21; found 399.2. The second product was the title compound of Example 250, which was obtained as a yellow-semi solid (37 mg, 11%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.62 - 1.89 (m, 2 H), 1.95 - 2.04 (m, 1 H), 2.27 (br s, 5 H), 2.30 (s, 3 H), 2.31 (s, 3 H), 2.32 - 2.39 (m, 1 H), 2.86 - 3.06 (m, 2 H), 3.08 - 3.18 (m, 1 H), 4.63 - 4.78 (m, 2 H), 4.91 - 5.01 (m, 1 H), 5.11 - 5.17 (m, 1 H), 6.69 - 6.76 (m, 2 H), 7.04 (d, *J*=7.53 Hz, 1 H); ESI-MS [M+H]⁺ calc'd for C₂₂H₂₇FN₄O₂ 398.21; found 399.2.

[0434] EXAMPLE 251: 2-(1-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)-5-methylphenol

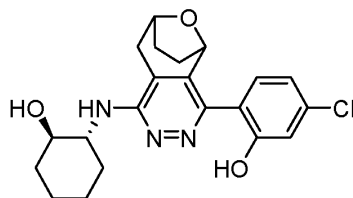


[0435] EXAMPLE 252: 2-((5*S*,8*R*)-1-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)-5-methylphenol



[0436] A mixture of 1-chloro-4-(2-(methoxymethoxy)-4-methylphenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine (300 mg, 0.865 mmol), Cs₂CO₃ (846 mg, 2.6 mmol), Pd₂(dba)₃ (79 mg, 0.0865 mmol), R-BINAP (108 mg, 0.173 mmol), and (3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-amine dihydrochloride (266 mg, 1.298 mmol) in toluene (5 mL) was stirred in a sealed tube on metal heating block at 100°C for 16 hours. The reaction mixture was added to solution of TFA (2 mL) in DCM (10 mL), stirred for 1 hour at 60°C, and then concentrated under vacuum to give a crude product mixture. The product mixture was purified by preparative HPLC (Phenomenex Gemini® C18 column) using a gradient of 10 to 30% ACN (0.035% TFA) in water (0.005% TFA). A TFA salt of the title compound of Example 251 was obtained as a light-yellow semi-solid (55 mg, 12.4%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.82 - 1.91 (m, 1 H), 2.04 - 2.33 (m, 4 H), 2.40 (s, 3 H), 2.50 - 2.66 (m, 2 H), 3.01 (d, *J*=2.38 Hz, 3 H), 3.04 - 3.20 (m, 2 H), 3.34 - 3.48 (m, 1 H), 3.74 - 3.88 (m, 2 H), 4.76 - 4.85 (m, 1 H), 4.90 - 4.96 (range, 2 H), 5.29 - 5.38 (m, 1 H), 6.92 (s, 2 H), 7.22 (s, 1 H); ESI-MS [*M*+*H*]⁺ calc'd for C₂₂H₂₇FN₄O₂ 398.21; found 399.2. The diastereomers were isolated via preparative SFC (Waters, Phenomenex Amylose-1 column) using a gradient of 25 to 50% MeOH (with 0.1% NH₄OH) in CO₂ to give the title compound of Example 252.

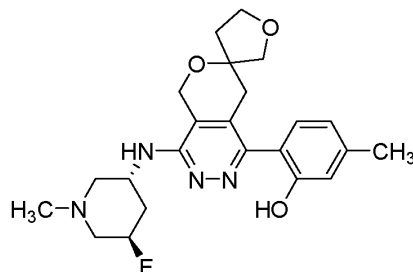
[0437] EXAMPLE 253: 5-chloro-2-(1-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)phenol



[0438] A mixture of 5-chloro-2-(1-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)phenol (100 mg, 0.309 mmol), Cs₂CO₃ (302 mg, 0.93 mmol), Pd₂(dba)₃ (28 mg, 0.0309 mmol), R-BINAP (108 mg, 0.173 mmol) (39 mg, 0.062 mmol), and (1*R*,2*R*)-2-aminocyclohexanol (39.1 mg, 0.34 mmol) in toluene (1 mL) was stirred in a sealed tube on metal heating block at 100°C for 16 hours. The mixture was then concentrated under vacuum to give a crude product mixture, which was purified by preparative HPLC (Phenomenex Gemini® C18 column) using a 10 to 30% gradient of ACN (0.035% TFA) in water (0.005% TFA). The title compound was obtained as a light-yellow semi-solid (6 mg, 5%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.22 - 1.54 (m, 4 H), 1.60 - 2.20 (m, 9 H), 2.27 - 2.41 (m, 1 H), 2.89 - 3.07 (m, 1 H), 3.46 - 3.58 (m, 1 H), 3.65 - 3.75 (m, 1

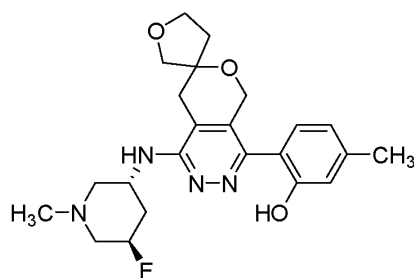
H), 4.72 - 4.74 (m, 1 H), 6.90 - 6.97 (m, 2 H), 7.15 (d, $J=8.03$ Hz, 1 H); ESI-MS $[M+H]^+$ calc'd for $C_{21}H_{24}ClN_3O_3$ 401.15; found 402.2.

[0439] EXAMPLE 254: 2-(4'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-4,5,5',8'-tetrahydro-2*H*-spiro[furan-3,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol



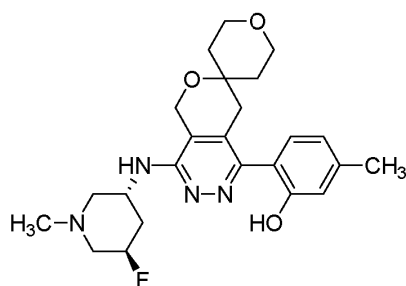
[0440] A mixture of *rac*-4'-chloro-1'-(2-(methoxymethoxy)-4-methylphenyl)-4,5,5',8'-tetrahydro-2*H*-spiro[furan-3,7'-pyrano[3,4-*d*]pyridazine] (17 mg, 0.0451 mmol), (3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-amine dihydrochloride (11 mg, 0.0541 mmol), $Pd_2(dba)_3$ (4.1 mg, 0.00451 mmol), R-BINAP (5.6 mg, 0.00902 mmol), and Cs_2CO_3 (59 mg, 0.180 mmol) in toluene (3 mL) was purged with nitrogen for 5 minutes. The vial was sealed and heated at 110°C overnight. The mixture was treated with water, extracted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated. The residue was dissolved in dioxane (2 mL) and HCl in dioxane (0.045 mL, 0.180 mmol) was added. The mixture was stirred at room temperature for 3 hours and purified by preparative HPLC (Phenomenex Gemini C18, 5 μm , 30 mm ID x 150 mm column) using a gradient of 10 to 100% ACN (0.035% TFA) in water (0.05% TFA) with a slow ramp from 10 to 60% ACN to give the title compound. 1H NMR (400 MHz, CD_3OD) δ ppm 1.91 - 2.20 (m, 2 H), 2.24 - 2.33 (m, 1 H), 2.38 (s, 3 H), 2.53 - 2.63 (m, 1 H), 2.88 - 2.91 (m, 2 H), 3.00 (s, 3 H), 3.03 - 3.14 (m, 1 H), 3.65 - 3.70 (m, 1 H), 3.78 - 3.88 (m, 2 H), 3.93 - 4.04 (m, 3 H), 4.72 (br d, $J=6.90$ Hz, 3 H), 5.23 - 5.39 (m, 1 H), 6.88 (s, 1 H), 6.89 - 6.93 (m, 1 H), 7.22 - 7.27 (m, 1 H); ESI-MS $[M+H]^+$ calc'd for $C_{23}H_{29}FN_4O_3$ 428.22; found 429.54.

[0441] EXAMPLE 255: 2-(1'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-4,5,5',8'-tetrahydro-2*H*-spiro[furan-3,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)-5-methylphenol



[0442] A mixture of *rac*-1'-chloro-4'-(2-(methoxymethoxy)-4-methylphenyl)-4,5,5',8'-tetrahydro-2H-spiro[furan-3,7'-pyrano[3,4-*d*]pyridazine] (80 mg, 0.212 mmol), (3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-amine dihydrochloride (52 mg, 0.255 mmol), Pd₂(dba)₃ (19 mg, 0.0212 mmol), R-BINAP (26 mg, 0.0425 mmol), and Cs₂CO₃ (277 mg, 0.849 mmol) in toluene (6 mL) was purged with nitrogen for 5 minutes. The vial was sealed, heated at 110°C overnight, and then filtered. The filtrate was concentrated and the residue was dissolved in dioxane (2 mL) and treated with HCl (0.21 mL, 0.849 mmol). The mixture was stirred at RT for 3 hours and purified by preparative HPLC (Phenomenex Gemini C18, 5 μm, 30 mm ID x 150 mm column) using a gradient of 10 to 100% ACN (0.035% TFA) in water (0.05% TFA) with a slow ramp from 10 to 60% ACN to give the title compound. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.78 - 1.88 (m, 1 H), 1.95 - 2.15 (m, 2 H), 2.17 - 2.26 (m, 1 H), 2.38 (s, 3 H), 2.53 - 2.64 (m, 1 H), 2.77 - 2.90 (m, 2 H), 2.99 (s, 4 H), 3.33 - 3.45 (m, 1 H), 3.51 - 3.56 (m, 1 H), 3.78 - 3.93 (m, 5 H), 3.96 - 4.03 (m, 1 H), 4.76 - 4.82 (m, 1 H), 5.21 - 5.39 (m, 1 H), 6.85 - 6.88 (m, 1 H), 6.90 - 6.95 (m, 1 H), 7.21 - 7.27 (m, 1 H); ESI-MS [M+H]⁺ calc'd for C₂₃H₂₉FN₄O₃ 428.22; found 429.54.

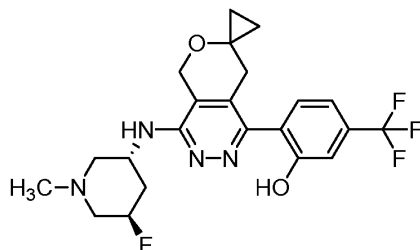
[0443] EXAMPLE 256: 2-(4'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-2,3,5,5',6,8'-hexahydrospiro[pyran-4,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol



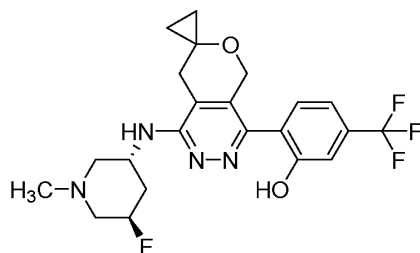
[0444] The title compound was synthesized from starting material 1,9-dioxaspiro[5.5]undecan-4-one, using a procedure analogous to Example 254. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.78 - 1.83 (m, 3 H), 2.01 - 2.22 (m, 1 H), 2.38 (s, 3 H), 2.53 - 2.64 (m,

1 H), 2.68 - 2.72 (m, 2 H), 3.00 (s, 3 H), 3.05 - 3.15 (m, 1 H), 3.67 (br d, $J=1.25$ Hz, 2 H), 3.73 - 3.84 (m, 6 H), 4.65 (s, 2 H), 4.76 - 4.85 (m, 1 H), 5.22 - 5.38 (m, 1 H), 6.87 - 6.89 (m, 1 H), 6.89 - 6.93 (m, 1 H), 7.23 - 7.26 (m, 1 H); ESI-MS $[M+H]^+$ calc'd for $C_{24}H_{31}FN_4O_3$ 442.24; found 443.48.

[0445] EXAMPLE 257: 2-(4'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



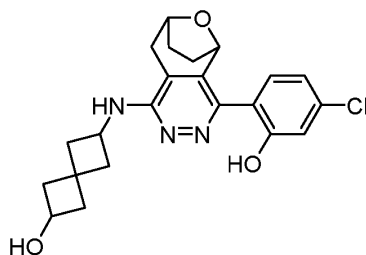
[0446] EXAMPLE 258: 2-(1'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)-5-(trifluoromethyl)phenol



[0447] To a stirred solution of a mixture of 4'-chloro-*N*-((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-amine and 1'-chloro-*N*-((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-amine (100 mg, 0.31 mmol) in a solution of dioxane (2 mL) and H₂O (0.5 mL) were added (2-hydroxy-4-(trifluoromethyl)phenyl)boronic acid (125 mg, 0.61 mmol), Cs₂CO₃ (403 mg, 1.24 mmol) and Pd(dppf)Cl₂.CH₂Cl₂ (25 mg, 0.031 μmol). The mixture was stirred at 100°C for 2 hours under N₂. LC-MS showed 48% desired mass was detected. The reaction mixture was evaporated and then partitioned between DCM/H₂O (5 mL/5 mL). The layers were separated and the aqueous phase was extracted with DCM (4 mL x 2). The combined organic layers were collected, dried, and concentrated to give a residue. The residue was purified by flash chromatography (ISCO® 4 g SepaFlash® silica gel column) using a gradient of 0 to 15% DCM in MeOH (30 mL/min) to give crude product (70 mg) which was further purified by preparative SFC (DAICEL CHIRALPAK® IG-10 μm, 30 mm ID x 250 mm column) using a mobile phase of CO₂ and 35% MeOH (with 0.1%

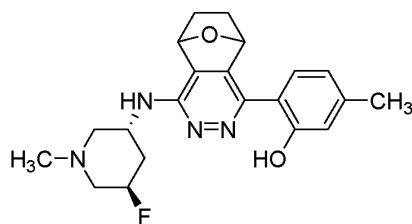
NH₃OH). The title compound of Example 258 was obtained as a white solid (12 mg, 57%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.58 - 0.76 (m, 2 H), 0.86 - 0.98 (m, 2 H), 1.71 - 1.98 (m, 1 H), 2.23 - 2.40 (m, 2 H), 2.42 - 2.48 (m, 3 H), 2.49 - 2.58 (m, 1 H), 2.58 - 2.66 (m, 2 H), 3.01 - 3.15 (m, 1 H), 4.44 - 4.50 (m, 2 H), 4.72 - 4.81 (m, 2 H), 4.96 - 5.08 (m, 1 H), 7.13 - 7.28 (m, 2 H), 7.34 - 7.48 (m, 1 H), 8.33 - 8.51 (m, 1 H); ESI-MS [M+H]⁺ calc'd for C₂₂H₂₄F₄N₄O₂ 452.18; found 452.9. The title compound of Example 257 was obtained as a white solid (8 mg, 38%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.33 - 0.62 (m, 2 H), 0.76 - 0.97 (m, 2 H), 1.74 - 1.99 (m, 1 H), 2.30 - 2.45 (m, 2 H), 2.47 - 2.54 (m, 3 H), 2.55 - 2.70 (m, 3 H), 3.10 - 3.24 (m, 2 H), 4.55 - 4.58 (m, 2 H), 4.74 - 4.80 (m, 2 H), 4.99 - 5.09 (m, 1 H), 7.12 - 7.27 (m, 2 H), 7.35 - 7.44 (m, 1 H), 8.38 - 8.45 (m, 1 H). ESI-MS [M+H]⁺ calc'd for C₂₂H₂₄F₄N₄O₂ 452.18; found 453.0.

[0448] EXAMPLE 259: 6-((4-(4-chloro-2-hydroxyphenyl)-6,7,8,9-tetrahydro-5H-5,8-epoxycyclohepta[d]pyridazin-1-yl)amino)spiro[3.3]heptan-2-ol



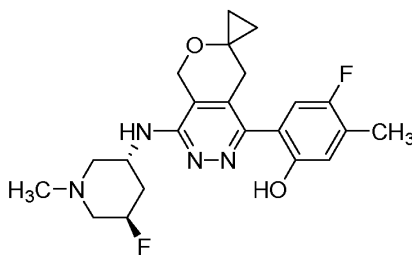
[0449] A mixture of 5-chloro-2-(1-chloro-6,7,8,9-tetrahydro-5H-5,8-epoxycyclohepta[d]pyridazin-4-yl)phenol (100 mg, 0.309 mmol), Cs₂CO₃ (302 mg, 0.93 mmol), Pd₂(dba)₃ (28 mg, 0.0309 mmol), R-BINAP (39 mg, 0.062 mmol), and 6-aminospiro[3.3]heptan-2-ol (43.2 mg, 0.34 mmol) in toluene (1 mL) was stirred in a sealed tube on metal heating block at 100°C for 16 hours. The reaction mixture was then concentrated under vacuum to give the crude product mixture. The product mixture was purified by Preparative HPLC (Phenomenex Gemini® C18 column) using a gradient of 10 to 30% ACN (0.035% TFA) in water (0.005% TFA). The title compound was obtained as a yellow semi-solid (25 mg, 19.6%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.55 - 1.69 (m, 1 H), 1.93 (s, 7 H), 2.03 - 2.22 (m, 3 H), 2.29 - 2.47 (m, 3 H), 2.72 - 2.82 (m, 1 H), 3.97 - 4.06 (m, 1 H), 4.34 - 4.42 (m, 1 H), 4.64 - 4.73 (m, 2 H), 6.80 - 6.87 (m, 2 H), 7.04 (d, *J*=8.78 Hz, 1 H); ESI-MS [M+H]⁺ calc'd for C₂₂H₂₄ClN₃O₃ 413.15; found 414.2.

[0450] EXAMPLE 260: 2-(4-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5,6,7,8-tetrahydro-5,8-epoxyphthalazin-1-yl)-5-methylphenol

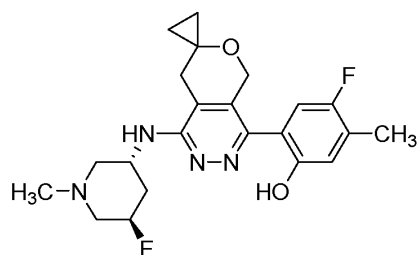


[0451] A mixture of 2-(4-chloro-5,6,7,8-tetrahydro-5,8-epoxyphthalazin-1-yl)-5-methylphenol (10 mg, 0.0346 mmol), Cs_2CO_3 (34 mg, 0.104 mmol), $\text{Pd}_2(\text{dba})_3$ (3.2 mg, 0.00346 mmol), R-BINAP (4.3 mg, 0.0069 mmol), and (3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-amine dihydrochloride (10.6 mg, 0.052 mmol) in toluene (1 mL) was stirred in a sealed tube on metal heating block at 100°C for 16 hours. The reaction mixture was then concentrated under vacuum to give a crude product mixture. The product mixture was purified by preparative HPLC (Phenomenex Gemini® C18 column) using a gradient of 10 to 100% ACN in water (10 mM NH_4HCO_3 , pH=9.5-10). The title compound was obtained as a yellow oil (1.0 mg, 7.5%). ^1H NMR (400 MHz, CD_3OD) δ ppm 1.42 - 1.49 (m, 1 H), 1.57 - 1.64 (m, 1 H), 1.72 - 1.85 (m, 1 H), 2.05 - 2.30 (m, 2 H), 2.05 - 2.29 (m, 1 H), 2.30 - 2.30 (m, 1 H), 2.31 - 2.40 (m, 6 H), 2.40 - 2.49 (m, 1 H), 2.94 - 3.02 (m, 1 H), 3.12 - 3.24 (m, 1 H), 4.64 - 4.71 (m, 1 H), 4.98 - 5.07 (m, 1 H), 5.61 - 5.69 (m, 1 H), 5.77 (d, $J=5.02$ Hz, 1 H), 6.76 - 6.88 (m, 1 H), 6.79 - 6.87 (m, 1 H), 7.33 (d, $J=8.53$ Hz, 1 H); ESI-MS $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{21}\text{H}_{25}\text{FN}_4\text{O}_2$ 384.20; found 385.2.

[0452] EXAMPLE 262: 4-fluoro-2-(4'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol



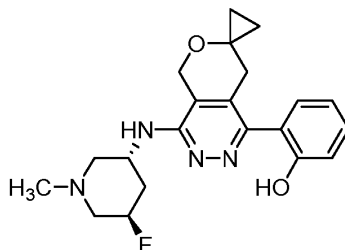
[0453] EXAMPLE 263: 4-fluoro-2-(1'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)-5-methylphenol



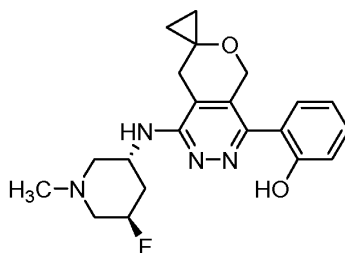
[0454] A mixture of 4'-chloro-*N*-((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-amine and 1'-chloro-*N*-((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-amine (70 mg, 214 μ mol) in THF (1 mL) was added 2-[5-fluoro-2-(methoxymethoxy)-4-methyl-phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (317.17 mg, 1.07 mmol), Xphos Pd G4 (18.43 mg, 21.42 μ mol), and K_3PO_4 (0.5 M, 2 mL). The mixture was stirred at 50°C for 3hr under N_2 . LC-MS showed 63% of desired mass was detected. The reaction mixture was evaporated, then partitioned between DCM/ H_2O (5 mL/5 mL). The layer was separated and the aq. Layer was extracted with DCM (4 mL x2). The combined organic layer was collected, dried, concentrated to give a residue, which was used directly in the next step without further purification. ESI-MS $[M+H]^+$ calc'd for $C_{24}H_{30}F_2N_4O_3$ 460.23; found, 460.8. The residue was taken up in DCM (4 mL) and was added TFA (1 mL). The mixture was stirred at 25°C for 1 hour. LC-MS showed 56% conversion to a product with the desired mass. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with 1 M HCl (3 mL) and extracted with EtOAc (3 mL x 2). The organic layer was discarded. The aqueous layer was adjusted with $NaHCO_3$ to pH 8-9 and extracted with dichloromethane/methanol (10/1, 10 mL x 2). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (ISCO® 4 g SepaFlash® silica gel column) using a gradient of 0 to 10% DCM in MeOH (30 mL/min) to give crude product (80 mg), which was further purified by preparative SFC (DAICEL CHIRALPAK® IG-10 μ m, 30 mm ID x 250 mm column) using a mobile phase of CO_2 and 60% MeOH (with 0.1% NH_3OH). The title compound of Example 262 was obtained as a white solid (11 mg, 52%). 1H NMR (400 MHz, CD_3OD) δ ppm 0.35 - 0.57 (m, 2 H), 0.85 - 0.91 (m, 2 H), 1.68 - 1.94 (m, 1 H), 2.13 - 2.20 (m, 1 H), 2.24 (d, $J=1.38$ Hz, 3 H), 2.28- 2.47 (m, 5 H), 2.63 (s, 2 H), 2.95 - 3.07 (m, 1 H), 3.17 - 3.24 (m, 1 H), 4.39 - 4.59 (m, 2 H), 4.71 - 4.82 (m, 1 H), 4.95 - 5.04 (m, 1 H), 6.72 (d, $J=6.50$ Hz, 1 H), 6.84 - 6.97 (m, 1 H); ESI-MS $[M+H]^+$ calc'd for $C_{22}H_{26}F_2N_4O_2$, 416.20; found, 417.3. The title compound of Example 263 was obtained as a white solid (10 mg,

91%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.59 - 0.68 (m, 2 H), 0.89 - 0.95 (m, 2 H), 1.73 - 1.92 (m, 1 H), 2.13 - 2.22 (m, 1 H), 2.23 - 2.27 (m, 3 H), 2.29 (br s, 5 H), 2.56 - 2.61 (m, 2 H), 2.89 - 3.03 (m, 1 H), 3.14 - 3.23 (m, 1 H), 4.44 - 4.51 (m, 2 H), 4.70 - 4.80 (m, 1 H), 4.93 - 5.03 (m, 1 H), 6.69 - 6.79 (m, 1 H), 6.87 - 6.93 (m, 1 H); ESI-MS [M+H]⁺ calc'd for C₂₂H₂₆F₂N₄O₂, 416.20; found, 417.3.

[0455] EXAMPLE 264: 2-(4'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol



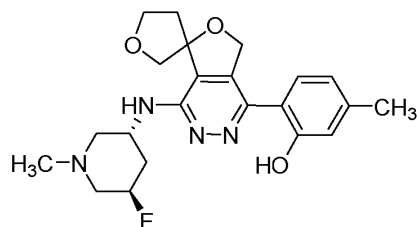
[0456] EXAMPLE 265: 2-(1'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)phenol



[0457] A mixture of 4'-chloro-*N*-((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-amine and 1'-chloro-*N*-((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-amine (70 mg, 214 μmol) in a solution of dioxane (2 mL) and H₂O (0.5 mL) were added (2-hydroxyphenyl)boronic acid (88.63 mg, 642.60 μmol), Cs₂CO₃ (139.58 mg, 428.40 μmol), and Pd(dppf)Cl₂.CH₂Cl₂ (34.98 mg, 42.84 μmol). The mixture was stirred at 100°C for 2 hours under N₂. LC-MS showed 37% desired mass was detected. The reaction mixture was evaporated and then partitioned between DCM/H₂O (5 mL/5 mL). The layers were separated and the aqueous phase was extracted with DCM (4 mL x 2). The combined organic layers were collected, dried and concentrated to give a residue, which was purified by flash chromatography (ISCO® 4 g SepaFlash® silica gel column) using a gradient of 0 to 15% DCM in MeOH (30 mL/min). The give crude product (40 mg) was further purified by preparative SFC (DAICEL CHIRALPAK® IG-10 μm, 30 mm ID x 250 mm column) using a

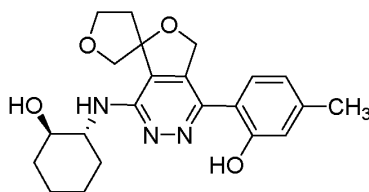
mobile phase of CO₂ and 60% EtOH (with 0.1% NH₃OH). The title compound of Example 265 was obtained as a white solid (16 mg). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.61 - 0.67 (m, 2 H), 0.89 - 0.95 (m, 2 H), 1.74 - 1.92 (m, 1 H), 2.11 - 2.22 (m, 1 H), 2.26 (br s, 5 H), 2.60 (s, 2 H), 2.87 - 3.00 (m, 1 H), 3.15 (br d, *J*=9.51 Hz, 1 H), 4.41 - 4.50 (m, 2 H), 4.67 - 4.80 (m, 1 H), 4.93 - 5.01 (m, 1 H), 6.85 - 6.97 (m, 2 H), 7.16 - 7.31 (m, 2 H); ESI-MS [M+H]⁺ calc'd for C₂₁H₂₅FN₄O₂, 384.20; found, 385.3. The title compound of Example 264 was obtained as a white solid (22 mg). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.45 - 0.51 (m, 2 H), 0.82 - 0.88 (m, 2 H), 1.70 - 1.89 (m, 1 H), 2.10 - 2.21 (m, 1 H), 2.26 - 2.45 (m, 5 H), 2.58 - 2.63 (m, 2 H), 2.98 (br t, *J*=10.26 Hz, 1 H), 3.11 - 3.24 (m, 1 H), 4.49 - 4.59 (m, 2 H), 4.68 - 4.80 (m, 1 H), 4.94 - 5.01 (m, 1 H), 6.85 - 6.96 (m, 2 H), 7.15 - 7.31 (m, 2 H); ESI-MS [M+H]⁺ calc'd for C₂₁H₂₅FN₄O₂, 384.20; found, 385.4.

[0458] EXAMPLE 266: 2-(4'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol



[0459] The title compound was prepared from starting material 1,7-dioxaspiro[4.4]nonan-3-one, using a procedure analogous to Example 254. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.89 - 2.10 (m, 1 H), 2.37 (s, 3 H), 2.38 - 2.51 (m, 2 H), 2.56 - 2.68 (m, 1 H), 3.00 (d, *J*=1.51 Hz, 3 H), 3.04 - 3.16 (m, 1 H), 3.34 - 3.42 (m, 1 H), 3.77 - 3.88 (m, 2 H), 3.88 - 3.95 (m, 1 H), 4.00 - 4.09 (m, 1 H), 4.29 - 4.39 (m, 2 H), 4.72 - 4.83 (m, 1 H), 5.26 (dd, *J*=10.23, 0.94 Hz, 3 H), 6.88 (s, 2 H), 7.26 - 7.32 (m, 1 H); ESI-MS [M+H]⁺ calc'd for C₂₂H₂₇FN₄O₃ 414.21; found 415.7.

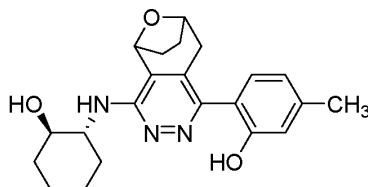
[0460] EXAMPLE 267: 2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol



[0461] The title compound was prepared from starting materials 1,7-dioxaspiro[4.4]nonan-3-one and (1*R*,2*R*)-2-aminocyclohexan-1-ol, using a procedure analogous to Example 254. ¹H

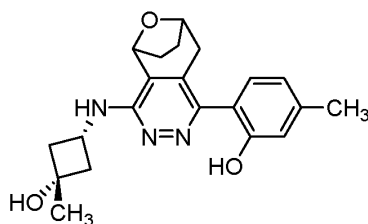
NMR (400 MHz, CD₃OD) δ ppm 1.24 - 1.55 (m, 4 H), 1.69 - 1.84 (m, 2 H), 2.02 - 2.10 (m, 1 H), 2.34 (s, 6 H), 3.45 - 3.56 (m, 1 H), 3.74 - 3.81 (m, 1 H), 3.90 - 4.05 (m, 2 H), 4.20 - 4.40 (m, 2 H), 5.35 (s, 2 H), 6.73 - 6.78 (m, 1 H), 6.82 - 6.85 (m, 1 H), 7.00 - 7.05 (m, 1 H); ESI-MS [M+H]⁺ calc'd for C₂₂H₂₇N₃O₄ 397.2; found 398.4.

[0462] EXAMPLE 268: 2-(4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-methylphenol



[0463] A mixture of 4-chloro-1-(2-(methoxymethoxy)-4-methylphenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine (107 mg, 0.31 mmol), Cs₂CO₃ (302 mg, 0.93 mmol), Pd₂(dba)₃ (28 mg, 0.031 mmol), R-BINAP (39 mg, 0.062 mmol), and (1*R*,2*R*)-2-aminocyclohexan-1-ol (71 mg, 0.62 mmol) in toluene (1 mL) was stirred in a sealed tube on metal heating block at 100°C for 16 hours. The reaction mixture was added to solution of TFA (2 mL) and DCM (10 mL), stirred for 1 hour at 60°C, and concentrated under vacuum to give a crude product mixture. The product mixture was purified by preparative HPLC (Phenomenex Gemini® C18 column) using a gradient of 10 to 30% ACN (0.035% TFA) in water (0.005% TFA). The title compound was obtained as a yellow solid (30 mg, 25%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.32 - 1.52 (m, 4 H) 1.59 - 1.81 (m, 3 H), 1.96 - 2.28 (m, 6 H), 2.32 (s, 3 H), 3.06 (s, 1 H), 3.53 - 3.62 (m, 1 H), 3.96 - 4.04 (m, 1 H), 4.66 - 4.74 (m, 1 H), 5.17 - 5.26 (m, 1 H), 6.69 - 6.80 (m, 2 H), 7.02 - 7.08 (m, 1 H); ESI-MS [M+H]⁺ calc'd for C₂₂H₂₇N₃O₃ 381.21; found 382.2.

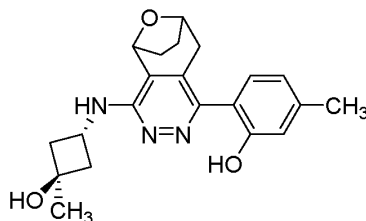
[0464] EXAMPLE 269: 2-(4-(((1*S*,3*S*)-3-hydroxy-3-methylcyclobutyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-methylphenol



[0465] A mixture of 4-chloro-1-(2-(methoxymethoxy)-4-methylphenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine (107 mg, 0.31 mmol), Cs₂CO₃ (302 mg, 0.93 mmol), Pd₂(dba)₃ (28 mg, 0.031 mmol), R-BINAP (39 mg, 0.062 mmol), and (1*S*,3*S*)-3-amino-1-

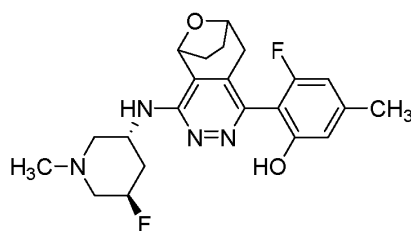
methylcyclobutan-1-ol (31 mg, 0.31 mmol) in toluene (1 mL) was stirred in a sealed tube on metal heating block at 100°C for 16 hours. The reaction mixture was added to solution of TFA (2 mL) and DCM (10 mL), stirred for 1 hour under 60°C, and concentrated under vacuum to give a crude product mixture. The product mixture was purified by preparative HPLC (Phenomenex Gemini® C18 column) using a gradient of 10 to 30% ACN (0.035% TFA) in water (0.005% TFA). The title compound was obtained as a yellow oil (50 mg, 44%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.41 (s, 3 H), 1.69 - 1.82 (m, 1 H), 2.09 - 2.39 (m, 9 H), 2.57 - 2.66 (m, 2 H), 3.13 (dd, *J*=18.45, 5.40 Hz, 1 H), 3.92 - 4.02 (m, 1 H), 4.72 - 4.79 (m, 1 H), 5.28 - 5.38 (m, 1 H), 6.78 - 6.88 (m, 2 H), 7.15 (d, *J*=7.78 Hz, 1 H); ESI-MS [M+H]⁺ calc'd for C₂₁H₂₅N₃O₃ 367.19; found 368.2.

[0466] EXAMPLE 270: 2-(4-(((1*R*,3*R*)-3-hydroxy-3-methylcyclobutyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-methylphenol



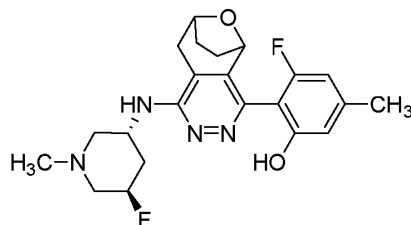
[0467] A mixture of 4-chloro-1-(2-(methoxymethoxy)-4-methylphenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine (107 mg, 0.31 mmol), Cs₂CO₃ (302 mg, 0.93 mmol), Pd₂(dba)₃ (28 mg, 0.031 mmol), R-BINAP (39 mg, 0.062 mmol), and (1*R*,3*R*)-3-amino-1-methylcyclobutan-1-ol (31 mg, 0.31 mmol) in toluene (1 mL) was stirred in a sealed tube on metal heating block at 100°C for 16 hours. The reaction mixture was added to solution of TFA (2 mL) and DCM (10 mL), stirred for 1 hour at 60°C, and concentrated under vacuum to give a crude product mixture. The product mixture was purified by preparative HPLC (Phenomenex Gemini® C18 column) using a gradient of 10 to 30% ACN (0.035% TFA) in water (0.005% TFA). The title compound was obtained as a yellow oil (53 mg, 47%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.43 (s, 3 H), 1.71 - 1.81 (m, 1 H), 2.11 - 2.17 (m, 1 H), 2.35 (s, 8 H), 2.53 - 2.62 (m, 2 H), 3.08 - 3.18 (m, 1 H), 4.51 (s, 1 H), 4.75 - 4.78 (m, 1 H), 5.35 (br d, *J*=6.27 Hz, 1 H), 6.83 - 6.87 (m, 2 H), 7.15 (d, *J*=7.53 Hz, 1 H); ESI-MS [M+H]⁺ calc'd for C₂₁H₂₅N₃O₃ 367.19; found 368.2.

[0468] EXAMPLE 271: 3-fluoro-2-(4-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-methylphenol



[0469] A mixture of 4-chloro-1-(2-fluoro-6-(methoxymethoxy)-4-methylphenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine (10 mg, 0.027 mmol), Cs₂CO₃ (27 mg, 0.082 mmol), Pd₂(dba)₃ (2.5 mg, 0.0027 mmol), R-BINAP (3.4 mg, 0.0055 mmol), and (3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-amine dihydrochloride (8.4 mg, 0.04 mmol) in toluene (1 mL) was stirred in a sealed tube on metal heating block at 100°C for 16 hours. The reaction mixture was added to solution of TFA (2 mL) and DCM (10 mL), stirred for 1 hour at 60°C, and concentrated under vacuum to give a crude product mixture. The product mixture was purified by preparative HPLC (Phenomenex Gemini® C18 column) using a gradient of 10 to 100% ACN in water (10 mM NH₄HCO₃, pH=9.5-10). The title compound was obtained as a colorless oil (2.8 mg, 25%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.66 - 2.32 (m, 7 H), 2.37 (s, 3 H), 2.55 - 2.64 (m, 1 H), 2.95 - 3.02 (m, 1 H), 2.99 (s, 2 H), 3.48 (d, *J*=1.76 Hz, 1 H), 3.80 - 3.88 (m, 2 H), 4.76 - 4.82 (m, 2 H), 5.24 - 5.37 (m, 2 H), 6.66 - 6.72 (m, 2 H); ESI-MS [M+H]⁺ calc'd for C₂₂H₂₆F₂N₄O₂ 416.20; found 417.2.

[0470] EXAMPLE 272: 3-fluoro-2-(1-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)-5-methylphenol

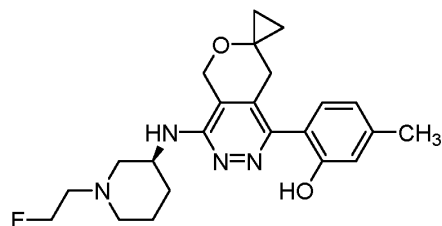


[0471] A mixture of 1-chloro-4-(2-fluoro-6-(methoxymethoxy)-4-methylphenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine (10 mg, 0.027 mmol), Cs₂CO₃ (27 mg, 0.082 mmol), Pd₂(dba)₃ (2.5 mg, 0.0027 mmol), R-BINAP (3.4 mg, 0.0055 mmol), and (3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-amine dihydrochloride (8.4 mg, 0.04 mmol) in toluene (1 mL) was stirred in a sealed tube on metal heating block at 100°C for 16 hours. The reaction mixture was added to solution of TFA (2 mL) and DCM (10 mL), stirred for 1 hour at 60°C, and concentrated under vacuum to give a crude product mixture. The product mixture was purified by preparative HPLC (Phenomenex Gemini® C18 column) using a

gradient of 10 to 100% ACN in water (10 mM NH_4HCO_3 , pH=9.5-10). The title compound was obtained as a colorless oil (0.8 mg, 7%). ^1H NMR (400 MHz, CD_3OD) δ ppm 1.69 - 2.35 (m, 7 H), 2.37 - 2.40 (m, 3 H), 2.53 - 2.62 (m, 1 H), 2.98 - 3.01 (m, 3 H), 3.01 - 3.08 (m, 1 H), 3.34 - 3.44 (m, 1 H), 3.76 - 3.89 (m, 2 H), 4.77 - 4.82 (m, 1 H), 4.89 - 4.94 (m, 1 H), 5.20 - 5.40 (m, 1 H), 6.66 - 6.75 (m, 1 H); ESI-MS $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{22}\text{H}_{26}\text{F}_2\text{N}_4\text{O}_2$ 416.20; found 417.2.

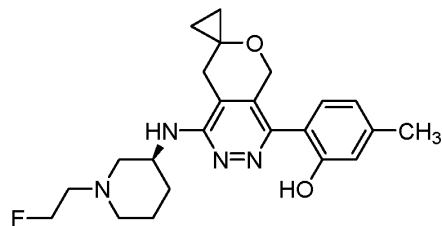
[0472] EXAMPLES 273 to 300 were prepared like the above examples.

[0473] EXAMPLE 273: (*R*)-2-(4'-((1-(2-fluoroethyl)piperidin-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol



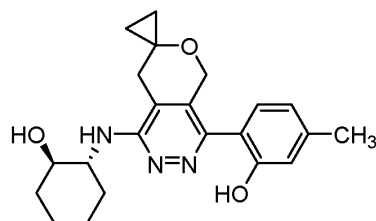
[0474] ^1H NMR (400 MHz, CDCl_3) δ ppm 0.46 - 0.53 (m, 2 H), 0.90 - 0.96 (m, 2 H), 1.61 - 1.66 (m, 2 H), 1.74 - 1.78 (m, 1 H), 1.96 - 2.00 (m, 1 H), 2.28 - 2.39 (m, 4 H), 2.62 - 2.72 (m, 2 H), 2.77 - 2.85 (m, 2 H), 2.92 - 2.98 (m, 2 H), 4.49 (dt, $J=2.89$, 1.57 Hz, 1 H), 4.51 - 4.59 (m, 3 H), 4.60 - 4.64 (m, 1 H), 4.89 - 4.93 (m, 1 H), 6.71 - 6.75 (m, 1 H), 6.92 - 6.94 (m, 1 H), 7.28 - 7.31 (m, 1 H), 11.43 (br s, 1 H); ESI-MS $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{23}\text{H}_{29}\text{FN}_4\text{O}_2$, 412.23; found, 413.2.

[0475] EXAMPLE 274: (*R*)-2-(1'-((1-(2-fluoroethyl)piperidin-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)-5-methylphenol



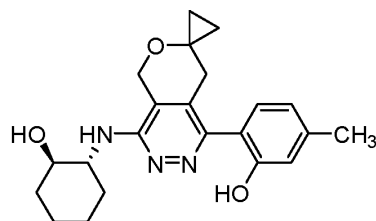
[0476] ^1H NMR (400 MHz, CDCl_3) δ ppm 0.69 - 0.75 (m, 2 H), 1.05 - 1.11 (m, 2 H), 1.64 - 1.67 (m, 1 H), 1.72 - 1.79 (m, 1 H), 1.93 - 1.99 (m, 1 H), 2.30 - 2.40 (m, 4 H), 2.55 (d, $J=6.78$ Hz, 2 H), 2.60 - 2.65 (m, 1 H), 2.66 - 2.77 (m, 2 H), 2.78 - 2.82 (m, 2 H), 4.49 (td, $J=4.96$, 1.13 Hz, 1 H), 4.53 - 4.58 (m, 1 H), 4.61 (td, $J=4.89$, 1.51 Hz, 1 H), 4.78 (d, $J=1.00$ Hz, 2 H), 5.08 - 5.17 (m, 1 H), 6.71 (dd, $J=7.91$, 1.13 Hz, 1 H), 6.94 (d, $J=1.00$ Hz, 1 H), 7.03 (d, $J=8.03$ Hz, 1 H), 11.88 (br s, 1 H); ESI-MS $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{23}\text{H}_{29}\text{FN}_4\text{O}_2$, 412.23; found, 413.2.

[0477] EXAMPLE 275: 2-(1'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)-5-methylphenol



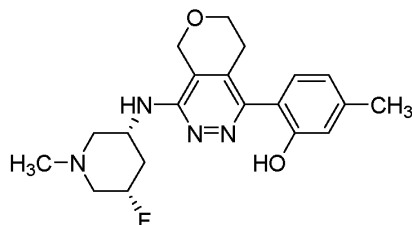
[0478] ¹H NMR (400 MHz, CDCl₃) δ ppm 0.65 - 0.75 (m, 2 H), 1.04 - 1.15 (m, 2 H), 1.26 - 1.38 (m, 2 H), 1.40 - 1.52 (m, 2 H), 1.72 - 1.86 (m, 2 H), 2.11 - 2.26 (m, 2 H), 2.35 (s, 3 H), 2.56 (s, 2 H), 3.44 - 3.55 (m, 1 H), 4.01 - 4.13 (m, 1 H), 4.18 (br d, *J*=6.53 Hz, 1 H), 4.77 (s, 2 H), 6.72 (dd, *J*=7.91, 1.13 Hz, 1 H), 6.93 (d, *J*=0.75 Hz, 1 H), 7.03 (d, *J*=8.03 Hz, 1 H), 11.53 (s, 1 H); ESI-MS [*M*+*H*]⁺ calc'd for C₂₂H₂₇N₃O₃, 381.21; found, 382.1.

[0479] EXAMPLE 276: 2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol



[0480] ¹H NMR (400 MHz, CDCl₃) δ ppm 0.44 - 0.60 (m, 2 H), 0.83 - 1.00 (m, 2 H), 1.29 - 1.39 (m, 2 H), 1.42 - 1.51 (m, 2 H), 1.72 - 1.92 (m, 2 H), 2.11 - 2.27 (m, 2 H), 2.35 (s, 3 H), 2.84 (br d, *J*=17.07 Hz, 1 H), 3.05 (br d, *J*=17.32 Hz, 1 H), 3.50 (td, *J*=10.16, 4.27 Hz, 1 H), 3.91 (br d, *J*=6.27 Hz, 1 H), 4.02 - 4.18 (m, 1 H), 4.53 (d, *J*=1.51 Hz, 2 H), 6.73 (dd, *J*=8.03, 1.25 Hz, 1 H), 6.92 (d, *J*=0.75 Hz, 1 H), 7.19 - 7.33 (m, 1 H), 11.43 (s, 1 H); ESI-MS [*M*+*H*]⁺ calc'd for C₂₂H₂₇N₃O₃, 381.21; found, 382.1.

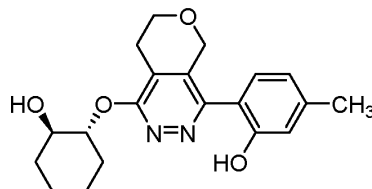
[0481] EXAMPLE 277: 2-(4-(((3*R*,5*S*)-5-fluoro-1-methylpiperidin-3-yl)amino)-7,8-dihydro-5*H*-pyrano[3,4-*d*]pyridazin-1-yl)-5-methylphenol



[0482] ¹H NMR (400 MHz, CD₃OD) δ ppm 1.90 - 2.00 (m, 1 H), 2.11 - 2.24 (m, 1 H), 2.32 (s, 3 H), 2.35 (s, 3 H), 2.57 - 2.61 (m, 2 H), 2.63 - 2.77 (m, 3 H), 3.86 (t, *J*=5.65 Hz, 2 H),

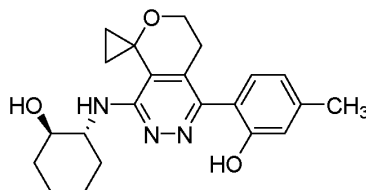
4.49 - 4.64 (m, 3 H), 4.74 - 4.84 (m, 1 H), 4.87 - 4.94 (m, 1 H), 6.74 (s, 1 H), 6.75 - 6.80 (m, 1 H), 7.09 (d, $J=7.53$ Hz, 1 H); ESI-MS $[M+H]^+$ calc'd for $C_{20}H_{25}FN_4O_2$, 372.20; found, 373.1.

[0483] EXAMPLE 278: 2-(1-(((1*R*,2*R*)-2-hydroxycyclohexyl)oxy)-7,8-dihydro-5*H*-pyrano[3,4-*d*]pyridazin-4-yl)-5-methylphenol



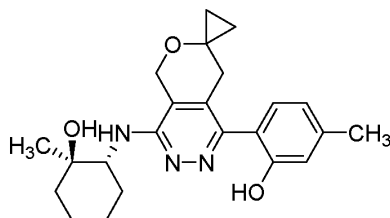
[0484] 1H NMR (400 MHz, $CDCl_3$) δ ppm 1.14 - 1.50 (m, 4 H), 1.59 - 1.77 (m, 2 H), 1.97 - 2.22 (m, 1 H), 2.21 - 2.22 (m, 1 H), 2.22 - 2.29 (m, 3 H), 2.56 - 2.85 (m, 2 H), 3.64 - 3.75 (m, 1 H), 3.83 - 3.92 (m, 1 H), 3.93 - 4.03 (m, 1 H), 4.55 - 4.72 (m, 2 H), 5.00 - 5.16 (m, 1 H), 6.67 (dd, $J=8.03, 1.00$ Hz, 1 H), 6.83 - 6.98 (m, 2 H); ESI-MS $[M+H]^+$ calc'd for $C_{20}H_{24}N_2O_4$, 356.17; found, 357.1.

[0485] EXAMPLE 279: 2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-7',8'-dihydrospiro[cyclopropane-1,5'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol



[0486] 1H NMR (400 MHz, $CDCl_3$) δ ppm 1.13 - 1.26 (m, 1 H), 1.26 - 1.50 (m, 5 H), 1.69 - 1.84 (m, 2 H), 1.84 - 1.99 (m, 2 H), 2.03 - 2.16 (m, 1 H), 2.16 - 2.27 (m, 1 H), 2.32 (s, 3 H), 2.83 (br t, $J=5.14$ Hz, 2 H), 3.45 - 3.61 (m, 1 H), 3.78 - 3.96 (m, 2 H), 4.06 - 4.22 (m, 1 H), 4.63 (br d, $J=5.52$ Hz, 1 H), 4.92 - 5.22 (m, 1 H), 6.76 (d, $J=7.78$ Hz, 1 H), 6.91 (s, 1 H), 7.01 (d, $J=7.24$ Hz, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{22}H_{27}N_3O_3$ 381.21; found 382.2.

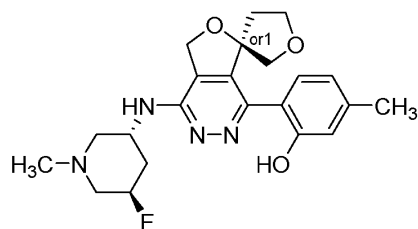
[0487] EXAMPLE 280: 2-(4'-(((1*R*,2*R*)-2-hydroxy-2-methylcyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol



[0488] 1H NMR (400 MHz, $CDCl_3$) δ ppm 0.43 - 0.60 (m, 2 H), 0.92 (dt, $J=8.72, 3.67$ Hz, 2 H), 1.23 (s, 3 H), 1.25 - 1.50 (m, 3 H), 1.58 - 1.73 (m, 2 H), 1.75 - 1.86 (m, 1 H), 1.89 -

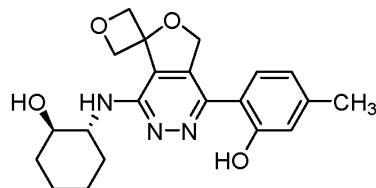
2.05 (m, 2 H), 2.34 (s, 3 H), 2.82 (d, $J=17.07$ Hz, 1 H), 3.07 (br d, $J=17.32$ Hz, 1 H), 3.80 (br d, $J=6.53$ Hz, 1 H), 4.17 - 4.29 (m, 1 H), 4.53 (s, 2 H), 6.73 (d, $J=7.56$ Hz, 1 H), 6.88 - 6.98 (m, 1 H), 7.25 (d, $J=8.03$ Hz, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{23}H_{29}N_3O_3$ 395.22; found 396.2.

