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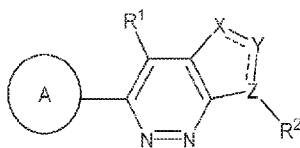
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(54) Title: HETEROCYCLIC AND HETEROARYL COMPOUNDS AS INHIBITORS OF NLRP3



(57) Abstract: The present invention relates to novel compounds of Formula (I): wherein each ring A, R¹, R², X, Y, and Z are as defined herein, which inhibit NOD-like receptor protein 3 (NLRP3) inflammasome activity. The invention further relates to the process for their preparation, pharmaceutical compositions and medicaments containing them, and their use in the treatment of diseases and disorders mediated by NLRP3.



HETEROCYCLIC AND HETEROARYL COMPOUNDS AS INHIBITORS OF NLRP3

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of, and priority to U.S. Provisional Patent Application
5 No. 63/477,864 filed on December 30, 2022, and U.S. Provisional Patent Application
No. 63/503,344 filed on May 19, 2023, the contents of which are herein incorporated by reference
in their entirety and for all purposes.

FIELD OF THE INVENTION

10 The present invention relates to compounds that are useful as inhibitors of NOD-like
receptor protein 3 (NLRP3) inflammasome pathway. The present invention also relates to
processes for the preparation of said compounds, pharmaceutical compositions comprising said
compounds, methods of using said compounds in the treatment of various diseases and disorders,
and medicaments containing them, and their use in diseases and disorders mediated by NLRP3.

BACKGROUND

The term inflammasome was coined by Martinon et al. to describe the molecular platform
triggering activation of inflammatory caspases and processing of interleukin 1 (IL-1) family
cytokines (Fabio Martinon et al., *Mol Cell* 10(2):417-26, 2002). Inflammasomes are part of the
15 innate immune system. Inflammasome activation is initiated by assembling of a multiprotein
complex, including nucleotide binding oligomerization domain (NOD)-like receptor (NLR), the
adapter apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC),
and the effector protease caspase-1. The assemble of the complex results in the activation of
caspase-1 and the release of the mature proinflammatory cytokines, such as IL-1 β and IL-18.

25 Among inflammasomes, the NLR family NACHT, LRR and PYD domains-containing
protein 3 (NLRP3) inflammasome has been studied extensively and was found to be activated by
a wide spectrum of stimuli. The regulatory mechanisms of NLRP3 activation are summarized in
a recent review paper (Seungwha Paik et al., *Cell Mol Immunol* 18(5):1141-1160, 2021).

NLRP3 activation is triggered by various infectious, non- infectious molecules, including
30 molecular byproducts of aging, physical inactivity and overnutrition. Once activated, it boosts

the downstream production of the inflammatory cytokines IL-1 β and IL-18. Gain-of function mutations of NLRP3 are associated with several genetic disorders including cryopyrin-associated periodic syndromes (CAPS). Additionally, NLRP3 is implicated in numerous common I) autoimmune, II) autoinflammatory, III) neurodegenerative, IV) cardiovascular and V) neuromuscular and muscular degenerative diseases e.g. (Matthew S J Mangan et al., *Nat Rev Drug Discov* 17(8):588-606, 2018; Corcoran et al., *Pharmacol Rev* 73(3):968-1000, 2021; Dubuisson et al., *Cells* 10(11):3023, 2021). Inflammasome activation has also been identified in retinal pigment epithelium (RPE) cells and proposed to be a causal factor for RPE dysfunction and degeneration (Gao et al., *Mediators Inflamm* 2015:690243, 2015). Further, NLRP3 activation is associated with severe COVID-19 cases and cytokine release syndrome (CRS) caused by cell-based therapeutics and biologic treatments (Tracey L Freeman and Talia H Swartz *Front Immunol* 11:1518, 2020; Lin et al., *PLoS Pathog* 6;15(6):e1007795, 2019).

Therefore, an NLRP3 inflammasome inhibitor could be used as a single or combination of agents clinically as novel therapies for these diseases. Thus, there is a need for inhibitors of the NLRP3 inflammasome pathway to provide new and/or alternative treatments for these inflammasome-related diseases, disorders, such as autoinflammatory fever syndrome cryopyrin-associated periodic syndrome (CAPS), sickle cell disease, chronic liver disease, nonalcoholic steatohepatitis (NASH), gout, hyperoxaluria, pseudogout (chondrocalcinosis), Type I/Type II diabetes and related complications (e.g. nephropathy, retinopathy), fibrosis, rheumatoid arthritis, inflammatory bowel diseases, asthma and allergic airway inflammation, neuroinflammation-related disorders (e.g. multiple sclerosis, brain infection, acute injury, Alzheimer's disease, Parkinson's disease, Huntington's disease), neuromuscular and muscular degenerative diseases, atherosclerosis and cardiovascular risk (e.g. cardiovascular risk reduction (CvRR), hypertension), hidradenitis suppurativa, wound healing and scar formation, and cancer (e.g. colon cancer, lung cancer, myeloproliferative neoplasms, leukemias, myelodysplastic syndromes (MDS), myelofibrosis).

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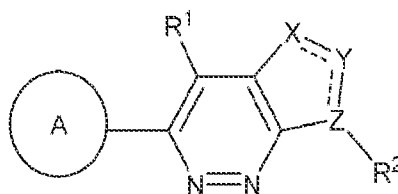
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20 to Streptococcal toxic shock-like syndrome (STSLS) *PLoS Pathog* 6;15(6):e1007795, 2019

SUMMARY OF THE INVENTION

An aspect of the application provides a compound of Formula (I):



(I)

wherein:

X and Y are independently selected from CR', C(R')(R'), N, NR'', O and S;

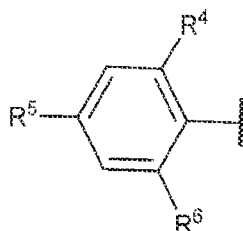
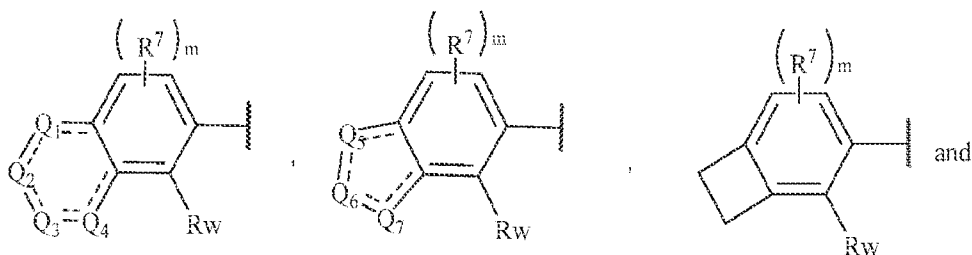
Z is selected from N, C and CH;

— is a single or double bond;

R' is independently selected from H, halogen, C₁₋₄alkyl, OH, C₃₋₆cycloalkyl, C₁₋₄alkoxy, C₃₋₆cycloalkoxy, halo-C₁₋₄alkoxy, C₁₋₄alkyl-thio, SH and halo-C₁₋₄alkyl;

R'' is independently selected from H, C₁₋₄alkyl, C₃₋₆cycloalkyl, and halo-C₁₋₄alkyl;

Ring A is selected from the group consisting of:



;

Q₁, Q₂, Q₃, Q₄, Q₅, Q₆, and Q₇ are independently selected from CR⁸, CR⁸R⁸, O, N, NR⁹ and S;

R_w is selected from OH, C₁₋₄alkyl, halo-C₁₋₄alkyl, C₃₋₆cycloalkyl, C₁₋₄alkoxy and halo-C₁₋₄alkoxy;

5 R¹ is selected from H, C₁₋₄alkyl, C₁₋₄alkyl-C₃₋₆cycloalkyl, C₁₋₄alkyl-C₃₋₆heterocycle, C₃₋₆cycloalkyl optionally substituted with halogen or R³, C₃₋₆heterocycle optionally substituted with halogen or R³, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, halo-C₁₋₄alkyl, C₁₋₄alkyl-thio, C₁₋₄alkoxy, C₃₋₆cycloalkoxy, and halo-C₁₋₄alkoxy;

10 R² is independently selected from C₃₋₇ cycloalkyl, C₁₋₄alkyl-aryl, C₁₋₄alkyl-C₃₋₇cycloalkyl, C₁₋₄alkyl-C₃₋₇heterocycle, C₃₋₇ heterocycle, wherein said C₃₋₇ heterocycle is a saturated or partially unsaturated membered monocyclic ring system having 1, 2, 3 heteroatom ring members independently selected from N, O and S, wherein said R² is optionally substituted with R³;

15 R³ is selected from C₁₋₄alkyl, deuterio-C₁₋₄alkyl, halogen, OH, halo-C₁₋₄alkyl, CN, C₃₋₆ cycloalkyl, C₁₋₄alkoxy, C₃₋₆cycloalkoxy, halo-C₁₋₄alkoxy, oxo and hydroxy-C₁₋₄alkyl;

R⁴, R⁵ and R⁶ are independently selected from H, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, OH, C₁₋₄alkoxy, halo-C₁₋₄alkyl, halo-C₁₋₄alkoxy, halogen, C₁₋₄alkyl-thio, C₃₋₆cycloalkyl, C₃₋₆ cycloalkoxy, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, and CN, wherein R⁴ is not H when R¹ is H;

20 R⁷ is independently selected from H, C₁₋₄alkyl, halo-C₁₋₄alkyl, C₃₋₆cycloalkyl, C₁₋₄alkoxy, halo-C₁₋₄alkoxy, halogen and CN;

R⁸ is selected from H, C₁₋₄ alkyl, halogen and halo-C₁₋₄alkyl, C₁₋₄alkoxy and halo-C₁₋₄alkoxy;

R⁹ is selected from H, C₁₋₄ alkyl, halo-C₁₋₄alkyl, C₃₋₆cycloalkyl; and

25 m is 0, 1 or 2;

wherein a form of the compound may be selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

An aspect of the invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound according to the definition of the compound of Formula (I) as disclosed herein, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers. The pharmaceutical composition is useful in the treatment of diseases and/or disorders related to the NLRP3 activity.

An aspect of the invention provides a compound of Formula (I) as disclosed herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease or disorder in which the NLRP3 signaling contributes to the pathology, and/or symptoms, and/or progression, of said disease or disorder. In another aspect, the invention provides a method of treating a disease or disorder in which the NLRP3 signaling contributes to the pathology, and/or symptoms, and/or progression, of said disease or disorder, comprising administering a therapeutically effective amount of a compound of Formula (I), or sub-formula thereof, as disclosed herein, or a pharmaceutically acceptable salt thereof.

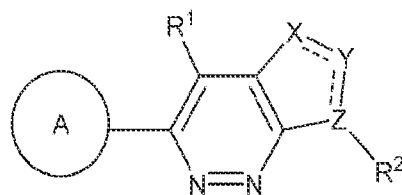
An aspect of the invention provides a method of inhibiting the NLRP3 inflammasome activity in a subject in need thereof, the method comprises administering to the subject in need thereof a therapeutically effective amount of a compound of Formula (I) as disclosed herein, or a pharmaceutically acceptable salt thereof.

An aspect of the invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, for use as a medicament.

An aspect of the invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease or disorder selected from inflammasome-related disease/disorders, immune diseases, inflammatory diseases, auto-immune diseases, or auto-inflammatory diseases.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides a compound of Formula (I)



(I)

wherein:

5 X and Y are independently selected from CR¹, C(R¹)(R¹), N, NR², O and S;

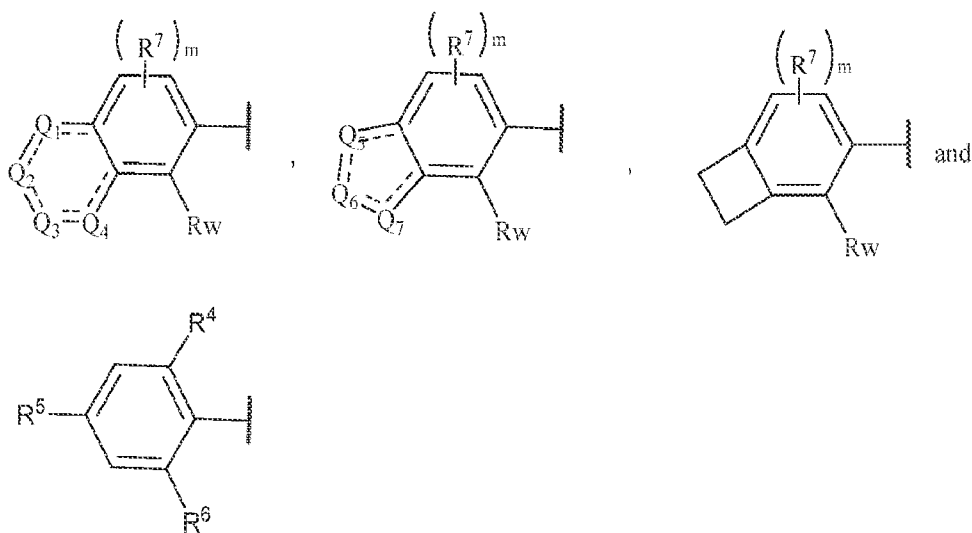
Z is selected from N, C and CH;

— is a single or double bond;

10 R¹ is independently selected from H, halogen, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, OH, C₃₋₆cycloalkyl, C₁₋₄alkoxy, C₃₋₆cycloalkoxy, halo-C₁₋₄alkoxy, C₁₋₄alkyl-thio, SH and halo-C₁₋₄alkyl;

R² is independently selected from H, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, C₃₋₆cycloalkyl, and halo-C₁₋₄alkyl;

Ring A is selected from the group consisting of:



15

Q₁, Q₂, Q₃, Q₄, Q₅, Q₆, and Q₇ are independently selected from CR⁸, C(R⁸)(R⁸), O, N, NR⁹, and S;

R_w is selected from OH, C₁₋₄alkyl, halo-C₁₋₄alkyl, C₃₋₆cycloalkyl, C₁₋₄alkoxy and halo-C₁₋₄alkoxy;

R¹ is selected from H, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, C₁₋₄alkyl-C₃₋₆cycloalkyl, C₁₋₄alkyl-C₃₋₆heterocycle, C₃₋₆cycloalkyl optionally substituted with halogen or R³, C₃₋₆heterocycle optionally substituted with halogen or R³, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, halo-C₁₋₄alkyl, C₁₋₄alkyl-thio, C₁₋₄alkoxy, C₃₋₆cycloalkoxy, and halo-C₁₋₄alkoxy;

R² is independently selected from C₃₋₇ cycloalkyl, C₁₋₄alkyl-aryl, C₁₋₄alkyl-C₃₋₇cycloalkyl, C₁₋₄alkyl-C₃₋₇heterocycle, C₃₋₇ heterocycle and aryl, wherein said C₃₋₇ heterocycle is a saturated or partially unsaturated membered monocyclic ring system having 1, 2, 3 heteroatom ring members independently selected from N, O and S, wherein said R² is optionally substituted with R³;

R³ is selected from C₁₋₄alkyl, deuterio-C₁₋₄alkyl, halogen, OH, halo-C₁₋₄alkyl, CN, C₃₋₆ cycloalkyl, C₁₋₄alkoxy, C₃₋₆cycloalkoxy, halo-C₁₋₄alkoxy, oxo and hydroxy-C₁₋₄alkyl;

R⁴, R⁵ and R⁶ are independently selected from H, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, OH, C₁₋₄alkoxy, halo-C₁₋₄alkyl, halo-C₁₋₄alkoxy, halogen, C₁₋₄alkyl-thio,

C₃₋₆cycloalkyl, C₃₋₆cycloalkoxy, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, CN, C₃₋₇ heteroaryl, wherein said C₃₋₇ heteroaryl ring system having 1, 2, 3 heteroatom ring members independently selected from N, O, S and C₁₋₄alkoxy-carbonyl;

R⁷ is selected from H, C₁₋₄alkyl, halo-C₁₋₄alkyl, C₃₋₆cycloalkyl, C₁₋₄alkoxy and halo-C₁₋₄alkoxy, halogen and CN;

R⁸ is selected from H, C₁₋₄ alkyl, halogen and halo-C₁₋₄alkyl, C₁₋₄alkoxy and halo-C₁₋₄alkoxy;

R⁹ is selected from H, C₁₋₄ alkyl, halo-C₁₋₄alkyl, C₃₋₆cycloalkyl; and

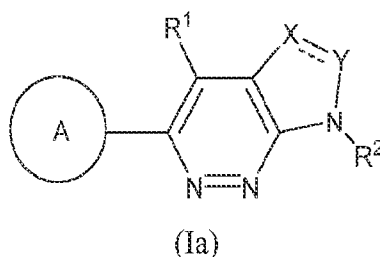
m is 0, 1 or 2;

wherein a form of the compound may be selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

Various embodiments of the invention are described herein, it will be recognized that features specified in each embodiment may be combined with other specified features to further embodiments of the present invention.

In embodiment 1, the invention provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as described above.

- 5 In embodiment 2, the invention provides a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, according to embodiment 1

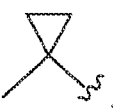


wherein:

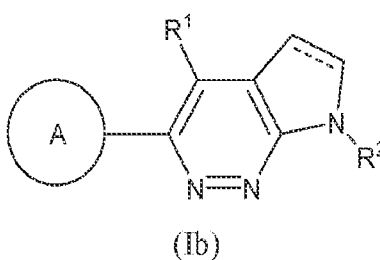
X and Y are independently selected from CR', C(R')(R');

- 10 R' is independently selected from H, halogen, C₁₋₄alkyl, OH, C₃₋₆cycloalkyl, C₁₋₄alkoxy, C₁₋₄alkyl-thio, SH and halo-C₁₋₄alkyl; and

R¹ is selected from H, CH₃, CH₃CH₂, cyclopropyl, cyclobutyl, isopropyl, tertbutyl, CF₃,

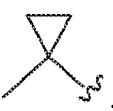
NHCH₃, CHF₂, SCH₃, OCH₃ and .

- 15 In embodiment 3, the invention provides a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, according to embodiment 1,

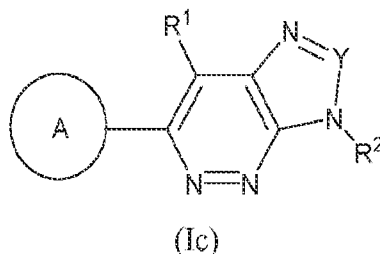


wherein:

R¹ is selected from H, CH₃, CH₃CH₂, cyclopropyl, cyclobutyl, isopropyl, tertbutyl, CF₃,

NHCH₃, CHF₂, SCH₃, OCH₃ and .

In embodiment 4, the invention provides a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, according to embodiment 1,

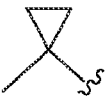


wherein:

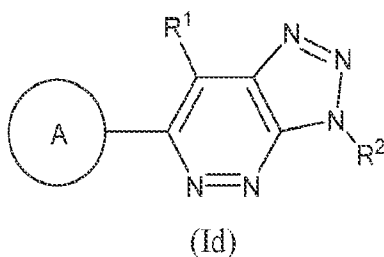
Y is selected from CR³;

5 R³ is independently selected from H, C₁₋₄alkyl and halo-C₁₋₄alkyl; and

R¹ is selected from H, CH₃, CH₃CH₂, cyclopropyl, cyclobutyl, isopropyl, tertbutyl, CF₃,

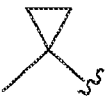
NHCH₃, CHF₂, SCH₃, OCH₃ and .

10 In embodiment 5, the invention provides a compound of Formula (Id), or a pharmaceutically acceptable salt thereof, according to embodiment 1,

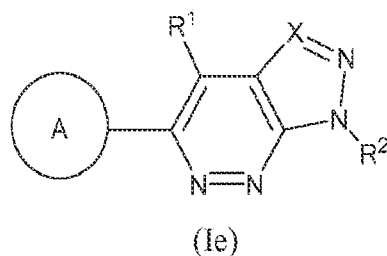


15 wherein:

R¹ is selected from H, CH₃, CH₃CH₂, cyclopropyl, cyclobutyl, isopropyl, tertbutyl, CF₃,

NHCH₃, CHF₂, SCH₃, OCH₃ and .

20 In embodiment 6, the invention provides a compound of Formula (Ie), or a pharmaceutically acceptable salt thereof, according to embodiment 1,



wherein:

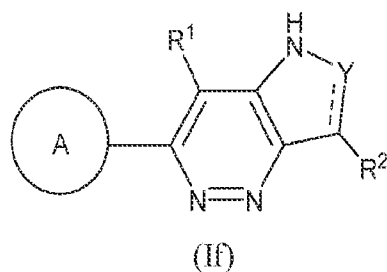
X is CR';

5 R' is selected from H and CH₃; and

R¹ is selected from H, CH₃, CH₃CH₂, cyclopropyl, cyclobutyl, isopropyl, tertbutyl, CF₃,

NHCH₃, CHF₂, SCH₃, OCH₃ and .

10 In embodiment 7, the invention provides a compound of Formula (If), or a pharmaceutically acceptable salt thereof, according to embodiment 1,



wherein:

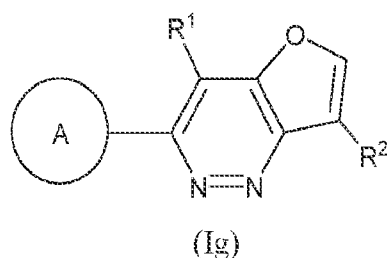
Y is selected from CH and CH₂;

15 --- is a single or double bond; and

R¹ is selected from H, CH₃, CH₃CH₂, cyclopropyl, cyclobutyl, isopropyl, tertbutyl, CF₃,

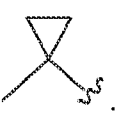
NHCH₃, CHF₂, SCH₃, OCH₃ and .

In embodiment 8, the invention provides a compound of Formula (Ig), or a pharmaceutically acceptable salt thereof, according to embodiment 1,

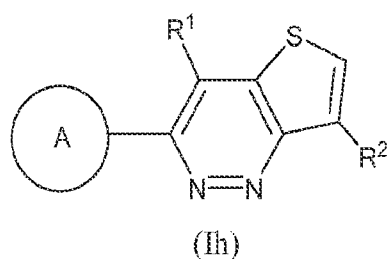


5 wherein:

R¹ is selected from H, CH₃, CH₃CH₂, cyclopropyl, cyclobutyl, isopropyl, tertbutyl, CF₃,

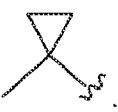
NHCH₃, CHF₂, SCH₃, OCH₃ and .

10 In embodiment 9 the invention provides a compound of Formula (Ih), or a pharmaceutically acceptable salt thereof, according to embodiment 1,



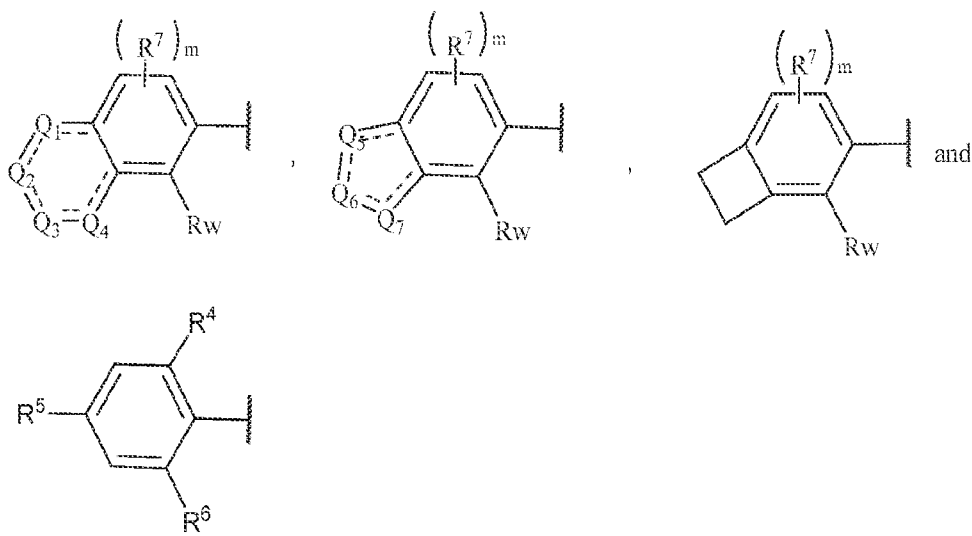
wherein:

R¹ is selected from H, CH₃, CH₃CH₂, cyclopropyl, cyclobutyl, isopropyl, tertbutyl, CF₃,

15 NHCH₃, CHF₂, SCH₃, OCH₃ and .

In embodiment 10, the invention provides a compound of Formula (I), or pharmaceutically acceptable salt thereof, wherein

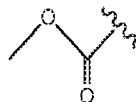
Ring A is selected from:



Q_1 , Q_2 , Q_3 , Q_4 , Q_5 , Q_6 , and Q_7 are independently selected from CR^8 , $C(R^8)(R^8)$, O, N, NR^9 and S;

R_w is selected from OH, $C_{1-4}alkyl$, halo- $C_{1-4}alkyl$, $C_{3-6}cycloalkyl$, $C_{1-4}alkoxy$ and halo- $C_{1-4}alkoxy$;

5 R^4 , R^5 and R^6 are independently selected from H, CH_3 , CH_2CH_3 , OH, OCH_3 , CF_3 , OCF_3 ,

CH_2CF_3 , $OCHF_2$, F, Cl, Br, cyclopropyl, isopropyl, SCH_3 , $N(CH_3)_2$, CN and  ;

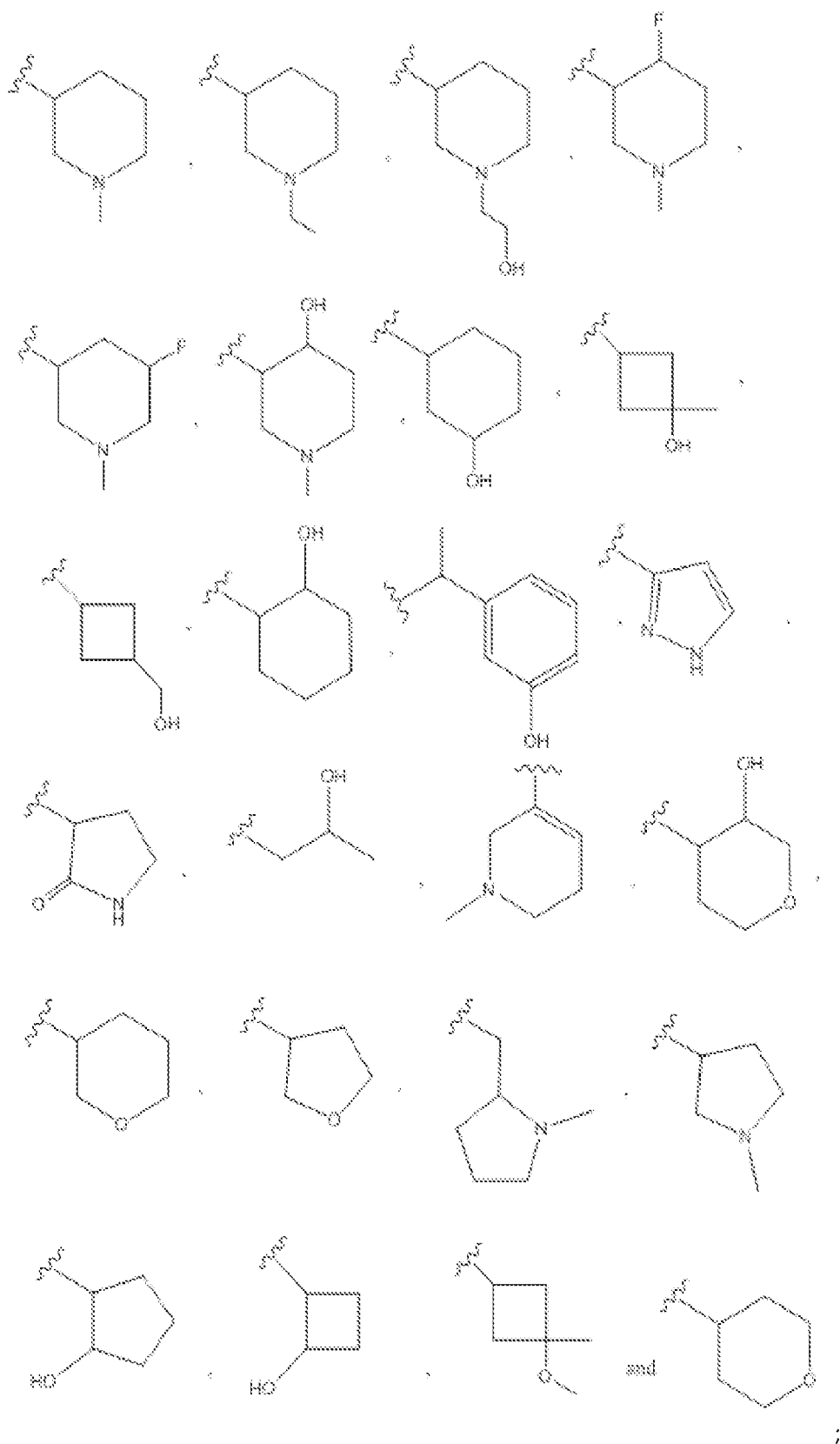
R^7 is independently selected from H, $C_{1-4}alkyl$, halo- $C_{1-4}alkyl$, $C_{3-6}cycloalkyl$, $C_{1-4}alkoxy$ and halo- $C_{1-4}alkoxy$, halogen and CN;

R^8 is selected from H, $C_{1-4}alkyl$, halogen and halo- $C_{1-4}alkyl$, $C_{1-4}alkoxy$, halo- $C_{1-4}alkoxy$;

10 R^9 is selected from H, $C_{1-4}alkyl$, halo- $C_{1-4}alkyl$, $C_{3-6}cycloalkyl$; and

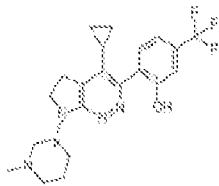
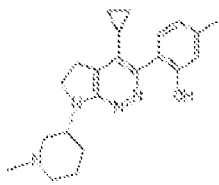
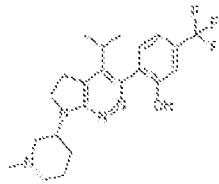
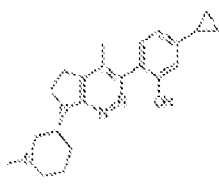
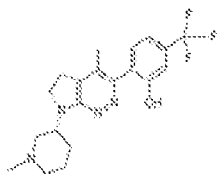
m is 0, 1 or 2; and

In embodiment 11, the invention provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, according to embodiment 1, wherein R² is selected from:



wherein a form of the compound may be selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

- 5 In embodiment 12, the invention provides a compound of Formula (I), or pharmaceutically acceptable salt thereof, according to embodiment 1, wherein:

Cmpd_ID	Structure	Name
I-1		2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
I-2		2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-methylphenol
I-3		2-[4-isopropyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
I-4		5-cyclopropyl-2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]phenol
I-5		2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol

Cmpd_ID	Structure	Name
I-6		2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol
I-7		2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-3-fluoro-5-methyl-phenol
I-8		2-[7-[(3R)-1-ethyl-3-piperidyl]-4-(1-methylcyclopropyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
I-9		2-[4-cyclobutyl-7-[(3R)-1-ethyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
I-10		2-[4-(3,3-difluorocyclobutyl)-7-[(3R)-1-ethyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
I-11		2-[4-cyclobutyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
I-12		2-[4-cyclobutyl-7-[(3R,5R)-5-fluoro-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol

Cmpd_ID	Structure	Name
I-13		5-cyclopropyl-2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]phenol
I-14		2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-methoxy-phenol
I-15		5-chloro-2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]phenol
I-16		3,5-dimethyl-2-[7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]phenol
I-17		3-methyl-2-[7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
I-18		3-methyl-2-[7-[(3R)-1-methylpyrrolidin-3-yl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
I-19		3-methyl-2-[7-(1-methyl-4-piperidyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol

Cmpd_ID	Structure	Name
I-20		3-methyl-2-[5-methyl-7-[rac-(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
I-21		5-chloro-3-fluoro-2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]phenol
I-22		5-chloro-2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]phenol
I-23		3-methyl-2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
I-24		2-[4-cyclopropyl-7-[(3R)-1-(2-hydroxyethyl)-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
I-25		2-[4-cyclopropyl-7-(3-hydroxy-3-methyl-cyclobutyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
I-26		2-[(7R)-4-cyclopropyl-7-tetrahydropyran-3-yl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol

Compd_ID	Structure	Name
I-27		3-methoxy-2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
I-28		2-(4-cyclopropyl-7-tetrahydrofuran-3-yl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol
I-29		2-[4-cyclopropyl-7-[(1R,2R)-2-hydroxycyclohexyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
I-30		2-[4-cyclopropyl-7-(1H-pyrazol-3-yl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
I-31		2-[4-cyclopropyl-7-[1-(3-hydroxyphenyl)ethyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
I-32		2-[(7R)-4-cyclopropyl-7-[(2S)-2-hydroxycyclohexyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
I-33		2-[4-cyclopropyl-7-[(1R,3S)-3-hydroxycyclohexyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol

Compd_ID	Structure	Name
I-34		2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-ethyl-phenol
I-35		5-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]indan-4-ol
I-36		5-methyl-2-[7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-3-(trifluoromethyl)phenol
I-37		5-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol
I-38		3-methoxy-2-[7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
I-39		3-methyl-2-[6-methyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
I-40		5-methyl-2-[6-methyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-3-(trifluoromethyl)phenol

Cmpd_ID	Structure	Name
I-41		3-[2,4-bis(trifluoromethyl)phenyl]-4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazine
I-42		3-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-4-(1-methylcyclopropyl)-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazine
I-43		5-[7-[(3R,5R)-5-fluoro-1-methyl-3-piperidyl]-4-methyl-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
I-44		5-[7-[(3S,4R)-4-fluoro-1-methyl-3-piperidyl]-4-methyl-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
I-45		5-[7-(3-hydroxy-3-methyl-cyclobutyl)-4-methyl-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
I-46		5-[4-cyclopropyl-7-[(3R,5R)-5-fluoro-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
I-47		5-[7-[(3R,5R)-5-fluoro-1-methyl-3-piperidyl]-4-methyl-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol

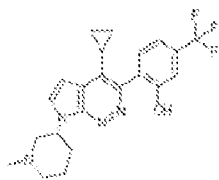
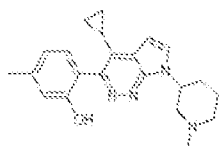
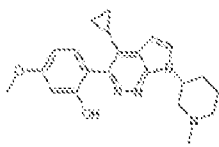
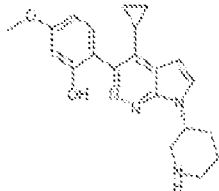
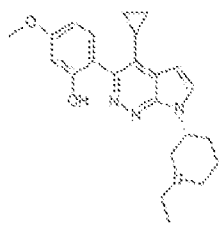
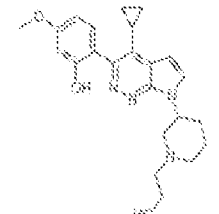
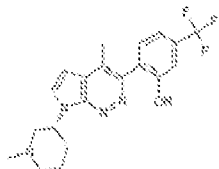
Cmpd_ID	Structure	Name
I-48		5-[4-cyclopropyl-7-[(3R,5R)-5-fluoro-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol
I-49		5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol
I-50		5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
I-51		5-[7-[(1R,2R)-2-hydroxycyclohexyl]-4-methyl-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
I-52		5-[7-[(3S,4R)-3-hydroxytetrahydropyran-4-yl]-4-methyl-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
I-53		5-[7-(3-hydroxy-3-methyl-cyclobutyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol
I-54		5-[7-[(1R,2R)-2-hydroxycyclohexyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol

Cmpd_ID	Structure	Name
I-55		5-[4-cyclopropyl-7-(3-hydroxy-3-methyl-cyclobutyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
I-56		5-[7-[(3S,4R)-3-hydroxytetrahydropyran-4-yl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol
I-57		2-[7-(3-hydroxy-3-methyl-cyclobutyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-methyl-3-(trifluoromethyl)phenol
I-58		3-[(7R)-7-tetrahydrofuran-3-yl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]bicyclo[4.2.0]octa-1,3,5-trien-2-ol
I-59		(3S,4R)-4-[3-(2-hydroxy-3-bicyclo[4.2.0]octa-1,3,5-trienyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-7-yl]tetrahydropyran-3-ol
I-60		5-[7-(3-hydroxy-3-methyl-cyclobutyl)-5-methyl-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol
I-61		(3S,4R)-4-[(5R)-3-[2-hydroxy-4-methyl-6-(trifluoromethyl)phenyl]-5-methyl-5,6-dihydropyrrolo[2,3-c]pyridazin-7-yl]tetrahydropyran-3-ol

Cmpd_ID	Structure	Name
I-62		(3S,4R)-4-[(5S)-3-[2-hydroxy-4-methyl-6-(trifluoromethyl)phenyl]-5-methyl-5,6-dihydropyrrolo[2,3-c]pyridazin-7-yl]tetrahydropyran-3-ol
I-63		2-[7-[(1R,2R)-2-hydroxycyclohexyl]-5-methyl-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-methyl-3-(trifluoromethyl)phenol
I-64		5-[7-[(1R,2R)-2-hydroxycyclohexyl]-5-methyl-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol
I-65		5-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-7-fluoro-benzofuran-4-ol
I-66		5-[7-[(1R,2R)-2-hydroxycyclopentyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol
I-67		5-[7-(3-hydroxy-3-methyl-cyclobutyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-2,3-dihydrobenzofuran-4-ol
I-68		2-[7-(3-methoxy-3-methyl-cyclobutyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol

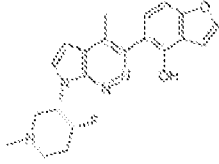
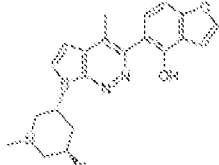
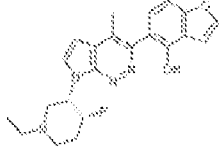
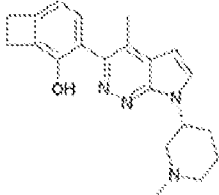
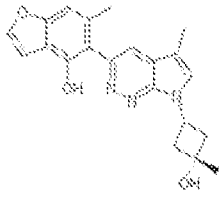
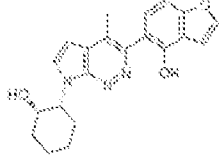
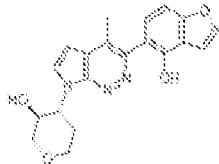
Compd_ID	Structure	Name
I-69		2-[7-(3-methoxy-3-methyl-cyclobutyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-methyl-3-(trifluoromethyl)phenol
I-70		5-[7-(3-methoxy-3-methyl-cyclobutyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol
I-71		6-(difluoromethyl)-5-[7-(3-methoxy-3-methyl-cyclobutyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
I-72		6-(difluoromethyl)-5-[7-(3-hydroxy-3-methyl-cyclobutyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
I-73		6-methyl-5-[7-(rac-(1R,2S)-2-hydroxycyclobutyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
I-74		6-methyl-5-[7-(rac-(1R,2R)-2-hydroxycyclobutyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
I-75		6-(difluoromethyl)-5-[7-[(3S,4R)-3-hydroxytetrahydropyran-4-yl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol

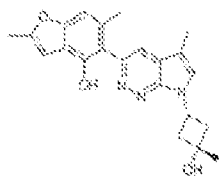
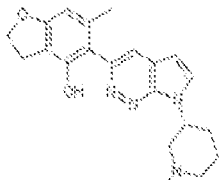
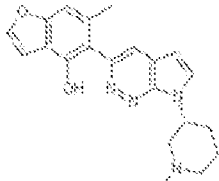
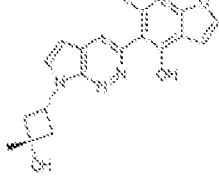
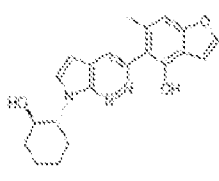
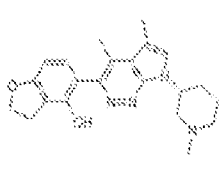
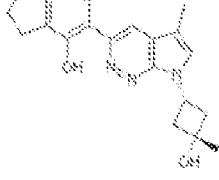
Compd_ID	Structure	Name
I-76		3-[7-[(1R,2R)-2-hydroxycyclohexyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-4-methyl-bicyclo[4.2.0]octa-1,3,5-trien-2-ol
I-77		3-(difluoromethyl)-2-[7-(3-hydroxy-3-methyl-cyclobutyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-methyl-phenol
I-78		5-[7-(3-hydroxy-3-methyl-cyclobutyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-6-(2,2,2-trifluoroethyl)benzofuran-4-ol
I-79		5-[7-[1-(3-hydroxyphenyl)ethyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol
IA-1		2-[7-[(3R)-1-methyl-3-piperidyl]-4-(trifluoromethyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
II-1		5-chloro-2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]phenol
II-2		5-cyclopropyl-2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]phenol

Cmpd_ID	Structure	Name
II-3		2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
II-4		2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-5-methyl-phenol
II-5		2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-5-methoxy-phenol
II-6		2-[4-cyclopropyl-7-[(3R)-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-5-methoxy-phenol
II-7		2-[4-cyclopropyl-7-[(3R)-1-ethyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-5-methoxy-phenol
II-8		2-[4-cyclopropyl-7-[(3R)-1-(2-hydroxyethyl)-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-5-methoxy-phenol
II-9		2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol

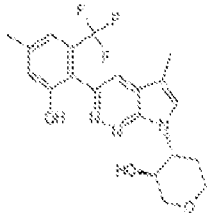
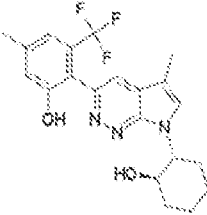
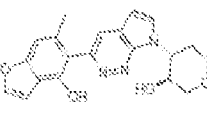
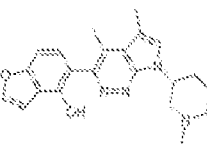
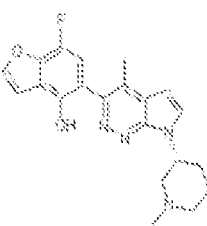
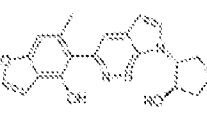
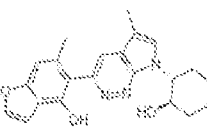
Compd_ID	Structure	Name
II-10		5-chloro-2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]phenol
II-11		5-methoxy-2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]phenol
II-12		5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
II-13		5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]benzothiophen-4-ol
II-14		5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]indan-4-ol
II-15		5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol
II-16		5-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol

Compd_ID	Structure	Name
II-17		3-methyl-2-[6-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
II-18		5-methyl-2-[6-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-3-(trifluoromethyl)phenol
II-19		2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-4-fluoro-5-methyl-phenol
II-20		6-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-2-fluoro-3-methyl-phenol
II-21		5-methyl-2-[7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-3-(trifluoromethyl)phenol
II-22		5-[7-(3-hydroxy-3-methyl-cyclobutyl)-4-methyl-pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
II-23		3-methyl-2-[7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol

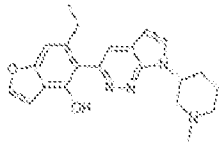
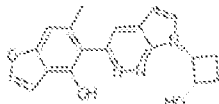
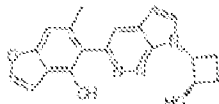
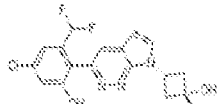
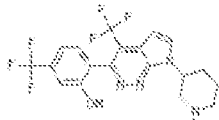
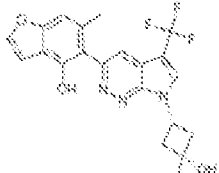
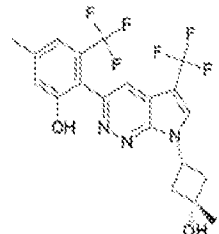
Cmpd_ID	Structure	Name
II-24		5-[7-[(3S,4R)-4-fluoro-1-methyl-3-piperidyl]-4-methyl-pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
II-25		5-[7-[(3R,5R)-5-fluoro-1-methyl-3-piperidyl]-4-methyl-pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
II-26		5-[7-[(3S,4R)-1-ethyl-4-fluoro-3-piperidyl]-4-methyl-pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
II-27		3-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]bicyclo[4.2.0]octa-1(6),2,4-trien-2-ol
II-28		5-[7-(3-hydroxy-3-methyl-cyclobutyl)-5-methyl-pyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol
II-29		5-[7-[(1R,2R)-2-hydroxycyclohexyl]-4-methyl-pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
II-30		5-[7-[(3S,4R)-3-hydroxytetrahydropyran-4-yl]-4-methyl-pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol

Cmpd_ID	Structure	Name
II-31		5-[7-(3-hydroxy-3-methyl-cyclobutyl)-5-methyl-pyrrolo[2,3-c]pyridazin-3-yl]-2,6-dimethyl-benzofuran-4-ol
II-32		6-methyl-5-[7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol
II-33		6-methyl-5-[7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
II-34		5-[7-(3-hydroxy-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol
II-35		5-[7-[(1R,2R)-2-hydroxycyclohexyl]pyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol
II-36		5-[4,5-dimethyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol
II-37		5-[7-(3-hydroxy-3-methyl-cyclobutyl)-5-methyl-pyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-2,3-dihydrobenzofuran-4-ol

Compd_ID	Structure	Name
II-38		6-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-7-ol
II-39		6-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-7-ol
II-40		2-fluoro-5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
II-41		5-[4-ethyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
II-42		2-[7-(3-hydroxy-3-methyl-cyclobutyl)-5-methyl-pyrrolo[2,3-c]pyridazin-3-yl]-5-methyl-3-(trifluoromethyl)phenol
II-43		3-[4-ethyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]bicyclo[4.2.0]octa-1,3,5-trien-2-ol
II-44		1,1-dimethyl-5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]indan-4-ol

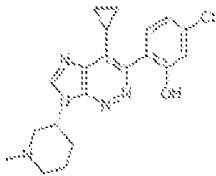
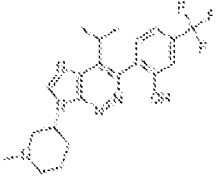
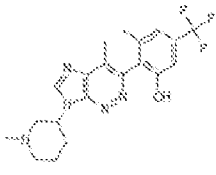
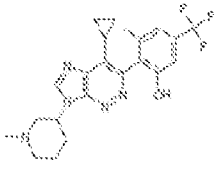
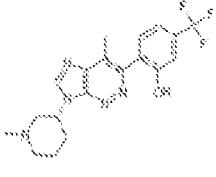
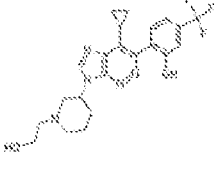
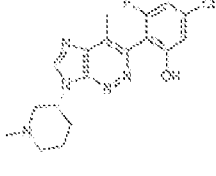
Cmpd_ID	Structure	Name
II-45		(3S,4R)-4-[3-[2-hydroxy-4-methyl-6-(trifluoromethyl)phenyl]-5-methyl-pyrrolo[2,3-c]pyridazin-7-yl]tetrahydropyran-3-ol
II-46		2-[7-[(1R,2R)-2-hydroxycyclohexyl]-5-methyl-pyrrolo[2,3-c]pyridazin-3-yl]-5-methyl-3-(trifluoromethyl)phenol
II-47		5-[7-[(3S,4R)-3-hydroxytetrahydropyran-4-yl]pyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol
II-48		5-[4,5-dimethyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
II-49		7-fluoro-5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
II-50		5-[7-[(1R,2R)-2-hydroxycyclopentyl]pyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol
II-51		5-[7-[(1R,2R)-2-hydroxycyclohexyl]-5-methyl-pyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol

Cmpd_ID	Structure	Name
II-52		5-[7-(3-hydroxy-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-2,3-dihydrobenzofuran-4-ol
II-53		6-(difluoromethyl)-5-[7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
II-54		2-[7-[(1R,2R)-2-hydroxycyclopentyl]pyrrolo[2,3-c]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol
II-55		2-[7-(3-methoxy-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol
II-56		2-[7-(3-methoxy-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazin-3-yl]-5-methyl-3-(trifluoromethyl)phenol
II-57		6-(difluoromethyl)-5-[7-(3-methoxy-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
II-58		6-(difluoromethyl)-5-[7-(3-hydroxy-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol

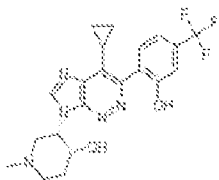
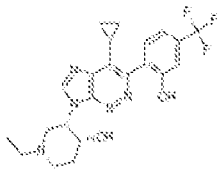
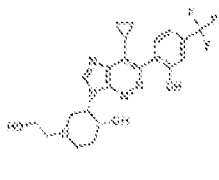
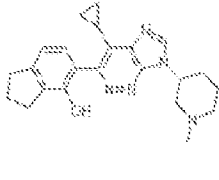
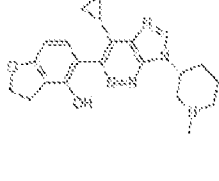
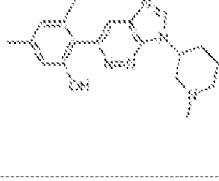
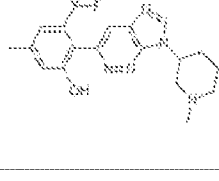
Compd_ID	Structure	Name
II-59		6-ethyl-5-[7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
II-60		6-methyl-5-[7-[rac-(1R,2S)-2-hydroxycyclobutyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
II-61		6-methyl-5-[7-[rac-(1R,2R)-2-hydroxycyclobutyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
II-62		5-chloro-3-(difluoromethyl)-2-[7-(3-hydroxy-3-methylcyclobutyl)pyrrolo[2,3-c]pyridazin-3-yl]phenol
IIA-1		2-[7-[(3R)-1-methyl-3-piperidyl]-4-(trifluoromethyl)pyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
IIB-1		5-[7-(3-hydroxy-3-methylcyclobutyl)-5-(trifluoromethyl)pyrrolo[2,3-c]pyridazin-3-yl]-6-methylbenzofuran-4-ol
IIB-2		2-[7-(3-hydroxy-3-methylcyclobutyl)-5-(trifluoromethyl)pyrrolo[2,3-c]pyridazin-3-yl]-5-methyl-3-(trifluoromethyl)phenol

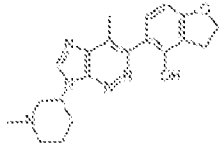
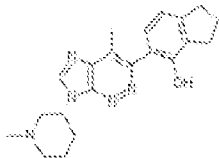
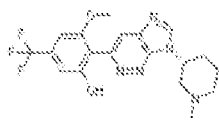
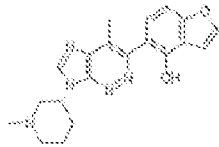
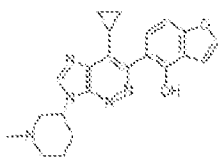
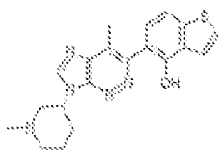
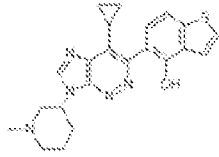
Cmpd_ID	Structure	Name
IIC-1		5-[5-(difluoromethyl)-7-(3-hydroxy-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol
IIC-2		3-(4-hydroxy-6-methyl-benzofuran-5-yl)-7-(3-hydroxy-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazine-5-carbaldehyde
IIC-3		2-[5-(difluoromethyl)-7-(3-hydroxy-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol
IIC-4		5-[5-(difluoromethyl)-7-(3-fluoro-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol
IIC-5		6-(difluoromethyl)-5-[5-(difluoromethyl)-7-(3-hydroxy-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
IID-1		3-(4-hydroxy-6-methyl-benzofuran-5-yl)-7-(3-hydroxy-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazine-5-carbonitrile
IIE-1		5-[5-cyclopropyl-7-(3-hydroxy-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol

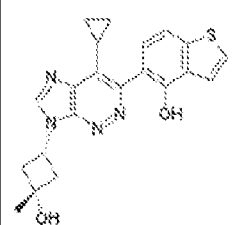
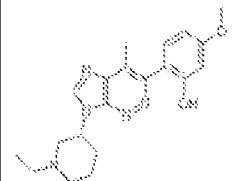
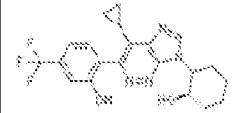
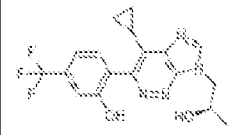
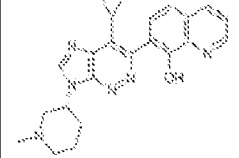
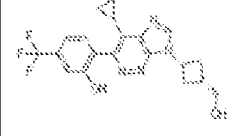
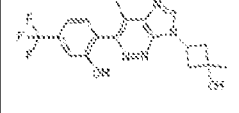
Cmpd_ID	Structure	Name
IIF-1		5-[5-fluoro-4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
IIF-2		5-[5-fluoro-4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol
IIF-3		5-[5-fluoro-7-(3-hydroxy-3-methyl-cyclobutyl)-4-methyl-pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol
IIG-1		5-[7-(3-hydroxy-3-methyl-cyclobutyl)-5-iodo-pyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-2,3-dihydrobenzofuran-4-ol
III-1		2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
III-2		3-methyl-2-[7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
III-3		5-chloro-3-fluoro-2-[6-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]phenol

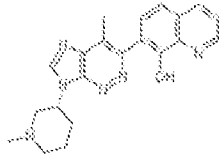
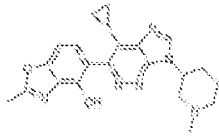
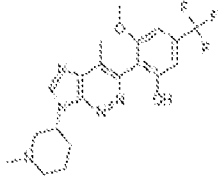
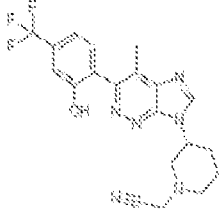
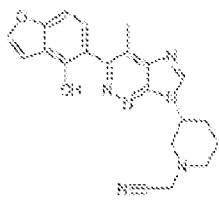
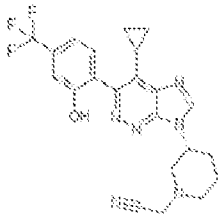
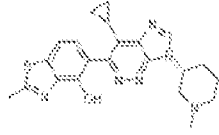
Cmpd_ID	Structure	Name
III-4		5-chloro-2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]phenol
III-5		2-[4-isopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
III-6		3-methyl-2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
III-7		2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol
III-8		2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
III-9		2-[4-cyclopropyl-7-[(3R)-1-(2-hydroxyethyl)-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
III-10		5-chloro-3-fluoro-2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]phenol

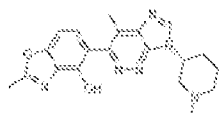
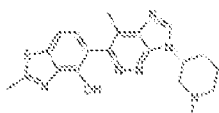
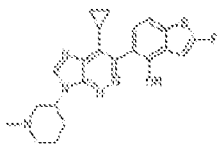
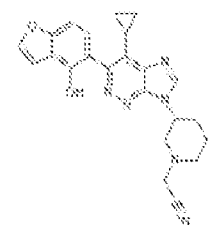
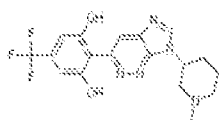
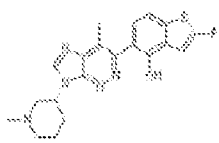
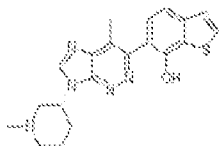
Cmpd_ID	Structure	Name
III-11		2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-3,5-dimethyl-phenol
III-12		5-methoxy-2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]phenol
III-13		2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-methoxy-phenol
III-14		4-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-3-hydroxy-benzonitrile
III-15		2-[4-cyclopropyl-7-(3-hydroxy-3-methyl-cyclobutyl)imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
III-16		(3S,4R)-4-[4-cyclopropyl-3-[2-hydroxy-4-(trifluoromethyl)phenyl]imidazo[4,5-c]pyridazin-7-yl]tetrahydropyran-3-ol
III-17		2-[4-cyclopropyl-7-(3-hydroxy-3-methyl-cyclobutyl)imidazo[4,5-c]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol

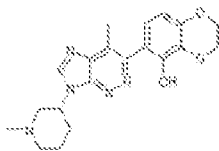
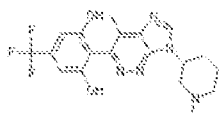
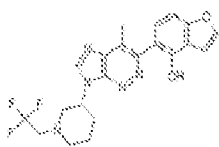
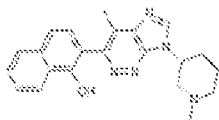
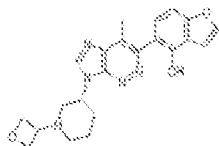
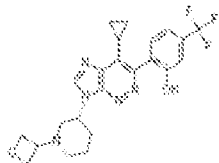
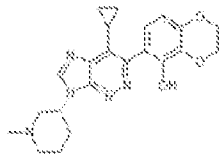
Compd_ID	Structure	Name
III-18		(3S,4R)-3-[4-cyclopropyl-3-[2-hydroxy-4-(trifluoromethyl)phenyl]imidazo[4,5-c]pyridazin-7-yl]-1-methylpiperidin-4-ol
III-19		(3S,4R)-3-[4-cyclopropyl-3-[2-hydroxy-4-(trifluoromethyl)phenyl]imidazo[4,5-c]pyridazin-7-yl]-1-ethylpiperidin-4-ol
III-20		(3S,4R)-3-[4-cyclopropyl-3-[2-hydroxy-4-(trifluoromethyl)phenyl]imidazo[4,5-c]pyridazin-7-yl]-1-(2-hydroxyethyl)piperidin-4-ol
III-21		5-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]indan-4-ol
III-22		5-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol
III-23		3,5-dimethyl-2-[7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]phenol
III-24		5-methyl-2-[7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-3-(trifluoromethyl)phenol

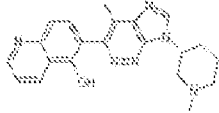
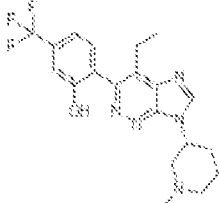
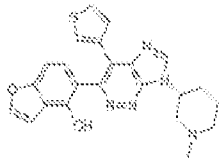
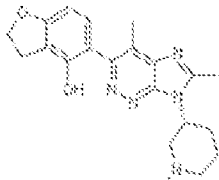
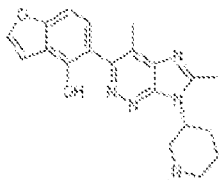
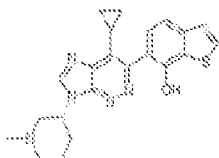
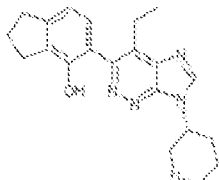
Cmpd_ID	Structure	Name
III-25		5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol
III-26		5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]indan-4-ol
III-27		3-methoxy-2-[7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
III-28		5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol
III-29		5-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol
III-30		5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzothiophen-4-ol
III-31		5-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzothiophen-4-ol

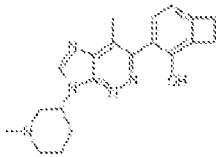
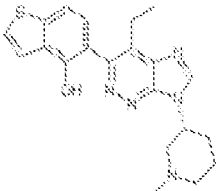
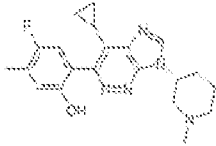
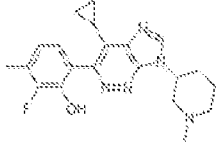
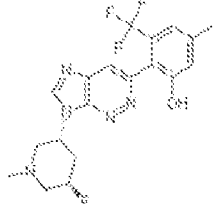
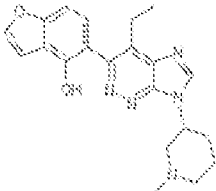
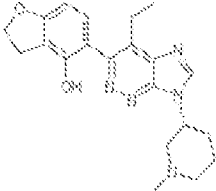
Cmpd_ID	Structure	Name
III-32		5-[4-cyclopropyl-7-(3-hydroxy-3-methyl-cyclobutyl)imidazo[4,5-c]pyridazin-3-yl]benzothiophen-4-ol
III-33		2-[7-[(3R)-1-ethyl-3-piperidyl]-4-methyl-imidazo[4,5-c]pyridazin-3-yl]-5-methoxy-phenol
III-34		2-[4-cyclopropyl-7-[(1R,2R)-2-hydroxycyclohexyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
III-35		2-[4-cyclopropyl-7-[(2R)-2-hydroxypropyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
III-36		7-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]quinolin-8-ol
III-37		2-[4-cyclopropyl-7-[3-(hydroxymethyl)cyclobutyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
III-38		2-[7-(3-hydroxy-3-methyl-cyclobutyl)-4-methyl-imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol

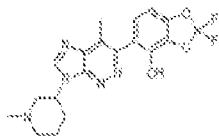
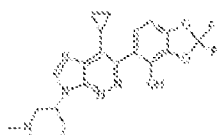
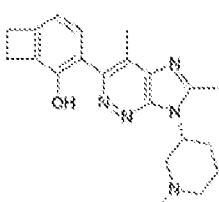
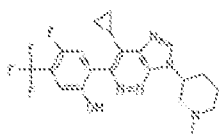
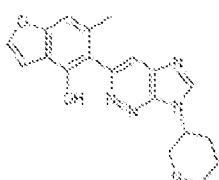
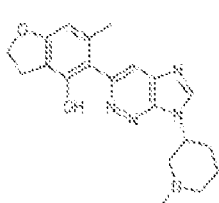
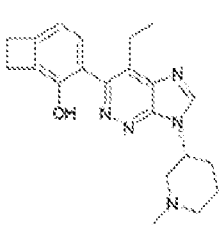
Cmpd_ID	Structure	Name
III-39		7-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]quinolin-8-ol
III-40		5-[4-cyclopropyl-7-[rac-(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-2-methyl-1,3-benzoxazol-4-ol
III-41		3-methoxy-2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
III-42		2-[(3R)-3-[3-[2-hydroxy-4-(trifluoromethyl)phenyl]-4-methyl-imidazo[4,5-c]pyridazin-7-yl]-1-piperidyl]acetonitrile
III-43		2-[(3R)-3-[3-(4-hydroxybenzofuran-5-yl)-4-methyl-imidazo[4,5-c]pyridazin-7-yl]-1-piperidyl]acetonitrile
III-44		2-[(3R)-3-[4-cyclopropyl-3-[2-hydroxy-4-(trifluoromethyl)phenyl]imidazo[4,5-c]pyridazin-7-yl]-1-piperidyl]acetonitrile
III-45		5-[4-cyclopropyl-7-[rac-(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-2-methyl-1,3-benzothiazol-4-ol

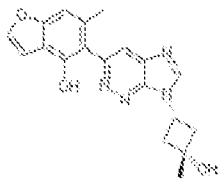
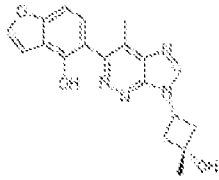
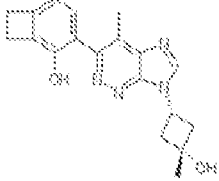
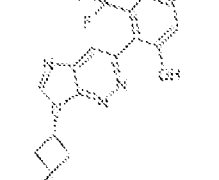
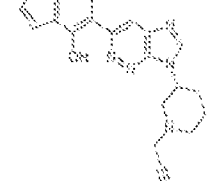
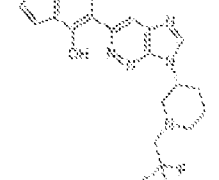
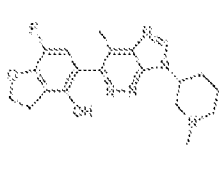
Compd_ID	Structure	Name
III-46		2-methyl-5-[4-methyl-7-[(rac-(3R)-1-methyl-3-piperidyl)]imidazo[4,5-c]pyridazin-3-yl]-1,3-benzoxazol-4-ol
III-47		2-methyl-5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]]imidazo[4,5-c]pyridazin-3-yl]-1,3-benzothiazol-4-ol
III-48		5-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]]imidazo[4,5-c]pyridazin-3-yl]-2-fluoro-benzothiophen-4-ol
III-49		2-[(3R)-3-[4-cyclopropyl-3-(4-hydroxybenzofuran-5-yl)]imidazo[4,5-c]pyridazin-7-yl]-1-piperidyl]acetonitrile
III-50		2-[7-[(3R)-1-methyl-3-piperidyl]]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)benzene-1,3-diol
III-51		2-fluoro-5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]]imidazo[4,5-c]pyridazin-3-yl]benzothiophen-4-ol
III-52		6-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]]imidazo[4,5-c]pyridazin-3-yl]benzothiophen-7-ol

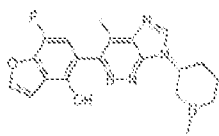
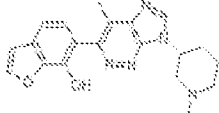
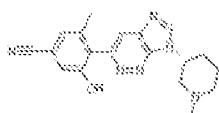
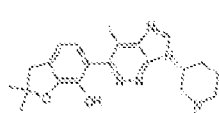
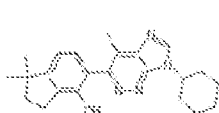
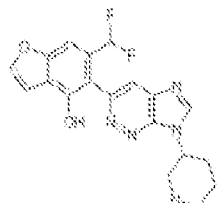
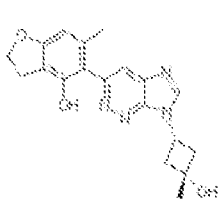
Cmpd_ID	Structure	Name
III-53		6-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-2,3-dihydro-1,4-benzodioxin-5-ol
III-54		2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)benzene-1,3-diol
III-55		5-[4-methyl-7-[(3R)-1-(2,2,2-trifluoroethyl)-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol
III-56		2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]naphthalen-1-ol
III-57		5-[4-methyl-7-[(3R)-1-(oxetan-3-yl)-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol
III-58		2-[4-cyclopropyl-7-[(3R)-1-(oxetan-3-yl)-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
III-59		6-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-2,3-dihydro-1,4-benzodioxin-5-ol

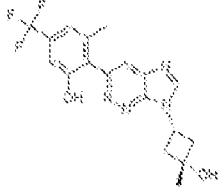
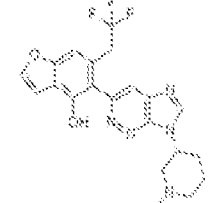
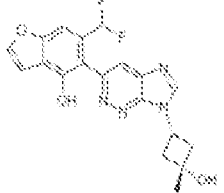
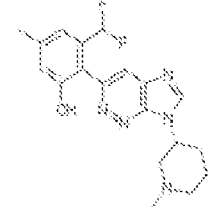
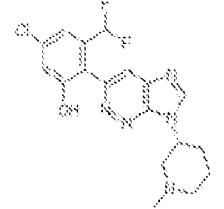
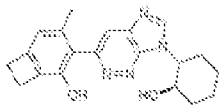
Compd_ID	Structure	Name
III-60		6-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]quinolin-5-ol
III-61		2-[4-ethyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
III-62		5-[7-[(3R)-1-methyl-3-piperidyl]-4-(3-thienyl)imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol
III-63		5-[4,6-dimethyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol
III-64		5-[4,6-dimethyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol
III-65		6-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzothiophen-7-ol
III-66		5-[4-ethyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]indan-4-ol

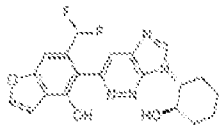
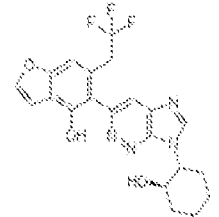
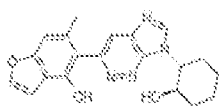
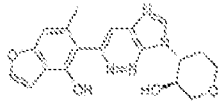
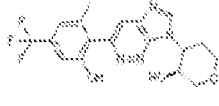
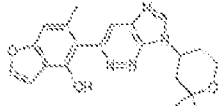
Compd_ID	Structure	Name
III-67		3-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]bicyclo[4.2.0]octa-1(6),2,4-trien-2-ol
III-68		5-[4-ethyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzothiophen-4-ol
III-69		2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-4-fluoro-5-methyl-phenol
III-70		6-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-2-fluoro-3-methyl-phenol
III-71		2-[7-[(3R,5R)-5-fluoro-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-methyl-3-(trifluoromethyl)phenol
III-72		5-[4-ethyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol
III-73		5-[4-ethyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol

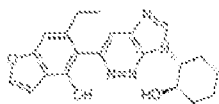
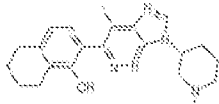
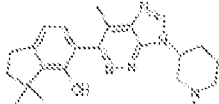
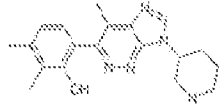
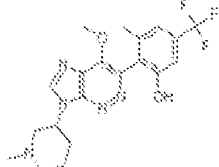
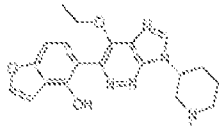
Cmpd_ID	Structure	Name
III-74		2,2-difluoro-5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-1,3-benzodioxol-4-ol
III-75		5-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-2,2-difluoro-1,3-benzodioxol-4-ol
III-76		3-[4,6-dimethyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]bicyclo[4.2.0]octa-1,3,5-trien-2-ol
III-77		2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-4-fluoro-5-(trifluoromethyl)phenol
III-78		6-methyl-5-[7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol
III-79		6-methyl-5-[7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol
III-80		3-[4-ethyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]bicyclo[4.2.0]octa-1(6),2,4-trien-2-ol

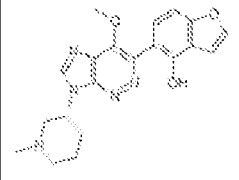
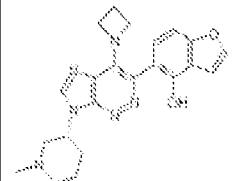
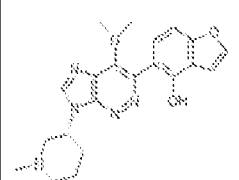
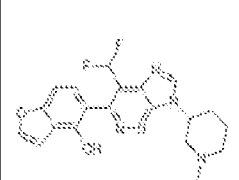
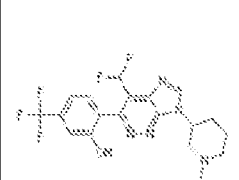
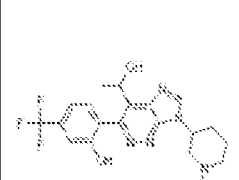
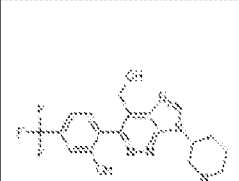
Compd_ID	Structure	Name
III-81		5-[7-(3-hydroxy-3-methyl-cyclobutyl)imidazo[4,5-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol
III-82		5-[7-(3-hydroxy-3-methyl-cyclobutyl)-4-methyl-imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol
III-83		3-[7-(3-hydroxy-3-methyl-cyclobutyl)-4-methyl-imidazo[4,5-c]pyridazin-3-yl]bicyclo[4.2.0]octa-1(6),2,4-trien-2-ol
III-84		2-[7-(3-hydroxy-3-methyl-cyclobutyl)imidazo[4,5-c]pyridazin-3-yl]-5-methyl-3-(trifluoromethyl)phenol
III-85		2-[(3R)-3-[3-(4-hydroxy-6-methyl-benzofuran-5-yl)imidazo[4,5-c]pyridazin-7-yl]-1-piperidyl]acetonitrile
III-86		6-methyl-5-[7-[(3R)-1-(2,2,2-trifluoroethyl)-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol
III-87		7-fluoro-5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol

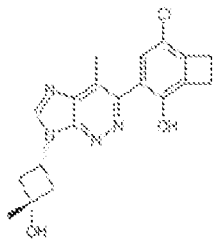
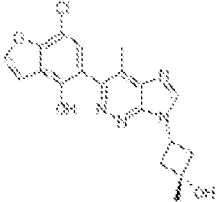
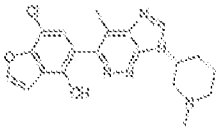
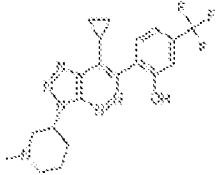
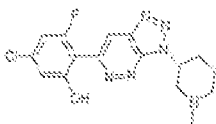
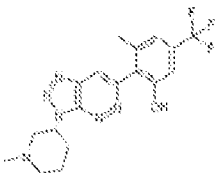
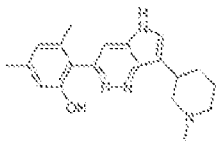
Compd_ID	Structure	Name
III-88		7-fluoro-5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol
III-89		6-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-7-ol
III-90		3-hydroxy-5-methyl-4-[7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzonitrile
III-91		2,2-dimethyl-6-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-3H-benzofuran-7-ol
III-92		1,1-dimethyl-5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]indan-4-ol
III-93		6-(difluoromethyl)-5-[7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol
III-94		5-[7-(3-hydroxy-3-methyl-cyclobutyl)imidazo[4,5-c]pyridazin-3-yl]-6-methyl-2,3-dihydrobenzofuran-4-ol

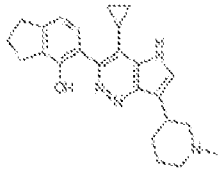
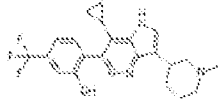
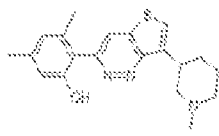
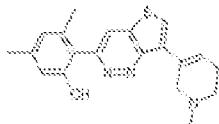
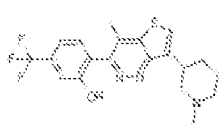
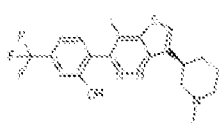
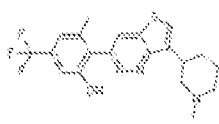
Cmpd_ID	Structure	Name
III-95		2-[7-(3-hydroxy-3-methyl-cyclobutyl)imidazo[4,5-c]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol
III-96		5-[7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-6-(2,2,2-trifluoroethyl)benzofuran-4-ol
III-97		6-(difluoromethyl)-5-[7-(3-hydroxy-3-methyl-cyclobutyl)imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol
III-98		3-(difluoromethyl)-5-methyl-2-[7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]phenol
III-99		5-chloro-3-(difluoromethyl)-2-[7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]phenol
III-100		5-[7-(3,3-dimethyltetrahydropyran-4-yl)imidazo[4,5-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol
III-101		3-[7-[(1R,2R)-2-hydroxycyclohexyl]imidazo[4,5-c]pyridazin-3-yl]-4-methyl-bicyclo[4.2.0]octa-1,3,5-trien-2-ol

Cmpd_ID	Structure	Name
III-102		6-(difluoromethyl)-5-[7-[(1R,2R)-2-hydroxycyclohexyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol
III-103		5-[7-[(1R,2R)-2-hydroxycyclohexyl]imidazo[4,5-c]pyridazin-3-yl]-6-(2,2,2-trifluoroethyl)benzofuran-4-ol
III-104		6-ethyl-5-[7-(3-hydroxy-3-methyl-cyclobutyl)imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol
III-105		5-[7-[(1R,2R)-2-hydroxycyclohexyl]imidazo[4,5-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol
III-106		5-[7-[(3S,4R)-3-hydroxytetrahydropyran-4-yl]imidazo[4,5-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol
III-107		(3S,4R)-4-[3-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]imidazo[4,5-c]pyridazin-7-yl]tetrahydropyran-3-ol
III-108		5-[7-(2,2-dimethyltetrahydropyran-4-yl)imidazo[4,5-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol

Cmpd_ID	Structure	Name
III-109		6-ethyl-5-[7-[(1R,2R)-2-hydroxycyclohexyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol
III-110		6-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]tetralin-5-ol
III-111		3,3-dimethyl-5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]indan-4-ol
III-112		2,3-dimethyl-6-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]phenol
IIIA-1		2-[4-methoxy-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol
IIIA-2		5-[4-(cyclopropoxy)-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol
IIIA-3		5-[4-ethoxy-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol

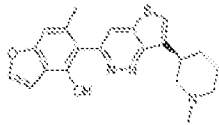
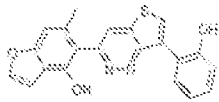
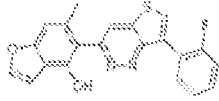
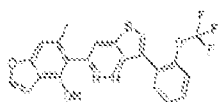
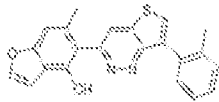
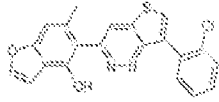
Compd_ID	Structure	Name
IIIA-4		5-[4-methoxy-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol
IIIA-5		5-[4-(azetidin-1-yl)-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol
IIIA-6		5-[4-(dimethylamino)-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol
IIIB-1		5-[4-(difluoromethyl)-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol
IIIB-2		2-[4-(difluoromethyl)-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
IIIC-1		2-[4-(1-hydroxyethyl)-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
IIID-1		2-[4-(hydroxymethyl)-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol

Cmpd_ID	Structure	Name
IIIE-1		5-chloro-3-[7-(3-hydroxy-3-methyl-cyclobutyl)-4-methyl-imidazo[4,5-c]pyridazin-3-yl]bicyclo[4.2.0]octa-1(6),2,4-trien-2-ol
IIIE-2		7-chloro-5-[7-(3-hydroxy-3-methyl-cyclobutyl)-4-methyl-imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol
IIIE-3		7-chloro-5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol
IV-1		2-[7-cyclopropyl-3-[(3R)-1-methyl-3-piperidyl]triazolo[4,5-c]pyridazin-6-yl]-5-(trifluoromethyl)phenol
IV-2		5-chloro-3-fluoro-2-[3-[(3R)-1-methyl-3-piperidyl]triazolo[4,5-c]pyridazin-6-yl]phenol
IV-3		3-methyl-2-[3-[(3R)-1-methyl-3-piperidyl]triazolo[4,5-c]pyridazin-6-yl]-5-(trifluoromethyl)phenol
V-1		3,5-dimethyl-2-[7-(1-methyl-3-piperidyl)-5H-pyrrolo[3,2-c]pyridazin-3-yl]phenol

Compd_ID	Structure	Name
V-2		5-[4-cyclopropyl-7-(1-methyl-3-piperidyl)-5H-pyrrolo[3,2-c]pyridazin-3-yl]indan-4-ol
V-3		2-[4-cyclopropyl-7-(1-methyl-3-piperidyl)-5H-pyrrolo[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
VI-1		3,5-dimethyl-2-[7-(1-methyl-3-piperidyl)thieno[3,2-c]pyridazin-3-yl]phenol
VI-2		3,5-dimethyl-2-[7-(1-methyl-3,6-dihydro-2H-pyridin-5-yl)thieno[3,2-c]pyridazin-3-yl]phenol
VI-3		2-[4-methyl-7-[(3S)-1-methyl-3-piperidyl]thieno[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
VI-4		2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]thieno[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
VI-5		3-methyl-2-[7-[(3S)-1-methyl-3-piperidyl]thieno[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol

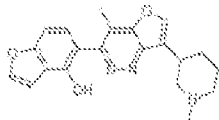
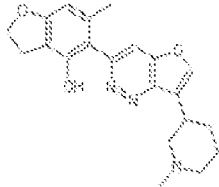
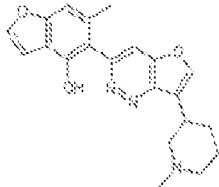
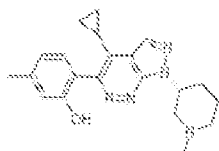
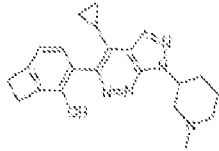
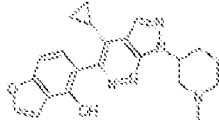
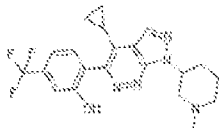
Compd_ID	Structure	Name
VI-6		3-methyl-2-[7-[(3R)-1-methyl-3-piperidyl]thieno[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
VI-7		2-[4-methyl-7-(1-methyl-3,6-dihydro-2H-pyridin-5-yl)thieno[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
VI-8		2-[4-cyclopropyl-7-(1-methyl-3-piperidyl)thieno[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
VI-9		3-methyl-2-[4-methyl-7-(1-methyl-3-piperidyl)thieno[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
VI-10		5-[4-methyl-7-[(3S)-1-methyl-3-piperidyl]thieno[3,2-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol
VI-11		5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]thieno[3,2-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol
VI-12		5-[4-methyl-7-(1-methyl-3-piperidyl)thieno[3,2-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol

Compd_ID	Structure	Name
VI-13		6-methyl-5-[7-(1-methyl-3-piperidyl)thieno[3,2-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol
VI-14		5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]thieno[3,2-c]pyridazin-3-yl]indan-4-ol
VI-15		5-[4-methyl-7-[(3S)-1-methyl-3-piperidyl]thieno[3,2-c]pyridazin-3-yl]indan-4-ol
VI-16		3-[4-methyl-7-(1-methyl-3-piperidyl)thieno[3,2-c]pyridazin-3-yl]bicyclo[4.2.0]octa-1(6),2,4-trien-2-ol
VI-17		6-methyl-5-[7-(1-methyl-3-piperidyl)thieno[3,2-c]pyridazin-3-yl]benzofuran-4-ol
VI-18		5-[4-methyl-7-(1-methyl-3-piperidyl)thieno[3,2-c]pyridazin-3-yl]indan-4-ol
VI-19		6-methyl-5-[7-[(3S)-1-methyl-3-piperidyl]thieno[3,2-c]pyridazin-3-yl]benzofuran-4-ol

Cmpd_ID	Structure	Name
VI-20		6-methyl-5-[7-[(3R)-1-methyl-3-piperidyl]thieno[3,2-c]pyridazin-3-yl]benzofuran-4-ol
VIA-1		5-[7-(2-hydroxyphenyl)thieno[3,2-c]pyridazin-3-yl]-6-methylbenzofuran-4-ol
VIA-2		5-[7-(2-fluorophenyl)thieno[3,2-c]pyridazin-3-yl]-6-methylbenzofuran-4-ol
VIA-3		6-methyl-5-[7-[2-(trifluoromethoxy)phenyl]thieno[3,2-c]pyridazin-3-yl]benzofuran-4-ol
VIA-4		6-methyl-5-[7-[2-(trifluoromethyl)phenyl]thieno[3,2-c]pyridazin-3-yl]benzofuran-4-ol
VIA-5		6-methyl-5-[7-(o-tolyl)thieno[3,2-c]pyridazin-3-yl]benzofuran-4-ol
VIA-6		5-[7-(2-chlorophenyl)thieno[3,2-c]pyridazin-3-yl]-6-methylbenzofuran-4-ol

Cmpd_ID	Structure	Name
VIB-1		5-[7-(3,6-dihydro-2H-pyran-4-yl)thieno[3,2-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol
VIB-2		6-methyl-5-(7-tetrahydropyran-4-ylthieno[3,2-c]pyridazin-3-yl)benzofuran-4-ol
VIB-3		5-methyl-2-(7-tetrahydropyran-3-ylthieno[3,2-c]pyridazin-3-yl)-3-(trifluoromethyl)phenol
VIB-4		6-methyl-5-(7-tetrahydrofuran-3-ylthieno[3,2-c]pyridazin-3-yl)benzofuran-4-ol
VIB-5		5-[7-(2,5-dihydrofuran-3-yl)thieno[3,2-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol
VIB-6		6-methyl-5-(7-tetrahydropyran-3-ylthieno[3,2-c]pyridazin-3-yl)benzofuran-4-ol
VII-1		3-methyl-2-[7-(1-methyl-3,6-dihydro-2H-pyridin-5-yl)furo[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol

Cmpd_ID	Structure	Name
VII-2		3-methyl-2-[7-(1-methyl-3-piperidyl)furo[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
VII-3		2-[4-methyl-7-(1-methyl-3-piperidyl)furo[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
VII-4		5-[4-methyl-7-(1-methyl-3-piperidyl)furo[3,2-c]pyridazin-3-yl]indan-4-ol
VII-5		5-[4-methyl-7-(1-methyl-3-piperidyl)furo[3,2-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol
VII-6		3-methyl-2-[4-methyl-7-(1-methyl-3-piperidyl)furo[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
VII-7		3-methyl-2-[7-[(3R)-1-methyl-3-piperidyl]furo[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol
VII-8		3-methyl-2-[7-[(3S)-1-methyl-3-piperidyl]furo[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol

Cmpd_ID	Structure	Name
VII-9		5-[4-methyl-7-(1-methyl-3-piperidyl)furo[3,2-c]pyridazin-3-yl]benzofuran-4-ol
VII-10		6-methyl-5-[7-(1-methyl-3-piperidyl)furo[3,2-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol
VII-11		6-methyl-5-[7-(1-methyl-3-piperidyl)furo[3,2-c]pyridazin-3-yl]benzofuran-4-ol
VIII-1		2-[4-cyclopropyl-1-(1-methyl-3-piperidyl)pyrazolo[3,4-c]pyridazin-5-yl]-5-methyl-phenol
VIII-2		3-[4-cyclopropyl-1-(1-methyl-3-piperidyl)pyrazolo[3,4-c]pyridazin-5-yl]bicyclo[4.2.0]octa-1,3,5-trien-2-ol
VIII-3		5-[4-cyclopropyl-1-(1-methyl-3-piperidyl)pyrazolo[3,4-c]pyridazin-5-yl]benzofuran-4-ol
VIII-4		2-[4-cyclopropyl-1-(1-methyl-3-piperidyl)pyrazolo[3,4-c]pyridazin-5-yl]-5-(trifluoromethyl)phenol

wherein a form of the compound may be selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

5

In embodiment 13, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of embodiments 1 to 12 or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers.