[0489] EXAMPLE 281: 2-((*R*^{*})-1'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-4,5-dihydro-2*H*,7*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-4'-yl)-5-methylphenol



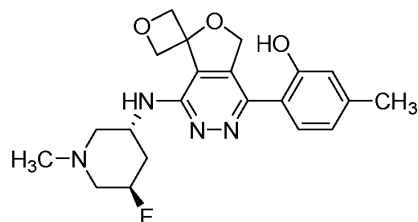
[0490] 1H NMR (400 MHz, CD_3OD) δ ppm 1.21 - 1.31 (m, 1 H), 1.69 - 1.88 (m, 1 H), 2.04 - 2.12 (m, 1 H), 2.17 - 2.28 (m, 2 H), 2.33 (s, 4 H), 2.39 (s, 3 H), 2.41 - 2.52 (m, 1 H), 2.99 - 3.28 (m, 2 H), 3.78 (s, 3 H), 4.70 - 4.78 (m, 1 H), 4.91 (br s, 1 H), 6.73 - 6.79 (m, 2 H), 6.99 - 7.04 (m, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{22}H_{27}N_4O_3$ 414.48; found 415.3.

[0491] EXAMPLE 282: 2-(4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-7*H*-spiro[furo[3,4-*d*]pyridazine-5,3'-oxetan]-1-yl)-5-methylphenol



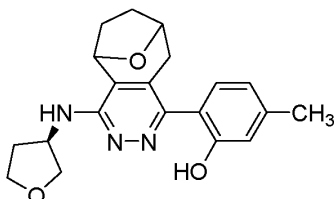
[0492] 1H NMR (400 MHz, CD_3OD) δ ppm 1.30 - 1.58 (m, 4 H), 1.71 - 1.86 (m, 2 H), 2.04 - 2.13 (m, 1 H), 2.34 (s, 4 H), 3.52 - 3.61 (m, 1 H), 4.05 - 4.14 (m, 1 H), 4.80 - 4.85 (m, 1 H), 4.92 - 4.97 (m, 1 H), 5.13 (d, $J=7.28$ Hz, 2 H), 5.36 (s, 2 H), 6.72 - 6.77 (m, 1 H), 6.82 - 6.85 (m, 1 H), 6.95 - 7.00 (m, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{21}H_{25}N_3O_4$ 383.4; found 384.38.

[0493] EXAMPLE 283: 2-(4-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-7*H*-spiro[furo[3,4-*d*]pyridazine-5,3'-oxetan]-1-yl)-5-methylphenol



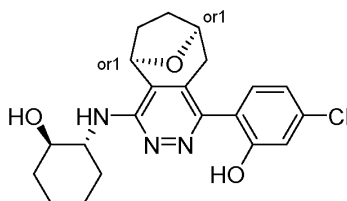
[0494] ^1H NMR (400 MHz, CD_3OD) δ ppm 1.88 - 2.05 (m, 1 H), 2.17 - 2.30 (m, 1 H), 2.36 (d, $J=14.43$ Hz, 7 H), 2.52 - 2.66 (m, 1 H), 2.71 - 2.81 (m, 1 H), 3.01 - 3.08 (m, 1 H), 4.75 - 5.01 (m, 4 H), 5.09 - 5.16 (m, 2 H), 5.39 (s, 2 H), 6.73 - 6.78 (m, 1 H), 6.82 - 6.86 (m, 1 H), 6.98 - 7.03 (m, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{21}\text{H}_{25}\text{FN}_4\text{O}_3$ 400.54; found 401.36.

[0495] EXAMPLE 284: 5-methyl-2-((5*RS*,8*SR*)-4-(((*R*)-tetrahydrofuran-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol



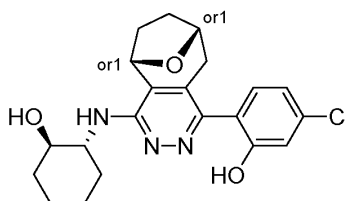
[0496] ^1H NMR (400 MHz, CD_3OD) δ ppm 1.69 - 1.94 (m, 1 H), 2.08 - 2.42 (m, 9 H), 3.15 (br dd, $J=18.32$, 5.02 Hz, 1 H), 3.76 - 3.93 (m, 2 H), 3.96 - 4.08 (m, 2 H), 4.57 (br s, 1 H), 4.77 (br s, 1 H), 5.28 - 5.39 (m, 1 H), 6.80 - 6.91 (m, 2 H), 7.14 - 7.22 (m, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_3$ 353.2; found 354.2.

[0497] EXAMPLE 285: 5-chloro-2-((5*R**,8*S**)-4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol



[0498] ^1H NMR (400 MHz, CD_3OD) δ ppm 1.32 - 1.56 (m, 4 H), 1.77 - 1.86 (m, 2 H), 2.33 (s, 6 H), 3.06 - 3.14 (m, 1 H), 3.60 - 3.68 (m, 1 H), 3.75 - 3.85 (m, 1 H), 4.72 - 4.81 (m, 2 H), 5.34 - 5.39 (m, 1 H), 6.96 - 7.02 (m, 2 H), 7.21 - 7.26 (m, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_3$ 401.2; found 402.2.

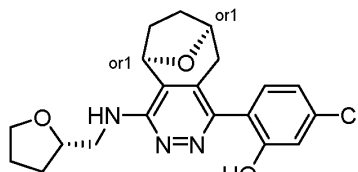
[0499] EXAMPLE 286: 5-chloro-2-((5*S**,8*R**)-4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol



[0500] ^1H NMR (400 MHz, CD_3OD) δ ppm 1.41 - 1.70 (m, 4 H), 1.81 - 2.11 (m, 4 H), 2.26 (br s, 4 H), 3.06 - 3.13 (m, 1 H), 3.66 (s, 1 H), 3.76 - 3.86 (m, 1 H), 4.74 - 4.78 (m, 1 H), 5.29

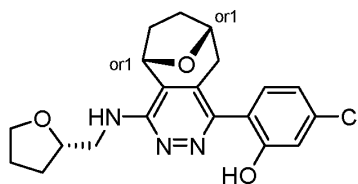
- 5.40 (m, 2 H), 6.92 - 7.05 (m, 2 H), 7.19 - 7.27 (m, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{20}H_{23}N_3O_3$ 401.2; found 402.2.

[0501] EXAMPLE 287: 5-chloro-2-(((5*R**,8*S**)-4-((((*S*)-tetrahydrofuran-2-yl)methyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol



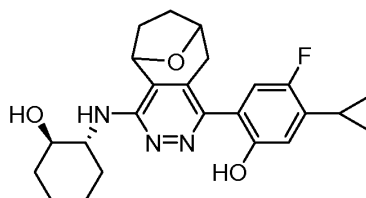
[0502] 1H NMR (400 MHz, CD_3OD) δ ppm 1.65 - 1.79 (m, 2 H), 1.90 - 2.04 (m, 2 H), 2.05 - 2.18 (m, 2 H), 2.32 (br d, $J=18.57$ Hz, 3 H), 3.07 - 3.16 (m, 1 H), 3.60 (s, 1 H), 3.66 (s, 1 H), 3.77 - 3.85 (m, 1 H), 3.88 - 3.95 (m, 1 H), 4.20 - 4.28 (m, 1 H), 4.73 - 4.80 (m, 1 H), 5.23 - 5.30 (m, 1 H), 6.97 - 7.07 (m, 2 H), 7.26 (d, $J=8.03$ Hz, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{20}H_{22}ClN_3O_3$ 387.1; found 388.1.

[0503] EXAMPLE 288: 5-chloro-2-(((5*S**,8*R**)-4-((((*S*)-tetrahydrofuran-2-yl)methyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol



[0504] 1H NMR (400 MHz, CD_3OD) δ ppm 1.65 - 1.79 (m, 2 H), 1.92 - 2.05 (m, 2 H), 2.05 - 2.19 (m, 2 H), 2.21 - 2.37 (m, 3 H), 3.06 - 3.17 (m, 1 H), 3.52 - 3.61 (m, 1 H), 3.63 - 3.70 (m, 1 H), 3.77 - 3.84 (m, 1 H), 3.88 - 3.96 (m, 1 H), 4.19 - 4.28 (m, 1 H), 4.74 - 4.79 (m, 1 H), 5.22 - 5.29 (m, 1 H), 7.00 (s, 2 H), 7.25 (s, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{20}H_{22}ClN_3O_3$ 387.1; found 388.1.

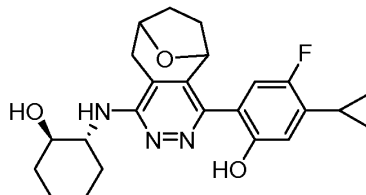
[0505] EXAMPLE 289: 5-cyclopropyl-4-fluoro-2-(4-((((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol



[0506] 1H NMR (400 MHz, CD_3OD) δ ppm 0.70 - 0.80 (m, 2 H), 1.05 (dd, $J=8.41$, 2.13 Hz, 2 H), 1.34 - 1.61 (m, 4 H), 1.70 - 1.89 (m, 3 H), 2.09 (br s, 3 H), 2.25 (br d, $J=3.76$ Hz, 4 H), 3.10 (br d, $J=5.27$ Hz, 1 H), 3.59 - 3.68 (m, 1 H), 3.76 - 3.85 (m, 1 H), 4.72 - 4.76 (m, 1

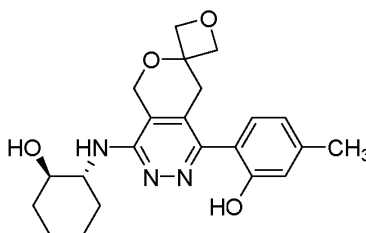
H), 5.32 (br s, 1 H), 6.47 (d, $J=6.27$ Hz, 1 H), 6.96 (d, $J=10.04$ Hz, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{24}H_{28}FN_3O_3$ 425.2; found 426.2.

[0507] EXAMPLE 290: 5-cyclopropyl-4-fluoro-2-(1-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)phenol



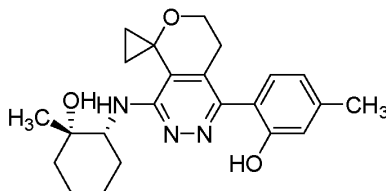
[0508] 1H NMR (400 MHz, CD_3OD) δ ppm 0.72 - 0.84 (m, 2 H), 1.00 - 1.13 (m, 2 H), 1.28 - 1.44 (m, 2 H), 1.31 - 1.61 (m, 2 H), 1.74 - 1.89 (m, 3 H), 1.99 - 2.15 (m, 5H), 2.17 - 2.33 (m, 1 H), 2.35 - 2.53 (m, 1 H), 3.00 - 3.22 (m, 1 H), 3.46 - 3.71 (m, 1 H), 3.74 - 3.86 (m, 1 H), 4.61 - 4.82 (m, 1 H), 4.91 - 5.00 (m, 1 H), 6.50 (d, $J=6.24$ Hz, 1 H), 6.98 (d, $J=9.90$ Hz, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{24}H_{28}FN_3O_3$ 425.2; found 426.2.

[0509] EXAMPLE 291: 2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5',8'-dihydrospiro[oxetane-3,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol



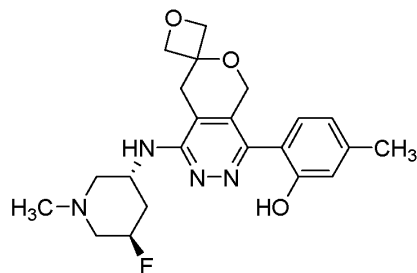
[0510] 1H NMR (400 MHz, CD_3OD) δ ppm 1.31 - 1.48 (m, 4 H), 1.71 - 1.82 (m, 2 H), 2.05 - 2.23 (m, 2 H), 2.32 (s, 3 H), 2.83 - 3.01 (m, 2 H), 3.54 - 3.64 (m, 1 H), 4.02 - 4.10 (m, 1 H), 4.51 - 4.55 (m, 2 H), 4.57 - 4.61 (m, 2 H), 4.70 - 4.74 (m, 2 H), 6.71 - 6.74 (m, 1 H), 6.74 - 6.79 (m, 1 H), 7.03 - 7.06 (m, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{22}H_{27}N_3O_4$ 397.47; found 398.4.

[0511] EXAMPLE 292: 2-(4'-(((1*R*,2*S*)-2-hydroxy-2-methylcyclohexyl)amino)-7',8'-dihydrospiro[cyclopropane-1,5'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol



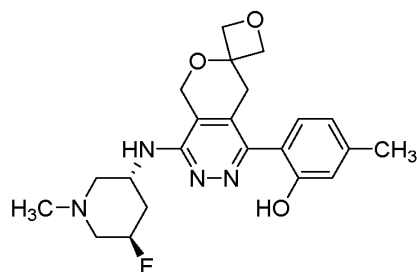
[0512] ^1H NMR (400 MHz, CD_3OD) δ ppm 1.15 - 1.20 (m, 2 H), 1.21 (s, 3 H), 1.29 - 1.55 (m, 4 H), 1.57 - 1.80 (m, 4 H), 1.85 - 1.97 (m, 2 H), 2.32 (s, 3 H), 2.67 (td, $J=5.65, 3.14$ Hz, 2 H), 3.33 - 3.36 (m, 1 H), 3.87 (t, $J=5.71$ Hz, 2 H), 4.05 (dd, $J=10.79, 4.39$ Hz, 1 H), 6.73 (s, 1 H), 6.77 (d, $J=7.49$ Hz, 1 H), 7.07 (d, $J=7.65$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_3$ 395.22; found 396.20.

[0513] EXAMPLE 293: 2-(1'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5',8'-dihydrospiro[oxetane-3,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)-5-methylphenol



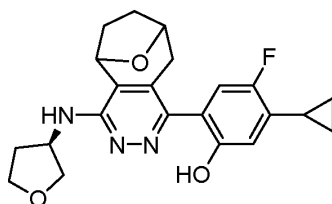
[0514] ^1H NMR (400 MHz, CD_3OD) δ ppm 1.69 - 1.88 (m, 1 H), 2.09 - 2.18 (m, 1 H), 2.33 (d, $J=4.77$ Hz, 8 H), 2.89 (s, 2 H), 2.91 - 3.16 (m, 2 H), 4.35 - 4.40 (m, 2 H), 4.69 (s, 5 H), 4.94 - 5.01 (m, 1 H), 6.76 (s, 1 H), 6.77 - 6.82 (m, 1 H), 7.09 - 7.15 (m, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{22}\text{H}_{27}\text{FN}_4\text{O}_3$ 414.48; found 415.4.

[0515] EXAMPLE 294: 2-(4'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5',8'-dihydrospiro[oxetane-3,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol



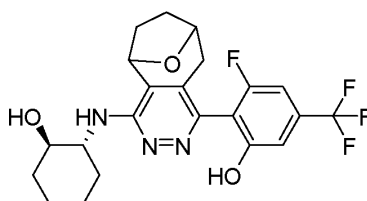
[0516] ^1H NMR (400 MHz, CD_3OD) δ ppm 1.98 - 2.22 (m, 1 H), 2.38 (s, 3 H), 2.53 - 2.66 (m, 1 H), 2.73 - 2.78 (m, 1 H), 3.00 (d, $J=2.38$ Hz, 3 H), 3.04 - 3.13 (m, 1 H), 3.14 - 3.18 (m, 1 H), 3.32 - 3.48 (m, 1 H), 3.68 (d, $J=1.63$ Hz, 2 H), 3.77 - 3.88 (m, 2 H), 4.53 - 4.59 (m, 1 H), 4.74 (dd, $J=14.12, 7.34$ Hz, 4 H), 5.22 - 5.40 (m, 1 H), 6.85 - 6.89 (m, 1 H), 6.89 - 6.93 (m, 1 H), 7.19 - 7.24 (m, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{22}\text{H}_{27}\text{FN}_4\text{O}_3$ 414.48; found 415.4.

[0517] EXAMPLE 295: 5-cyclopropyl-4-fluoro-2-(4-(((*R*)-tetrahydrofuran-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol



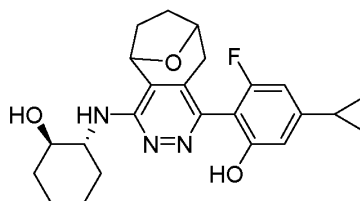
[0518] ^1H NMR (400 MHz, CD_3OD) δ ppm 0.78 (br d, $J=5.32$ Hz, 2 H), 1.09 (br d, $J=8.44$ Hz, 2 H), 1.71 - 1.85 (m, 1 H), 2.06 - 2.49 (m, 7 H), 3.13 - 3.23 (m, 1 H), 3.88 (br d, $J=5.32$ Hz, 2 H), 4.04 (br s, 2 H), 4.53 - 4.65 (m, 1 H), 4.76 - 4.81 (m, 1 H), 5.37 (br d, $J=5.69$ Hz, 1 H), 6.53 (d, $J=6.05$ Hz, 1 H), 7.08 (d, $J=9.90$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{22}\text{H}_{24}\text{FN}_3\text{O}_3$ 397.2; found 398.2.

[0519] EXAMPLE 296: 3-fluoro-2-(4-(((1R,2R)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5H-5,8-epoxycyclohepta[d]pyridazin-1-yl)-5-(trifluoromethyl)phenol



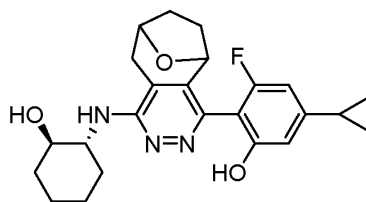
[0520] ^1H NMR (400 MHz, CD_3OD) δ ppm 1.49 (br d, $J=9.54$ Hz, 4 H), 1.56 - 1.77 (m, 3 H), 1.91 - 2.28 (m, 5 H), 2.91 - 3.06 (m, 1 H), 3.45 - 3.59 (m, 1 H), 3.63 - 3.77 (m, 1 H), 4.42 - 4.73 (m, 2 H), 5.14 - 5.35 (m, 1 H), 6.91 - 7.10 (m, 2 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{22}\text{H}_{23}\text{F}_4\text{N}_3\text{O}_3$ 453.2; found 454.2.

[0521] EXAMPLE 297: 5-cyclopropyl-3-fluoro-2-(4-(((1R,2R)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5H-5,8-epoxycyclohepta[d]pyridazin-1-yl)phenol



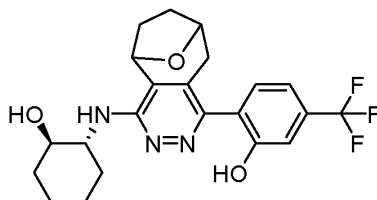
[0522] ^1H NMR (400 MHz, CD_3OD) δ ppm 0.75 (dt, $J=6.59$, 4.61 Hz, 2 H), 0.97 - 1.11 (m, 2 H), 2.29 (br s, 14 H), 3.01 - 3.26 (m, 1 H), 3.57 - 3.72 (m, 1 H), 3.76 - 3.93 (m, 1 H), 4.70 - 4.81 (m, 1 H), 5.28 - 5.46 (m, 1 H), 6.53 (br d, $J=2.76$ Hz, 2 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{24}\text{H}_{28}\text{FN}_3\text{O}_3$ 425.2; found 426.2.

[0523] EXAMPLE 298: 5-cyclopropyl-3-fluoro-2-(1-(((1R,2R)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5H-5,8-epoxycyclohepta[d]pyridazin-4-yl)phenol



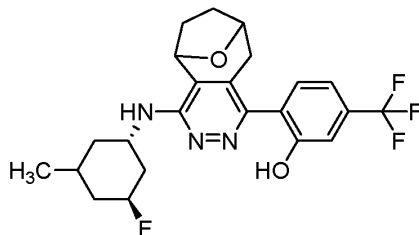
[0524] ^1H NMR (400 MHz, CD_3OD) δ ppm 0.68 - 0.82 (m, 2 H), 1.00 - 1.12 (m, 2 H), 1.42 (br s, 4 H), 1.79 - 2.31 (m, 10 H), 3.03 - 3.19 (m, 1 H), 3.64 (s, 1 H), 3.80 - 3.89 (m, 1 H), 4.67 - 4.79 (m, 1 H), 5.28 - 5.51 (m, 1 H), 6.56 (br s, 2 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{24}\text{H}_{28}\text{FN}_3\text{O}_3$ 425.2; found 426.2.

[0525] EXAMPLE 299: 2-(4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol



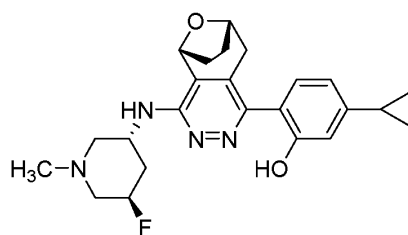
[0526] ^1H NMR (400 MHz, CD_3OD) δ ppm 1.37 - 1.65 (m, 4 H), 1.73 - 1.88 (m, 3 H), 2.04 (s, 3 H), 2.37 (m, 6 H), 3.08 - 3.17 (m, 1 H), 3.60 - 3.70 (m, 1 H), 3.77 - 3.86 (m, 1 H), 4.75 - 4.81 (m, 1 H), 5.33 - 5.42 (m, 1 H), 7.23 (d, $J=1.25$ Hz, 1 H), 7.29 - 7.34 (m, 1 H), 7.45 (s, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{22}\text{H}_{24}\text{F}_3\text{N}_3\text{O}_3$ 435.2; found 436.2.

[0527] EXAMPLE 300: 2-(4-(((1*S*,3*S*)-3-fluoro-5-methylcyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol

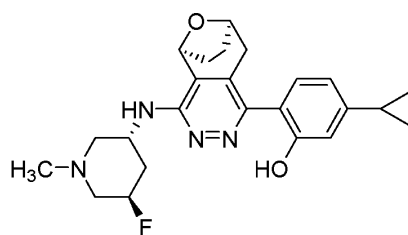


[0528] ^1H NMR (400 MHz, CD_3OD) δ ppm 2.33 (br d, $J=4.40$ Hz, 7 H), 2.49 - 2.71 (m, 2 H), 3.00 - 3.07 (m, 3 H), 3.08 - 3.23 (m, 2 H), 3.77 - 3.95 (m, 2 H), 4.79 - 4.83 (m, 1 H), 5.24 - 5.42 (m, 2 H), 7.30 (s, 2 H), 7.56 (br d, $J=7.70$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{22}\text{H}_{24}\text{F}_4\text{N}_4\text{O}_2$ 452.2; found 453.2.

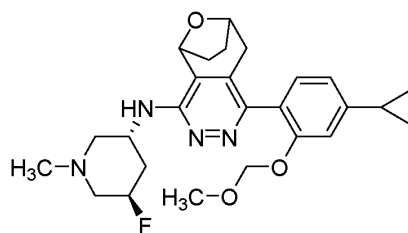
[0529] EXAMPLE 301: 5-cyclopropyl-2-(((5*R*,8*S*)-4-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol



[0530] EXAMPLE 302: 5-cyclopropyl-2-(((5*S*,8*R*)-4-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol



[0531] STEP 1: 1-(4-cyclopropyl-2-(methoxymethoxy)phenyl)-*N*-((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-amine



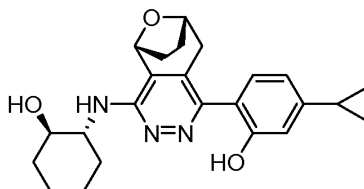
[0532] A mixture of 4-chloro-1-(4-cyclopropyl-2-(methoxymethoxy)phenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine (100 mg, 268.21 μ mol), (3*R*,5*R*)-5-fluoro-1-methyl-piperidin-3-amine (110.02 mg, 536.42 μ mol, 2 HCl), Cs₂CO₃ (436.94 mg, 1.34 mmol), BINAP (50.10 mg, 80.46 μ mol) and Pd(OAc)₂ (12.04 mg, 53.64 μ mol) in toluene (4 mL) was degassed and purged with N₂ (3 x) and then stirred at 120°C for 12 hours under N₂ atmosphere. LC-MS showed the starting material was consumed completely and one main peak with desired mass was detected. The residue was diluted with H₂O (80 mL) and extracted with DCM (100 mL x 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (ISCO® 12 g SepaFlash® silica gel column) using a gradient of 0 to 20% MeOH in DCM (15 mL/min) to give the title compound as a white solid (100 mg, crude). ESI-MS *m/z* [M+H]⁺ 468.3.

[0533] STEP 2: 5-cyclopropyl-2-(((5*R*,8*S*)-4-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol and 5-

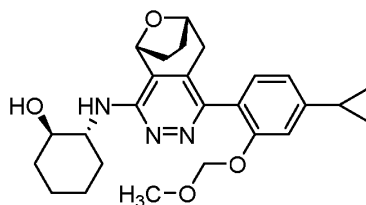
cyclopropyl-2-((5*S*,8*R*)-4-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol

[0534] To a solution of 1-(4-cyclopropyl-2-(methoxymethoxy)phenyl)-*N*-((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-amine (80 mg, 170.74 μ mol) in DCM (3 mL) was added TFA (0.6 mL). The mixture was stirred at 25°C for 2 hours. LC-MS showed starting material was consumed completely and one main peak with desired mass. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by preparative HPLC (Xtimate C18-10 μ m, 40 mm x 150 mm column) using a gradient of 16 to 56% ACN in water (with $\text{NH}_3\text{H}_2\text{O}+\text{NH}_4\text{HCO}_3$) over 36 minutes to give a mixture of the title compounds as a white solid (40 mg, yield 90%, purity 100%). The diastereomers were separated by SFC (DAICEL CHIRALPAK® AD-10 μ m, 30 mm x 250 mm column) using a mobile phase of CO_2 and 50% iPrOH (with 0.1% NH_3OH). The title compound of Example 301 was obtained as a white solid (11.5 mg, 23.7% yield, 99.4% purity). ^1H NMR (400 MHz, CD_3OD) δ ppm 0.53 - 0.61 (m, 2 H), 0.81 - 0.91 (m, 2 H), 1.54 - 1.63 (m, 1 H), 1.71 - 1.96 (m, 3 H), 2.04 - 2.16 (m, 3 H), 2.25 (m, 2 H), 2.41 (s, 3 H), 2.46 - 2.62 (m, 1 H), 2.93 (m, 1 H), 3.02 - 3.13 (m, 1 H), 3.24 - 3.30 (m, 1 H), 4.57 - 4.68 (m, 2 H), 4.84 - 5.01 (m, 1 H), 5.06 (d, $J=5.63$ Hz, 1H), 6.50 (s, 1 H), 6.54 - 6.54 (m, 1 H), 6.56 (d, $J=7.63$ Hz, 1 H), 6.94 (d, $J=7.75$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ 424.2. The title compound of Example 302 was obtained as a white solid (17.1 mg, 35.3% yield, 99.4% purity). ^1H NMR (400 MHz, CD_3OD) δ ppm 0.51 - 0.63 (m, 2 H), 0.83 - 0.91 (m, 2 H), 1.53 - 1.62 (m, 1 H), 1.70 - 1.94 (m, 3 H), 2.05 - 2.15 (m, 3 H), 2.18 - 2.32 (m, 2 H), 2.39 (s, 3 H), 2.43 - 2.58 (m, 1 H), 2.92 (m, 1 H), 3.09 (br t, $J=10.82$ Hz, 1 H), 3.25 (br s, 1 H), 4.57 - 4.70 (m, 2 H), 4.84 - 5.00 (m, 1 H), 5.06 (d, $J=5.63$ Hz, 1 H), 6.50 (d, $J=1.13$ Hz, 1 H), 6.52 - 6.60 (m, 1 H), 6.94 (d, $J=7.75$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ 424.2.

[0535] EXAMPLE 303: 5-cyclopropyl-2-((5*R*,8*S*)-4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol



[0536] STEP 1: (1*R*,2*R*)-2-(((5*R*,8*S*)-1-(4-cyclopropyl-2-(methoxymethoxy)phenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol

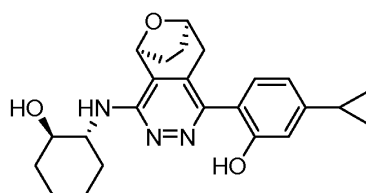


[0537] A mixture of (1*R*,2*R*)-2-(((5*R*,8*S*)-1-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol (180.00 mg, 581.04 μ mol), 2-(4-cyclopropyl-2-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (212.09 mg, 697.25 μ mol), Cs₂CO₃ (757.26 mg, 2.32 mmol), and Pd(dppf)Cl₂.CH₂Cl₂ (94.90 mg, 116.21 μ mol) in dioxane (4 mL) and H₂O (1 mL) was degassed and purged with N₂ (3 x) and stirred at 100°C for 1 hour under N₂ atmosphere. LC-MS showed starting material was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by flash chromatography (ISCO® 20 g SepaFlash® silica gel column) using a gradient of 0 to 10% MeOH in DCM (35 mL/min) to give the title compound as a white solid (350 mg, crude). ESI-MS *m/z* [M+H]⁺ 451.3.

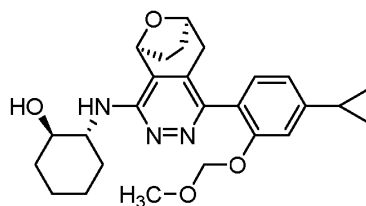
[0538] STEP 2: 5-cyclopropyl-2-((5*R*,8*S*)-4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol

[0539] To a solution of (1*R*,2*R*)-2-(((5*R*,8*S*)-1-(4-cyclopropyl-2-(methoxymethoxy)phenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol (300 mg, 664.37 μ mol) in DCM (12 mL) was added TFA (4.61 g, 40.39 mmol, 3 mL). The mixture was stirred at 45°C for 2 hours. LC-MS showed 29% desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by preparative HPLC (Xtimate C18-10 μ m, 40 mm x 150 mm column) using a gradient of 0 to 36% ACN in water (with FA) over 30 minutes. The title compound was obtained as a white solid (42.8 mg, 100%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.55 - 0.68 (m, 2 H), 0.88 - 0.98 (m, 2 H), 1.15 - 1.30 (m, 4 H), 1.41 - 1.69 (m, 3 H), 1.82 - 2.09 (m, 7 H), 2.78 - 2.91 (m, 1 H), 3.40 - 3.51 (m, 1 H), 3.85 - 3.90 (m, 1 H), 4.53 - 4.62 (m, 1 H), 5.06 - 5.16 (m, 1 H), 6.43 - 6.61 (m, 2 H), 6.84 - 7.01 (m, 1 H), 8.19 (s, 1 H); ESI-MS *m/z* [M+H]⁺ 407.2.

[0540] EXAMPLE 304: 5-cyclopropyl-2-((5*S*,8*R*)-4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol



[0541] STEP 1: (1*R*,2*R*)-2-(((5*S*,8*R*)-1-(4-cyclopropyl-2-(methoxymethoxy)phenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol



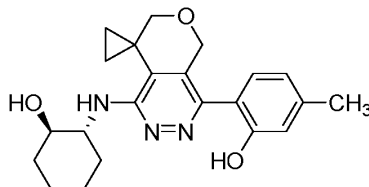
[0542] A mixture of (1*R*,2*R*)-2-(((5*S*,8*R*)-1-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol (130.00 mg, 419.64 μ mol), 2-(4-cyclopropyl-2-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (153.18 mg, 503.57 μ mol), Cs₂CO₃ (546.91 mg, 1.68 mmol), and Pd(dppf)Cl₂.CH₂Cl₂ (68.54 mg, 83.93 μ mol) in dioxane (4 mL) and H₂O (1 mL) was degassed and purged with N₂ (3 x) and stirred at 100°C for 1 hour under N₂ atmosphere. LC-MS showed starting material was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by flash chromatography (ISCO® 20 g SepaFlash® silica gel column) using a gradient of 0 to 10% MeOH in DCM (35 mL/min) to give the title compound as a white solid (240 mg, crude). ESI-MS *m/z* [M+H]⁺ 451.3.

[0543] STEP 2: 5-cyclopropyl-2-(((5*S*,8*R*)-4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol

[0544] To a solution of (1*R*,2*R*)-2-(((5*S*,8*R*)-1-(4-cyclopropyl-2-(methoxymethoxy)phenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol (240 mg, 531.49 μ mol) in DCM (8 mL) was added TFA (3.07 g, 26.92 mmol, 2 mL). The mixture was stirred at 40°C for 2 hours. LC-MS showed 34% desired mass was detected. The reaction was filtered and concentrated under reduced pressure to give a residue. The residue was purified by preparative HPLC (Xtimate C18-10 μ m, 40 mm x 150 mm column) using a gradient of 0 to 36% ACN in water (with FA) over 30 minutes. The title compound was obtained as a white solid (51.8 mg, 100%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.57 - 0.66 (m, 2 H), 0.86 - 0.99 (m, 2 H), 1.17 - 1.30 (m, 4 H), 1.45

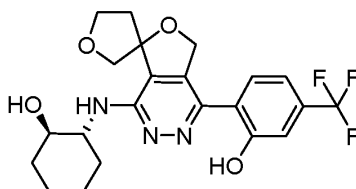
- 1.70 (m, 3 H), 1.78 - 2.08 (m, 7 H), 2.82 - 2.96 (m, 1 H), 3.41 - 3.53 (m, 1 H), 3.83 - 3.88 (m, 1 H), 4.56 - 4.68 (m, 1 H), 5.16 - 5.23 (m, 1 H), 6.51 - 6.62 (m, 2 H), 6.92 - 7.04 (m, 1 H), 8.03 - 8.17 (m, 1 H); ESI-MS m/z $[M+H]^+$ 407.2.

[0545] EXAMPLE 305: 2-(1'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5'*H*,7'*H*-spiro[cyclopropane-1,8'-pyrano[3,4-*d*]pyridazin]-4'-yl)-5-methylphenol



[0546] To a mixture of (1*R*,2*R*)-2-((4'-chloro-5'*H*,7'*H*-spiro[cyclopropane-1,8'-pyrano[3,4-*d*]pyridazin]-1'-yl)amino)cyclohexan-1-ol (70 mg, 225.96 μ mol) in dioxane (2 mL) and H₂O (0.5 mL) were added 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (58.19 mg, 248.56 μ mol), Pd(dppf)Cl₂.CH₂Cl₂ (36.91 mg, 45.19 μ mol) and Cs₂CO₃ (294.49 mg, 903.84 μ mol) and the mixture was stirred at 100°C for 2 hours under N₂. LC-MS showed one main peak with desired mass. The mixture was treated with HCl (1 M, 8 mL) and extracted with EtOAc (10 mL). The organic layer was discarded. The aqueous layer was filtered. The filtrate was purified by preparative HPLC (Boston Prime C18-5 μ m, 30 mm x 150 mm column) using a gradient of 0 to 39% ACN in water (with FA) over 9 minutes. A formic acid salt of the title compound was obtained as a white solid (15 mg, 16% yield, 100% purity). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.71 - 0.91 (m, 2 H), 1.03 - 1.37 (m, 5 H), 1.56 - 1.80 (m, 3 H), 1.83 - 1.97 (m, 2 H), 2.28 (s, 3 H), 2.33 (dt, $J=3.61$, 1.86 Hz, 1 H), 3.48 (br d, $J=11.62$ Hz, 1 H), 3.52 - 3.57 (m, 1 H), 3.58 - 3.66 (m, 1 H), 4.26 - 4.62 (m, 2 H), 4.87 - 5.09 (m, 1 H), 6.46 - 6.85 (m, 2 H), 6.99 (d, $J=7.58$ Hz, 1 H), 8.11 - 8.25 (m, 1 H), 9.57 - 9.67 (m, 1 H); ESI-MS m/z $[M+H]^+$ 382.2.

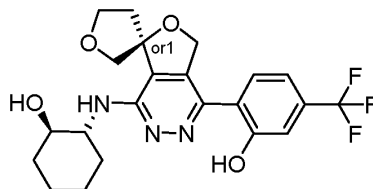
[0547] EXAMPLE 306: 2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



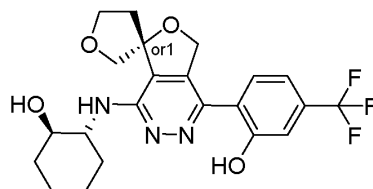
[0548] The title compound was synthesized from starting material (1*R*,2*R*)-2-aminocyclohexan-1-ol, using a procedure analogous to Example 254. ¹H NMR (400 MHz,

CD₃OD) δ ppm 1.42 (br s, 4 H), 1.68 - 1.82 (m, 2 H), 2.03 (s, 1 H), 2.25 - 2.48 (m, 3 H), 3.46 - 3.57 (m, 1 H), 3.72 - 3.78 (m, 1 H), 3.99 (s, 2 H), 4.20 - 4.38 (m, 2 H), 5.33 (s, 2 H), 7.20 (s, 2 H), 7.39 - 7.44 (m, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for C₂₂H₂₄F₃N₃O₄ 451.2; found 452.7.

[0549] EXAMPLE 307: 2-((*S*^{*})-4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol

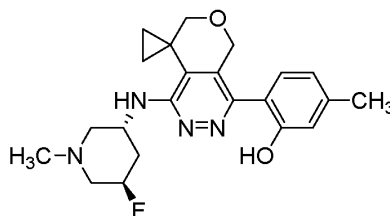


[0550] EXAMPLE 308: 2-((*R*^{*})-4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol

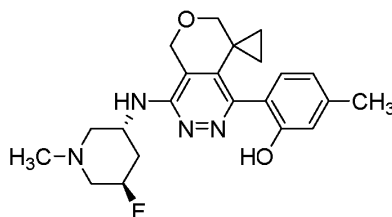


[0551] The title compounds were obtained from chiral separation of Example 306 by supercritical fluid chromatography. The first peak was assigned as the title compound of Example 307. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.42 (br s, 4 H) 1.68 - 1.82 (m, 2 H), 2.03 (s, 1 H), 2.25 - 2.48 (m, 3 H), 3.46 - 3.57 (m, 1 H), 3.72 - 3.78 (m, 1 H), 3.99 (s, 2 H), 4.20 - 4.38 (m, 2 H), 5.33 (s, 2 H), 7.20 (s, 2 H), 7.39 - 7.44 (m, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for C₂₂H₂₄F₃N₃O₄ 451.2; found 452.7. The second peak was assigned as the title compound of Example 308. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.42 (br s, 4 H), 1.68 - 1.82 (m, 2 H), 2.03 (s, 1 H), 2.25 - 2.48 (m, 3 H), 3.46 - 3.57 (m, 1 H), 3.72 - 3.78 (m, 1 H), 3.99 (s, 2 H), 4.20 - 4.38 (m, 2 H), 5.33 (s, 2 H), 7.20 (s, 2 H), 7.39 - 7.44 (m, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for C₂₂H₂₄F₃N₃O₄ 451.2; found 452.7.

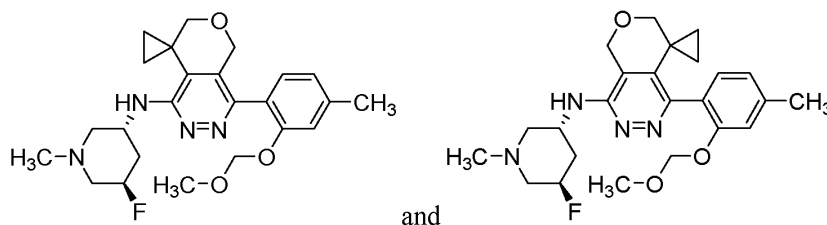
[0552] EXAMPLE 309: 2-(1'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5'*H*,7'*H*-spiro[cyclopropane-1,8'-pyrano[3,4-*d*]pyridazin]-4'-yl)-5-methylphenol



[0553] EXAMPLE 310: 2-(4'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5'*H*,7'*H*-spiro[cyclopropane-1,8'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol



[0554] STEP 1: *N*-((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)-4'-(2-(methoxymethoxy)-4-methylphenyl)-5'*H*,7'*H*-spiro[cyclopropane-1,8'-pyrano[3,4-*d*]pyridazin]-1'-amine and *N*-((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)-1'-(2-(methoxymethoxy)-4-methylphenyl)-5'*H*,7'*H*-spiro[cyclopropane-1,8'-pyrano[3,4-*d*]pyridazin]-4'-amine



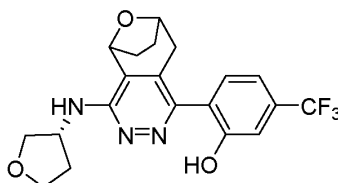
[0555] To a mixture of 4'-chloro-1'-(2-(methoxymethoxy)-4-methylphenyl)-5'*H*,7'*H*-spiro[cyclopropane-1,8'-pyrano[3,4-*d*]pyridazine] and 1'-chloro-4'-(2-(methoxymethoxy)-4-methylphenyl)-5'*H*,7'*H*-spiro[cyclopropane-1,8'-pyrano[3,4-*d*]pyridazine] (in total, 280 mg) in toluene (5 mL) were added (3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-amine (248.39 mg, 1.21 mmol, 2HCl), Pd(OAc)₂ (9.06 mg, 40.37 μmol), BINAP (50.27 mg, 80.74 μmol) and Cs₂CO₃ (526.11 mg, 1.61 mmol) and the mixture was stirred at 100°C for 12 hours under N₂. LC-MS showed desired mass. The reaction mixture was quenched with H₂O (10 mL) and extracted with DCM (10 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuum to give a mixture of the title compounds as a yellow solid (in total, 340 mg, crude). ESI-MS *m/z* [M+H]⁺ 443.3.

[0556] STEP 2: 2-(1'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5'*H*,7'*H*-spiro[cyclopropane-1,8'-pyrano[3,4-*d*]pyridazin]-4'-yl)-5-methylphenol and 2-(4'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5'*H*,7'*H*-spiro[cyclopropane-1,8'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol

[0557] To a mixture of *N*-((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)-4'-(2-(methoxymethoxy)-4-methylphenyl)-5'*H*,7'*H*-spiro[cyclopropane-1,8'-pyrano[3,4-*d*]pyridazin]-1'-amine and *N*-((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)-1'-(2-

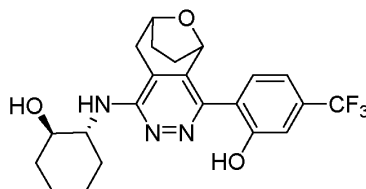
(methoxymethoxy)-4-methylphenyl)-5'*H*,7'*H*-spiro[cyclopropane-1,8'-pyrano[3,4-*d*]pyridazin]-4'-amine (340 mg, crude) in DCM (8 mL) was added TFA (1.30 g, 11.44 mmol, 850.00 μ L). The mixture was stirred at 25°C for 12 hours. LC-MS showed one main peak with desired mass. The mixture was evaporated to dryness and purified by preparative HPLC (Boston Prime C18-5 μ m, 30 mm x 150 mm column) using a gradient of 16 to 56% ACN in water (with NH_4OH) over 9 minutes. The title compound of Example 310 was obtained as a white solid (80.8 mg). ^1H NMR (400 MHz, CD_3OD) δ ppm 0.57 (br d, $J=1.54$ Hz, 2 H), 0.82 - 0.90 (m, 1 H), 1.15 (br d, $J=7.48$ Hz, 1 H), 1.35 - 1.39 (m, 1 H), 1.79 - 1.99 (m, 1 H), 2.30 - 2.46 (m, 5 H), 2.53 (s, 3 H), 2.60 - 2.77 (m, 1 H), 3.18 - 3.27 (m, 1 H), 3.40 (br s, 1 H), 3.47 - 3.60 (m, 2 H), 4.68 - 4.81 (m, 3 H), 4.96 - 5.12 (m, 1 H), 6.68 - 6.75 (m, 2 H), 6.94 (br d, $J=7.70$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ 399.2. The title compound of Example 309 was obtained as a white solid (71 mg). ^1H NMR (400 MHz, CD_3OD) δ ppm 0.83 - 0.93 (m, 2 H), 1.74 - 1.88 (m, 2 H), 1.97 - 2.12 (m, 2 H), 2.34 (d, $J=11.44$ Hz, 7 H), 2.64 (br d, $J=18.05$ Hz, 2 H), 2.75 - 2.80 (m, 1 H), 2.88 (br s, 1 H), 3.58 (d, $J=1.98$ Hz, 2 H), 4.50 - 4.67 (m, 3 H), 4.76 (br s, 1 H), 6.71 - 6.81 (m, 2 H), 7.04 (d, $J=7.70$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ 399.2.

[0558] EXAMPLE 311: 2-(4-(((*R*)-tetrahydrofuran-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol



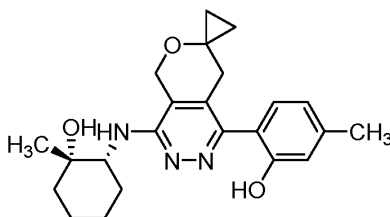
[0559] Using a procedure analogous to Example 237, the title compound was obtained as a light-yellow oil (3.0 mg, 0.007 mmol, 7%). ^1H NMR (400 MHz, CD_3OD) δ ppm 1.73 - 1.82 (m, 1 H), 2.13 - 2.42 (range, 6 H), 3.11 - 3.19 (m, 1 H), 3.86 - 3.96 (m, 2 H), 3.99 - 4.08 (m, 2 H), 4.54 - 4.60 (m, 1 H), 4.75 - 4.80 (m, 1 H), 5.36 - 5.42 (m, 1 H), 7.27 (s, 2 H), 7.51 - 7.55 (m, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{20}\text{H}_{20}\text{F}_3\text{N}_3\text{O}_3$ 407.1; found 408.1.

[0560] EXAMPLE 312: 2-(1-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)-5-(trifluoromethyl)phenol

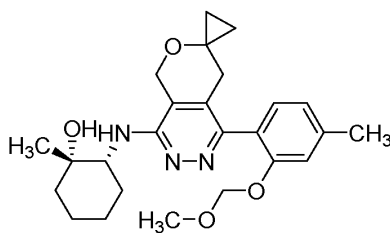


[0561] Using a procedure analogous to Example 237, the title compound was obtained as a white semi-solid (8.0 mg, 18%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.43 (br s, 4 H), 1.84 (br d, *J*=7.28 Hz, 3 H), 2.05 (s, 4 H), 2.21 - 2.32 (m, 1 H), 2.40 - 2.54 (m, 1 H), 3.03 - 3.19 (m, 1 H), 3.58 - 3.68 (m, 1 H), 3.76 - 3.86 (m, 1 H), 4.82 - 4.84 (m, 1 H), 4.91 - 4.94 (m, 1 H), 7.26 (s, 1 H), 7.33 (d, *J*=8.03 Hz, 1 H), 7.48 (d, *J*=8.03 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₂H₂₄F₃N₃O₃ 435.2; found 436.2.

[0562] EXAMPLE 313: 2-(4'-(((1*R*,2*S*)-2-hydroxy-2-methylcyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol



[0563] STEP 1: (1*S*,2*R*)-2-((1'-(2-(methoxymethoxy)-4-methylphenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)-1-methylcyclohexan-1-ol



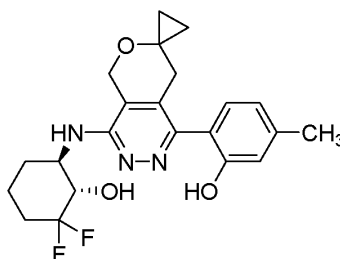
[0564] A mixture of 4'-chloro-1'-(2-(methoxymethoxy)-4-methylphenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (25 mg, 0.072 mmol), (1*S*,2*R*)-2-amino-1-methylcyclohexanol (37 mg, 0.29 mmol), Cs₂CO₃ (0.14 g, 0.43 mmol), (*R*)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (18 mg, 0.029 mmol), palladium(II) acetate (3.2 mg, 0.014 mmol), and toluene (1 mL) was heated at 100°C for 18 hours. The mixture was diluted with DMSO (1 mL), filtered, and purified by HPLC (Gemini 30 mm ID x 150 mm column) using a 10-100% gradient of ACN (0.05% TFA) in water (0.035% TFA) to give the title compound. ESI-MS [M+H]⁺ calc'd for C₂₅H₃₄N₃O₄, 440.2; found, 440.2.

[0565] STEP 2: 2-(4'-(((1*R*,2*S*)-2-hydroxy-2-methylcyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol

[0566] To a solution of (1*S*,2*R*)-2-((1'-(2-(methoxymethoxy)-4-methylphenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)-1-methylcyclohexan-1-

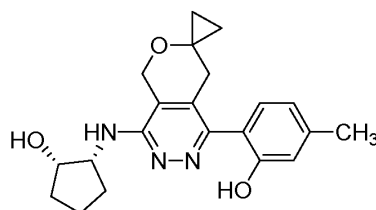
ol in DCE (1 mL) was added TFA (0.5 mL). The solution was stirred at RT for 3 hours. The solution was concentrated under reduced pressure and purified by HPLC (Gemini 30 mm ID x 150 mm column) using a 10-100% gradient of ACN (0.05% TFA) in water (0.035% TFA) to give the title compound (7.7 mg, 26% over two steps). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.52 - 0.62 (m, 2 H), 0.91 - 1.00 (m, 2 H), 1.22 - 1.25 (m, 3 H), 1.35 - 1.35 (m, 1 H), 1.36 - 1.58 (m, 3 H), 1.48 - 1.57 (m, 2 H), 1.63 - 1.85 (m, 5 H), 1.77 - 1.84 (m, 4 H), 2.02 - 2.04 (m, 4 H), 2.34 - 2.37 (m, 3 H), 2.65 - 2.66 (m, 1 H), 2.66 - 2.84 (m, 2 H), 3.96 - 4.02 (m, 1 H), 4.72 - 4.75 (m, 2 H), 6.80 - 6.84 (m, 1 H), 6.84 - 6.88 (m, 1 H), 7.16 - 7.23 (m, 1 H); ESI-MS [M+H]⁺ calc'd for C₂₃H₂₉N₃O₃, 395.2; found, 396.1.

[0567] EXAMPLE 314: 2-(4'-(((1*R*,2*S*)-3,3-difluoro-2-hydroxycyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol



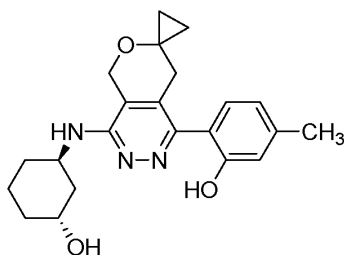
[0568] The title compound was prepared using a procedure analogous to Example 313. ¹H NMR (400 MHz, CD₃OD) δ ppm 0.54 - 0.59 (m, 2 H), 0.91 - 0.96 (m, 2 H), 1.52 - 1.64 (m, 2 H), 1.71 - 1.86 (m, 2 H), 2.09 - 2.20 (m, 2 H), 2.34 - 2.36 (m, 3 H), 2.65 - 2.66 (m, 1 H), 2.73 - 2.76 (m, 2 H), 3.81 - 3.91 (m, 1 H), 4.22 - 4.31 (m, 1 H), 4.68 - 4.70 (m, 2 H), 6.80 - 6.83 (m, 1 H), 6.84 - 6.88 (m, 1 H), 7.17 - 7.21 (m, 1 H); ESI-MS [M+H]⁺ calc'd for C₂₂H₂₅F₂N₃O₃, 417.2; found, 418.1.