10 In embodiment 14, the invention provides a method for treating or ameliorating a disease modulated by NLRP3 in a subject in need thereof comprising, administering to the subject an effective amount of the compound according to of any one of embodiments 1 to 12.

In embodiment 15, the invention provides a method of treating or ameliorating a disease modulated by NLRP3 according to embodiment 14 selected from Alzheimer disease,
15 Frontotemporal dementia (FTD), Huntington's disease, Parkinson's disease, Perioperative neurocognitive disorders, Post-cardiac arrest cognitive impairment, Poststroke cognitive impairment, Sepsis, Sepsis associated encephalopathy, Subarachnoid hemorrhage, Macular Degeneration, Retinal neovascularization, Uveitis, Colitis, Endothelial dysfunction, Gout,
20 Pseudogout, Graft-versus-host-disease (GvHD), Systemic lupus erythematosus-lupus nephritis, Cryopyrin-associated periodic syndromes (CAPS), Cystic fibrosis, Sickle-cell disease, VCP-associated disease, Liver fibrosis, Nonalcoholic fatty liver disease (NASH), muscle atrophy, inherited and acquired myopathies, e.g. Duchenne Muscular Dystrophy (DMD), Hyperalgesia, Multiple sclerosis-associated neuropathic pain, Acute Kidney Injury, Chronic crystal
25 nephropathy, Chronic Kidney Disease, asthma and allergic airway inflammation Diabetes-associated atherosclerosis, Diabetic encephalopathy, Diabetic kidney disease, Islet transplantation rejection, Obesity-associated renal disease, Oxalate-induced nephropathy, Renal fibrosis, Renal hypertension, Type I diabetes, Type II diabetes, Psoriasis, Hidradenitis suppurativa, Atherosclerosis and Cytokine Release Syndrome (CRS).

30

In embodiment 16, the invention provides a method of any one of embodiments 14 to 15, wherein the effective amount of the compound is in a range of from about 0.001 mg/kg/day to about 500 mg/kg/day.

5 In embodiment 17, the invention provides a compound according to any one of embodiments 1 to 12 or a pharmaceutically acceptable salt thereof, for use in treating or ameliorating a disease modulated by NLRP3 selected from Alzheimer disease, Frontotemporal dementia (FTD), Huntington's disease, Parkinson's disease, Perioperative neurocognitive disorders, Post-cardiac arrest cognitive impairment, Poststroke cognitive impairment, Sepsis, Sepsis associated encephalopathy, Subarachnoid
10 hemorrhage, Macular Degeneration, Retinal neovascularization, Uveitis, Colitis, Endothelial dysfunction, Gout, Pseudogout, Graft-versus-host-disease (GvHD), Systemic lupus erythematosus-lupus nephritis, Cryopyrin-associated periodic syndromes (CAPS), Cystic fibrosis, Sickle-cell disease, VCP-associated disease, Liver fibrosis, Nonalcoholic fatty liver disease (NAFLD), muscle atrophy, inherited and acquired myopathies, Hyperalgesia, Multiple sclerosis-associated neuropathic pain, Acute Kidney Injury, Chronic
15 crystal nephropathy, Chronic Kidney Disease, asthma and allergic airway inflammation Diabetes-associated atherosclerosis, Diabetic encephalopathy, Diabetic kidney disease, Islet transplantation rejection, Obesity-associated renal disease, Oxalate-induced nephropathy, Renal fibrosis, Renal hypertension, Type I diabetes, Type II diabetes, Psoriasis, Hidradenitis suppurativa, Atherosclerosis and Cytokine Release Syndrome (CRS).

20

In embodiment 18, the invention provides the use of a compound according to embodiment 17, wherein the effective amount of the compound is in a range of from about 0.001 mg/kg/day to about 500 mg/kg/day.

25 In embodiment 19, the invention provides the use of a compound according to any one of embodiments 1 to 12 in the preparation of a pharmaceutical composition for treating or ameliorating a disease modulated by NLRP3 in a subject in need thereof comprising, administering to the subject an effective amount of the compound or a form thereof in admixture with one or more of the pharmaceutically acceptable excipients.

30

METHOD OF USE OF THE INVENTION

There is evidence for a role of NLRP3-induced IL-1 and IL-18 in the inflammatory responses occurring in connection with, or as a result of, a multitude of different disorders (Menu et al, *Clinical and Experimental Immunology*, 2011, 166, 1-15; Strowig et al, *Nature*, 2012, 481, 278-286). NLRP3 mutations have been found to be responsible for a set of rare autoinflammatory diseases known as CAPS (Ozaki et al, *J. Inflammation Research*, 2015, 8, 15-27; Schroder et al, *Cell*, 2010, 140:821-832; Menu et al, *Clinical and Experimental Immunology*, 2011, 166, 1-15). CAPS are heritable diseases characterized by recurrent fever and inflammation and are comprised of three autoinflammatory disorders that form a clinical continuum. These

diseases, in order of increasing severity, are familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and chronic infantile cutaneous neurological articular syndrome (CINCA; also called neonatal-onset multisystem inflammatory disease, NOMID), and all have been shown to result from gain-of-function mutations in the NLRP3 gene, which leads to increased secretion of IL-1 beta. NLRP3 has also been implicated in a number of

autoinflammatory diseases, including pyogenic arthritis, pyoderma gangrenosum and acne (PAPA), Sweet's syndrome, chronic nonbacterial osteomyelitis (CNO), and acne vulgaris (Cook et al, *Eur J. Immunol.*, 2010, 40, 595-653). A number of autoimmune diseases have been shown to involve NLRP3 including, in particular, multiple sclerosis, type-1 diabetes (T1D), psoriasis, rheumatoid arthritis (RA), Behcet's disease, Schnitzler syndrome, macrophage

activation syndrome (Braddock et al. *Nat. Rev. Drug Disc.* 2004, 3, 1-10; Inoue et al, *Immunology*, 2013, 139, 11-18, Coll et al, *Nat. Med.* 2015, 21(3), 248-55; Scott et al, *Clin. Exp. Rheumatol.* 2016, 34(1), 88-93), systemic lupus erythematosus and its complications such as lupus nephritis (Lu et al, *J. Immunol.*, 2017, 198(3), 1119-29), and systemic sclerosis (Artlett et al, *Arthritis Rheum.* 2011, 63(11), 3563-74). NLRP3 has also been shown to play a role in a number of lung diseases including chronic obstructive pulmonary disorder (COPD), asthma (including steroidresistant asthma), asbestosis, and silicosis (De Nardo et al, *Am. J. Pathol.*, 2014, 184: 42-54; Kim et al. *Am. J. Respir Crit Care Med*, 2017, 196(3), 283-97). NLRP3 has also been suggested to have a role in a number of central nervous system conditions, including Multiple Sclerosis (MS), Parkinson's disease (PD), Alzheimer's disease (AD), dementia,

Huntington's disease, cerebral malaria, brain injury from pneumococcal meningitis (Walsh et al, *Nature Reviews*, 2014, 15, 84-97; and Dempsey et al. *Brain. Behav. Immun.* 2017, 61, 306-16), intracranial aneurysms (Zhang et al. *J. Stroke and Cerebrovascular Dis.*, 2015, 24, 5, 972-9), and traumatic brain injury (Ismael et al. *J. Neurotrauma.*, 2018, 35(11), 1294-1303).

5 NLRP3 activity has also been shown to be involved in various metabolic diseases including type 2

diabetes (T2D) and its organ-specific complications, atherosclerosis, obesity, gout, pseudo-gout, metabolic syndrome (Wen et al, *Nature Immunology*, 2012, 13, 352-357; Duewell et al, *Nature*, 2010, 464, 1357-1361; Strowig et al, *Nature*, 2014, 481, 278-286), and non-
10 alcoholic steatohepatitis (Mridha et al. *J. Hepatol.* 2017, 66(5), 1037-46). NLRP3 is also suggested to play a key pathological role in the development and progression of several skeletal muscle diseases, e.g. muscle atrophy, inherited and acquired myopathies (Dubussion et al. *Cells* 2021, 10(11):3023). A role for NLRP3 via IL-1 beta has also been suggested in atherosclerosis, myocardial infarction (van Hout et al. *Eur Heart J.*

15 2017, 38(11), 828-3-6), heart failure (Sano et al. *J. Am. Coll. Cardiol.* 2018, 71(8), 875-66), aortic aneurysm and dissection (Wu et al. *Arterioscler Thromb. Vase. Biol.*, 2017, 37(4), 694-706), and other cardiovascular events (Ridker et al, *N. Engl. J. Med.*, 2017, 377(12), 1119-31). Other diseases in which NLRP3 has been shown to be involved include: ocular diseases

such as both wet and dry age-related macular degeneration (Doyle et al. *Nature Medicine*, 2012, 18, 791-798; Tarallo et al. *Cell* 2012, 149(4), 847-59), diabetic retinopathy (Loukovaara et al.

20 *Acta Ophthalmol.*, 2017, 95(8), 803-8), non-infectious uveitis and optic nerve damage (Puyang et al. *Sci. Rep.* 2016, 6, 20998); liver diseases including non-alcoholic steatohepatitis (NASH) and acute alcoholic hepatitis (Henao-Mejia et al, *Nature*, 2012, 482, 179-185); inflammatory

reactions in the lung and skin (Primiano et al. *J. Immunol.* 2016, 197(6), 2421-33) including

25 contact hypersensitivity (such as bullous pemphigoid (Fang et al. *J Dermatol Sci.* 2016, 83(2),

116-23)), atopic dermatitis (Niebuhr et al. *Allergy*, 2014, 69(8), 1058-67), Hidradenitis suppurativa (Alikhan et al. *J. Am. Acad. Dermatol.*, 2009, 60(4), 539-61), and sarcoidosis (Jager et al. *Am. J. Respir Crit. Care Med.*, 2015, 191, A5816); inflammatory reactions in the joints

(Braddock et al, *Nat. Rev. Drug Disc.*, 2004, 3, 1-10); amyotrophic lateral sclerosis (Gugliandolo et al. *Int. J. Mol. Sci.*, 2018, 19(7), E1992); cystic fibrosis (Iarmiti et al. *Nat. Commun.*, 2016,

30

7, 10791); stroke (Walsh et al, *Nature Reviews*, 2014, 15, 84-97); chronic kidney disease (Granata et al. *PLoS One* 2015, 10(3), e022272); and inflammatory bowel diseases including ulcerative colitis and Crohn's disease (Braddock et al, *Nat. Rev. Drug Disc.* 2004, 3, 1-10; Neudecker et al. *J. Exp. Med.* 2017, 214(6), 1737-52; Lazaridis et al. *Dig. Dis. Sci.* 2017, 62(9), 2348-56). The NLRP3 inflammasome has been found to be activated in response to oxidative stress. NLRP3 has also been shown to be involved in inflammatory hyperalgesia (Dolunay et al, *Inflammation*, 2017, 40, 3-66-86). US application US202003-61898 is incorporated herein by reference.

COMPOUND FORMS

To assist in understanding the scope of the compounds of Formula (I) or a form thereof described herein, the following Specific Examples are included. The experiments relating to the compounds of Formula (I) or a form thereof described herein should not, of course, be construed as specifically limiting the scope of the compounds of Formula (I) or a form thereof described herein and such variations of the compounds of Formula (I) or a form thereof as described herein, now known or later developed, which would be within the purview of one skilled in the art are considered to fall within the scope as described herein and hereinafter claimed.

Other than in the working examples, unless indicated to the contrary, all numbers expressing quantities of ingredients, reaction conditions, experimental data, and so forth used in the specification and claims are to be understood as being modified by the term "about". Accordingly, all such numbers represent approximations that may vary depending upon the desired properties sought to be obtained by a reaction or as a result of variable experimental conditions. Therefore, within an expected range of experimental reproducibility, the term "about" in the context of the resulting data, refers to a range for data provided that may vary according to a standard deviation from the mean. As well, for experimental results provided, the resulting data may be rounded up or down to present data consistently, without loss of significant figures. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should be construed in light of the number of significant digits and ordinary rounding techniques.

While the numerical ranges and parameters setting forth the characterization of the compounds of Formula (I) or a form thereof described herein are approximations, the numerical values set forth in the working examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements.

The compounds of Formula (I) or a form thereof provided herein are described in more detail with reference to the following non-limiting examples, which are offered to more fully illustrate the scope of the compounds of Formula (I) or a form thereof described herein, but are not to be construed as limiting the scope thereof. The examples illustrate the preparation of compounds of Formula (I) or a form thereof described herein, and the testing of these compounds of Formula (I) or a form thereof *in vitro* and/or *in vivo*. Those of skill in the art will understand that the synthesis techniques described in these examples represent techniques that fall within the practice of those having ordinary skill in the chemical arts, and as such constitute preferred modes for the practice thereof. However, it should be appreciated that those having skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific methods that are disclosed herein while still obtaining a like or similar result without departing from the spirit and scope described herein.

In certain embodiments described herein, the compound of Formula (I) or a form thereof is isolated for use.

As used herein, the term “isolated” means the physical state of a compound of Formula (I) or a form thereof after being isolated and/or separated and/or purified from a synthetic process (*e.g.*, from a reaction mixture) or natural source or combination thereof according to an isolation, separation or purification process or processes described herein or which are well known to the skilled artisan (*e.g.*, chromatography, recrystallization and the like) in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

As used herein, the term “protected” means that a functional group on a compound of Formula (I) or a form thereof is in a form modified to preclude undesired side reactions of the functional group when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks

such as, for example, T. W. Greene *et al*, *Protective Groups in Organic Synthesis* (2007), Wiley, New York.

Prodrugs and solvates of the compounds of Formula (I) or a form thereof described herein are also contemplated.

5 As used herein, the term “prodrug” means that a functional group on a compound of Formula (I) is in a form (*e.g.*, acting as an active or inactive drug precursor) that is transformed *in vivo* to yield an active or more active compound of Formula (I) or a form thereof. The transformation may occur by various mechanisms (*e.g.*, by metabolic and/or non-metabolic chemical processes), such as, for example, by hydrolysis and/or metabolism in blood, liver
10 and/or other organs and tissues. A discussion of the use of prodrugs is provided by V.J. Stella, *et. al.*, “Biotechnology: Pharmaceutical Aspects, Prodrugs: Challenges and Rewards,” American Association of Pharmaceutical Scientists and Springer Press, 2007.

In one example, when a compound of Formula (I) or a form thereof contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the
15 hydrogen atom of the acid group with a functional group such as alkyl and the like. In another example, when a compound of Formula (I) or a form thereof contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a functional group such as alkyl or carbonyloxy and the like. In another example, when a compound of Formula (I) or a form thereof contains an amine functional group, a prodrug can be
20 formed by the replacement of one or more amine hydrogen atoms with a functional group such as alkyl or substituted carbonyl.

Pharmaceutically acceptable prodrugs of compounds of Formula (I) or a form thereof include those compounds substituted with one or more of the following groups: carboxylic acid esters, sulfonate esters, amino acid esters, phosphonate esters (*e.g.*, a phosphoramidic acid used
25 to derive a phosphoramidic acid) and mono-, di- or triphosphate esters further substituted with alkyl, where appropriate. As described herein, it is understood by a person of ordinary skill in the art that one or more of such substituents may be used to provide a compound of Formula (I) or a form thereof as a prodrug.

The compounds of Formula (I) or a form thereof can form salts, which are intended to be
30 included within the scope of this description. Reference to a compound of Formula (I) or a form

thereof herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula (I) or a form thereof contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein.

The term "pharmaceutically acceptable salt(s)", as used herein, means those salts of compounds of Formula (I) or a form thereof described herein that are safe and effective (*i.e.*, non-toxic, physiologically acceptable) for use in mammals and that possess biological activity, although other salts are also useful. Salts of the compounds of the Formula (I) may be formed, for example, by reacting a compound of Formula (I) with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Pharmaceutically acceptable salts include one or more salts of acidic or basic groups present in compounds of Formula (I) or a form thereof described herein. Embodiments of acid addition salts include, and are not limited to, acetate, acid phosphate, ascorbate, benzoate, benzenesulfonate, bisulfate, bitartrate, borate, butyrate, chloride, citrate, camphorate, camphorsulfonate, ethanesulfonate, formate, fumarate, gentisinate, gluconate, glucaronate, glutamate, hydrobromide, hydrochloride, dihydrochloride, hydroiodide, isonicotinate, lactate, maleate, methanesulfonate, naphthalenesulfonate, nitrate, oxalate, pamoate, pantothenate, phosphate, propionate, saccharate, salicylate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate (also known as tosylate), trifluoroacetate, trifluoroacetic acid salt and the like. One or more embodiments of acid addition salts include chloride, hydrochloride, dihydrochloride, trihydrochloride, hydrobromide, acetate, diacetate, methanesulfonate, sulfate, trifluoroacetate, trifluoroacetic acid salt and the like. More particular embodiments include a chloride, hydrochloride, dihydrochloride, hydrobromide, methanesulfonate, sulfate, trifluoroacetate, trifluoroacetic acid salt and the like.

In certain embodiments of the compounds of Formula (I) or a form thereof described herein, the compound is isolated as a salt form, wherein the compound is conjugated with the salt

in a ratio represented as, in a non-limiting example, "compound:salt (A:B)," wherein "A" and "B" represent the equivalents of compound to salt in the isolated form.

Additionally, acids which are considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*,
5 Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use*. (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33, 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated
10 herein by reference thereto.

Suitable basic salts include, but are not limited to, aluminum, ammonium, calcium, lithium, magnesium, potassium, sodium, zinc, and diethanolamine salts. Certain compounds of Formula (I) or a form thereof described herein can also form pharmaceutically acceptable salts with organic bases (for example, organic amines) such as, but not limited to,
15 dicyclohexylamines, *tert*-butyl amines and the like, and with various amino acids such as, but not limited to, arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (*e.g.*, methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (*e.g.*, dimethyl, diethyl, and dibutyl sulfates), long chain halides (*e.g.*, decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (*e.g.*, benzyl and
20 phenethyl bromides), and others.

All such acid salts and base salts are intended to be included within the scope of pharmaceutically acceptable salts as described herein. In addition, all such acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of this description.

25 Compounds of Formula (I), and forms thereof, may further exist in a tautomeric form. All such tautomeric forms are contemplated and intended to be included within the scope of the compounds of Formula (I) or a form thereof as described herein.

The compounds of Formula (I) or a form thereof may contain asymmetric or chiral centers, and, therefore, may exist in different stereoisomeric forms. The present description is

intended to include all stereoisomeric forms of the compounds of Formula (I) as well as mixtures thereof, including racemic mixtures.

The compounds of Formula (I) or a form thereof described herein may include one or more chiral centers, and as such may exist as racemic mixtures (*R/S*) or as substantially pure enantiomers and diastereomers. The compounds may also exist as substantially pure (*R*) or (*S*) enantiomers (when one chiral center is present). In one embodiment, the compounds of Formula (I) or a form thereof described herein are (*S*) isomers and may exist as enantiomerically pure compositions substantially comprising only the (*S*) isomer. In another embodiment, the compounds of Formula (I) or a form thereof described herein are (*R*) isomers and may exist as enantiomerically pure compositions substantially comprising only the (*R*) isomer. As one of skill in the art will recognize, when more than one chiral center is present, the compounds of Formula (I) or a form thereof described herein may also exist as a (*R,R*), (*R,S*), (*S,R*) or (*S,S*) isomer, as defined by *IUPAC* Nomenclature Recommendations.

As used herein, the term “substantially pure” refers to compounds of Formula (I) or a form thereof consisting substantially of a single isomer in an amount greater than or equal to 90%, in an amount greater than or equal to 92%, in an amount greater than or equal to 95%, in an amount greater than or equal to 98%, in an amount greater than or equal to 99%, or in an amount equal to 100% of the single isomer.

In one aspect of the description, a compound of Formula (I) or a form thereof is a substantially pure (*S*) enantiomer present in an amount greater than or equal to 90%, in an amount greater than or equal to 92%, in an amount greater than or equal to 95%, in an amount greater than or equal to 98%, in an amount greater than or equal to 99%, or in an amount equal to 100%.

In one aspect of the description, a compound of Formula (I) or a form thereof is a substantially pure (*R*) enantiomer present in an amount greater than or equal to 90%, in an amount greater than or equal to 92%, in an amount greater than or equal to 95%, in an amount greater than or equal to 98%, in an amount greater than or equal to 99%, or in an amount equal to 100%.

As used herein, the term "racemate" refers to any mixture of isometric forms that are not "enantiomerically pure", including mixtures such as, without limitation, in a ratio of about 50/50, about 60/40, about 70/30, or about 80/20, about 85/15 or about 90/10.

5 In addition, the compounds of Formula (I) or a form thereof described herein embrace all geometric and positional isomers. For example, if a compound of Formula (I) or a form thereof incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures thereof, are embraced within the scope of the compounds of Formula (I) or a form thereof described herein.

10 Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by use of a chiral HPLC column or other chromatographic methods known to those skilled in the art.

15 Enantiomers can also be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (*e.g.*, chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (*e.g.*, hydrolyzing) the individual diastereomers to the corresponding pure enantiomers.

20 All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds of Formula (I) or a form thereof (including salts, solvates, esters and prodrugs and transformed prodrugs thereof), which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, diastereomeric and regioisomeric forms, are contemplated within the scope of the description herein. Individual stereoisomers of the
25 compounds of Formula (I) or a form thereof described herein may, for example, be substantially free of other isomers, or may be present in a racemic mixture, as described *supra*.

The use of the terms "salt," "solvate," "ester," "prodrug" and the like, is intended to apply equally to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates, isotopologues or prodrugs of the instant compounds.

One or more compounds of Formula (I) or a form thereof described herein may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and the description herein is intended to embrace both solvated and unsolvated forms.

5 As used herein, the term “solvate” means a physical association of a compound of Formula (I) or a form thereof described herein with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. As used
10 herein, “solvate” encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like.

One or more compounds of Formula (I) or a form thereof described herein may optionally be converted to a solvate. Preparation of solvates is generally known. A typical, non-limiting process involves dissolving a compound of Formula (I) or a form thereof in a desired
15 amount of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example infrared spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

As used herein, the term “hydrate” means a solvate wherein the solvent molecule is
20 water.

Polymorphic crystalline and amorphous forms of the compounds of Formula (I) or a form thereof, and of the salts, solvates, esters and prodrugs of the compounds of Formula (I) or a form thereof, are further intended to be included in the scope of the compounds of Formula (I) or a form thereof described herein.

25 As used herein, the term “isotope enriched” means a compounds of Formula (I) or a form thereof which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of Formula (I) or a form thereof described herein include isotopes of hydrogen,
30 carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as H², H³, C¹³, C¹⁴, N¹⁵, O¹⁸,

O¹⁷, P³¹, P³², S³⁵, F¹⁸, Cl³⁵ and Cl³⁶, respectively, each of which is also within the scope of this description.

DEFINITIONS

5 The chemical terms used above and throughout the description herein, unless specifically defined otherwise, shall be understood by one of ordinary skill in the art to have the following indicated meanings.

 As used herein, the term “C₁₋₈alkyl” refers to saturated hydrocarbon radicals having from one to eight carbon atoms in a straight or branched chain configuration, including, without
10 limitation, methyl, ethyl, npropyl, isopropyl, nbutyl, isobutyl, secbutyl, tertbutyl and the like. In some embodiments, C₁₋₈alkyl includes C₁₋₆alkyl, C₁₋₄alkyl and the like. A C₁₋₈alkyl radical may be optionally substituted where allowed by available valences.

 As used herein, the term “C₁₋₈alkoxy” refers to saturated hydrocarbon radicals of from one to eight carbon atoms having a straight or branched chain configuration of the formula: OC<sub>1-
15 8</sub>alkyl, including, without limitation, methoxy, ethoxy, npropoxy, isopropoxy, nbutoxy, isobutoxy, secbutoxy, tertbutoxy, npentoxy, nhexoxy and the like. In some embodiments, C₁₋₈alkoxy includes C₁₋₆alkoxy, C₁₋₄alkoxy and the like. A C₁₋₈alkoxy radical may be optionally substituted where allowed by available valences.

 As used herein, the term “C₃₋₇cycloalkyl” and “C₃₋₇cycloalkyl” refers to a saturated
20 monocyclic, bicyclic or polycyclic hydrocarbon radical, including, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. A C₃₋₇cycloalkyl and C₃₋₇cycloalkyl radical may be optionally substituted where allowed by available valences.

 As used herein, the term “heterocyclyl” or “heterocycle” refers to a saturated or partially unsaturated monocyclic, bicyclic or polycyclic carbon atom ring structure radical in which one or
25 more carbon atom ring members have been replaced, where allowed by structural stability, with a heteroatom, such as an O, S or N atom, including without limitation, piperidinyl, tetrahydro-2H-pyran or pyrrolidinyl. A heterocyclyl or heterocycle radical may be optionally substituted on a carbon or nitrogen atom ring member where allowed by available valences.

As used herein, the term “aryl” refers to a monocyclic, bicyclic or polycyclic aromatic carbon atom ring structure radical, including, without limitation, phenyl, naphthyl (also referred to as naphthalenyl), anthracenyl, fluorenyl, azulenyl, phenanthrenyl and the like. An aryl radical may be optionally substituted where allowed by available valences.

5 As used herein, the term “heteroaryl” refers to a monocyclic, bicyclic or polycyclic aromatic carbon atom ring structure radical in which one or more carbon atom ring members have been replaced, where allowed by structural stability, with one or more heteroatoms, such as an O, S or N atom. A heteroaryl radical may be optionally substituted on a carbon or nitrogen atom ring member where allowed by available valences.

10 As used herein, the term “halo” or “halogen” generally refers to a halogen atom radical, including fluoro, chloro, bromo and iodo.

As used herein, the term “C₁₋₄alkoxy-C₁₋₄alkyl” refers to a radical of the formula: C₁₋₄alkylOC₁₋₄alkyl.

15 As used herein, the term “C₁₋₄alkyl-amino” refers to a radical of the formula: NHC₁₋₄alkyl.

As used herein, the term “(C₁₋₄alkyl)₂-amino” refers to a radical of the formula: N(C₁₋₄alkyl)₂.

As used herein, the term “C₁₋₄alkyl-thio” refers to a radical of the formula: -S-C₁₋₄alkyl.

20 As used herein, the term “amino-C₁₋₄alkoxy” refers to a radical of the formula: OC₁₋₄alkylNH₂.

As used herein, the term “amino-C₁₋₄alkyl” refers to a radical of the formula: C₁₋₄alkylNH₂.

As used herein, the term “aryl-C₁₋₄alkyl” refers to a radical of the formula: -C₁₋₄alkyl-aryl.

25 As used herein, the term “arylC₁₋₄alkylamino” refers to a radical of the formula: NHC₁₋₄alkylaryl.

As used herein, the term “C₃₋₆cycloalkyl-C₁₋₄alkyl” refers to a radical of the formula: C₁₋₄alkylC₃₋₆cycloalkyl.

As used herein, the term “C₃₋₆cycloalkyl-amino” refers to a radical of the formula: -NH-C₃₋₆cycloalkyl.

As used herein, the term “C₁₋₄alkoxy-carbonyl” refers to a radical of the formula -C(O)-C₁₋₄alkoxy.

5 As used herein, the term “deutero-C₁₋₄alkyl,” refers to a radical of the formula: C₁₋₄alkyldeutero, wherein C₁₋₄alkyl is partially or completely substituted with one or more deuterium atoms where allowed by available valences.

As used herein, the term “halo-C₁₋₄alkoxy” refers to a radical of the formula: OC₁₋₄alkylhalo, wherein C₁₋₄alkyl is partially or completely substituted with one or more halogen
10 atoms where allowed by available valences.

As used herein, the term “halo-C₁₋₄alkyl” refers to a radical of the formula: C₁₋₄alkylhalo, wherein C₁₋₄alkyl is partially or completely substituted with one or more halogen atoms where allowed by available valences.

As used herein, the term “hydroxy” refers to a radical of the formula: -OH.

15 As used herein, the term “hydroxy-C₁₋₄alkoxy-C₁₋₄alkyl” refers to a radical of the formula: -C₁₋₄alkyl-O-C₁₋₄alkyl-OH.

As used herein, the term “hydroxy-C₁₋₄alkyl” refers to a radical of the formula: C₁₋₄alkylOH, wherein C₁₋₄alkyl is partially or completely substituted with one or more hydroxy radicals where allowed by available valences.

20 As used herein, “oxo” refers to a carbonyl, i.e., -C(O)-.

As used herein, the term “and the like,” with reference to the definitions of chemical terms provided herein, means that variations in chemical structures that could be expected by one skilled in the art include, without limitation, isomers (including chain, branching or positional structural isomers), hydration of ring systems (including saturation or partial unsaturation of
25 monocyclic, bicyclic or polycyclic ring structures) and all other variations where allowed by available valences which result in a stable compound.

As used herein, the term “substituent” means positional variables on the atoms of a core molecule that are attached at a designated atom position, replacing one or more hydrogen atoms

on the designated atom, provided that the atom of attachment does not exceed the available valence or shared valences, such that the substitution results in a stable compound. Accordingly, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. It should also be noted that any carbon as well as heteroatom with a valence
5 level that appears to be unsatisfied as described or shown herein is assumed to have a sufficient number of hydrogen atom(s) to satisfy the valences described or shown.

For the purposes of this description, where one or more substituent variables for a compound of Formula (I) encompass functionalities incorporated into a compound of Formula I-VII, each functionality appearing at any location within the disclosed compound may be
10 independently selected, and as appropriate, independently and/or optionally substituted.

As used herein, the terms “independently selected,” or “each selected” refer to functional variables in a substituent list that may be attached more than once on the structure of a core molecule, where the pattern of substitution at each occurrence is independent of the pattern at any other occurrence. Further, the use of a generic substituent on a core structure for a
15 compound provided herein is understood to include the replacement of the generic substituent with specie substituents that are included within the particular genus, e.g., aryl may be independently replaced with phenyl or naphthalenyl (also referred to as naphthyl) and the like, such that the resulting compound is intended to be included within the scope of the compounds described herein.

As used herein, the term “each instance of” or “each variable is independently” when
20 used in a phrase such as “...aryl, arylC₁₋₄alkyl, heterocycle and heterocyclyl-C₁₋₄alkyl, wherein each instance of aryl and heterocycle is optionally substituted with one or two substituents...” is intended to include optional, independent substitution on each of the aryl and heterocycle rings and on the aryl and heterocycle portions of arylC₁₋₄alkyl and heterocyclyl-C₁₋₄alkyl.

As used herein, the term “optionally substituted” means that the specified substituent --
25 variables, groups, radicals or moieties represent the scope of the genus and may be independently chosen as needed to replace one or more hydrogen atoms on the designated atom of attachment of a core molecule.

As used herein, the terms “stable compound” or “stable structure” means a compound that is sufficiently robust to be isolated to a useful degree of purity from a reaction mixture and formulations thereof into an efficacious therapeutic agent.

As used herein, the terms “subject” and “patient” are used interchangeably to refer to an animal or any living organism having sensation and the power of voluntary movement, and which requires for its existence oxygen and organic food. Nonlimiting examples include members of the human, equine, porcine, bovine, rattus, murine, canine and feline species. In some embodiments, the subject is a mammal or a warm-blooded vertebrate animal. In certain embodiments, the subject is a non-human animal. In specific embodiments, the subject is a human.

Compound names provided herein were obtained using ACD Labs Index Name software provided by ACD Labs and/or ChemDraw Ultra software provided by CambridgeSoft®. When the compound name disclosed herein conflicts with the structure depicted, the structure shown will supercede the use of the name to define the compound intended. Nomenclature for substituent radicals defined herein may differ slightly from the chemical name from which they are derived; one skilled in the art will recognize that the definition of the substituent radical is intended to include the radical as found in the chemical name.

DOSAGE AND ADMINISTRATION

The compounds of the present invention may be formulated in a wide variety of oral administration dosage forms and carriers. Oral administration can be in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions, syrups, or suspensions. Compounds of the present invention are efficacious when administered by other routes of administration including continuous (intravenous drip) topical parenteral, intramuscular, intravenous, subcutaneous, transdermal (which may include a penetration enhancement agent), buccal, nasal, inhalation and suppository administration, among other routes of administration. The preferred manner of administration is generally oral using a convenient daily dosing regimen which can be adjusted according to the degree of affliction and the patient's response to the active ingredient.

A compound or compounds of the present invention, as well as their pharmaceutically useable salts, together with one or more conventional excipients, carriers, or diluents, may be placed into the form of pharmaceutical compositions and unit dosages. The pharmaceutical compositions and unit dosage forms may be comprised of conventional ingredients in conventional proportions, with or without additional active compounds or principles, and the unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. The pharmaceutical compositions may be employed as solids, such as tablets or filled capsules, semisolids, powders, sustained release formulations, or liquids such as solutions, suspensions, emulsions, elixirs, or filled capsules for oral use; or in the form of suppositories for rectal or vaginal administration; or in the form of sterile injectable solutions for parenteral use. A typical preparation will contain from about 5% to about 95% active compound or compounds (w/w). The term "preparation" or "dosage form" is intended to include both solid and liquid formulations of the active compound and one skilled in the art will appreciate that an active ingredient can exist in different preparations depending on the target organ or tissue and on the desired dose and pharmacokinetic parameters.

The term "excipient" as used herein refers to a compound that is useful in preparing a pharmaceutical composition, generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipients that are acceptable for veterinary use as well as human pharmaceutical use. The compounds of this invention can be administered alone but will generally be administered in admixture with one or more suitable pharmaceutical excipients, diluents or carriers selected with regard to the intended route of administration and standard pharmaceutical practice.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary as well as human pharmaceutical use.

A "pharmaceutically acceptable salt" form of an active ingredient may also initially confer a desirable pharmacokinetic property on the active ingredient which were absent in the non-salt form, and may even positively affect the pharmacodynamics of the active ingredient with respect to its therapeutic activity in the body. The phrase "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the

desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier may be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. In powders, the carrier generally is a finely divided solid which is a mixture with the finely divided active component. In tablets, the active component generally is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. Suitable carriers include but are not limited to magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. Solid form preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

Liquid formulations also are suitable for oral administration include liquid formulation including emulsions, syrups, elixirs, aqueous solutions, aqueous suspensions. These include solid form preparations which are intended to be converted to liquid form preparations shortly before use. Emulsions may be prepared in solutions, for example, in aqueous propylene glycol

solutions or may contain emulsifying agents such as lecithin, sorbitan monooleate, or acacia. Aqueous solutions can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents. Aqueous suspensions can be prepared by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well known suspending agents.