[0569] EXAMPLE 315: 2-(4'-(((1*R*,2*S*)-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol



[0570] The title compound was prepared using a procedure analogous to Example 313. ESI-MS [M+H]⁺ calc'd for C₂₁H₂₅N₃O₃, 367.2; found, 368.1.

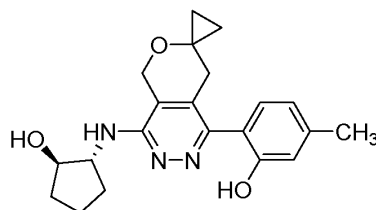
[0571] EXAMPLE 316: 2-(4'-(((1*R*,3*R*)-3-hydroxycyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol



[0572] The title compound was prepared using a procedure analogous to Example 313.

ESI-MS $[M+H]^+$ calc'd for $C_{22}H_{27}N_3O_3$, 381.2; found, 382.1.

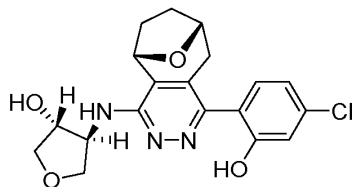
[0573] EXAMPLE 317: 2-(4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol



[0574] The title compound was prepared using a procedure analogous to Example 313.

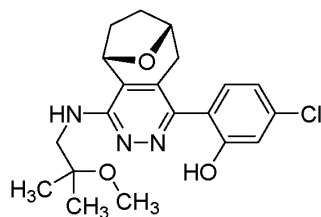
ESI-MS $[M+H]^+$ calc'd for $C_{21}H_{25}N_3O_3$, 367.2; found, 368.2.

[0575] EXAMPLE 318: (3*R*,4*S*)-4-(((5*S*,8*R*)-1-(4-chloro-2-hydroxyphenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)tetrahydrofuran-3-ol



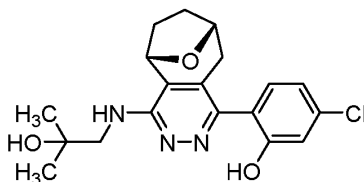
[0576] To a 4 mL vial fitted with a stir bar were added R-BINAP (12 mg, 0.0186 mmol), 5-chloro-2-((5*R*,8*S*)-4-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol (15 mg, 0.0464 mmol), Cs_2CO_3 (60 mg, 0.186 mmol), (3*R*,4*S*)-4-aminotetrahydrofuran-3-ol hydrochloride (26 mg, 186 mmol), and palladium(II) acetate (2.1 mg, 0.00928 mmol) in toluene (0.8 mL). The resulting solution was heated to 100°C for 18 hours and then purified by HPLC (Phenomenex Gemini® C18, 5 μ m, ID 30 mm x 150 mm) using a gradient of 5 to 60% ACN (with 0.035% TFA) in H_2O (with 0.05% TFA). The pure fractions were combined and dried *in vacuo* to afford a TFA salt of the title compound as an orange film (1.2 mg, 6.4%). ESI-MS m/z $[M+H]^+$ calc'd for $C_{19}H_{20}ClN_3O_4$ 389.11; found, 390.10.

[0577] EXAMPLE 319: 5-chloro-2-((5*S*,8*R*)-4-((2-methoxy-2-methylpropyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol



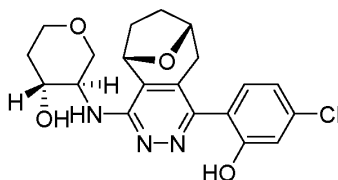
[0578] The title compound was prepared like Example 318, using R-BINAP (12 mg, 0.0186 mmol), 5-chloro-2-((5*R*,8*S*)-4-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol (15 mg, 0.0464 mmol), Cs₂CO₃ (60 mg, 0.186 mmol), 2-methoxy-2-methylpropan-1-amine (19.2 mg, 0.186 mmol), and palladium(II) acetate (2.1 mg, 0.00928 mmol) in toluene (0.8 mL) to give the title compound as an orange film (1.6 mg, 8.8%). ESI-MS *m/z* [M+H]⁺ calc'd for C₂₀H₂₄ClN₃O₃ 389.15; found 390.10.

[0579] EXAMPLE 320: 5-chloro-2-((5*S*,8*R*)-4-((2-hydroxy-2-methylpropyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol



[0580] The title compound was prepared like Example 318, using R-BINAP (12 mg, 0.0186 mmol), 5-chloro-2-((5*R*,8*S*)-4-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol (15 mg, 0.0464 mmol), Cs₂CO₃ (60 mg, 0.186 mmol), 1-amino-2-methyl-propan-2-ol (16.55 mg, 0.186 mmol), and palladium(II) acetate (2.1 mg, 0.00928 mmol) in toluene (0.8 mL) to give the title compound as an orange film (4.2 mg, 24.1%). ESI-MS *m/z* [M+H]⁺ calc'd for C₁₉H₂₂ClN₃O₃ 376.10.

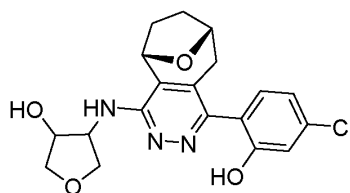
[0581] EXAMPLE 321: (3*R*,4*R*)-3-(((5*S*,8*R*)-1-(4-chloro-2-hydroxyphenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)tetrahydro-2*H*-pyran-4-ol



[0582] The title compound was prepared like Example 318, using R-BINAP (12 mg, 0.0186 mmol), 5-chloro-2-((5*R*,8*S*)-4-chloro-6,7,8,9-tetrahydro-5*H*-5,8-

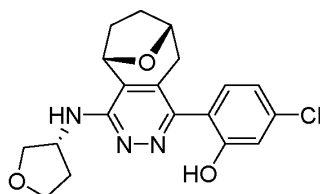
epoxycyclohepta[*d*]pyridazin-1-yl)phenol (15 mg, 0.0464 mmol), Cs₂CO₃ (60 mg, 0.186 mmol), (3*R*,4*R*)-3-aminotetrahydropyran-4-ol (21.7 mg, 0.186 mmol), and palladium(II) acetate (2.1 mg, 0.00928 mmol) in toluene (0.8 mL) to give the title compound as an orange solid (5.3 mg, 27.4%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.55 - 1.81 (m, 2 H), 1.88 - 2.13 (m, 2 H), 2.18 - 2.36 (m, 4 H), 3.05 - 3.18 (m, 1 H), 3.41 - 3.61 (m, 1 H), 4.48 (td, *J*=9.98, 5.02 Hz, 1 H), 3.83 - 4.10 (m, 2 H), 4.16 (dd, *J*=11.48, 4.96 Hz, 1 H), 4.75 - 4.81 (m, 1 H), 5.26 - 5.43 (m, 1 H), 7.00 - 7.10 (m, 1 H), 7.02 (d, *J*=1.88 Hz, 1 H), 7.27 - 7.34 (m, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₀H₂₂ClN₃O₄ 403.13; found 404.10.

[0583] EXAMPLE 322: 4-(((5*S*,8*R*)-1-(4-chloro-2-hydroxyphenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)tetrahydrofuran-3-ol



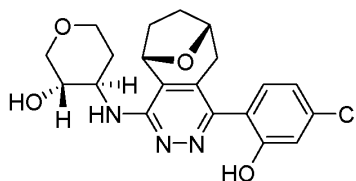
[0584] The title compound was prepared like Example 318, using R-BINAP (12 mg, 0.0186 mmol), 5-chloro-2-((5*R*,8*S*)-4-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol (15 mg, 0.0464 mmol), Cs₂CO₃ (60 mg, 0.186 mmol), (3*R*,4*S*)-4-aminotetrahydrofuran-3-ol hydrochloride (25.9 mg, 0.186 mmol), and palladium(II) acetate (2.1 mg, 0.00928 mmol) in toluene (0.8 mL) to give the title compound as a brown film (10.6 mg, 58.5%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.70 - 1.82 (m, 1 H), 2.14 (td, *J*=9.38, 3.95 Hz, 1 H), 2.23 - 2.38 (m, 3 H), 3.14 (dd, *J*=18.26, 5.33 Hz, 1 H), 3.74 (dd, *J*=9.79, 2.64 Hz, 1 H), 3.89 (ddd, *J*=11.64, 9.57, 3.39 Hz, 1 H), 4.09 (ddd, *J*=9.79, 7.15, 4.89 Hz, 1 H), 4.24 (ddd, *J*=9.54, 5.90, 1.51 Hz, 1 H), 4.37 (dt, *J*=5.27, 2.89 Hz, 1 H), 4.45 (ddt, *J*=7.33, 4.85, 2.38, 2.38 Hz, 1 H), 4.74 - 4.81 (m, 1 H), 5.35 (br t, *J*=7.28 Hz, 1 H), 7.05 (s, 1 H), 7.07 (d, *J*=8.01 Hz, 1 H), 7.32 (d, *J*=8.16 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₁₉H₂₀ClN₃O₄ 389.11; 390.10.

[0585] EXAMPLE 323: 5-chloro-2-((5*S*,8*R*)-4-(((*R*)-tetrahydrofuran-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol



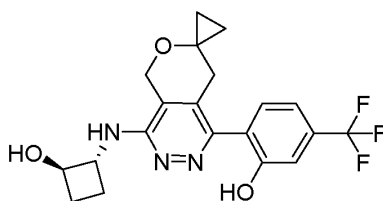
[0586] The title compound was prepared like Example 318, using R-BINAP (12 mg, 0.0186 mmol), 5-chloro-2-((5*R*,8*S*)-4-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol (15 mg, 0.0464 mmol), Cs₂CO₃ (60 mg, 0.186 mmol), (3*R*)-tetrahydrofuran-3-amine (16.2 mg, 0.186 mmol), and palladium(II) acetate (2.1 mg, 0.00928 mmol) in toluene (0.8 mL) to give the title compound as an orange film (2.5 mg, 14.1%); ESI-MS *m/z* [M+H]⁺ calc'd for C₁₉H₂₀ClN₃O₃ 373.12; found 374.10.

[0587] EXAMPLE 324: (3*S*,4*R*)-4-(((5*S*,8*R*)-1-(4-chloro-2-hydroxyphenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)tetrahydro-2*H*-pyran-3-ol



[0588] The title compound was prepared like Example 318, using R-BINAP (12 mg, 0.0186 mmol), 5-chloro-2-((5*R*,8*S*)-4-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol (15 mg, 0.0464 mmol), Cs₂CO₃ (60 mg, 0.186 mmol), (3*S*,4*R*)-4-aminotetrahydropyran-3-ol hydrochloride (28.5 mg, 0.186 mmol), and palladium(II) acetate (2.1 mg, 0.00928 mmol) in toluene (0.8 mL) to give the title compound as a brown film (2.8 mg, 14.6%). ¹H NMR (400 MHz, CD₃OD) δ ppm 2.21 - 2.35 (m, 4 H), 3.02 - 3.25 (m, 3 H), 3.37 - 3.60 (m, 2 H), 3.72 (td, *J*=9.88, 5.08 Hz, 1 H), 3.91 - 4.08 (m, 4 H), 4.73 - 4.81 (m, 1 H), 5.28 - 5.36 (m, 1 H), 6.98 - 7.06 (m, 2 H), 7.24 - 7.29 (m, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₀H₂₂ClN₃O₄ 403.13; found 404.10.

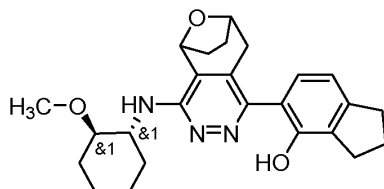
[0589] EXAMPLE 325: 2-(4'-(((1*R*,2*R*)-2-hydroxycyclobutyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



[0590] To a 5 mL vial fitted with a stir bar was added R-BINAP (19 mg, 0.0299 mmol), (1*R*,2*R*)-2-aminocyclobutanol hydrochloride (37 mg, 0.299 mmol), 4'-chloro-1'-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (30 mg, 0.0749 mmol), Cs₂CO₃ (122 mg, 0.374 mmol), and palladium(II) acetate (3.4 mg, 0.0150 mmol) in toluene (1.947 mL). The reaction mixture was heated at 100°C overnight. The solution was concentrated and stirred in DCM (1.298 mL)

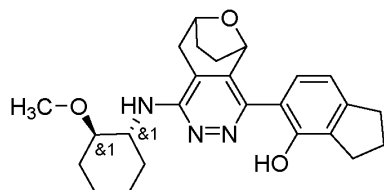
and trifluoroacetic acid (0.58 mL, 7.49 mmol) for 3 hours. The reaction mixture was concentrated and extracted with EtOAc (2 x 10 mL) and saturated NaHCO₃ (10 mL). The organics were separated, dried with MgSO₄, and concentrated under reduced pressure. The resulting solid was dissolved in DMF (1 mL) and MeOH (1 mL). The solution was filtered and purified via Shimadzu preparative HPLC using a TFA-containing mobile phase to give a TFA salt of the title compound (2.3 mg, 7.5%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.49 - 0.67 (m, 2 H), 0.88 - 0.99 (m, 2 H), 1.51 - 1.81 (m, 2 H), 2.11 - 2.33 (m, 2 H), 2.73 (d, *J*=1.76 Hz, 2 H), 4.14 (m, 1 H), 4.25 (m, 1 H), 4.70 (s, 2 H), 7.17 - 7.25 (m, 1 H), 7.30 (dd, *J*=8.03, 1.00 Hz, 1 H), 7.50 (d, *J*=7.78 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₀H₂₀F₃N₃O₃ 407.15; found 408.2.

[0591] EXAMPLE 326: *rac*-5-(4-(((1*R*,2*R*)-2-methoxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-2,3-dihydro-1*H*-inden-4-ol



[0592] Using a procedure analogous to Example 268, starting from 4-chloro-1-(4-(methoxymethoxy)-2,3-dihydro-1*H*-inden-5-yl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine, the title compound was obtained as a colorless oil (10.0 mg, 24%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.28 (br dd, *J*=11.80, 9.79 Hz, 3 H), 1.40 - 1.54 (m, 1 H), 1.63 - 1.81 (m, 3 H), 1.93 - 2.10 (m, 4 H), 2.13 - 2.29 (m, 4 H), 2.77 - 2.94 (m, 4 H), 2.98 - 3.07 (m, 1 H), 3.24 (s, 1 H), 3.28 - 3.32 (m, 3 H), 3.75 - 3.91 (m, 1 H), 4.67 (br t, *J*=5.14 Hz, 1 H), 5.12 - 5.30 (m, 1 H), 6.83 (d, *J*=7.78 Hz, 1 H), 6.94 (s, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₅H₃₁N₃O₃ 421.2; found 422.2.

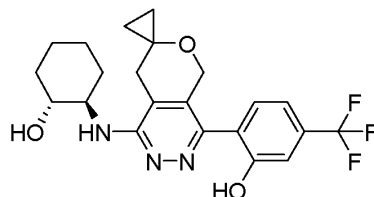
[0593] EXAMPLE 327: *rac*-5-(1-(((1*R*,2*R*)-2-methoxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)-2,3-dihydro-1*H*-inden-4-ol



[0594] Using a procedure analogous to Example 268, starting from 1-chloro-4-(4-(methoxymethoxy)-2,3-dihydro-1*H*-inden-5-yl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine, the title compound was obtained as a colorless oil (14.0 mg,

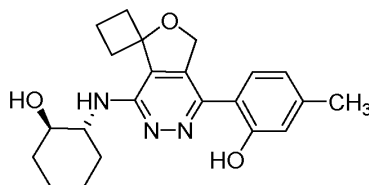
33%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.23 - 1.46 (m, 3 H), 1.48 - 1.61 (m, 1 H), 1.75 - 1.91 (m, 3 H), 2.00 - 2.49 (m, 8 H), 2.91 - 2.97 (m, 2 H), 2.97 - 3.03 (m, 2 H), 3.03 - 3.15 (m, 1 H), 3.34 (s, 1 H), 3.37 - 3.40 (m, 3 H), 3.85 - 3.98 (m, 1 H), 4.92 - 4.99 (m, 2 H), 6.95 (d, *J*=7.53 Hz, 1 H), 7.06 (dd, *J*=7.53, 5.02 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₅H₃₁N₃O₃ 421.2; found 422.2.

[0595] EXAMPLE 328: 2-(1'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)-5-(trifluoromethyl)phenol



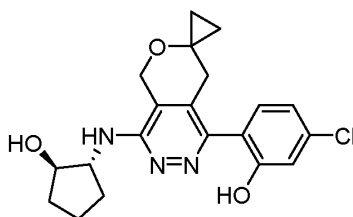
[0596] The title compound was prepared using a procedure analogous to Example 313. ¹H NMR (400 MHz, CD₃OD) δ ppm 0.63 - 0.70 (m, 2 H), 0.88 - 0.95 (m, 2 H), 1.25 - 1.42 (m, 4 H), 1.70 - 1.83 (m, 2 H), 2.02 - 2.11 (m, 1 H), 2.16 - 2.24 (m, 1 H), 2.62 - 2.67 (m, 2 H), 3.53 - 3.60 (m, 1 H), 4.03 - 4.11 (m, 1 H), 4.45 - 4.48 (m, 2 H), 7.14 - 7.18 (m, 1 H), 7.20 - 7.25 (m, 1 H), 7.37 - 7.42 (m, 1 H); ESI-MS [M+H]⁺ calc'd for C₂₂H₂₄F₃N₃O₃, 435.2; found, 436.2.

[0597] EXAMPLE 329: 2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-7'*H*-spiro[cyclobutane-1,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol



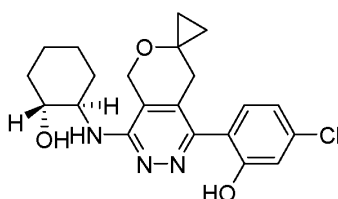
[0598] The title compound was prepared from starting material 5-oxaspiro[3.4]octan-7-one, using a procedure analogous to Example 254. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.35 - 1.61 (m, 4 H), 1.76 - 1.85 (m, 2 H), 2.05 - 2.18 (m, 2 H), 2.27 (br d, *J*=2.64 Hz, 2 H), 2.35 (s, 3 H), 2.54 (br dd, *J*=5.65, 4.14 Hz, 2 H), 2.87 - 3.03 (m, 2 H), 3.70 - 3.90 (m, 2 H), 5.13 (s, 2 H), 6.83 (s, 2 H), 7.23 - 7.28 (m, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₂H₂₇N₃O₃ 381.5; found 382.2.

[0599] EXAMPLE 330: 5-chloro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol



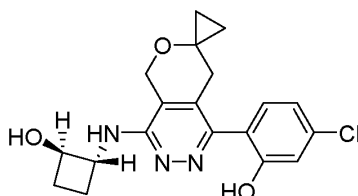
[0600] A mixture of (1*R*,2*R*)-2-(((1'-chloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclopentan-1-ol (30 mg, 0.101 mmol), 5-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (34 mg, 0.132 mmol), XPhos palladacycle G4 (8.7 mg, 0.0101 mmol), and tripotassium phosphate (43 mg, 0.203 mmol) in THF (2.3 mL) and water (0.6 mL) was stirred in a metal heating block at 70°C for 16 hours. The reaction mixture was concentrated via rotary evaporation, diluted with in MeOH (1 mL) and DMF (1 mL), filtered through a 0.45 µm PTFE Membrane filter (VWR), rinsed with MeOH (0.5 mL), and purified via preparative HPLC (Shimadzu) using a gradient of 10 to 100% ACN in H₂O (0.05% TFA). The appropriate fractions were combined and concentrated via rotary evaporation at 45°C. The resulting mixture was dried *in vacuo* to provide a crude TFA salt of the title compound (15.0 mg) as a white solid. The TFA salt was dissolved in MeOH (1 mL), passed through a 100 mg Agilent StratoSpheres SPE cartridge (PL-HCO₃ MP SPE) to remove TFA, and the cartridge was rinsed with MeOH (3 x 1 mL). The filtrate was concentrated via rotary evaporation and dried *in vacuo* to provide the impure title compound as a yellow film. The impure material was dissolved in MeOH (0.5 mL), filtered through a 0.45 µm PTFE Membrane filter (VWR), rinsed with MeOH (0.5 mL), and purified via preparative HPLC (Shimadzu) using a gradient of 40 to 100% ACN (4:1 ACN/H₂O with 10mM NH₄HCO₃) in H₂O (10mM NH₄HCO₃). The pure fractions were combined and concentrated via rotary evaporation at 45°C. The resulting mixture was dried *in vacuo* to provide the title compound as a light-yellow solid (7.2 mg, 18%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.50 - 0.58 (m, 2 H), 0.92 - 0.98 (m, 2 H), 1.58 - 1.66 (m, 1 H), 1.76 - 1.85 (m, 2 H), 1.88 - 1.95 (m, 1 H), 2.09 - 2.18 (m, 1 H), 2.30 - 2.39 (m, 1 H), 2.88 - 2.99 (m, 2 H), 4.02 - 4.16 (m, 3 H), 4.52 (s, 2 H), 5.29 - 5.37 (m, 1 H), 6.90 (dd, *J*=8.53, 2.01 Hz, 1 H), 7.12 (d, *J*=2.26 Hz, 1 H), 7.32 (d, *J*=8.28 Hz, 1 H), 11.83 (br s, 1 H); ESI-MS [*M*+*H*]⁺ calc'd for C₂₀H₂₂ClN₃O₃, 387.13; found, 388.1.

[0601] EXAMPLE 331: 5-chloro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol



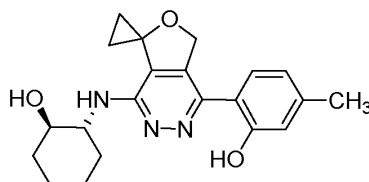
[0602] The title compound was prepared using a procedure analogous to Example 318, starting from R-BINAP (22 mg, 0.0359 mmol), 5-chloro-2-(4'-chloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol (29 mg, 0.0897 mmol), Cs₂CO₃ (117 mg, 0.359 mmol), (1*R*,2*R*)-2-aminocyclohexanol (41.3 mg, 0.359 mmol), and palladium(II) acetate (4.0 mg, 0.0179 mmol) in toluene (0.8 mL) to give the title compound as an orange film (3.5 mg, 9.7%). ESI-MS *m/z* [M+H]⁺ calc'd for C₂₁H₂₄ClN₃O₃ 401.15; found 402.10.

[0603] EXAMPLE 332: 5-chloro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclobutyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol



[0604] The title compound was prepared using a procedure analogous to Example 318, starting from R-BINAP (22 mg, 0.0359 mmol), 5-chloro-2-(4'-chloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol (29 mg, 0.0897 mmol), Cs₂CO₃ (117 mg, 0.359 mmol), (1*R*,2*R*)-2-aminocyclobutanol hydrochloride (44.3 mg, 0.359 mmol), and palladium(II) acetate (4.0 mg, 0.0179 mmol) in toluene (0.8 mL) to give the title compound as a light yellow solid (2.9 mg, 8.6%). ESI-MS *m/z* [M+H]⁺ calc'd for C₁₉H₂₀ClN₃O₃ 373.12; found 374.10.

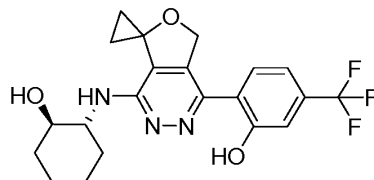
[0605] EXAMPLE 333: 2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-7*H*-spiro[cyclopropane-1,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol



[0606] The title compound was prepared from starting material 4-oxaspiro[2.4]heptan-6-one using a procedure analogous to Example 254. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.17 -

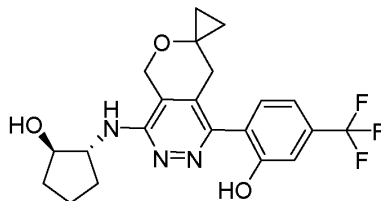
1.61 (m, 8 H), 1.68 - 1.84 (m, 2 H), 2.06 (s, 1 H), 2.35 (s, 4 H), 3.41 - 3.52 (m, 1 H), 3.79 - 3.88 (m, 1 H), 5.41 (s, 2 H), 6.72 - 6.80 (m, 1 H), 6.82 - 6.87 (m, 1 H), 7.04 - 7.10 (m, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{21}H_{25}N_3O_3$ 367.45; found 368.2.

[0607] EXAMPLE 334: 2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-7'*H*-spiro[cyclopropane-1,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



[0608] The title compound was prepared from starting material 4-oxaspiro[2.4]heptan-6-one using a procedure analogous to Example 254. 1H NMR (400 MHz, CD_3OD) δ ppm 1.22 - 1.46 (m, 6 H), 1.50 - 1.64 (m, 2 H), 1.68 - 1.83 (m, 2 H), 1.98 - 2.13 (m, 1 H), 2.24 - 2.38 (m, 1 H), 3.41 - 3.63 (m, 1 H), 3.83 - 4.04 (m, 1 H), 5.34 (d, $J=0.75$ Hz, 2 H), 7.11 - 7.27 (m, 2 H), 7.35 - 7.56 (m, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{21}H_{22}F_3N_3O_3$ 421.42; found 422.2.

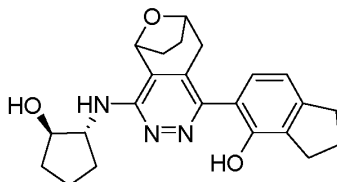
[0609] EXAMPLE 335: 2-(4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



[0610] To a 5 mL vial fitted with a stir bar were added R-BINAP (28 mg, 0.0449 mmol), (1*R*,2*R*)-2-aminocyclopentan-1-ol hydrochloride (62 mg, 0.449 mmol), 4'-chloro-1'-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (45 mg, 0.112 mmol), Cs_2CO_3 (183 mg, 0.561 mmol), and palladium(II) acetate (5.0 mg, 0.0225 mmol) in toluene (2.9205 mL). The reaction mixture was heated at 100°C overnight. The solution was concentrated and stirred in DCM (1.947 mL) and trifluoroacetic acid (0.87 mL, 11.2 mmol) for 3 hours. The solution was concentrated and extracted with EtOAc (2 x 10 mL) and saturated $NaHCO_3$ (10 mL). The organics were separated, dried with $MgSO_4$, and concentrated under reduced pressure. The resulting solid was dissolved in DMF (1 mL) and MeOH (1 mL). The solution was filtered and purified via Shimadzu preparative HPLC using a TFA-containing mobile phase. The title compound was obtained as a TFA salt (5.3 mg, 11%). 1H NMR (400 MHz, CD_3OD) δ ppm 0.42 - 0.55 (m, 2 H), 0.81 - 0.93 (m, 2 H), 1.56 - 1.76 (m, 2 H), 1.76 - 1.91 (m, 2 H), 1.96 -

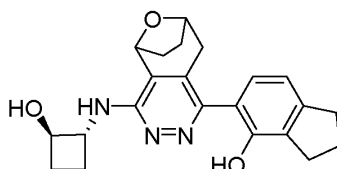
2.12 (m, 1 H), 2.21 - 2.39 (m, 1 H), 2.61 (s, 2 H), 4.08 (dt, $J=7.03$, 5.40 Hz, 1 H), 4.18 (td, $J=7.59$, 5.14 Hz, 1 H), 4.59 (s, 2 H), 7.16 (s, 1 H), 7.23 (d, $J=7.64$ Hz, 1 H), 7.41 (d, $J=7.78$ Hz, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{21}H_{22}F_3N_3O_3$ 421.16; found 422.2.

[0611] EXAMPLE 336: 5-(4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-2,3-dihydro-1*H*-inden-4-ol



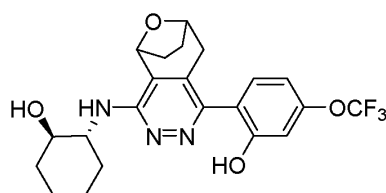
[0612] Using a procedure analogous to Example 268, starting from 4-chloro-1-(4-(methoxymethoxy)-2,3-dihydro-1*H*-inden-5-yl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine, the title compound was obtained as a light-yellow semi-solid (7.0 mg, 18%). 1H NMR (400 MHz, CD_3OD) δ ppm 1.49 - 1.75 (m, 3 H), 2.05 (s, 2 H), 2.08 - 2.09 (m, 1 H), 2.09 - 2.29 (m, 6 H), 2.10 (br s, 1 H), 2.85 - 2.98 (m, 4 H), 3.04 (dd, $J=17.82$, 5.27 Hz, 1 H), 4.03 - 4.10 (m, 1 H), 4.22 - 4.31 (m, 1 H), 4.67 - 4.73 (m, 1 H), 5.18 (dd, $J=12.67$, 5.90 Hz, 1 H), 6.84 (d, $J=7.53$ Hz, 1 H), 6.94 - 7.01 (m, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{23}H_{27}N_3O_3$ 393.2; found 394.2.

[0613] EXAMPLE 337: 5-(4-(((1*R*,2*R*)-2-hydroxycyclobutyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-2,3-dihydro-1*H*-inden-4-ol



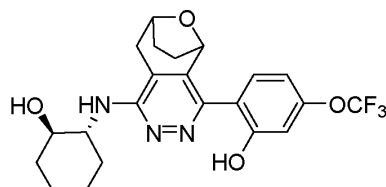
[0614] Using a procedure analogous to Example 268, starting from 4-chloro-1-(4-(methoxymethoxy)-2,3-dihydro-1*H*-inden-5-yl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine, the title compound was obtained as a light-yellow semi-solid (1.2 mg, 3%). 1H NMR (400 MHz, CD_3OD) δ ppm 1.65 - 1.91 (m, 5 H), 2.08 - 2.33 (m, 6 H), 2.85 - 3.00 (m, 4 H), 3.04 (dt, $J=17.63$, 4.36 Hz, 1 H), 4.03 - 4.19 (m, 2 H), 4.67 - 4.74 (m, 1 H), 5.19 - 5.26 (m, 1 H), 6.85 (d, $J=7.53$ Hz, 1 H), 6.98 (d, $J=7.53$ Hz, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{22}H_{25}N_3O_3$ 379.2; found 380.2.

[0615] EXAMPLE 338: 2-(4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethoxy)phenol



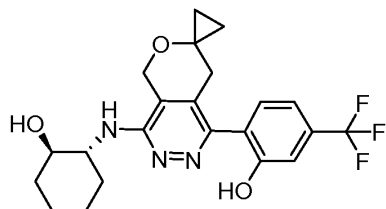
[0616] Using a procedure analogous to Example 237, starting from 2-(4-chloro-6,7,8,9-tetrahydro-5H-5,8-epoxycyclohepta[d]pyridazin-1-yl)-5-(trifluoromethoxy)phenol, the title compound was obtained as a light-yellow semi-solid (3.0 mg, 7%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.40 (br d, *J*=2.01 Hz, 4 H), 1.73 - 1.84 (m, 2 H), 2.03 (s, 2 H), 2.14 - 2.28 (m, 4 H), 2.99 - 3.10 (m, 1 H), 3.56 - 3.66 (m, 1 H), 4.00 - 4.13 (m, 1 H), 4.54 - 4.66 (m, 1 H), 4.68 - 4.75 (m, 1 H), 5.23 (s, 1 H), 6.82 (dd, *J*=2.01, 1.00 Hz, 1 H), 6.83 - 6.89 (m, 1 H), 7.28 (d, *J*=8.53 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₂H₂₄F₃N₃O₄ 451.2; found 452.2.

[0617] EXAMPLE 339: 2-(1-(((1R,2R)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5H-5,8-epoxycyclohepta[d]pyridazin-4-yl)-5-(trifluoromethoxy)phenol



[0618] Using a procedure analogous to Example 237, starting from 2-(1-chloro-6,7,8,9-tetrahydro-5H-5,8-epoxycyclohepta[d]pyridazin-4-yl)-5-(trifluoromethoxy)phenol, the title compound was obtained as a light-yellow semi-solid (4.8 mg, 11%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.30 - 1.48 (m, 4 H), 1.70 - 1.82 (m, 3 H), 2.00 - 2.14 (m, 3 H), 2.24 (s, 2 H), 2.88 - 3.03 (m, 1 H), 3.53 - 3.61 (m, 1 H), 3.99 - 4.10 (m, 1 H), 4.78 - 4.81 (m, 1 H), 4.81 - 4.86 (m, 2 H), 6.85 (d, *J*=1.00 Hz, 1 H), 6.86 - 6.90 (m, 1 H), 7.28 (d, *J*=8.28 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₂H₂₄F₃N₃O₄ 451.2; found 452.2.

[0619] EXAMPLE 340: 2-(4'-(((1R,2R)-2-hydroxycyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol

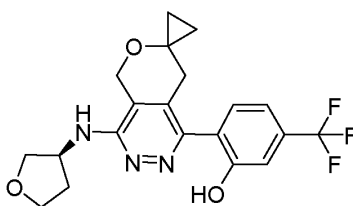


[0620] To a 5 mL vial fitted with a stir bar were added (1R,2R)-2-aminocyclohexan-1-ol (32 mg, 0.280 mmol), 2-(4'-chloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-

d]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol (25 mg, 0.0701 mmol), Cs₂CO₃ (114 mg, 0.350 mmol), palladium(II) acetate (1.6 mg, 0.00701 mmol), and (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine) (4.1 mg, 0.00701 mmol) in dioxane (2 mL). The vial was flushed with nitrogen and the reaction mixture heated at 90°C overnight. The reaction was allowed to cool to room temperature and extracted with EtOAc/acetone (1:1, 100 mL) and water (100 mL). The organics were separated, dried with MgSO₄, and concentrated under reduced pressure. The resulting solid was dissolved in DMF (1 mL) and MeOH (1 mL). The solution was filtered and purified via Shimadzu preparative HPLC using a TFA-containing mobile phase. The title compound was obtained as a TFA salt (1.9 mg, 4.9%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.53 - 0.64 (m, 2 H), 0.88 - 0.98 (m, 2 H), 1.31 - 1.60 (m, 4 H), 1.82 (m, 2 H), 1.99 - 2.15 (m, 2 H), 2.70 - 2.76 (m, 2 H), 3.54 - 3.67 (m, 1 H), 3.76 - 3.90 (m, 1 H), 4.63 - 4.79 (m, 2 H), 7.21 (s, 1 H), 7.29 (dd, *J*=7.91, 0.88 Hz, 1 H), 7.48 (d, *J*=8.03 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₂H₂₄F₃N₃O₃ 435.18; found 436.2.

[0621] EXAMPLE 341: (*S*)-2-(4'-((tetrahydrofuran-3-yl)amino)-5',8'-

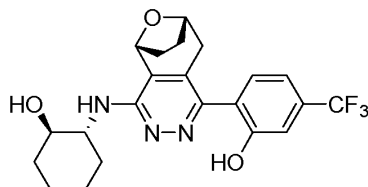
dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



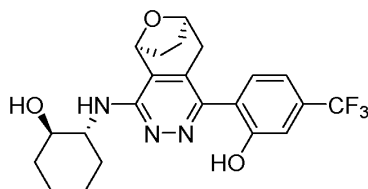
[0622] To a 5 mL vial fitted with a stir bar were added (3*S*)-tetrahydrofuran-3-amine (29 mg, 0.336 mmol), 2-(4'-chloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol (30 mg, 0.0841 mmol), Cs₂CO₃ (137 mg, 0.420 mmol), palladium(II) acetate (1.9 mg, 0.00841 mmol), and (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine) (4.9 mg, 0.00841 mmol) in dioxane (2.4 mL). The vial was flushed with nitrogen and the reaction mixture heated at 90°C overnight. The reaction mixture was allowed to cool to room temperature and extracted with EtOAc/acetone (1:1, 100 mL) and water (100 mL). The organics were separated, dried with MgSO₄, and concentrated under reduced pressure. The resulting solid was dissolved in DMF (1 mL) and MeOH (1 mL). The solution was filtered and purified via Shimadzu preparative HPLC using a TFA-containing mobile phase. The title compound was obtained as a TFA salt (0.60 mg, 1.4%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.53 - 0.63 (m, 2 H), 0.89 - 0.99 (m, 2 H), 2.07 - 2.20 (m, 1 H), 2.42 (m, 1 H), 2.74 (s, 2 H), 3.84 - 3.95 (m, 2 H), 3.98 - 4.12 (m, 2 H), 4.53 - 4.65 (m, 1

H), 4.72 (s, 2 H), 7.25 (s, 1 H), 7.33 (d, $J=8.25$ Hz, 1 H), 7.54 (d, $J=7.89$ Hz, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{20}H_{20}F_3N_3O_3$ 407.15; found 408.1.

[0623] EXAMPLE 342: 2-((5*R*,8*S*)-4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol

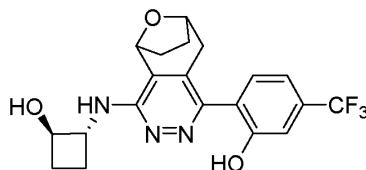


[0624] EXAMPLE 343: 2-((5*S*,8*R*)-4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol



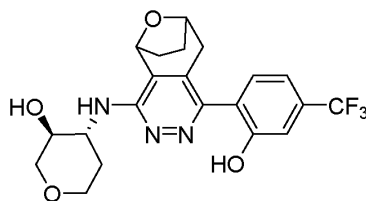
[0625] A mixture of (1*R*,2*R*)-2-((1-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol (62 mg, 0.2 mmol), (2-hydroxy-4-(trifluoromethyl)phenyl)boronic acid (82 mg, 0.400 mmol), and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (15 mg, 0.0200 mmol) in THF (1.0 mL) and 0.5M K_3PO_4 (0.3 mL) was stirred in a sealed tube on metal heating block at 100°C for 1 hour. The reaction mixture was purified by preparative HPLC (Phenomenex Gemini® C18 column) using a gradient of 10 to 30% ACN (0.035% TFA) in water (0.005% TFA). A TFA salt of the title compound of Example 342 was obtained as a white semi-solid (50.0 mg, 45%). 1H NMR (400 MHz, CD_3OD) δ ppm 1.35 - 1.54 (m, 3 H), 1.56 - 1.67 (m, 1 H), 1.73 - 1.88 (m, 3 H), 2.05 - 2.15 (m, 2 H), 2.23 - 2.37 (m, 4 H), 3.05 - 3.17 (m, 1 H), 3.58 - 3.72 (m, 1 H), 3.76 - 3.87 (m, 1 H), 4.74 - 4.80 (m, 1 H), 5.37 (br d, $J=2.51$ Hz, 1 H), 7.24 (s, 1 H), 7.27 - 7.32 (m, 1 H), 7.46 (d, $J=8.03$ Hz, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{22}H_{24}F_3N_3O_3$ 435.2; found 436.2. A TFA salt of the title compound of Example 343 was obtained as a yellow semi-solid (60.0 mg, 55%). 1H NMR (400 MHz, CD_3OD) δ ppm 1.30 - 1.51 (m, 3 H), 1.52 - 1.64 (m, 1 H), 1.70 - 1.88 (m, 3 H), 2.02 - 2.21 (m, 3 H), 2.22 - 2.36 (m, 3 H), 3.08 - 3.17 (m, 1 H), 3.64 - 3.71 (m, 1 H), 3.77 - 3.87 (m, 1 H), 4.76 (br t, $J=5.02$ Hz, 1 H), 5.41 (d, $J=6.02$ Hz, 1 H), 7.24 (d, $J=1.00$ Hz, 1 H), 7.29 (dd, $J=7.91, 0.88$ Hz, 1 H), 7.46 (d, $J=7.78$ Hz, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{22}H_{24}F_3N_3O_3$ 435.2; found 436.2.

[0626] EXAMPLE 344: 2-(4-(((1*R*,2*R*)-2-hydroxycyclobutyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol



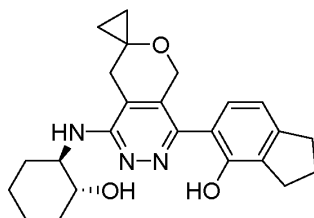
[0627] Using a procedure analogous to Example 237, the title compound was obtained as a yellow oil (6.0 mg, 15%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.38 - 1.48 (m, 1 H), 1.51 - 1.64 (m, 2 H), 1.88 - 1.98 (m, 1 H), 2.02 - 2.17 (m, 5 H), 2.88 - 2.97 (m, 1 H), 3.99 (s, 1 H), 4.15 - 4.23 (m, 1 H), 4.60 (s, 1 H), 5.05 (br d, *J*=5.77 Hz, 1 H), 7.05 (d, *J*=1.25 Hz, 1 H), 7.10 - 7.14 (m, 1 H), 7.26 (d, *J*=7.78 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₀H₂₀F₃N₃O₃ 407.1; found 408.1.

[0628] EXAMPLE 345: (3*S*,4*R*)-4-((1-(2-hydroxy-4-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)tetrahydro-2*H*-pyran-3-ol



[0629] Using a procedure analogous to Example 237, the title compound was obtained as a light-yellow oil (1.0 mg, 2%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.66 - 1.77 (m, 2 H), 2.02 - 2.28 (m, 4 H), 2.02 - 2.13 (m, 1 H), 3.00 - 3.09 (m, 1 H), 3.21 - 3.28 (m, 1 H), 3.49 - 3.57 (m, 1 H), 3.70 - 3.77 (m, 1 H), 3.92 - 4.05 (m, 2 H), 4.22 - 4.30 (m, 1 H), 4.67 - 4.76 (m, 1 H), 5.21 - 5.26 (m, 1 H), 7.17 (s, 1 H), 7.22 - 7.26 (m, 1 H), 7.36 - 7.42 (m, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₁H₂₂F₃N₃O₄ 437.1; found 438.1.

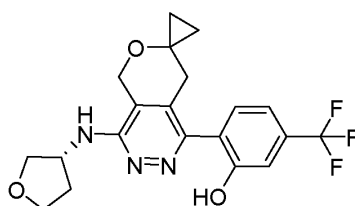
[0630] EXAMPLE 346: 5-(1'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)-2,3-dihydro-1*H*-inden-4-ol



[0631] 1'-chloro-4'-(4-(methoxymethoxy)-2,3-dihydro-1*H*-inden-5-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (23 mg, 0.062 mmol), (1*R*,2*R*)-2-

aminocyclohexan-1-ol (7.1 mg, 0.062 mmol), Pd₂(dba)₃ (5.7 mg, 0.006 mmol), (*R*)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (7.7 mg, 0.012 mmol) and Cs₂CO₃ (6.1 mg, 0.186 mmol) were taken up into a microwave tube in THF (2.7 mL, 0.02 M). The sealed tube was heated in a microwave reactor at 100°C for 3 hours. The reaction was quenched with saturated aq NaHCO₃ and extracted with DCM. The organic phase was dried over Na₂SO₄ and concentrated under vacuum. Trifluoroacetic acid (0.67 mL, 0.08 M) and DCM (2.7 mL, 0.02 M) were added to the crude mixture, which was stirred for 1 hour at 30°C. The reaction mixture was then concentrated under vacuum to give a crude product mixture. The product mixture was purified by preparative HPLC (Phenomenex Gemini® C18) using a 10 to 100% gradient of ACN in water (10 mM NH₄HCO₃, pH=9.5-10). The title compound was obtained as a light-brown powder (5.0 mg, 20%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.63 - 0.74 (m, 2 H), 0.90 - 1.00 (m, 2 H), 1.26 - 1.52 (m, 4 H), 1.67 - 1.84 (m, 2 H), 2.06 - 2.28 (m, 4 H), 2.67 (s, 2 H), 2.90 (dt, *J*=1.00 Hz, 2 H), 2.96 (dt, *J*=1.00 Hz, 2 H), 3.58 (ddd, *J*=1.00 Hz, 1 H), 4.05 (ddd, *J*=1.00 Hz, 1 H), 4.49 (s, 2 H), 6.87 (d, *J*=1.00 Hz, 1 H), 6.99 (d, *J*=1.00 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₄H₂₉N₃O₃ 407.2; found 408.2.

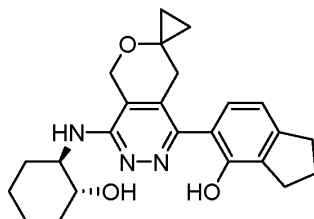
[0632] EXAMPLE 347: (*R*)-2-(4'-((tetrahydrofuran-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



[0633] To a 5 mL vial fitted with a stir bar were added R-BINAP (17 mg, 0.0280 mmol), (3*R*)-oxolan-3-amine hydrochloride (35 mg, 0.280 mmol), 2-(4'-chloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol (25 mg, 0.0701 mmol), Cs₂CO₃ (114 mg, 0.350 mmol), and palladium(II) acetate (3.1 mg, 0.0140 mmol) in dioxane (2 mL). The reaction mixture was heated at 100°C overnight and then concentrated and extracted with EtOAc (2 x 10 mL) and brine (10 mL). The organics were separated and dried with MgSO₄. The solution was filtered and concentrated under reduced pressure. The resulting solid was dissolved in DMF (1 mL) and MeOH (1 mL), filtered and purified via Shimadzu preparative HPLC using a TFA-containing mobile phase. The title compound was obtained as a TFA salt (3.4 mg, 9.3%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.48 - 0.68 (m, 2 H), 0.90 - 1.02 (m, 2 H), 2.13 (m, 1 H), 2.36 - 2.51 (m, 1 H), 2.74 (s, 2 H), 3.78 - 3.94 (m, 2 H), 3.97 - 4.08 (m, 2 H), 4.49 - 4.66 (m, 1 H), 4.73 (s, 2 H), 7.25 (s, 1 H),

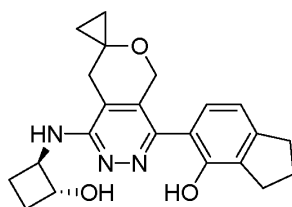
7.33 (dd, $J=8.03$, 0.75 Hz, 1 H), 7.55 (d, $J=8.03$ Hz, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{20}H_{20}F_3N_3O_3$ 407.15; found 408.1.

[0634] EXAMPLE 348: 5-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-2,3-dihydro-1*H*-inden-4-ol



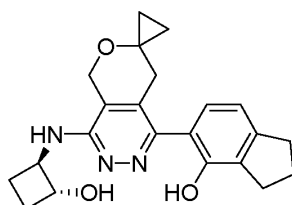
[0635] A microwave vial was charged with 4'-chloro-1'-(4-(methoxymethoxy)-2,3-dihydro-1*H*-inden-5-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (18.3 mg, 0.049 mmol), (1*R*,2*R*)-2-aminocyclohexan-1-ol (5.7 mg, 0.049 mmol), $Pd_2(dba)_3$ (4.5 mg, 0.005 mmol), (*R*)-(+)-(1,1'-binaphthalene-2,2'-diyl)bis(diphenylphosphine) (6.1 mg, 0.010 mmol), and Cs_2CO_3 (48.0 mg, 0.147 mmol) in THF (2.5 mL, 0.02 M). The vial was capped, and a stream of nitrogen was bubbled through the reaction mixture for 15 minutes. The reaction mixture was heated to 100°C in a microwave reactor and stirred for 3 hours. The reaction was quenched with saturated aq NH_4Cl and extracted with DCM. The organic phase was dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. A solution of TFA in DCM (1:4, 2.5 mL, 0.02 M) was added to the crude mixture and stirred for 1 hour at 30°C. The reaction mixture was concentrated under vacuum and purified by preparative HPLC (Phenomenex Gemini® C18 column) using a gradient of 10 to 100% ACN in water (10 mM NH_4HCO_3 , pH=9.5-10). The title compound was obtained as a light-yellow film (1.2 mg, 6%). 1H NMR (400 MHz, CD_3OD) δ ppm 0.47 - 0.58 (m, 2 H), 0.78 - 0.94 (m, 2 H), 1.40 (br d, $J=7.34$ Hz, 5 H), 1.68 - 1.84 (m, 2 H), 1.99 - 2.16 (m, 3 H), 2.16 - 2.27 (m, 1 H), 2.58 - 2.70 (m, 2 H), 2.80 - 3.05 (m, 4 H), 3.47 - 3.63 (m, 1 H), 4.02 - 4.16 (m, 1 H), 4.53 - 4.68 (m, 2 H), 6.79 - 6.88 (m, 1 H), 6.96 - 7.11 (m, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{24}H_{29}N_3O_3$ 407.22; found 408.2.

[0636] EXAMPLE 349: 5-(1'-(((1*R*,2*R*)-2-hydroxycyclobutyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)-2,3-dihydro-1*H*-inden-4-ol



[0637] A microwave vial was charged with 4'-chloro-1'-(4-(methoxymethoxy)-2,3-dihydro-1*H*-inden-5-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (16.7 mg, 0.045 mmol), (1*R*,2*R*)-2-aminocyclobutanol (3.9 mg, 0.045 mmol), palladium (II) acetate (2.0 mg, 0.009 mmol), (*R*)-(+)-(1,1'-binaphthalene-2,2'-diyl)bis(diphenylphosphine) (11.2 mg, 0.018 mmol), and Cs₂CO₃ (73.0 mg, 0.224 mmol) in toluene (2.7 mL, 0.02 M). The vial was capped, and a stream of nitrogen was bubbled through the reaction mixture for 15 minutes. The reaction mixture was heated to 100°C in a microwave reactor and stirred for 3 hours. The reaction was quenched with saturated aq NH₄Cl and extracted with DCM. The organic phase was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. A solution of TFA in DCM (1:4, 2.7 mL, 0.02 M) was added to the crude mixture and stirred for 1 hour at 30°C. The reaction mixture was concentrated under vacuum and purified by preparative HPLC (Phenomenex Gemini® C18 column) using a 10 to 100% gradient of ACN in water (10 mM NH₄HCO₃, pH=9.5-10). The title compound was obtained as a light-yellow film (1.1 mg, 6%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.64 - 0.73 (m, 2 H), 0.92 - 1.02 (m, 2 H), 1.43 - 1.59 (m, 1 H), 1.60 - 1.77 (m, 1 H), 2.09 - 2.30 (m, 4 H), 2.54 - 2.70 (m, 2 H), 2.87 - 3.01 (m, 4 H), 4.09 (m, 1 H), 4.29 (m, 1 H), 4.46 - 4.57 (m, 1 H), 4.50 (br s, 1 H), 6.85 (m, 1 H), 7.00 (m, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₂H₂₅N₃O₃ 379.2; found 380.2.

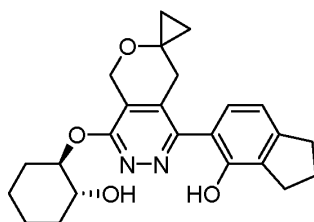
[0638] EXAMPLE 350: 5-(4'-(((1*R*,2*R*)-2-hydroxycyclobutyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-2,3-dihydro-1*H*-inden-4-ol



[0639] A microwave vial was charged with 4'-chloro-1'-(4-(methoxymethoxy)-2,3-dihydro-1*H*-inden-5-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (20.0 mg, 0.054 mmol), (1*R*,2*R*)-2-aminocyclobutanol hydrochloride (26.5 mg, 0.215 mmol), palladium (II) acetate (2.4 mg, 0.011 mmol), (*R*)-(+)-(1,1'-binaphthalene-2,2'-diyl)bis(diphenylphosphine) (13.4 mg, 0.021 mmol), and Cs₂CO₃ (87.4 mg, 0.268 mmol) in toluene (2.7 mL, 0.02 M). The vial was capped, and a stream of nitrogen was bubbled through the reaction mixture for 15 minutes. The reaction mixture was heated to 100°C in a microwave reactor and stirred for 3 hours. The reaction was quenched with saturated aq NH₄Cl and extracted with DCM. The organic phase was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. A solution of TFA in DCM (1:4, 2.7 mL, 0.02 M) was

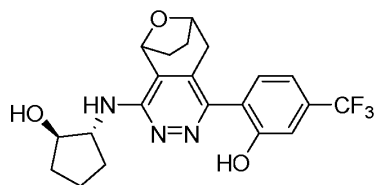
added to the crude mixture and stirred for 1 hour at 30°C. The reaction mixture was concentrated under vacuum and purified by preparative HPLC (Phenomenex Gemini® C18 column) using a 10 to 100% gradient of ACN in water (10 mM NH₄HCO₃, pH=9.5-10). The title compound was obtained as a light-yellow film (2.2 mg, 11%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.47 - 0.57 (m, 2 H), 0.84 - 0.92 (m, 2 H), 1.46 - 1.60 (m, 1 H), 1.60 - 1.75 (m, 1 H), 2.07 - 2.30 (m, 4 H), 2.65 (br s, 2 H), 2.85 - 3.01 (m, 4 H), 4.01 - 4.15 (m, 1 H), 4.29 (m, 1 H), 4.58 (br s, 2 H), 6.85 (m, 1 H), 7.01 (m, 1 H); ESI-MS m/z [M+H]⁺ calc'd for C₂₂H₂₅N₃O₃ 379.2; found 380.2.

[0640] EXAMPLE 351: 5-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)oxy)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-2,3-dihydro-1*H*-inden-4-ol



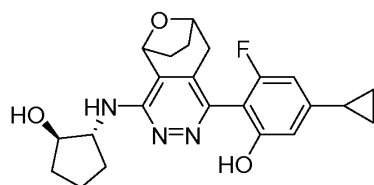
[0641] A microwave vial was charged with NaH (4.8 mg, 0.119 mmol), (1*R*,2*R*)-cyclohexane-1,2-diol (5.9 mg, 0.119 mmol) and 4'-chloro-1'-(4-(methoxymethoxy)-2,3-dihydro-1*H*-inden-5-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (12.7 mg, 0.034 mmol) and THF (1.7 mL, 0.02 M). The vial was capped, and a stream of nitrogen was bubbled through the reaction mixture for 15 minutes. The reaction mixture was heated to 100°C in a microwave reactor and stirred for 3 hours. The reaction was quenched with saturated aq NH₄Cl and extracted with DCM. The organic phase was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. A solution of TFA in DCM (1:4, 2.7 mL, 0.02 M) was added to the crude mixture and stirred for 1 hour at 30°C. The reaction mixture was concentrated under vacuum and purified by preparative HPLC (Phenomenex Gemini® C18 column) using a 10 to 100% gradient of ACN in water (10 mM NH₄HCO₃, pH=9.5-10). The title compound was obtained as a white film (0.6 mg, 4%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.53 (s, 2 H), 0.86 - 0.94 (m, 2 H), 1.34 - 1.58 (m, 4 H), 1.78 (br s, 2 H), 2.03 - 2.22 (m, 3 H), 2.32 - 2.45 (m, 1 H), 2.68 (m, 2 H), 2.90 (dd, *J*=1.00 Hz, 2 H), 2.96 (m, 2 H), 3.69 - 3.83 (m, 1 H), 4.67 (m, 1 H), 4.84 (d, *J*=1.00 Hz, 1 H), 5.12 - 5.26 (m, 1 H), 6.88 (m, 1 H), 7.04 (m, 1 H); ESI-MS m/z [M+H]⁺ calc'd for C₂₄H₂₈N₂O₄ 408.2; found 409.2.

[0642] EXAMPLE 352: 2-(4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol



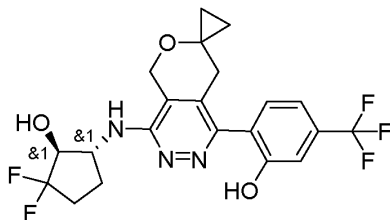
[0643] Using a procedure analogous to Example 237 under 0.1 mmol scale, the title compound was obtained as an orange oil (TFA salt, 12.0 mg, 22%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.55 - 1.84 (m, 5 H), 1.96 - 2.26 (m, 6 H), 2.92 - 3.08 (m, 1 H), 3.92 - 4.04 (m, 1 H), 4.16 (d, *J*=6.78 Hz, 1 H), 4.61 - 4.71 (m, 1 H), 5.24 - 5.29 (m, 1 H), 7.12 (d, *J*=1.00 Hz, 1 H), 7.19 (dd, *J*=7.78, 1.00 Hz, 1 H), 7.36 (d, *J*=8.03 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₁H₂₂F₃N₃O₃ 421.2; found 422.2.

[0644] EXAMPLE 353: 5-cyclopropyl-3-fluoro-2-(4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol



[0645] Using a procedure analogous to Example 268 under 0.1 mmol scale, the title compound was obtained as a white semi-solid (3.0 mg, 7%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.55 - 0.65 (m, 2 H), 0.86 - 0.95 (m, 2 H), 1.54 - 1.81 (m, 6 H), 1.88 - 1.93 (m, 1 H), 1.94 - 2.22 (m, 5 H), 2.74 - 2.90 (m, 1 H), 3.93 - 4.10 (m, 2 H), 4.55 - 4.63 (m, 1 H), 5.06 - 5.14 (m, 1 H), 6.36 (s, 2 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₃H₂₆FN₃O₃ 411.2; found 412.2.

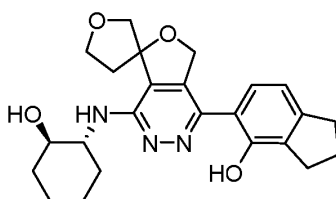
[0646] EXAMPLE 354: *rac*-2-(4'-(((1*R*,2*S*)-3,3-difluoro-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



[0647] To a 5 mL vial fitted with a stir bar were added R-BINAP (17 mg, 0.0280 mmol), *rac*-(1*R*,5*S*)-5-amino-2,2-difluorocyclopentan-1-ol hydrochloride (49 mg, 0.280 mmol), 2-(4'-

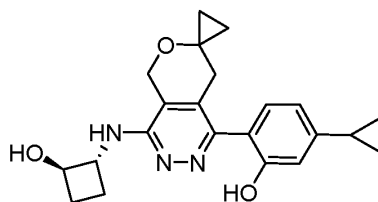
chloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol (25 mg, 0.0701 mmol), Cs₂CO₃ (114 mg, 0.350 mmol), and palladium(II) acetate (3.1 mg, 0.0140 mmol) in dioxane (2 mL). The vial was flushed with nitrogen and the reaction mixture was heated to 100°C overnight. The solution was extracted with EtOAc (2 x 10 mL) and brine (10 mL). The organics were separated and dried with MgSO₄. The solution was filtered, concentrated under reduced pressure, and dissolved in MeOH (1 mL) and DMF (1 mL). The solution was filtered and purified via Shimadzu preparative HPLC using a TFA-containing mobile phase. The title compound was obtained as a TFA salt (2.6 mg, 6.5%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.45 - 0.70 (m, 2 H), 0.89 - 1.03 (m, 2 H), 1.69 - 1.88 (m, 1 H), 2.08 - 2.28 (m, 1 H), 2.28 - 2.47 (m, 2 H), 2.74 (s, 2 H), 4.14 - 4.31 (m, 1 H), 4.31 - 4.45 (m, 1 H), 4.73 (d, *J*=1.51 Hz, 2 H), 7.25 (s, 1 H), 7.33 (d, *J*=8.05 Hz, 1 H), 7.54 (d, *J*=7.78 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₁H₂₀F₃N₃O₃ 457.14; found 458.1.

[0648] EXAMPLE 355: 5-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-2,3-dihydro-1*H*-inden-4-ol



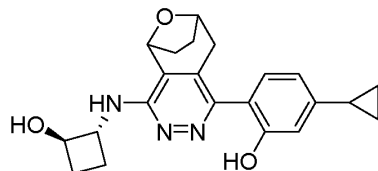
[0649] The title compound was prepared using a procedure analogous to Example 318, starting from R-BINAP (17 mg, 0.0267 mmol), 4-chloro-1-[4-(methoxymethoxy)indan-5-yl]spiro[7*H*-furo[3,4-*d*]pyridazine-5,3'-tetrahydrofuran] (26 mg, 0.0669 mmol), Cs₂CO₃ (87 mg, 0.267 mmol), (1*R*,2*R*)-2-aminocyclohexanol (30.8 mg, 0.267 mmol), and palladium(II) acetate (3.0 mg, 0.0134 mmol) in toluene (0.8 mL) and was obtained as an orange solid (6.5 mg, 22.9%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.22 - 1.55 (m, 4 H), 1.71 - 1.84 (m, 2 H), 2.03 - 2.17 (m, 3 H), 2.28 - 2.49 (m, 3 H), 2.94 (t, *J*=7.40 Hz, 4 H), 3.52 (qd, *J*=9.03, 4.27 Hz, 1 H), 3.76 (dd, *J*=10.23, 2.82 Hz, 1 H), 3.91 - 4.05 (m, 2 H), 4.23 - 4.39 (m, 2 H), 5.34 - 5.42 (m, 2 H), 6.84 (d, *J*=7.91 Hz, 1 H), 7.03 (d, *J*=8.03 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₄H₂₉N₃O₄ 423.22; found 424.20.

[0650] EXAMPLE 356: 5-cyclopropyl-2-(4'-(((1*R*,2*R*)-2-hydroxycyclobutyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol



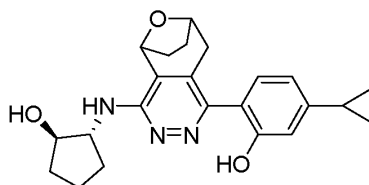
[0651] To a 5 mL vial fitted with a stir bar were added R-BINAP (28 mg, 0.0451 mmol), (1*R*,2*R*)-2-aminocyclobutanol hydrochloride (56 mg, 0.451 mmol), 4'-chloro-1'-(4-cyclopropyl-2-(methoxymethoxy)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (42 mg, 0.113 mmol), Cs₂CO₃ (184 mg, 0.563 mmol), and palladium(II) acetate (5.1 mg, 0.0225 mmol) in toluene (2.93 mL). The vial was flushed with nitrogen and the reaction mixture was heated to 100°C overnight. The mixture was concentrated under reduced pressure and stirred in DCM (1.9533 mL) and TFA (0.87 mL, 11.3 mmol) for 3 hours. The reaction was concentrated and dissolved in MeOH (1 mL) and DMF (1 mL). The solution was filtered and purified via Shimadzu preparative HPLC using a TFA-containing mobile phase. The title compound was obtained as a TFA salt (0.50 mg, 0.90%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.41 - 0.52 (m, 2 H), 0.58 - 0.68 (m, 2 H), 0.77 - 0.89 (m, 2 H), 0.89 - 1.00 (m, 2 H), 1.37 - 1.58 (m, 2 H), 1.78 - 1.89 (m, 1 H), 2.12 (m, 2 H), 2.66 (s, 2 H), 4.01 - 4.21 (m, 2 H), 4.59 (s, 2 H), 6.58 (s, 1 H), 6.65 (d, *J*=7.55 Hz, 1 H), 7.08 (d, *J*=8.28 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₂H₂₅N₃O₃ 379.19; found 380.2.

[0652] EXAMPLE 357: 5-cyclopropyl-2-(4-(((1*R*,2*R*)-2-hydroxycyclobutyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol



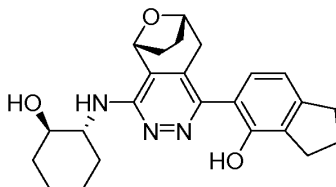
[0653] Using a procedure analogous to Example 268 under 0.1 mmol scale, the title compound was obtained as a white semi-solid (TFA salt, 5.0 mg, 10%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.69 - 0.79 (m, 2 H), 0.99 - 1.10 (m, 2 H), 1.55 - 1.80 (m, 3 H), 1.94 (s, 1 H), 2.12 - 2.40 (m, 6 H), 3.12 - 3.20 (m, 1 H), 4.24 (s, 2 H), 4.75 - 4.80 (m, 1 H), 5.28 - 5.35 (m, 1 H), 6.70 (d, *J*=1.51 Hz, 1 H), 6.76 (dd, *J*=7.91, 1.63 Hz, 1 H), 7.16 (d, *J*=8.03 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₃H₂₆FN₃O₃ 379.2; found 380.2.

[0654] EXAMPLE 358: 5-cyclopropyl-2-(4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol

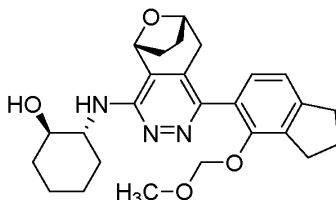


[0655] Using a procedure analogous to Example 268 under 0.1 mmol scale, the title compound was obtained as a white semi-solid (TFA salt, 4.0 mg, 8%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.73 (s, 2 H), 1.02 - 1.10 (m, 2 H), 1.66 - 1.81 (m, 3 H), 1.83 - 1.98 (m, 3 H), 2.05 - 2.21 (m, 2 H), 2.26 - 2.41 (m, 4 H), 3.12 - 3.20 (m, 1 H), 4.11 - 4.19 (m, 1 H), 4.22 - 4.29 (m, 1 H), 4.75 - 4.80 (m, 1 H), 5.33 - 5.38 (m, 1 H), 6.70 (s, 1 H), 6.74 - 6.79 (m, 1 H), 7.16 (d, *J*=7.78 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₃H₂₇N₃O₃ 393.2; found 394.2.

[0656] EXAMPLE 359: 5-((5*R*,8*S*)-4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-2,3-dihydro-1*H*-inden-4-ol



[0657] STEP 1: (1*R*,2*R*)-2-(((5*R*,8*S*)-1-(4-(methoxymethoxy)-2,3-dihydro-1*H*-inden-5-yl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol



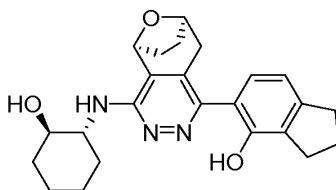
[0658] To a solution of (1*R*,2*R*)-2-(((5*R*,8*S*)-1-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol (50 mg, 161.40 μmol) and 2-(4-(methoxymethoxy)-2,3-dihydro-1*H*-inden-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (98.19 mg, 322.80 μmol) in dioxane (0.4 mL) and H₂O (0.1 mL) were added Pd(dppf)Cl₂ (23.62 mg, 32.28 μmol) and Cs₂CO₃ (210.35 mg, 645.60 μmol). The mixture was stirred at 100°C for 12 hours under N₂. LC-MS showed starting material was consumed completely. Several new peaks were shown on LC-MS and ~70% of desired compound was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by preparative TLC (SiO₂, PE/EtOAc = 0:1) to give the title compound as a light-yellow solid (42 mg, 55% yield, 95% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm

1.45 - 1.69 (m, 5 H), 1.98 (br d, $J=8.25$ Hz, 2 H), 2.23 - 2.49 (m, 8 H), 3.14 - 3.23 (m, 4 H), 3.39 (s, 3 H), 3.64 - 3.71 (m, 2 H), 4.19 - 4.31 (m, 2 H), 4.87 - 5.01 (m, 3 H), 5.13 (d, $J=5.75$ Hz, 1 H), 7.46 (s, 2 H).

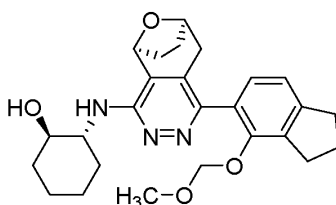
[0659] STEP 2: 5-((5*R*,8*S*)-4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-2,3-dihydro-1*H*-inden-4-ol

[0660] To a solution of (1*R*,2*R*)-2-(((5*R*,8*S*)-1-(4-(methoxymethoxy)-2,3-dihydro-1*H*-inden-5-yl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol (30 mg, 66.44 μ mol) in EtOH (0.2 mL) was added HCl (12 M, 0.2 mL). The mixture was stirred at 25°C for 3 hours. LC-MS showed the starting material was consumed completely and ~94% of desired compound was detected. The reaction was quenched by addition of NaHCO_3 (20 mL) and then extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by preparative TLC (SiO_2 , PE/EtOAc = 0:1) followed by preparative HPLC (Waters Xbridge C18-10 μ m, 50 mm ID x 150 mm column) using a gradient of 32 to 62% ACN in water ($\text{NH}_3/\text{H}_2\text{O}$) over 11 minutes. The title compound was obtained as a light-yellow solid (9.7 mg, 35% yield, 97% purity). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.24 - 1.49 (m, 5 H), 1.53 - 1.68 (m, 2 H), 1.76 (br d, $J=2.25$ Hz, 1 H), 2.00 - 2.27 (m, 8 H), 2.40 (br d, $J=17.64$ Hz, 1 H), 2.89 - 3.03 (m, 4 H), 3.49 (br dd, $J=17.20, 4.94$ Hz, 2 H), 4.01 (br s, 1 H), 4.08 - 4.30 (m, 1 H), 4.74 - 4.82 (m, 1 H), 4.97 (br d, $J=2.25$ Hz, 1 H), 6.78 (d, $J=7.88$ Hz, 1 H), 7.16 (d, $J=7.75$ Hz, 1 H).

[0661] EXAMPLE 360: 5-((5*S*,8*R*)-4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-2,3-dihydro-1*H*-inden-4-ol



[0662] STEP 1: (1*R*,2*R*)-2-(((5*S*,8*R*)-1-(4-(methoxymethoxy)-2,3-dihydro-1*H*-inden-5-yl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol

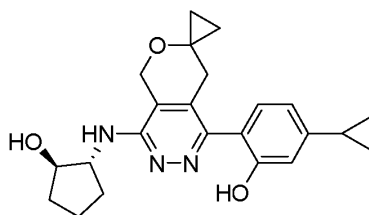


[0663] A mixture of (1*R*,2*R*)-2-(((5*S*,8*R*)-1-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol (30 mg, 96.84 μ mol), 2-(4-(methoxymethoxy)-2,3-dihydro-1*H*-inden-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (58.91 mg, 193.68 μ mol), Pd(dppf)Cl₂ (14.17 mg, 19.37 μ mol), and Cs₂CO₃ (126.21 mg, 387.36 μ mol) in dioxane (1 mL) and H₂O (0.24 mL) was degassed and purged with N₂ (3 x) and then stirred at 100°C for 6 hours under N₂ atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by preparative TLC (SiO₂, EtOAc/PE = 1:0). The title compound was obtained as a white solid (40.6 mg, 92.9%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.29 - 1.51 (m, 5 H), 1.78 (br d, *J*=10.01 Hz, 3 H), 1.92 - 2.04 (m, 2 H), 2.07 - 2.18 (m, 4 H), 2.20 - 2.47 (m, 3 H), 2.86 - 3.07 (m, 4 H), 3.20 (s, 3 H), 3.42 - 3.63 (m, 1 H), 3.94 - 4.12 (m, 1 H), 4.22 (br s, 1 H), 4.71 (br s, 1 H), 4.74 - 4.83 (m, 2 H), 5.04 (br s, 1 H), 7.07 (s, 2 H).

[0664] STEP 2: 5-((5*S*,8*R*)-4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-2,3-dihydro-1*H*-inden-4-ol

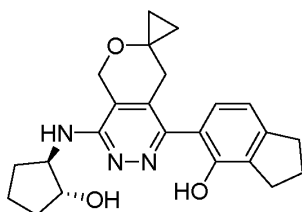
[0665] To a solution of (1*R*,2*R*)-2-(((5*S*,8*R*)-1-(4-(methoxymethoxy)-2,3-dihydro-1*H*-inden-5-yl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol (35 mg, 77.51 μ mol) in EtOH (2 mL) was added HCl (12 M, 645.91 μ L). The mixture was stirred at 25°C for 1 hour. LC-MS showed desired product was detected. The reaction was quenched with NaHCO₃ (5 mL) at 25°C and the mixture was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with H₂O (10 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by preparative TLC (SiO₂, PE/EtOAc = 0:1) followed by preparative HPLC (Waters Xbridge C18-10 μ m, 50 mm x 150 mm column) using a 33 to 63% gradient of ACN in water (NH₃/H₂O) over 11 minutes. The title compound was obtained as a white solid (9.8 mg, 30% yield, 97% purity). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.27 (br d, *J*=4.50 Hz, 4 H), 1.57 (br d, *J*=11.01 Hz, 1 H), 1.62 - 1.71 (m, 2 H), 1.83 - 1.90 (m, 1 H), 1.90 - 2.22 (m, 8 H), 2.80 - 2.90 (m, 4 H), 2.93 (br d, *J*=5.25 Hz, 1 H), 3.45 - 3.58 (m, 1 H), 3.83 - 3.99 (m, 1 H), 4.59 - 4.71 (m, 1 H), 5.26 (br d, *J*=5.38 Hz, 1 H), 5.72 - 6.52 (m, 1 H), 6.77 (d, *J*=7.63 Hz, 1 H), 6.97 (d, *J*=7.63 Hz, 1 H), 8.88 - 10.22 (m, 1 H).

[0666] EXAMPLE 361: 5-cyclopropyl-2-(4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol



[0667] To a 5 mL vial fitted with a stir bar were added R-BINAP (25 mg, 0.0408 mmol), (1*R*,2*R*)-2-aminocyclopentan-1-ol (41 mg, 0.408 mmol), 4'-chloro-1'-(4-cyclopropyl-2-(methoxymethoxy)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (38 mg, 0.102 mmol), Cs₂CO₃ (166 mg, 0.510 mmol), and palladium(II) acetate (4.6 mg, 0.0204 mmol) in toluene (2.651 mL). The vial was flushed with nitrogen and the reaction mixture was heated to 100°C overnight. The solution was extracted with EtOAc (2 x 10 mL) and brine (10 mL). The organics were separated and dried with MgSO₄. The mixture was filtered and concentrated under reduced pressure. The resulting material was dissolved in MeOH (1 mL) and DMF (1 mL), filtered and purified via Shimadzu preparative HPLC using a TFA-containing mobile phase. The title compound was obtained as a TFA salt. ¹H NMR (400 MHz, CD₃OD) δ ppm 0.44 - 0.65 (m, 2 H), 0.72 (q, *J*=5.14 Hz, 2 H), 0.85 - 0.98 (m, 2 H), 0.98 - 1.09 (m, 2 H), 1.58 - 1.77 (m, 2 H), 1.77 - 1.97 (m, 3 H), 1.99 - 2.16 (m, 1 H), 2.29 (m, 1 H), 2.76 (s, 2 H), 4.00 - 4.29 (m, 2 H), 4.71 (s, 2 H), 6.68 (s, 1 H), 6.75 (d, *J*=8.07 Hz, 1 H), 7.18 (d, *J*=8.07 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₃H₂₇N₃O₃ 393.21; found 394.2.

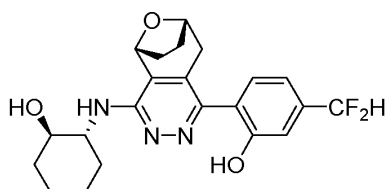
[0668] EXAMPLE 362: 5-(4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino))-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-2,3-dihydro-1*H*-inden-4-ol



[0669] A microwave vial was charged with 4'-chloro-1'-(4-(methoxymethoxy)-2,3-dihydro-1*H*-inden-5-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (26.6 mg, 0.713 mmol), (1*R*,2*R*)-2-aminocyclopentan-1-ol (28.9 mg, 0.285 mmol), palladium (II) acetate (3.2 mg, 0.014 mmol), (*R*)-(+)-(1,1'-Binaphthalene-2,2'-diyl)bis(diphenylphosphine) (17.8 mg, 0.029 mmol), and Cs₂CO₃ (116 mg, 0.357 mmol) in toluene (3.6 mL, 0.02 M). The vial was capped and a stream of nitrogen was bubbled through the reaction mixture for 15 minutes. The reaction mixture was heated at 100°C in a microwave reactor and stirred for 3

hours. The reaction was quenched with saturated aq NH_4Cl and extracted with DCM. The organic phase was dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude material and 2,2'-bipyridine (104 mg, 0.666 mmol) were dissolved in DCM (1.5 mL, 0.05 M) under N_2 atmosphere. The mixture was cooled to 0°C and trimethylsilyl trifluoromethane sulfonate (0.08 mL, 0.444 mmol) was added dropwise. The solution was stirred at room temperature until the spot on a TLC plate associated with methoxymethyl ether had disappeared. Water was added to the solution and the resulting solution was stirred at 23°C until TMS ether disappeared from the TLC plate. The reaction mixture was extracted with DCM and the organic phase was dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The product mixture was purified by preparative HPLC (Phenomenex Gemini® C18 column) using a 10 to 100% gradient of ACN in water (10 mM NH_4HCO_3 , pH=9.5-10). The title compound was obtained as a light-brown film. ^1H NMR (400 MHz, CD_3OD) δ ppm 0.45 - 0.58 (m, 2 H), 0.85 - 0.95 (m, 2 H), 1.63 - 1.95 (m, 4 H), 1.99 - 2.21 (m, 3 H), 2.22 - 2.40 (m, 1 H), 2.65 (s, 2 H), 2.90 (t, $J=7.47$ Hz, 2 H), 2.97 (m, 2 H), 4.02 - 4.23 (m, 2 H), 4.62 (br s, 2 H), 6.86 (m, 1 H), 7.03 (m, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{23}\text{H}_{27}\text{N}_3\text{O}_3$ 393.2; found 394.2.

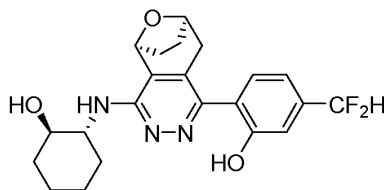
[0670] EXAMPLE 363: 5-(difluoromethyl)-2-((5*R*,8*S*)-4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol



[0671] A mixture of or (1*R*,2*R*)-2-(((5*R*,8*S*)-1-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol (32 mg, 0.1 mmol), 2-(4-(difluoromethyl)-2-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3-dioxolane (63 mg, 0.200 mmol), and $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (8 mg, 0.0100 mmol) in THF (1.0 mL) and 0.5M K_3PO_4 (0.3 mL) was stirred in a sealed tube on metal heating block at 100°C for 1 hour. The reaction mixture was concentrated, treated with TFA (1 mL) and DCM (2 mL) and allowed to stir for 1 hour at 50°C . The reaction mixture was concentrated and purified by preparative HPLC (Phenomenex Gemini® C18 column) using a 10 to 100% gradient of ACN in water (10 mM NH_4HCO_3 , pH=9.5-10). The title compound was obtained as a light-yellow semi-solid (7.0 mg, 16%). ^1H NMR (400 MHz, CD_3OD) δ ppm 1.30 - 1.53 (m, 4 H), 1.75 (br s, 3

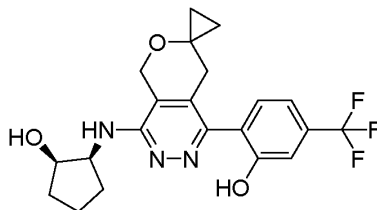
H), 2.05 - 2.13 (m, 1 H), 2.14 - 2.29 (m, 5 H), 3.04 (dd, $J=17.82, 5.27$ Hz, 1 H), 3.53 - 3.63 (m, 1 H), 4.07 (br s, 1 H), 4.68 - 4.73 (m, 1 H), 5.21 (d, $J=3.76$ Hz, 1 H), 6.58 - 6.91 (m, 1 H), 7.08 (s, 1 H), 7.09 - 7.14 (m, 1 H), 7.30 (d, $J=7.78$ Hz, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{22}H_{25}F_2N_3O_3$ 417.2; found 418.2.

[0672] EXAMPLE 364: 5-(difluoromethyl)-2-(((5*S*,8*R*)-4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol



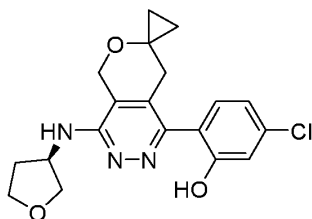
[0673] A mixture of (1*R*,2*R*)-2-(((5*S*,8*R*)-1-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol (32 mg, 0.1 mmol), 2-(4-(difluoromethyl)-2-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3-dioxolane (63 mg, 0.200 mmol), and Pd(dppf)Cl₂.CH₂Cl₂ (8 mg, 0.0100 mmol) in THF (1.0 mL) and 0.5M K₃PO₄ (0.3 mL) was stirred in a sealed tube on metal heating block at 100°C for 1 hour. The reaction mixture was concentrated, treated with TFA (1 mL) and DCM (2 mL) and allowed to stir for 1 hour at 50°C. The reaction mixture was concentrated and purified by preparative HPLC (Phenomenex Gemini® C18 column) using a 10 to 30% gradient of ACN (0.035% TFA) in water (0.005% TFA). A TFA salt of the title compound was obtained as a light-yellow oil (7.5 mg, 14%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.43 (br s, 4 H), 1.72 - 1.88 (m, 3 H), 2.17 (s, 3 H), 2.23 - 2.38 (m, 3 H), 3.08 - 3.20 (m, 1 H), 3.64 - 3.71 (m, 1 H), 3.80 - 3.88 (m, 1 H), 4.75 - 4.80 (m, 1 H), 5.39 (d, $J=6.27$ Hz, 1 H), 6.64 - 6.94 (m, 1 H), 7.15 (s, 1 H), 7.19 (s, 1 H), 7.39 (d, $J=7.78$ Hz, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{22}H_{25}F_2N_3O_3$ 417.2; found 418.2.

[0674] EXAMPLE 365: 2-(4'-(((1*S*,2*R*)-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



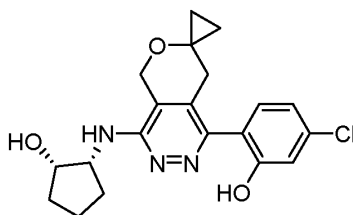
[0675] The title compound was prepared using a procedure analogous to Example 318, starting from R-BINAP (17 mg, 0.0272 mmol), 2-(4'-chloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol (24 mg, 0.0680 mmol), Cs₂CO₃ (111 mg, 0.340 mmol), (1*S*,2*R*)-2-aminocyclopentanol hydrochloride (37.4 mg, 0.272 mmol), and palladium(II) acetate (3.1 mg, 0.0136 mmol) in dioxane (0.8 mL). The title compound was obtained as a yellow solid (1.1 mg, 3.8%); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₁H₂₂F₃N₃O₃ 421.16; found 422.10.

[0676] EXAMPLE 366: (*R*)-5-chloro-2-(4'-((tetrahydrofuran-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol



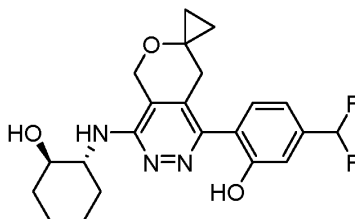
[0677] To a 5 mL vial fitted with a stir bar were added R-BINAP (23 mg, 0.0371 mmol), (3*R*)-oxolan-3-amine hydrochloride (46 mg, 0.371 mmol), 5-chloro-2-(4'-chloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol (30 mg, 0.0928 mmol), Cs₂CO₃ (151 mg, 0.464 mmol), and palladium(II) acetate (4.2 mg, 0.0186 mmol) in dioxane (2 mL). The vial was flushed with nitrogen and the reaction mixture was heated to 100°C overnight. The mixture was extracted with EtOAc (2 x 10 mL) and brine (10 mL). The organics were separated, dried with MgSO₄, filtered, and concentrated under reduced pressure. The resulting material was dissolved in MeOH (1 mL) and DMF (1 mL). The solution was filtered and purified via basic Shimadzu preparative HPLC to give the title compound (3.3 mg, 9.5%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.41 - 0.54 (m, 2 H), 0.81 - 0.92 (m, 2 H), 1.99 - 2.12 (m, 1 H), 2.31 - 2.43 (m, 1 H), 2.61 (s, 2 H), 3.71 - 3.92 (m, 2 H), 3.95 - 4.12 (m, 2 H), 4.57 (s, 2 H), 4.69 - 4.78 (m, 1 H), 6.91 (s, 1 H), 6.94 (d, *J*=7.90 Hz, 1 H), 7.20 (d, *J*=8.03 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₁₉H₂₀ClN₃O₃ 373.12; found 374.1.

[0678] EXAMPLE 367: 5-chloro-2-(4'-(((1*R*,2*S*)-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol

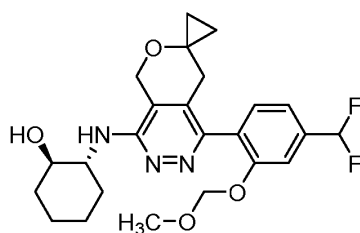


[0679] A mixture of 5-chloro-2-(4'-chloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol (25 mg, 0.0774 mmol), (1*S*,2*R*)-2-aminocyclopentanol hydrochloride (43 mg, 0.309 mmol), palladium(II) acetate (3.5 mg, 0.0155 mmol), R-BINAP (19 mg, 0.0309 mmol), and Cs₂CO₃ (126 mg, 0.387 mmol) in 1,4-dioxane (2.2 mL) was stirred in a metal heating block for 4 hours at 100°C. The reaction mixture was concentrated via rotary evaporation, diluted with MeOH (1 mL) and DMF (1 mL), filtered through a 0.45 μm PTFE membrane filter (VWR), rinsed with MeOH (0.5 mL), and purified via preparative HPLC (Shimadzu) using a gradient of 10-100% ACN in H₂O (0.05% TFA). The appropriate fractions were combined and concentrated via rotary evaporation at 45°C. The resulting mixture was dried *in vacuo* to provide a TFA salt of the title compound. The TFA salt was dissolved in MeOH (1 mL), passed through a 100 mg Agilent StratoSpheres SPE cartridge (PL-HCO₃ MP SPE) to remove TFA, and the cartridge was rinsed with MeOH (3 x 1 mL). The filtrate was concentrated via rotary evaporation and dried *in vacuo* to provide the title compound as a light-yellow solid (4.8 mg, 16%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.45 (br t, *J*=5.14 Hz, 2 H), 0.73 - 0.84 (m, 2 H), 1.48 - 1.57 (m, 1 H), 1.60 - 1.77 (m, 3 H), 1.77 - 1.86 (m, 1 H), 1.90 - 1.98 (m, 1 H), 2.52 - 2.70 (m, 2 H), 4.14 - 4.21 (m, 1 H), 4.26 - 4.35 (m, 1 H), 4.44 - 4.58 (m, 2 H), 4.62 - 4.71 (m, 1 H), 5.45 (br d, *J*=7.28 Hz, 1 H), 6.83 - 6.96 (m, 2 H), 7.17 (d, *J*=8.03 Hz, 1 H), 9.73 (s, 1 H); ESI-MS [M+H]⁺ calc'd for C₂₀H₂₂ClN₃O₃, 387.13; found, 388.1.

[0680] EXAMPLE 368: 5-(difluoromethyl)-2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol



[0681] STEP 1: (1*R*,2*R*)-2-((1'-(4-(difluoromethyl)-2-(methoxymethoxy)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclohexan-1-ol



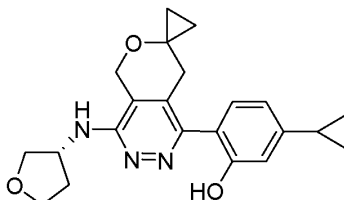
[0682] A mixture of 4'-chloro-1'-(4-(difluoromethyl)-2-(methoxymethoxy)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (38 mg, 99.27 μ mol), (1*R*,2*R*)-2-aminocyclohexanol (45.73 mg, 397.09 μ mol), Pd(OAc)₂ (4.46 mg, 19.85 μ mol), Cs₂CO₃ (161.72 mg, 496.36 μ mol) and BINAP (24.73 mg, 39.71 μ mol) in toluene (1.9 mL) was degassed and purged with N₂ (3 x) and then stirred at 100°C for 12 hours under N₂ atmosphere. TLC (PE/EtOAc = 0:1) indicated starting material was consumed completely and one new spot had formed. The reaction mixture was diluted with EtOAc (3 mL) and H₂O (3 mL). The organic layers were washed with brine (3 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash chromatography (ISCO® 4 g SepaFlash® silica gel column) using a gradient of 0 to 50% EtOAc in PE (20 mL/min). The title compound was obtained as a white solid (30 mg, 46% yield, 70% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.38 - 0.54 (m, 2 H), 0.92 (br d, *J*=1.63 Hz, 2 H), 1.35 - 1.44 (m, 2 H), 1.47 - 1.53 (m, 2 H), 1.74 - 1.82 (m, 2 H), 2.08 - 2.20 (m, 2 H), 3.39 (s, 2 H), 3.45 - 3.55 (m, 1 H), 4.23 - 4.39 (m, 1 H), 4.47 - 4.64 (m, 2 H), 5.12 (s, 2 H), 6.50 - 6.83 (m, 2 H), 7.19 - 7.25 (m, 3 H), 7.64 - 7.72 (m, 1 H), 7.77 - 7.87 (m, 1 H).

[0683] STEP 2: 5-(difluoromethyl)-2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol

[0684] A mixture of (1*R*,2*R*)-2-((1'-(4-(difluoromethyl)-2-(methoxymethoxy)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclohexan-1-ol (30 mg, 65.01 μ mol) in TFA (0.3 mL) and DCM (0.9 mL) was degassed and purged with N₂ (3 x) and then stirred at 25°C for 3 hours under N₂ atmosphere. LC-MS showed the starting material was consumed completely. Several new peaks were shown on LC-MS and ~73% of desired compound was detected. The reaction mixture was diluted with NaHCO₃ (3 mL) and EtOAc (3 mL). The organic layers were washed with brine (3 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography (ISCO® 4 g SepaFlash® silica gel column) using a gradient of 0 to 40% EtOAc in PE (18 mL/min). The title compound was obtained as a white solid (7.8 mg, 12% yield, 95% purity). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.43 - 0.49 (m, 2 H), 0.75 -

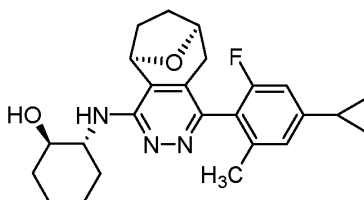
0.81 (m, 2 H), 1.15 - 1.35 (m, 5 H), 1.60 - 1.71 (m, 2 H), 1.89 - 2.11 (m, 2 H), 3.54 (br d, $J=2.50$ Hz, 1 H), 3.89 - 4.04 (m, 1 H), 4.39 - 4.60 (m, 2 H), 4.69 - 4.82 (m, 1 H), 5.66 (br d, $J=6.88$ Hz, 1 H), 7.07 (s, 2 H), 7.31 (d, $J=8.25$ Hz, 1 H), 10.26 (s, 1 H).

[0685] EXAMPLE 369: (*R*)-5-cyclopropyl-2-(4'-((tetrahydrofuran-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol



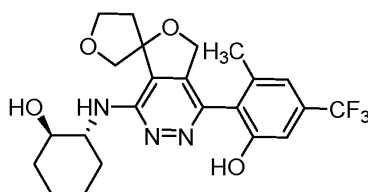
[0686] To a 5 mL vial fitted with a stir bar was added R-BINAP (30 mg, 0.0483 mmol), (3*R*)-oxolan-3-amine hydrochloride (60 mg, 0.483 mmol), 4'-chloro-1'-(4-cyclopropyl-2-(methoxymethoxy)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (45 mg, 0.121 mmol), Cs₂CO₃ (197 mg, 0.603 mmol), and palladium(II) acetate (5.4 mg, 0.0241 mmol) in toluene (3.1393 mL). The vial was flushed with nitrogen and the reaction mixture was heated to 100°C overnight and then extracted with EtOAc (2 x 10 mL) and brine (10 mL). The organics were separated, dried with MgSO₄, filtered, and concentrated under reduced pressure. The crude material was dissolved and stirred in DCM (2.0929 mL) and TFA (0.28 mL, 3.62 mmol) for 3 hours. The reaction mixture was concentrated and dissolved in MeOH (1 mL) and DMF (1 mL). The solution was filtered and purified via Shimadzu preparative HPLC using a TFA-containing mobile phase. The title compound was obtained as a TFA salt (6.8 mg, 11%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.47 - 0.64 (m, 2 H), 0.68 - 0.79 (m, 2 H), 0.89 - 0.99 (m, 2 H), 1.00 - 1.09 (m, 2 H), 1.85 - 1.99 (m, 1 H), 2.10 (m, 1 H), 2.31 - 2.44 (m, 1 H), 2.77 (s, 2 H), 3.76 - 3.92 (m, 2 H), 3.97 - 4.08 (m, 2 H), 4.59 (dt, $J=5.90, 3.95$ Hz, 1 H), 4.72 (s, 2 H), 6.70 (d, $J=1.51$ Hz, 1 H), 6.77 (dd, $J=8.03, 1.51$ Hz, 1 H), 7.21 (d, $J=8.03$ Hz, 1 H); ESI-MS m/z [M+H]⁺ calc'd for C₂₂H₂₅N₃O₃ 379.19; found 380.2.

[0687] EXAMPLE 370: (1*R*,2*R*)-2-(((5*R*,8*S*)-1-(4-cyclopropyl-2-fluoro-6-methylphenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol



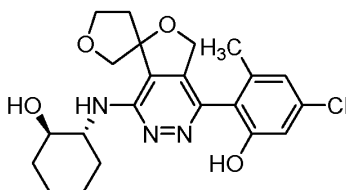
[0688] A solution of (1*R*,2*R*)-2-(((5*R*,8*S*)-1-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol (20 mg, 0.065 mmol), 2-(4-cyclopropyl-2-fluoro-6-methyl-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.097 mmol, 27 mg), XPhos Palladacycle G4 (11 mg, 0.0129 mmol), 0.5M K₃PO₄ (0.6 mL), and THF (0.5 mL) was stirred at 80°C overnight. Dioxane (0.75 mL) was added and the biphasic mixture was purified by HPLC (Gemini prep column 30 mm x 150mm) using a 10 to 100% gradient of ACN (0.035% TFA) in water (0.05% TFA) to give the title compound (20 mg, 73%). ESI-MS [M+H]⁺ calc'd for C₂₅H₃₀FN₃O₂, 423.2; found 424.2.

[0689] EXAMPLE 371: 2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-3-methyl-5-(trifluoromethyl)phenol



[0690] Using a procedure analogous to Example 268 at 0.1 mmol scale, the title compound was obtained as a colorless oil (TFA salt, 14.0 mg, 24%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.45 (br d, *J*=7.28 Hz, 4 H), 1.83 (br d, *J*=6.78 Hz, 2 H), 2.06 - 2.15 (m, 1 H), 2.19 - 2.25 (m, 1 H), 2.28 (s, 3 H), 2.53 (s, 2 H), 3.56 (br s, 1 H), 3.82 (br dd, *J*=10.29, 5.02 Hz, 2 H), 4.03 - 4.14 (m, 1 H), 4.41 (br dd, *J*=15.56, 10.29 Hz, 2 H), 4.94 - 5.04 (m, 1 H), 5.09 - 5.24 (m, 1 H), 7.08 (s, 1 H), 7.18 (s, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₃H₂₆F₃N₃O₄ 465.2; found 466.2.

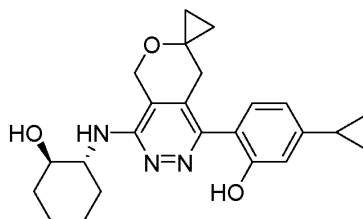
[0691] EXAMPLE 372: 5-chloro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-3-methylphenol



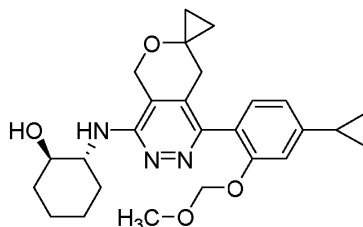
[0692] Using a procedure analogous to Example 268 at 0.1 mmol scale, the title compound was obtained as a colorless oil (TFA salt, 7.0 mg, 13%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.40 - 1.56 (m, 4 H), 1.78 - 1.88 (m, 2 H), 2.07 - 2.14 (m, 1 H), 2.20 (s, 3 H), 2.21 - 2.28 (m, 1 H), 2.38 - 2.58 (m, 2 H), 3.55 (br s, 1 H), 3.82 (br dd, *J*=10.16, 4.64 Hz, 2 H), 4.03 - 4.13 (m, 1 H), 4.40 (dd, *J*=16.06, 10.29 Hz, 2 H), 4.94 (br s, 1 H), 5.09 - 5.23 (m, 1 H), 6.85 (d,

$J=1.76$ Hz, 1 H), 6.93 (d, $J=1.25$ Hz, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{22}H_{26}ClN_3O_4$ 431.2; found 432.2.

[0693] EXAMPLE 373: 5-cyclopropyl-2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol



[0694] STEP 1: (1*R*,2*R*)-2-((1'-(4-cyclopropyl-2-(methoxymethoxy)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclohexan-1-ol

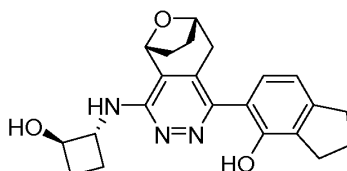


[0695] To a solution of 4'-chloro-1'-(4-cyclopropyl-2-(methoxymethoxy)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (50 mg, 134.10 μ mol) and (1*R*,2*R*)-2-aminocyclohexanol (38.61 mg, 335.26 μ mol) in toluene (0.5 mL) were added CS_2CO_3 (218.47 mg, 670.52 μ mol) and BINAP (33.40 mg, 53.64 μ mol), followed by $Pd(OAc)_2$ (6.02 mg, 26.82 μ mol). The mixture was stirred at 100°C for 12 hours under N_2 . LC-MS showed starting material was consumed completely. A new peak was shown on LC-MS and ~25% of desired compound was detected. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL x 2). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography (ISCO® 4 g SepaFlash® silica gel column) using a gradient of 0 to 20% EtOAc in PE (30 mL/min). The title compound was obtained as a yellow oil (40 mg, 59% yield, 89% purity). 1H NMR (400 MHz, $CDCl_3$) δ ppm 0.46 (br s, 2 H), 0.70 - 0.78 (m, 2 H), 0.87 - 0.94 (m, 2 H), 0.97 - 1.05 (m, 2 H), 1.24 - 1.28 (m, 2 H), 1.77 (br d, $J=6.6$ Hz, 3 H), 1.92 (ddd, $J=13.3, 8.4, 5.1$ Hz, 2 H), 2.13 (br d, $J=8.9$ Hz, 2 H), 3.37 (s, 3 H), 3.51 (td, $J=10.2, 4.2$ Hz, 1 H), 4.02 - 4.31 (m, 2 H), 4.42 - 4.66 (m, 2 H), 5.07 (s, 2 H), 6.77 (dd, $J=7.7, 1.2$ Hz, 1 H), 6.95 (s, 1 H), 7.17 (d, $J=7.8$ Hz, 1 H).

[0696] STEP 2: 5-cyclopropyl-2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol

[0697] To a solution of (1*R*,2*R*)-2-((1'-(4-cyclopropyl-2-(methoxymethoxy)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclohexan-1-ol (47 mg, 104.08 μ mol) in DCM (0.4 mL) was added TFA (240.48 mg, 2.11 mmol, 156.67 μ L). The mixture was stirred at 25°C for 3 hours. LC-MS showed the starting material was consumed completely and a new peak indicated about 77% of desired compound was detected. The reaction mixture was quenched by addition saturated NaHCO₃ (5 mL), and extracted with EtOAc (5 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash chromatography (ISCO® 4 g SepaFlash® silica gel column) using a gradient of 0 to 50% EtOAc in PE (30 mL/min) to give the title compound as a white solid (2.1 mg, 30% yield, 95% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.41 - 0.58 (m, 2 H) 0.69 - 0.81 (m, 2 H) 0.88 - 0.94 (m, 2 H) 0.96 - 1.06 (m, 2 H) 1.25 - 1.28 (m, 1 H) 1.39 - 1.49 (m, 2 H) 1.78 (br d, *J*=10.1 Hz, 2 H) 1.91 - 1.84 (m, 1 H) 1.97 - 2.09 (m, 1 H) 2.13 - 2.27 (m, 2 H) 2.83 (br d, *J*=17.0 Hz, 1 H) 3.04 (br d, *J*=17.1 Hz, 1 H) 3.45 - 3.55 (m, 1 H) 3.93 - 4.13 (m, 2 H) 4.61 - 4.45 (m, 2 H) 6.65 (br d, *J*=7.9 Hz, 1 H) 6.76 (s, 1 H) 7.25 (d, *J*=8.3 Hz, 1 H).

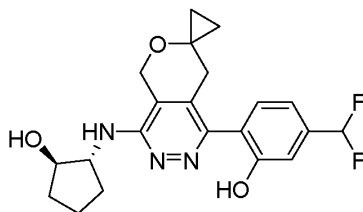
[0698] EXAMPLE 374: 5-((5*R*,8*S*)-4-(((1*R*,2*R*)-2-hydroxycyclobutyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-2,3-dihydro-1*H*-inden-4-ol



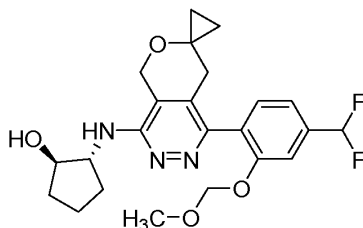
[0699] The title compound was prepared like Example 268 under 0.1 mmol scale. Two diastereomers were isolated by preparative HPLC (Phenomenex Gemini® C18 column) using a gradient of 10 to 30% ACN (0.035% TFA) in water (0.005% TFA) before the deprotection of methoxymethyl-group. The first-eluting isomer was added to a solution of TFA (2 mL) and DCM (10 mL) and stirred for 1 hour at 60°C. The reaction mixture was purified by preparative HPLC (Phenomenex Gemini® C18 column) using a 10 to 100% gradient of ACN in water (10 mM NH₄HCO₃, pH=9.5-10). The title compound was obtained as a light-yellow oil (2.2 mg, 4%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.40 - 1.63 (m, 3 H), 1.88 - 2.14 (m, 8 H), 2.74 - 2.80 (m, 2 H), 2.80 - 2.86 (m, 2 H), 2.89 - 2.95 (m, 1 H), 3.98 (d, *J*=8.03 Hz, 1 H),

4.09 - 4.20 (m, 1 H), 4.59 (br s, 1 H), 5.05 (br d, $J=6.27$ Hz, 1 H), 6.72 (d, $J=7.78$ Hz, 1 H), 6.85 (d, $J=7.53$ Hz, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{22}H_{25}N_3O_3$ 379.2; found 380.2.