The compounds of the present invention may be formulated for parenteral administration (*e.g.*, by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, for example solutions in aqueous polyethylene glycol. Examples of oily or nonaqueous carriers, diluents, solvents or vehicles include propylene glycol, polyethylene glycol, vegetable oils (*e.g.*, olive oil), and injectable organic esters (*e.g.*, ethyl oleate), and may contain formulatory agents such as preserving, wetting, emulsifying or suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution for constitution before use with a suitable vehicle, *e.g.*, sterile, pyrogen-free water.

The compounds of the present invention may be formulated for topical administration to the epidermis as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also containing one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. Formulations suitable for topical administration in the mouth include lozenges comprising active agents in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

The compounds of the present invention may be formulated for administration as suppositories. A low melting wax, such as a mixture of fatty acid glycerides or cocoa butter is

first melted and the active component is dispersed homogeneously, for example, by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and to solidify.

The compounds of the present invention may be formulated for vaginal administration.

5 Pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

The compounds of the present invention may be formulated for nasal administration. The solutions or suspensions are applied directly to the nasal cavity by conventional means, for example, with a dropper, pipette or spray. The formulations may be provided in a single or
10 multidose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomizing spray pump.

The compounds of the present invention may be formulated for aerosol administration, particularly to the respiratory tract and including intranasal administration. The compound will
15 generally have a small particle size for example of the order of five (5) microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. The active ingredient is provided in a pressurized pack with a suitable propellant such as a chlorofluorocarbon (CFC), for example, dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, or carbon dioxide or other suitable gas. The aerosol may conveniently
20 also contain a surfactant such as lecithin. The dose of drug may be controlled by a metered valve. Alternatively the active ingredients may be provided in a form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). The powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit
25 dose form for example in capsules or cartridges of *e.g.*, gelatin or blister packs from which the powder may be administered by means of an inhaler.

When desired, formulations can be prepared with enteric coatings adapted for sustained or controlled release administration of the active ingredient. For example, the compounds of the present invention can be formulated in transdermal or subcutaneous drug delivery devices.

30 These delivery systems are advantageous when sustained release of the compound is necessary

and when patient compliance with a treatment regimen is crucial. Compounds in transdermal delivery systems are frequently attached to an skin-adhesive solid support. The compound of interest can also be combined with a penetration enhancer, e.g., Azone (1-dodecylazacycloheptan-2-one). Sustained release delivery systems are inserted subcutaneously into to the subdermal layer by surgery or injection. The subdermal implants encapsulate the compound in a lipid soluble membrane, e.g., silicone rubber, or a biodegradable polymer, e.g., polyactic acid.

Suitable formulations along with pharmaceutical carriers, diluents and excipients are described in *Remington: The Science and Practice of Pharmacy* 1995, edited by E. W. Martin, Mack Publishing Company, 19th edition, Easton, Pennsylvania. A skilled formulation scientist may modify the formulations within the teachings of the specification to provide numerous formulations for a particular route of administration without rendering the compositions of the present invention unstable or compromising their therapeutic activity.

The modification of the present compounds to render them more soluble in water or other vehicle, for example, may be easily accomplished by minor modifications (salt formulation, esterification, etc.), which are well within the ordinary skill in the art. It is also well within the ordinary skill of the art to modify the route of administration and dosage regimen of a particular compound in order to manage the pharmacokinetics of the present compounds for maximum beneficial effect in patients.

The term "therapeutically effective amount" as used herein means an amount required to reduce symptoms of the disease in an individual. The dose will be adjusted to the individual requirements in each particular case. That dosage can vary within wide limits depending upon numerous factors such as the severity of the disease to be treated, the age and general health condition of the patient, other medicaments with which the patient is being treated, the route and form of administration and the preferences and experience of the medical practitioner involved. For oral administration, a daily dosage of between about 0.01 and about 1000 mg/kg body weight per day should be appropriate in monotherapy and/or in combination therapy. A preferred daily dosage is between about 0.1 and about 500 mg/kg body weight, more preferred 0.1 and about 100 mg/kg body weight and most preferred 1.0 and about 10 mg/kg body weight per day. Thus, for administration to a 70 kg person, the dosage range would be about 7 mg to 0.7 g per day. The daily dosage can be administered as a single dosage or in divided dosages, typically

between 1 and 5 dosages per day. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect for the individual patient is reached. One of ordinary skill in treating diseases described herein will be able, without undue experimentation and in reliance on personal knowledge, experience and the disclosures of this application, to ascertain a therapeutically effective amount of the compounds of the present invention for a given disease and patient.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Examples of representative compounds encompassed by the present invention and within the scope of the invention are provided in the following Table. These examples and preparations which follow are provided to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

In general, the nomenclature used in this Application is based on AUTONOMTM v.4.0, a Beilstein Institute computerized system for the generation of IUPAC systematic nomenclature. If there is a discrepancy between a depicted structure and a name given that structure, the depicted structure is to be accorded more weight. In addition, if the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it.

The reagents and solvents were used as purchased (from a variety of vendors), except where noted. Where applicable, the term "Celite" is used as shown in the following examples to represent the tradename CELITE® (brand of diatomaceous earth). Where applicable, chromatographic separations were performed using techniques and equipment commonly available such as, for example, by using an ISCO CombiFlash® Rf system. Where applicable, NMR spectra were obtained using techniques and equipment commonly available such as, for

example, by using a Bruker Avance III⁵⁰⁰ spectrometer with deuterated solvents such as, for example, DMSO-*d*₆ or residual solvent as standard. Where applicable, melting points were determined using techniques and equipment commonly available such as, for example, by using a SRS OptiMelt[®] MPA100 (values as obtained without correction/calibration). Where
5 applicable, TLC analysis was performed using techniques and equipment commonly available such as, for example, by using Aldrich 254 nm glass-backed plates (60 Å, 250 µm), visualized using UV and I₂ stains. Where applicable, ESI mass spectra were obtained using techniques and equipment commonly available such as, for example, by using an ACQUITY UPLC[®] System, with values shown as [M+H]⁺ or [M-H]⁻, unless otherwise indicated. Where applicable, the
10 structure of the product was obtained via a 2D NOESY (Nuclear Overhauser Spectroscopy) experiment.

The following abbreviations are provided to ensure the terms used herein are unambiguous to one skilled in the art:

Abbreviation	Meaning
AcOH or HOAc	acetic acid
ACN or MeCN	Acetonitrile
AlMe ₃	Trimethylaluminum
APC	allylpalladium (II) chloride dimer
Boc	<i>tert</i> -butoxycarbonyl
CsOAc	cesium acetate
DCM or CH ₂ Cl ₂	Dichloromethane
DME	dimethyl ether
DMF	dimethyl formamide
DMA	Dimethylacetamide
DMAP	4-dimethylaminopyridine
DMSO	Dimethylsulfoxide
EtOAc	ethyl acetate
EtOH	Ethanol
HPLC	high performance liquid chromatography
h, hr, min, s	hour (h or hr), minute (min), second (s)
iPrMgCl*LiCl	isopropylmagnesium chloride lithium chloride complex
iPrOAc	isopropyl acetate
K ₂ CO ₃	potassium carbonate
K ₃ PO ₄	potassium phosphate
KOtBu or t-BuOK	potassium <i>tert</i> -butoxide

Abbreviation	Meaning
LC/MS, LCMS or LC-MS	liquid chromatographic mass spectroscopy
MeOH	Methanol
MeNH ₂ x HCl	methanamine hydrochloride
MS	mass spectroscopy
m.p.	melting point (shown in °Centigrade)
MPS	potassium peroxymonosulfate (2KHSO ₅ ·KHSO ₄ ·K ₂ SO ₄)
NaH	sodium hydride
NaHCO ₃	sodium bicarbonate
NaHMDS	sodium hexamethyldisilazide
NaIO ₄	sodium periodate
NaOH	sodium hydroxide
NaOtAm	sodium <i>tert</i> -pentoxide
NaOMe	sodium methoxide
NaOEt	sodium ethoxide
NaOtBu	sodium <i>tert</i> -butoxide
NCS	N-chlorosuccinimide
NH ₄ Cl	ammonium chloride
NH ₄ OH	ammonium hydroxide
NIS	N-iodosuccinimide
NMP	N-methylpyrrolidone
NMR	nuclear magnetic resonance
Oxone	potassium peroxymonosulfate
PCl ₅	phosphorus perchloride or phosphorus pentachloride
PCy ₃	Tricyclohexylphosphine
[Pd]	Palladium

Abbreviation	Meaning
Pd/C ^o	palladium on carbon
Pd ₂ (dba) ₃ or Pd ₂ dba ₃	tris(dibenzylideneacetone)dipalladium(0)
Pd(dppf)Cl ₂	[1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II)
PdCl ₂ (ACN)	bis(acetonitrile)dichloropalladium(II)
PdCl ₂ (allyl)	chloroallylpalladium(II) dimer
[Pd(OAc) ₂] ₃	palladium (II) acetate
Pd(PPh ₃) ₄	tetrakis(triphenylphosphine)palladium
POCl ₃	phosphorus oxychloride
PPh ₃	Triphenylphosphine
psi	pounds per square inch pressure
Pt/C	platinum on carbon
PTSA	p-toluenesulfonic acid
Q-Phos or QPhos	1,2,3,4,5-pentaphenyl-1'-(di- <i>tert</i> -butylphosphino)ferrocene
RT	room temperature
TBSO or OTBS	<i>tert</i> -butyldimethylsilyloxy
TCDI	1,1'-thiocarbonyldiimidazole
t-Bu	tert-butyl
TEA, NEt ₃ , Et ₃ N	Triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	Tetrahydrofuran
TosMIC or TsMIC	Toluenesulfonylmethyl isocyanide
TsOH X H ₂ O	p-toluenesulfonic acid monohydrate
UPLC	Ultra Performance Liquid Chromatography
Xphos or XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

COMPOUNDS AND PREPARATION

EXPERIMENTAL

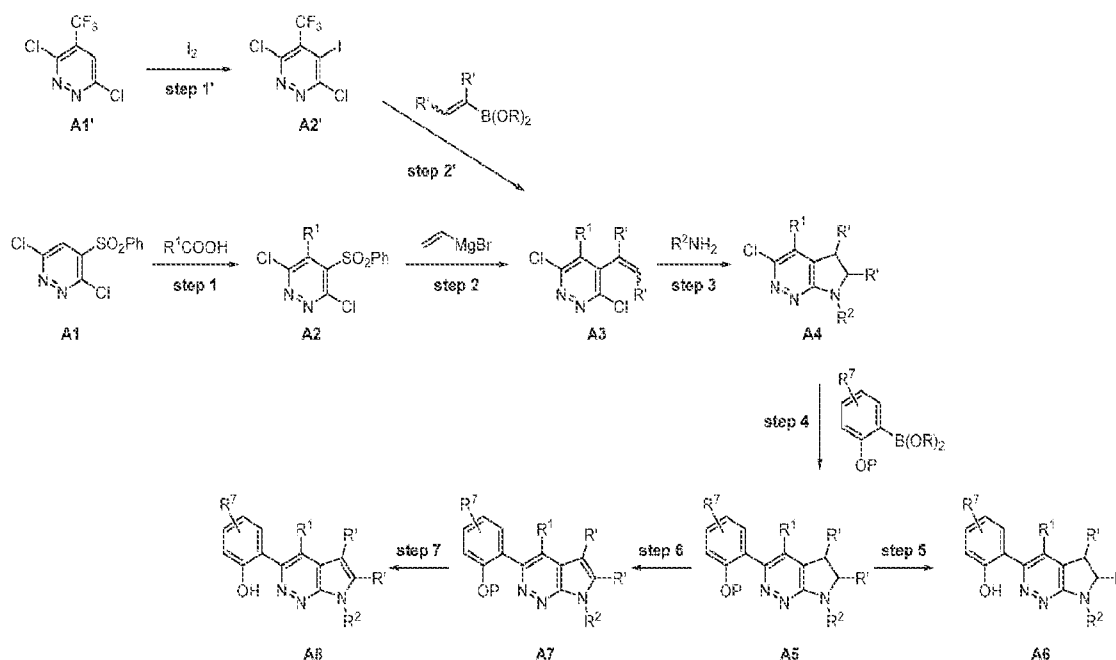
General synthetic Methods

As disclosed herein, general methods for preparing the compounds of Formula I or a
5 form thereof as described herein can be prepared using the methods summarized in Schemes A-G
by the suitable selection of reagents with appropriate substitution, solvents, temperatures,
pressures, and other reaction conditions readily selected by one of ordinary skilled in the art.
Many of the starting materials are commercially available or, when not available, can be
prepared via standard, well-known synthetic methodology or using the routes described below
10 using techniques known to those skilled in the art. The synthetic schemes provided herein
comprise multiple reaction steps, each of which is intended to stand on its own and can be
carried out with or without any preceding or succeeding step(s). In other words, each of the
individual reaction steps of the synthetic schemes provided herein in isolation is contemplated.

Depending on the nature of the groups depicted in the schemes below, the final
15 compounds or their precursors may be further elaborated using the standard, well-known
synthetic methods such as S_NAr displacement reaction, metal catalyzed coupling reactions like
Suzuki coupling, Negishi coupling and Buchwald coupling, reductive amination, etc. to afford
the compounds of the general Formula I.

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Scheme A:

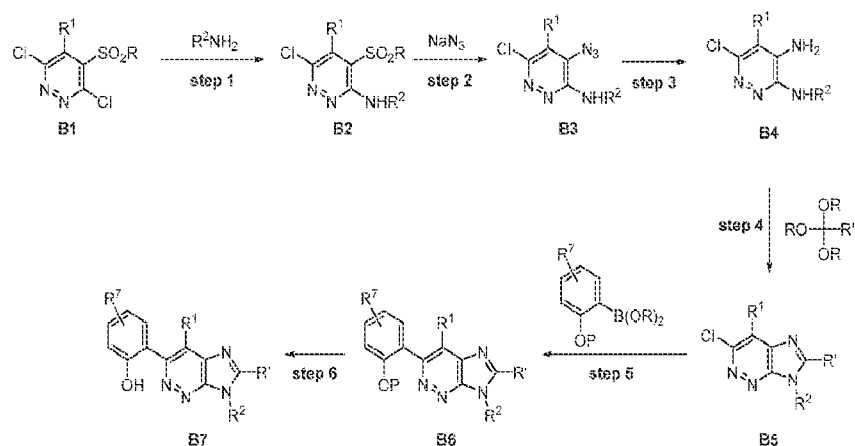


Compound **A1** is converted to compound **A2** by Minisci reaction with an appropriate carboxylic acid in the presence of a silver salt and a suitable oxidizing agent (such as ammonium persulfate and the like) in a suitable solvent (such as acetonitrile and the like). Compound **A2** is converted to compound **A3** by reacting with vinylmagnesium bromide in a suitable solvent (such as THF and the like). Alternatively, compound **A2'** can be synthesized by reacting compound **A1'** with iodine in the presence of a suitable base (such as $\text{TMPZn}(\text{OPiv})_2\text{MgCl} \cdot \text{LiCl}$ and the like) in a suitable solvent (such as THF and the like). Suzuki coupling of compound **A2'** with vinyl boronic acid (or pinacol boronic ester) in the presence of a catalyst (such as $\text{Pd}(\text{dppf})\text{Cl}_2$ and the like) and a base (such as aqueous K_2CO_3 and the like) in a suitable solvent (such as 1,4-dioxane and the like) affords compound **A3**. Compound **A3** is cyclized to compound **A4** by treatment with optionally protected amine in the presence of a base (such as DIPEA and the like) in a suitable solvent (such as acetonitrile and the like) at an elevated temperature (such as 110°C and the like). Suzuki coupling of compound **A4** with an optionally protected aryl- or heteroaryl-boronic acid (or pinacol boronic ester) in the presence of a catalyst (such as $\text{Pd}(\text{dppf})\text{Cl}_2$ and the like) and a base (such as aqueous K_2CO_3 and the like) in a suitable solvent (such as 1,4-dioxane and the like) provides compound **A5**. Removal of protecting groups leads to compound **A6**.

Compound **A5** can be oxidized to compound **A7** by an oxidant (such as MnO_2 and the like) in a suitable solvent (such as toluene and the like) at an elevated temperature (such as

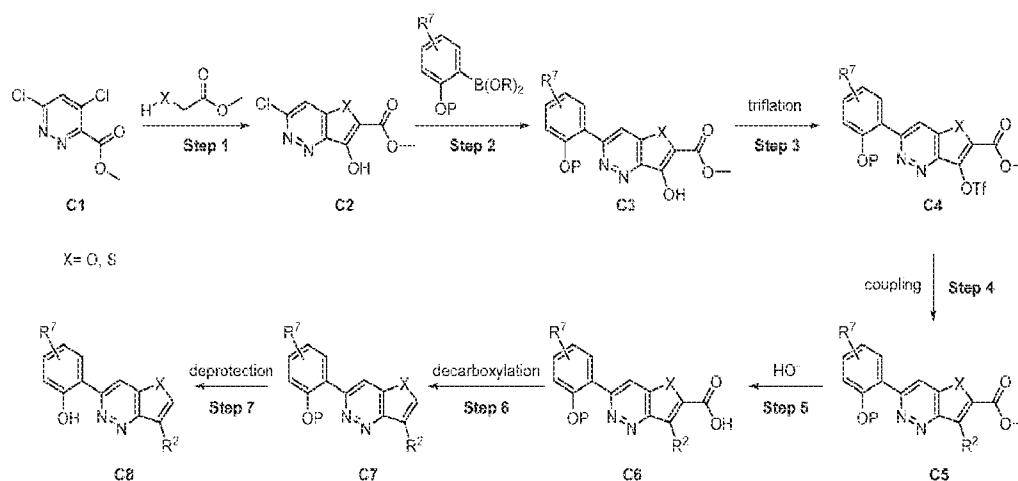
110°C and the like). Deprotection of compound **A7** provides compound **A8**.

Scheme B:



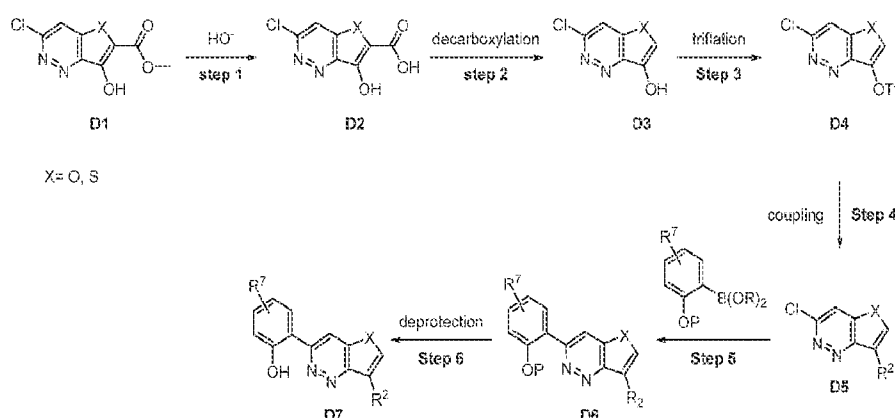
- 5 Compound **B1** is reacted with an optionally protected amine in the presence of a base (such as K_2CO_3 and the like) in a suitable solvent (such as dioxane and the like) at an elevated temperature (such as 60°C and the like) to give compound **B2**, which is further converted to compound **B3** by reacting with NaN_3 in a suitable solvent (such as DMSO and the like) at an elevated temperature (such as 80°C and the like). Compound **B3** is reduced to compound **B4** by
- 10 an appropriate reducing agent (such as zinc and the like), which is cyclized to compound **B5** upon treatment with an ortho ester at an elevated temperature (such as 100°C and the like). Suzuki coupling of compound **B5** with an optionally protected aryl- or heteroaryl-boronic acid (or pinacol boronic ester) in the presence of a catalyst (such as $Pd(dppf)Cl_2$ and the like) and a base (such as aqueous K_2CO_3 and the like) in a suitable solvent (such as 1,4-dioxane and the
- 15 like) provides compound **B6**. Removal of protecting groups leads to compound **B7**.

Scheme C:



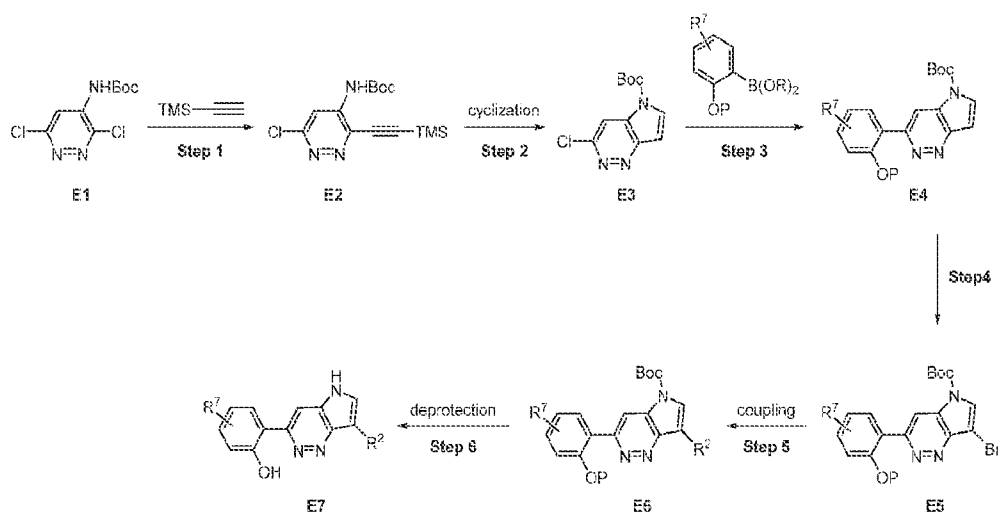
- Compound **C1** is converted to compound **C2** by reacting with 2-hydroxy or 2-mercaptoacetate in the presence of a base (such as Et_3N , NaH and the like) in a suitable solvent (such as THF and the like). Suzuki coupling of compound **C2** with an optionally protected aryl- or heteroaryl-boronic acid (or pinacol boronic ester) in the presence of a catalyst (such as Pd(dppf)Cl_2 and the like) and a base (such as aqueous K_2CO_3 and the like) in a suitable solvent (such as 1,4-dioxane and the like) provides compound **C3**, which is further converted to compound **C4** by reacting with a triflating reagent (such as triflic anhydride and the like) in the presence of a base (such as DIPEA and the like) in a suitable solvent (such as DCM and the like). Compound **C4** is converted to compound **C5** by coupling with an appropriate coupling partner (such as a boronic acid, organozinc reagent, and the like) in the presence of a catalyst (such as Pd(dppf)Cl_2 and the like). Hydrolysis of compound **C5** by an appropriate base (such as LiOH and the like) in a suitable solvent (such as THF and the like) affords compound **C6**, which is decarboxylated to give compound **C7** in the presence of a metal salt (such as Ag_2CO_3 and the like) in a suitable solvent (such as DMSO and the like) at an elevated temperature. Removal of protecting groups leads to compound **C8**.

Scheme D:



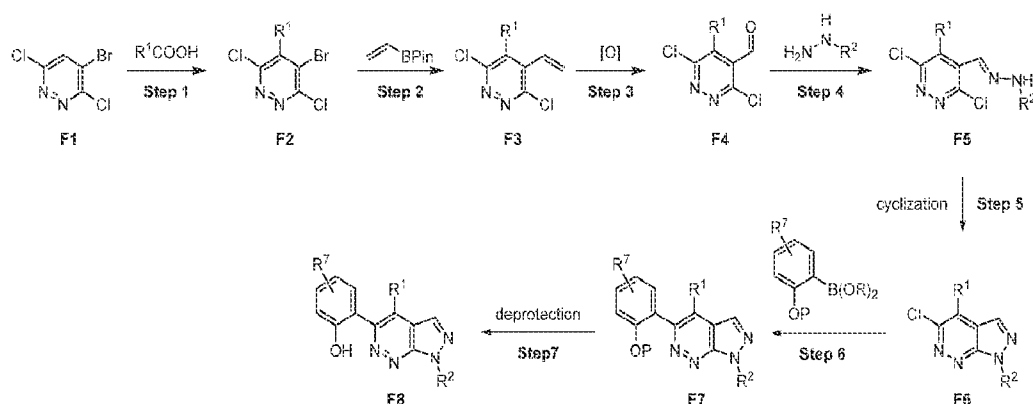
- Compound **D1**, prepared by the method described in scheme C, is hydrolyzed to compound **D2** by reacting with a base (such as LiOH and the like) in a suitable solvent (such as dioxane and the like). Decarboxylation of compound **D2** in the presence of a metal salt (such as Ag_2CO_3 and the like) in a suitable solvent (such as DMSO and the like) at an elevated temperature (such as 120°C and the like) affords compound **D3**, which is subjected to a reaction with a triflating reagent (such as triflic anhydride and the like) in the presence of a base (such as pyridine and the like) in a suitable solvent (such as DCM and the like). Compound **D4** is converted to compound **D5** by coupling with an appropriate coupling partner (such as a boronic acid, organozinc reagent, and the like) in the presence of a catalyst (such as $\text{Pd}(\text{dppf})\text{Cl}_2$ and the like). Compound **D5** is further coupled with an optionally protected aryl- or heteroaryl-boronic acid (or pinacol boronic ester) in the presence of a catalyst (such as $\text{Pd}(\text{dppf})\text{Cl}_2$ and the like) and a base (such as aqueous K_2CO_3 and the like) in a suitable solvent (such as 1,4-dioxane and the like) to provide compound **D6**. Removal of protecting groups leads to compound **D7**.

Scheme E:



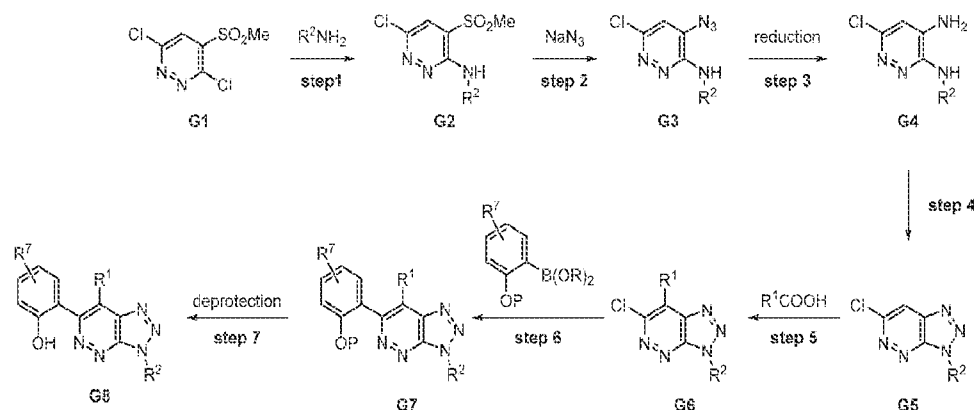
Compound **E1** is converted to compound **E2** by Sonogashira reaction with TMS-acetylene in the presence of a catalyst (such as $\text{Pd(PPh}_3)_4$ and the like) and a base (such as NEt_3 and the like) in a suitable solvent (such as THF and the like), which is cyclized to compound **E3** in the presence of a base (such as K_2CO_3 and the like) in a suitable solvent (such as DMF and the like). Compound **E3** is coupled with an optionally protected aryl- or heteroaryl-boronic acid (or pinacol boronic ester) in the presence of a catalyst (such as XPhos-Pd-G3 and the like) and a base (such as aqueous K_2CO_3 and the like) in a suitable solvent (such as 1,4-dioxane and the like) to provide compound **E4**. Reaction of compound **E4** with a halogenation reagent (such as NBS and the like) in a suitable solvent (such as NBS and the like) affords compound **E5**. Compound **E5** is converted to compound **E6** by coupling with an appropriate coupling partner (such as a boronic acid, organozinc reagent, and the like) in the presence of a catalyst (such as Pd(dppf)Cl_2 and the like). Removal of protecting groups leads to compound **E7**.

Scheme F:



Compound **F1** is converted to compound **F2** by Minisci reaction with an appropriate carboxylic acid in the presence of a silver salt and a suitable oxidizing agent (such as ammonium persulfate and the like) in a suitable solvent (such as acetonitrile and the like). Suzuki coupling of compound **F2** with vinyl pinacol borate in the presence of a catalyst (such as Pd(dppf)Cl₂ and the like) and a base (such as K₂CO₃ and the like) in a suitable solvent (such as THF and the like) affords compound **F3**, which is subjected to oxidation by an oxidant (such as sodium periodate and the like) to give compound **F4**. Compound **F4** is condensed with a substituted hydrazine to give compound **F5**, which is subsequently cyclized to compound **F6** at an elevated temperature (such as 150°C and the like). Suzuki coupling of compound **F6** with an optionally protected aryl- or heteroaryl-boronic acid (or pinacol boronic ester) in the presence of a catalyst (such as XPhos-Pd-G3 and the like) and a base (such as aqueous K₂CO₃ and the like) in a suitable solvent (such as 1,4-dioxane and the like) provides compound **F7**. Removal of protecting groups leads to compound **F8**.

Scheme G:

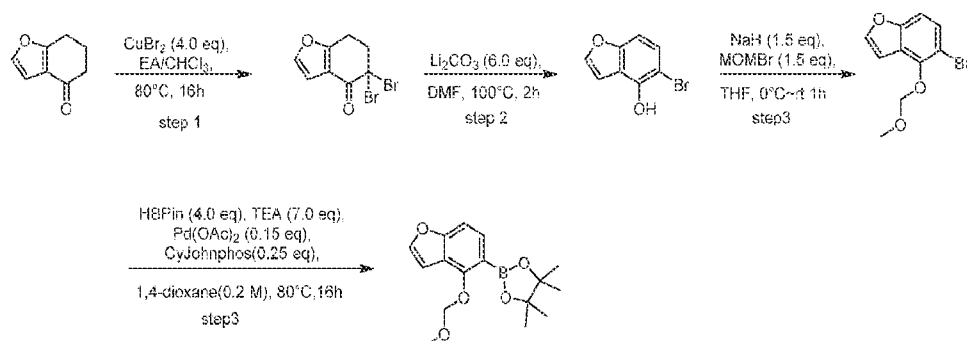


Compound **G1** is reacted with an optionally protected amine in the presence of a base (such as K_2CO_3 and the like) in a suitable solvent (such as THF and the like) at an elevated temperature (such as $50^\circ C$ and the like) to give compound **G2**, which is converted to compound **G3** by reacting with NaN_3 in a suitable solvent (such as DMSO and the like) at an elevated temperature (such as $80^\circ C$ and the like). Compound **G3** is reduced to compound **G4** by an appropriate reducing agent (such as zinc and the like), which is cyclized to compound **G5** upon treatment with sodium nitrite in the presence of an acid (such as HOAc and the like) in water.

Compound **G5** is converted to compound **G6** by Minisci reaction with an appropriate carboxylic acid in the presence of a silver salt and a suitable oxidizing agent (such as ammonium persulfate and the like) in a suitable solvent (such as acetonitrile and the like). Suzuki coupling of compound **G6** with an optionally protected aryl- or heteroaryl-boronic acid (or pinacol boronic ester) in the presence of a catalyst (such as $Pd(dppf)Cl_2$ and the like) and a base (such as aqueous K_2CO_3 and the like) in a suitable solvent (such as 1,4-dioxane and the like) provides compound **G7**. Removal of protecting groups leads to compound **G8**.

COMPOUNDS AND PREPARATION

Intermediate 1: Preparation of 2-(4-(methoxymethoxy)benzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1: A mixture of CuBr_2 (58.7 g, 263 mmol) in anhydrous ethyl acetate (150 mL) was stirred at 80°C for 10 min, followed by addition of 6,7-dihydrobenzofuran-4(5H)-one (10.0 g, 65.7 mmol) in CHCl_3 (25 mL). The mixture was stirred continuously at 80°C for 16 h. Upon completion, the reaction was cooled to room temperature and filtered to remove the solid. The filtrate was concentrated, and the residue was purified by flash column chromatography on silica gel eluting with 0-10% ethyl acetate in petroleum ether to afford 5,5-dibromo-6,7-dihydrobenzofuran-4(5H)-one as yellow solids (9.4 g, 46% yield). MS m/z 294.9 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 7.84 (d, $J = 2.0$ Hz, 1H), 6.84 (d, $J = 2.0$ Hz, 1H), 3.16 (t, $J = 6.0$ Hz, 2H), 3.00 (t, $J = 5.6$ Hz, 2H).

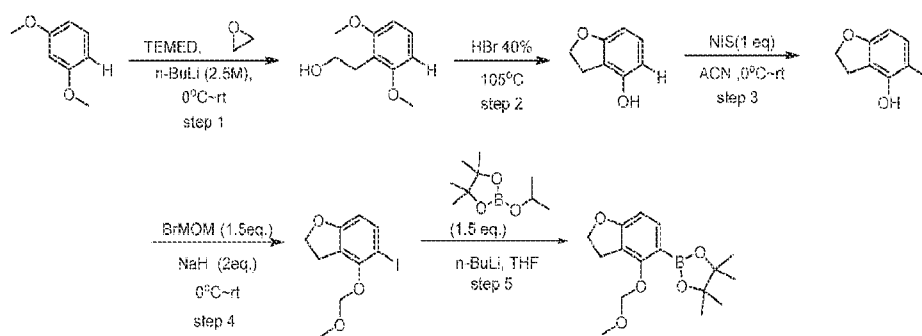
Step 2: To a solution of 5,5-dibromo-6,7-dihydrobenzofuran-4(5H)-one (9.4 g, 32 mmol) in DMF (150 mL) was added Li_2CO_3 (14.2 g, 192 mmol) at room temperature. The reaction mixture was stirred at 100°C for 2h. Upon completion, the mixture was cooled to room temperature and filtered to remove the solid. The filtrate was concentrated, and the residue was diluted with water (500 mL) and then extracted with ethyl acetate (300 mL). The organic layer was washed with water (500 mL x 2) and brine (500 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 0-20% ethyl acetate in petroleum ether to afford 5-bromobenzofuran-4-ol as yellow solids (6.4 g, 94% yield). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 10.48 (s, 1H), 7.88 (d, $J = 2.0$ Hz, 1H), 7.38 (d, $J = 8.8$ Hz, 1H), 7.15 (d, $J = 1.6$ Hz, 1H), 7.05 (d, $J = 8.4$ Hz, 1H).

Step 3: To a solution of 5-bromobenzofuran-4-ol (7.8 g, 36.6 mmol) in THF (150 mL) was added NaH (2.2 g, 54.9 mmol, 60%) at 0°C. The reaction mixture was stirred at 0°C for 0.5 h, followed by addition of bromomethyl methyl ether (6.86 g, 54.9 mmol) dropwise. The reaction mixture was stirred at room temperature for 0.5h. Upon completion, the reaction was quenched with water (150 mL) and extracted with EtOAc (100 mL). The organic layer was washed with water

(150 mL x 1) and brine (150 mL x 1), dried over Na_2SO_4 , filtered, and concentrated to afford 5-bromo-4-(methoxymethoxy)benzofuran as yellow oil (9.0 g, 96% yield), which was applied to the next step without further purification. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 8.02 (d, $J = 2.4$ Hz, 1H), 7.51 (d, $J = 8.4$ Hz, 1H), 7.35 (dd, $J = 0.8$ Hz, $J = 8.4$ Hz, 1H), 7.12 (dd, $J = 0.8$ Hz, $J = 2.0$ Hz, 1H), 5.36 (s, 2H), 3.55 (s, 3H).

Step 4: To a solution of 5-bromo-4-(methoxymethoxy)benzofuran (8.0 g, 31.1 mmol) in 1,4-dioxane (150 mL) were added pinacolborane (15.9 g, 124 mmol), TEA (22.0 g, 218 mmol), $\text{Pd}(\text{OAc})_2$ (777 mg, 4.67 mmol) and CyJohnphos (1.73 g, 7.78 mmol) under Ar. The reaction mixture was stirred at 80°C under Ar for 16h, then filtered through a pad of Celite and washed with EtOAc. The filtrate was concentrated and the residue was purified by flash column chromatography on silica gel eluting with 0-6% ethyl acetate in petroleum ether to afford 2-(4-(methoxymethoxy)benzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as a yellow solid (4.17 g, 44% yield). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 7.96 (d, $J = 2.0$ Hz, 1H), 7.55 (d, $J = 8.4$ Hz, 1H), 7.35 (d, $J = 8.4$ Hz, 1H), 7.03 (d, $J = 2.4$ Hz, 1H), 5.22 (s, 2H), 3.51 (s, 3H), 1.30 (s, 12H).

Intermediate 2: Preparation of 2-(4-(Difluoromethoxy)-2,3-dihydrobenzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1: To a solution of 1,3-dimethoxybenzene (55.0 g, 398 mmol, 1.0 eq.) in dry THF (500 mL), tetramethylethylenediamine (55.5 g, 1.2 eq.) was added and the mixture was stirred for 30 min at 0°C , n-butyllithium (25.50 g, 398 mmol, 1.0 eq, 2.5 M) was slowly added dropwise. The mixture was stirred for 3 h at 0°C . Ethylene oxide (35.1 g, 796 mmol, 2.0 eq.) was slowly added dropwise for 1 h at 0°C . Naturally warmed to room temperature. The reaction was stirred at room temperature for 16 h. The reaction mixture was diluted with water (500 mL) and extracted with

EtOAc (500 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a yellow solid. The solid was washed with ether (100 mL x 2) to afford 2-(2,6-dimethoxyphenyl)ethan-1-ol (20.1 g, 28% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ: 7.16 (t, *J* = 8.3 Hz, 1H), 6.56 (d, *J* = 8.3 Hz, 2H), 3.82 (s, 6H), 3.80 – 3.73 (m, 2H), 2.99 (t, *J* = 6.4 Hz, 2H).

Step 2: A solution of 2-(2,6-dimethoxyphenyl)ethan-1-ol (40.2 g, 220 mmol, 1.0 eq.) in 40% aqueous HBr solution (700 mL, HBr-H₂O) was stirred at 105 °C for 16 h. The reaction solution was diluted with water (1 L) and extracted with EtOAc (500 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a residue. The residue was purified by flash chromatography on silica gel (EA in PE = 9.32%) to afford 2,3-dihydrobenzofuran-4-ol (2.8 g, 9.3% yield) as yellow solids. ¹H NMR (400 MHz, CDCl₃) δ: 7.01 – 6.95 (m, 1H), 6.41 (d, *J* = 8.0 Hz, 1H), 6.31 (d, *J* = 8.2 Hz, 1H), 4.60 (t, *J* = 8.6 Hz, 2H), 3.16 (t, *J* = 8.8 Hz, 2H).

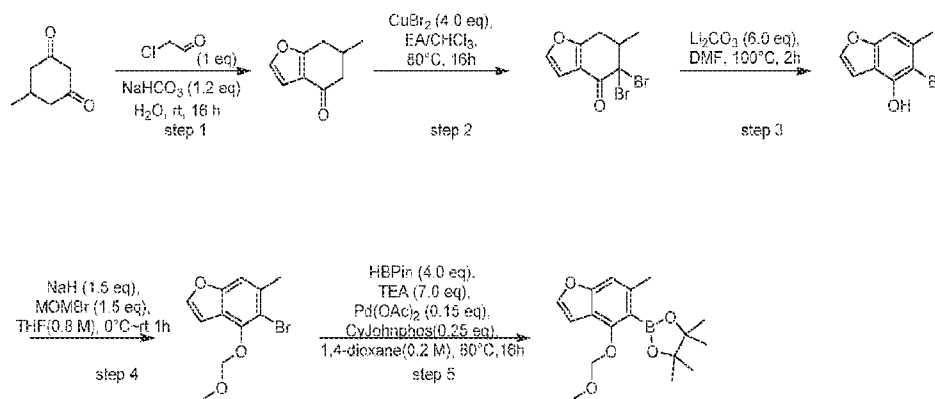
Step 3: To a solution of 2,3-dihydrobenzofuran-4-ol (6.08 g, 44.63 mmol, 1.0 eq.) in acetonitrile (60 mL) was slowly added NIS (10.04 g, 44.63 mmol, 1.0 eq.) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was diluted with water (50 mL) and extracted with DCM (40 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a residue. The residue was purified by flash chromatography on silica gel (SiO₂, EA in PE = 0.7%) to afford 5-iodo-2,3-dihydrobenzofuran-4-ol (4.76 g, 41 % yield) as brown solids. MS *m/z* 262.0 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ: 7.89 (brs, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 6.26 (d, *J* = 8.4 Hz, 1H), 4.62 (t, *J* = 8.8 Hz, 2H), 3.22 (t, *J* = 8.8 Hz, 2H).

Step 4: To a mixture of 5-iodo-2,3-dihydrobenzofuran-4-ol (4.60 g, 17.6 mmol, 1.00 eq) in THF (50.0 mL) was added NaH (60%) (1.40 g, 35.11 mmol, 2.00 eq) at 0 °C, the mixture was stirred at 0 °C for 0.5 h. Then MOMBr (3.29 g, 26.33 mmol, 1.5 eq) was added and the reaction mixture was stirred at rt for 2 h. The reaction mixture was quenched with sat. aqueous NH₄Cl (50 mL), the mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL x 3). The organics were washed with brine (50 mL x 3), dried with Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (SiO₂, Petroleum ether/ethyl acetate=100/1~10/1) to give 5-iodo-4-(methoxymethoxy)-2,3-dihydrobenzofuran (3.4 g, 63%

yield) as white solids. ^1H NMR (400 MHz, CDCl_3) δ : 7.49 (d, $J = 8.4$ Hz, 1H), 6.38 (d, $J = 8.4$ Hz, 1H), 5.13 (s, 2H), 4.57 (t, $J = 8.7$ Hz, 2H), 3.59 (s, 3H), 3.34 (t, $J = 8.7$ Hz, 2H).

Step 5: To a mixture of 5-iodo-4-(methoxymethoxy)-2,3-dihydrobenzofuran (2.90 g, 9.47 mmol, 1.00 eq) in THF (30 mL) was added dropwise n-BuLi (4.55 mL, 2.5 M, 11.37 mmol, 1.2 eq) at -78°C under N_2 atmosphere, the mixture was stirred at -78°C for 0.5 h. Then 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.64 g, 14.21 mmol, 1.5 eq) in THF (10 mL) was added dropwise under N_2 atmosphere and the reaction mixture was stirred at rt for 3 h. The reaction mixture was quenched with saturated NH_4Cl aqueous solution (30 mL) and extracted with ethyl acetate (40 mL x 3), the combined organic layer was washed with brine (40 mL x 3), dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by column chromatography (SiO_2 , Petroleum ether/ethyl acetate=100/1~10/1) to give 2-(4-(methoxymethoxy)-2,3-dihydrobenzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.2 g, 76% Yield) as white solids. ^1H NMR (400 MHz, CDCl_3) δ : 7.58 (d, $J = 8.0$ Hz, 1H), 6.58 (d, $J = 8.0$ Hz, 1H), 5.11 (s, 2H), 4.59 (t, $J = 8.7$ Hz, 2H), 3.56 (s, 3H), 3.27 (t, $J = 8.7$ Hz, 2H), 1.32 (s, 12H).

Intermediate 3: Preparation of 2-(4-(methoxymethoxy)-6-methylbenzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1: To a solution of sodium bicarbonate (79.9 g, 951.2 mmol, 1.2 eq) and chloroacetaldehyde (155.5 g, 792.6 mmol, 1.0 eq) in water (1380 mL) at 0°C was added dropwise a solution of 4,4-dimethylcyclohexane-1,3-dione in THF (1100 mL). The resulting mixture was stirred at room temperature for 18 h and ethyl acetate (1000 mL) was added. The mixture was adjusted to pH=1 with 50% H_2SO_4 and vigorously stirred for 3 h. The organic layer was collected, and the acidic layer was extracted with ethyl acetate (3 x 400 mL). The combined organic extracts were washed

with water, saturated NaHCO_3 , brine, and dried over Na_2SO_4 . The solvent was evaporated under reduced pressure and the residue was purified on silica gel (Petroleum ether/Ethyl acetate=20/1 to 1/1) to afford the 6-methyl-6,7-dihydrobenzofuran-4(5H)-one (54 g, 359.5 mmol, 45.3% yield) as yellow oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.69 (d, J = 2.1 Hz, 1H), 6.65 (d, J = 2.1 Hz, 1H), 2.97 (dd, J = 17.1, 4.8 Hz, 1H), 2.59 (dd, J = 17.0, 9.4 Hz, 1H), 2.41 (dt, J = 17.0, 2.1 Hz, 2H), 2.28 (dd, J = 13.5, 3.7 Hz, 1H), 1.09 (d, J = 6.3 Hz, 3H).

Step 2: CuBr_2 (321.2 g, 1.44 mol, 4.0 eq) was added into EA (770 mL). The reaction was allowed to stir at 80°C for 10 min. To this was added a solution of 6-methyl-6,7-dihydrobenzofuran-4(5H)-one (54 g, 359.5 mmol, 1.0 eq) in CHCl_3 (128 mL) at 80°C in one portion. The reaction was allowed to stir at 80°C for 16 h. Upon completion, the reaction was cooled to rt, filtered to remove the solid. The filtrate was concentrated and purified by silica gel column chromatography (PE: EA =50:1~5:1) to afford the 5,5-dibromo-6-methyl-6,7-dihydrobenzofuran-4(5H)-one (33 g, 107.1 mmol, 29.8% yield) as yellow solid.

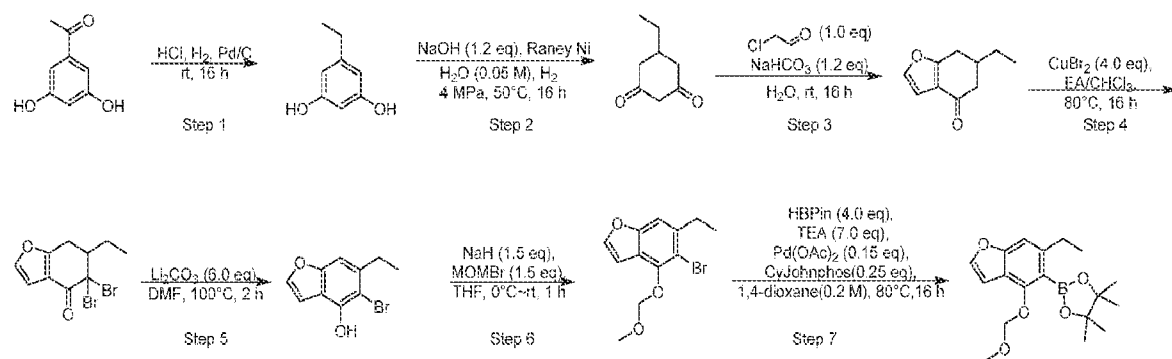
Step 3: 5,5-dibromo-6-methyl-6,7-dihydrobenzofuran-4(5H)-one (33 g, 107.1 mmol, 1.0 eq) was dissolved in anhydrous DMF (535mL). To this solution was added Li_2CO_3 (47.5 g, 642.9 mmol, 6.0 eq). The reaction was allowed to stir at 100°C for 2 h. Upon completion, the reaction was cooled to rt, filtered to remove the solid and concentrated. The residue was diluted with water (500 mL), extracted with EA (200 mL). The organic layer was washed with water (500 mL x 2) and brine (500 mL x 1), dried over Na_2SO_4 , decanted, and concentrated. The residue was purified by silica gel column chromatography (EA:PE = 1: 50) to afford the 5-bromo-6-methylbenzofuran-4-ol (19.5 g, 85.8 mmol, 80.1% yield) as white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 10.38 (s, 1H), 7.80 (d, J = 2.2 Hz, 1H), 7.12 (d, J = 0.9 Hz, 1H), 7.09 (dd, J = 2.2, 1.0 Hz, 1H), 2.41 (d, J = 0.6 Hz, 3H).

Step 4: To a solution of 5-bromo-6-methylbenzofuran-4-ol (19.5 g, 85.8 mmol, 1.0 eq) in THF (110 mL) was added NaH (6.8 g, 171.7 mmol, 2.0 eq) at 0°C in portions. The reaction mixture was warmed to rt for 1 hour and then MOMBr (16.1 g, 128.8 mmol, 1.5 eq) was added. The reaction was stirred at rt for 1 h. The mixture was quenched with H_2O (200 mL), extracted with EA (100 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated to afford the 5-bromo-4-(methoxymethoxy)-6-methylbenzofuran (21 g, 77.4 mmol, 90.1% yield) as brown oil, which was used for the next step without further purification. ^1H

NMR (400 MHz, DMSO-*d*₆) δ 7.95 (d, *J* = 2.3 Hz, 1H), 7.42 (t, *J* = 0.9 Hz, 1H), 7.06 (dd, *J* = 2.3, 1.0 Hz, 1H), 5.35 (s, 2H), 3.55 (s, 3H), 2.46 (d, *J* = 0.7 Hz, 3H).

Step 5. To a solution of 5-bromo-4-(methoxymethoxy)-6-methylbenzofuran (21 g, 77.4 mmol, 1.0 eq) in dioxane (370 mL) were added HBPIn (37.7 g, 295.0 mmol, 4.0 eq), TEA (52.2 g, 516.4 mmol, 7.0 eq), Pd(OAc)₂ (2.4 g, 11.0 mmol, 0.15 eq) and CyJohnphos (6.4 g, 18.4 mmol, 0.25 eq). The mixture was then purged with N₂. The reaction was allowed to be stirred at 80°C for 16 h. Upon completion, the reaction was cooled to room temperature, filtered through a pad of Celite and rinsed with EA. The filtrate was concentrated to get crude oil. The residue was purified by column chromatography on silica gel (Petroleum ether/Ethyl acetate=80/1 to 10/1) to afford the 2-(4-(methoxymethoxy)-6-methylbenzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10 g, 31.4 mmol, 42.6% yield) as brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.84 (d, *J* = 2.4 Hz, 1H), 7.14 (s, 1H), 6.93 (dd, *J* = 2.0, 0.8 Hz, 1H), 5.22 (s, 2H), 3.48 (s, 3H), 2.37 (s, 3H), 1.33 (s, 12H).

Intermediate 4. Preparation of 2-(6-ethyl-4-(methoxymethoxy)benzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1. To a solution of 1-(3,5-dihydroxyphenyl)ethan-1-one (50.0 g, 0.330 mol, 1.0 eq.) in HCl (4% w/w) (3750 mL) was added Pd/C (12 g, 25% w/w). The mixture was stirred for 16 h at room temperature under H₂ (4 MPa). The reaction mixture was filtered through a pad of Celite, rinsed with EA. The filtrate was then extracted with tert-Butyl methyl ether (1 L). The combined organic layer was washed with water (500 mL x 3) and brine (500 mL), dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel (Petroleum ether/Ethyl acetate = 1:0 to 5:1) to afford 5-ethylbenzene-1,3-diol (33.0 g, 0.240 mol,

72.7% yield) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 6.27 – 6.27 (m, 1H), 6.21 – 6.20 (m, 2H), 2.51 (q, J = 7.6 Hz, 2H), 1.26 (t, J = 7.2 Hz, 3H).

Step 2. To a mixture of 5-ethylbenzene-1,3-diol (42.0 g, 0.300 mol, 1.0 eq.) in H_2O (420 mL) was added Raney Ni (3.60 g, 8.5% w/w) and NaOH (14.6 g, 0.360 mol, 1.2 eq.). The reaction was stirred at 50°C for 16 h under H_2 (4 MPa). Upon completion, the reaction mixture was cooled to room temperature. The pH was adjusted to around 4–5 with 2M HCl and the mixture was extracted with EtOAc (500 mL x 3). The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (Petroleum ether/Ethyl acetate = 1:0 to 1:1) to afford 5-ethylcyclohexane-1,3-dione (22.0 g, 0.160 mol, 51.6% yield) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 5.19 (s, 1H), 2.27 (dd, J = 16.4, 3.2 Hz, 2H), 2.03 (d, J = 11.2 Hz, 1H), 1.98 (s, 1H), 1.36 – 1.32 (m, 2H), 0.87 (t, J = 7.6 Hz, 3H).

Step 3. To a solution of NaHCO_3 (11.5 g, 0.140 mol, 1.2 eq.) and 2-chloroacetaldehyde (22.4 g, 0.110 mol, 1.0 eq.) in water (160 mL) was added a solution of 5-ethylcyclohexane-1,3-dione (16.0 g, 0.110 mol, 1.0 eq.) in THF (20 mL) dropwise at 0°C. The reaction was stirred at room temperature for 16 h, then diluted with ethyl acetate. The pH was adjusted to pH = 1 with H_2SO_4 (50% w/w in H_2O) and the mixture was vigorously stirred for 3 h. The organic layer was collected, and the aqueous layer was extracted with ethyl acetate (500 mL x 3). The combined organic phase was washed with water, saturated NaHCO_3 and brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography on silica gel (Petroleum ether/Ethyl acetate = 1:0 to 3:1) to afford 6-ethyl-6,7-dihydrobenzofuran-4(5H)-one (10.5 g, 0.060 mol, 56.2% yield) as yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.32 (d, J = 1.6 Hz, 1H), 6.66 (d, J = 2.0 Hz, 1H), 3.03 – 2.98 (m, 1H), 2.62 – 2.51 (m, 2H), 2.29 – 2.22 (m, 2H), 1.61 (s, 2H), 0.99 (t, J = 7.6 Hz, 3H).

Step 4: A mixture of CuBr_2 (57.1 g, 0.260 mol, 4 eq.) in ethyl acetate (180 mL) was heated and stirred at 80°C for 10 min. Then a solution of 6-ethyl-6,7-dihydrobenzofuran-4(5H)-one (10.5 g, 0.060 mol, 1 eq.) in CHCl_3 (100 mL) was added into the mixture at 80°C. The reaction was stirred at 80°C for 16 h. Upon completion, the reaction mixture was cooled to room temperature, filtered through a pad of Celite and rinsed with EtOAc. The filtrate was concentrated in vacuo. The residue was purified by flash chromatography on silica gel (PE: EA = 1:0 ~ 20:1) to afford

5,5-dibromo-6-ethyl-6,7-dihydrobenzofuran-4(5H)-one (8.00 g, 24.8 mmol, 38.8% yield) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 7.39 (d, $J = 2.0$ Hz, 1H), 6.77 (d, $J = 2.0$ Hz, 1H), 3.07 (dd, $J = 17.6, 4.8$ Hz, 1H), 2.67 (dd, $J = 17.6, 9.6$ Hz, 1H), 2.43 – 2.36 (m, 2H), 1.78 – 1.61 (m, 1H), 1.11 (t, $J = 7.2$ Hz, 3H).

5 Step 5: To a mixture of 5,5-dibromo-6-ethyl-6,7-dihydrobenzofuran-4(5H)-one (8.00 g, 24.9 mmol, 1.0 eq.) in DMF (80 mL) was added Li_2CO_3 (11.0 g, 149 mmol, 4.0 eq.). The reaction mixture was stirred for 2 h at 100°C . Upon completion, the reaction was cooled to room temperature, filtered through a pad of Celite and rinsed with EtOAc. The filtrate was diluted with water (800 mL) and extracted with EtOAc (200 mL x 3). The combined organic layer was dried
10 over anhydrous Na_2SO_4 , filtered and concentrated. The residue was purified by flash chromatography on silica gel (PE: EA = 1:0 ~ 20:1) to afford 5-bromo-6-ethylbenzofuran-4-ol (4.50 g, 18.7 mmol, 75.1% yield) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.38 (s, 1H), 7.81 (d, $J = 2.4$ Hz, 1H), 7.10 (s, 1H), 7.08 (s, 1H), 2.77 (q, $J = 7.6$ Hz, 2H), 1.19 (t, $J = 7.2$ Hz, 3H).

15 Step 6: To a solution of 5-bromo-6-ethylbenzofuran-4-ol (5.00 g, 20.7 mmol, 1.0 eq.) in THF (50 mL) was added NaH (1.24 g, 31.0 mmol, 1.5 eq.) in portions at 0°C . The resulting mixture was stirred at room temperature for 0.5 h. Then bromomethyl methyl ether (3.89 g, 31.0 mmol, 1.5 eq.) was added slowly at 0°C . The reaction was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched by the addition of water, diluted with water (500 mL) and
20 extracted with EtOAc (200 mL x 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated to afford 5-bromo-6-ethyl-4-(methoxymethoxy)benzofuran (5.50 g, 19.3 mmol, 93.0% yield) as yellow oil, which was used for the next step without further purification. ^1H NMR (400 MHz, CDCl_3) δ 7.52 (d, $J = 2.4$ Hz, 1H), 7.20 (s, 1H), 6.88 (d, $J = 2.0$ Hz, 1H), 5.31 (s, 2H), 3.67 (s, 3H), 2.88 (q, $J = 7.6$ Hz, 2H),
25 1.27 (t, $J = 7.6$ Hz, 3H).

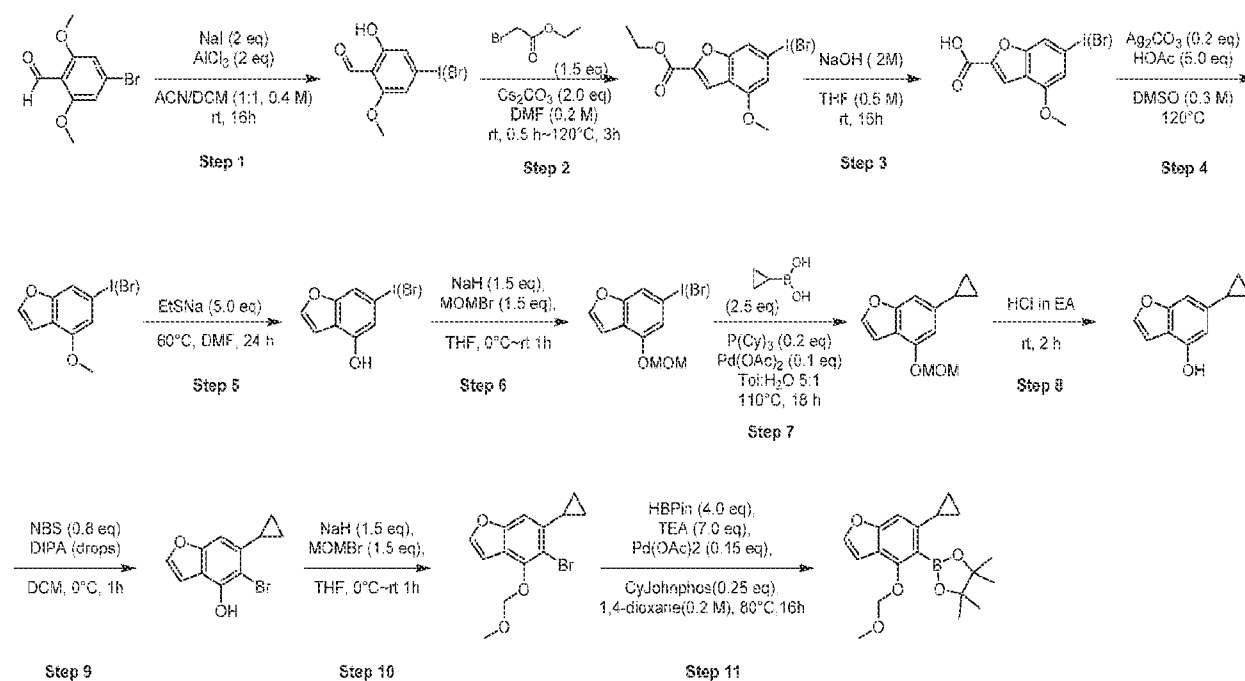
Step 7: To a solution of 5-bromo-6-ethyl-4-(methoxymethoxy)benzofuran (5.90 g, 20.7 mmol, 1.0 eq.) in 1,4-dioxane (60 mL) were added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10.6 g, 83.0 mmol, 4.0 eq.), $\text{Pd}(\text{OAc})_2$ (517 mg, 3.10 mmol, 0.15 eq.), Et_3N (20.1 mL, 145 mmol, 7.0 eq.) and 2-(dicyclohexylphosphino)biphenyl (1.80 g, 5.20 mmol, 0.25 eq.). The reaction was
30 stirred at 80°C for 16 h under N_2 atmosphere. Upon completion, the reaction was cooled to room

temperature, filtered through a pad of Celite and rinsed with EtOAc. The filtrate was diluted with water (500 mL) and extracted with EtOAc (100 mL x 3). The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated.

The residue was purified by flash chromatography on silica gel (PE: EA = 1:0 ~ 20:1) to afford

2-(6-ethyl-4-(methoxymethoxy)benzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.70 g, 14.2 mmol, 68.3% yield) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.47 (d, J = 2.4 Hz, 1H), 7.08 (s, 1H), 6.86 (d, J = 2.0 Hz, 1H), 5.24 (s, 2H), 3.59 (s, 3H), 2.76 (dd, J = 15.2 Hz, 7.6 Hz, 2H), 1.40 (s, 12H), 1.25 (t, J = 7.6 Hz, 3H).

Intermediate 5. Preparation of 2-(6-cyclopropyl-4-(methoxymethoxy)benzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1: To a mixture of 4-bromo-2,6-dimethoxybenzaldehyde (25.0 g, 102 mmol, 1.0 eq.) and NaI (30.6 g, 204 mmol, 2.0 eq.) in MeCN (150 mL) and DCM (150 mL) was added AlCl₃ (27.2 g, 204 mmol, 2.0 eq.) at 0°C. The reaction was stirred at room temperature for 16 h. Upon completion, the reaction was quenched with aq. NH₄Cl (100 mL) and extracted with EtOAc (500 mL x 2). The organic phase was washed with brine (200 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo to afford 2-hydroxy-4-iodo(bromo)-6-methoxybenzaldehyde as a yellow solid (23.0 g, 97.6% yield), which was used into next step without further purification. ¹H NMR

(400 MHz, CDCl₃) δ 12.07 (s, 1H), 11.97 (s, 0.6 H), 10.28 (s, 0.6 H), 10.26 (s, 1H), 7.00 (s, 0.6 H), 6.76 (s, 1+0.6 H), 6.55 (d, J = 1.4 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 2H).

Step 2: To a solution of 2-hydroxy-4-iodo(bromo)-6-methoxybenzaldehyde (23.0 g, 100 mmol, 1.0 eq.) in DMF (230 mL) were added ethyl 2-bromoacetate (25.1 g, 150 mmol, 1.5 eq.) and Cs₂CO₃ (65.4 g, 200 mmol, 2.0 eq.). The reaction was stirred at room temperature for 0.5 h, then stirred at 120°C for 3 h under Ar atmosphere. Upon completion, the reaction mixture was cooled to room temperature, diluted with H₂O (1000 mL) and extracted with EtOAc (400 mL x 2). The organic layer was washed with brine (500 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo to afford ethyl 6-iodo (bromo) -4-methoxybenzofuran-2-carboxylate as a yellow solid (18.0 g, 59.9% yield), which was used into next step without further purification. MS m/z 210.9 [M-H]

Step 3: To a solution of ethyl 6-iodo(bromo)-4-methoxybenzofuran-2-carboxylate (18.0 g, 52.0 mmol, 1.0 eq.) in THF (150 mL) and H₂O (50 mL) was added NaOH (3.12 g, 78.0 mmol, 1.5 eq.). The reaction was stirred at 25°C for 16 h. Upon completion, the reaction mixture was poured into 4 N HCl to pH = 4 and extracted with EtOAc (200 mL x 3). The organic phase was washed with brine (200 mL), dried over Na₂SO₄, filtered and evaporated under reduced pressure to afford 6-iodo(bromo)-4-methoxybenzofuran-2-carboxylic acid as a white solid (17.0 g, 92.5% yield), which was used into next step without further purification. MS m/z 225.0 [M-H].

Step 4: To a mixture of 6-iodo(bromo)-4-methoxybenzofuran-2-carboxylic acid (17.0 g, 53.5 mmol, 1.0 eq.) and AgCO₃ (2.9 g, 10.7 mmol, 0.2 eq.) in DMSO (170 mL) was added AcOH (16.1 g, 267 mmol, 5.0 eq.). The reaction was stirred at 120°C for 2 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with H₂O (1000 mL) and extracted with EtOAc (300 mL x 2). The organic layer was washed with brine (500 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by silica gel column (100% PE) to get 6-iodo(bromo)-4-methoxybenzofuran as a white solid (12.0 g, 95% purity, 77.8% yield).

Step 5: To a suspension of NaH (5.7 g, 91.2 mmol, 5.0 eq.) in DMF (50 mL) was added ethanethiol (3.7 g, 91.2 mmol, 5.0 eq.) at 0°C. The mixture was stirred at 0°C for 30 min under N₂ atmosphere. 6-iodo(bromo)benzofuran-4-ol (5.0 g, 18.2 mmol, 1.0 eq.) was added into the EtSNa solution at 0°C. The reaction was stirred at 60°C for 24 h under N₂ atmosphere. Upon

completion, the reaction mixture was cooled to room temperature, diluted with H₂O (500 mL) and extracted with EtOAc (200 mL x 3). The organic phase was washed with brine (200 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The crude was purified by reversed phase flash chromatography (80 g flash column, eluting with 0-100% MeCN in H₂O) to give 6-iodo(bromo)benzofuran-4-ol as a white solid (4.5 g, 94.9% yield). MS m/z 213.1 [M-H]⁻.

Step 6: To a solution of 6-iodo(bromo)benzofuran-4-ol (7.3 g, 34.2 mmol, 1.0 eq.) in THF (80 mL) was added NaH (2.1 g, 51.4 mmol, 1.5 eq.) at 0°C. The reaction was allowed to stir at 0°C for 0.5 h. Then bromomethyl methyl ether (6.4 g, 51.4 mmol, 1.5 eq.) was added at 0°C. The reaction was warmed to room temperature and stirred for 0.5 h. The mixture was quenched with water and extracted with EtOAc (70 mL x 3). The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford 6-iodo(bromo)-4-(methoxymethoxy)benzofuran as yellow oil (8.3 g, 94.2% yield), which was used into next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.57 (s, 0.4 H), 7.52 (d, J = 2.0 Hz, 1H), 7.47 (d, J = 2.0 Hz, 0.4 H), 7.37 (s, 1H), 7.22 (s, 0.4 H), 7.07 (d, J = 1.2 Hz, 1H), 6.84 (s, 0.4 H), 6.84 (s, 1H), 5.28 (s, 2H), 5.27 (s, 1H), 3.52 (s, 5H).

Step 7: To a solution of 6-iodo(bromo)-4-(methoxymethoxy)benzofuran (5.0 g, 19.5 mmol, 1.0 eq.) and cyclopropylboronic acid (5.0 g, 58.4 mmol, 3.0 eq.) in Tol (80 mL) and H₂O (20 mL) were added K₃PO₄ (12.4 g, 58.4 mmol, 3.0 eq.), P(Cy)₃ (1.1 g, 3.9 mmol, 0.2 eq.) and Pd(OAc)₂ (437 mg, 1.9 mmol, 0.1 eq.). The reaction was stirred at 100°C in microwave reactor for 1 h under N₂. The reaction mixture was cooled to room temperature, diluted with water (100 mL) and extracted with EtOAc (300 mL x 3). The organic phase was washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column (petroleum ether: EtOAc = 20:1) to get 6-cyclopropyl-4-(methoxymethoxy)benzofuran as a white solid (3.3 g, 77.7% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.47 (d, J = 2.4 Hz, 1H), 6.88 (s, 1H), 6.83 – 6.77 (m, 1H), 6.71 (s, 1H), 5.29 (s, 2H), 3.53 (s, 3H), 2.04 – 1.92 (m, 1H), 1.03 – 0.92 (m, 2H), 0.75 – 0.67 (m, 2H).

Step 8: A solution of 6-cyclopropyl-4-(methoxymethoxy)benzofuran (3.0 g, 13.7 mmol, 1.0 eq.) in 2.0 M HCl in EA (30 mL) was stirred at 25°C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure. The crude product was purified by reversed phase

flash chromatography (40 g flash column, eluting with 0-100% MeCN in H₂O) to give 6-cyclopropylbenzofuran-4-ol as a white solid (777 mg, 32.5% yield). MS m/z 175.2 [M+H]⁺.

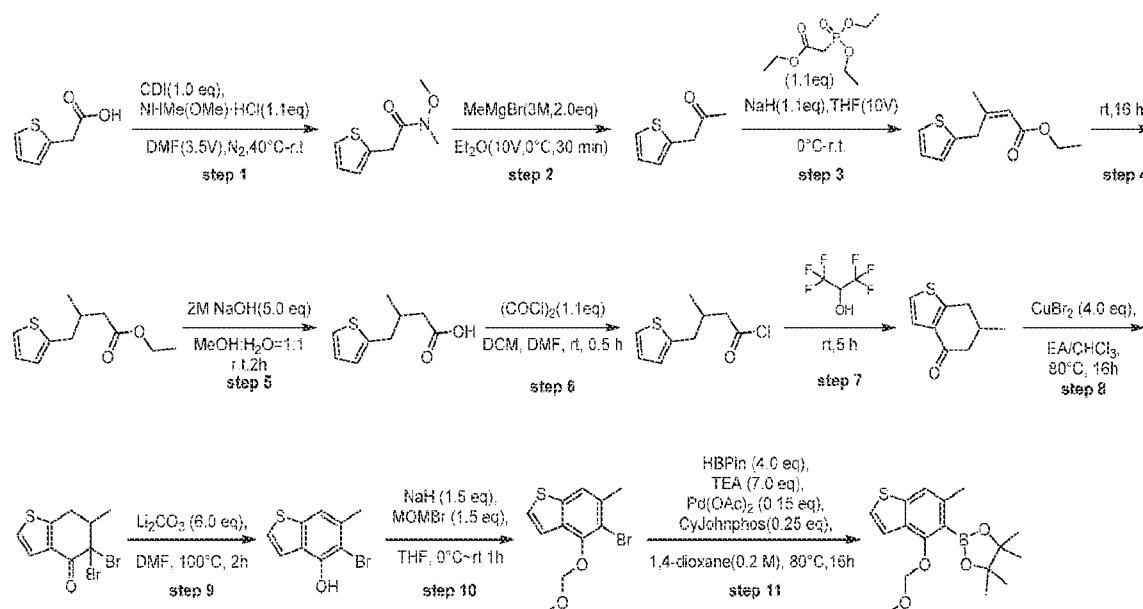
Step 9: To a solution of 6-cyclopropylbenzofuran-4-ol (777 mg, 4.5 mmol, 1.0 eq.) in DCM (20 mL) were added 1-bromopyrrolidine-2,5-dione (715 mg, 4.0 mmol, 0.9 eq.) and

diisopropylamine (drops) at 0°C. The resulting mixture was stirred at 0°C for 1 h. Upon completion, the reaction mixture was diluted with water and extracted with EtOAc. The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was chromatographed on silica gel eluted with petroleum ether to give the 5-bromo-6-cyclopropylbenzofuran-4-ol as a yellow solid (708 mg, 62.7% yield). MS m/z 253.0 [M-H]⁻.

Step 10: To a solution of 5-bromo-6-cyclopropylbenzofuran-4-ol (708 mg, 2.8 mmol, 1.0 eq.) in DCM (10 mL) were added DIEA (1.1 g, 8.4 mmol, 3.0 eq.) and bromomethyl methyl ether (385 mg, 3.1 mmol, 1.1 eq.). The reaction was stirred at 25°C for 1 h. Upon completion, the reaction mixture was quenched with water and extracted with EtOAc (30 mL x 3). The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford 5-bromo-6-cyclopropyl-4-(methoxymethoxy)benzofuran as yellow oil (800 mg, 96.2% yield), which was used into next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.52 (d, J = 2.4 Hz, 1H), 6.97 (s, 1H), 6.87 (d, J = 2.0 Hz, 1H), 5.32 (s, 2H), 3.68 (s, 3H), 2.04 – 1.92 (m, 1H), 1.10 – 1.01 (m, 2H), 0.69 (q, J = 5.4 Hz, 2H).

Step 11: To a solution of 5-bromo-6-cyclopropyl-4-(methoxymethoxy)benzofuran (980 mg, 3.3 mmol, 1.0 eq.) in 1,4-dioxane (10 mL) were added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.7 g, 13.2 mmol, 4.0 eq.), Pd(OAc)₂ (111 mg, 0.5 mmol, 0.15 eq.), TEA (2.3 g, 23.1 mmol, 7.0 eq.) and 2-(dicyclohexylphosphino)biphenyl (289 mg, 0.8 mmol, 0.25 eq.). The reaction was stirred at 100°C for 16 h under N₂ atmosphere. Upon completion, the reaction mixture was cooled to room temperature, filtered through a pad of celite and rinsed with EtOAc. The filtrate was concentrated in vacuo. The residue was purified by flash chromatography (40 g flash column, eluting with 0-12% EA in PE) to afford 2-(6-cyclopropyl-4-(methoxymethoxy)benzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (500 mg, 44.1% yield) as a brown solid. ¹H NMR (400 MHz, CDCl₃) δ 7.46 (d, J = 2.0 Hz, 1H), 6.86 (s, 1H), 6.84 (d, J = 1.2 Hz, 1H), 5.24 (s, 2H), 3.59 (s, 3H), 2.18 – 2.09 (m, 1H), 1.41 (s, 12H), 0.92 – 0.87 (m, 2H), 0.76 – 0.68 (m, 2H).

Intermediate 6. Preparation of 2-(4-(methoxymethoxy)-6-methylbenzo[b]thiophen-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1: To a solution of 2-(thiophen-2-yl)acetic acid (10.0 g, 70.3 mmol, 1.0 eq.) in DMF (70 mL, 1 M) was added CDI (11.4 g, 70.3 mmol, 1.0 eq.). After being stirred at 40°C for 30 min, N,O-dimethylhydroxylamine hydrochloride (7.6 g, 77.4 mmol, 1.1 eq.) was added. The reaction mixture was stirred at room temperature for 0.5 h. Upon completion, the mixture was diluted with saturated NH₄Cl (50 mL) and extracted with EtOAc (2 x 100 mL). The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (ethyl acetate/hexane = 0% ~ 20%) to obtain N-methoxy-N-methyl-2-(thiophen-2-yl)acetamide (7.0 g, 37.8 mmol, yield 53%) as colorless oil. MS m/z 186.2 [M+H]⁺.

Step 2: To a solution of N-methoxy-N-methyl-2-(thiophen-2-yl)acetamide (7.0 g, 37.8 mmol, 1.0 eq.) in Et₂O (70 mL) at 0°C under N₂ atmosphere was added CH₃MgBr (3M in Et₂O, 25.2 mL, 75.6 mmol, 2.0 eq.). The reaction mixture was stirred at 0°C for 0.5 h. Upon completion, the reaction mixture was quenched with aq. NH₄Cl and extracted with ethyl acetate (50 mL x 3). The organic layer was dried over Na₂SO₄, filtered and concentrated. The concentrated residue was purified by silica gel column chromatography eluting with 0-20% EtOAc in hexanes to give 1-(thiophen-2-yl)propan-2-one (1.5 g, 10.7 mmol, 28% yield) as a brown solid. MS m/z 141.1 [M+H]⁺, ¹H NMR (400 MHz, CDCl₃) δ 7.20 (m, 1H), 6.96 (m, 1H), 6.87 (d, J = 3.2 Hz, 1H), 3.87 (s, 2H), 2.18 (s, 3H).

Step 3: To a mixture of NaH (471 mg, 11.8 mmol, 1.1 eq.) in THF (15 mL) was added ethyl 2-(diethoxyphosphoryl)acetate (2.6 g, 11.8 mmol, 1.1 eq.) at 0°C. The reaction mixture was warmed to room temperature and stirred for 0.5 h. 1-(thiophen-2-yl)propan-2-one (1.5 g, 10.7 mmol, 1.0 eq.) was added to the mixture at 0°C. The reaction mixture was warmed to room temperature and stirred for another 1 h. Upon completion, the mixture was quenched with water (20 mL) and extracted with EtOAc (50 mL x 3). The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (ethyl acetate/hexane = 0% ~ 30%) to obtain ethyl (Z)-3-methyl-4-(thiophen-2-yl)but-2-enoate (1.4 g, 6.7 mmol, yield 62%) as a brown solid. MS m/z 211.2 [M+H]⁺.

Step 4: A mixture of ethyl (Z)-3-methyl-4-(thiophen-2-yl)but-2-enoate (1.4 g, 6.7 mmol, 1.0 eq.), Raney-Ni (280 mg, 20% w/w) in MeOH (14 mL) was stirred at room temperature under H₂ atmosphere for 16 h. Upon completion, the reaction mixture was filtered through a Celite pad and washed with MeOH. The filtrate was concentrated to afford ethyl 3-methyl-4-(thiophen-2-yl)butanoate (0.9 g, 4.2 mmol, 62% yield) as a brown solid, which was used to the next step without purification. ¹H NMR (400 MHz, CDCl₃) δ 7.13 – 7.11(m, 1H), 6.91 – 6.90 (m, 1H), 6.78 (d, J = 2.4 Hz, 1H), 4.15 – 4.09 (m, 2H), 2.86 – 2.81 (m, 1H), 2.77 – 2.72 (m, 1H), 2.43 – 2.33 (m, 1H), 2.40 – 2.35 (m, 1H), 2.34 – 2.26 (m, 1H), 2.16 – 2.09 (m, 1H), 1.25 (t, J = 7.2 Hz, 3H), 0.99 (d, J = 6.4 Hz, 3H).

Step 5: To a solution of ethyl 3-methyl-4-(thiophen-2-yl)butanoate (0.9 g, 4.2 mmol, 1.0 eq.) in a mixture of tetrahydrofuran and methanol (16 mL, 1:1) was added NaOH (0.8 g, 21.2 mmol, 5.0 eq.) at room temperature. The reaction mixture was stirred at room temperature for 4 hours and then the solvent evaporated. The residue was dissolved in water, acidified with hydrochloric acid (4N) and extracted with EA (20 mL x 3). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to obtain 3-methyl-4-(thiophen-2-yl)butanoic acid (0.7 g, 3.8 mmol, 90% yield) as a white solid, which was used to the next step without purification. MS m/z 185.3 [M+H]⁺.

Step 6: To a solution of 3-methyl-4-(thiophen-2-yl)butanoic acid (0.7 g, 3.8 mmol, 1.0 eq.) in DCM (7 mL) was added (COCl)₂ (0.4 mL, 4.2 mmol, 1.1 eq.). The reaction mixture was stirred at room temperature for 0.5 h. The mixture was concentrated in vacuo to give crude 3-methyl-4-

(thiophen-2-yl)butanoyl chloride (0.8 g) as yellow oil, which was used to the next step without further purification.

Step 7: A mixture of 3-methyl-4-(thiophen-2-yl)butanoyl chloride (0.8 g, 4.0 mmol, 1.0 eq.) in 1,1,1,3,3,3-hexafluoropropan-2-ol (8 mL) was stirred at room temperature for 2 h. Upon completion, the reaction mixture was concentrated to remove 1,1,1,3,3,3-hexafluoropropan-2-ol. The residue was quenched with water (50 mL) and extracted with ethyl acetate (50 mL x 3). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with hexanes to afford 6-methyl-6,7-dihydrobenzo[b]thiophen-4(5H)-one (250 mg, 1.5 mmol, 35% yield) as a white solid. MS m/z 167.0 [M+H]⁺.

Step 8: To a mixture of CuBr₂ (1.3 g, 6.0 mmol, 4.0 eq.) in EtOAc (5 mL) was added a solution of 6-methyl-6,7-dihydrobenzo[b]thiophen-4(5H)-one (250 mg, 1.5 mmol, 1.0 eq.) in CHCl₃ (1 mL) at 80°C. The reaction was stirred at 80°C for 16 h. Upon completion, the reaction mixture was cooled to room temperature, filtered and collected organic phase. The organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with 0-3% EtOAc in hexanes to afford 5, 5-dibromo-6-methyl-6, 7-dihydrobenzo[b]thiophen-4(5H)-one (260 mg, 0.8 mmol, 53% yield) as a white solid. MS m/z 324.8 [M+H]⁺.