[0700] EXAMPLE 375: 5-(difluoromethyl)-2-(4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol



[0701] STEP 1: (1*R*,2*R*)-2-((1'-4-(difluoromethyl)-2-(methoxymethoxy)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclopentan-1-ol



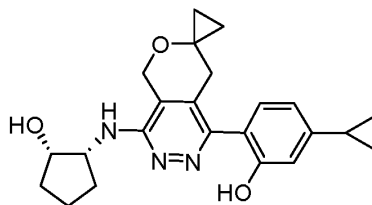
[0702] A mixture of 4'-chloro-1'-(4-(difluoromethyl)-2-(methoxymethoxy)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (45 mg, 117.56 μ mol), (1*R*,2*R*)-2-aminocyclopentanol hydrochloride (40.44 mg, 293.90 μ mol), $Pd(OAc)_2$ (5.28 mg, 23.51 μ mol), Cs_2CO_3 (191.51 mg, 587.79 μ mol) and BINAP (29.28 mg, 47.02 μ mol) in toluene (5 mL) was degassed and purged with N_2 (3 x) and then stirred at 120°C for 12 hours. TLC (PE/EtOAc = 0:1) indicated the starting material was consumed completely and one new spot had formed. The reaction mixture was diluted with EtOAc (3 mL) and H_2O (3 mL). The organic layers were washed with brine (3 mL x 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give the title compound as a white solid (28 mg, 48% yield, 90% purity).

[0703] STEP 2: 5-(difluoromethyl)-2-(4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol

[0704] A mixture of (1*R*,2*R*)-2-((1'-4-(difluoromethyl)-2-(methoxymethoxy)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclopentan-1-ol (28 mg, 62.57 μ mol) in TFA (0.13 mL) and DCM (0.35 mL) was degassed and purged with N_2 (3 x) and then stirred at 25°C for 3 hours. TLC (PE/EtOAc = 0:1) indicated the starting material was consumed completely and one new spot had formed. The reaction mixture was diluted

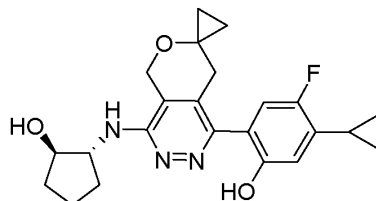
with NaHCO₃ (2 mL) and EtOAc (2 mL). The organic layers were washed with brine (2 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography (ISCO® 4 g SepaFlash® silica gel column) using a gradient of 0 to 40% PE in EtOAc (20 mL/min). The title compound was obtained as a white solid (4.4 mg, 17% yield, 95% purity). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.43 - 0.49 (m, 2 H), 0.73 - 0.80 (m, 2 H), 1.23 (s, 2 H), 1.48 - 1.58 (m, 2 H), 1.63 - 1.72 (m, 2 H), 1.85 - 1.94 (m, 1 H), 2.11 - 2.19 (m, 1 H), 3.95 - 4.21 (m, 2 H), 4.41 - 4.56 (m, 2 H), 5.14 (br s, 1 H), 5.89 (br d, *J*=5.75 Hz, 1 H), 6.85 - 7.06 (m, 1 H), 7.07 - 7.16 (m, 2 H), 7.32 (d, *J*=8.00 Hz, 1 H), 10.23 (s, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₁H₂₃F₂N₃O₃ 403.2; found 404.0.

[0705] EXAMPLE 376: 5-cyclopropyl-2-(4'-(((1*R*,2*S*)-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol



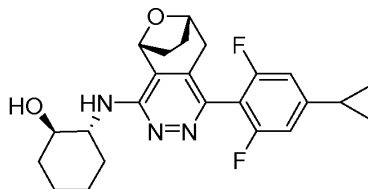
[0706] To a 5 mL vial fitted with a stir bar were added R-BINAP (20 mg, 0.0322 mmol), (1*S*,2*R*)-2-aminocyclopentanol hydrochloride (44 mg, 0.322 mmol), 4'-chloro-1'-(4-cyclopropyl-2-(methoxymethoxy)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (30 mg, 0.0805 mmol), Cs₂CO₃ (131 mg, 0.402 mmol), and palladium(II) acetate (3.6 mg, 0.0161 mmol) in dioxane (2.0929 mL). The vial was flushed with nitrogen and the reaction mixture was heated to 80°C overnight. The solution was extracted with EtOAc (2 x 10 mL) and brine (10 mL). The organics were separated and dried with MgSO₄. The mixture was filtered, concentrated under reduced pressure, dissolved in DCM (1.3952 mL) and TFA (0.31 mL, 4.02 mmol) and allowed to stir at room temperature overnight. The solution was concentrated under reduced pressure, dissolved in MeOH (1 mL) and DMF (1 mL), filtered and purified via Shimadzu preparative HPLC using a TFA-containing mobile phase. The title compound was obtained as a TFA salt (6.9 mg, 17%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.54 - 0.63 (m, 2 H), 0.69 - 0.78 (m, 2 H), 0.89 - 0.99 (m, 2 H), 0.99 - 1.09 (m, 2 H), 1.66 (m, 1 H), 1.74 - 1.86 (m, 1 H), 1.87 - 2.02 (m, 4 H), 2.12 (m, 1 H), 2.76 (s, 2 H), 4.15 (br dd, *J*=8.53, 3.76 Hz, 1 H), 4.39 (td, *J*=4.71, 2.38 Hz, 1 H), 4.72 - 4.78 (m, 2 H), 6.69 (s, 1 H), 6.76 (dd, *J*=7.78, 1.25 Hz, 1 H), 7.19 (d, *J*=8.03 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₃H₂₇N₃O₃ 393.21; found 394.2.

[0707] EXAMPLE 377: 5-cyclopropyl-4-fluoro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol



[0708] To a 5 mL vial fitted with a stir bar were added R-BINAP (29 mg, 0.0461 mmol), (1*R*,2*R*)-2-aminocyclopentan-1-ol (47 mg, 0.461 mmol), 4'-chloro-1'-(4-cyclopropyl-5-fluoro-2-(methoxymethoxy)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (45 mg, 0.115 mmol), Cs₂CO₃ (188 mg, 0.576 mmol), and palladium(II) acetate (5.2 mg, 0.023 mmol) in dioxane (2.9948 mL). The vial was flushed with nitrogen and the reaction mixture was heated to 80°C overnight. The solution was extracted with EtOAc (2 x 10 mL) and brine (10 mL), and the organics were separated and dried with MgSO₄. The mixture was filtered and concentrated under reduced pressure, dissolved in DCM (1.9965 mL) and TFA (0.27 mL, 3.45 mmol) and allowed to stir at room temperature overnight. The solution was concentrated and dissolved in MeOH (1 mL) and DMF (1 mL), filtered and purified via Shimadzu preparative HPLC using a TFA-containing mobile phase. The title compound was obtained as a TFA salt (7.5 mg, 12%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.52 - 0.63 (m, 2 H), 0.69 - 0.80 (m, 2 H), 0.89 - 0.97 (m, 2 H), 1.02 - 1.12 (m, 2 H), 1.61 - 1.79 (m, 2 H), 1.79 - 1.94 (m, 2 H), 2.01 - 2.18 (m, 2 H), 2.21 - 2.37 (m, 1 H), 2.76 (s, 2 H), 4.11 (m, 1 H), 4.21 (m, 1 H), 4.70 (s, 2 H), 6.48 (d, *J*=6.27 Hz, 1 H), 7.04 (d, *J*=10.04 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₃H₂₆FN₃O₃ 411.20; found 412.2.

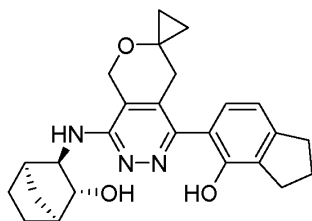
[0709] EXAMPLE 378: (1*R*,2*R*)-2-(((5*R*,8*S*)-1-(4-cyclopropyl-2,6-difluorophenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol



[0710] Using a procedure analogous to Example 237 under 0.1 mmol scale and (1*R*,2*R*)-2-(((5*S*,8*R*)-1-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol as starting material, the title compound was obtained as a light-

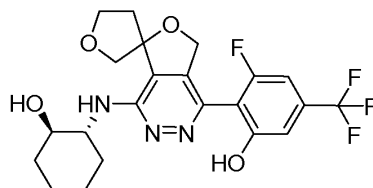
yellow oil (16.0 mg, 37%). ^1H NMR (400 MHz, CD_3OD) δ ppm 0.71 (br d, $J=5.14$ Hz, 2 H), 1.02 (br d, $J=8.07$ Hz, 2 H), 1.30 (br s, 3 H), 1.44 - 1.56 (m, 1 H), 1.58 - 1.66 (m, 1 H), 1.70 (br s, 2 H), 1.90 - 2.03 (m, 3 H), 2.09 - 2.25 (m, 4 H), 2.78 - 2.95 (m, 1 H), 3.46 - 3.59 (m, 1 H), 3.63 - 3.73 (m, 1 H), 4.62 - 4.69 (m, 1 H), 5.23 (br s, 1 H), 6.79 (br s, 1 H), 6.82 (br s, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{24}\text{H}_{27}\text{F}_2\text{N}_3\text{O}_2$ 427.5; found 428.5.

[0711] EXAMPLE 379: 5-(4'-(((1*R*,2*R*,3*R*,4*S*)-3-hydroxybicyclo[2.2.1]heptan-2-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-2,3-dihydro-1*H*-inden-4-ol



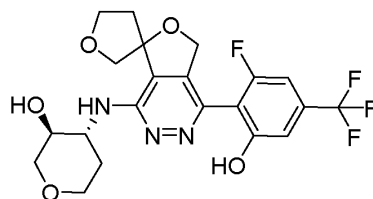
[0712] A microwave vial was charged with a mixture of 4'-chloro-1'-(4-(methoxymethoxy)-2,3-dihydro-1*H*-inden-5-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (10.9 mg, 0.029 mmol), (1*S*,2*R*,3*R*,4*R*)-3-aminonorboman-2-ol hydrochloride (9.6 mg, 0.058 mmol), palladium (II) acetate (1.3 mg, 0.006 mmol), (*R*)-(+)-(1,1'-binaphthalene-2,2'-diyl)bis(diphenylphosphine) (7.3 mg, 0.012 mmol), and Cs_2CO_3 (47.6 mg, 0.146 mmol) in toluene (1.5 mL, 0.02 M). The reaction mixture was heated to 100°C in a microwave reactor and stirred for 3 hours. The reaction mixture was quenched with saturated aq NaHCO_3 and extracted with DCM. The organic phase was dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The concentrate was taken up in a solution of DCM and toluene (1.5 mL, 0.02 M). Trifluoroacetic acid (23 μL , 0.292 mmol) was added, and the solution was stirred for 1 hour at 40°C. After the completion of reaction was observed by LC-MS, the reaction was quenched with saturated aq NaHCO_3 and extracted with DCM. The organic phase was dried over Na_2SO_4 , filtered, concentrated under reduced pressure, and purified by preparative HPLC (Phenomenex Gemini® C18 column) using a 10 to 100% gradient of ACN in water (10 mM NH_4HCO_3 , pH=9.5-10). The title compound was obtained as a white powder (2.5 mg, 20%). ^1H NMR (400 MHz, CD_3OD) δ ppm 0.52 (d, $J=1.38$ Hz, 2 H), 0.80 - 0.96 (m, 2 H), 1.17 - 1.52 (m, 4 H), 1.55 - 1.74 (m, 2 H), 1.83 - 1.98 (m, 1 H), 2.08 - 2.19 (m, 2 H), 2.21 - 2.28 (m, 1 H), 2.65 (s, 3 H), 2.84 - 2.98 (m, 4 H), 3.40 - 3.47 (m, 1 H), 3.74 - 3.89 (m, 1 H), 4.54 - 4.74 (m, 2 H), 6.80 - 6.93 (m, 1 H), 6.98 - 7.07 (m, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{25}\text{H}_{29}\text{N}_3\text{O}_3$ 419.2; found 420.2.

[0713] EXAMPLE 380: 3-fluoro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-4,5-dihydro-2*H*,7*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



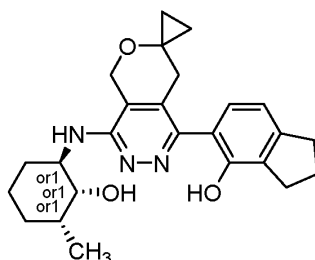
[0714] The title compound was synthesized from starting material (1*R*,2*R*)-2-aminocyclohexan-1-ol and 4'-chloro-1'-(2-fluoro-6-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-4,5-dihydro-2*H*,7*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazine] using a procedure analogous to Example 254. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.23 - 1.53 (m, 4 H), 1.65 - 1.83 (m, 2 H), 1.99 - 2.10 (m, 1 H), 2.23 - 2.50 (m, 3 H), 3.46 - 3.58 (m, 1 H), 3.69 - 3.79 (m, 1 H), 3.92 - 4.13 (m, 2 H), 4.18 - 4.38 (m, 2 H), 4.94 (s, 2 H), 6.99 - 7.08 (m, 2 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₂H₂₃F₄N₃O₄ 469.2; found 470.7.

[0715] EXAMPLE 381: (3*S*,4*R*)-4-((1'-(2-fluoro-6-hydroxy-4-(trifluoromethyl)phenyl)-4,5-dihydro-2*H*,7*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-4'-yl)amino)tetrahydro-2*H*-pyran-3-ol



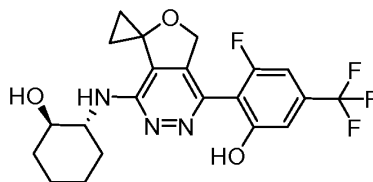
[0716] The title compound was synthesized from starting materials (3*S*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ol and 4'-chloro-1'-(2-fluoro-6-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-4,5-dihydro-2*H*,7*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazine] using a procedure analogous to Example 254; ¹H NMR (400 MHz, CD₃OD) δ ppm 1.63 - 1.81 (m, 1 H), 2.16 - 2.30 (m, 1 H), 2.33 - 2.56 (m, 2 H), 3.27 (s, 1 H), 3.46 - 3.57 (m, 1 H), 3.64 (s, 1 H), 3.81 (dd, *J*=10.23, 4.58 Hz, 1 H), 3.91 - 4.13 (m, 4 H), 4.37 (s, 2 H), 5.05 - 5.20 (m, 2 H), 7.10 (s, 2 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₁H₂₁F₄N₃O₅ 471.1; found 472.7.

[0717] EXAMPLE 382: *rel*-5-(4'-(((1*R*,2*R*,3*R*)-2-hydroxy-3-methylcyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-2,3-dihydro-1*H*-inden-4-ol



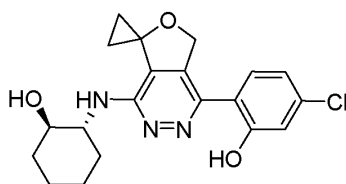
[0718] A microwave vial was charged with a mixture of 4'-chloro-1'-(4-(methoxymethoxy)-2,3-dihydro-1*H*-inden-5-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (11.4 mg, 0.031 mmol), (1*R*,2*R*,6*R*)-2-amino-6-methylcyclohexanol hydrochloride (10.1 mg, 0.061 mmol), palladium (II) acetate (1.4 mg, 0.006 mmol), (*R*)-(+)-(1,1'-binaphthalene-2,2'-diyl)bis(diphenylphosphine) (7.6 mg, 0.012 mmol), and Cs₂CO₃ (49.8 mg, 0.153 mmol) in 1,4-dioxane (1.5 mL, 0.02 M). The reaction mixture was heated to 120°C in a microwave reactor and stirred for 1 hour. The reaction mixture was then quenched with saturated aq NaHCO₃ and extracted with DCM. The organic phase was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The concentrate was dissolved in DCM (1.5 mL, 0.02 M), and TFA (24 µL, 0.306 mmol) was added. The solution was stirred for 1 hour at 40°C. After the completion of reaction was observed by LC-MS, the reaction was quenched with saturated aq NaHCO₃ and the mixture extracted with DCM. The organic phase was dried over Na₂SO₄, filtered, concentrated under reduced pressure, and purified by preparative HPLC (Phenomenex Gemini® C18 column) using a 10 to 100% gradient of ACN in water (10 mM NH₄HCO₃, pH=9.5-10). The title compound was obtained as a white solid (2.7 mg, 21%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.45 - 0.64 (m, 2 H), 0.80 - 0.96 (m, 2 H), 1.01 - 1.19 (m, 3 H), 1.35 - 1.48 (m, 1 H), 1.50 - 1.77 (m, 4 H), 2.08 - 2.25 (m, 4 H), 2.55 - 2.75 (m, 2 H), 2.78 - 2.96 (m, 3 H), 3.71 - 3.84 (m, 1 H), 4.27 - 4.41 (m, 1 H), 4.53 - 4.69 (m, 2 H), 6.78 - 6.89 (m, 1 H), 6.98 - 7.10 (m, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₅H₃₁N₃O₃ 421.2; found 422.2.

[0719] EXAMPLE 383: 3-fluoro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-7'*H*-spiro[cyclopropane-1,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



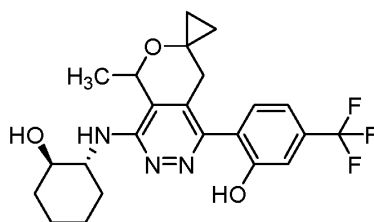
[0720] The title compound was prepared from starting materials (1*R*,2*R*)-2-aminocyclohexan-1-ol and 4'-chloro-1'-(2-fluoro-6-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-7'*H*-spiro[cyclopropane-1,5'-furo[3,4-*d*]pyridazine] using a procedure analogous to Example 254. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.20 - 1.47 (m, 6 H), 1.51 - 1.63 (m, 2 H), 1.67 - 1.81 (m, 2 H), 1.99 - 2.10 (m, 1 H), 2.27 - 2.39 (m, 1 H), 3.48 - 3.60 (m, 1 H), 3.92 - 4.04 (m, 1 H), 4.97 (s, 2 H), 6.98 - 7.10 (m, 2 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₁H₂₁F₄N₃O₃ 439.2; found 440.7.

[0721] EXAMPLE 384: 5-chloro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-7'*H*-spiro[cyclopropane-1,5'-furo[3,4-*d*]pyridazin]-1'-yl)phenol

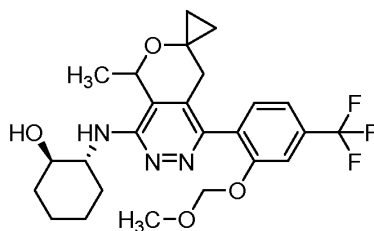


[0722] The title compound was prepared from starting materials (1*R*,2*R*)-2-aminocyclohexan-1-ol and 4'-chloro-1'-(2-fluoro-6-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-7'*H*-spiro[cyclopropane-1,5'-furo[3,4-*d*]pyridazine] using a procedure analogous to Example 254. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.39 (br d, *J*=1.88 Hz, 6 H), 1.55 - 1.69 (m, 2 H), 1.71 - 1.84 (m, 2 H), 2.03 - 2.15 (m, 1 H), 2.25 - 2.34 (m, 1 H), 3.46 - 3.56 (m, 1 H), 3.76 - 3.87 (m, 1 H), 5.34 (s, 2 H), 6.93 - 7.00 (m, 1 H), 7.02 - 7.06 (m, 1 H), 7.18 - 7.22 (m, 1 H), 7.56 - 7.60 (m, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₀H₂₂ClN₃O₃ 387.1; found 388.1.

[0723] EXAMPLE 385: 2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



[0724] STEP 1: (1*R*,2*R*)-2-((1'-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclohexan-1-ol



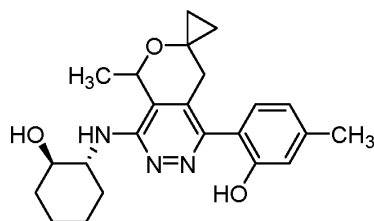
[0725] A mixture of 4'-chloro-1'-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (80 mg, 192.86 μ mol), (1*R*,2*R*)-2-aminocyclohexanol (44.42 mg, 385.72 μ mol), Pd(OAc)₂ (4.33 mg, 19.29 μ mol), Cs₂CO₃ (251.35 mg, 771.45 μ mol) and BINAP (24.02 mg, 38.57 μ mol) in toluene (1 mL) was degassed and purged with N₂ (3 x) and then stirred at 120°C for 1 hour. TLC (PE/EtOAc = 1:1) indicated the starting material was consumed completely and three new spots had formed. The reaction mixture was diluted with H₂O (5 mL) and extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (5 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography (ISCO® 4 g SepaFlash® silica gel column) using a gradient of 0 to 50% EtOAc in PE (30 mL/min). The title compound was obtained as a colorless oil (60 mg, 48% yield, 96% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.16 - 0.37 (m, 1 H), 0.60 (td, *J*=10.4, 5.9 Hz, 1 H), 0.73 - 0.87 (m, 1 H), 1.02 (br dd, *J*=11.3, 5.7 Hz, 1 H), 1.31 - 1.48 (m, 4 H), 1.62 (t, *J*=6.5 Hz, 3 H), 1.74 - 1.85 (m, 3 H), 2.12 - 2.27 (m, 2 H), 3.13 - 3.29 (m, 1 H), 3.40 (br s, 3 H), 3.48 - 3.59 (m, 1 H), 4.15 - 4.40 (m, 1 H), 4.67 - 4.88 (m, 1 H), 5.05 - 5.19 (m, 2 H), 7.33 - 7.54 (m, 3 H).

[0726] STEP 2: 2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol

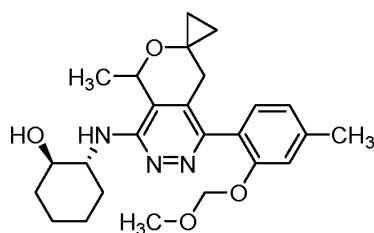
[0727] To a solution of (1*R*,2*R*)-2-((1'-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclohexan-1-ol (60 mg, 121.58 μ mol) was added TFA (0.25 mL) in DCM (0.7 mL). The mixture was stirred at 25°C for 3 hours. LC-MS showed the starting material was consumed completely. Several new peaks were shown on LC-MS and ~79% of desired compound was detected. The reaction mixture was diluted with NaHCO₃ (5 mL) and EtOAc (5 mL). The organic layers were washed with brine (5 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by preparative HPLC (Waters Xbridge, 10 μ m, 25 mm x 150 mm column) using a 40 to 70% gradient of ACN in water (NH₄HCO₃) over 10 minutes. The title compound was obtained as a white

solid (15.6 mg, 27.1% yield, 95% purity). ^1H NMR (400 MHz, CDCl_3) δ ppm 0.20 - 0.28 (m, 1 H), 0.65 - 0.79 (m, 2 H), 0.99 - 1.09 (m, 1 H), 1.30 - 1.39 (m, 2 H), 1.42 - 1.51 (m, 2 H), 1.61 (t, $J=6.07$ Hz, 3 H), 1.80 (br t, $J=11.69$ Hz, 2 H), 2.11 - 2.19 (m, 1 H), 2.22 (s, 1 H), 3.46 - 3.63 (m, 2 H), 4.00 - 4.14 (m, 1 H), 4.16 - 4.27 (m, 1 H), 4.63 - 4.81 (m, 1 H), 7.15 (br d, $J=8.13$ Hz, 1 H), 7.35 (br s, 1 H), 7.46 (dd, $J=8.13, 2.13$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{23}\text{H}_{26}\text{F}_3\text{N}_3\text{O}_3$ 449.2; found 450.3.

[0728] EXAMPLE 386: 2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol



[0729] STEP 1: (1*R*,2*R*)-2-((1'-(2-(methoxymethoxy)-4-methylphenyl)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclohexan-1-ol



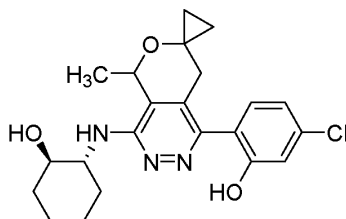
[0730] To a solution of 4'-chloro-1'-(2-(methoxymethoxy)-4-methylphenyl)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (100 mg, 277.14 μmol) in toluene (1 mL) were added $\text{Pd}(\text{OAc})_2$ (6.22 mg, 27.71 μmol), (1*R*,2*R*)-2-aminocyclohexanol (63.84 mg, 554.27 μmol), BINAP (34.51 mg, 55.43 μmol) and Cs_2CO_3 (361.18 mg, 1.11 mmol). The mixture was stirred at 120°C for 2 hours. LC-MS showed the starting material was consumed completely and ~56% of desired compound was detected. The mixture was diluted with H_2O (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (30 mL x 2), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography (ISCO® 4 g SepaFlash® silica gel column) using a gradient of 0 to 50% EtOAc in PE (20 mL/min). The title compound was obtained as a colorless oil (60 mg). ^1H NMR (400 MHz, CDCl_3) δ ppm 0.20 - 0.33 (m, 1 H), 0.54 - 0.63 (m, 1 H), 0.71 - 0.81 (m, 1 H), 0.94 - 1.05 (m, 1 H), 1.31 - 1.53 (m, 5 H), 1.61 (t, $J=6.3$ Hz, 3 H), 1.78 (br d, $J=8.4$ Hz, 3 H), 2.09 - 2.24 (m, 3 H), 2.39

(s, 3 H), 3.34 - 3.41 (m, 3 H), 3.44 - 3.58 (m, 1 H), 3.96 - 4.07 (m, 1 H), 4.67 - 4.85 (m, 1 H), 5.02 - 5.13 (m, 2 H), 6.92 (d, $J=7.5$ Hz, 1 H), 7.02 (s, 1 H), 7.19 (dd, $J=7.6, 3.2$ Hz, 1 H).

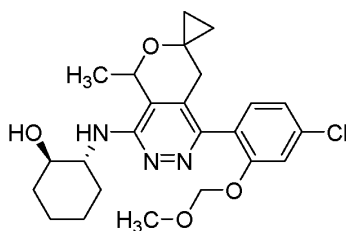
[0731] STEP 2: 2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol

[0732] To a solution of (1*R*,2*R*)-2-((1'-(2-(methoxymethoxy)-4-methylphenyl)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclohexan-1-ol (60 mg, 136.50 μ mol) in DCM (0.7 mL) was added TFA (3.37 mmol, 0.25 mL). The mixture was stirred at 25°C for 3 hours. LC-MS showed the starting material was consumed completely and ~75% of desired compound was detected. The reaction was quenched with saturated NaHCO_3 (10 mL), diluted with H_2O (10 mL) and extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue, which was purified by preparative HPLC (Waters Xbridge, 10 μ m, 25 mm x 150 mm column) using a 30 to 60% gradient of ACN in water (NH_4HCO_3) over 10 minutes. The title compound was obtained as a white solid (9.1 mg, 16% yield, 95% purity). ^1H NMR (400 MHz, CDCl_3) δ ppm 0.13 - 0.33 (m, 1 H), 0.58 - 0.81 (m, 2 H), 0.93 - 1.11 (m, 1 H), 1.27 - 1.38 (m, 2H), 1.38 - 1.39 (m, 1 H), 1.40 - 1.53 (m, 2 H), 1.58 - 1.61 (m, 3 H), 1.75 - 1.85 (m, 2 H), 2.02 (s, 1 H), 2.16 - 2.29 (m, 2 H), 2.35 (s, 3 H), 3.46 - 3.66 (m, 2 H), 4.00 - 4.14 (m, 2 H), 4.64 - 4.78 (m, 1 H), 6.73 (br d, $J=8.0$ Hz, 1 H), 6.93 (s, 1 H), 7.22 - 7.26 (m, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_3$ 395.2; found 396.6.

[0733] EXAMPLE 387: 5-chloro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol



[0734] STEP 1: (1*R*,2*R*)-2-((1'-(4-chloro-2-(methoxymethoxy)phenyl)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclohexan-1-ol



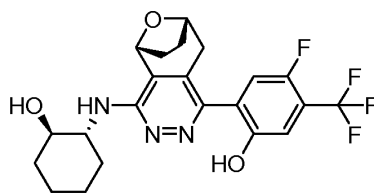
[0735] A mixture of 4'-chloro-1'-(4-chloro-2-(methoxymethoxy)phenyl)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (25 mg, 65.57 μ mol), (1*R*,2*R*)-2-aminocyclohexanol (30.21 mg, 262.29 μ mol), Pd(OAc)₂ (2.94 mg, 13.11 μ mol), Cs₂CO₃ (106.83 mg, 327.87 μ mol) and BINAP (16.33 mg, 26.23 μ mol) in toluene (2.5 mL) was degassed and purged with N₂ (3 x) and then stirred at 100°C for 2 hours. TLC (PE/EtOAc = 0:1) indicated the starting material was consumed completely and three new spots had formed. The reaction mixture was diluted with EtOAc (3 mL) and H₂O (3 mL). The organic layers were washed with brine (3 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography (ISCO® 4 g SepaFlash® silica gel column) using a gradient of 0 to 38% EtOAc in PE (30 mL/min). The title compound was obtained as a white solid (28 mg, 76% yield, 82% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.19 - 0.34 (m, 1 H), 0.55 - 0.64 (m, 1 H), 0.76 - 0.82 (m, 1 H), 0.83 - 0.92 (m, 2 H), 0.99 - 1.04 (m, 1 H), 1.52 (br d, *J*=11.76 Hz, 2 H), 1.60 - 1.62 (m, 3 H), 1.77 (br d, *J*=10.26 Hz, 2 H), 2.04 (s, 1 H), 2.09 - 2.21 (m, 2 H), 2.44 (s, 1 H), 3.38 (s, 3 H), 3.47 - 3.60 (m, 1 H), 3.87 (s, 1 H), 4.08 - 4.15 (m, 1 H), 4.19 (br s, 1 H), 4.64 - 4.79 (m, 1 H), 4.83 - 4.96 (m, 1 H), 5.03 - 5.14 (m, 2 H), 7.09 (dd, *J*=8.13, 1.88 Hz, 1 H), 7.20 - 7.25 (m, 2 H).

[0736] STEP 2: 5-chloro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol

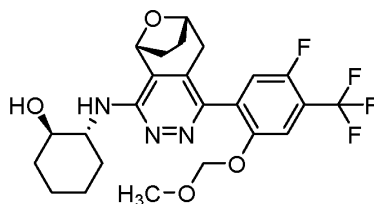
[0737] A solution of (1*R*,2*R*)-2-((1'-(4-chloro-2-(methoxymethoxy)phenyl)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclohexan-1-ol (28 mg, 60.87 μ mol) and TFA (0.3 mL) in DCM (0.9 mL) was stirred at 25°C for 3 hours. TLC (PE/EtOAc = 0:1) indicated the starting material was consumed completely and one new spot had formed. The reaction mixture was diluted with NaHCO₃ (3 mL) and EtOAc (3 mL). The organic layers were washed with brine (3 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography (ISCO® 4 g SepaFlash® silica gel column) using a gradient of 0 to 30% EtOAc in PE (18 mL/min). The title compound was obtained as a white solid (4.1 mg, 16%

yield, 98% purity). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 0.24 - 0.33 (m, 1 H), 0.56 - 0.68 (m, 2 H), 0.81 - 0.93 (m, 1 H), 1.20 - 1.34 (m, 4 H), 1.45 (dd, $J=15.32$, 6.44 Hz, 3 H), 1.61 - 1.73 (m, 2 H), 1.90 - 1.99 (m, 1 H), 2.10 - 2.16 (m, 1 H), 2.21 (br dd, $J=17.32$, 4.44 Hz, 1 H), 2.70 - 2.81 (m, 1 H), 3.48 - 3.56 (m, 1 H), 3.84 - 4.03 (m, 1 H), 4.58 - 4.87 (m, 1 H), 4.89 - 4.99 (m, 1 H), 5.58 (dd, $J=13.13$, 6.88 Hz, 1 H), 6.90 - 6.96 (m, 2 H), 7.20 (dd, $J=8.63$, 1.75 Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{22}\text{H}_{26}\text{ClN}_3\text{O}_3$ 415.2; found 416.0.

[0738] EXAMPLE 388: 4-fluoro-2-(((5*R*,8*S*)-4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol



[0739] STEP 1: (1*R*,2*R*)-2-(((5*R*,8*S*)-1-(5-fluoro-2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol



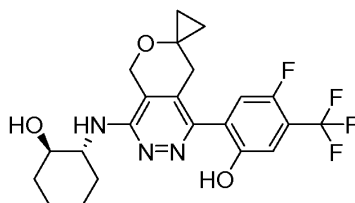
[0740] A mixture of (1*R*,2*R*)-2-(((5*R*,8*S*)-1-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol (40 mg, 129.12 μmol), 2-(5-fluoro-2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (67.81 mg, 193.68 μmol), K_3PO_4 (54.82 mg, 258.24 μmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (9.45 mg, 12.91 μmol) in dioxane (2 mL) and H_2O (0.4 mL) was stirred at 100°C for 1 hour under N_2 . LC-MS showed one main peak with desired mass was detected. The mixture was concentrated in vacuum to give the title compound as a yellow liquid (64 mg, crude) which was used without further purification. ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{24}\text{H}_{27}\text{F}_4\text{N}_3\text{O}_4$ 497.2; found 498.3

[0741] STEP 2: 4-fluoro-2-(((5*R*,8*S*)-4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol

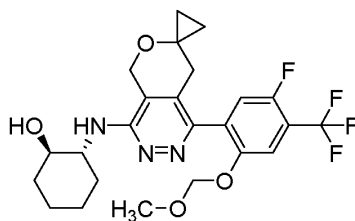
[0742] A solution of (1*R*,2*R*)-2-(((5*R*,8*S*)-1-(5-fluoro-2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-

yl)amino)cyclohexan-1-ol (64 mg crude) in HCl (4M, 5 mL) was stirred at 25°C for 2 hours. LC-MS showed one main peak with desired mass was detected. The reaction mixture was extracted with EtOAc (10 mL x 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by preparative HPLC (C18 30 mm x 150 mm column) using ACN in water (FA). The title compound was obtained as a yellow solid (5 mg, 13% yield, 100% purity). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.29 - 1.50 (m, 4 H), 1.64 - 1.86 (m, 3 H), 2.01 - 2.45 (m, 6 H), 2.99 - 3.14 (m, 1 H), 3.59 (br s, 1 H), 4.03 - 4.12 (m, 1 H), 4.59 - 4.63 (m, 1 H), 5.20 (br s, 1 H), 7.15 (d, *J*=5.72 Hz, 1 H), 7.20 (d, *J*=10.12 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₂H₂₃F₄N₃O₃ 453.2; found 454.2.

[0743] EXAMPLE 389: 4-fluoro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



[0744] STEP 1: (1*R*,2*R*)-2-((1'-(5-fluoro-2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclohexan-1-ol

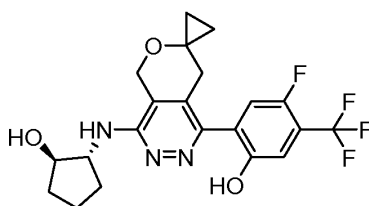


[0745] To a mixture of (1*R*,2*R*)-2-[(1-chlorospiro[5,8-dihydropyrano[3,4-*d*]pyridazine-7,1'-cyclopropane]-4-yl)amino]cyclohexanol (42 mg, 135.58 μmol) and 2-(5-fluoro-2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (71.20 mg, 203.36 μmol) in dioxane (1 mL) and H₂O (0.25 mL) were added K₃PO₄ (57.56 mg, 271.15 μmol) and Pd(dppf)Cl₂.CH₂Cl₂ (11.07 mg, 13.56 μmol) in one portion. The mixture was stirred at 100°C for 2 hours. LC-MS showed the desired mass was detected. The reaction mixture was concentrated in vacuum to give a crude product, which was purified by flash chromatography (ISCO® 4 g SepaFlash® silica gel column) using a gradient of 0 to 5% MeOH in DCM (20mL/min). The title compound was obtained as a yellow oil (57.8 mg, 81.2% yield, 94.8% purity). ESI-MS *m/z* [M+H]⁺ calc'd for C₂₄H₂₇F₄N₃O₄ 497.2; found 498.2.

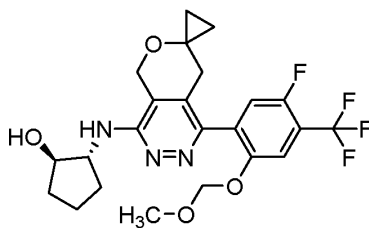
[0746] STEP 2: 4-fluoro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol

[0747] A mixture of (1*R*,2*R*)-2-((1'-(5-fluoro-2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclohexan-1-ol (57 mg, 108.57 μ mol) in DCM (2 mL) and TFA (0.5 mL) was stirred at 21°C for 1.5 hours. LC-MS showed the desired mass was detected. The reaction mixture was concentrated in vacuum to give a crude product, which was purified by preparative HPLC (C18 30 mm x150 mm column) using a gradient of 8 to 48% ACN in water (FA) over 9 minutes. A formic acid salt of the title compound was obtained as a yellow solid (18 mg, 34% yield, 99% purity). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.50 - 0.54 (m, 2 H), 0.85 - 0.90 (m, 2 H), 1.30 - 1.46 (m, 4 H), 1.69 - 1.84 (m, 2 H), 2.03 - 2.24 (m, 2 H), 2.56 - 2.69 (m, 2 H), 3.57 (td, *J*=9.97, 4.31 Hz, 1 H), 4.05 - 4.14 (m, 1 H), 4.53 - 4.68 (m, 2 H), 7.12 (d, *J*=5.88 Hz, 1 H), 7.23 (d, *J*=10.63 Hz, 1 H); ¹⁹F NMR (376 MHz, CD₃OD) δ ppm -129.47 (q, *J*=13.47 Hz, 1 F), -63.02 (br d, *J*=13.46 Hz, 1 F); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₂H₂₃F₄N₃O₃ 453.2; found 454.4.

[0748] EXAMPLE 390: 4-fluoro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



[0749] STEP 1: (1*R*,2*R*)-2-((1'-(5-fluoro-2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclopentan-1-ol



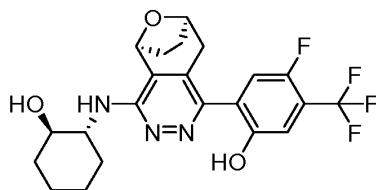
[0750] To a mixture of (1*R*,2*R*)-2-((1'-chloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclopentan-1-ol (35 mg, 118.34 μ mol) and 2-(5-fluoro-2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (62.15 mg, 177.51 μ mol) in dioxane (1 mL) and H₂O (0.25 mL) were added K₃PO₄ (50.24 mg, 236.68 μ mol) and Pd(dppf)Cl₂.CH₂Cl₂ (9.66 mg, 11.83 μ mol) in one portion. The

mixture was stirred at 100°C for 2 hours. LC-MS showed the starting material was consumed completely and the desired mass was detected. The reaction mixture was concentrated in vacuum to give a crude product, which was purified by flash chromatography (ISCO® 4 g SepaFlash® silica gel column) using a gradient of 0 to 5% MeOH in DCM (20mL/min). The title compound was obtained as a yellow oil (38.1 mg, 58% yield, 87.2% purity). ESI-MS m/z $[M+H]^+$ calc'd for $C_{23}H_{25}F_4N_3O_4$ 483.2; found 484.4.

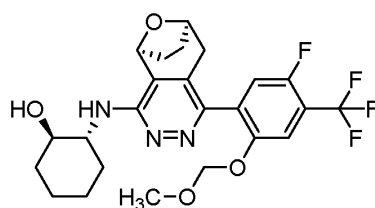
[0751] STEP 2: 4-fluoro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol

[0752] A mixture of (1*R*,2*R*)-2-((1'-(5-fluoro-2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclopentan-1-ol (38 mg, 68.51 μ mol) in DCM (2 mL) and TFA (0.5 mL) was stirred at 27°C for 1 hour. LC-MS showed desired mass was detected. The reaction mixture was concentrated in vacuum to give a crude product, which was purified by preparative HPLC (C18 30 mm x 150 mm column) using a 9 to 49% gradient of ACN in water (FA) over 9 minutes. A formic acid salt of the title compound was obtained as a white solid (5.5 mg, 18% yield, 100% purity). 1H NMR (400 MHz, CD_3OD) δ ppm 0.48 - 0.55 (m, 2 H), 0.85 - 0.91 (m, 2 H), 1.62 - 1.86 (m, 4 H), 1.96 - 2.11 (m, 1 H), 2.22 - 2.35 (m, 1 H), 2.63 (s, 2 H), 4.04 - 4.22 (m, 2 H), 4.58 (s, 2 H), 7.13 (d, $J=5.88$ Hz, 1 H), 7.24 (d, $J=10.38$ Hz, 1 H); ^{19}F NMR (376 MHz, CD_3OD) δ ppm -129.39 (q, $J=12.71$ Hz, 1 F), -63.07 - -63.00 (m, 1 F); ESI-MS m/z $[M+H]^+$ calc'd for $C_{21}H_{21}F_4N_3O_3$ 439.2; found 440.3.

[0753] EXAMPLE 391: 4-fluoro-2-((5*S*,8*R*)-4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol



[0754] STEP 1: (1*R*,2*R*)-2-(((5*S*,8*R*)-1-(5-fluoro-2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol

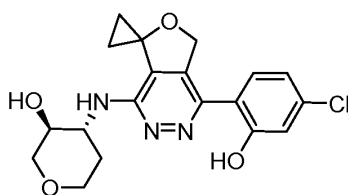


[0755] A mixture of (1*R*,2*R*)-2-(((5*S*,8*R*)-1-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol (40 mg, 129.12 μ mol), 2-(5-fluoro-2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (58.77 mg, 167.86 μ mol), K_3PO_4 (54.82 mg, 258.24 μ mol), and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (10.54 mg, 12.91 μ mol) in dioxane (0.5 mL) and H_2O (0.1 mL) was stirred at 100°C for 1 hour under N_2 . LC-MS showed one main peak with desired mass was detected. The mixture was concentrated *in vacuo* to give the title compound as a black solid (150 mg, crude) which was used without further purification. ESI-MS m/z $[M+H]^+$ calc'd for $C_{24}H_{27}F_4N_3O_4$ 497.2; found 498.3.

[0756] STEP 2: 4-fluoro-2-((5*S*,8*R*)-4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol

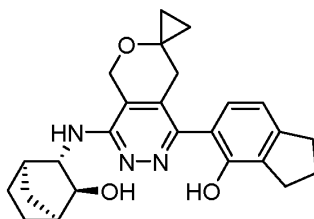
[0757] A solution of (1*R*,2*R*)-2-(((5*S*,8*R*)-1-(5-fluoro-2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol (150 mg crude) in HCl (4M, 5 mL) was stirred at 20°C for 2 hours. LC-MS showed one main peak with desired mass. The reaction mixture was extracted with EtOAc (10 mL x 2). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated in vacuum. The residue was purified by preparative HPLC (C18 30 mm x 150 mm column) using a gradient of 16 to 56% ACN in water (TFA) over 9 minutes. The title compound was obtained as a yellow solid (7.5 mg, 12% yield over two steps, 97% purity). 1H NMR (400 MHz, CD_3OD) δ ppm 1.34 - 1.64 (m, 4 H), 1.72 - 1.87 (m, 3 H), 2.01 - 2.19 (m, 3 H), 2.21 - 2.36 (m, 3 H), 3.13 (br dd, $J=18.51, 4.75$ Hz, 1 H), 3.59 - 3.69 (m, 1 H), 3.77 (br s, 1 H), 4.77 (br d, $J=5.00$ Hz, 1 H), 5.37 (br d, $J=5.50$ Hz, 1 H), 7.19 (d, $J=5.75$ Hz, 1 H), 7.29 (d, $J=10.01$ Hz, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{22}H_{23}F_4N_3O_3$ 453.2; found 454.2.

[0758] EXAMPLE 392: (3*S*,4*R*)-4-((1'-(4-chloro-2-hydroxyphenyl)-7'*H*-spiro[cyclopropane-1,5'-furo[3,4-*d*]pyridazin]-4'-yl)amino)tetrahydro-2*H*-pyran-3-ol



[0759] The title compound was prepared from starting materials (3*S*,4*R*)-4-aminotetrahydro-2*H*-pyran-3-ol and 4'-chloro-1'-(2-fluoro-6-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-7'*H*-spiro[cyclopropane-1,5'-furo[3,4-*d*]pyridazine] using a procedure analogous to Example 254. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.29 - 1.42 (m, 2 H), 1.51 - 1.68 (m, 3 H), 2.30 - 2.43 (m, 1 H), 3.22 - 3.31 (m, 1 H), 3.52 - 3.66 (m, 2 H), 3.91 - 3.98 (m, 1 H), 3.99 - 4.14 (m, 2 H), 5.37 - 5.43 (m, 2 H), 6.89 - 6.96 (m, 1 H), 7.01 - 7.06 (m, 1 H), 7.12 - 7.19 (m, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₁₉H₂₀ClN₃O₄ 389.1; found 390.3.

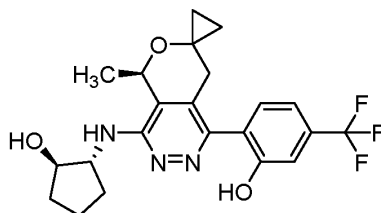
[0760] EXAMPLE 393: 5-(4'-(((1*R*,2*S*,3*S*,4*S*)-3-hydroxybicyclo[2.2.1]heptan-2-yl) amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-2,3-dihydro-1*H*-inden-4-ol



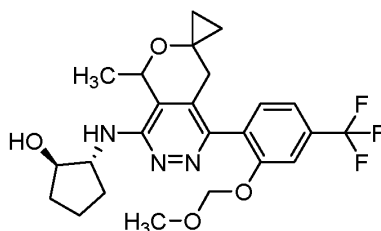
[0761] A microwave vial was charged with 4'-chloro-1'-(4-(methoxymethoxy)-2,3-dihydro-1*H*-inden-5-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (13.4 mg, 0.036 mmol), (1*S*,2*S*,3*S*,4*R*)-3-aminonorbornan-2-ol hydrochloride (11.8 mg, 0.072 mmol), palladium (II) acetate (1.6 mg, 0.007 mmol), (*R*)-(+)-(1,1'-binaphthalene-2,2'-diyl)bis(diphenylphosphine) (9.0 mg, 0.014 mmol), and Cs₂CO₃ (58.5 mg, 0.180 mmol) in 1,4-dioxane (1.8 mL, 0.02 M). The reaction mixture was heated to 120°C in a microwave reactor and stirred for 1 hour. The reaction mixture was quenched with saturated aq NaHCO₃ and extracted with DCM. The organic phase was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude mixture was dissolved in DCM (1.8 mL, 0.02 M) and TFA (28 μL, 0.359 mmol) was added. The solution was stirred for 1 hour at 40°C. After the completion of reaction was observed by LC-MS, the reaction was quenched with saturated aq NaHCO₃ and extracted with DCM. The organic phase was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The product mixture was purified

by preparative HPLC (Phenomenex Gemini® C18 column) using a gradient of 10 to 100% ACN in water (10 mM NH₄HCO₃, pH=9.5-10). The title compound was obtained as a light-yellow powder (4.7 mg, 31%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.43 - 0.59 (m, 2 H), 0.74 - 0.97 (m, 2 H), 1.28 - 1.55 (m, 3 H), 1.62 - 1.83 (m, 2 H), 1.87 - 2.02 (m, 1 H), 2.06 - 2.19 (m, 2 H), 2.35 - 2.46 (m, 2 H), 2.65 (s, 2 H), 2.82 - 3.01 (m, 4 H), 3.84 (br s, 1 H), 4.60 (br d, *J*=5.65 Hz, 2 H), 6.85 (d, *J*=7.53 Hz, 1 H), 6.98 - 7.07 (m, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₅H₂₉N₃O₃ 419.2; found 420.2.

[0762] EXAMPLE 394: 2-((*R*)-4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



[0763] STEP 1: (1*R*,2*R*)-2-((1'-2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclopentan-1-ol



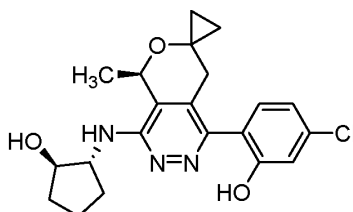
[0764] To a solution of 4'-chloro-1'-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (54 mg, 130.18 μmol) in dioxane (2 mL) were added BINAP (16.21 mg, 26.04 μmol), Cs₂CO₃ (127.25 mg, 390.54 μmol), (1*R*,2*R*)-2-aminocyclopentanol (71.66 mg, 520.73 μmol, HCl), and Pd₂(dba)₃ (11.92 mg, 13.02 μmol). The mixture was stirred at 120°C for 6 hours. LC-MS showed the starting material was consumed completely. New peaks were shown on LC-MS and ~29% of desired product was detected. The reaction mixture was diluted with H₂O (50 mL) and extracted with DCM (50 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography (ISCO® 4 g SepaFlash® silica gel column) using a gradient of 0 to 50% EtOAc in PE (20 mL/min). The title compound was obtained as a

colorless oil (36 mg, 55% yield, 95% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.55 - 0.67 (m, 2 H), 0.73 - 0.96 (m, 2 H), 0.97 - 1.12 (m, 1 H), 1.59 (br s, 7 H), 1.72 - 1.98 (m, 4 H), 2.07 - 2.20 (m, 1 H), 2.27 - 2.42 (m, 1 H), 3.22 - 3.56 (m, 3 H), 4.16 (s, 1 H), 4.66 - 4.92 (m, 1 H), 5.05 - 5.23 (m, 2 H), 7.35 - 7.59 (m, 3 H).