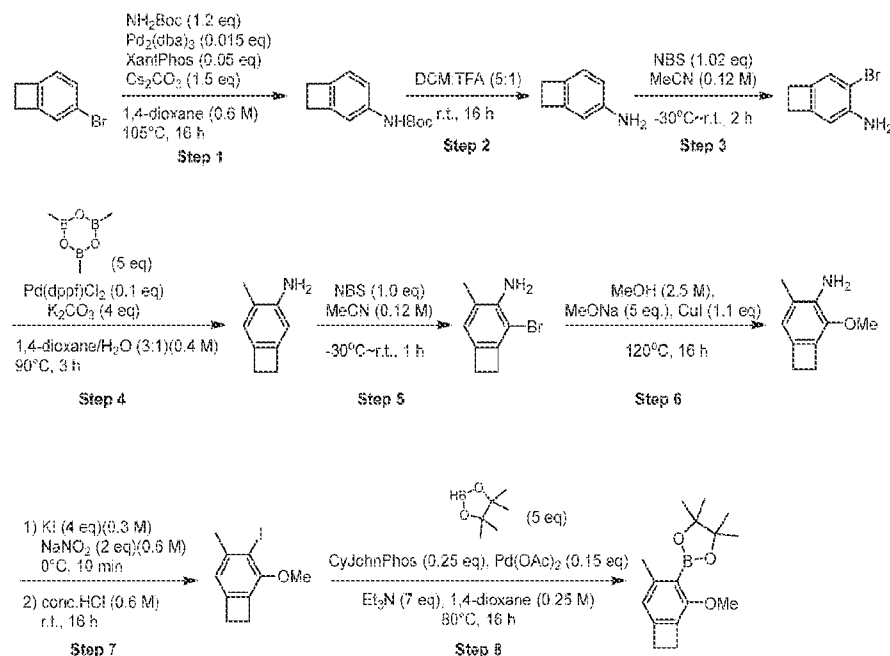
Step 9: To a mixture of 5, 5-dibromo-6-methyl-6, 7-dihydrobenzo[b]thiophen-4(5H)-on (260 mg, 0.8 mmol, 1.0 eq.) in DMF (3 mL) was added Li₂CO₃ (356 mg, 4.8 mmol, 6.0 eq.). The reaction was stirred at 100°C for 2 h. Upon completion, the reaction mixture was cooled to room temperature, quenched with water (10 mL) and extracted with EtOAc (10 mL x 3). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with hexanes to afford 5-bromo-6-methylbenzo[b]thiophen-4-ol (60 mg, 0.2 mmol, 31% yield) as a white solid. MS m/z 243.0 [M-H]⁻.

Step 10: To a solution of 5-bromo-6-methylbenzo[b]thiophen-4-ol (60 mg, 0.200 mmol, 1.0 eq.) in THF (1 mL) was added NaH (17.0 mg, 0.400 mmol, 2.0 eq.) at 0°C. The reaction mixture was warmed to room temperature and stirred for 0.5 h. Bromo(methoxy)methane (39 mg, 0.300 mmol, 1.5 eq.) was added to the mixture at 0°C. The reaction mixture was warmed to room

temperature and stirred for 2 h. Upon completion, the mixture was quenched with water (10 mL) and extracted with EtOAc (10 mL x 3). The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated to obtain ethyl (Z)-3-methyl-4-(thiophen-2-yl)but-2-enoate (60 mg, 6.7 mmol, yield 62%) as a brown solid, which was used to the next step without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.81 (s, 1H), 7.73 (d, J = 4.0 Hz, 1H), 7.45 (d, J = 4.0 Hz, 1H), 5.24 (s, 2H), 3.60 (s, 3H), 2.48 (s, 3H).

Step 11: To a mixture of ethyl (Z)-3-methyl-4-(thiophen-2-yl)but-2-enoate (60 mg, 6.70 mmol, 1.0 eq.), CyJohnPhos (18 mg, 0.052 mmol, 0.25 eq.), Pd(OAc)₂ (7 mg, 0.031 mmol, 0.15 eq.) and Et₃N (148 mg, 1.46 mmol, 7.0 eq.) in anhydrous 1,4-dioxane (2 mL) under N₂ atmosphere was added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (107 mg, 0.835 mmol, 4.0 eq.) dropwise at room temperature. The reaction was stirred at 80°C for 16 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with water (5 mL) and extracted with EtOAc (5 mL x 3). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with 0-10% EtOAc in hexanes to afford 2-(4-(methoxymethoxy)-6-methylbenzo[b]thiophen-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (30 mg, 0.089 mmol, 43% yield) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.60 (d, J = 5.6 Hz, 1H), 7.56 (s, 1H), 7.42 – 7.40 (m, 1H), 5.12 (s, 2H), 3.52 (s, 3H), 2.41 (s, 3H), 1.34 (s, 12H).

Intermediate 7. Preparation of 2-(2-methoxy-4-methylbicyclo[4.2.0]octa-1(6),2,4-trien-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1: A mixture of 3-bromobicyclo[4.2.0]octa-1(6),2,4-triene (57.8 g, 315 mmol, 1.0 eq.), NH₂Boc (44.4 g, 379 mmol, 1.2 eq.), Cs₂CO₃ (154 g, 474 mmol, 1.5 eq.), Xantphos (9.14 g, 15.8 mmol, 0.05 eq.), Pd₂(dba)₃ (4.34 g, 4.74 mmol, 0.01 eq.) and 1,4-dioxane (525 mL) was stirred at 105°C under N₂ atmosphere for 16 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with water (1000 mL) and extracted with EtOAc (1000 mL x 3). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with 0-10% EtOAc in hexanes to afford tert-butyl bicyclo[4.2.0]octa-1(6),2,4-trien-3-ylcarbamate (69.0 g, 315 mmol, 99.7% yield) as a pale yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 7.21 (s, 1H), 7.01 (d, J = 7.6 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.39 (s, 1H), 3.12 (s, 4H), 1.51 (s, 9H). MS m/z 164.4 [M-t-Bu+H]⁺.

Step 2: To a solution of tert-butyl bicyclo[4.2.0]octa-1(6),2,4-trien-3-ylcarbamate (73.2 g, 334 mmol, 1.0 eq.) in DCM (700 mL) was added TFA (140 mL). The reaction was stirred at room temperature for 16 h. Upon completion, the reaction mixture was concentrated in vacuum. The residue was diluted with water (1000 mL), neutralized with aq. NaHCO₃ to pH = 8 and extracted with DCM (1000 mL x 3). The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford bicyclo[4.2.0]octa-1(6),2,4-trien-3-amine (36.6 g, 307 mmol, 92.0% yield) as yellow oil, which was used to next step without further purification. ¹H NMR

(400MHz, CDCl₃) δ 6.82 (d, J = 8.0 Hz, 1H), 6.52 (dd, J = 7.6, 1.6 Hz, 1H), 6.46 (s, 1H), 3.50 (s, 2H), 3.07 (s, 4H). MS m/z 120.3 [M+H]⁺.

Step 3: To a solution of bicyclo[4.2.0]octa-1(6),2,4-trien-3-amine (36.6 g, 307 mmol, 1.0 eq.) in MeCN (1400 mL) was added a solution of NBS (53.6 g, 301 mmol, 0.98 eq.) in MeCN (1000 mL) at -30°C dropwise. The reaction was allowed to warm to room temperature and stirred for 2 h. Upon completion, the reaction mixture was diluted with water (1000 mL) and extracted with EtOAc (1000 mL x 3). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with 0-12% EtOAc in hexanes to afford 4-bromobicyclo[4.2.0]octa-1(6),2,4-trien-3-amine (17.0 g, 85.8 mmol, 28.0% yield) as a black solid. ¹H NMR (400 MHz, CDCl₃) δ 7.08 (s, 1H), 6.53 (s, 1H), 3.96 (s, 2H), 3.10 – 3.06 (m, 2H), 3.06 – 3.03 (m, 2H). MS m/z 239.3 [M+Na+H₂O+H]⁺, 241.3 [M+Na+H₂O+H]⁺.

Step 4: A mixture of 4-bromobicyclo[4.2.0]octa-1(6),2,4-trien-3-amine (12.0 g, 60.6 mmol, 1.0 eq.), K₂CO₃ (25.1 g, 182 mmol, 3.0 eq.), Pd(dppf)Cl₂ (4.40 g, 6.06 mmol, 0.1 eq.), H₂O (50 mL), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (3.5 M in THF, 86.6 mL, 303 mmol, 5 eq.) and 1,4-dioxane (250 mL) was stirred at 90°C under N₂ atmosphere for 3 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with water (1000 mL) and extracted with EtOAc (1000 mL x 2). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with 0-10% EtOAc in hexanes to afford 4-methylbicyclo[4.2.0]octa-1(6),2,4-trien-3-amine (4.94 g, 37.1 mmol, 61.2% yield) as an orange solid. ¹H NMR (400 MHz, CDCl₃) δ 6.74 (s, 1H), 6.44 (s, 1H), 3.49 (s, 2H), 3.07 (s, 4H), 2.15 (s, 3H). MS m/z 134.1 [M+H]⁺.

Step 5: To a solution of 4-methylbicyclo[4.2.0]octa-1(6),2,4-trien-3-amine (4.94 g, 37.1 mmol, 1.0 eq.) in MeCN (200 mL) was added a solution of NBS (6.60 g, 37.1 mmol, 1.0 eq.) in MeCN (100 mL) at -30°C dropwise. The reaction was allowed to warm to room temperature and stirred for 1 h. Upon completion, the reaction mixture was diluted with water (300 mL) and extracted with EtOAc (100 mL x 3). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with 0-10% EtOAc in hexanes to afford 2-bromo-4-methylbicyclo[4.2.0]octa-1(6),2,4-trien-3-

amine (3.1 g, 14.6 mmol, 39.4% yield) as an off-white solid. ^1H NMR (400 MHz, CDCl_3) δ 6.70 (s, 1H), 3.07 – 3.04 (m, 2H), 3.03 – 3.01 (m, 2H), 2.19 (s, 3H). MS m/z 212.2, 214.2 $[\text{M}+\text{H}]^+$.

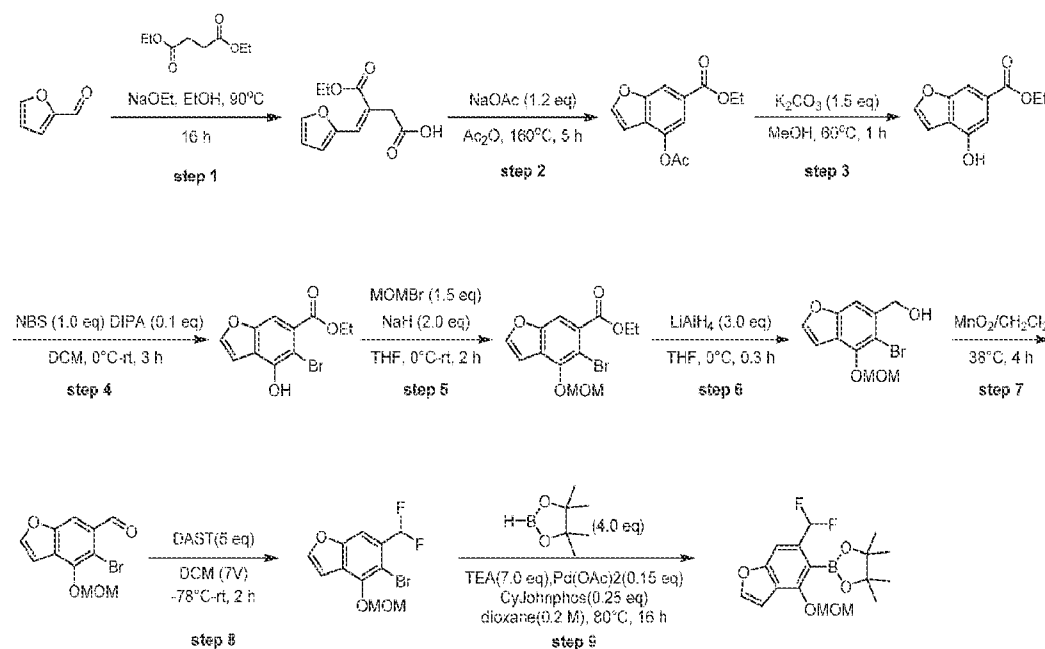
Step 6: Solid Na (1.84 g, 80.2 mmol, 5.0 eq.) was added in portions into MeOH (20 mL) at 0°C and the mixture was warmed to room temperature until the solid was consumed completely. A 50 mL autoclave was charged with the mixture of fresh MeONa solution, 2-bromo-4-methylbicyclo[4.2.0]octa-1(6),2,4-trien-3-amine (3.40 g, 16.0 mmol, 1.0 eq.) and CuI (3.36 g, 17.6 mmol, 1.1 eq.). The reaction was sealed and stirred at 120°C for 16 h. The reaction mixture was cooled to room temperature, diluted with water (100 mL) and extracted with EtOAc (100 mL x 3). The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with 0-10% EtOAc in hexanes to afford 2-methoxy-4-methylbicyclo[4.2.0]octa-1(6),2,4-trien-3-amine (700 mg, 4.29 mmol, 26.8% yield) as an off-white solid. ^1H NMR (400 MHz, CDCl_3) δ 6.42 (s, 1H), 3.94 (s, 3H), 3.57 (s, 2H), 3.37 – 3.31 (m, 2H), 3.12 – 3.08 (m, 2H), 2.15 (s, 3H). MS m/z 164.4 $[\text{M}+\text{H}]^+$.

Step 7: To a suspension of 2-methoxy-4-methylbicyclo[4.2.0]octa-1(6),2,4-trien-3-amine (1.00 g, 6.13 mmol, 1.0 eq.) in conc. HCl (37 % w/w, 10 mL) was added a solution of NaNO_2 (845 mg, 12.3 mmol, 2.0 eq.) in water (10 mL) at 0°C . After being stirred at 0°C for 10 min, an orange suspension was obtained forming diazonium salts compound. A solution of KI (4.07 g, 24.5 mmol, 4.0 eq.) in water (20 mL) was added into the diazonium salt. During the addition, lots of solid stuff was generated. The reaction was then stirred overnight at room temperature for 16 h. The reaction mixture was extracted with EtOAc (30 mL x 3). The organic layer was washed with aq. $\text{Na}_2\text{S}_2\text{O}_3$ (100 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with hexanes to afford 3-iodo-2-methoxy-4-methylbicyclo[4.2.0]octa-1(6),2,4-triene (277 mg, 1.01 mmol, 16.5% yield) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 6.55 (s, 1H), 3.92 (s, 3H), 3.40 – 3.30 (m, 2H), 3.09 – 3.03 (m, 2H), 2.37 (s, 4H).

Step 8: To a mixture of 3-iodo-2-methoxy-4-methylbicyclo[4.2.0]octa-1(6),2,4-triene (277 mg, 1.01 mmol, 1.0 eq.), CyJohnPhos (88.6 mg, 0.253 mmol, 0.25 eq.), $\text{Pd}(\text{OAc})_2$ (34.0 mg, 0.152 mmol, 0.15 eq.) and Et_3N (716 mg, 7.07 mmol, 7.0 eq.) in anhydrous 1,4-dioxane (4 mL) under N_2 atmosphere was added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (647 mg, 5.05 mmol, 5.0 eq.)

dropwise at room temperature. The reaction was stirred at 80°C for 16 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with water (20 mL) and extracted with EtOAc (20 mL x 3). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with 0-10% EtOAc in hexanes to afford 2-(2-methoxy-4-methylbicyclo[4.2.0]octa-1(6),2,4-trien-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (137 mg, 0.500 mmol, 49.5% yield) as an orange solid. ¹H NMR (400 MHz, CDCl₃) δ 6.46 (s, 1H), 3.85 (s, 3H), 3.37 – 3.29 (m, 2H), 3.14 – 3.06 (m, 2H), 2.30 (s, 3H), 1.36 (s, 12H).

10 Intermediate 8. Preparation of 2-(6-(difluoromethyl)-4-(methoxymethoxy)benzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1. To a stirred solution of furan-2-carbaldehyde (63.2 mL, 763 mmol, 1.0 eq.) and diethyl butanedioate (190 mL, 1.14 mol, 1.5 eq.) in anhydrous ethanol (1280 mL) was added NaOEt (130 g, 1.91 mol, 2.5 eq.). The resulting mixture was refluxed at 90°C for 16 hours. After cooling to room temperature, the reaction solvent was evaporated under reduced pressure. The crude residue was then dissolved in water and the pH of the solution was acidified to pH = 1 with concentrated HCl. The acidic solution was then extracted with EtOAc (3 × 1000 mL). The combined organic layer was extracted with 10% Na₂CO₃ solution (3 × 500 mL). The basic aqueous solution was collected and combined, washed with Et₂O (2 × 1000 mL), and then

acidified to pH = 1 with concentrated HCl. The resulting acidic solution was back-extracted with EtOAc (3 × 500 mL). The combined EtOAc solution was then washed with water (2 × 500 mL) and brine, dried over Na₂SO₄, filtered and evaporated under reduced pressure to give (Z)-3-(ethoxycarbonyl)-4-(furan-2-yl)but-3-enoic acid as a black oil (178 g, 104% yield).

- 5 Step 2. The resulting crude 3-ethoxycarbonyl-4-(2-furyl)but-3-enoic acid (178 g, 794 mmol, 1.0 eq.) was dissolved in acetic anhydride (750 mL) and treated with sodium acetate (78.2 g, 953 mmol, 1.2 eq.). The resulting mixture was refluxed at 160°C for 5 hours. Upon completion of the reaction, the reaction was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc, washed with water and brine, dried over
- 10 Na₂SO₄, filtered, and evaporated under reduced pressure to give ethyl 4-acetoxybenzofuran-6-carboxylate as black oil (137 g, 69.5% yield).

- Step 3. To a solution of the resulting crude ethyl 4-acetoxybenzofuran-6-carboxylate (137 g, 552 mmol, 1.0 eq.) in methanol (400 mL) was added potassium carbonate (114 g, 828 mmol, 1.5 eq.). The mixture was refluxed at 60°C for 1 hour. After complete consumption of the starting
- 15 material, the solvent was evaporated, and the residue was diluted with water. The aqueous solution was acidified with solid citric acid until pH = 3, then extracted with EtOAc (3 × 300 mL). The combined organic solution was washed with water and brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (gradient elution of petroleum ether: EtOAc = 4:1 ~ 2:3) to afford ethyl
- 20 4-hydroxybenzofuran-6-carboxylate (48.5 g, 42.6% yield) as a yellow solid. MS m/z 207.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 10.37 (s, 1H), 8.04 (d, J = 2.2 Hz, 1H), 7.62 (t, J = 1.1 Hz, 1H), 7.26 (d, J = 1.2 Hz, 1H), 7.03 (dd, J = 2.3, 1.0 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H).

- Step 4. To a mixture of ethyl 4-hydroxybenzofuran-6-carboxylate (50.0 g, 243 mmol, 1.0 eq.)
- 25 and DIPA (3.4 mL, 24.3 mmol, 0.1 eq.) in DCM (500 mL) at 0°C was added NBS (43.2 g, 243 mmol, 1.0 eq.). The mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with water (500 mL) and extracted with DCM (400 mL x 3). The organic layer was dried over Na₂SO₄, decanted, and concentrated. The crude product was chromatographed on silica gel (gradient elution of petroleum ether: EtOAc = 20:1~10:1~5:1) to give the ethyl 5-
- 30 bromo-4-hydroxybenzofuran-6-carboxylate as yellow oil (37.0 g, 53.5% yield). ¹H NMR (400

MHz, DMSO-*d*₆) δ 10.90 (s, 1H), 8.05 (d, *J* = 4.0 Hz, 1H), 7.48 (s, 1H), 7.31 -7.11 (m, 1H), 4.35 (q, *J* = 7.2 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H).

Step 5. To a solution of ethyl 5-bromo-4-hydroxybenzofuran-6-carboxylate (37.0 g, 130 mmol, 1.0 eq.) in anhydrous THF (370 mL) at 0°C was added NaH (10.4 g, 260 mmol, 2.0 eq.) in portions. The reaction was stirred at room temperature for 1 hour. Bromomethyl methyl ether (24.3 g, 195 mmol, 1.5 eq.) was added to the mixture at 0°C. The reaction was stirred at room temperature for 1 hour. The mixture was diluted with H₂O (350 mL) and extracted with EtOAc (300 mL x 3). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was chromatographed on silica gel (gradient elution of petroleum ether :

EtOAc = 10 : 1) to give ethyl 5-bromo-4-(methoxymethoxy)benzofuran-6-carboxylate as yellow oil (38.9 g, 91.1% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.18 (d, *J* = 4.0 Hz, 1H), 7.76 (s, 1H), 7.26 – 7.12 (m, 1H), 5.40 (s, 2H), 4.35 (q, *J* = 7.2 Hz, 2H), 3.57 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H).

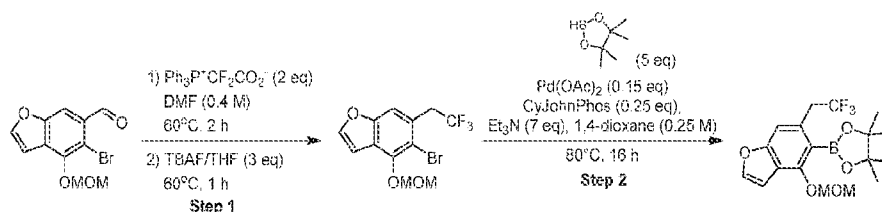
Step 6. To a mixture of LiAlH₄ (5.19 g, 137 mmol, 3.0 eq.) in THF (840 mL) was added ethyl 5-bromo-4-(methoxymethoxy)benzo[b]thiophene-6-carboxylate (15.0 g, 45.6 mmol, 1.0 eq.) under N₂ atmosphere at -20°C and the mixture was stirred for 20 min. Upon completion, the reaction mixture was warmed to room temperature, treated with Na₂SO₄•10H₂O and stirred for 5 min. The mixture was filtered through a Celite pad and rinsed with EtOAc. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with 0~5% EtOAc in petroleum ether to afford (5-bromo-4-(methoxymethoxy)benzo[b]thiophen-6-yl)methanol (12.0 g, 41.8 mmol, 92.0% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.98 (d, *J* = 2.0 Hz, 1H), 7.49 (s, 1H), 7.23 – 6.70 (m, 1H), 5.56 – 5.53 (t, *J* = 5.4 Hz, 1H), 5.35 (d, *J* = 0.4 Hz, 2H), 4.59 (d, *J* = 5.6 Hz, 2H), 3.54 (d, *J* = 0.4 Hz, 3H).

Step 7. To a mixture of (5-bromo-4-(methoxymethoxy)benzo[b]thiophen-6-yl)methanol (12.0 g, 41.8 mmol, 1.0 eq.) in DCM (120 mL) was added MnO₂ (21.8 g, 251 mmol, 6.0 eq.). The reaction was stirred at 38°C for 4 hours. Upon completion, the reaction mixture was cooled to room temperature, filtered through a Celite pad and rinsed with DCM. The filtrate was concentrated under reduced pressure to afford 5-bromo-4-(methoxymethoxy)benzofuran-6-carbaldehyde (10.1 g, 35.4 mmol, 85% yield) as a white solid. MS *m/z* 284.9 [M+H]⁺.

Step 8. To a solution of 5-bromo-4-(methoxymethoxy)benzofuran-6-carbaldehyde (10.1 g, 35.4 mmol, 1.0 eq.) in DCM (70 mL) was added DAST (23.4 mL, 177 mmol, 5.0 eq.) at -60°C. The reaction mixture was warmed to room temperature and stirred for 4 hours. Upon completion, the mixture was added dropwise into saturated NaHCO₃ (50 mL) and the mixture was extracted with EtOAc (50 mL x 3). The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography eluting with 0~10% EtOAc in petroleum ether to obtain 5-bromo-6-(difluoromethyl)-4-(methoxymethoxy)benzo[b]thiophene (9.5 g, 30.9 mmol, yield 87%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.17 (d, J = 2.0 Hz, 1H), 7.72 (s, 1H), 7.38 – 7.1 (t, J = 54.8 Hz, 1H), 7.20 (d, J = 1.6 Hz, 1H), 5.41 (s, 2H), 3.55 (s, 3H).

Step 9. To a mixture of 5-bromo-6-(difluoromethyl)-4-(methoxymethoxy)benzo[b]thiophene (9.5 g, 30.9 mmol, 1.0 eq.), CyJohnPhos (2.7 g, 7.7 mmol, 0.25 eq.), Pd(OAc)₂ (1.0 g, 4.6 mmol, 0.15 eq.) and Et₃N (30.1 mL, 216.5 mmol, 7.0 eq.) in anhydrous 1,4-dioxane (95 mL) under N₂ atmosphere was added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (15.8 mg, 123.7 mmol, 4.0 eq.) dropwise at room temperature. The reaction was stirred at 80°C for 16 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with water (50 mL) and extracted with EtOAc (50 mL x 3). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with 0~10% EtOAc in petroleum ether to afford 2-(6-(difluoromethyl)-4-(methoxymethoxy)benzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.2 g, 14.7 mmol, 47% yield) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.08 (d, J = 2.0 Hz, 1H), 7.57 (s, 1H), 7.09 (d, J = 1.6 Hz, 1H), 7.20 – 6.92 (t, J = 56.4 Hz, 1H), 5.30 (s, 2H), 3.50 (s, 3H), 1.32 (s, 12H).

Intermediate 9. Preparation of 2-(4-(methoxymethoxy)-6-(2,2,2-trifluoroethyl)benzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



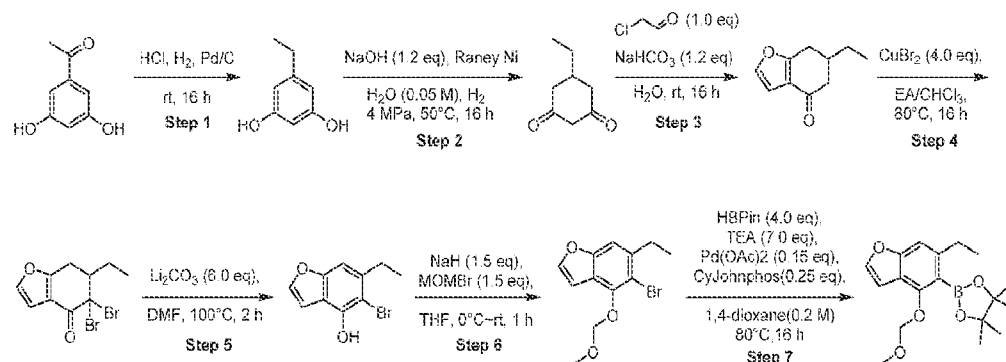
Step 1. A 20 mL microwave tube was charged with a mixture of 5-bromo-4-

(methoxymethoxy)benzofuran-6-carbaldehyde (1.0 g, 3.51 mmol, 1.0 eq.) and 2,2-difluoro-2-(triphenylphosphonio)acetate (2.50 g, 7.02 mmol, 2.0 eq.) in anhydrous DMF (6 mL) under N₂ atmosphere at room temperature. The vessel was sealed and stirred at 60°C for 2 h. The reaction

5 was repeated 4 more times at the same time. Once the start material was consumed completely monitored with TLC, the reaction mixture was cooled to room temperature and poured into a 250 mL round-bottom flask. A solution of TBAF (1.0 M, 52.6 mL, 52.6 mmol, 3.0 eq.) was added into the mixture. The reaction was stirred at 60°C under N₂ atmosphere for 1 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with water (100 mL) and extracted with EtOAc (100 mL x 3). The organic layer was washed with water (100 mL x 2) and brine (100 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with 0-10% EtOAc in hexanes to afford 5-bromo-4-(methoxymethoxy)-6-(2,2,2-trifluoroethyl)benzofuran (1.6 g, 4.72 mmol, 26.9% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.59 (d, J = 2.0 Hz, 1H), 7.35 (s, 1H), 6.94 (d, J = 2.0 Hz, 1H), 5.32 (s, 2H), 3.78 (q, J = 10.4 Hz, 2H), 3.67 (s, 3H).

Step 2. To a mixture of 5-bromo-4-(methoxymethoxy)-6-(2,2,2-trifluoroethyl)benzofuran (1.64 g, 4.84 mmol, 1.0 eq.), CyJohnPhos (424 mg, 1.21 mmol, 0.25 eq.), Pd(OAc)₂ (163 mg, 0.725 mmol, 0.15 eq.) and Et₃N (4.71 mL, 33.9 mmol, 7.0 eq.) in anhydrous 1,4-dioxane (20 mL) under N₂ atmosphere was added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.51 mL, 0.882 g/mL, 24.2 mmol, 5.0 eq.) dropwise at room temperature. The reaction was stirred at 80°C for 16 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with water (100 mL) and extracted with EtOAc (100 mL x 3). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with 0-10% EtOAc in hexanes to afford 2-(4-(methoxymethoxy)-6-(2,2,2-trifluoroethyl)benzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.18 g, 3.06 mmol, 63.2% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.54 (d, J = 2.4 Hz, 1H), 7.23 (s, 1H), 6.95 – 6.88 (m, 1H), 5.23 (s, 2H), 3.68 (q, J = 10.8 Hz, 2H), 3.60 (s, 3H), 1.39 (s, 12H).

Intermediate 10. Preparation of 2-(6-ethyl-4-(methoxymethoxy)benzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1. To a solution of 1-(3,5-dihydroxyphenyl)ethan-1-one (50.0 g, 0.330 mol, 1.0 eq.) in HCl (4% w/w) (3750 mL) was added Pd/C (12 g, 25% w/w). The mixture was stirred for 16 h at room temperature under H₂ (4 MPa). The reaction mixture was filtered through a pad of Celite, rinsed with EA. The filtrate was then extracted with tert-Butyl methyl ether (1 L). The combined organic layer was washed with water (500 mL x 3) and brine (500 mL), dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel (Petroleum ether/Ethyl acetate = 1.0 to 5:1) to afford 5-ethylbenzene-1,3-diol (33.0 g, 0.240 mol, 72.7% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 6.27 – 6.27 (m, 1H), 6.21 – 6.20 (m, 2H), 2.51 (q, J = 7.6 Hz, 2H), 1.26 (t, J = 7.2 Hz, 3H).

Step 2. To a mixture of 5-ethylbenzene-1,3-diol (42.0 g, 0.300 mol, 1.0 eq.) in H₂O (420 mL) was added Raney Ni (3.60 g, 8.5% w/w) and NaOH (14.6 g, 0.360 mol, 1.2 eq.). The reaction was stirred at 50°C for 16 h under H₂ (4 MPa). Upon completion, the reaction mixture was cooled to room temperature. The PH was adjusted to around 4~5 with 2M HCl and the mixture was extracted with EtOAc (500 mL x 3). The organic phase was washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel (Petroleum ether/Ethyl acetate = 1:0 to 1:1) to afford 5-ethylcyclohexane-1,3-dione (22.0 g, 0.160 mol, 51.6% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 5.19 (s, 1H), 2.27 (dd, J = 16.4, 3.2 Hz, 2H), 2.03 (d, J = 11.2 Hz, 1H), 1.98 (s, 1H), 1.36 – 1.32 (m, 2H), 0.87 (t, J = 7.6 Hz, 3H).

Step 3. To a solution of NaHCO₃ (11.5 g, 0.140 mol, 1.2 eq.) and 2-chloroacetaldehyde (22.4 g, 0.110 mol, 1.0 eq.) in water (160 mL) was added a solution of 5-ethylcyclohexane-1,3-dione (16.0 g, 0.110 mol, 1.0 eq.) in THF (20 mL) dropwise at 0°C. The reaction was stirred at room

temperature for 16 h, then diluted with ethyl acetate. The pH was adjusted to pH = 1 with H₂SO₄ (50% w/w in H₂O) and the mixture was vigorously stirred for 3 h. The organic layer was collected, and the aqueous layer was extracted with ethyl acetate (500 mL x 3). The combined organic phase was washed with water, saturated NaHCO₃ and brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel (Petroleum ether/Ethyl acetate = 1:0 to 3:1) to afford 6-ethyl-6,7-dihydrobenzofuran-4(5H)-one (10.5 g, 0.060 mol, 56.2% yield) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.32 (d, J = 1.6 Hz, 1H), 6.66 (d, J = 2.0 Hz, 1H), 3.03 – 2.98 (m, 1H), 2.62 – 2.51 (m, 2H), 2.29 – 2.22 (m, 2H), 1.61 (s, 2H), 0.99 (t, J = 7.6 Hz, 3H).

Step 4. A mixture of CuBr₂ (57.1 g, 0.260 mol, 4 eq.) in ethyl acetate (180 mL) was heated and stirred at 80°C for 10 min. Then a solution of 6-ethyl-6,7-dihydrobenzofuran-4(5H)-one (10.5 g, 0.060 mol, 1 eq.) in CHCl₃ (100 mL) was added into the mixture at 80°C. The reaction was stirred at 80°C for 16 h. Upon completion, the reaction mixture was cooled to room temperature, filtered through a pad of Celite and rinsed with EtOAc. The filtrate was concentrated in vacuo.

The residue was purified by flash chromatography on silica gel (PE: EA = 1:0 ~ 20:1) to afford 5,5-dibromo-6-ethyl-6,7-dihydrobenzofuran-4(5H)-one (8.00 g, 24.8 mmol, 38.8% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 7.39 (d, J = 2.0 Hz, 1H), 6.77 (d, J = 2.0 Hz, 1H), 3.07 (dd, J = 17.6, 4.8 Hz, 1H), 2.67 (dd, J = 17.6, 9.6 Hz, 1H), 2.43 – 2.36 (m, 2H), 1.78 – 1.61 (m, 1H), 1.11 (t, J = 7.2 Hz, 3H).

Step 5. To a mixture of 5,5-dibromo-6-ethyl-6,7-dihydrobenzofuran-4(5H)-one (8.00 g, 24.9 mmol, 1.0 eq.) in DMF (80 mL) was added Li₂CO₃ (11.0 g, 149 mmol, 4.0 eq.). The reaction mixture was stirred for 2 h at 100°C. Upon completion, the reaction was cooled to room temperature, filtered through a pad of Celite and rinsed with EtOAc. The filtrate was diluted with water (800 mL) and extracted with EtOAc (200 mL x 3). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography on silica gel (PE: EA = 1:0 ~ 20:1) to afford 5-bromo-6-ethylbenzofuran-4-ol (4.50 g, 18.7 mmol, 75.1% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.38 (s, 1H), 7.81 (d, J = 2.4 Hz, 1H), 7.10 (s, 1H), 7.08 (s, 1H), 2.77 (q, J = 7.6 Hz, 2H), 1.19 (t, J = 7.2 Hz, 3H).

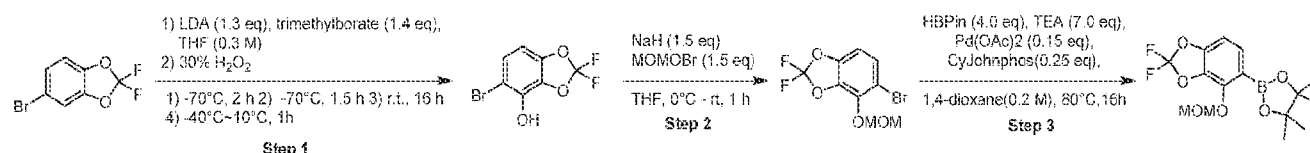
Step 6. To a solution of 5-bromo-6-ethylbenzofuran-4-ol (5.00 g, 20.7 mmol, 1.0 eq.) in THF (50 mL) was added NaH (1.24 g, 31.0 mmol, 1.5 eq.) in portions at 0°C. The resulting mixture was stirred at room temperature for 0.5 h. Then bromomethyl methyl ether (3.89 g, 31.0 mmol, 1.5 eq.) was added slowly at 0°C. The reaction was warmed to room temperature and stirred for 1 h.

The reaction mixture was quenched by the addition of water, diluted with water (500 mL) and extracted with EtOAc (200 mL x 3). The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to afford 5-bromo-6-ethyl-4-(methoxymethoxy)benzofuran (5.50 g, 19.3 mmol, 93.0% yield) as yellow oil, which was used for the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.52 (d, J = 2.4 Hz, 1H), 7.20 (s, 1H), 6.88 (d, J = 2.0 Hz, 1H), 5.31 (s, 2H), 3.67 (s, 3H), 2.88 (q, J = 7.6 Hz, 2H), 1.27 (t, J = 7.6 Hz, 3H).

Step 7. To a solution of 5-bromo-6-ethyl-4-(methoxymethoxy)benzofuran (5.90 g, 20.7 mmol, 1.0 eq.) in 1,4-dioxane (60 mL) were added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10.6 g, 83.0 mmol, 4.0 eq.), Pd(OAc)₂ (517 mg, 3.10 mmol, 0.15 eq.), Et₃N (20.1 mL, 145 mmol, 7.0 eq.) and 2-(dicyclohexylphosphino)biphenyl (1.80 g, 5.20 mmol, 0.25 eq.). The reaction was stirred at 80°C for 16 h under N₂ atmosphere. Upon completion, the reaction was cooled to room temperature, filtered through a pad of Celite and rinsed with EtOAc. The filtrate was diluted with water (500 mL) and extracted with EtOAc (100 mL x 3). The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated.

The residue was purified by flash chromatography on silica gel (PE: EA = 1:0 ~ 20:1) to afford 2-(6-ethyl-4-(methoxymethoxy)benzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.70 g, 14.2 mmol, 68.3% yield) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.47 (d, J = 2.4 Hz, 1H), 7.08 (s, 1H), 6.86 (d, J = 2.0 Hz, 1H), 5.24 (s, 2H), 3.59 (s, 3H), 2.76 (dd, J = 15.2 Hz, 7.6 Hz, 2H), 1.40 (s, 12H), 1.25 (t, J = 7.6 Hz, 3H).

Intermediate 11. Preparation of (1s, 3s)-1-methyl-3-((1-(2-(2,2,2-trifluoroethyl)-4-(trifluoromethyl)phenyl)imidazo[1,5-d][1,2,4]triazin-4-yl)amino)cyclobutan-1-ol

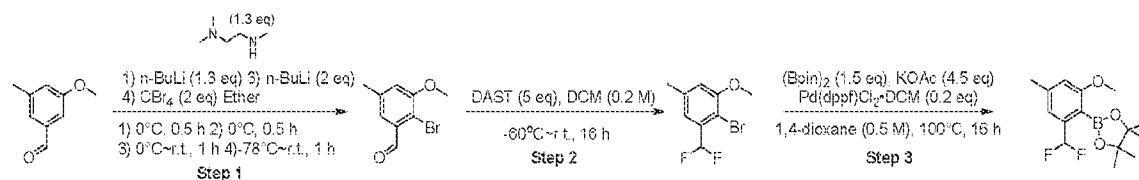


Step 1. A solution of 5-bromo-2,2-difluorobenzo[d][1,3]dioxole (700 mg, 2.95 mmol, 1.0 eq) in THF (10 mL) was added LDA (2.5 M in Hexane, 1.8 mL, 4.43 mmol, 1.5 eq) slowly at -70°C and allowed to stir for 2 h at -70°C. The mixture was added trimethylborate (460 mg, 4.43 mmol, 1.5 eq) at -70°C and allowed to stir at -70°C for 2 h under N₂. The mixture was warmed to -30°C dropping with H₂O₂, allowed to stir at -30°C for 0.5 h. The mixture was warmed to 5°C, quenched with Na₂S₂O₃ aq. and extracted with EtOAc (30 mL x 3). The organic phase was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by reversed phase flash chromatography (12 g flash column, eluting with 0-100% MeCN in H₂O) to afford 5-bromo-2,2-difluorobenzo[d][1,3]dioxol-4-ol (200 mg, 0.80 mmol, 26.8% yield) as a yellow oil. MS m/z 250.9 [M-H]⁻.