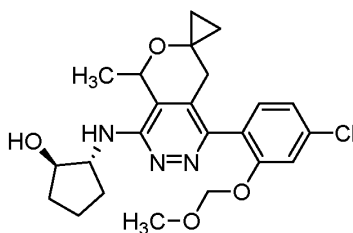
[0765] STEP 2: 2-((*R*)-4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol

[0766] To a solution of (1*R*,2*R*)-2-((1'-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclopentan-1-ol (36 mg, 75.08 μmol) in DCM (0.5 mL) was added TFA (307.00 mg, 2.69 mmol, 0.2 mL). The mixture was stirred at 25°C for 3 hours. LC-MS showed starting material was consumed completely. New peaks were shown on LC-MS and ~53% of the desired compound was detected. The reaction was quenched with saturated NaHCO₃ (10 mL) and the mixture diluted with H₂O (10 mL) and extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography (ISCO® 4 g SepaFlash® silica gel column) using a gradient of 0 to 50% EtOAc in PE (30 mL/min). The title compound was obtained as a white solid (2.6 mg, 7.6% yield, 95% purity). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.18 - 0.31 (m, 1 H), 0.67 - 0.86 (m, 2 H), 0.97 - 1.11 (m, 1 H), 1.23 - 1.32 (m, 2 H), 1.58 - 1.61 (m, 3 H), 1.76 - 1.84 (m, 2 H), 1.91 (td, *J*=7.1, 3.1 Hz, 1 H), 2.01 (s, 1 H), 2.07 - 2.18 (m, 1 H), 2.24 (br d, *J*=16.8 Hz, 1 H), 2.30 - 2.43 (m, 1 H), 3.49 - 3.66 (m, 1 H), 3.98 - 4.12 (m, 1 H), 4.12 - 4.42 (m, 1 H), 4.61 - 4.85 (m, 1 H), 7.15 (br d, *J*=8.4 Hz, 1 H), 7.36 (s, 1 H), 7.43 - 7.50 (m, 1 H).

[0767] EXAMPLE 395: 5-chloro-2-((*R*)-4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol



[0768] STEP 1: (1*R*,2*R*)-2-((1'-(4-chloro-2-(methoxymethoxy)phenyl)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclopentan-1-ol



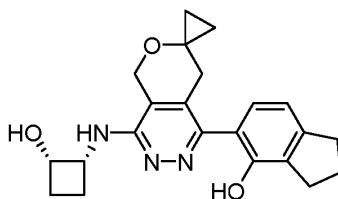
[0769] A mixture of 4'-chloro-1'-(4-chloro-2-(methoxymethoxy)phenyl)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (30 mg, 78.69 μmol), (1*R*,2*R*)-2-aminocyclopentanol (43.31 mg, 314.75 μmol , HCl), BINAP (9.80 mg, 15.74 μmol), Cs_2CO_3 (76.91 mg, 236.06 μmol) and $\text{Pd}_2(\text{dba})_3$ (7.21 mg, 7.87 μmol) in dioxane (1.4 mL) was degassed and purged with N_2 (3 x) and then stirred at 120°C for 2 hours under N_2 atmosphere. TLC (PE/EtOAc = 3:1 and PE/EtOAc = 1:2) indicated the starting material was consumed completely and many new spots were formed. The reaction mixture was diluted with EtOAc (3 mL) and H_2O (3 mL). The organic layers were washed with brine (3 mL x 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography (ISCO® 4 g SepaFlash® silica gel column) using a gradient of 0 to 38% EtOAc in PE (40 mL/min). The title compound was obtained as a white solid (32 mg, 43% yield, 95% purity). ^1H NMR (400 MHz, CDCl_3) δ ppm 0.20 - 0.35 (m, 1 H), 0.56 - 0.66 (m, 1 H), 0.86 - 0.91 (m, 1 H), 0.98 - 1.07 (m, 1 H), 1.22 - 1.31 (m, 4 H), 1.59 - 1.62 (m, 3 H), 1.73 - 1.94 (m, 4 H), 2.00 - 2.18 (m, 2 H), 2.26 - 2.42 (m, 2 H), 2.84 (s, 1 H), 3.35 - 3.42 (m, 3 H), 4.05 - 4.13 (m, 1 H), 4.69 - 4.87 (m, 1 H), 5.04 - 5.15 (m, 2 H), 7.11 (dd, $J=8.19$, 1.81 Hz, 1 H), 7.22 - 7.25 (m, 2 H).

[0770] STEP 2: 5-chloro-2-((*R*)-4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol

[0771] To (1*R*,2*R*)-2-((1'-(4-chloro-2-(methoxymethoxy)phenyl)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclopentan-1-ol (30 mg, 67.27 μmol) was added TFA (0.2 mL) in DCM (0.6 mL). The mixture was stirred at 25°C for 2 hours. TLC (PE/EtOAc = 1:2) indicated the starting material was consumed completely and one new spot had formed. The reaction mixture was diluted with aq NaHCO_3 (5 mL) and extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (5 mL x 2), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography (ISCO® 4 g SepaFlash® silica gel column) using a gradient of 0 to 38% EtOAc in PE (30 mL/min). The title compound was obtained as a white solid (3.2 mg, 11% yield, 97% purity). ^1H NMR (400 MHz, CDCl_3) δ

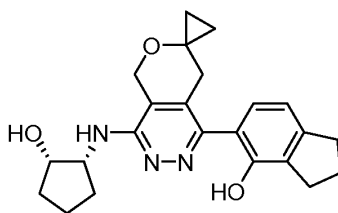
ppm 0.17 - 0.29 (m, 1 H), 0.65 - 0.79 (m, 2 H), 0.88 (br t, $J=6.19$ Hz, 1 H), 0.99 - 1.11 (m, 1 H), 1.24 - 1.27 (m, 1 H), 1.32 (br d, $J=7.75$ Hz, 1 H), 1.57 - 1.61 (m, 3 H), 1.79 - 1.82 (m, 1 H), 1.89 (br dd, $J=8.07, 2.56$ Hz, 1 H), 2.06 - 2.17 (m, 1 H), 2.22 (br d, $J=15.63$ Hz, 1 H), 2.30 - 2.42 (m, 1 H), 3.56 (br d, $J=16.63$ Hz, 1 H), 4.00 - 4.22 (m, 2 H), 4.30 (br s, 1 H), 4.63 - 4.76 (m, 1 H), 6.89 (dd, $J=8.44, 1.19$ Hz, 1 H), 7.11 (d, $J=1.00$ Hz, 1 H), 7.29 (dd, $J=8.44, 4.31$ Hz, 1 H).

[0772] EXAMPLE 396: 5-(4'-(((1*R*,2*S*)-2-hydroxycyclobutyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-2,3-dihydro-1*H*-inden-4-ol



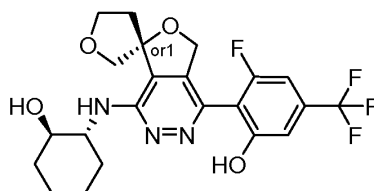
[0773] A microwave vial was charged with 4'-chloro-1'-(4-(methoxymethoxy)-2,3-dihydro-1*H*-inden-5-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (11.8 mg, 0.032 mmol), (1*S*,2*R*)-2-aminocyclobutanol hydrochloride (7.8 mg, 0.063 mmol), palladium (II) acetate (1.4 mg, 0.006 mmol), (*R*)-(+)-(1,1'-binaphthalene-2,2'-diyl)bis(diphenylphosphine) (7.9 mg, 0.013 mmol), and Cs₂CO₃ (20.6 mg, 0.063 mmol) in 1,4-dioxane and *tert*-butyl alcohol (9:1 mixture, 1.4 mL:0.16 mL, 0.02 M). The reaction mixture was heated to 120°C in a microwave reactor and stirred for 5 hours. The reaction was quenched with saturated aq NaHCO₃ and the mixture extracted with DCM. The organic phase was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude mixture was dissolved in DCM (1.6 mL, 0.02 M). TFA (49 µL, 0.633 mmol) was added and the solution was stirred for 1 hour at 40°C. After the completion of reaction was observed by LC-MS, the reaction was quenched with saturated aq NaHCO₃ and extracted with DCM. The organic phase was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The product mixture was purified by preparative HPLC (Phenomenex Gemini® C18 column) using a gradient of 10 to 100% ACN in water (10 mM NH₄HCO₃, pH=9.5-10). The title compound was obtained as a white powder (1.3 mg, 11%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.40 (s, 2 H), 0.73 - 0.83 (m, 2 H), 1.73 - 1.89 (m, 1 H), 1.94 - 2.26 (m, 5 H), 2.43 - 2.62 (m, 2 H), 2.71 - 2.90 (m, 4 H), 4.31 - 4.57 (m, 4 H), 6.64 - 6.79 (m, 1 H), 6.83 - 6.96 (m, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₂H₂₅N₃O₃ 379.19; found 380.2.

[0774] EXAMPLE 397: 5-(4'-(((1*R*,2*S*)-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-2,3-dihydro-1*H*-inden-4-ol



[0775] A microwave vial was charged with 4'-chloro-1'-(4-(methoxymethoxy)-2,3-dihydro-1*H*-inden-5-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (13.8 mg, 0.037 mmol), (1*S*,2*R*)-2-aminocyclopentan-1-ol hydrochloride (10.2 mg, 0.074 mmol), palladium (II) acetate (1.7 mg, 0.007 mmol), (*R*)-(+)-(1,1'-binaphthalene-2,2'-diyl)bis(diphenylphosphine) (9.2 mg, 0.015 mmol), and Cs₂CO₃ (60.3 mg, 0.185 mmol) in 1,4-dioxane and tert-butyl alcohol (9:1 mixture, 1.7 mL:0.19 mL, 0.02 M). The reaction mixture was heated to 120°C in a microwave reactor and stirred for 3 hours. The reaction was quenched with saturated aq NaHCO₃ and the mixture extracted with DCM. The organic phase was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude mixture was dissolved in DCM (1.9 mL, 0.02 M), and TFA (57 µL, 0.74 mmol) was added. The solution was stirred for 1 hour at 40°C. After the completion of reaction was observed by LC-MS, the reaction was quenched with saturated aq NaHCO₃ and the mixture extracted with DCM. The organic phase was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The product mixture was purified by preparative HPLC (Phenomenex Gemini® C18 column) using a gradient of 10 to 100% ACN in water (10 mM NH₄HCO₃, pH=9.5-10). The title compound was obtained as a white powder (4.0 mg, 0.01 mmol, 30%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.33 - 0.48 (m, 2 H), 0.78 (s, 2 H), 1.65 (br s, 5 H), 2.01 (quin, *J*=7.29 Hz, 3 H), 2.42 - 2.59 (m, 2 H), 2.71 - 2.89 (m, 4 H), 4.14 - 4.30 (m, 2 H), 4.37 - 4.54 (m, 2 H), 6.65 - 6.77 (m, 1 H), 6.87 - 6.98 (m, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₃H₂₇N₃O₃ 393.2; found 394.2.

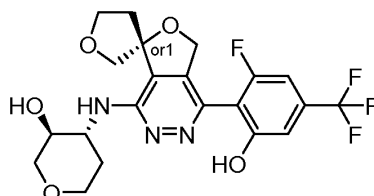
[0776] EXAMPLE 398: 3-fluoro-2-((3*R**)-4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



[0777] The title compound was prepared from starting material (1*R*,2*R*)-2-aminocyclohexan-1-ol hydrochloride using a procedure analogous to Example 381. ¹H NMR

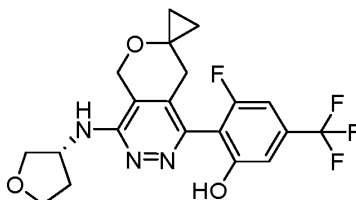
(400 MHz, CD₃OD) δ ppm 1.42 (br s, 4 H), 1.66 - 1.83 (m, 2 H), 2.01 - 2.08 (m, 1 H), 2.23 - 2.31 (m, 1 H), 2.33 - 2.50 (m, 2 H), 3.45 - 3.56 (m, 1 H), 3.74 (d, $J=10.04$ Hz, 1 H), 3.91 - 4.07 (m, 2 H), 4.22 (d, $J=10.04$ Hz, 1 H), 4.29 - 4.39 (m, 1 H), 4.95 (d, $J=3.89$ Hz, 2 H), 6.99 - 7.08 (m, 2 H); ESI-MS m/z $[M+H]^+$ calc'd for C₂₂H₂₃F₄N₃O₄ 469.2; found 470.3.

[0778] EXAMPLE 399: 3-fluoro-2-((3*R**)-4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



[0779] The title compound was prepared from starting material (3*R*,4*S*)-4-aminooxan-3-ol hydrochloride using a procedure analogous to Example 381. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.52 - 1.70 (m, 1 H), 2.42 (s, 3 H), 3.21 - 3.29 (m, 1 H), 3.50 - 3.64 (m, 2 H), 3.76 (d, $J=10.04$ Hz, 1 H), 3.86 - 3.94 (m, 1 H), 3.94 - 4.04 (m, 2 H), 4.15 - 4.27 (m, 2 H), 4.30 - 4.40 (m, 1 H), 4.96 (d, $J=4.39$ Hz, 2 H), 7.00 - 7.07 (m, 2 H); ESI-MS m/z $[M+H]^+$ calc'd for C₂₁H₂₁F₄N₃O₅ 471.1; found 472.3.

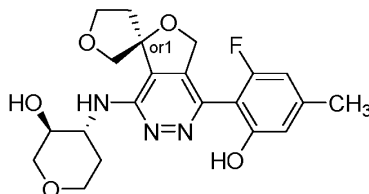
[0780] EXAMPLE 400: 3-fluoro-2-(4'-(((*R*)-tetrahydrofuran-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



[0781] To a 5 mL vial fitted with a stir bar were added R-BINAP (13 mg, 0.0213 mmol), (3*R*)-oxolan-3-amine hydrochloride (16 mg, 0.133 mmol), 2-(4-chlorospiro[5,8-dihydropyrano[3,4-*d*]pyridazine-7,1'-cyclopropane]-1-yl)-3-fluoro-5-(trifluoromethyl)phenol (20 mg, 0.0534 mmol), Cs₂CO₃ (52 mg, 0.160 mmol), and palladium(II) acetate (2.4 mg, 0.0107 mmol) in DMA (2 mL). The vial was flushed with nitrogen and the reaction mixture was heated to 130°C in a Biotage microwave reactor for 30 minutes. The solution was extracted with EtOAc (2 mL) and brine (1 mL). The organics were separated and concentrated under reduced pressure. The resulting oil was dissolved in MeOH (2 mL) and DMF (0.3 mL), filtered, and purified via basic Shimadzu preparative HPLC to give the title compound (1.6 mg, 7.1%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.45 - 0.58 (m, 2 H), 0.84 -

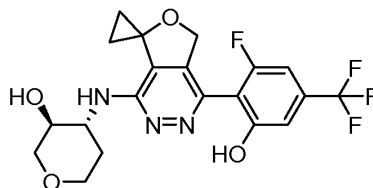
0.96 (m, 2 H), 1.99 - 2.14 (m, 1 H), 2.35 - 2.44 (m, 1 H), 2.50 (br s, 2 H), 3.78 (m, 1 H), 3.86 (m, 1 H), 3.96 - 4.06 (m, 1 H), 4.09 (m, 1 H), 4.59 (s, 2 H), 4.76 (m, 1 H), 7.02 (s, 1 H), 7.03 (s, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{20}H_{19}F_4N_3O_3$ 425.1; found 426.1.

[0782] EXAMPLE 401: (3*S*,4*R*)-4-(((3*R**)-1'-(2-fluoro-6-hydroxy-4-methylphenyl)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-4'-yl)amino)tetrahydro-2*H*-pyran-3-ol



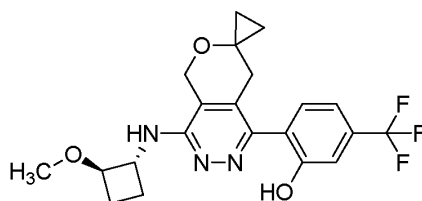
[0783] The title compound was prepared from starting material (3*R*,4*S*)-4-aminooxan-3-ol hydrochloride using a procedure analogous to Example 381. 1H NMR (400 MHz, CD_3OD) δ ppm 1.53 - 1.68 (m, 1 H), 2.31 (s, 6 H), 3.22 - 3.28 (m, 1 H), 3.50 - 3.66 (m, 2 H), 3.72 - 3.78 (m, 1 H), 3.87 - 4.04 (m, 3 H), 4.13 - 4.37 (m, 3 H), 4.94 (d, $J=5.65$ Hz, 2 H), 6.51 - 6.56 (m, 1 H), 6.57 - 6.61 (m, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{21}H_{24}FN_3O_5$ 417.2; found 418.3.

[0784] EXAMPLE 402: (3*S*,4*R*)-4-((1'-(2-fluoro-6-hydroxy-4-(trifluoromethyl)phenyl)-7'*H*-spiro[cyclopropane-1,5'-furo[3,4-*d*]pyridazin]-4'-yl)amino)tetrahydro-2*H*-pyran-3-ol



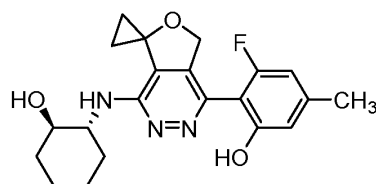
[0785] The title compound was prepared from starting material (3*R*,4*S*)-4-aminooxan-3-ol hydrochloride using a procedure analogous to Example 381. 1H NMR (400 MHz, CD_3OD) δ ppm 1.26 (br d, $J=1.00$ Hz, 2 H), 1.60 (br d, $J=1.00$ Hz, 3 H), 2.23 - 2.34 (m, 1 H), 3.14 - 3.25 (m, 1 H), 3.44 - 3.56 (m, 1 H), 3.69 (d, $J=4.89$ Hz, 1 H), 3.90 (br d, $J=4.02$ Hz, 1 H), 3.97 (dd, $J=11.17, 4.89$ Hz, 1 H), 4.16 - 4.27 (m, 1 H), 4.98 (s, 2 H), 7.00 - 7.09 (m, 2 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{20}H_{19}F_4N_3O_4$ 441.1; found 442.3.

[0786] EXAMPLE 403: 2-(4'-(((1*R*,2*R*)-2-methoxycyclobutyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



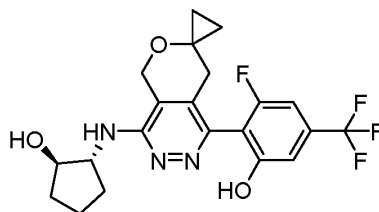
[0787] A mixture of 2-(4'-chloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol (25 mg, 0.0701 mmol), (1*R*,2*R*)-2-methoxycyclobutan-1-amine (19 mg, 0.14 mmol), sodium *tert*-butoxide (24 mg, 0.245 mmol), *rac*-BINAP Pd G3 (7.0 mg, 0.007 mmol), and toluene (1 mL) was heated at 100°C for 2 hours. The mixture was diluted with DMSO (1 mL), filtered, and purified by HPLC (Gemini 30 mm x 150 mm column) using a 10-70% gradient of ACN (0.035% TFA) in water (0.05% TFA) followed by SFC (Waters, IC-5 μ m, 21 mm x 250 mm column) using a mobile phase of CO₂ and 10 to 35% MeOH (with 0.05% NH₃OH) to give the title compound (0.6 mg, 2.03%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.46 - 0.53 (m, 2 H), 0.85 - 0.90 (m, 2 H), 1.43 - 1.66 (m, 2 H), 2.06 - 2.18 (m, 1 H), 2.23 - 2.32 (m, 1 H), 2.54 - 2.66 (m, 1 H), 2.64 - 2.66 (m, 1 H), 3.34 (s, 3 H), 3.97 (q, *J*=7.32 Hz, 1 H), 4.50 - 4.67 (m, 3 H), 7.15 (s, 1 H), 7.22 (d, *J*=7.45 Hz, 1 H), 7.41 (d, *J*=7.91 Hz, 1 H); ESI-MS [M+H]⁺ calc'd for C₂₁H₂₂F₃N₃O₃, 421.2; found, 422.10.

[0788] EXAMPLE 404: 3-fluoro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-7'*H*-spiro[cyclopropane-1,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol

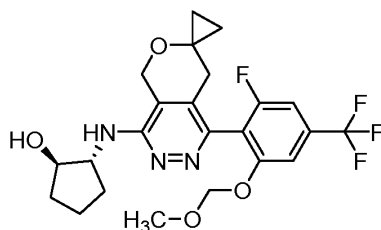


[0789] The title compound was prepared from starting material (1*R*,2*R*)-2-aminocyclohexan-1-ol hydrochloride using a procedure analogous to Example 381. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.19 - 1.46 (m, 6 H), 1.50 - 1.60 (m, 2 H), 1.65 - 1.79 (m, 2 H), 1.98 - 2.09 (m, 1 H), 2.31 (s, 4 H), 3.46 - 3.57 (m, 1 H), 3.88 - 4.01 (m, 1 H), 4.90 - 5.03 (m, 2 H), 6.51 - 6.56 (m, 1 H), 6.57 - 6.61 (m, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₁H₂₄FN₃O₃ 385.2; found 386.4.

[0790] EXAMPLE 405: 3-fluoro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



[0791] STEP 1 (1*R*,2*R*)-2-((1'-(2-fluoro-6-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclopentan-1-ol



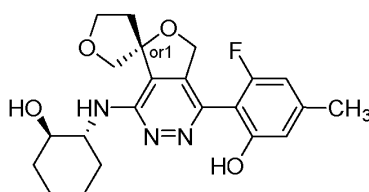
[0792] A mixture of (1*R*,2*R*)-2-((1'-chloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclopentan-1-ol (90 mg, 304.30 μ mol), 2-(2-fluoro-6-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (213.08 mg, 608.59 μ mol), K_3PO_4 (0.5 M in H_2O (5 mL)), and Xphos Pd G4 (52.37 mg, 60.86 μ mol) in THF (2.5 mL) was degassed and purged with N_2 (3 x) and then stirred at 60°C for 1 hour under N_2 atmosphere. LC-MS showed the starting material was consumed completely and two main peaks with desired mass were detected. The mixture was diluted with H_2O (5 mL) and extracted with EtOAc (10 mL x 2). The combined organic layers were concentrated in vacuum to give a crude product, which was purified by flash chromatography (ISCO® 4 g SepaFlash® silica gel column) using a gradient of 0 to 3% MeOH in DCM (20 mL/min). The title compound was obtained as a yellow oil (145 mg, 98.6%). 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 0.48 (br d, $J=6.1$ Hz, 1 H), 0.80 (br s, 1 H), 1.43 - 1.58 (m, 2 H), 1.61 - 1.76 (m, 2 H), 1.89 (br dd, $J=12.4, 6.5$ Hz, 1 H), 2.14 (br dd, $J=13.1, 7.7$ Hz, 1 H), 3.10 (br dd, $J=15.1, 5.2$ Hz, 1 H), 3.22 - 3.29 (m, 5 H), 3.94 (s, 3 H), 4.01 (br s, 1 H), 4.11 - 4.24 (m, 1 H), 4.25 - 4.36 (m, 1 H), 4.46 - 4.71 (m, 2 H), 4.75 - 5.04 (m, 2 H), 5.25 (d, $J=6.8$ Hz, 1 H), 5.28 - 5.38 (m, 1 H), 5.87 - 6.05 (m, 1 H), 7.37 - 7.44 (m, 1 H), 7.45 - 7.54 (m, 1 H); ESI-MS m/z $[M+H]^+$ 484.2.

[0793] STEP 2: 3-fluoro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol

[0794] A solution of (1*R*,2*R*)-2-((1'-(2-fluoro-6-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclopentan-1-ol (140 mg, 289.58 μ mol) in HCl (4 M in H_2O , 2 mL) was stirred at 25°C for 12 hours. LC-MS showed 12% of the starting material remained and one main peak with desired mass was detected. The reaction mixture was adjusted to pH = 9 with $NH_3 \cdot H_2O$, then diluted with H_2O (5 mL) and extracted with DCM (5 mL x 2). The combined organic layers were concentrated under reduced pressure to give a crude product, which was purified

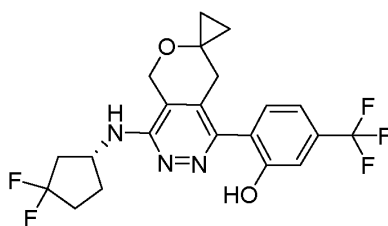
by preparative HPLC (C18 40 mm x 150 mm column) using a gradient of 15 to 55% ACN in water ($\text{NH}_3\text{H}_2\text{O}+\text{NH}_4\text{HCO}_3$) over 9 minutes, and then further purified by SFC (DAICEL CHIRALPAK® AD-10 μm , 30 mm x 250 mm column) using a mobile phase of CO_2 and 25% EtOH (with 0.1% NH_3OH). The title compound was obtained as a white solid (5.6 mg, 10% yield, 90% purity). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 0.48 (s, 2 H), 0.79 (s, 2 H), 1.43 - 1.78 (m, 4 H), 1.83 - 1.98 (m, 1 H), 2.09 - 2.23 (m, 1 H), 2.33 (br s, 2 H), 3.97 - 4.24 (m, 2 H), 4.42 - 4.57 (m, 2 H), 5.06 (d, $J=3.1$ Hz, 1 H), 5.96 (d, $J=6.4$ Hz, 1 H), 7.05 (s, 1 H), 7.16 (br d, $J=8.8$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{21}\text{H}_{21}\text{F}_4\text{N}_3\text{O}_3$ 439.2; found 440.2.

[0795] EXAMPLE 406: 3-fluoro-2-((3*R**)-4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol



[0796] The title compound was prepared from starting material (1*R*,2*R*)-2-aminocyclohexan-1-ol hydrochloride using a procedure analogous to Example 381. ^1H NMR (400 MHz, CD_3OD) δ ppm 1.22 - 1.51 (m, 4 H), 1.66 - 1.83 (m, 2 H), 2.03 - 2.09 (m, 1 H), 2.31 (s, 4 H), 2.32 - 2.48 (m, 2 H), 3.43 - 3.56 (m, 1 H), 3.73 (d, $J=10.04$ Hz, 1 H), 3.90 - 4.04 (m, 2 H), 4.16 - 4.23 (m, 1 H), 4.17 - 4.17 (m, 1 H), 4.27 - 4.38 (m, 1 H), 4.88 - 4.98 (m, 2 H), 6.51 - 6.57 (m, 1 H), 6.57 - 6.61 (m, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{22}\text{H}_{26}\text{FN}_3\text{O}_4$ 415.2; found 416.4.

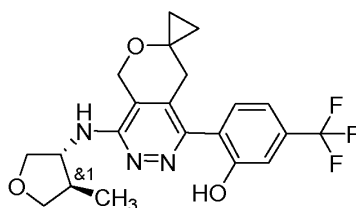
[0797] EXAMPLE 407: (*R*)-2-(4'-((3,3-difluorocyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



[0798] To a 5 mL vial fitted with a stir bar were added R-BINAP (17 mg, 0.0280 mmol), (1*R*)-3,3-difluorocyclopentanamine hydrochloride (44 mg, 0.280 mmol), 2-(4'-chloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol (25 mg, 0.0701 mmol), Cs_2CO_3 (114 mg, 0.350 mmol), and palladium(II) acetate (3.1 mg, 0.0140 mmol) in DMA (2.6 mL). The vial was flushed with nitrogen and the reaction mixture was

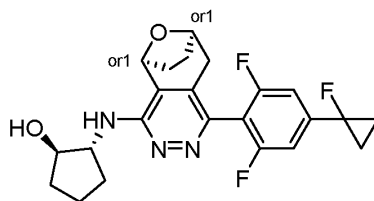
heated to 130°C in a Biotage microwave reactor for 30 minutes. The mixture was extracted with EtOAc (2 mL) and brine (1 mL). The organics were separated and concentrated. The crude material was dissolved in MeOH (2 mL) and DMF (0.3 mL), filtered, and purified via basic Shimadzu preparative HPLC to give the title compound (6.4 mg, 21%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.40 - 0.58 (m, 2 H), 0.80 - 0.96 (m, 2 H), 1.80 - 1.98 (m, 1 H), 2.05 - 2.24 (m, 2 H), 2.24 - 2.44 (m, 2 H), 2.60 (s, 2 H), 2.71 (m, 1 H), 4.57 (s, 2 H), 4.64 - 4.77 (m, 1 H), 7.15 (s, 1 H), 7.23 (d, *J*=7.89 Hz, 1 H), 7.41 (d, *J*=7.89 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₁H₂₀F₅N₃O₂ 441.2; found 442.1.

[0799] EXAMPLE 408: *rac*-2-(4'-(((3*R*,4*R*)-4-methyltetrahydrofuran-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



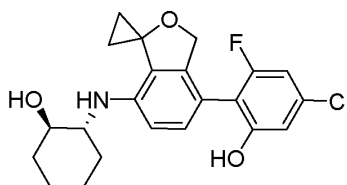
[0800] To a 5 mL vial fitted with a stir bar were added R-BINAP (17 mg, 0.0280 mmol), *rac*-(3*R*,4*R*)-4-methyltetrahydrofuran-3-amine;hydrochloride (39 mg, 0.280 mmol), 2-(4'-chloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol (25 mg, 0.0701 mmol), Cs₂CO₃ (114 mg, 0.350 mmol), and palladium(II) acetate (3.1 mg, 0.0140 mmol) in DMA (2.5 mL). The vial was flushed with nitrogen and the reaction mixture was heated to 130°C for 30 minutes in a Biotage microwave reactor. The mixture was extracted with EtOAc (2 mL) and brine (1 mL). The organics were separated and concentrated under reduced pressure. The crude material was dissolved in DMF (1 mL) and MeOH (1 mL), filtered, and purified via basic Shimadzu preparative HPLC to give the title compound (0.70 mg, 2.4%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.45 - 0.56 (m, 2 H), 0.83 - 0.94 (m, 2 H), 1.19 (d, *J*=6.79 Hz, 3 H), 2.34 - 2.49 (m, 1 H), 2.61 (s, 2 H), 3.41 - 3.53 (m, 1 H), 3.70 (dd, *J*=8.99, 4.95 Hz, 1 H), 4.12 (t, *J*=7.79 Hz, 1 H), 4.24 (dd, *J*=8.89, 6.51 Hz, 1 H), 4.34 - 4.44 (m, 1 H), 4.59 (s, 2 H), 7.16 (s, 1 H), 7.23 (d, *J*=8.07 Hz, 1 H), 7.41 (d, *J*=7.89 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₁H₂₂F₃N₃O₃ 421.2; found 422.1.

[0801] EXAMPLE 409: (1*R*,2*R*)-2-(((5*S**,8*R**)-1-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclopentan-1-ol



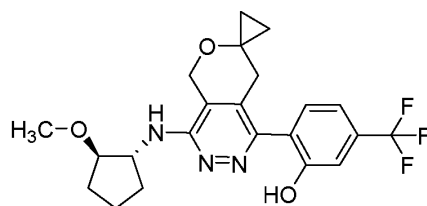
[0802] A mixture of (1*R*,2*R*)-2-(((5*S*,8*R*)-1-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclopentan-1-ol (30 mg, 0.100 mmol), 2-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (60 mg, 0.200 mmol), and Xphos Pd G4 (8.6 mg, 0.0100 mmol) in THF (1.4 mL) and aqueous 0.5M K₃PO₄ (0.35 mL) was stirred in a metal heating block at 100°C for 60 minutes. The reaction mixture was concentrated and diluted with MeOH (3 mL) and filtered using a syringe filter. The crude product was purified by preparative HPLC (Phenomenex Gemini® C18 column) using a gradient of 10 to 100% ACN in water (10 mM NH₄HCO₃, pH=9.5-10). The title compound was obtained as an orange semi-solid (8.0 mg, 19%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.22 - 1.30 (m, 2 H), 1.60 (dd, *J*=19.20, 1.63 Hz, 2 H), 1.73 (s, 5 H), 2.09 (d, *J*=17.82 Hz, 3 H), 2.17 - 2.37 (m, 3 H), 2.87 - 2.97 (m, 1 H), 4.13 (s, 1 H), 4.18 - 4.28 (m, 1 H), 4.70 - 4.78 (m, 1 H), 5.25 (d, *J*=5.77 Hz, 1 H), 6.99 - 7.10 (m, 2 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₃H₂₄F₃N₃O₂ 431.2; found 432.2.

[0803] EXAMPLE 410: 5-chloro-3-fluoro-2-(7'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-3'*H*-spiro[cyclopropane-1,1'-isobenzofuran]-4'-yl)phenol



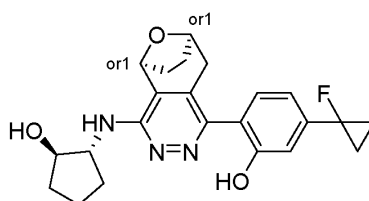
[0804] The title compound was prepared from starting material (1*R*,2*R*)-2-aminocyclohexan-1-ol hydrochloride using a procedure analogous to Example 254. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.34 - 1.46 (m, 5 H), 1.50 - 1.59 (m, 1 H), 1.71 - 1.82 (m, 4 H), 2.01 - 2.12 (m, 2 H), 3.59 - 3.69 (m, 1 H), 3.79 - 3.88 (m, 1 H), 5.12 (s, 2 H), 6.88 (d, *J*=1.51 Hz, 1 H), 6.90 - 6.95 (m, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₂H₂₃ClFNO₃ 403.1; found 404.1.

[0805] EXAMPLE 411: 2-(4'-(((1*R*,2*R*)-2-methoxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



[0806] To a 5 mL vial fitted with a stir bar were added R-BINAP (21 mg, 0.0329 mmol), (1*R*,2*R*)-2-methoxycyclopentan-1-amine hydrochloride (50 mg, 0.329 mmol), 4'-chloro-1'-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (33 mg, 0.0823 mmol), Cs₂CO₃ (134 mg, 0.412 mmol), and palladium(II) acetate (3.7 mg, 0.0165 mmol) in DMA (3 mL). The vial was flushed with nitrogen and the reaction mixture was heated to 130°C in a Biotage microwave reactor for 30 minutes. The mixture was extracted with EtOAc (2 mL) and brine (1 mL). The organics were separated and concentrated. The crude material was dissolved in DCM (5 mL) and TFA (0.19 mL, 2.47 mmol) and allowed to stir at room temperature overnight. The solution was concentrated and extracted with saturated aq NaHCO₃ (2 mL) and EtOAc (2 mL). The organics were separated and dried with MgSO₄ and concentrated under reduced pressure. The material was dissolved in MeOH (2 mL) and DMF (1 mL), filtered, and purified via basic Shimadzu preparative HPLC to give the title compound (5.2 mg, 15%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.40 - 0.57 (m, 2 H), 0.80 - 0.93 (m, 2 H), 1.55 - 1.84 (m, 4 H), 1.94 - 2.12 (m, 1 H), 2.28 (m, 1 H), 2.60 - 2.61 (s, 2 H), 3.43 (s, 3 H), 3.78 - 3.97 (m, 1 H), 4.46 - 4.64 (m, 3 H), 7.15 (s, 1 H), 7.22 (d, *J*=7.89 Hz, 1 H), 7.42 (d, *J*=7.89 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₂H₂₄F₃N₃O₃ 435.2; found 436.1.

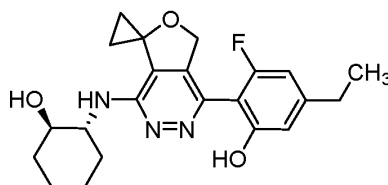
[0807] EXAMPLE 412: 5-(1-fluorocyclopropyl)-2-((5*S**,8*R**)-4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol



[0808] A mixture of (1*R*,2*R*)-2-(((5*S*,8*R*)-1-chloro-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclopentan-1-ol (30 mg, 0.100 mmol), 2-(4-(1-fluorocyclopropyl)-2-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (64 mg, 0.200 mmol), and Pd(dppf)Cl₂.CH₂Cl₂ (7.3 mg, 0.0100 mmol) in THF (1.4 mL) and

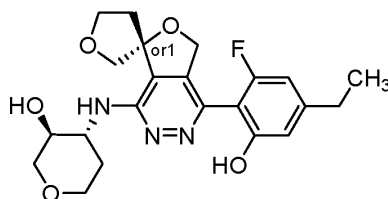
aqueous 0.5M K₃PO₄ (0.35 mL) was stirred in a metal heating block at 100°C for 60 minutes. After cooling to room temperature, the reaction mixture was concentrated. TFA (1 mL) and DCM (2 mL) were added and the reaction mixture was stirred for 1 hour at 50°C. The reaction mixture was again concentrated and diluted with MeOH (3 mL) and filtered with a syringe filter. The crude product was purified by preparative HPLC (Phenomenex Gemini® C18 column) using a 10 to 100% gradient of ACN in water (10 mM NH₄HCO₃, pH=9.5-10). The title compound was obtained as a brown oil (20.0 mg, 49%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.10 (dd, *J*=8.78, 1.76 Hz, 2 H), 1.46 (dd, *J*=19.20, 1.63 Hz, 2 H), 1.68 (br s, 5 H), 2.04 (s, 2 H), 2.22 (br d, *J*=17.82 Hz, 4 H), 2.98 - 3.11 (m, 1 H), 3.99 - 4.18 (m, 2 H), 4.65 - 4.71 (m, 1 H), 5.21 (br s, 1 H), 6.69 - 6.89 (m, 2 H), 7.16 (d, *J*=7.78 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₃H₂₆FN₃O₃ 411.2; found 412.2.

[0809] EXAMPLE 413: 5-ethyl-3-fluoro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-7'*H*-spiro[cyclopropane-1,5'-furo[3,4-*d*]pyridazin]-1'-yl)phenol



[0810] The title compound was prepared from starting material (1*R*,2*R*)-2-aminocyclohexan-1-ol hydrochloride using a procedure analogous to Example 254. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.19 - 1.47 (m, 9 H), 1.53 - 1.63 (m, 2 H), 1.68 - 1.83 (m, 2 H), 2.03 - 2.11 (m, 1 H), 2.31 - 2.40 (m, 1 H), 2.58 - 2.68 (m, 2 H), 3.50 - 3.61 (m, 1 H), 3.92 - 4.03 (m, 1 H), 4.98 (s, 2 H), 6.54 - 6.61 (m, 1 H), 6.62 - 6.67 (m, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₂H₂₆FN₃O₃ 399.2, found 400.4.

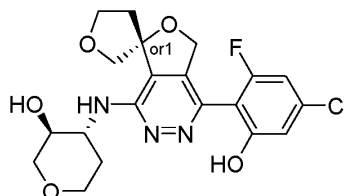
[0811] EXAMPLE 414: (3*S*,4*R*)-4-(((3*R**)-1'-(4-ethyl-2-fluoro-6-hydroxyphenyl)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-4'-yl)amino)tetrahydro-2*H*-pyran-3-ol



[0812] The title compound was prepared from starting material (3*R*,4*S*)-4-aminooxan-3-ol hydrochloride using a procedure analogous to Example 381. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.26 (t, *J*=7.59 Hz, 3 H), 1.55 - 1.70 (m, 1 H), 2.26 - 2.50 (m, 3 H), 2.58 - 2.69 (m, 2 H), 3.25 - 3.31 (m, 1 H), 3.52 - 3.67 (m, 2 H), 3.77 (dd, *J*=10.10, 0.69 Hz, 1 H), 3.89 - 4.05 (m, 3

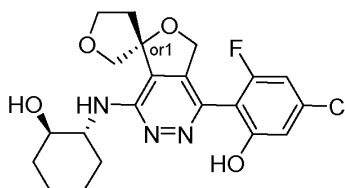
H), 4.15 - 4.39 (m, 3 H), 4.91 - 5.03 (m, 2 H), 6.56 - 6.62 (m, 1 H), 6.62 - 6.67 (m, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{22}H_{26}FN_3O_5$ 431.2, found 432.4.

[0813] EXAMPLE 415: (3*S*,4*R*)-4-(((3*R**)-1'-(4-chloro-2-fluoro-6-hydroxyphenyl)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-4'-yl)amino)tetrahydro-2*H*-pyran-3-ol



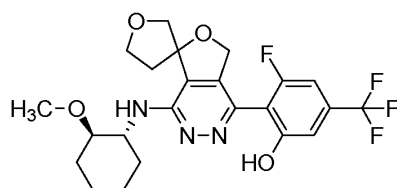
[0814] The title compound was prepared from starting material (3*R*,4*S*)-4-aminooxan-3-ol hydrochloride using a procedure analogous to Example 381. 1H NMR (400 MHz, CD_3OD) δ ppm 1.56 - 1.69 (m, 1 H), 2.26 - 2.35 (m, 1 H), 2.37 - 2.50 (m, 2 H), 3.24 - 3.31 (m, 1 H), 3.52 - 3.66 (m, 2 H), 3.77 (d, $J=10.04$ Hz, 1 H), 3.88 - 3.96 (m, 1 H), 3.96 - 4.06 (m, 2 H), 4.16 - 4.28 (m, 2 H), 4.31 - 4.41 (m, 1 H), 4.91 - 5.03 (m, 2 H), 6.78 - 6.84 (m, 2 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{20}H_{21}ClFN_3O_5$ 437.1; found 438.3.

[0815] EXAMPLE 416: 5-chloro-3-fluoro-2-(((3*R**)-4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)phenol

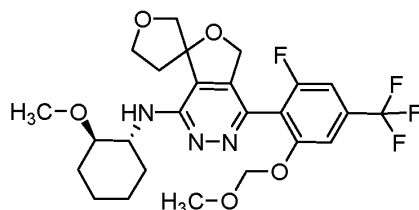


[0816] The title compound was prepared from starting material (1*R*,2*R*)-2-aminocyclohexan-1-ol using a procedure analogous to Example 381. 1H NMR (400 MHz, CD_3OD) δ ppm 1.22 - 1.52 (m, 4 H), 1.68 - 1.85 (m, 2 H), 1.98 - 2.11 (m, 1 H), 2.24 - 2.34 (m, 2 H), 2.35 - 2.49 (m, 1 H), 3.41 - 3.55 (m, 1 H), 3.75 (d, $J=10.04$ Hz, 1 H), 3.91 - 4.05 (m, 2 H), 4.21 (d, $J=10.04$ Hz, 1 H), 4.29 - 4.41 (m, 1 H), 4.88 - 5.06 (m, 2 H), 6.67 - 6.75 (m, 1 H), 6.77 - 6.84 (m, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{21}H_{23}ClFN_3O_4$ 435.1; found 436.3.

[0817] EXAMPLE 417: 3-fluoro-2-((4'-(((1*R*,2*R*)-2-methoxycyclohexyl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



[0818] STEP 1: 1'-(2-fluoro-6-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-N-((1R,2R)-2-methoxycyclohexyl)-4,5-dihydro-2H,7'H-spiro[furan-3,5'-furo[3,4-d]pyridazin]-4'-amine

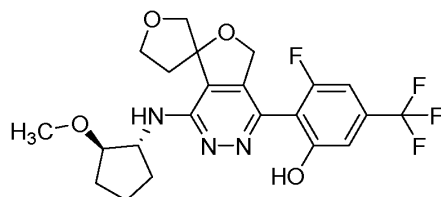


[0819] A mixture of 4'-chloro-1'-(2-fluoro-6-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-4,5-dihydro-2H,7'H-spiro[furan-3,5'-furo[3,4-d]pyridazine] (40 mg, 0.0920 mmol), *trans*-(1R,2R)-2-methoxycyclohexanamine hydrochloride (23 mg, 0.14 mmol), Cs₂CO₃ (105 mg, 0.322 mmol), *rac*-BINAP Pd G3 (9.3 mg, 0.0092 mmol), and toluene (1 mL) was heated at 100°C for 6 hours. The mixture was diluted with DMSO (1 mL), filtered, and purified by HPLC (Gemini 30 mm x 150 mm column) using a gradient of 10-100% ACN (0.035% TFA) in water (0.05% TFA) to give the title compound (12.3 mg, 25.3%). ESI-MS [M+H]⁺ calc'd for C₂₅H₂₉F₄N₃O₅, 527.2; found, 528.20.

[0820] STEP 2: 3-fluoro-2-(4'-(((1R,2R)-2-methoxycyclohexyl)amino)-4,5-dihydro-2H,7'H-spiro[furan-3,5'-furo[3,4-d]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol

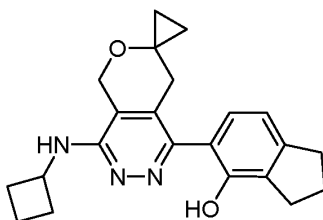
[0821] To a solution 1'-(2-fluoro-6-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-N-((1R,2R)-2-methoxycyclohexyl)-4,5-dihydro-2H,7'H-spiro[furan-3,5'-furo[3,4-d]pyridazin]-4'-amine (12.3 mg, 23 μmol) in DCM (0.8 mL) was added TFA (0.2 mL). The mixture was stirred at 25°C for 2 hours. LC-MS showed starting material was consumed completely and one main peak with desired mass. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by preparative HPLC (Gemini 30 mm x150 mm column) using a gradient of 10-90% ACN (0.035% TFA) in water (0.05% TFA) to give the title compound (6.0 mg, 52.2%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.28 - 1.51 (m, 4 H), 1.76 - 1.88 (m, 2 H), 2.19 - 2.34 (m, 2 H), 2.36 - 2.50 (m, 2 H), 3.21 - 3.29 (m, 1 H), 3.39 (d, *J*=4.14 Hz, 3 H), 3.77 - 3.90 (m, 2 H), 4.07 (q, *J*=9.16 Hz, 1 H), 4.29 - 4.40 (m, 2 H), 5.06 - 5.18 (m, 2 H), 7.09 (s, 1 H), 7.13 (d, *J*=9.28 Hz, 1 H); ESI-MS [M+H]⁺ calc'd for C₂₃H₂₅F₄N₃O₄, 483.2; found, 484.2.

[0822] EXAMPLE 418: 3-fluoro-2-(4'-(((1*R*,2*R*)-2-methoxycyclopentyl)amino)-4,5-dihydro-2*H*,7*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



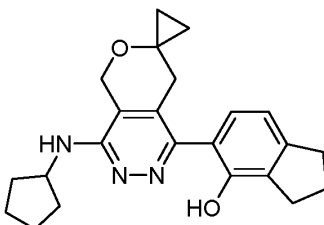
[0823] Using a procedure analogous to Example 417, the title compound was obtained as a light-yellow film (5.5 mg, 13%). ESI-MS $[M+H]^+$ calc'd for $C_{22}H_{23}F_4N_3O_4$, 469.2; found, 470.2.

[0824] EXAMPLE 419: 5-(4'-(cyclobutylamino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-2,3-dihydro-1*H*-inden-4-ol



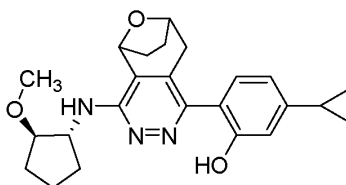
[0825] Using a procedure analogous to Example 417, the title compound was obtained as a yellow solid (2.9 mg, 29%). ESI-MS $[M+H]^+$ calc'd for $C_{22}H_{23}N_3O_2$, 363.2; found, 364.2.

[0826] EXAMPLE 420: 5-(4'-(cyclopentylamino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-2,3-dihydro-1*H*-inden-4-ol



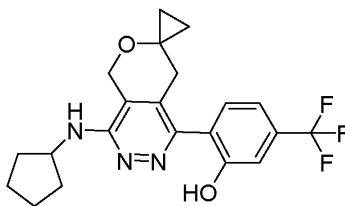
[0827] Using a procedure analogous to Example 417, the title compound was obtained as an orange solid (2.4 mg, 24%). 1H NMR (400 MHz, CD_3OD) δ ppm 0.54 - 0.60 (m, 2 H), 0.90 - 0.96 (m, 2 H), 1.64 - 1.76 (m, 4 H), 1.76 - 1.90 (m, 2 H), 2.08 - 2.23 (m, 4 H), 2.73 (s, 2 H), 2.90 (t, $J=7.40$ Hz, 2 H), 2.97 (t, $J=7.53$ Hz, 2 H), 4.25 - 4.34 (m, 1 H), 4.69 (s, 2 H), 6.93 (d, $J=7.65$ Hz, 1 H), 7.08 (d, $J=7.53$ Hz, 1 H); ESI-MS $[M+H]^+$ calc'd for $C_{23}H_{27}N_3O_2$, 377.2; found, 378.2.

[0828] EXAMPLE 421: 5-cyclopropyl-2-(4'-(((1*R*,2*R*)-2-methoxycyclopentyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol



[0829] The title compound was prepared using a procedure analogous to Example 268 under 0.1 mmol scale. The crude product was purified by preparative HPLC (Phenomenex Gemini® C18 column) using a gradient of 10 to 100% ACN in water (10 mM NH_4HCO_3 , pH=9.5-10). The title compound was obtained as a yellow oil (5.0 mg, 12%). ^1H NMR (400 MHz, CD_3OD) δ ppm 0.67 (dd, $J=4.89, 1.88$ Hz, 2 H), 0.96 (br d, $J=6.53$ Hz, 2 H), 1.30 - 1.35 (m, 1 H), 1.54 - 1.63 (m, 1 H), 1.64 - 1.71 (m, 2 H), 1.73 - 1.82 (m, 2 H), 1.83 - 1.90 (m, 1 H), 1.95 - 1.99 (m, 1 H), 2.15 - 2.30 (m, 4 H), 2.97 - 3.06 (m, 1 H), 3.34 (s, 3 H), 3.84 - 3.92 (m, 1 H), 4.47 - 4.54 (m, 1 H), 4.66 - 4.71 (m, 1 H), 5.10 - 5.23 (m, 1 H), 6.59 (d, $J=1.51$ Hz, 1 H), 6.64 - 6.69 (m, 1 H), 7.04 (d, $J=7.78$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_3$ 407.2; found 408.2.

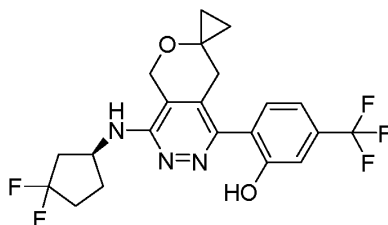
[0830] EXAMPLE 422: 2-(4'-(cyclopentylamino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



[0831] To a 5 mL vial fitted with a stir bar were added R-BINAP (21 mg, 0.0336 mmol), cyclopentylamine (29 mg, 0.336 mmol), 2-(4'-chloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol (30 mg, 0.0841 mmol), Cs_2CO_3 (137 mg, 0.420 mmol), and palladium(II) acetate (3.8 mg, 0.0168 mmol) in DMA (3 mL). The vial was flushed with nitrogen and the reaction mixture was heated to 130°C for 30 minutes in a Biotage microwave reactor. The mixture was extracted with EtOAc (2 mL) and brine (1 mL). The organics were separated and concentrated under reduced pressure. The crude material was dissolved in DMF (1 mL) and MeOH (1 mL), filtered, and purified via basic Shimadzu preparative HPLC, which was followed by Shimadzu preparative HPLC using a TFA-containing mobile phase. The title compound was obtained as a TFA salt (1.0 mg, 2.3%). ^1H NMR (400 MHz, CD_3OD) δ ppm 0.52 - 0.63 (m, 2 H), 0.84 - 0.98 (m, 2 H), 1.62 - 1.82 (m, 4 H), 1.82 - 1.91 (m, 2 H), 2.15 - 2.25 (m, 2 H), 2.72 (s, 2 H), 4.14 - 4.31 (m,

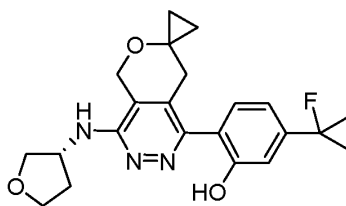
1 H), 4.69 (s, 2 H), 7.22 (s, 1 H), 7.30 (d, $J=8.78$ Hz, 1 H), 7.50 (d, $J=7.78$ Hz, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{21}H_{22}F_3N_3O_2$ 405.2; found 406.1.