Step 2. 5-bromo-2,2-difluorobenzo[d][1,3]dioxol-4-ol (1 g, 3.95 mmol, 1.0 eq) was dissolved in THF (anhydrous SDS) (10 mL) and cooled to 0°C. To this was added NaH (237 mg, 5.93 mmol, 1.5 eq) in portions at 0°C. The reaction was allowed to stir at 0°C for 0.5 h. To this was added MOMBr (749 mg, 5.93 mmol, 1.5 eq). The reaction was allowed to stir at rt for 0.5 h, with TLC monitoring. Upon completion, the reaction was quenched with water (100 mL), extracted with EtOAc (100 mL). The organic layer was washed with water (150 mL x 1) and brine (150 mL x 1). The organic layer was dried over Na₂SO₄, decanted, and concentrated to get 5-bromo-2,2-difluoro-4-(methoxymethoxy)benzo[d][1,3]dioxole (1 g, 3.37 mmol, 85.2% yield) as a yellow oil, which was used for the next step without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.57 (d, *J* = 8.8 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 5.38 (s, 2H), 3.56 (s, 3H).

Step 3. To a solution of 5-bromo-2,2-difluoro-4-(methoxymethoxy)benzo[d][1,3]dioxole (1.1 g, 3.70 mmol, 1.0 eq) in 1,4-dioxane (15 mL) were added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.9 g, 14.81 mmol, 4.0 eq), Pd(OAc)₂ (92.5 mg, 0.55 mmol, 0.15 eq), TEA (2.62 g, 25.92 mmol, 7.0 eq) and 2-(dicyclohexylphosphino)biphenyl (324 mg, 0.92 mmol, 0.25 eq). The reaction was allowed to stir at 100°C for 16 h under N₂, with TLC monitoring. The reaction mixture was cooled to 25°C and filtered through a pad of celite and rinsed with EtOAc. The filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (Petroleum ether/Ethyl acetate = 1:0 to 10:1) to afford the 2-(2,2-difluoro-4-(methoxymethoxy)benzo[d][1,3]dioxol-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (200 mg, 0.58 mmol, 15.7% yield) as colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.50 (d, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 5.25 (s, 2H), 3.59 (s, 3H), 1.34 (s, 12H).

Intermediate 12. Preparation of 2-(2-(difluoromethyl)-6-methoxy-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

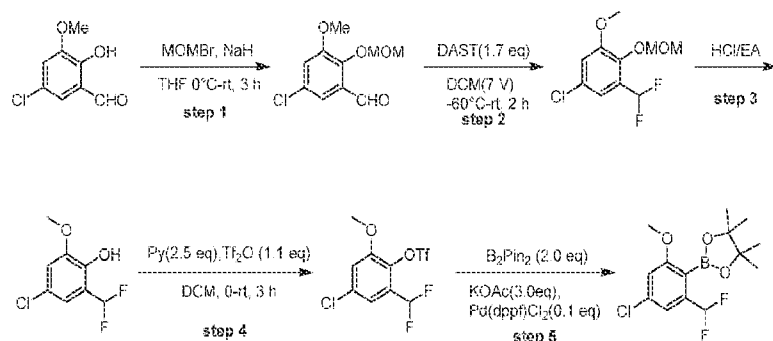


- 5 Step 1. To a solution of N,N,N'-trimethylethylenediamine (27.60 g, 270.08 mmol, 1.3 eq) in anhydrous THF under argon atmosphere was added n-BuLi (2.5 M, 108 mL, 270.08 mmol, 1.3 eq) dropwise at 0°C. The reaction mixture was stirred at 0°C for 30 min. A solution of 3-methoxy-5-methylbenzaldehyde (31.2 g, 207.75 mmol, 1.0 eq) in anhydrous THF was added dropwise at 0°C. The reaction mixture was stirred at 0°C for 30 min. n-BuLi (2.5 M, 166 mL, 415.51 mmol, 2.0 eq) was added dropwise at 0°C. The reaction mixture was warmed to room temperature and stirred for one hour. A solution of CBr₄ (137.79 g, 415.51 mmol, 2 eq) in anhydrous THF was added dropwise at -78°C. The reaction mixture was warmed to room temperature and stirred for one hour. The reaction mixture was quenched with NH₄Cl and extracted with EtOAc (1000 mL x 3). The organic phase was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel eluted with (PE/EtOAc = 100:1~50:1~20:1) and reversed phase flash chromatography (330 g flash column, eluting with 0-100% MeCN in H₂O) to afford 2-bromo-3-methoxy-5-methylbenzaldehyde (8.3 g, 36.23 mmol, 17.44% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 10.41 (s, 1H), 7.34 (d, J = 1.1 Hz, 1H), 6.95 (d, J = 1.3 Hz, 1H), 3.94 (s, 3H), 2.38 (s, 3H).

- 25 Step 2. DAST (29.20 g, 181.16 mmol, 5.0 eq) was added dropwise into a round-bottom flask under an inert atmosphere containing 2-bromo-3-methoxy-5-methylbenzaldehyde (8.3 g, 36.23 mmol, 1.0 eq) in DCM at -78°C. The reaction was stirred at rt for 16 h. The mixture was added dropwise into a sat. aq. NaHCO₃ at 0°C. The resulting mixture was extracted with DCM (200 mL x 3). The organic phase was dried over Na₂SO₄, decanted, concentrated to afford 2-bromo-1-(difluoromethyl)-3-methoxy-5-methylbenzene (6.4 g, 25.73 mmol, 71.01% yield) as brown oil, which was used for the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.09 (s, 1H), δ 6.93 (t, J = 55.2 Hz, 1H) 6.82 (s, 1H), 3.91 (s, 3H), 2.38 (s, 3H).

Step 3. A mixture of 2-bromo-1-(difluoromethyl)-3-methoxy-5-methylbenzene (2.3 g, 9.16 mmol, 1.0 eq), B₂PIN₂ (2.44 g, 9.62 mmol, 1.05 eq), KOAc (2.7 g, 27.48 mmol, 3 eq) and Pd(dppf)Cl₂ (742.56 mg, 0.916 mmol, 0.1 eq) in anhydrous 1,4-dioxane was stirred at 100°C under Ar atmosphere for 16 h. The reaction mixture was cooled to room temperature, filtered through a pad of Celite and rinsed with EtOAc (50 mL). The filtrate was concentrated in vacuo. The residue was purified by flash chromatography (40 g flash column, eluting with 0-10% EtOAc in PE) to afford 2-(2-(difluoromethyl)-6-methoxy-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.10 g, 3.69 mmol, 40.28% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 6.96 (s, 1H), 6.79 (t, *J*=56.8, 1H), 6.79 (s, 1H), 6.73 (s, 1H), 6.65 (s, 1H), 3.79 (s, 3H), 2.37 (s, 3H), 1.37 (s, 12H).

Intermediate 13. Preparation of 2-(4-chloro-2-(difluoromethyl)-6-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1. To a solution of 5-chloro-2-hydroxy-3-methoxybenzaldehyde (10.0 g, 53.6 mmol, 1.0 eq) in THF (100 mL) was added NaH (4.29 g, 107.2 mmol, 2.0 eq) at 0°C. The mixture was stirred at rt for 0.5 h. Then MOMBr (10.1 g, 80.4 mmol, 1.5 eq) was added slowly at 0°C. The reaction was allowed to stir at room temperature for 1 h. The reaction mixture was quenched with water (50 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated to afford 5-chloro-3-methoxy-2-(methoxymethoxy)benzaldehyde (10.0 g, 43.4 mmol, 81% yield) as a yellow oil, which was used for the next step without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.27 (s, 1H), 7.46 (s, 1H), 7.24 (d, *J* = 2.4 Hz, 1H), 5.17 (s, 2H), 3.89 (s, 3H), 3.47 (s, 3H).

Step 2. To a solution of 5-chloro-3-methoxy-2-(methoxymethoxy)benzaldehyde (10.0 g, 43.4 mmol, 1.0 eq.) in DCM (70 mL) was added DAST (28.6 mL, 216.8 mmol, 5.0 eq.) at -60°C. The

reaction mixture was warmed to room temperature and stirred for 4 h. Upon completion, the mixture was added to saturated NaHCO₃ (50 mL) and extracted with DCM (50 mL x 3). The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography (ethyl acetate/hexane = 0% ~ 10%) to obtain 5-chloro-1-(difluoromethyl)-3-methoxy-2-(methoxymethoxy)benzene (6.0 g, 23.8 mmol, yield 55%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.34 (d, J = 2.0 Hz, 1H), 7.14 (d, J = 2.4 Hz, 1H), 7.10 (t, J = 54.8 Hz, 1H), 5.11 (s, 2H), 3.87 (s, 3H).

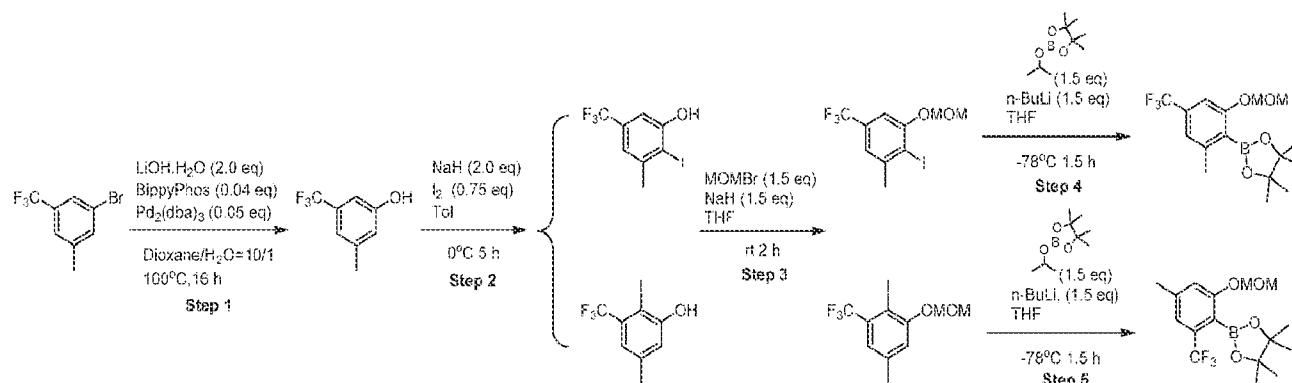
Step 3. A solution of 5-chloro-1-(difluoromethyl)-3-methoxy-2-(methoxymethoxy)benzene (6.0 g, 23.8 mmol, 1.0 eq.) in HCl in EA (60 mL) was stirred at 25 °C for 2 h with LCMS monitoring. Upon completion, the reaction mixture was concentrated under reduced pressure to afford 4-chloro-2-(difluoromethyl)-6-methoxyphenol as a yellow oil (5.7 g), which was used for the next step without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ 9.78 (s, 1H), 7.17 (d, J = 2.0 Hz, 2H), 7.06 (t, J = 55.2 Hz, 1H), 7.00 (d, J = 2.0 Hz, 1H), 3.86 (s, 3H).

Step 4. To a solution of 4-chloro-2-(difluoromethyl)-6-methoxyphenol (5.7 g, 27.3 mmol, 1.0 eq.) in DCM (60 mL) was added pyridine (5.5 mL, 68.3 mmol, 2.5 eq.) and Tf₂O (5.1 mL, 30.1 mmol, 1.1 eq.) at 0°C. The reaction mixture was warmed to room temperature and stirred for 4 h. Upon completion, the mixture was quenched with water (30 mL) and extracted with DCM (50 mL x 3). The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography (ethyl acetate/hexane = 0% ~ 10%) to obtain 4-chloro-2-(difluoromethyl)-6-methoxyphenyl trifluoromethanesulfonate (5.9 g, 17.3 mmol, yield 63%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.70 (d, J = 2.0 Hz, 1H), 7.39 (d, J = 2.0 Hz, 1H), 7.13 (t, J = 53.6 Hz, 1H), 3.97 (s, 3H).

Step 5. To a solution of 4-chloro-2-(difluoromethyl)-6-methoxyphenyl trifluoromethanesulfonate (3.0 g, 8.8 mmol, 1.0 eq.) in 1,4-dioxane was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (3.4 g, 13.2 mmol, 1.5 eq.), Pd(dppf)Cl₂ (639.1 mg, 0.9 mmol, 0.1 eq.), KOAc (2.6 g, 26.4 mmol, 3.0 eq.). The reaction was allowed to stir at 100°C for 16 h under N₂. Upon completion, the reaction was cooled to room temperature, filtered through a pad of celite and rinsed with EtOAc. The filtrate was diluted with water (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by flash chromatography on silica gel (PE: EA = 1:0

~ 20:1) to afford 2-(4-chloro-2-(difluoromethyl)-6-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.3 g, 4.1 mmol, 46% yield) as yellow oil. ^1H NMR (400 MHz, DMSO- d_6) δ 7.22 (s, 1H), 7.18 (s, 1H), 6.94(t, J = 55.6 Hz, 1H), 3.80 (s, 3H), 1.25 (s, 12H).

- 5 Intermediate 14. Preparation of 2-(2-(methoxymethoxy)-4-methyl-6-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and intermediate 15 2-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



- Step 1. A mixture of 1-bromo-3-methyl-5-(trifluoromethyl)benzene (51.0 g, 213.0 mmol, 1.0 eq.), LiOH.H₂O (17.9 g, 426.7 mmol, 2 eq.), BippyPhos (4.3 g, 8.5 mmol, 0.04 eq.) and Pd₂(dba)₃ (9.7 g, 10.7 mmol, 0.05 eq.) in dioxane (500 mL) was stirred at 100°C for 16 h under N₂. Upon completion, the reaction mixture was cooled to room temperature. The reaction mixture was filtered through a pad of celite and rinsed with EtOAc (1000 mL). The filtrate was concentrated, purified by reversed phase column (0.1% TFA, 35%-40% ACN) to give a pale-yellow oil (32 g, 181.6 mmol, 85.1% yield). MS m/z 175.1 [M-H]⁻. ^1H NMR (400 MHz, DMSO- d_6) δ 10.99 (s, 1H), 7.13 (s, 1H), 6.95 (s, 1H), 2.28 (s, 3H)
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- 15

- Step 2. To a solution of 3-methyl-5-(trifluoromethyl)phenol (32.0 g, 181.7 mmol, 1.0 eq.) in anhydrous Tol (500 mL) at 0°C was added NaH (8.72 g, 363.3 mmol, 2 eq.) and the mixture was stirred at 0°C for 1 h. I₂ (34.6 g, 136.3 mmol, 0.75 eq.) was added to reaction at 0°C and the mixture was stirred for another 4 h. Upon completion, the reaction was poured into water, acidified with 1 M HCl to pH 5-6, diluted with EtOAc (100 mL). The organic phase was separated and dried over Na₂SO₄, filtered and concentrated, purified by reversed phase column (0.1% TFA, 40%-45% ACN) to afford a mixture of 2-iodo-3-methyl-5-(trifluoromethyl)phenol
- 20

and 2-iodo-5-methyl-3-(trifluoromethyl)phenol (33 g, 109.3 mmol, 60.1% yield) as a yellow oil, which was used in the next step without further purification. MS m/z 301.0 $[M-H]^+$.

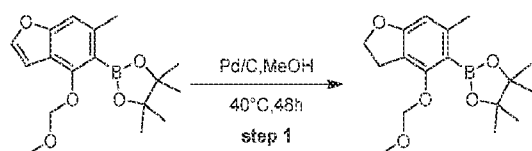
Step 3. A mixture of 2-iodo-3-methyl-5-(trifluoromethyl)phenol and 2-iodo-5-methyl-3-(trifluoromethyl)phenol obtained above (33 g, 109.3 mmol, 1.0 eq) was dissolved in anhydrous THF (300 mL) at 0°C, to which was added NaH (3.9 g, 163.9 mmol, 1.5 eq.) slowly at 0°C and the mixture was stirred for 1 h. MOMBr (20.5 g, 163.9 mmol, 1.5 eq.) was then added at 0°C and stirred for another 1 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with EtOAc (200 mL) and quenched with water. The organic phase was separated and dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography eluting with 0-10% EA in hexanes to afford 2-iodo-1-(methoxymethoxy)-3-methyl-5-(trifluoromethyl)benzene (17 g, 49.1 mmol, 44.9% yield) ^1H NMR (400 MHz, $DMSO-d_6$): δ 7.36 (s, 1H), 7.18 (s, 1H), 5.39 (s, 2H), 3.39 (s, 3H), 2.49 (s, 3H); and 2-iodo-1-(methoxymethoxy)-5-methyl-3-(trifluoromethyl)benzene (5.5 g, 15.89 mmol, 14.5% yield) ^1H NMR (400 MHz, $DMSO-d_6$): δ 7.24 (s, 1H), 7.22 (s, 1H), 5.33 (s, 2H), 3.43 (s, 3H), 2.34 (s, 3H).

Step 4. 2-Iodo-1-(methoxymethoxy)-3-methyl-5-(trifluoromethyl)benzene (17 g, 49.1 mmol, 1.0 eq.) was dissolved in anhydrous THF (200 mL) under N_2 at -78°C, to which was added $n-BuLi$ (46.0 mL, 73.7 mmol, 1.5 eq.) dropwise at -78°C and the mixture was stirred for 1 h. Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (13.7 g, 73.6 mmol, 1.5 eq.) was then added at -78°C and the reaction mixture was stirred for another 1 h. Upon completion, the reaction mixture was diluted with EtOAc (200 mL) and quenched with saturated NH_4Cl (40 mL). The organic phase was separated, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography eluting with 0-10% EA in hexanes to afford 2-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10 g, 28.9 mmol, 58.8% yield) as a white solid. ^1H NMR (400 MHz, $DMSO-d_6$) δ 7.16 (s, 1H), 7.12 (s, 1H), 5.24 (s, 2H), 3.38 (s, 3H), 2.33 (s, 3H), 1.33 (s, 12H).

Step 5. 2-Iodo-1-(methoxymethoxy)-5-methyl-3-(trifluoromethyl)benzene (5.5 g, 15.9 mmol, 1.0 eq.) was dissolved in anhydrous THF (60 mL) under N_2 at -78°C, to which was added $n-BuLi$ (14.9 mL, 23.8 mmol, 1.5 eq.) dropwise at -78°C and the mixture was stirred for 1 h. 2-

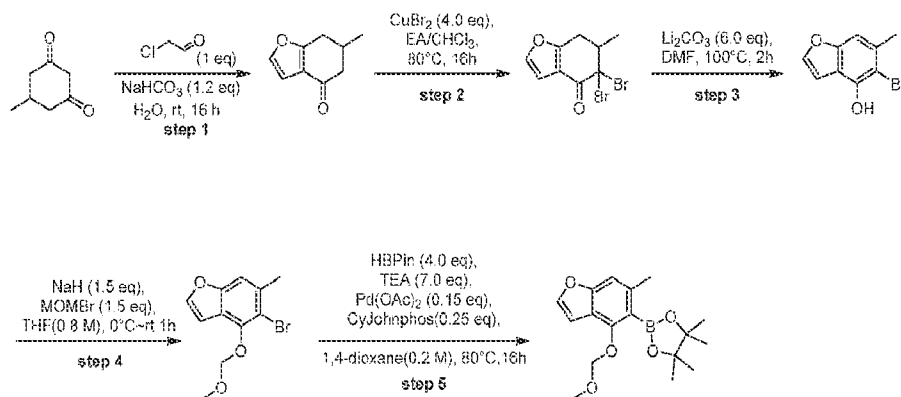
Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.4 g, 23.8 mmol, 1.5 eq.) was then added at -78°C and stirred for 1 h. Upon completion, the reaction mixture was diluted with EtOAc (100 mL) and quenched with saturated NH₄Cl (20 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography eluting with 0-10% EA in in hexanes to afford 2-(2-(methoxymethoxy)-4-methyl-6-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.9 g, 8.4 mmol, 52.7% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.14 (s, 2H), 5.22 (s, 2H), 3.37 (s, 3H), 2.36 (s, 3H), 1.29 (s, 12H).

10 Intermediate 16. Preparation of 2-(4-(methoxymethoxy)-6-methyl-2,3-dihydrobenzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1. A mixture of 2-(4-(methoxymethoxy)-6-methylbenzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5 g, 15.7 mmol, 1.0 eq.) and Pd/C (10%, 0.5 g) in MeOH (100 mL) was stirred at 40°C for 48h under hydrogen (balloon). The mixture was filtered. The filtrate was concentrated under reduced pressure to afford 2-(4-(methoxymethoxy)-6-methyl-2,3-dihydrobenzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as white solid (3.0 g, 9.3 mmol, 59.6% yield). ¹H NMR (400 MHz, CDCl₃) δ 6.39 (s, 1H), 5.07 (s, 2H), 4.52 (t, *J* = 8.4 Hz, 2H), 3.52 (s, 3H), 3.24 (t, *J* = 8.8 Hz, 2H), 2.34 (s, 3H), 1.36 (s, 12H).

Intermediate 17. Preparation of 2-(4-(methoxymethoxy)-6-methylbenzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1. To a solution of sodium bicarbonate (79.9 g, 951.2 mmol, 1.2 eq) and chloroacetaldehyde (155.5 g, 792.6 mmol, 1.0 eq) in water (1380 mL) at 0°C was added dropwise a solution of 4,4-dimethylcyclohexane-1,3-dione in THF (1100 mL). The resulting mixture was stirred at room temperature for 18 h and ethyl acetate (1000 mL) was added. The mixture was adjusted to pH=1 with 50% H₂SO₄ and vigorously stirred for 3 h. The organic layer was collected and the acidic layer was extracted with ethyl acetate (3 x 400 mL). The combined organic extracts were washed with water, saturated NaHCO₃, brine, and dried over Na₂SO₄. The solvent was evaporated under reduced pressure and the residue was purified on silica gel (Petroleum ether/Ethyl acetate=20/1 to 1/1) to afford the 6-methyl-6,7-dihydrobenzofuran-4(5H)-one (54 g, 359.5 mmol, 45.3% yield) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.69 (d, J = 2.1 Hz, 1H), 6.65 (d, J = 2.1 Hz, 1H), 2.97 (dd, J = 17.1, 4.8 Hz, 1H), 2.59 (dd, J = 17.0, 9.4 Hz, 1H), 2.41 (dt, J = 17.0, 2.1 Hz, 2H), 2.28 (dd, J = 13.5, 3.7 Hz, 1H), 1.09 (d, J = 6.3 Hz, 3H).

Step 2. CuBr₂ (321.2 g, 1.44 mol, 4.0 eq) was added into EA (770 mL). The reaction was allowed to stir at 80°C for 10 min. To this was added a solution of 6-methyl-6,7-dihydrobenzofuran-4(5H)-one (54 g, 359.5 mmol, 1.0 eq) in CHCl₃ (128 mL) at 80°C in one portion. The reaction was allowed to stir at 80°C for 16 h. Upon completion, the reaction was cooled to rt, filtered to remove the solid. The filtrate was concentrated and purified by silica gel column chromatography (PE: EA =50:1~5:1) to afford the 5,5-dibromo-6-methyl-6,7-dihydrobenzofuran-4(5H)-one (33 g, 107.1 mmol, 29.8% yield) as yellow solid.

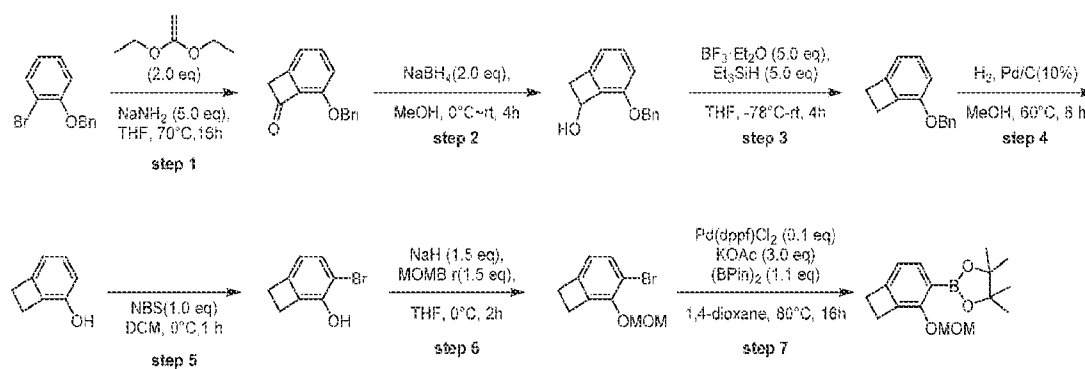
Step 3. 5,5-dibromo-6-methyl-6,7-dihydrobenzofuran-4(5H)-one (33 g, 107.1 mmol, 1.0 eq) was dissolved in anhydrous DMF (535mL). To this solution was added Li₂CO₃ (47.5 g, 642.9 mmol, 6.0 eq). The reaction was allowed to stir at 100°C for 2 h. Upon completion, the reaction was cooled to rt, filtered to remove the solid and concentrated. The residue was diluted with water

(500 mL), extracted with EA (200 mL). The organic layer was washed with water (500 mL x 2) and brine (500 mL x 1), dried over Na₂SO₄, decanted, and concentrated. The residue was purified by silica gel column chromatography (EA:PE = 1: 50) to afford the 5-bromo-6-methylbenzofuran-4-ol (19.5 g, 85.8 mmol, 80.1% yield) as white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.38 (s, 1H), 7.80 (d, J = 2.2 Hz, 1H), 7.12 (d, J = 0.9 Hz, 1H), 7.09 (dd, J = 2.2, 1.0 Hz, 1H), 2.41 (d, J = 0.6 Hz, 3H).

Step 4. To a solution of 5-bromo-6-methylbenzofuran-4-ol (19.5 g, 85.8 mmol, 1.0 eq) in THF (110 mL) was added NaH (6.8 g, 171.7 mmol, 2.0 eq) at 0 °C in portions. The reaction mixture was warmed to r.t. for 1 hour and then MOMBr (16.1 g, 128.8 mmol, 1.5 eq) was added. The reaction was stirred at r.t. for 1 h. The mixture was quenched with H₂O (200 mL), extracted with EA (100 mL x 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated to afford the 5-bromo-4-(methoxymethoxy)-6-methylbenzofuran (21 g, 77.4 mmol, 90.1% yield) as brown oil, which was used for the next step without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.95 (d, J = 2.3 Hz, 1H), 7.42 (t, J = 0.9 Hz, 1H), 7.06 (dd, J = 2.3, 1.0 Hz, 1H), 5.35 (s, 2H), 3.55 (s, 3H), 2.46 (d, J = 0.7 Hz, 3H).

Step 5. To a solution of 5-bromo-4-(methoxymethoxy)-6-methylbenzofuran (21 g, 77.4 mmol, 1.0 eq) in dioxane (370 mL) were added HBPIn (37.7 g, 295.0 mmol, 4.0 eq), TEA (52.2 g, 516.4 mmol, 7.0 eq), Pd(OAc)₂ (2.4 g, 11.0 mmol, 0.15 eq) and CyJohnphos (6.4 g, 18.4 mmol, 0.25 eq). The mixture was then purged with N₂. The reaction was allowed to be stirred at 80°C for 16 h. Upon completion, the reaction was cooled to room temperature, filtered through a pad of Celite and rinsed with EA. The filtrate was concentrated to get crude oil. The residue was purified by column chromatography on silica gel (Petroleum ether/Ethyl acetate=80/1 to 10/1) to afford the 2-(4-(methoxymethoxy)-6-methylbenzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10 g, 31.4 mmol, 42.6% yield) as brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.84 (d, J = 2.4 Hz, 1H), 7.14 (s, 1H), 6.93 (dd, J = 2.0, 0.8 Hz, 1H), 5.22 (s, 2H), 3.48 (s, 3H), 2.37 (s, 3H), 1.33 (s, 12H).

Intermediate 18. Preparation of 2-(2-(methoxymethoxy)bicyclo[4.2.0]octa-1,3,5-trien-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1. To a solution of 1-(benzyloxy)-2-bromobenzene (30.0 g, 114.01 mmol) in THF (600 mL) were added 1,1-diethoxyethene (26.49 g, 228.02 mmol) and NaNH₂ (22.24 g, 570.05 mmol). The reaction was stirred at 70°C for 6 h. Upon completion, the reaction mixture was cooled to rt and poured into ice water. The pH of reaction mixture was adjusted to pH = 2 with 4N HCl. The reaction mixture was extracted with EA (500 mL x 3). The organic phases were dried over Na₂SO₄, filtered, concentrated and purified by silica gel column chromatography (0~6% EA/PE) to afford yellow solid 5-(benzyloxy)bicyclo[4.2.0]octa-1,3,5-trien-7-one (8.0 g, 31.3% Yield). MS m/z 225.1[M+H]⁺.

Step 2. To a solution of 5-(benzyloxy)bicyclo[4.2.0]octa-1,3,5-trien-7-one (16.1 g, 71.79 mmol) in anhydrous MeOH (300 mL) was added NaBH₄ (5.43 g, 143.58 mmol) at 0°C. The reaction mixture was stirred at rt for 4h. Upon completion, the reaction mixture was quenched with water (300 mL), extracted with EA (300 mL x 2). The organic layers were dried over by anhydrous Na₂SO₄, filtered, concentrated and purified by silica gel column chromatography (0~10% EA/PE) to afford yellow solid 5-(benzyloxy)bicyclo[4.2.0]octa-1,3,5-trien-7-ol (12.2 g, 75.1% Yield). MS m/z 225.2[M-H]⁺.

Step 3. To a solution of 5-(benzyloxy)bicyclo[4.2.0]octa-1,3,5-trien-7-ol (14.0 g, 61.8 mmol, 1.0 eq) in anhydrous DCM (300 mL) was added BF₃·Et₂O (43.9 g, 309.3 mmol, 5.0 eq) and Et₃SiH (35.97 g, 309.3 mmol, 5.0 eq) at -78°C under Ar. The reaction was allowed to stir at -78°C for 4 h. Upon completion, the reaction mixture was quenched with saturated aqueous NaHCO₃ (300 mL), extracted with DCM (500 mL x 2). The organic layer was dried over Na₂SO₄, decanted, concentrated, and purified by silica gel column chromatography (100% PE) to afford yellow solid 2-(benzyloxy)bicyclo[4.2.0]octa-1,3,5-triene (2.1 g, 61.8 mmol, 16.1% Yield). ¹H NMR (400 MHz, CDCl₃) δ 7.42-7.28 (m, 6H), 7.14-7.10 (m, 1H), 6.76 (d, J = 8.4 Hz, 1H), 6.68 (d, J = 7.2 Hz, 1H), 5.16 (s, 2H), 3.28 (t, J = 4.0 Hz, 2H), 3.14 (t, J = 4.0 Hz, 2H).

Step 4. A mixture of 2-(benzyloxy)bicyclo[4.2.0]octa-1,3,5-triene (2.1 g, 9.9 mmol, 1 eq) and Pd/C (10%, 0.2 g) in MeOH (20 mL) was stirred at 60°C for 8 h under hydrogen (balloon). The mixture was filtered. The filtrate was concentrated under reduced pressure. The crude yellow oil (1.2 g, 9.9 mmol, 100.0% yield) was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.08 (t, *J* = 8.0 Hz, 1H), 6.65 (dd, *J* = 10.8 Hz, 7.2 Hz, 2H), 3.12 (s, 4H).

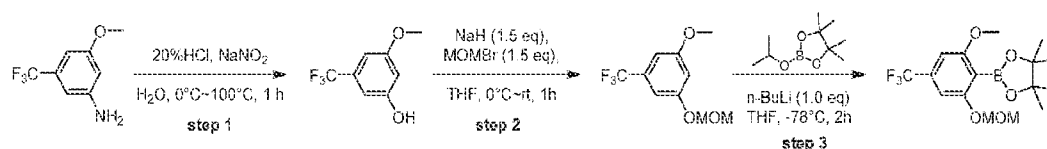
Step 5. To a solution of bicyclo[4.2.0]octa-1,3,5-trien-2-ol (1.2 g, 9.9 mmol, 1.0 eq) in anhydrous DCM (20 mL) was added NBS (1.78 g, 9.9 mmol, 1.0 eq) at 0°C. The reaction was allowed to stir at 0°C for 1 h. Upon completion, the reaction mixture was quenched with water (30 mL), extracted with DCM (20 mL x 2). The organic layer was dried over Na₂SO₄, decanted, concentrated, and purified by silica gel column chromatography (100% PE) to afford yellow solid 3-bromobicyclo[4.2.0]octa-1,3,5-trien-2-ol (1.1 g, 5.5 mmol, 55.3% Yield). ¹H NMR (400 MHz, CDCl₃) δ 7.32 (d, *J* = 7.6 Hz, 1H), 6.55 (d, *J* = 7.6 Hz, 1H), 5.44 (s, 1H), 3.16 (dd, *J* = 6.0 Hz, 3.6 Hz, 2H), 3.09 (dd, *J* = 5.2 Hz, 2.8 Hz, 2H).

Step 6. To a solution of 3-bromobicyclo[4.2.0]octa-1,3,5-trien-2-ol (1.1 g, 5.5 mmol, 1.0 eq) in THF (20 mL) was added NaH (0.2 g, 8.3 mmol, 1.5 eq) at 0°C. The reaction mixture was stirred at 0°C for 0.5 h. Then MOMBr (1.04 g, 8.3 mmol, 1.5 eq) was added. The reaction mixture was stirred at rt for 0.5 h. The reaction was quenched with water (30 mL), extracted with EtOAc (30 mL). The organic layer was washed with water (20 mL x 1) and brine (20 mL x 1). The organic layer was dried over Na₂SO₄, decanted, and concentrated to afford yellow oil 3-bromo-2-(methoxymethoxy)bicyclo[4.2.0]octa-1,3,5-triene (1.2 g, 4.9 mmol, 89.3% Yield) without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.39 (d, *J* = 7.6 Hz, 1H), 6.60 (d, *J* = 7.6 Hz, 1H), 5.22 (s, 2H), 3.49 (s, 3H), 3.30 (t, *J* = 4.0 Hz, 2H), 3.10 (t, *J* = 4.0 Hz, 2H).

Step 7. To a solution of 3-bromo-2-(methoxymethoxy)bicyclo[4.2.0]octa-1,3,5-triene (1.3 g, 5.3 mmol, 1.0 eq) in 1,4-dioxane (20 mL) were added (Bpin)₂ (1.49 g, 5.8 mmol, 1.1 eq), Pd(dppf)Cl₂ (0.39 g, 0.5 mmol, 0.1 eq) and AcOK (1.57 g, 16.0 mmol, 3.0 eq). The reaction mixture was stirred at 80°C under Ar for 16 h. The reaction mixture was filtered through a pad of celite and rinsed with EA. The organic phase was concentrated and purified by silica gel column chromatography (0~6% PE/EA) to afford a white solid 2-(2-(methoxymethoxy)bicyclo[4.2.0]octa-1,3,5-trien-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.7 g, 2.4 mmol, 45.1% Yield). ¹H NMR (400 MHz, CDCl₃) δ 7.59 (d, *J* = 7.2 Hz, 1H), 6.73 (d,

$J = 7.2$ Hz, 1H), 5.20 (s, 2H), 3.48 (s, 3H), 3.32 – 3.24 (m, 2H), 3.18 – 3.09 (m, 2H), 1.33 (s, 12H).

Intermediate 19. Preparation of 2-(2-methoxy-6-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



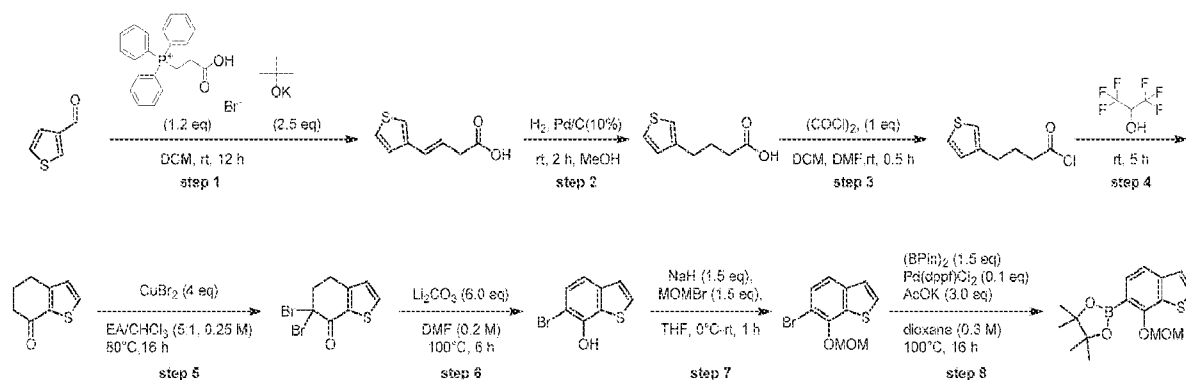
Step 1. To a solution of 3-methoxy-5-(trifluoromethyl)aniline (5.0 g, 26.16 mmol) in 20% HCl aqueous solution (200 mL) was added NaNO_2 (2.17 g, 31.39 mmol) at 0°C . The reaction was allowed to stir at 0°C for 0.5 h. After that, the reaction mixture was added to water (200 mL) at 100°C . The reaction was allowed to stir at 110°C for 15 min. Upon completion, the reaction was cooled to rt. taken up in EtOAc (200 mL) and washed with water (200 mL x 2) and brine (200 mL x 1). The organic phase was dried over Na_2SO_4 , filtered, concentrated and purified by silica gel column chromatography (0~10% EA/PE) to afford yellow oil 3-methoxy-5-(trifluoromethyl)phenol (3.0 g, 59.7% Yield). MS m/z 191.1 $[\text{M}+\text{H}]^+$.

Step 2. To a solution of 3-methoxy-5-(trifluoromethyl)phenol (3.0 g, 15.61 mmol) in anhydrous THF (60 mL) was added NaH (937 mg, 23.42 mmol) at 0°C . The reaction mixture was stirred at 0°C for 0.5 h. Then MOMBr (2.93 g, 23.42 mmol) was added. The reaction mixture was stirred at rt for another 0.5h. Upon completion, the reaction mixture was quenched with water (50 mL), extracted with EA (50 mL). The organic layer was washed with water (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 , filtered, concentrated and purified by silica gel column chromatography (100% PE) to afford yellow oil 1-methoxy-3-(methoxymethoxy)-5-(trifluoromethyl)benzene (2.8 g, 75.9% Yield). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 6.91 (s, 1H), 6.88 – 6.87 (m, 2H), 5.26 (s, 2H), 3.81 (s, 3H), 3.39(s, 3H).

Step 3. To a solution of 1-methoxy-3-(methoxymethoxy)-5-(trifluoromethyl)benzene (1.0 g, 4.23 mmol) in anhydrous THF (10 mL) was added $n\text{-BuLi}$ (2.65 mL, 4.23 mmol, 1.6 M) at -78°C under Ar. The reaction mixture was stirred at -78°C for 1 h. Then 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.58 g, 8.47 mmol) was added at -78°C . The reaction mixture was stirred at -78°C for another 1 h. Upon completion, the reaction was quenched with saturated

NH₄Cl (30 mL), extracted with EtOAc (30 mL). The organic layer was washed with water (30 mL x 2) and brine (30 mL x 1), dried over Na₂SO₄, decanted, concentrated, and purified by silica gel column chromatography (100% PE) to afford yellow solid 2-(2-methoxy-6-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (861 mg, 56.2% Yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.96 (s, 1H), 6.89 (s, 1H), 5.22 (s, 2H), 3.79 (s, 3H), 3.37 (s, 3H), 1.29 (s, 12H).

Intermediate 20. Preparation of 2-(7-(methoxymethoxy)benzo[b]thiophen-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1. To a solution of thiophene-3-carbaldehyde (20 g, 178.3 mmol, 1 eq) in DCM (200 mL) were added (2-carboxyethyl) triphenylphosphonium bromide (88.8 g, 214.0 mmol, 1.2 eq) and t-BuOK (50.0 g, 445.8 mmol, 2.5 eq). The reaction was stirred at rt for 8 h. The reaction was quenched with water (300 mL), extracted with DCM (300 mL). The organic layer was washed with water (200 mL x 2) and brine (300 mL x 1), dried over Na₂SO₄, decanted, concentrated and purified by silica gel column chromatography (0~50% PE/EA) to afford a yellow solid (E)-4-(thiophen-3-yl) but-3-enoic acid (14 g, 83.2 mmol, 46.7% Yield) MS m/z 167.1 [M-H].