[0832] EXAMPLE 423: (*S*)-2-(4'-((3,3-difluorocyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



[0833] To a 5 mL vial fitted with a stir bar were added R-BINAP (21 mg, 0.0336 mmol), (1*S*)-3,3-difluorocyclopentanamine hydrochloride (53 mg, 0.336 mmol), 2-(4'-chloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol (30 mg, 0.0841 mmol), Cs_2CO_3 (137 mg, 0.420 mmol), and palladium(II) acetate (3.8 mg, 0.0168 mmol) in DMA (3 mL). The vial was flushed with nitrogen and the reaction mixture was heated to 130°C in a Biotage microwave reactor for 30 minutes. The mixture was extracted with EtOAc (2 mL) and brine (1 mL). The organics were separated and concentrated. The crude material was dissolved in MeOH (2 mL) and DMF (0.3 mL), filtered, and purified via basic Shimadzu preparative HPLC to give the title compound (2.2 mg, 5.93%). 1H NMR (400 MHz, CD_3OD) δ ppm 0.44 - 0.56 (m, 2 H), 0.81 - 0.94 (m, 2 H), 1.80 - 1.97 (m, 1 H), 2.07 - 2.23 (m, 2 H), 2.23 - 2.45 (m, 2 H), 2.61 (s, 2 H), 2.65 - 2.81 (m, 1 H), 4.57 (s, 2 H), 4.65 - 4.77 (m, 1 H), 7.12 - 7.20 (m, 1 H), 7.22 (dd, $J=7.78$, 1.00 Hz, 1 H), 7.41 (d, $J=8.03$ Hz, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{21}H_{20}F_5N_3O_2$ 441.2; found 442.1.

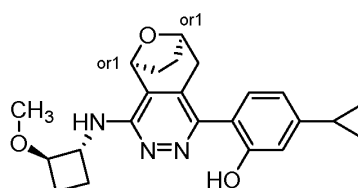
[0834] EXAMPLE 424: (*R*)-5-(1-fluorocyclopropyl)-2-(4'-((tetrahydrofuran-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol



[0835] To a 5 mL vial were added (*R*)-1'-chloro-*N*-(tetrahydrofuran-3-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-amine (30 mg, 0.106 mmol), 2-(4-(1-fluorocyclopropyl)-2-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (34 mg, 0.106 mmol), XPhos Palladacycle G4 (9.2 mg, 0.0106 mmol), and tripotassium phosphate (45 mg, 0.213 mmol) in THF (2 mL) and water (0.5 mL). The vial

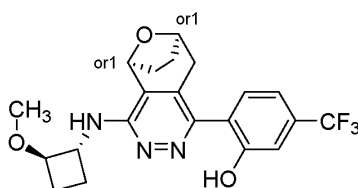
was flushed with nitrogen and the reaction mixture was heated at 70°C for 3 hours. The mixture was allowed to cool to room temperature and extracted with EtOAc (2 mL) and brine (2 mL). The organics were concentrated, dissolved in DCM (2 mL) and trifluoroacetic acid (0.25 mL, 3.19 mmol), and allowed to stir at room temperature for 4 hours. The solution was concentrated and extracted with saturated aq NaHCO₃ (2 mL) and EtOAc (2 mL). The organics were concentrated via rotary evaporation, dissolved in MeOH (1 mL) and DMF (1 mL), and purified by basic preparative HPLC to give the title compound (5.4 mg, 13%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.44 - 0.58 (m, 2 H), 0.83 - 0.95 (m, 2 H), 1.05 - 1.16 (m, 2 H), 1.37 - 1.53 (m, 2 H), 2.03 - 2.06 (m, 1 H), 2.37 (dd, *J*=12.80, 6.78 Hz, 1 H), 2.63 (s, 2 H), 3.69 - 3.91 (m, 2 H), 3.96 - 4.14 (m, 2 H), 4.58 (s, 2 H), 4.69 - 4.79 (m, 1 H), 6.79 (dd, *J*=8.03, 1.25 Hz, 1 H), 6.86 (d, *J*=1.51 Hz, 1 H), 7.22 (d, *J*=7.78 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₂H₂₄N₃O₃ 397.2; found 398.1.

[0836] EXAMPLE 425: 5-cyclopropyl-2-((5*S**,8*R**)-4-(((1*R*,2*R*)-2-methoxycyclobutyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol



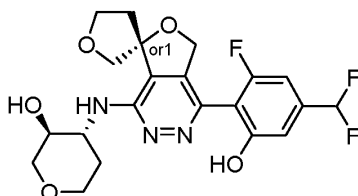
[0837] The title compound was prepared using a procedure analogous to Example 268 under 0.1 mmol scale. The crude product was first purified by preparative HPLC (Phenomenex Gemini® C18 column) using a 10 to 100% gradient of ACN in water (10 mM NH₄HCO₃, pH=9.5-10) to give a mixture of stereoisomers. The diastereomers were purified via preparative SFC (Waters, ChiralTech IC column-5 μm, 21 mm x 150 mm) using a gradient of 35 to 50% MeOH (with 0.1% NH₄OH) in CO₂. The title compound was obtained as a light-yellow semi-solid (7.0 mg, 18%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.67 (dd, *J*=5.02, 2.01 Hz, 2 H), 0.96 (br d, *J*=6.53 Hz, 2 H), 1.43 - 1.72 (m, 3 H), 1.83 - 1.91 (m, 1 H), 1.97 - 2.05 (m, 1 H), 2.20 (br d, *J*=17.82 Hz, 5 H), 2.98 - 3.06 (m, 1 H), 3.33 (s, 3 H), 3.92 - 4.03 (m, 1 H), 4.53 - 4.63 (m, 1 H), 4.65 - 4.72 (m, 1 H), 5.19 (d, *J*=6.27 Hz, 1 H), 6.59 (d, *J*=1.76 Hz, 1 H), 6.65 (dd, *J*=7.78, 1.76 Hz, 1 H), 7.04 (d, *J*=7.78 Hz, 1 H). ESI-MS *m/z* [M+H]⁺ calc'd for C₂₃H₂₇N₃O₃ 393.2; found 394.2.

[0838] EXAMPLE 426: 2-((5*S**,8*R**)-4-(((1*R*,2*R*)-2-methoxycyclobutyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol



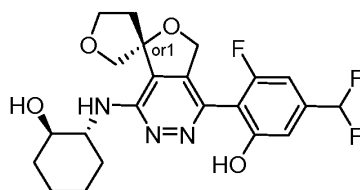
[0839] The title compound was prepared using a procedure analogous to Example 268 under 0.1 mmol scale. The crude product was first purified by preparative HPLC (Phenomenex Gemini® C18 column) using a 10 to 100% gradient of ACN in water (10 mM NH_4HCO_3 , pH=9.5-10) to give a mixture of stereoisomers. The diastereomers were purified via preparative SFC (Waters, ChiralTech IC column-5 μm , 21 mm x 150 mm) using a gradient of 25 to 50% MeOH (with 0.1% NH_4OH) in CO_2 . The title compound was obtained as a light-yellow semi-solid (2.5 mg, 6%). ^1H NMR (400 MHz, CD_3OD) δ ppm 1.47 - 1.56 (m, 1 H), 1.58 - 1.65 (m, 1 H), 1.68 - 1.76 (m, 1 H), 2.02 - 2.05 (m, 1 H), 2.20 (br d, $J=17.82$ Hz, 5 H), 2.98 - 3.10 (m, 1 H), 3.35 - 3.36 (m, 3 H), 3.98 - 4.06 (m, 1 H), 4.62 - 4.66 (m, 1 H), 4.70 - 4.73 (m, 1 H), 5.23 (d, $J=5.77$ Hz, 1 H), 7.18 (s, 1 H), 7.23 (dd, $J=7.78, 0.75$ Hz, 1 H), 7.39 (d, $J=8.03$ Hz, 1 H). ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{21}\text{H}_{22}\text{F}_3\text{N}_3\text{O}_3$ 421.2; found 422.2.

[0840] EXAMPLE 427: (3S,4R)-4-(((3R*)-1'-(4-(difluoromethyl)-2-fluoro-6-hydroxyphenyl)-4,5-dihydro-2H,7'H-spiro[furan-3,5'-furo[3,4-d]pyridazin]-4'-yl)amino)tetrahydro-2H-pyran-3-ol



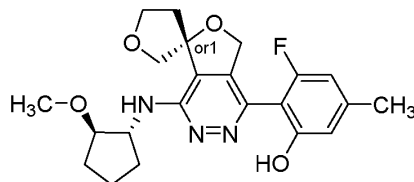
[0841] The title compound was prepared from starting material (3R,4S)-4-aminooxan-3-ol hydrochloride using a procedure analogous to Example 381. ^1H NMR (400 MHz, CD_3OD) δ ppm 1.55 - 1.72 (m, 1 H), 2.27 - 2.36 (m, 1 H), 2.37 - 2.51 (m, 2 H), 3.24 - 3.30 (m, 1 H), 3.53 - 3.67 (m, 2 H), 3.78 (d, $J=10.04$ Hz, 1 H), 3.89 - 3.96 (m, 1 H), 4.00 (s, 2 H), 4.25 (s, 2 H), 4.31 - 4.40 (m, 1 H), 4.98 (d, $J=4.77$ Hz, 2 H), 6.59 - 6.79 (m, 1 H), 6.87 - 6.95 (m, 1 H), 6.95 - 6.98 (m, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{21}\text{H}_{22}\text{F}_3\text{N}_3\text{O}_5$ 453.2 found 454.4.

[0842] EXAMPLE 428: 5-(difluoromethyl)-3-fluoro-2-((3R*)-4'-(((1R,2R)-2-hydroxycyclohexyl)amino)-4,5-dihydro-2H,7'H-spiro[furan-3,5'-furo[3,4-d]pyridazin]-1'-yl)phenol



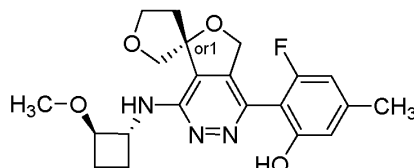
[0843] The title compound was prepared from starting material (1*R*,2*R*)-2-aminocyclohexan-1-ol using a procedure analogous to Example 381. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.36 - 1.56 (m, 4 H), 1.77 - 1.91 (m, 2 H), 2.06 - 2.27 (m, 2 H), 2.37 - 2.61 (m, 2 H), 3.48 - 3.63 (m, 1 H), 3.81 (d, *J*=10.29 Hz, 2 H), 4.02 - 4.14 (m, 1 H), 4.34 - 4.45 (m, 2 H), 5.05 - 5.22 (m, 2 H), 6.62 - 6.84 (m, 1 H), 6.93 - 7.06 (m, 2 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₂H₂₄F₃N₃O₄ 451.2 found 452.4.

[0844] EXAMPLE 429: 3-fluoro-2-((3*R**)-4'-(((1*R*,2*R*)-2-methoxycyclopentyl)amino)-4,5-dihydro-2*H*,7*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol



[0845] The title compound was prepared from starting material (1*R*,2*R*)-2-methoxycyclopentan-1-amine hydrochloride using a procedure analogous to Example 381. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.53 - 1.65 (m, 1 H), 1.68 - 1.90 (m, 3 H), 1.95 - 2.08 (m, 1 H), 2.33 (s, 6 H), 3.46 (s, 3 H), 3.75 (d, *J*=10.04 Hz, 1 H), 3.79 - 3.87 (m, 1 H), 3.94 - 4.05 (m, 1 H), 4.18 - 4.23 (m, 1 H), 4.25 - 4.35 (m, 1 H), 4.51 - 4.58 (m, 1 H), 4.90 - 5.02 (m, 2 H), 6.52 - 6.59 (m, 1 H), 6.60 - 6.63 (m, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₂H₂₆FN₃O₄ 415.2 found 416.4.

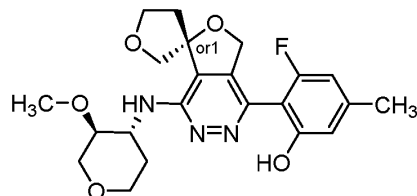
[0846] EXAMPLE 430: 3-fluoro-2-((3*R**)-4'-(((1*R*,2*R*)-2-methoxycyclobutyl)amino)-4,5-dihydro-2*H*,7*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol



[0847] The title compound was prepared from starting material *trans*-(1*R*,2*R*)-2-methoxycyclobutanamine hydrochloride using a procedure analogous to Example 381. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.40 - 1.56 (m, 1 H), 1.59 - 1.72 (m, 1 H), 2.05 (s, 1 H), 2.13 - 2.22 (m, 1 H), 2.33 (s, 6 H), 3.37 (s, 3 H), 3.79 (s, 1 H), 3.86 - 3.93 (m, 1 H), 3.98 -

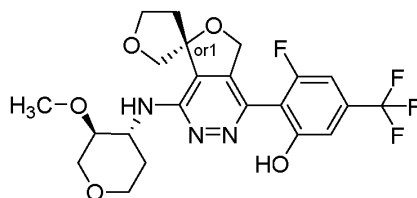
4.07 (m, 1 H), 4.19 - 4.25 (m, 1 H), 4.29 - 4.38 (m, 1 H), 4.58 - 4.69 (m, 1 H), 4.94 (s, 2 H), 6.52 - 6.59 (m, 1 H), 6.60 - 6.63 (m, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{21}H_{24}FN_3O_4$ 401.2 found 402.4.

[0848] EXAMPLE 431: 3-fluoro-2-((3*R**)-4'-(((3*S*,4*R*)-3-methoxytetrahydro-2*H*-pyran-4-yl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol



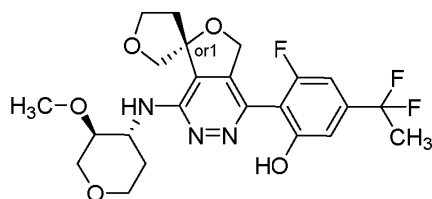
[0849] The title compound was prepared from starting material (3*S*,4*R*)-3-methoxytetrahydro-2*H*-pyran-4-amine using a procedure analogous to Example 381. 1H NMR (400 MHz, CD_3OD) δ ppm 1.54 - 1.65 (m, 1 H), 2.31 (s, 5 H), 2.40 - 2.51 (m, 1 H), 3.33 - 3.41 (m, 2 H), 3.47 (s, 3 H), 3.53 - 3.63 (m, 1 H), 3.75 (d, $J=10.16$ Hz, 1 H), 3.81 - 3.89 (m, 1 H), 3.95 - 4.05 (m, 1 H), 4.05 - 4.14 (m, 1 H), 4.21 - 4.26 (m, 1 H), 4.27 - 4.35 (m, 2 H), 4.89 - 5.01 (m, 2 H), 6.50 - 6.57 (m, 1 H), 6.57 - 6.62 (m, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{22}H_{26}FN_3O_5$ 431.2 found 432.4.

[0850] EXAMPLE 432: 3-fluoro-2-((3*R**)-4'-(((3*S*,4*R*)-3-methoxytetrahydro-2*H*-pyran-4-yl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



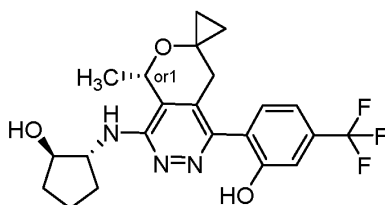
[0851] The title compound was prepared from starting material (3*S*,4*R*)-3-methoxytetrahydro-2*H*-pyran-4-amine using a procedure analogous to Example 381. 1H NMR (400 MHz, CD_3OD) δ ppm 1.55 - 1.67 (m, 1 H), 2.28 - 2.50 (m, 3 H), 3.32 - 3.41 (m, 2 H), 3.48 (s, 3 H), 3.54 - 3.64 (m, 1 H), 3.74 - 3.80 (m, 1 H), 3.81 - 3.90 (m, 1 H), 3.97 - 4.05 (m, 1 H), 4.07 - 4.15 (m, 1 H), 4.21 - 4.28 (m, 1 H), 4.29 - 4.37 (m, 2 H), 4.91 - 5.02 (m, 2 H), 6.98 - 7.09 (m, 2 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{22}H_{23}F_4N_3O_5$ 485.2 found 486.4.

[0852] EXAMPLE 433: 5-(1,1-difluoroethyl)-3-fluoro-2-((3*R**)-4'-(((3*S*,4*R*)-3-methoxytetrahydro-2*H*-pyran-4-yl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)phenol



[0853] The title compound was prepared from starting material (3*S*,4*R*)-3-methoxytetrahydro-2*H*-pyran-4-amine using a procedure analogous to Example 381. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.53 - 1.68 (m, 1 H), 1.91 (t, *J*=18.32 Hz, 3 H), 2.28 - 2.40 (m, 2 H), 2.40 - 2.51 (m, 1 H), 3.34 - 3.42 (m, 2 H), 3.47 (d, *J*=5.27 Hz, 3 H), 3.52 - 3.66 (m, 1 H), 3.72 - 3.80 (m, 1 H), 3.82 - 3.91 (m, 1 H), 3.96 - 4.05 (m, 1 H), 4.06 - 4.15 (m, 1 H), 4.21 - 4.28 (m, 1 H), 4.28 - 4.38 (m, 2 H), 4.90 - 5.04 (m, 2 H), 6.84 - 6.91 (m, 1 H), 6.91 - 6.95 (m, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₃H₂₆F₃N₃O₅ 481.2 found 482.4.

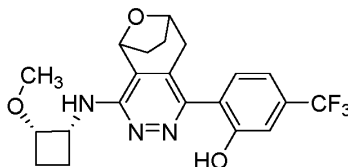
[0854] EXAMPLE 434: 2-((*R*^{*})-4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol



[0855] To a 5 mL vial fitted with a stir bar were added *rel*-(*R*)-4'-chloro-1'-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (66 mg, 0.159 mmol), (1*R*,2*R*)-2-aminocyclopentan-1-ol hydrochloride (66 mg, 0.477 mmol), Cs₂CO₃ (207 mg, 0.636 mmol), and [3-(2-aminophenyl)phenyl]-methylsulfonyloxy-palladium;[1-(2-diphenylphosphanyl)-1-naphthyl]-2-naphthyl]-diphenyl-phosphane (32 mg, 0.0318 mmol) in 1,4-dioxane (2 mL). The vial was flushed with nitrogen and the reaction mixture was heated to 100°C for 2 hours. The reaction was allowed to cool to room temperature and extracted with EtOAc (2 mL) and brine (1 mL). The organics were separated and concentrated. The crude material was dissolved in DCM (2 mL) and TFA (0.37 mL, 4.77 mmol) and allowed to stir at room temperature for 4 hours. The reaction mixture was concentrated and extracted with EtOAc (2 x 5 mL) and saturated aq NaHCO₃ (5 mL). The organics were concentrated and dissolved in DMF (1 mL) and MeOH (2 mL), filtered, and purified via basic Shimadzu preparative HPLC to give the title compound (4.4 mg, 6.4%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.13 - 0.37 (m, 1 H), 0.63 (m, 1 H), 0.68 - 0.82 (m, 1 H), 0.90 - 1.04 (m, 1 H), 1.54 (d, *J*=6.53 Hz, 3 H), 1.62 - 1.77 (m,

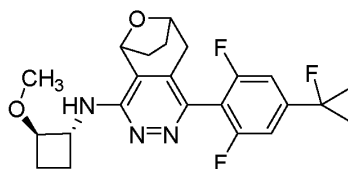
2 H), 1.77 - 1.93 (m, 2 H), 1.99 - 2.13 (m, 1 H), 2.16 - 2.35 (m, 2 H), 2.98 (d, $J=17.57$ Hz, 1 H), 4.03 - 4.21 (m, 2 H), 4.93 - 5.06 (m, 1 H), 7.16 (s, 1 H), 7.23 (d, $J=7.60$ Hz, 1 H), 7.41 (d, $J=8.03$ Hz, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{22}H_{24}F_3N_3O_3$ 435.2; found 436.1.

[0856] EXAMPLE 435: 2-(4-(((1*R*,2*S*)-2-methoxycyclobutyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol



[0857] The title compound was prepared using a procedure analogous to Example 268 under 0.1 mmol scale. The crude product was purified by preparative HPLC (Phenomenex Gemini® C18 column) using a gradient of 10 to 100% ACN in water (10 mM NH_4HCO_3 , pH=9.5-10). The title compound was obtained as a light-yellow semi-solid (14.0 mg, 33%). 1H NMR (400 MHz, CD_3OD) δ ppm 1.63 - 1.79 (m, 1 H), 1.99 - 2.33 (m, 8 H), 2.98 - 3.11 (m, 1 H), 3.29 - 3.32 (m, 3 H), 4.13 - 4.21 (m, 1 H), 4.67 - 4.72 (m, 1 H), 4.72 - 4.80 (m, 1 H), 5.16 - 5.24 (m, 1 H), 7.16 (s, 1 H), 7.18 - 7.24 (m, 1 H), 7.35 (s, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{21}H_{22}F_3N_3O_3$ 421.2; found 422.2.

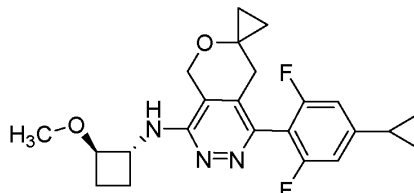
[0858] EXAMPLE 436: 1-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-*N*-(((1*R*,2*R*)-2-methoxycyclobutyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-amine



[0859] A mixture of $Pd_2(dba)_3$ (7.5 mg, 0.00818 mmol), Cs_2CO_3 (107 mg, 0.327 mmol), R-BINAP (0.010 mL, 0.0164 mmol), *trans*-(1*R*,2*R*)-2-methoxycyclobutanamine hydrochloride (23 mg, 0.164 mmol) and 4-chloro-1-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine (30 mg, 0.0818 mmol) in DMF (7.4 mL) was stirred in an oil bath at 100°C for 16 hours under nitrogen. The reaction mixture was concentrated and 3 mL of MeOH was added to dissolve the mixture. The resulting suspension was filtered using a syringe filter and the filtrate was purified by preparative HPLC (Phenomenex Gemini® C18 column) using a gradient of 10 to 100% ACN in water (10 mM NH_4HCO_3 , pH=9.5-10). The title compound was obtained as an orange semi-solid (16.0 mg, 45%). 1H NMR (400 MHz, CD_3OD) δ ppm 1.19 - 1.28 (m, 2 H), 1.44 - 1.71 (m, 5 H), 1.97 -

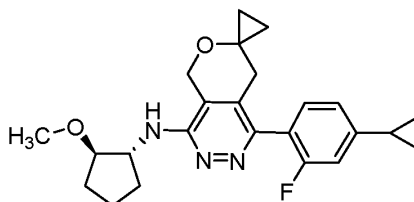
2.03 (m, 1 H), 2.03 - 2.32 (m, 5 H), 2.81 - 2.95 (m, 1 H), 3.34 (s, 3 H), 3.94 - 4.05 (m, 1 H), 4.63 (s, 1 H), 4.70 (s, 1 H), 5.20 (s, 1 H), 6.96 - 7.05 (m, 2 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{23}H_{24}F_3N_3O_2$ 431.2; found 432.2.

[0860] EXAMPLE 437: 1'-(4-cyclopropyl-2,6-difluorophenyl)-*N*-((1*R*,2*R*)-2-methoxycyclobutyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-amine



[0861] To a 5 mL vial fitted with a stir bar were added R-BINAP (39 mg, 0.0619 mmol), a mixture of 4'-chloro-1'-(4-cyclopropyl-2,6-difluorophenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] and 1'-chloro-4'-(4-cyclopropyl-2,6-difluorophenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (54 mg, 0.0774 mmol), Cs_2CO_3 (252 mg, 0.774 mmol), and palladium(II) acetate (7.0 mg, 0.0310 mmol) in DMA (2 mL). The vial was flushed with nitrogen and the reaction mixture was heated in a Biotage microwave reactor at 130°C for 30 minutes. The mixture was extracted with EtOAc (5 mL) and brine (5 mL). The organics were separated and dried with $MgSO_4$. The solution was concentrated and purified via flash chromatography (amine column) using a gradient of 10 to 50% EtOAc in heptane. The mixture was separated via SFC to give the title compound as the second eluting peak (3.6 mg, 5.6%). 1H NMR (400 MHz, CD_3OD) δ ppm 0.44 - 0.53 (m, 2 H), 0.70 - 0.81 (m, 2 H), 0.82 - 0.90 (m, 2 H), 0.99 - 1.11 (m, 2 H), 1.41 - 1.62 (m, 2 H), 1.94 - 2.01 (m, 1 H), 2.07 - 2.15 (m, 1 H), 2.20 - 2.30 (m, 1 H), 2.37 - 2.48 (m, 2 H), 3.32 (s, 3 H), 3.91 - 3.99 (m, 1 H), 4.48 - 4.64 (m, 3 H), 6.80 (d, $J=9.03$ Hz, 2 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{23}H_{25}F_2N_3O_2$ 413.2; found 414.2.

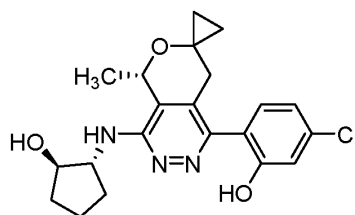
[0862] EXAMPLE 438: 1'-(4-cyclopropyl-2-fluorophenyl)-*N*-((1*R*,2*R*)-2-methoxycyclopentyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-amine



[0863] To a 20 mL vial fitted with a stir bar were added R-BINAP (45 mg, 0.0726 mmol), a mixture of 4'-chloro-1'-(4-cyclopropyl-2-fluorophenyl)-5',8'-dihydrospiro[cyclopropane-

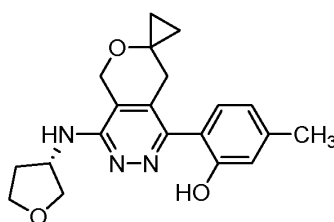
1,7'-pyrano[3,4-*d*]pyridazine] and 1'-chloro-4'-(4-cyclopropyl-2-fluorophenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (60 mg, 0.0907 mmol), Cs₂CO₃ (295 mg, 0.907 mmol), and palladium(II) acetate (8.1 mg, 0.0363 mmol) in DMA (1.1716 mL). The vial was flushed with nitrogen and the reaction mixture was heated in a Biotage microwave reactor at 130°C for 30 minutes. The reaction was extracted with EtOAc (2 x 5 mL) and brine (5 mL). The organics were dried with MgSO₄, filtered, concentrated. The crude material was purified via flash chromatography (amine column) using a gradient of 10 to 50% EtOAc in heptane. Both isomers were isolated as a single peak. The mixture was purified via SFC to give the title compound as the second eluting peak (2.3 mg, 6.2%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.44 - 0.55 (m, 2 H), 0.72 - 0.81 (m, 2 H), 0.84 - 0.93 (m, 2 H), 0.99 - 1.12 (m, 2 H), 1.54 - 1.72 (m, 2 H), 1.73 - 1.84 (m, 2 H), 1.93 - 2.08 (m, 2 H), 2.19 - 2.36 (m, 1 H), 2.51 (br s, 2 H), 3.42 (s, 3 H), 3.87 (dt, *J*=6.34, 4.11 Hz, 1 H), 4.48 - 4.60 (m, 3 H), 6.91 (dd, *J*=11.29, 1.51 Hz, 1 H), 7.03 (dd, *J*=7.91, 1.63 Hz, 1 H), 7.27 (t, *J*=7.91 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₄H₂₈FN₃O₂ 409.2; found 410.2.

[0864] EXAMPLE 439: 5-chloro-2-((*S**)-4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol



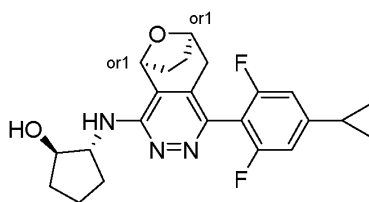
[0865] The title compound is obtained like Example 395.

[0866] EXAMPLE 440: (*S*)-5-methyl-2-(4'-(((tetrahydrofuran-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol



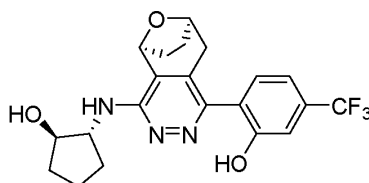
[0867] The title compound was prepared using a procedure analogous to Example 313. ESI-MS [M+H]⁺ calc'd for C₂₀H₂₃N₃O₃, 353.2; found, 354.1.

[0868] EXAMPLE 441: (1*R*,2*R*)-2-(((5*S**,8*R**)-1-(4-cyclopropyl-2,6-difluorophenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclopentan-1-ol

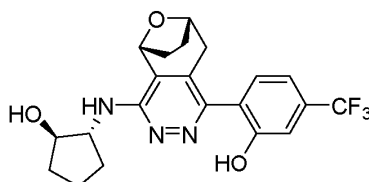


[0869] The title compound was prepared like Example 343 and was obtained as a colorless oil (TFA salt, 20.0 mg, 38%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.82 - 0.88 (m, 2 H), 1.14 (dd, *J*=8.28, 2.01 Hz, 2 H), 1.70 - 1.81 (m, 2 H), 1.88 (br d, *J*=0.75 Hz, 3 H), 2.02 - 2.10 (m, 1 H), 2.12 - 2.20 (m, 1 H), 2.26 (br d, *J*=18.57 Hz, 5 H), 2.97 - 3.07 (m, 1 H), 4.03 - 4.12 (m, 1 H), 4.27 (d, *J*=6.78 Hz, 1 H), 4.73 - 4.83 (m, 1 H), 5.39 (br s, 1 H), 6.93 (s, 1 H), 6.94 (s, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₃H₂₅F₂N₃O₂ 413.2; found 414.2.

[0870] EXAMPLE 442: 2-((5*S*,8*R*)-4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol



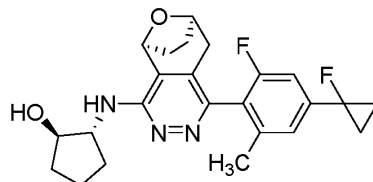
[0871] EXAMPLE 443: 2-((5*R*,8*S*)-4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol



[0872] The title compounds were prepared using a procedure analogous to Example 342 and Example 343 under 0.1 mmol scale. The title compound of Example 442 was obtained as a light-yellow solid (TFA salt, 37.0 mg, 69%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.69 - 1.93 (m, 5 H), 2.09 - 2.18 (m, 1 H), 2.32 (s, 5 H), 3.08 - 3.17 (m, 1 H), 4.05 - 4.13 (m, 1 H), 4.26 (s, 1 H), 4.74 - 4.80 (m, 1 H), 5.37 - 5.43 (m, 1 H), 7.25 (s, 1 H), 7.30 (dd, *J*=7.91, 0.88 Hz, 1 H), 7.47 (d, *J*=7.78 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₁H₂₂F₃N₃O₃ 421.2; found 422.2. The title compound Example 443 was obtained as a light-yellow semi-solid (TFA salt, 37.0 mg, 69%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.68 - 1.95 (m, 5 H), 2.08 - 2.22 (m, 2 H), 2.24 - 2.38 (m, 4 H), 3.08 - 3.18 (m, 1 H), 4.04 - 4.14 (m, 1 H), 4.27 (s, 1 H),

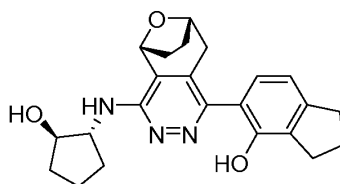
4.74 - 4.80 (m, 1 H), 5.36 - 5.43 (m, 1 H), 7.25 (s, 1 H), 7.31 (d, $J=1.00$ Hz, 1 H), 7.47 (d, $J=7.78$ Hz, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{21}H_{22}F_3N_3O_3$ 421.2; found 422.2.

[0873] EXAMPLE 444: (1*R*,2*R*)-2-(((5*S*,8*R*)-1-(2-fluoro-4-(1-fluorocyclopropyl)-6-methylphenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclopentan-1-ol

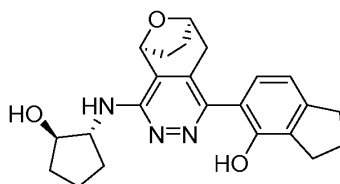


[0874] Using a procedure analogous to Example 364 under 0.1 mmol scale, the title compound was obtained as an orange oil (4.0 mg, 9%). 1H NMR (400 MHz, CD_3OD) δ ppm 1.20 (dt, $J=9.03$, 1.51 Hz, 2 H), 1.48 - 1.60 (m, 2 H), 1.62 - 1.95 (m, 6 H), 2.10 (d, $J=8.03$ Hz, 5 H), 2.25 (br d, $J=2.76$ Hz, 3 H), 2.69 - 2.94 (m, 1 H), 4.12 (s, 1 H), 4.18 - 4.26 (m, 1 H), 4.67 - 4.76 (m, 1 H), 5.25 (d, $J=5.27$ Hz, 1 H), 6.97 - 7.03 (m, 1 H), 7.03 - 7.08 (m, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{24}H_{27}F_2N_3O_2$ 427.2; found 428.2.

[0875] EXAMPLE 445: 5-((5*R*,8*S*)-4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-2,3-dihydro-1*H*-inden-4-ol



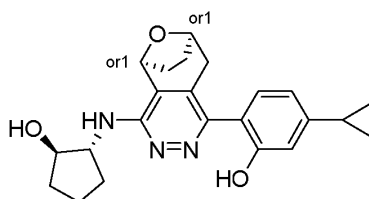
[0876] EXAMPLE 446: 5-((5*S*,8*R*)-4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-2,3-dihydro-1*H*-inden-4-ol



[0877] The title compounds were prepared using a procedure analogous to Example 363 and Example 364 under 0.1 mmol scale. The title compound Example 445 was obtained as a colorless semi-solid (3.5 mg, 9%). 1H NMR (400 MHz, CD_3OD) δ ppm 1.53 - 1.78 (m, 5 H), 1.89 - 2.22 (m, 8 H), 2.78 (s, 2 H), 2.83 (s, 2 H), 2.88 - 2.97 (m, 1 H), 3.92 - 4.13 (m, 2 H), 4.59 (br s, 1 H), 5.10 (d, $J=5.77$ Hz, 1 H), 6.73 (d, $J=7.53$ Hz, 1 H), 6.86 (d, $J=7.78$ Hz, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{23}H_{27}N_3O_3$ 393.2; found 394.2. The title compound of

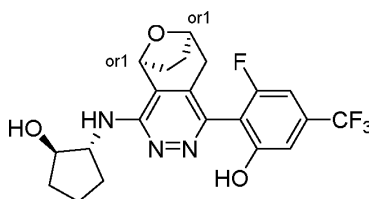
Example 446 was obtained as a colorless semi-solid (17.0 mg, 43%). ^1H NMR (400 MHz, CD_3OD) δ ppm 1.58 (br s, 5 H), 1.93 - 2.19 (m, 8 H), 2.77 (s, 2 H), 2.82 (t, $J=7.40$ Hz, 2 H), 2.87 - 2.98 (m, 1 H), 3.94 (d, $J=7.03$ Hz, 1 H), 4.02 (s, 1 H), 4.57 (br s, 1 H), 5.11 (d, $J=5.77$ Hz, 1 H), 6.72 (d, $J=7.53$ Hz, 1 H), 6.85 (d, $J=7.53$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{23}\text{H}_{27}\text{N}_3\text{O}_3$ 393.2; found 394.2.

[0878] EXAMPLE 447: 5-cyclopropyl-2-((5*S**,8*R**)-4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol



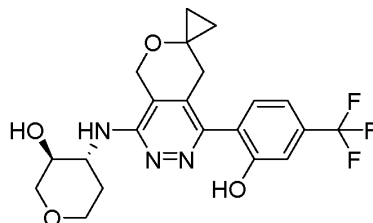
[0879] Using a procedure analogous to Example 364 under 0.1 mmol scale, the title compound was obtained as a brown oil (9.0 mg, 23%). ^1H NMR (400 MHz, CD_3OD) δ ppm 0.66 - 0.73 (m, 2 H), 0.99 (dd, $J=8.53$, 2.01 Hz, 2 H), 1.66 - 1.94 (m, 6 H), 2.01 - 2.05 (m, 1 H), 2.06 - 2.11 (m, 1 H), 2.24 (br d, $J=18.07$ Hz, 4 H), 2.99 - 3.12 (m, 1 H), 4.03 - 4.09 (m, 1 H), 4.11 - 4.18 (m, 1 H), 4.66 - 4.74 (m, 1 H), 5.19 - 5.26 (m, 1 H), 6.62 (d, $J=1.76$ Hz, 1 H), 6.66 - 6.71 (m, 1 H), 7.05 (d, $J=7.78$ Hz, 1 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{23}\text{H}_{27}\text{N}_3\text{O}_3$ 393.2; found 394.2.

[0880] EXAMPLE 448: 3-fluoro-2-((5*S**,8*R**)-4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol



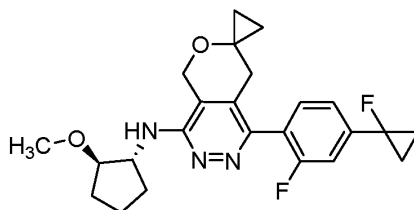
[0881] Using a procedure analogous to Example 364 under 0.1 mmol scale, the title compound was obtained as a light-yellow semi-solid (9.0 mg, 20%). ^1H NMR (400 MHz, CD_3OD) δ ppm 1.56 - 1.77 (m, 5 H), 1.90 - 2.04 (m, 3 H), 2.08 - 2.25 (m, 3 H), 2.74 - 2.89 (m, 1 H), 3.95 - 4.02 (m, 1 H), 4.06 - 4.14 (m, 1 H), 4.57 - 4.62 (m, 1 H), 5.10 - 5.15 (m, 1 H), 6.92 (s, 2 H); ESI-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{21}\text{H}_{21}\text{F}_4\text{N}_3\text{O}_3$ 439.2; found 440.2.

[0882] EXAMPLE 449: (3*S*,4*R*)-4-((1'-(2-hydroxy-4-(trifluoromethyl)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)tetrahydro-2*H*-pyran-3-ol



[0883] To a 5 mL vial fitted with a stir bar were added R-BINAP (21 mg, 0.0336 mmol), (3*R*,4*S*)-4-aminooxan-3-ol hydrochloride (52 mg, 0.336 mmol), 2-(4'-chloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol (30 mg, 0.0841 mmol), Cs₂CO₃ (137 mg, 0.420 mmol), and palladium(II) acetate (3.8 mg, 0.0168 mmol) in DMA (3 mL). The vial was flushed with nitrogen and the reaction mixture was heated to 130°C in a Biotage microwave reactor for 30 minutes. The solution was extracted with EtOAc (2 mL) and brine (1 mL). The organics were separated and concentrated, dissolved in MeOH (2 mL) and DMF (0.3 mL), filtered and purified by Shimadzu preparative HPLC using a TFA-containing mobile phase. The title compound was obtained as a TFA salt (1.8 mg, 3.9%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.55 - 0.66 (m, 2 H), 0.90 - 1.01 (m, 2 H), 1.85 (dd, *J*=12.67, 4.39 Hz, 1 H), 2.00 - 2.12 (m, 1 H), 2.69 - 2.79 (m, 2 H), 3.24 (dd, *J*=11.04, 10.29 Hz, 1 H), 3.49 (td, *J*=12.05, 2.01 Hz, 1 H), 3.72 (td, *J*=9.85, 5.14 Hz, 1 H), 3.93 - 4.15 (m, 3 H), 4.67 - 4.78 (m, 2 H), 7.23 (s, 1 H), 7.31 (dd, *J*=7.91, 0.88 Hz, 1 H), 7.51 (d, *J*=7.78 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₁H₂₂F₃N₃O₄ 437.2; found 438.1.

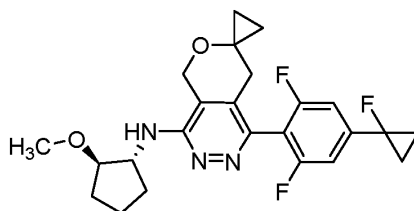
[0884] EXAMPLE 450: 1'-(2-fluoro-4-(1-fluorocyclopropyl)phenyl)-*N*-((1*R*,2*R*)-2-methoxycyclopentyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-amine



[0885] To a 5 mL vial fitted with a stir bar were added 1'-chloro-*N*-((1*R*,2*R*)-2-methoxycyclopentyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-amine (28 mg, 0.0904 mmol), 2-[2-fluoro-4-(1-fluorocyclopropyl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (38 mg, 0.136 mmol), Pd(dppf)Cl₂·CH₂Cl₂ (7.4 mg, 0.00904 mmol), tripotassium hydrogen phosphate (39 mg, 0.181 mmol) in 1,4-dioxane (2 mL) and water (0.5

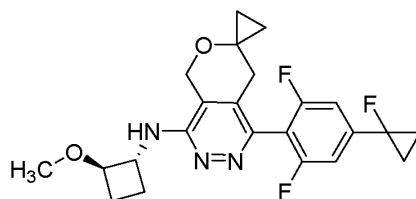
mL). The vial was flushed with nitrogen and the reaction mixture was heated to 80°C with stirring overnight. The mixture was allowed to cool to room temperature and was extracted with EtOAc (5 mL) and brine (5 mL). The organics were separated and concentrated, dissolved in DMF (0.5 mL) and MeOH (1 mL), filtered and purified by Shimadzu preparative HPLC using a TFA-containing mobile phase. The title compound was obtained as a TFA salt (5.2 mg, 11%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.54 - 0.64 (m, 2 H), 0.87 - 0.99 (m, 2 H), 1.16 - 1.27 (m, 2 H), 1.50 - 1.66 (m, 2 H), 1.66 - 1.91 (m, 4 H), 2.07 - 2.15 (m, 1 H), 2.23 - 2.36 (m, 1 H), 2.69 (s, 2 H), 3.41 (s, 3 H), 3.85 - 4.01 (m, 1 H), 4.17 - 4.28 (m, 1 H), 4.71 (s, 2 H), 7.12 - 7.31 (m, 2 H), 7.51 (t, *J*=7.40 Hz, 1 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₄H₂₇F₂N₃O₂ 427.2; found 428.2.

[0886] EXAMPLE 451: 1'-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-*N*-((1*R*,2*R*)-2-methoxycyclopentyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-amine



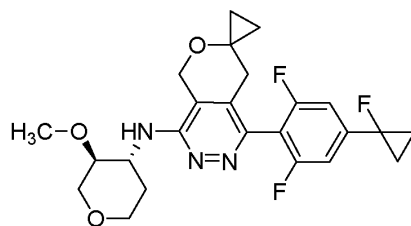
[0887] To a 5 mL vial fitted with a stir bar were added 2-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (16 mg, 0.0531 mmol), 1'-chloro-*N*-((1*R*,2*R*)-2-methoxycyclopentyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-amine 2,2,2-trifluoroacetate (15 mg, 0.0354 mmol), and XPhos Palladacycle G4 (3.0 mg, 0.00354 mmol), in THF (0.5 mL) and K₃PO₄ (0.5M) (1 mL). The vial was flushed with nitrogen and the reaction mixture was heated to 50°C for 4 hours and then allowed to cool to room temperature. The mixture was extracted with EtOAc (5 mL) and brine (5 mL). The organics were separated and concentrated, dissolved in DMF (0.5 mL) and MeOH (1 mL), filtered and purified by Shimadzu preparative HPLC using a TFA-containing mobile phase. The title compound was obtained as a TFA salt (3.2 mg, 16%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.57 - 0.67 (m, 2 H), 0.88 - 1.00 (m, 2 H), 1.19 - 1.36 (m, 2 H), 1.58 - 1.68 (m, 2 H), 1.69 - 1.90 (m, 4 H), 2.08 - 2.20 (m, 1 H), 2.20 - 2.33 (m, 1 H), 2.65 (s, 2 H), 3.41 (s, 3H), 3.87 - 4.04 (m, 1 H), 4.14 - 4.27 (m, 1 H), 4.66 - 4.76 (m, 2 H), 7.10 (d, *J*=8.78 Hz, 2 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₄H₂₆F₃N₃O₂ 445.2; found 446.2.

[0888] EXAMPLE 452: 1'-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-*N*-((1*R*,2*R*)-2-methoxycyclobutyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-amine



[0889] To a 5 mL microwave vial fitted with a stir bar were added 1-chloro-*N*-[(1*R*,2*R*)-2-methoxycyclobutyl]spiro[5,8-dihydropyrano[3,4-*d*]pyridazine-7,1'-cyclopropane]-4-amine (25 mg, 0.0845 mmol), 2-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (38 mg, 0.127 mmol), and XPhos Palladacycle G4 (7.3 mg, 0.00845 mmol) in THF (0.5 mL) and K₃PO₄ (0.5M) (1 mL). The vial was flushed with nitrogen and the reaction mixture was heated to 50°C for 4 hours. The mixture was allowed to cool to room temperature and was extracted with EtOAc (2 mL) and brine (2 mL). The organics were separated and concentrated, dissolved in DMF (0.5 mL) and MeOH (2 mL), filtered and purified by Shimadzu preparative HPLC using a TFA-containing mobile phase. The title compound was obtained as a TFA salt (2.1 mg, 4.6%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.52 - 0.65 (m, 2 H), 0.87 - 1.01 (m, 2 H), 1.18 - 1.35 (m, 2 H), 1.53 - 1.76 (m, 4 H), 2.24 (t, *J*=7.89 Hz, 1 H), 2.36 (t, *J*=7.70 Hz, 1 H), 2.55 - 2.70 (m, 2 H), 3.37 (s, 3 H), 4.07 (q, *J*=7.58 Hz, 1 H), 4.24 - 4.38 (m, 1 H), 4.68 (s, 2 H), 7.09 (d, *J*=8.99 Hz, 2 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₃H₂₄F₃N₃O₂ 431.2; found 432.2.

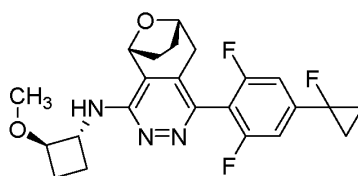
[0890] EXAMPLE 453: 1'-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-*N*-((3*S*,4*R*)-3-methoxytetrahydro-2*H*-pyran-4-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-amine



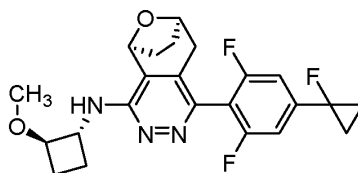
[0891] To a 5 mL vial fitted with a stir bar were added 1'-chloro-*N*-((3*S*,4*R*)-3-methoxytetrahydro-2*H*-pyran-4-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-amine (21 mg, 0.0645 mmol), 2-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (29 mg, 0.0967 mmol), and XPhos Palladacycle G4 (5.5 mg, 0.00645 mmol) in THF (0.4 mL) and K₃PO₄ (0.5M) (0.8 mL). The vial was flushed with nitrogen and the reaction mixture was heated to 50°C for 4 hours. The mixture was allowed to cool to room temperature and was extracted with EtOAc

(2 mL) and brine (2 mL). The organics were separated and concentrated, dissolved in DMF (0.5 mL) and MeOH (2 mL), filtered and purified by Shimadzu preparative HPLC using a TFA-containing mobile phase. The title compound was obtained as a TFA salt of (5.0 mg, 13%). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.56 - 0.68 (m, 2 H), 0.89 - 1.01 (m, 2 H), 1.23 - 1.35 (m, 2 H), 1.57 - 1.70 (m, 2 H), 1.85 - 1.99 (m, 1 H), 2.01 - 2.12 (m, 1 H), 2.66 (s, 2 H), 3.17 - 3.25 (m, 1 H), 3.37 - 3.51 (m, 5 H), 3.99 (dd, $J=11.74$, 4.40 Hz, 1 H), 4.09 (ddd, $J=11.32$, 9.67, 4.68 Hz, 1 H), 4.28 (dd, $J=11.19$, 4.77 Hz, 1 H), 4.72 (s, 2 H), 7.10 (d, $J=9.17$ Hz, 2 H); ESI-MS m/z [M+H]⁺ calc'd for C₂₄H₂₆F₃N₃O₃ 461.2; found 462.2.

[0892] EXAMPLE 454: (5*R*,8*S*)-1-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-*N*-((1*R*,2*R*)-2-methoxycyclobutyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-amine



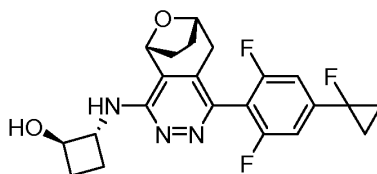
[0893] EXAMPLE 455: (5*S*,8*R*)-1-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-*N*-((1*R*,2*R*)-2-methoxycyclobutyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-amine



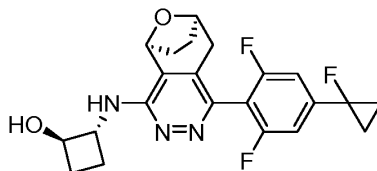
[0894] A mixture of Pd₂(dba)₃ (37 mg, 0.0409 mmol), Cs₂CO₃ (533 mg, 1.64 mmol), R-BINAP (0.051 mL, 0.0818 mmol), *trans*-(1*R*,2*R*)-2-methoxycyclobutanamine hydrochloride (113 mg, 0.818 mmol) and 4-chloro-1-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine (150 mg, 0.409 mmol) in DMF (10 mL) was stirred in an oil bath at 100°C for 16 hours under nitrogen. The reaction mixture was concentrated and dispersed in MeOH (10 mL). The resulting suspension was filtered through a syringe filter and the filtrate was purified by preparative HPLC (basic-ACCQ-prep) using a gradient of 10 to 100% ACN in water (with NH₄HCO₃). The product-containing fractions were collected, concentrated and dried *in vacuo*. The mixture components were separated by preparative SFC (Waters, Phenomenex Cellulose-2 column) using a gradient of 5 to 30% MeOH (modified with 0.1% NH₄OH) in CO₂. The first eluting product was dried *in vacuo* to

give the title compound of Example 454 as a white semi-solid (40.7 mg, 23%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.20 - 1.27 (m, 2 H), 1.46 - 1.69 (m, 5 H), 1.99 - 2.09 (m, 2 H), 2.11 - 2.29 (m, 4 H), 2.84 - 2.93 (m, 1 H), 3.34 (s, 3 H), 3.97 - 4.04 (m, 1 H), 4.60 - 4.68 (m, 1 H), 4.68 - 4.73 (m, 1 H), 5.16 (d, *J*=5.77 Hz, 1 H), 6.98 - 7.03 (m, 2 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₃H₂₄F₃N₃O₂ 431.2; found 432.2. The second eluting product was dried *in vacuo* to give the title compound of Example 455 as a white semi-solid (39.8 mg, 23%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.19 - 1.28 (m, 2 H), 1.47 - 1.68 (m, 5 H), 2.03 (s, 2 H), 2.11 - 2.32 (m, 4 H), 2.84 - 2.92 (m, 1 H), 3.33 (s, 3 H), 4.01 (d, *J*=7.53 Hz, 1 H), 4.57 - 4.65 (m, 1 H), 4.66 - 4.73 (m, 1 H), 5.21 (d, *J*=5.77 Hz, 1 H), 7.00 (dd, *J*=8.91, 1.38 Hz, 2 H). ESI-MS *m/z* [M+H]⁺ calc'd for C₂₃H₂₄F₃N₃O₂ 431.2; found 432.2.

[0895] EXAMPLE 456: (1*R*,2*R*)-2-(((5*R*,8*S*)-1-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclobutan-1-ol



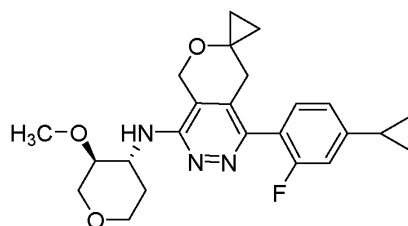
[0896] EXAMPLE 457: (1*R*,2*R*)-2-(((5*S*,8*R*)-1-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclobutan-1-ol



[0897] A mixture of Pd₂(dba)₃ (37 mg, 0.0409 mmol), Cs₂CO₃ (533 mg, 1.64 mmol), R-BINAP (0.051 mL, 0.0818 mmol), *trans*-(1*R*,2*R*)-2-aminocyclobutanol hydrochloride (101 mg, 0.818 mmol) and 4-chloro-1-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazine (150 mg, 0.409 mmol) in DMF (10 mL) was stirred in an oil bath at 100°C for 16 hours under nitrogen. The reaction mixture was concentrated and dispersed in MeOH (10 mL). The resulting suspension was filtered through a syringe filter and the filtrate was purified by preparative HPLC (basic-ACCQ-prep.) using a gradient of 10 to 100% ACN in water (with NH₄HCO₃). The product-containing fractions were collected, concentrated and dried *in vacuo*. The mixture components were separated by

preparative SFC (Waters, Phenomenex i-Amylose-3 column) using a gradient of 25 to 50% MeOH (modified with 0.1% NH₄OH) in CO₂. The first eluting product was dried *in vacuo* to give the title compound of Example 456 as a light-yellow semi-solid (27 mg, 16%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.24 (dd, *J*=8.91, 1.63 Hz, 2 H), 1.49 - 1.71 (m, 5 H), 2.06 (br d, *J*=17.57 Hz, 2 H), 2.23 (br d, *J*=7.78 Hz, 4 H), 2.84 - 2.94 (m, 1 H), 4.13 (d, *J*=7.78 Hz, 1 H), 4.29 - 4.38 (m, 1 H), 4.68 - 4.74 (m, 1 H), 5.16 (d, *J*=5.77 Hz, 1 H), 7.01 (dd, *J*=8.91, 1.38 Hz, 2 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₂H₂₂F₃N₃O₂ 417.2; found 418.2. The second eluting product was dried *in vacuo* to give the title compound of Example 457 as a light-brown semi-solid (23.3 mg, 14%). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.20 - 1.26 (m, 2 H), 1.48 - 1.70 (m, 5 H), 2.02 - 2.10 (m, 2 H), 2.13 - 2.29 (m, 4 H), 2.89 (dd, *J*=17.69, 5.14 Hz, 1 H), 4.11 (d, *J*=7.78 Hz, 1 H), 4.33 (s, 1 H), 4.70 (s, 1 H), 5.19 (d, *J*=5.77 Hz, 1 H), 6.98 - 7.06 (m, 2 H); ESI-MS *m/z* [M+H]⁺ calc'd for C₂₂H₂₂F₃N₃O₂ 417.2; found 418.2.

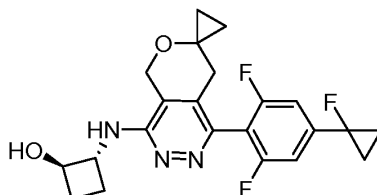
[0898] EXAMPLE 458: 1'-(4-cyclopropyl-2-fluorophenyl)-*N*-((3*S*,4*R*)-3-methoxytetrahydro-2*H*-pyran-4-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-amine



[0899] To a 5 mL microwave vial fitted with a stir bar were added R-BINAP (27 mg, 0.0441 mmol), (3*R*,4*S*)-3-methoxyoxan-4-amine hydrochloride (55 mg, 0.331 mmol), a mixture of 4'-chloro-1'-(4-cyclopropyl-2-fluorophenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] and 1'-chloro-4'-(4-cyclopropyl-2-fluorophenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazine] (73 mg, 0.110 mmol), Cs₂CO₃ (108 mg, 0.331 mmol), and palladium(II) acetate (5.0 mg, 0.0221 mmol) in DMA (2 mL). The vial was flushed with nitrogen, and the reaction mixture was heated in a Biotage microwave reactor at 130°C for 30 minutes and then extracted with EtOAc (5 mL) and brine (5 mL). The organics were separated and dried with MgSO₄, concentrated and purified by flash chromatography (amine column) using a gradient of 30 to 90% EtOAc in heptane. The crude product was purified by SFC to give the title compound (7.2 mg, 15%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.42 - 0.55 (m, 2 H), 0.71 - 0.79 (m, 2 H), 0.86 - 0.96 (m, 2 H), 1.00 - 1.09 (m, 2 H), 1.53 - 1.67 (m, 1 H), 1.85 - 1.99 (m, 1 H), 2.41 - 2.59 (m, 1 H), 2.62 - 2.78 (m, 2 H),

3.28 - 3.36 (m, 1 H), 3.42 (dt, $J=9.16$, 4.45 Hz, 1 H), 3.47 (s, 3 H), 3.58 (td, $J=11.48$, 2.38 Hz, 1 H), 3.91 (dt, $J=11.61$, 3.61 Hz, 1 H), 4.19 (dd, $J=11.04$, 4.02 Hz, 1 H), 4.23 - 4.35 (m, 1 H), 4.55 (s, 2 H), 6.81 (dd, $J=11.42$, 1.63 Hz, 1 H), 6.96 (dd, $J=7.91$, 1.63 Hz, 1 H), 7.35 (t, $J=7.78$ Hz, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{24}H_{28}FN_3O_3$ 425.2; found 426.2.

[0900] EXAMPLE 459: (1*R*,2*R*)-2-((1'-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclobutan-1-ol



[0901] To a 5 mL vial fitted with a stir bar were added (1*R*,2*R*)-2-((1'-chloro-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclobutan-1-ol (30 mg, 0.106 mmol), 2-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (32 mg, 0.106 mmol), and XPhos Palladacycle G4 (9.2 mg, 0.0106 mmol) in THF (0.7 mL) and K_3PO_4 (0.5M) (1.4 mL). The vial was flushed with nitrogen and the reaction mixture was heated to 50°C overnight. The mixture was allowed to cool to room temperature and then extracted with EtOAc (2 mL) and brine (2 mL). The organics were separated and concentrated, dissolved in DMF (0.5 mL) and MeOH (2 mL), filtered and purified by Shimadzu preparative HPLC using a TFA-containing mobile phase to give the title compound was a TFA salt (5.8 mg, 10%). 1H NMR (400 MHz, $CDCl_3$) δ ppm 0.44 - 0.59 (m, 2 H), 0.93 - 1.02 (m, 2 H), 1.11 - 1.23 (m, 2 H), 1.56 - 1.71 (m, 2 H), 1.71 - 1.86 (m, 2 H), 2.11 - 2.31 (m, 2 H), 2.54 (s, 2 H), 4.16 (br d, $J=7.03$ Hz, 1 H), 4.27 (br d, $J=7.28$ Hz, 1 H), 4.65 - 4.89 (m, 2 H), 5.72 - 6.01 (br s, 1 H), 6.88 (d, $J=8.78$ Hz, 2 H), 9.30 (br s, 1 H); ESI-MS m/z $[M+H]^+$ calc'd for $C_{22}H_{22}F_3N_3O_2$ 417.2; found 418.1.

[0902] Table 5 lists *in vitro* biological assay data (IL-1 β and TNF- α) for some of the compounds shown in the examples. These assays are described in the section entitled Biological Activity, above.

[0903] TABLE 5: Biological Assay Data

Example No.	IL-1 β IC ₅₀ (nM)	TNF- α IC ₅₀ (nM)
233	15.6	10000
234	163.4	10000
235	81.4	10000

Example No.	IL-1 β IC ₅₀ (nM)	TNF- α IC ₅₀ (nM)
236	13.5	10000
237	12.3	
238	8.1	
239	106.9	
240	7.0	
241	11.4	
242	7.4	
243	11.8	
244	155.4	
245	5.6	
246	768.0	
247	36.1	
248	10.3	
249	7.5	
250	19.6	
251	23.5	
252	17.4	
253	71.7	
254	131.9	
255	70.2	
256	108.7	
257	7.3	
258	15.3	
259	761.3	
260	19.1	
261	188.2	
262	40.6	
263	742.0	
264	50.1	
265	1226.0	
266	25.8	

Example No.	IL-1 β IC ₅₀ (nM)	TNF- α IC ₅₀ (nM)
267	101.8	
268	79.7	
269	299.3	
270	559.4	
271	91.2	
272	110.3	
273	9.4	
274	48.9	
275	419.1	
276	21.4	
277	24.3	
278	308.6	
279	379.1	
280	74.2	
281	208.6	
282	282.7	
283	90.7	
284	227.6	
285	196.2	
286	159.5	
287	459.8	
288	207.3	
289	53.8	
290	254.8	
291	399.1	
292	467.6	
293	21.9	
294	58.1	
295	206.5	
296	84.8	
297	28.1	

Example No.	IL-1 β IC ₅₀ (nM)	TNF- α IC ₅₀ (nM)
298	114.7	
299	27.3	
300	30.7	
301	17.8	
302	15.6	
303	19.7	
304	50.8	
305	376.5	
306	36.0	
307	16.8	
308	124.9	
309	73.7	
310	101.2	
311	100.1	
312	29.5	
313	95.7	
314	60.4	
315	86.6	
316	129.1	
317	43.6	
318	187.4	
319	452.3	
320	154.2	
321	464.8	
322	145.6	
323	142.2	
324	89.6	
325	21.8	
326	64.9	
327	267.6	
328	170.9	

Example No.	IL-1 β IC ₅₀ (nM)	TNF- α IC ₅₀ (nM)
329	282.0	
330	12.5	
331	24.5	
332	25.1	
333	142.0	
334	42.7	
335	16.3	
336	32.6	
337	79.6	
338	54.0	
339	99.2	
340	22.0	
341	231.5	
342	24.0	
343	20.7	
344	43.4	
345	167.9	
346	134.2	
347	34.9	
348	24.5	
349	331.9	
350	22.5	
351	74.5	
352	40.2	
353	63.6	
354	32.7	
355	91.8	
356	85.4	
357	43.9	
358	62.4	
359	28.5	

Example No.	IL-1 β IC ₅₀ (nM)	TNF- α IC ₅₀ (nM)
360	13.2	
361	21.4	
362	22.3	
363	70.8	
364	53.9	
365	21.1	
366	35.6	
367	99.6	
368	43.4	
369	47.2	
370	69.6	
371	36.0	
372	42.8	
373	24.8	
374	53.9	
375	56.9	
376	48.8	
377	74.3	
378	90.0	
379	68.0	10000
380	16.1	
381	48.3	
382	25.1	
383	18.4	
384	86.4	
385	37.9	
386	41.4	
387	38.8	
388	60.5	
389	26.0	
390	56.3	

Example No.	IL-1 β IC ₅₀ (nM)	TNF- α IC ₅₀ (nM)
391	95.1	
392	36.0	
393	7.3	
394	33.4	
395	46.7	
396	39.3	
397	28.3	
398	14.6	
399	22.2	
400	42.8	
401	32.5	
402	31.8	
403	14.9	
404	25.0	
405	27.1	
406	11.2	
407	20.5	
408	29.0	
409	30.1	
410	24.5	
411	10.7	
412	22.0	
413	19.7	
414	49.6	
415	27.2	
416	17.1	
417	30.8	
418	37.2	
419	31.5	
420	26.1	
421	23.8	

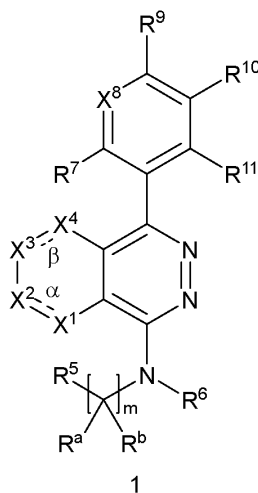
Example No.	IL-1 β IC ₅₀ (nM)	TNF- α IC ₅₀ (nM)
422	44.2	
423	40.1	
424	32.7	
425	11.6	
426	14.3	
427	35.6	
428	25.0	
429	33.0	
430	48.8	
431	32.8	
432	28.3	
433	40.6	
434	8.3	
435	36.1	
436	46.4	
437	56.7	
438	61.7	
439	18.0	
440	242.9	
441	36.9	
442	15.7	
443	66.8	
444	46.0	
445	38.2	
446	33.8	
447	18.2	
448	24.6	
449	20.4	
450	43.7	
451	18.8	
452	40.2	

Example No.	IL-1 β IC ₅₀ (nM)	TNF- α IC ₅₀ (nM)
453	15.0	
454	1843.1	
455	13.2	
456	1307.8	
457	14.8	
458	23.5	
459	21.9	

[0904] As used in this specification and the appended claims, singular articles such as “a,” “an,” and “the,” may refer to a single object or to a plurality of objects unless the context clearly indicates otherwise. Thus, for example, reference to a composition containing “a compound” may include a single compound or two or more compounds. The above description is intended to be illustrative and not restrictive. Many embodiments will be apparent to those of skill in the art upon reading the above description. Therefore, the scope of the invention should be determined with reference to the appended claims and includes the full scope of equivalents to which such claims are entitled. The disclosures of all articles and references cited in the disclosure, including patents, patent applications and publications, are herein incorporated by reference in their entirety and for all purposes.

WHAT IS CLAIMED IS

1. A compound of Formula 1,



or a pharmaceutically acceptable salt thereof in which:

α is a single bond and β is a single bond; and

- (i) X^1 is CH_2 , $\text{CH}(\text{CH}_3)$, or X^C ;
 X^2 is O and X^3 is CH_2 or X^C , or
 X^2 is CH_2 or X^C and X^3 is O; and
 X^4 is a bond, CH_2 , CH_2CH_2 , or X^C ;

wherein X^C is selected from C₃₋₆ cycloalkylidene and C₃₋₅

oxacycloalkylidene, each substituted with 0 to 4 substituents

independently selected from halo, and wherein one, and no more than one, of X^1 , X^2 , X^3 and X^4 is X^C ; or

- (ii) X^1 is $C(HR^1)$;
 X^2 is O;
 X^3 is $C(HR^3)$; and
 X^4 is CH_2 ;

wherein R¹ and R³ taken together represent a C₁₋₃ alkanediyl bridging the carbon atoms to which R¹ and R² are attached; or

- (iii) X^1 is CH_2 ;
 X^2 is $\text{C}(\text{HR}^2)$;
 X^3 is O ;
and X^4 is $\text{C}(\text{HR}^4)$;

wherein R^2 and R^4 taken together represent a C_{1-3} alkanediyl bridging the carbon atoms to which R^2 and R^4 are attached; or

- (iv) X^1 is $C(HR^1)$;
 X^2 is O and X^3 is CH_2 , or
 X^2 is CH_2 and X^3 is O; and
 X^4 is $C(HR^4)$;

wherein R^1 and R^4 taken together represent a C_{1-3} alkanediyl; or

- (v) X^1 is $C(HR^1)$;
 X^2 is CH_2 ;
 X^3 is $C(HR^3)$; and
 X^4 is CH_2 ;

wherein R^1 and R^3 taken together represent a C_{1-2} alkanediyloxy or O bridging the carbon atoms to which R^1 and R^3 are attached; or

- (vi) X^1 is $C(HR^1)$;
 X^2 is CH_2 ;
 X^3 is CH_2 ; and
 X^4 is $C(HR^4)$;

wherein R^1 and R^4 taken together represent a C_{1-2} alkanediyloxy or O bridging the carbon atoms to which R^1 and R^4 are attached;

m is selected from 0, 1 and 2;

each R^a and R^b is independently selected from hydrogen and C_{1-4} alkyl, or R^a and R^b , together with a carbon atom to which both R^a and R^b are attached, form a C_{3-6} cycloalkylidene, provided if m is 2, then no more than one R^a and R^b , together with the carbon atom to which R^a and R^b are attached, form a C_{3-6} cycloalkylidene;

R^5 is selected from:

- (a) C_{3-8} cycloalkyl, which is substituted with 0 to 5 substituents independently selected from:
- (i) halo, hydroxy, cyano and oxo;
 - (ii) amino, which is substituted with 0 to 2 substituents independently selected from C_{1-4} alkyl; and
 - (iii) C_{1-4} alkyl, C_{1-4} alkylcarbonyl and C_{1-4} alkoxy, each substituted with 0 to 3 substituents independently selected from halo;

(b) C₃₋₈ heterocyclyl in which up to 3 carbon ring atoms are each independently substituted with 0 to 2 substituents independently selected from:

- (i) halo, hydroxy, cyano and oxo;
- (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
- (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;

and in which a nitrogen ring atom, if present, is unsubstituted or substituted with a substituent selected from:

- (i) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;
- (ii) C₃₋₈ cycloalkyl-(CH₂)_n, which C₃₋₈ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl, C₁₋₄ alkoxy and oxo; and
- (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl and C₁₋₄ alkoxy;

wherein the C₃₋₈ heterocyclyl has only one ring heteroatom, the ring heteroatom selected from nitrogen, oxygen, and sulfur; and

n is selected from 0 and 1;

provided:

if m is 0, X¹ is C(HR¹), X² is CH₂, X³ is CH₂, X⁴ is C(HR⁴), X⁸ is CH, α and β are both single bonds, R¹ and R⁴ taken together represent an ethan-1,2-diyl bridging the carbon atoms to which R¹ and R⁴ are attached, R⁶, R¹⁰ and R¹¹ are each hydrogen, R⁷ is hydroxy, and R⁹ is cyano, methyl or cyclopropyl, then R⁵ is not 1-methylpiperidin-3-yl; and

if m is 0, X¹ is C(HR¹), X² is CH₂, X³ is CH₂, X⁴ is C(HR⁴), X⁸ is CH, α and β are both single bonds, R¹ and R⁴ taken together represent a methan-1,1-diyl or O bridging the carbon atoms to which R¹ and R⁴ are attached, R⁶, R¹⁰ and R¹¹ are each hydrogen, R⁷ is hydroxy, and R⁹ is cyano, methyl or cyclopropyl, then R⁵ is not 1-methylpiperidin-3-yl;

- (c) phenyl, which is substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl and C₁₋₄ alkoxy, provided at least one of the substituents is hydroxy;

R⁶ is selected from hydrogen and C₁₋₄ alkyl;

X⁸ is selected from N and CR⁸;

R⁷, R⁸ and R¹¹ are each independently selected from:

- (i) hydrogen, halo, hydroxy and cyano;
- (ii) C₁₋₄ alkyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo; and
- (iii) C₃₋₈ cycloalkyl which is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl and C₁₋₄ alkoxy; and

R⁹ and R¹⁰ are each independently selected from:

- (i) hydrogen, halo, hydroxy and cyano;
- (ii) C₁₋₄ alkyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo; and
- (iii) C₃₋₈ cycloalkyl which is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl and C₁₋₄ alkoxy; or

R⁹ and R¹⁰ form an ethan-1,2-dioxy moiety bridging the carbon atoms to which they are attached.

2. The compound or pharmaceutically acceptable salt according to claim 1, wherein:

X¹ is CH₂, CH(CH₃), or X^C;

X² is O and X³ is CH₂ or X^C, or

X² is CH₂ or X^C and X³ is O; and

X⁴ is a bond, CH₂, CH₂CH₂, or X^C;

wherein X^C is selected from C₃₋₆ cycloalkylidene and C₃₋₅ oxacycloalkylidene, each substituted with 0 to 4 substituents independently selected from halo, and wherein one, and no more than one, of X¹, X², X³ and X⁴ is X^C.

3. The compound or pharmaceutically acceptable salt according to claim 1, wherein:

X¹ is CH₂, (CH(CH₃), or X^C;

X² is O and X³ is CH₂ or X^C, or

X² is CH₂ or X^C and X³ is O; and

X⁴ is CH₂ or X^C;

wherein X^C is selected from C_{3-6} cycloalkylidene and C_{3-5} oxacycloalkylidene, each substituted with 0 to 4 substituents independently selected from halo, and wherein one, and no more than one, of X^1 , X^2 , X^3 and X^4 is X^C .

4. The compound or pharmaceutically acceptable salt according to claim 1, wherein:
 X^1 is $C(HR^1)$;
 X^2 is O;
 X^3 is $C(HR^3)$; and
 X^4 is CH_2 ;
wherein R^1 and R^3 taken together represent a C_{1-3} alkanediyl bridging the carbon atoms to which R^1 and R^2 are attached.
5. The compound or pharmaceutically acceptable salt according to claim 1, wherein:
 X^1 is CH_2 ;
 X^2 is $C(HR^2)$;
 X^3 is O;
and X^4 is $C(HR^4)$;
wherein R^2 and R^4 taken together represent a C_{1-3} alkanediyl bridging the carbon atoms to which R^2 and R^4 are attached.
6. The compound or pharmaceutically acceptable salt according to claim 1, wherein:
 X^1 is $C(HR^1)$;
 X^2 is O and X^3 is CH_2 , or
 X^2 is CH_2 and X^3 is O; and
 X^4 is $C(HR^4)$;
wherein R^1 and R^4 taken together represent a C_{1-3} alkanediyl.
7. The compound or pharmaceutically acceptable salt according to claim 1, wherein:
 X^1 is $C(HR^1)$;
 X^2 is CH_2 ;
 X^3 is $C(HR^3)$; and
 X^4 is CH_2 ;
wherein R^1 and R^3 taken together represent a C_{1-2} alkanediyloxy or O bridging the carbon atoms to which R^1 and R^3 are attached.

8. The compound or pharmaceutically acceptable salt according to claim 1, wherein:
X¹ is C(HR¹);
X² is CH₂;
X³ is CH₂; and
X⁴ is C(HR⁴);
wherein R¹ and R⁴ taken together represent a C₁₋₂ alkanediyloxy or O bridging the carbon atoms to which R¹ and R⁴ are attached.
9. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 8, wherein m is 0.
10. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 8, wherein m is 1 or 2.
11. The compound or pharmaceutically acceptable salt according to claim 10, wherein each R^a and R^b is independently selected from hydrogen and C₁₋₄ alkyl.
12. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 11, wherein R⁵ is C₃₋₈ cycloalkyl, which is substituted with 0 to 5 substituents independently selected from:
- (i) halo, hydroxy, cyano and oxo;
 - (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
 - (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo.
13. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 11, wherein R⁵ is C₃₋₈ heterocyclyl in which up to 3 carbon ring atoms are each independently substituted with 0 to 2 substituents independently selected from:
- (i) halo, hydroxy, cyano and oxo;
 - (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
 - (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;

and in which a nitrogen ring atom, if present, is unsubstituted or substituted with a substituent selected from:

- (i) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;
- (ii) C₃₋₈ cycloalkyl-(CH₂)_n, which C₃₋₈ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl, C₁₋₄ alkoxy and oxo; and
- (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl and C₁₋₄ alkoxy.

14. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 11, wherein R⁵ is C₃₋₈ heterocyclyl in which the ring heteroatom is selected from nitrogen and oxygen and up to 3 carbon ring atoms are each independently substituted with 0 to 2 substituents independently selected from:

- (i) halo, hydroxy, cyano and oxo;
- (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
- (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;

and in which a nitrogen ring atom, if present, is unsubstituted or substituted with a substituent selected from:

- (i) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;
- (ii) C₃₋₈ cycloalkyl-(CH₂)_n, which C₃₋₈ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl, C₁₋₄ alkoxy and oxo; and
- (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl and C₁₋₄ alkoxy.

15. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 11, wherein R⁵ is C₃₋₈ heterocyclyl in which the ring heteroatom is nitrogen and up to 3

carbon ring atoms are each independently substituted with 0 to 2 substituents independently selected from:

- (i) halo, hydroxy, cyano and oxo;
- (ii) amino, which is substituted with 0 to 2 substituents independently selected from C₁₋₄ alkyl; and
- (iii) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkoxy, each substituted with 0 to 3 substituents independently selected from halo;

and in which the nitrogen ring atom is unsubstituted or substituted with a substituent selected from:

- (i) C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl and C₁₋₄ alkylsulfonyl, each substituted with 0 to 3 substituents independently selected from halo;
- (ii) C₃₋₈ cycloalkyl-(CH₂)_n, which C₃₋₈ cycloalkyl moiety is substituted with 0 to 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ alkylcarbonyl, C₁₋₄ alkoxy and oxo; and
- (iii) phenyl-(CH₂)_n and pyridinyl-(CH₂)_n, which phenyl and pyridinyl moieties are substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl and C₁₋₄ alkoxy.

16. The compound or pharmaceutically acceptable salt according to any one of claims 13 to 15, wherein R⁵ is C₃₋₈ heterocyclyl and n is 0.

17. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 11, wherein R⁵ is phenyl, which is substituted with 0 to 3 substituents independently selected from halo, hydroxy, cyano, C₁₋₄ alkyl and C₁₋₄ alkoxy, provided at least one of the substituents is hydroxy.

18. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 17, wherein R⁶ is selected from hydrogen and methyl.

19. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 17, wherein R⁶ is hydrogen.

20. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 19, wherein X⁸ is CR⁸.

21. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 20, wherein R⁷ and R⁸ are both hydrogen, and R¹¹ is selected from:

- (i) hydrogen, halo and hydroxy; and
- (ii) C₁₋₃ alkyl and C₁₋₃ alkoxy, each substituted with 0 to 3 substituents independently selected from halo.

22. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 21, wherein R⁹ and R¹⁰ are each independently selected from:

- (i) hydrogen, halo, hydroxy and cyano;
- (ii) C₁₋₄ alkyl and C₁₋₃ alkoxy, each substituted with 0 to 3 fluoro; and
- (iii) C₃₋₅ cycloalkyl which is substituted with 0 to 3 substituents independently selected from methyl and methoxy.

23. The compound according to claim 1, which is selected from the following compounds:

2-(4'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-7',8'-dihydrospiro[cyclopropane-1,5'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol;

2-(1'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-7',8'-dihydrospiro[cyclopropane-1,5'-pyrano[3,4-*d*]pyridazin]-4'-yl)-5-methylphenol;

2-(1'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)-5-methylphenol;

2-(4'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol;

5-chloro-2-(((5*R*,8*S*)-4-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol;

5-chloro-2-(((5*S*,8*R*)-4-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol;

5-chloro-2-(((5*S*,8*R*)-1-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)phenol;

5-chloro-2-((5*R*,8*S*)-1-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)phenol;
2-((5*R*,8*S*)-1-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5,7,8,9-tetrahydro-5,8-epoxyoxepino[3,4-*d*]pyridazin-4-yl)-5-methylphenol;
2-((5*R*,8*S*)-4-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5,7,8,9-tetrahydro-5,8-epoxyoxepino[3,4-*d*]pyridazin-1-yl)-5-methylphenol;
2-(4-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-methylphenol;
2-((5*R*,8*S*)-4-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-methylphenol;
2-((5*S*,8*R*)-4-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-methylphenol;
2-(1-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)-5-methylphenol;
2-((5*S*,8*R*)-1-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)-5-methylphenol;
5-chloro-2-(1-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)phenol;
2-(4'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-4,5,5',8'-tetrahydro-2*H*-spiro[furan-3,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol;
2-(1'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-4,5,5',8'-tetrahydro-2*H*-spiro[furan-3,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)-5-methylphenol;
2-(4'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-2,3,5,5',6,8'-hexahydrospiro[pyran-4,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol;
2-(4'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;
2-(1'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)-5-(trifluoromethyl)phenol;
6-((4-(4-chloro-2-hydroxyphenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)amino)spiro[3.3]heptan-2-ol;

2-(4-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5,6,7,8-tetrahydro-5,8-epoxyphthalazin-1-yl)-5-methylphenol;

4-fluoro-2-(4'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol;

4-fluoro-2-(1'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)-5-methylphenol;

2-(4'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol;

2-(1'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)phenol;

2-(4'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol;

2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol;

2-(4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-methylphenol;

2-(4-(((1*S*,3*S*)-3-hydroxy-3-methylcyclobutyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-methylphenol;

2-(4-(((1*R*,3*R*)-3-hydroxy-3-methylcyclobutyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-methylphenol;

3-fluoro-2-(4-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-methylphenol;

3-fluoro-2-(1-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)-5-methylphenol;

(*R*)-2-(4'-((1-(2-fluoroethyl)piperidin-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol;

(*R*)-2-(1'-((1-(2-fluoroethyl)piperidin-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)-5-methylphenol;

2-(1'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)-5-methylphenol;

2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol;

2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-7',8'-dihydrospiro[cyclopropane-1,5'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol;

2-(4'-(((1*R*,2*R*)-2-hydroxy-2-methylcyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol;

2-((*R*^{*})-1'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-4'-yl)-5-methylphenol;

2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-7*H*-spiro[furo[3,4-*d*]pyridazine-5,3'-oxetan]-1-yl)-5-methylphenol;

2-(4'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-7*H*-spiro[furo[3,4-*d*]pyridazine-5,3'-oxetan]-1-yl)-5-methylphenol;

5-methyl-2-((5*RS*,8*SR*)-4-(((*R*)-tetrahydrofuran-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol;

5-chloro-2-((5*R*^{*},8*S*^{*})-4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol;

5-chloro-2-((5*S*^{*},8*R*^{*})-4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol;

5-chloro-2-((5*R*^{*},8*S*^{*})-4-(((*S*)-tetrahydrofuran-2-yl)methyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol;

5-chloro-2-((5*S*^{*},8*R*^{*})-4-(((*S*)-tetrahydrofuran-2-yl)methyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol;

5-cyclopropyl-4-fluoro-2-(4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol;

5-cyclopropyl-4-fluoro-2-(1-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)phenol;

2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5',8'-dihydrospiro[oxetane-3,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol;

2-(4'-(((1*R*,2*S*)-2-hydroxy-2-methylcyclohexyl)amino)-7',8'-dihydrospiro[cyclopropane-1,5'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol;

2-(1'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5',8'-dihydrospiro[oxetane-3,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)-5-methylphenol;
2-(4'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5',8'-dihydrospiro[oxetane-3,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol;
5-cyclopropyl-4-fluoro-2-(4-(((*R*)-tetrahydrofuran-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol;
3-fluoro-2-(4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol;
5-cyclopropyl-3-fluoro-2-(4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol;
5-cyclopropyl-3-fluoro-2-(1-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)phenol;
2-(4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol;
2-(4-(((1*S*,3*S*)-3-fluoro-5-methylcyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol;
5-cyclopropyl-2-((5*R*,8*S*)-4-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol;
5-cyclopropyl-2-((5*S*,8*R*)-4-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol;
5-cyclopropyl-2-((5*R*,8*S*)-4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol;
5-cyclopropyl-2-((5*S*,8*R*)-4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol;
2-(1'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5'*H*,7'*H*-spiro[cyclopropane-1,8'-pyrano[3,4-*d*]pyridazin]-4'-yl)-5-methylphenol;
2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;
2-((*S*^{*})-4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;
2-((*R*^{*})-4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;

2-(1'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5'*H*,7'*H*-
 spiro[cyclopropane-1,8'-pyrano[3,4-*d*]pyridazin]-4'-yl)-5-methylphenol;
 2-(4'-(((3*R*,5*R*)-5-fluoro-1-methylpiperidin-3-yl)amino)-5'*H*,7'*H*-
 spiro[cyclopropane-1,8'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol;
 2-(4-(((*R*)-tetrahydrofuran-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-
 epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol;
 2-(1-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-
 epoxycyclohepta[*d*]pyridazin-4-yl)-5-(trifluoromethyl)phenol;
 2-(4'-(((1*R*,2*S*)-2-hydroxy-2-methylcyclohexyl)amino)-5',8'-
 dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-
 methylphenol;
 2-(4'-(((1*R*,2*S*)-3,3-difluoro-2-hydroxycyclohexyl)amino)-5',8'-
 dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-
 methylphenol;
 2-(4'-(((1*R*,2*S*)-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-
 pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol;
 2-(4'-(((1*R*,3*R*)-3-hydroxycyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-
 pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol;
 2-(4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-
 pyrano[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol;
 (3*R*,4*S*)-4-(((5*S*,8*R*)-1-(4-chloro-2-hydroxyphenyl)-6,7,8,9-tetrahydro-5*H*-5,8-
 epoxycyclohepta[*d*]pyridazin-4-yl)amino)tetrahydrofuran-3-ol;
 5-chloro-2-((5*S*,8*R*)-4-((2-methoxy-2-methylpropyl)amino)-6,7,8,9-tetrahydro-5*H*-
 5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol;
 5-chloro-2-((5*S*,8*R*)-4-((2-hydroxy-2-methylpropyl)amino)-6,7,8,9-tetrahydro-5*H*-
 5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol;
 (3*R*,4*R*)-3-(((5*S*,8*R*)-1-(4-chloro-2-hydroxyphenyl)-6,7,8,9-tetrahydro-5*H*-5,8-
 epoxycyclohepta[*d*]pyridazin-4-yl)amino)tetrahydro-2*H*-pyran-4-ol;
 4-(((5*S*,8*R*)-1-(4-chloro-2-hydroxyphenyl)-6,7,8,9-tetrahydro-5*H*-5,8-
 epoxycyclohepta[*d*]pyridazin-4-yl)amino)tetrahydrofuran-3-ol;
 5-chloro-2-((5*S*,8*R*)-4-(((*R*)-tetrahydrofuran-3-yl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-
 epoxycyclohepta[*d*]pyridazin-1-yl)phenol;

(3*S*,4*R*)-4-(((5*S*,8*R*)-1-(4-chloro-2-hydroxyphenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)tetrahydro-2*H*-pyran-3-ol;
2-(4'-(((1*R*,2*R*)-2-hydroxycyclobutyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;
rac-5-(4-(((1*R*,2*R*)-2-methoxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-2,3-dihydro-1*H*-inden-4-ol;
rac-5-(1-(((1*R*,2*R*)-2-methoxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)-2,3-dihydro-1*H*-inden-4-ol;
2-(1'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)-5-(trifluoromethyl)phenol;
2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-7'*H*-spiro[cyclobutane-1,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol;
5-chloro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol;
5-chloro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol;
5-chloro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclobutyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol;
2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-7'*H*-spiro[cyclopropane-1,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol;
2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-7'*H*-spiro[cyclopropane-1,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;
2-(4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;
5-(4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-2,3-dihydro-1*H*-inden-4-ol;
5-(4-(((1*R*,2*R*)-2-hydroxycyclobutyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-2,3-dihydro-1*H*-inden-4-ol;
2-(4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethoxy)phenol;
2-(1-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)-5-(trifluoromethoxy)phenol;

2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;

(*S*)-2-(4'-(((tetrahydrofuran-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;

2-(((5*R*,8*S*)-4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(((5*S*,8*R*)-4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-(((1*R*,2*R*)-2-hydroxycyclobutyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

(3*S*,4*R*)-4-((1-(2-hydroxy-4-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)tetrahydro-2*H*-pyran-3-ol;

5-(1'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)-2,3-dihydro-1*H*-inden-4-ol;

(*R*)-2-(4'-(((tetrahydrofuran-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;

5-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5',8'-dihydrospiro [cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-2,3-dihydro-1*H*-inden-4-ol;

5-(1'-(((1*R*,2*R*)-2-hydroxycyclobutyl)amino)-5',8'-dihydrospiro [cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)-2,3-dihydro-1*H*-inden-4-ol;

5-(4'-(((1*R*,2*R*)-2-hydroxycyclobutyl)amino)-5',8'-dihydrospiro [cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-2,3-dihydro-1*H*-inden-4-ol;

5-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)oxy)-5',8'-dihydrospiro [cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-2,3-dihydro-1*H*-inden-4-ol;

2-(4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

5-cyclopropyl-3-fluoro-2-(4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol;

rac-2-(4'-(((1*R*,2*S*)-3,3-difluoro-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;

5-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-4,5-dihydro-2*H*,7*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-2,3-dihydro-1*H*-inden-4-ol;

5-cyclopropyl-2-(4'-(((1*R*,2*R*)-2-hydroxycyclobutyl)amino)-5',8'-
dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol;
5-cyclopropyl-2-(4'-(((1*R*,2*R*)-2-hydroxycyclobutyl)amino)-6,7,8,9-tetrahydro-5*H*-
5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol;
5-cyclopropyl-2-(4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-6,7,8,9-tetrahydro-5*H*-
5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol;
5-((5*R*,8*S*)-4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-
epoxycyclohepta[*d*]pyridazin-1-yl)-2,3-dihydro-1*H*-inden-4-ol;
5-((5*S*,8*R*)-4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-
epoxycyclohepta[*d*]pyridazin-1-yl)-2,3-dihydro-1*H*-inden-4-ol;
5-cyclopropyl-2-(4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5',8'-
dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol;
5-(4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-
pyrano[3,4-*d*]pyridazin]-1'-yl)-2,3-dihydro-1*H*-inden-4-ol;
5-(difluoromethyl)-2-((5*R*,8*S*)-4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-
tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol;
5-(difluoromethyl)-2-((5*S*,8*R*)-4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-
tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol;
2-(4'-(((1*S*,2*R*)-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-
pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;
(*R*)-5-chloro-2-(4'-((tetrahydrofuran-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-
1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol;
5-chloro-2-(4'-(((1*R*,2*S*)-2-hydroxycyclopentyl)amino)-5',8'-
dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol;
5-(difluoromethyl)-2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5',8'-
dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol;
(*R*)-5-cyclopropyl-2-(4'-((tetrahydrofuran-3-yl)amino)-5',8'-
dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol;
(1*R*,2*R*)-2-(((5*R*,8*S*)-1-(4-cyclopropyl-2-fluoro-6-methylphenyl)-6,7,8,9-tetrahydro-
5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol;
2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-4,5-dihydro-2*H*,7*H*-spiro[furan-3,5'-
furo[3,4-*d*]pyridazin]-1'-yl)-3-methyl-5-(trifluoromethyl)phenol;

5-chloro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-3-methylphenol;

5-cyclopropyl-2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol;

5-((5*R*,8*S*)-4'-(((1*R*,2*R*)-2-hydroxycyclobutyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-2,3-dihydro-1*H*-inden-4-ol;

5-(difluoromethyl)-2-(4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol;

5-cyclopropyl-2-(4'-(((1*R*,2*S*)-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol;

5-cyclopropyl-4-fluoro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol;

(1*R*,2*R*)-2-(((5*R*,8*S*)-1-(4-cyclopropyl-2,6-difluorophenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclohexan-1-ol;

5-(4'-(((1*R*,2*R*,3*R*,4*S*)-3-hydroxybicyclo[2.2.1]heptan-2-yl) amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-2,3-dihydro-1*H*-inden-4-ol;

3-fluoro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;

(3*S*,4*R*)-4-((1'-(2-fluoro-6-hydroxy-4-(trifluoromethyl)phenyl)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-4'-yl)amino)tetrahydro-2*H*-pyran-3-ol;

rel-5-(4'-(((1*R*,2*R*,3*R*)-2-hydroxy-3-methylcyclohexyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-2,3-dihydro-1*H*-inden-4-ol;

3-fluoro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-7'*H*-spiro[cyclopropane-1,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;

5-chloro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-7'*H*-spiro[cyclopropane-1,5'-furo[3,4-*d*]pyridazin]-1'-yl)phenol;

2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;

2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5'-methyl-5',8'-
dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-
methylphenol;

5-chloro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5'-methyl-5',8'-
dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol;

4-fluoro-2-((5*R*,8*S*)-4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-
5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

4-fluoro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-5',8'-
dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-
(trifluoromethyl)phenol;

4-fluoro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5',8'-
dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-
(trifluoromethyl)phenol;

4-fluoro-2-((5*S*,8*R*)-4-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-6,7,8,9-tetrahydro-
5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

5-(4'-(((1*R*,2*S*,3*S*,4*S*)-3-hydroxybicyclo[2.2.1]heptan-2-yl) amino)-5',8'-
dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-2,3-
dihydro-1*H*-inden-4-ol;

2-((*R*)-4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5'-methyl-5',8'-
dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-
(trifluoromethyl)phenol;

5-chloro-2-((*R*)-4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5'-methyl-5',8'-
dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol;

5-(4'-(((1*R*,2*S*)-2-hydroxycyclobutyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-
pyrano[3,4-*d*]pyridazin]-1'-yl)-2,3-dihydro-1*H*-inden-4-ol;

5-(4'-(((1*R*,2*S*)-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-
pyrano[3,4-*d*]pyridazin]-1'-yl)-2,3-dihydro-1*H*-inden-4-ol;

3-fluoro-2-((3*R*^{*})-4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-4,5-dihydro-2*H*,7*H*-
spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;

3-fluoro-2-((3*R*^{*})-4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-4,5-dihydro-2*H*,7*H*-
spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;

3-fluoro-2-(4'-(((*R*)-tetrahydrofuran-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-
1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;

(3*S*,4*R*)-4-(((3*R**)-1'-(2-fluoro-6-hydroxy-4-methylphenyl)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-4'-yl)amino)tetrahydro-2*H*-pyran-3-ol;

(3*S*,4*R*)-4-((1'-(2-fluoro-6-hydroxy-4-(trifluoromethyl)phenyl)-7'*H*-spiro[cyclopropane-1,5'-furo[3,4-*d*]pyridazin]-4'-yl)amino)tetrahydro-2*H*-pyran-3-ol;

2-(4'-(((1*R*,2*R*)-2-methoxycyclobutyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;

3-fluoro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-7'*H*-spiro[cyclopropane-1,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol;

3-fluoro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;

3-fluoro-2-((3*R**)-4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol;

(*R*)-2-(4'-((3,3-difluorocyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;

rac-2-(4'-(((3*R*,4*R*)-4-methyltetrahydrofuran-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;

(1*R*,2*R*)-2-(((5*S**,8*R**)-1-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclopentan-1-ol;

5-chloro-3-fluoro-2-(7'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-3'*H*-spiro[cyclopropane-1,1'-isobenzofuran]-4'-yl)phenol;

2-(4'-(((1*R*,2*R*)-2-methoxycyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;

5-(1-fluorocyclopropyl)-2-((5*S**,8*R**)-4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol;

5-ethyl-3-fluoro-2-(4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-7'*H*-spiro[cyclopropane-1,5'-furo[3,4-*d*]pyridazin]-1'-yl)phenol;

(3*S*,4*R*)-4-(((3*R**)-1'-(4-ethyl-2-fluoro-6-hydroxyphenyl)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-4'-yl)amino)tetrahydro-2*H*-pyran-3-ol;

(3*S*,4*R*)-4-(((3*R**)-1'-(4-chloro-2-fluoro-6-hydroxyphenyl)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-4'-yl)amino)tetrahydro-2*H*-pyran-3-ol;

5-chloro-3-fluoro-2-((3*R**)-4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)phenol;

3-fluoro-2-(4'-(((1*R*,2*R*)-2-methoxycyclohexyl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;

3-fluoro-2-(4'-(((1*R*,2*R*)-2-methoxycyclopentyl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;

5-(4'-(cyclobutylamino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-2,3-dihydro-1*H*-inden-4-ol;

5-(4'-(cyclopentylamino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-2,3-dihydro-1*H*-inden-4-ol;

5-cyclopropyl-2-(4-(((1*R*,2*R*)-2-methoxycyclopentyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol;

2-(4'-(cyclopentylamino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;

(*S*)-2-(4'-((3,3-difluorocyclopentyl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;

(*R*)-5-(1-fluorocyclopropyl)-2-(4'-((tetrahydrofuran-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol;

5-cyclopropyl-2-((5*S**,8*R**)-4-(((1*R*,2*R*)-2-methoxycyclobutyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol;

2-((5*S**,8*R**)-4-(((1*R*,2*R*)-2-methoxycyclobutyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

(3*S*,4*R*)-4-(((3*R**)-1'-(4-(difluoromethyl)-2-fluoro-6-hydroxyphenyl)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-4'-yl)amino)tetrahydro-2*H*-pyran-3-ol;

5-(difluoromethyl)-3-fluoro-2-((3*R**)-4'-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)phenol;

3-fluoro-2-((3*R**)-4'-(((1*R*,2*R*)-2-methoxycyclopentyl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol;

3-fluoro-2-((3*R**)-4'-(((1*R*,2*R*)-2-methoxycyclobutyl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol;

3-fluoro-2-((3*R**)-4'-(((3*S*,4*R*)-3-methoxytetrahydro-2*H*-pyran-4-yl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-methylphenol;

3-fluoro-2-((3*R**)-4'-(((3*S*,4*R*)-3-methoxytetrahydro-2*H*-pyran-4-yl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;

5-(1,1-difluoroethyl)-3-fluoro-2-((3*R**)-4'-(((3*S*,4*R*)-3-methoxytetrahydro-2*H*-pyran-4-yl)amino)-4,5-dihydro-2*H*,7'*H*-spiro[furan-3,5'-furo[3,4-*d*]pyridazin]-1'-yl)phenol;

2-((*R**)-4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)-5-(trifluoromethyl)phenol;

2-(4-(((1*R*,2*S*)-2-methoxycyclobutyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

1-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-*N*-((1*R*,2*R*)-2-methoxycyclobutyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-amine;

1'-(4-cyclopropyl-2,6-difluorophenyl)-*N*-((1*R*,2*R*)-2-methoxycyclobutyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-amine;

1'-(4-cyclopropyl-2-fluorophenyl)-*N*-((1*R*,2*R*)-2-methoxycyclopentyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-amine;

5-chloro-2-((*S**)-4'-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-5'-methyl-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol;

(*S*)-5-methyl-2-(4'-((tetrahydrofuran-3-yl)amino)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-1'-yl)phenol;

(1*R*,2*R*)-2-(((5*S**,8*R**)-1-(4-cyclopropyl-2,6-difluorophenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclopentan-1-ol;

2-((5*S*,8*R*)-4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-((5*R*,8*S*)-4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol;
 (1*R*,2*R*)-2-(((5*S*,8*R*)-1-(2-fluoro-4-(1-fluorocyclopropyl)-6-methylphenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclopentan-1-ol;
 5-((5*R*,8*S*)-4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-2,3-dihydro-1*H*-inden-4-ol;
 5-((5*S*,8*R*)-4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-2,3-dihydro-1*H*-inden-4-ol;
 5-cyclopropyl-2-((5*S*^{*},8*R*^{*})-4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)phenol;
 3-fluoro-2-((5*S*^{*},8*R*^{*})-4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol;
 (3*S*,4*R*)-4-((1'-(2-hydroxy-4-(trifluoromethyl)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)tetrahydro-2*H*-pyran-3-ol;
 1'-(2-fluoro-4-(1-fluorocyclopropyl)phenyl)-*N*-((1*R*,2*R*)-2-methoxycyclopentyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-amine;
 1'-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-*N*-((1*R*,2*R*)-2-methoxycyclopentyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-amine;
 1'-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-*N*-((1*R*,2*R*)-2-methoxycyclobutyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-amine;
 1'-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-*N*-((3*S*,4*R*)-3-methoxytetrahydro-2*H*-pyran-4-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-amine;
 (5*R*,8*S*)-1-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-*N*-((1*R*,2*R*)-2-methoxycyclobutyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-amine ;
 (5*S*,8*R*)-1-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-*N*-((1*R*,2*R*)-2-methoxycyclobutyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-amine;

(1*R*,2*R*)-2-(((5*R*,8*S*)-1-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclobutan-1-ol;

(1*R*,2*R*)-2-(((5*S*,8*R*)-1-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-6,7,8,9-tetrahydro-5*H*-5,8-epoxycyclohepta[*d*]pyridazin-4-yl)amino)cyclobutan-1-ol;

1'-(4-cyclopropyl-2-fluorophenyl)-*N*-((3*S*,4*R*)-3-methoxytetrahydro-2*H*-pyran-4-yl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-amine;
and

(1*R*,2*R*)-2-((1'-(2,6-difluoro-4-(1-fluorocyclopropyl)phenyl)-5',8'-dihydrospiro[cyclopropane-1,7'-pyrano[3,4-*d*]pyridazin]-4'-yl)amino)cyclobutan-1-ol;

or a pharmaceutically acceptable salt of any one of the aforementioned compounds.

24. A compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 23 for use as a medicament.

25. A pharmaceutical composition comprising:
a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 23; and
a pharmaceutically acceptable excipient.

26. A compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 23 for use in treating a disease, disorder or condition associated with NLRP3.

27. A compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 23 for use in treating a disease, disorder or condition associated with a heterozygous gain of function mutation in the NLRP3 gene.

28. A compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 23 for use in treating a cryopyrin-associated periodic syndrome (CAPS).

29. A method of treating a disease, disorder or condition in a subject, the method comprising administering to the subject a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 23, wherein the disease, disorder or condition is associated with NLRP3.

30. A method of treating a disease, disorder or condition in a subject, the method comprising administering to the subject a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 23, wherein the disease, disorder or condition is associated with a heterozygous gain of function mutation in the NLRP3 gene.
31. A method of treating a disease, disorder or condition in a subject, the method comprising administering to the subject a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 23, wherein the disease, disorder or condition is cryopyrin-associated periodic syndrome (CAPS).
32. The method according to claim 31, wherein the cryopyrin-associated periodic syndrome is selected from neonatal-onset multisystem inflammatory disease (NOMID/CINCA), Muckle-Wells syndrome (MWS), and familial cold autoinflammatory syndrome (FCAS).
33. A method of treating a neurodegenerative disease, disorder or condition in a subject, the method comprising administering to the subject a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 23.
34. A method of treating a disease, disorder or condition in a subject, the method comprising administering to the subject a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 23, wherein the disease, disorder or condition is selected from Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis and prion disease.
35. A combination comprising a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 23, and at least one additional pharmacologically active agent.
36. The combination according to claim 35, wherein the additional pharmacologically active agent is selected from beta-secretase inhibitors, gamma-secretase inhibitors, HMG-CoA reductase inhibitors, nonsteroidal anti-inflammatory drugs, vitamin E, anti-amyloid antibodies, antidepressants, antipsychotics, anxiolytics, and anticonvulsants.