Step 2. A mixture of (E)-4-(thiophen-3-yl) but-3-enoic acid (14 g, 83.2 mmol, 1.0 eq.) and Pd/C (10%, 1.4 g) in MeOH (100 mL) was stirred at rt for 2 h under hydrogen (balloon). The mixture was filtered. The filtrate was concentrated under reduced pressure. The crude yellow solid (11.3 g, 59.9 mmol, 101.9% yield) was used in the next step without further purification. MS m/z 169.2 [M+H].

Step 3. A mixture of 4-(thiophen-3-yl) butanoic acid (10 g, 58.7 mmol, 1.0 eq.), (COCl)₂ (7.4 g, 58.7 mmol, 1.0 eq.) and DMF (1 mL) in DCM (100 mL) was stirred at rt for 0.5 h under N₂. The

mixture was concentrated under reduced pressure. The crude yellow oil (10.0 g, 58.7 mmol, 70.6% yield) was used in the next step without further purification. MS m/z 240.1 $[M+H]^+$.

Step 4. A solution of 4-(thiophen-3-yl) butanoyl chloride (11.3 g, 59.9 mmol, 1 eq) in 1,1,1,3,3,3-hexafluoro-2-propanol (100 mL) was stirred at rt for 5 h under N₂. The reaction was quenched with water (300 mL), extracted with DCM (300 mL). The organic layer was washed with water (200 mL x 2) and brine (300 mL x 1). The organic layer was dried over Na₂SO₄, decanted, concentrated and purified by silica gel column chromatography (0~30% PE/EA) to afford a yellow oil 5,6-dihydrobenzo[b]thiophen-7(4H)-one (7.6 g, 49.9 mmol, 83.4% Yield). MS m/z 153.1 $[M+H]^+$. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.87 (d, J = 5.2 Hz, 1H), 7.13 (d, J = 4.8 Hz, 1H), 2.85 (t, J = 6.0 Hz, 2H), 2.53 (t, J = 5.6 Hz, 2H), 2.06-2.11(m, 2H).

Step 5. A mixture of CuBr₂ (44.6 g, 199.7 mmol, 4.0 eq) in anhydrous EA (200 mL) was allowed to stir at 80°C for 10 min. Then a solution of 5,6-dihydrobenzo[b]thiophen-7(4H)-one (7.6 g, 49.9 mmol, 1.0 eq) in CHCl₃ (40 mL) was added at 80°C. The reaction was stirred at 80°C for 16 h. Upon completion, the reaction was cooled to rt. The reaction mixture was filtered to remove the solid and the filtrate was concentrated. The residue was purified by silica gel column chromatography (0~10% PE/EA) to afford black solid 6,6-dibromo-5,6-dihydrobenzo[b]thiophen-7(4H)-one (13 g, 41.9 mmol, 84.0% Yield). MS m/z 310.8 $[M+H]^+$. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.18 (d, J = 5.2 Hz, 1H), 6.84 (d, J = 4.8 Hz, 1H), 3.13 (t, J = 5.6 Hz, 2H), 2.96 (t, J = 5.6 Hz, 2H).

Step 6. To a solution of 6,6-dibromo-5,6-dihydrobenzo[b]thiophen-7(4H)-one (13.4 g, 43.23 mmol, 1.0 eq) in DMF (216 mL) was added Li₂CO₃ (19.2 g, 259.3 mmol, 6.0 eq). The reaction mixture was stirred at 100°C for 2 h. Upon completion, the reaction was cooled to rt, filtered to remove the solid. The filtrate was concentrated. The residue was diluted with water (500 mL), extracted with EA (300 mL). The organic layer was washed with water (500 mL x 2) and brine (500 mL x 1), dried over anhydrous Na₂SO₄, decanted, concentrated, and purified by silica gel column chromatography (0~2% PE/EA) to afford yellow solid 6-bromobenzo[b]thiophen-7-ol (4.4 g, 19.21 mmol, 44.4% Yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.22 (s, 1H), 7.72 (d, J = 5.6 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.41 (d, J = 5.2 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H).

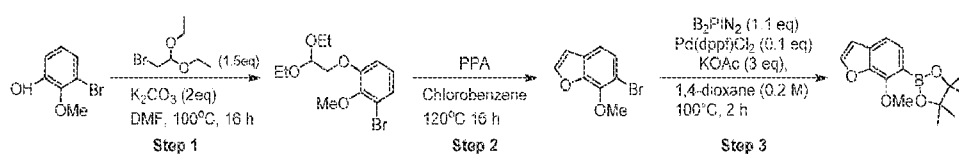
Step 7. To a solution of 6-bromobenzo[b]thiophen-7-ol (4.5 g, 19.6 mmol, 1.0 eq) in THF (50 mL) was added NaH (0.7 g, 29.5 mmol, 1.5 eq) at 0°C. The reaction mixture was stirred at 0°C

for 0.5 h. Then MOMBr (3.68 g, 29.5 mmol, 1.5 eq) was added. The reaction mixture was stirred at rt for another 0.5h. The reaction was quenched with water (150 mL), extracted with EtOAc (100 mL). The organic layer was washed with water (150 mL x 1) and brine (150 mL x 1), dried over Na₂SO₄, decanted, concentrated to afford yellow oil 6-bromo-7-

(methoxymethoxy)benzo[b]thiophene (4.7 g, 17.2 mmol, 87.6% Yield) without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.81 (d, *J* = 5.2 Hz, 1H), 7.64-7.59(m, 2H), 7.49 (d, *J* = 5.6 Hz, 1H), 5.31 (s, 2H), 3.62 (s, 3H).

Step 8. To a solution of 6-bromo-7-(methoxymethoxy)benzo[b]thiophene (4.7 g, 17.2 mmol, 1.0 eq) in 1,4- dioxane (50 mL) were added (Bpin)₂ (6.55 g, 25.8 mmol, 1.5 eq), Pd(dppf)Cl₂ (1.25 g, 1.72 mmol, 0.1 eq) and AcOK (5.07 g, 51.6 mmol, 3.0 eq). The reaction mixture was stirred at 100°C under Ar for 16 h. The reaction mixture was filtered through a pad of celite and rinsed with EA. The filtrate was concentrated and purified by silica gel column chromatography (0~6% PE/EA) to afforded a yellow solid 2-(7-(methoxymethoxy)benzo[b]thiophen-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.1 g, 6.6 mmol, 38.1% Yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.86 (d, *J* = 5.2 Hz, 1H), 7.66 – 7.60 (m, 2H), 7.48 (d, *J* = 5.2 Hz, 1H), 5.23 (s, 2H), 3.54 (s, 3H), 1.32 (s, 12H).

Intermediate 21. Preparation of 2-(7-methoxybenzofuran-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



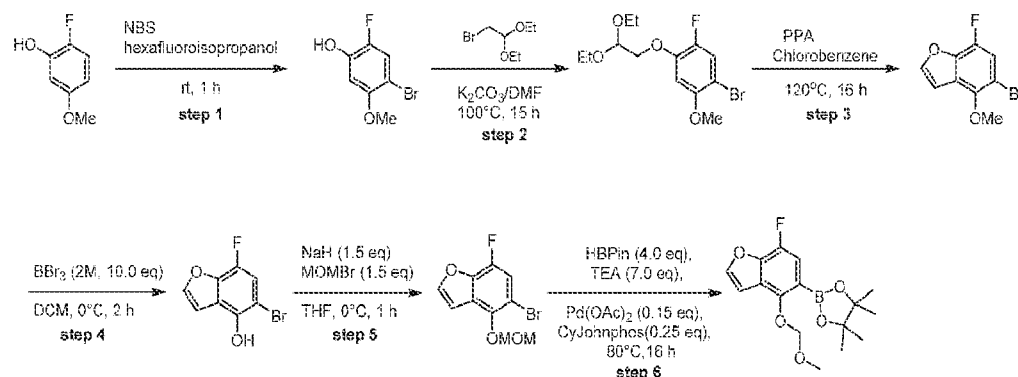
Step 1. To a mixture of 3-bromo-2-methoxyphenol (5 g, 24.63mmol, 1 eq) and 2-bromo-1,1-diethoxyethane (7.25 g, 36.94 mmol, 1.5 eq) in DMF was added K₂CO₃ (6.81 g, 49.25 mmol, 2.0 eq) at rt. After completion of the addition, the mixture was heated at 100°C for 16 h. Upon completion, the reaction was cooled to room temperature. The mixture was diluted with H₂O (50 mL) and extracted with EA (10 mL x 3). The organic layer was washed with brine (50 mL x 2), dried with Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography on silica gel eluted with (PE/EA = 1:0~10:1) to give 1-bromo-3-(2,2-diethoxyethoxy)-2-methoxybenzene (8.5 g, 24.44 mmol, 99.2% yield) as colorless oil. ¹H NMR

(400 MHz, DMSO-*d*₆) δ 7.16 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.10 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.99 (t, *J* = 8.2 Hz, 1H), 4.85 (t, *J* = 5.2 Hz, 1H), 4.00 (d, *J* = 5.2 Hz, 2H), 3.77 (s, 3H), 3.73 – 3.65 (m, 2H), 3.63 – 3.56 (m, 2H), 1.14 (t, *J* = 7.2 Hz, 6H).

Step 2. To a mixture of 1-bromo-3-(2,2-diethoxyethoxy)-2-methoxybenzene (8.5 g, 26.63 mmol, 1.0 eq) in Chlorobenzene (85 mL) was added PPA (7.83 g, 79.89 mmol, 3.0 eq). After completion of the addition, the mixture was heated at 120°C for 16 h. Upon completion, the reaction was cooled to room temperature, the mixture was diluted with H₂O (500 mL) and extracted with EA (300 mL x 3). The organic layer was washed with brine (100 mL x 2), dried over Na₂SO₄, filtered, and concentrated in vacuum. The crude product was purified by column chromatography on silica gel eluted with (PE/EA = 1:0~10:1) to give 6-bromo-7-methoxybenzofuran (3.5 g, 15.41 mmol, 57.89% yield) as colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.59 (d, *J* = 2.4 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 2.4 Hz, 1H), 4.22 (s, 3H).

Step 3. A flask was charged with a mixture of 6-bromo-7-methoxybenzofuran (3.5 g, 15.41 mmol, 1 eq), B₂Pin₂ (4.31 g, 16.96 mmol, 1.1 eq), KOAc (4.54 g, 46.24 mmol, 3 eq) and Pd(dppf)Cl₂ (1.12 g, 1.54 mmol, 0.1 eq) in anhydrous 1,4-dioxane (35 mL) at rt. The mixture was then degassed/purged with N₂. The reaction was heated to 100°C and stirred for 2 h. Upon completion, the reaction mixture was cooled to room temperature, filtered through a pad of Celite and rinsed with EtOAc. The filtrate was concentrated in vacuum. The crude product was purified by column chromatography on silica gel eluted with (PE/EA = 1:0~10:1) to give 2-(7-methoxybenzofuran-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.5 g, 9.12 mmol, 59.16% yield) as colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.56 (d, *J* = 2.0 Hz, 1H), 7.46 (d, *J* = 7.2 Hz, 1H), 7.19 (d, *J* = 4.8 Hz, 1H), 6.68 (d, *J* = 2.0 Hz, 1H), 4.09 (s, 3H), 1.30 (s, 12H).

Intermediate 22. Preparation of 2-(7-fluoro-4-(methoxymethoxy)benzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1. To a solution of 2-fluoro-5-methoxyphenol (9.0 g, 63.4 mmol, 1.0 eq) in

5 hexafluoroisopropanol (100 mL) was added NBS (12.4 g, 69.7 mmol, 1.1 eq) slowly at 0°C. The mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with NaHCO₃ aq (100 mL) and extracted with EtOAc (200 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, concentrated in vacuo and purified by silica gel column, eluted with PE/EtOAc=20/1 to afford 4-bromo-2-fluoro-5-methoxyphenol

10 (12.8 g, 57.76 mmol, 91.1% yield) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.26 (d, J = 9.6 Hz, 1H), 6.61 (d, J = 7.6 Hz, 1H), 6.14 (d, J = 3.2 Hz, 1H), 3.83 (s, 3H).

Step 2. A mixture of 4-bromo-2-fluoro-5-methoxyphenol (10.0 g, 45.2 mmol, 1.0 eq), 2-bromo-1,1-diethoxyethane (9.3 g, 47.5 mmol, 1.05 eq) and K₂CO₃ (12.5 g, 90.4 mmol, 2.0 eq) in DMF (200 mL) was stirred at 100°C for 16 h. Upon completion, the reaction was cooled to room

15 temperature, diluted with EtOAc (200 mL) and washed with water (500 mLx3), dried over anhydrous Na₂SO₄ and concentrated to afford 1-bromo-4-(2,2-diethoxyethoxy)-5-fluoro-2-methoxybenzene (15.0 g, 44.49 mmol, 98.3% yield) as yellow oil, which was used for the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.27 (d, J = 10.4 Hz, 1H), 6.65 (d, J = 7.6 Hz, 1H), 4.83 (t, J = 5.2 Hz, 1H), 4.08 (t, J = 4.4 Hz, 2H), 3.84 (s, 3H), 3.81-3.77 (m, 2H), 3.66-3.62 (m, 2H), 1.26-1.24 (m, 9H).

20

Step 3. To a solution of 1-bromo-4-(2,2-diethoxyethoxy)-5-fluoro-2-methoxybenzene (15.0 g, 44.49 mmol, 1.0 eq) in chlorobenzene (200 mL) was added PPA (15.0 g, 182.94 mmol, 4.1 eq). The reaction mixture was stirred at 100°C for 16 h. Upon completion, the reaction was cooled to room temperature, diluted with H₂O (500 mL), extracted with EtOAc (300 mLx2). The

25 combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and

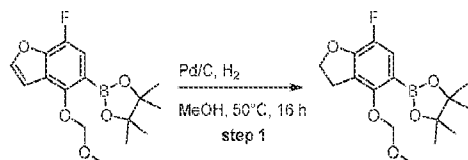
concentrated, purified by silica gel column, eluted with PE/EtOAc=20/1 to afford 5-bromo-7-fluoro-4-methoxybenzofuran (6.5 g, 26.53 mmol, 59.6% yield) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.63 (d, J = 2.0 Hz, 1H), 7.23 (d, J = 9.6 Hz, 1H), 6.94 (t, J = 2.4 Hz, 1H), 4.01 (s, 3H).

- 5 Step 4. To a solution of 5-bromo-7-fluoro-4-methoxybenzofuran (5.0 g, 20.5 mmol, 1.0 eq) in DCM (50 mL) was added BBr₃ (51.1 g, 2.0 M, 204.04 mmol, 10.0 eq) at 0°C. The mixture was stirred for 2 h at 0°C. The reaction mixture was quenched with MeOH (30 mL) at 0°C and the pH was adjusted to around 7~8 by progressively adding NaHCO₃. The reaction was extracted with EtOAc (200 mLx2), washed with brine (300 mL). The organic phase was dried over
- 10 Na₂SO₄, filtered, concentrated in vacuo, and purified by silica gel column, eluted with PE/EtOAc=20/1 to afford 5-bromo-7-fluorobenzofuran-4-ol (1.4 g, 6.06 mmol, 29.7% yield) as yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 7.60 (d, J = 2.0 Hz, 1H), 7.15 (d, J = 9.6 Hz, 1H), 6.92 (t, J = 2.8 Hz, 1H), 5.63 (s, 1H).

- Step 5. To a solution of 5-bromo-7-fluorobenzofuran-4-ol (1.4 g, 6.09 mmol, 1.0 eq) in THF (20
- 15 mL) was added NaH (0.365 g, 9.13 mmol, 1.5 eq) at 0°C and stirred at 0°C for 0.5 h. MOMBr (1.14 g, 9.13 mmol, 1.5 eq) was added to the mixture at 0 °C and stirred at 0 °C for another 1 h. The reaction mixture was quenched with NH₄Cl aq (10 mL), extracted with EtOAc (100 mL), washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated to afford 5-bromo-7-fluoro-4-(methoxymethoxy)benzofuran (1.2 g, 4.36 mmol, 72.0% yield) as yellow oil. ¹H NMR
- 20 (400 MHz, CDCl₃) δ 7.61 (d, J = 2.0 Hz, 1H), 7.24 (d, J = 9.6 Hz, 1H), 6.96 (t, J = 2.4 Hz, 1H), 5.64 (s, 2H), 3.66 (s, 3H).

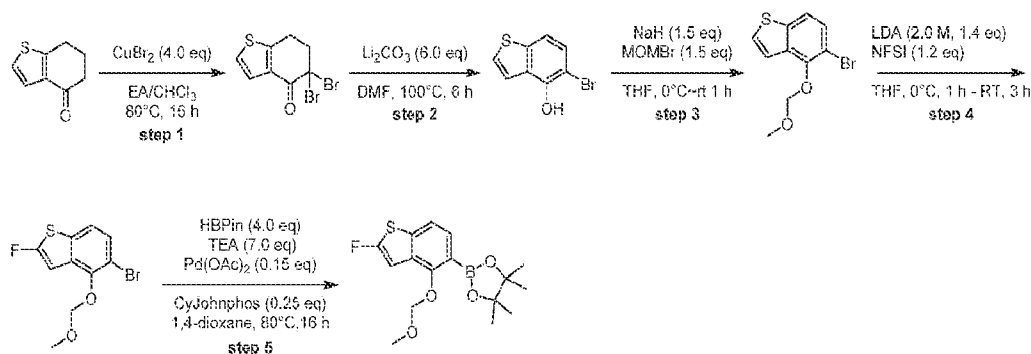
- Step 6. A mixture of 5-bromo-7-fluoro-4-(methoxymethoxy) benzofuran (1.2 g, 4.36 mmol, 1.0 eq), HBPIn (2.2 g, 17.52 mmol, 4.0 eq), TEA (3.1 g, 30.66 mmol, 7.0 eq), Pd(OAc)₂ (0.148 g, 0.66 mmol, 0.15 eq) and CyJohnphos (0.383 g, 1.10 mmol, 0.25 eq) in dioxane (10 mL) was
- 25 stirred at 80°C for 16 h. Upon completion, the reaction was cooled to room temperature, diluted with EtOAc (50 mL) and filtered through a pad of celite. The filtrate was concentrated in vacuo, purified by silica gel column, eluted with PE/EtOAc=10/1 to afford 2-(7-fluoro-4-(methoxymethoxy) benzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.5 g, 1.55 mmol, 35.6% yield) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.59 (d, J = 2.0 Hz, 1H), 7.39 (d, J =
- 30 10.8 Hz, 1H), 6.92 (t, J = 2.4 Hz, 1H), 5.19 (s, 2H), 3.62 (s, 3H), 1.36 (s, 12H).

Intermediate 23. Preparation of 2-(7-fluoro-4-(methoxymethoxy)-2,3-dihydrobenzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



- 5 Step 1. To a solution of 2-(7-fluoro-4-(methoxymethoxy)benzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.2 g, 0.62 mmol, 1.0 eq) in MeOH (5 mL) was added dry Pd/C (0.02 g). The mixture was stirred for 16 h at 50°C under H₂. Upon completion, the reaction mixture was cooled to room temperature and filtered through a pad of celite. The filtrate was concentrated in vacuo to afford 2-(7-fluoro-4-(methoxymethoxy)-2,3-dihydrobenzofuran-5-yl)-4,4,5,5-
- 10 tetramethyl-1,3,2-dioxaborolane (0.14 g, 50% purity, 0.22 mol, 34.8% yield) as a yellow oil, which was used for the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.33 (d, J = 10.8 Hz, 1H), 5.05 (s, 2H), 3.59 (s, 3H), 3.34 (t, J = 8.8 Hz, 1H), 3.22 (t, J = 8.8 Hz, 1H), 1.35 (s, 12H).

- 15 Intermediate 24. Preparation of 2-(2-fluoro-4-(methoxymethoxy)benzo[b]thiophen-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



- Step 1. A suspension of CuBr₂ (58.8 g, 263.16 mmol, 4.0 eq) in EtOAc (200 mL) was stirred at 80°C for 10 min. A solution of 6,7-dihydrobenzo[b]thiophen-4(5H)-one (10.0 g, 65.79 mmol, 1.0
- 20 eq) in CHCl₃ (40 mL) was added to the suspension. The mixture was stirred at 80°C for 16 h. Upon completion, the reaction mixture was cooled to room temperature and filtered through a pad of celite. The filtrate was concentrated, washed with PE/EtOAc=10/1 and filtered again. The

solid was dried in vacuo to afford 5,5-dibromo-6,7-dihydrobenzo[b]thiophen-4(5H)-one (17.6 g, 56.77 mmol, 86.4% yield) as a yellow solid. MS m/z 310.9 $[M+H]^+$.

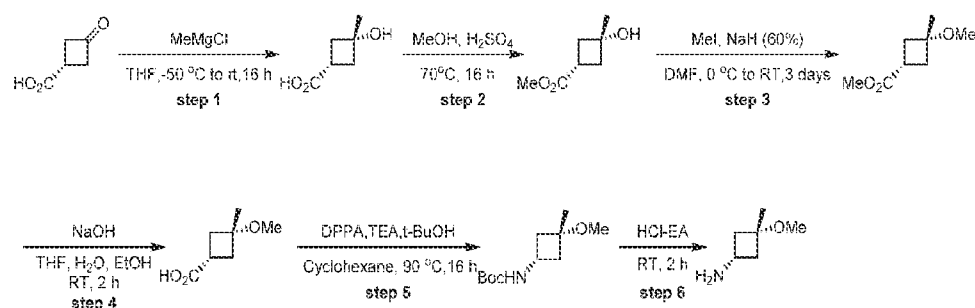
Step 2. To a solution of 5,5-dibromo-6,7-dihydrobenzo[b]thiophen-4(5H)-one (17.6 g, 56.77 mmol, 1.0 eq) in DMF (300 mL) was added Li_2CO_3 (25.2 g, 340.64 mmol, 6.0 eq). The reaction mixture was stirred for 6 h at 100°C. Upon completion, the reaction mixture was cooled to room temperature, diluted with EtOAc (300 mL), washed with H_2O (500 mL $\times$ 3). The organic phase was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column, eluted with PE/EtOAc=50/1 to afford 5-bromobenzo[b]thiophen-4-ol (8.3 g, 36.23 mmol, 63.81% yield) as white solid. MS m/z 226.9 $[M-H]^-$.

Step 3. To a solution of 5-bromobenzo[b]thiophen-4-ol (8.3 g, 36.23 mmol, 1.0 eq) in THF (150 mL) was added NaH (2.2 g, 54.37 mmol, 1.5 eq) at 0°C and stirred at 0°C for 0.5 h. MOMBr (6.8 g, 54.37 mmol, 1.5 eq) was added to the mixture at 0 °C and stirred at 0 °C for another 1 h. The reaction mixture was quenched with NH_4Cl aq (10 mL), extracted with EtOAc (300 mL). The organic phase was washed with brine (200 mL), dried over anhydrous Na_2SO_4 and concentrated to afford 5-bromo-4-(methoxymethoxy)benzo[b]thiophene (10.9 g, 90% purity, 35.91 mmol, 99.1% yield) as yellow oil. ^1H NMR (400 MHz, $DMSO-d_6$) δ 7.83 (d, J = 5.6 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.52 (d, J = 5.6 Hz, 1H), 5.26 (s, 2H), 3.60 (s, 3H).

Step 4. To a solution of LDA (12.8 mL, 2.0 M, 25.6 mmol, 1.4 eq) in THF (100 mL) at -78°C was added a solution of 5-bromo-4-(methoxymethoxy)benzo[b]thiophene (5.0 g, 18.3 mmol, 1.0 eq) in THF (50 mL). The mixture was stirred at 0°C for 1 h under Ar atmosphere. NFSI (5.76 g, 18.3 mmol, 1.0 eq) in THF (50 mL) was added to the solution at 0°C. The mixture was stirred at 0°C for another 1 h under Ar atmosphere, then warmed to RT and stirred for 16 h. The reaction mixture was quenched with NH_4Cl aq. (10 mL), extracted with EtOAc (300 mL). The organic phase was washed with brine (200 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column, eluted with 100% PE to afford 5-bromo-2-fluoro-4-(methoxymethoxy)benzo[b]thiophene (0.88 g, 3.02 mmol, 16.5% yield) as yellow oil. ^1H NMR (400 MHz, $DMSO-d_6$) δ 7.69 (d, J = 8.8 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.17 (d, J = 2.8 Hz, 1H), 5.21 (s, 2H), 3.59 (s, 3H).

Step 5. A mixture of 5-bromo-2-fluoro-4-(methoxymethoxy)benzo[b]thiophene (0.2 g, 0.69 mmol, 1.0 eq), HBPIn (0.352 g, 2.75 mmol, 4.0 eq), TEA (0.486 g, 4.81 mmol, 7.0 eq), Pd(OAc)₂ (0.023 g, 0.10 mmol, 0.15 eq) and CyJohnphos (0.06 g, 0.17 mmol, 0.25 eq) in dioxane (2 mL) was stirred at 80°C for 16 h. Upon completion, the reaction was cooled to room temperature, diluted with EtOAc (10 mL) and filtered through a pad of celite. The filtrate was concentrated. The residue was purified by silica gel column, eluted with PE/EtOAc=20/1 to afford 2-(2-fluoro-4-(methoxymethoxy)benzo[b]thiophen-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.035 g, 0.10 mmol, 15.1% yield) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.67 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 2.8 Hz, 1H), 5.14 (s, 2H), 3.51 (s, 3H), 1.32 (s, 12H).

Intermediate 25. Preparation of (1*s*,3*s*)-3-methoxy-3-methylcyclobutan-1-amine



Step 1. To a solution of 3-oxocyclobutane-1-carboxylic acid (38.80 g, 340.05 mmol, 1.0 eq.) in dry THF (750 mL) under N₂ was added MeMgCl (250 mL, 3.00 M, 2.2 eq.) dropwise at a rate such that the temperature did not rise above -40°C. The resulting mixture was stirred at rt for 16 h under N₂. The mixture was cooled to internal temperature 5°C and Phosphoric acid (750 mL, 1 M) was added to the mixture slowly (maintaining temperature below 15°C) under N₂. Once the phosphoric acid addition was completed, the mixture was stirred at rt for 1 hour. The mixture was diluted with H₂O (300 mL) and extracted with EA (300 mL x 3). The organic phase was washed with brine (300 mL x 3), dried over anhydrous Na₂SO₄ and concentrated. Tert-Butyl methyl ether (80 mL) was added to the residue to precipitate the solid. The suspension was filtered, the solid was dried under vacuum to afford (1*s*,3*s*)-3-hydroxy-3-methylcyclobutane-1-carboxylic acid (26.30 g, 202.09 mmol, 59.43% Yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.00 (s, 1H), 5.03 (s, 1H), 2.61 – 2.52 (m, 1H), 2.17 – 2.04 (m, 4H), 1.22 (s, 3H).

Step 2. To a solution of (1s,3s)-3-hydroxy-3-methylcyclobutane-1-carboxylic acid (15.00 g, 115.26 mmol, 1.0 eq.) in MeOH (255 mL) was added H₂SO₄ (2.34 mL, 16 M) at rt. The resulting mixture was stirred at 70°C for 16 h. The mixture was concentrated to afford the residue. The residue was diluted with H₂O (100 mL) and extracted with EA (100 mL x 3). The organic phase
5 was washed with Saturated NaHCO₃ (100 mL x 2) and brine (100 mL x 3), dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/23) to afford methyl (1s,3s)-3-hydroxy-3-methylcyclobutane-1-carboxylate (14.3 g, 99.19 mmol, 86.06% Yield) as a colorless oil. ¹H NMR (400 MHz, DMSO-d₆) δ 5.08 (s, 1H), 3.59 (s, 3H), 2.67 (p, *J* = 8.9 Hz, 1H), 2.19 – 2.06 (m, 4H), 1.23 (s, 3H).

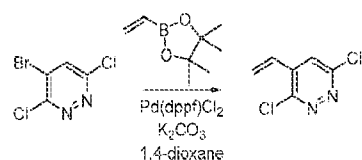
Step 3. To a solution of methyl (1s,3s)-3-hydroxy-3-methylcyclobutane-1-carboxylate (15.00 g, 104.04 mmol, 1.0 eq.) in DMF (250 mL) was added NaH (60%, 12.48 g, 312.13 mmol, 3.0 eq.) at 0°C. The mixture was stirred at rt for 1 h. Then MeI (58.29 mL, 936.39 mmol, 9.0 eq.) was added to the mixture at 0°C. The mixture was stirred at rt for 3 days. The mixture was quenched with H₂O (200 mL) and extracted with EA (200 mL x 3). The organic phase was washed with
15 brine (200 mL x 3), dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/5) to afford methyl (1s,3s)-3-methoxy-3-methylcyclobutane-1-carboxylate (10.80 g, 68.27 mmol, 65.62% Yield) as a yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ 3.60 (s, 3H), 3.05 (s, 3H), 2.80 (p, *J* = 8.8 Hz, 1H), 2.25 – 2.11 (m, 2H), 2.10 – 1.99 (m, 2H), 1.27 (s, 3H).

Step 4. To a solution of methyl (1s,3s)-3-methoxy-3-methylcyclobutane-1-carboxylate (6.20 g, 39.19 mmol, 1.0 eq.) in THF/EtOH/H₂O (25 mL/25 mL/10 mL) was added NaOH (6.27 g, 156.77 mmol, 4.0 eq.) at rt. The mixture was stirred at rt for 2 h. The mixture was concentrated under reduced pressure. The residue was diluted with water (100 mL) and washed with EtOAc (100 mL x 2). The aqueous phase was adjusted to pH = 5-6 with citric acid (1M) and then
25 extracted with EtOAc (100 mL x 3). The organic phase was washed with brine (80 mL x 3), dried over anhydrous Na₂SO₄ and concentrated to afford (1s,3s)-3-methoxy-3-methylcyclobutane-1-carboxylic acid (5.5 g, 38.15 mmol, 97.34% Yield) as a yellow oil which was used to next step without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ 12.06 (s, 1H), 3.05 (s, 3H), 2.73 – 2.62 (m, 1H), 2.21 – 2.12 (m, 2H), 2.06 – 1.98 (m, 2H), 1.26 (s, 3H).

Step 5. To a solution of (1s,3s)-3-methoxy-3-methylcyclobutane-1-carboxylic acid (5.50 g, 38.15 mmol, 1.0 eq.) in Cyclohexane (5 mL) was added DPPA (11.13 g, 45.78 mmol, 1.2 eq.), t-BuOH (145.95 mL, 1.53 mol, 40.0 eq.) and TEA (6.36 mL, 45.78 mmol, 1.2 eq.) at 0°C. The resulting mixture was stirred at 90°C for 16 h. The mixture was diluted with H₂O (100 mL) and extracted with EA (100 mL x 3). The organic phase was washed with brine (100 mL x 3), dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/8) to afford tert-butyl ((1s,3s)-3-methoxy-3-methylcyclobutyl)carbamate (3.20 g, 14.86 mmol, 38.96% Yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.09 (d, *J* = 7.7 Hz, 1H), 3.69 – 3.51 (m, 1H), 3.03 (s, 3H), 2.19 – 2.05 (m, 2H), 2.02 – 1.86 (m, 2H), 1.36 (s, 9H), 1.20 (s, 3H).

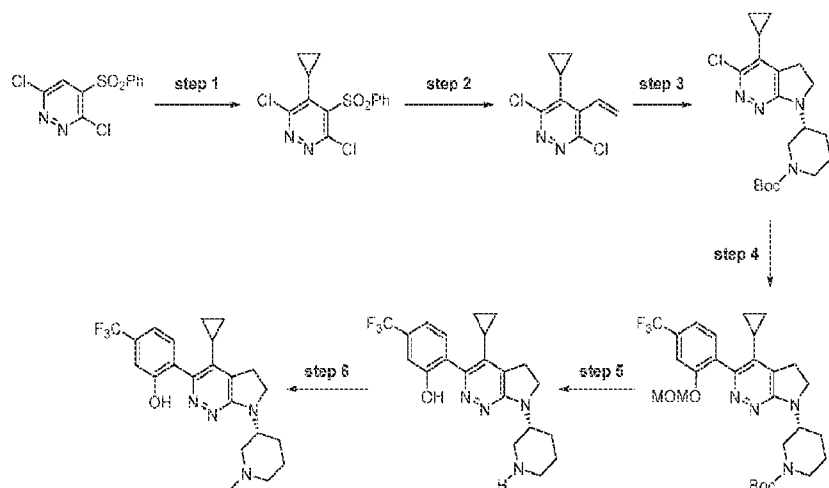
Step 6. To a solution of tert-butyl ((1s,3s)-3-methoxy-3-methylcyclobutyl) carbamate (5.50 g, 38.15 mmol, 1.0 eq.) in EA (6 mL) was added HCl-EtOAc (20 mL, 4M). The mixture was stirred at rt for 2 h. The mixture was concentrated to afford (1s,3s)-3-methoxy-3-methylcyclobutan-1-amine (3.20 g, 14.86 mmol, 38.96% Yield) as white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.30 (s, 3H), 3.43 – 3.37 (m, 1H), 3.08 (s, 3H), 2.19 (s, 2H), 2.17 (s, 2H), 1.24 (s, 3H).

Intermediate 26. Preparation of 3,6-dichloro-4-vinylpyridazine



To a degassed solution of 4-bromo-3,6-dichloro-pyridazine (1.08 g, 4.74 mmol) in 1,4-dioxane (21 mL) was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (Pd(dppf)Cl₂) (347 mg, 0.474 mmol), vinylboronic acid pinacol ester (0.88 mL, 5.21 mmol), and a 2 M solution of aqueous potassium carbonate (7.1 mL, 14.2 mmol). The reaction stirred at 70 °C for 2 hours. Upon completion the mixture was diluted with water, extracted with ethyl acetate, and combined organics were evaporated under reduced pressure. The crude residue was purified via flash chromatography eluting 0 to 100% EtOAc/Hexanes to afford 3,6-dichloro-4-vinylpyridazine (574 mg, 69% yield). MS *m/z* 176.9, 178.9 [M+H]⁺.

Example 1. Preparation of (R)-2-(4-cyclopropyl-7-(1-methylpiperidin-3-yl)-6,7-dihydro-5H-pyrrolo[2,3-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol (I-1)



Step 1: To a flask containing 3,6-dichloro-4-(phenylsulfonyl)pyridazine (20.0 g, 69.1 mmol) was added acetonitrile (200 mL), then silver nitrate (14.1 g, 82.9 mmol) and cyclopropanecarboxylic acid (17.8 g, 207.3 mmol). The resulting mixture was heated to 80°C, then ammonium persulfate (78.8 g, 345.5 mmol) in water (150 mL) was added dropwise over a period of 5 min. The reaction mixture was stirred at 80°C for another 15 min. TLC (10% ethyl acetate in petroleum ether) showed starting material was consumed and a new spot formed. The reaction mixture was quenched with saturated aqueous sodium bicarbonate solution (50 mL), and the mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic phase was washed with water (2 x 100 mL) and brine (100 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with a gradient EtOAc/petroleum ether (0 - 4% EtOAc) to afford 3,6-dichloro-4-cyclopropyl-5-(phenylsulfonyl)pyridazine (7.0 g, 31% yield, 21.3 mmol) as a white solid. MS m/z 328.9 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ : 7.95 – 7.84 (m, 2H), 7.77 – 7.67 (m, 1H), 7.62 – 7.56 (m, 2H), 2.33 – 2.18 (m, 1H), 1.52 – 1.39 (m, 2H), 0.93 (q, J = 6.0 Hz, 2H).

Step 2: To an oven-dried three-necked flask were added 3,6-dichloro-4-cyclopropyl-5-(phenylsulfonyl)pyridazine (4.0 g, 12.1 mmol) and anhydrous tetrahydrofuran (8 mL). The resulting mixture was cooled to -10 °C, then vinylmagnesium bromide (1M in THF, 24 mL, 24.0 mmol) was added dropwise. The resulting mixture was stirred at -10°C for 1 hour. TLC (10% EtOAc in petroleum ether) showed starting material was consumed. Saturated aqueous ammonium chloride (5 mL) was added to quench the reaction, and the mixture was extracted

with EtOAc (3 x 20 mL). The organic phase was washed with water (2 x 20 mL) and brine (20 mL). The organic phase was dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with a gradient EtOAc/petroleum ether (0 - 10% EtOAc) to afford 3,6-dichloro-4-cyclopropyl-5-vinylpyridazine (700 mg, 27% yield, 3.25 mmol) as a yellow solid. MS m/z 215.0 $[M+H]^+$.

Step 3: To a sealed tube were added 3,6-dichloro-4-cyclopropyl-5-vinylpyridazine (700 mg, 3.22 mmol), *tert*-butyl (*R*)-3-aminopiperidine-1-carboxylate (4.73 g, 1.84 mmol), acetonitrile (10 mL) and diisopropylethyl amine (1.68 mL, 9.66 mmol). The resulting solution was heated at 110°C under N₂ for 16 h. TLC (30% EtOAc in petroleum ether) showed the starting material was completely consumed. The reaction mixture was allowed to cool to room temperature, then concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with a gradient EtOAc/petroleum ether (0 - 30% EtOAc) to afford *tert*-butyl (*R*)-3-(3-chloro-4-cyclopropyl-5,6-dihydro-7*H*-pyrrolo[2,3-*c*]pyridazin-7-yl)piperidine-1-carboxylate (1.1 g, 90% yield, 2.90 mmol) as a white solid. MS m/z 379.3 $[M+H]^+$; ¹H NMR (400 MHz, CDCl₃) δ : 4.16 – 3.88 (m, 3H), 3.66 – 3.52 (m, 2H), 3.05 (t, *J* = 8.0 Hz, 3H), 2.84 – 2.68 (m, 1H), 1.98 – 1.88 (m, 1H), 1.85 – 1.80 (m, 1H), 1.80 – 1.68 (m, 2H), 1.66 – 1.54 (m, 1H), 1.45 (s, 9H), 1.08 – 1.00 (m, 2H), 0.82 – 0.72 (m, 2H).

Step 4: To a screw top vial were added *tert*-butyl (*R*)-3-(3-chloro-4-cyclopropyl-5,6-dihydro-7*H*-pyrrolo[2,3-*c*]pyridazin-7-yl)piperidine-1-carboxylate (165 mg, 0.44 mmol), 2-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (175 mg, 0.5 mmol), and XPhos Pd G3 (38 mg, 0.04 mmol). The tube was degassed with Ar for 15 min and 1,4-dioxane (1 mL) and potassium carbonate (2M aqueous solution, 0.66 mL, 1.32 mmol) were added then. The resulting mixture was heated to 90 °C for 2 h. Upon completion, the reaction mixture was loaded directly onto precolumn and purified via flash chromatography eluting with a gradient of CH₂Cl₂/MeOH/NH₄OH (0-30% MeOH/NH₄OH) to afford *tert*-butyl (*R*)-3-(4-cyclopropyl-3-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-5,6-dihydro-7*H*-pyrrolo[2,3-*c*]pyridazin-7-yl)piperidine-1-carboxylate (155 mg, 64% yield) as a yellow oil. MS m/z 549.3 $[M+H]^+$.

Step 5: A solution of *tert*-butyl (*R*)-3-(4-cyclopropyl-3-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-5,6-dihydro-7*H*-pyrrolo[2,3-*c*]pyridazin-7-yl)piperidine-1-carboxylate

(155 mg, 0.3 mmol) in trifluoroacetic acid (0.5 mL) was stirred for 3 hours at room temperature. Upon completion, trifluoroacetic acid was evaporated by blowing air and the crude material was taken to the next step without further purification. MS m/z 405.3 $[M+H]^+$.

Step 6: The crude residue from step 5 was dissolved in CH_2Cl_2 (1.5 mL) and MeOH (0.5 mL),

- 5 and triethylamine (276 μ L, 1.98 mmol) was added then. The mixture was stirred for 5 minutes, then cooled to 0 °C and sodium triacetoxyborohydride (254 mg, 1.2 mmol) and formaldehyde (37 % in water, 80 μ L, 1.2 mmol) were added. The solution was stirred for 5 minutes at 0 °C before being quenched with sodium bicarbonate (10 mL) and extracted with CH_2Cl_2 . The combined organic phases were washed with water, brine, dried over sodium sulfate, filtered, and
- 10 concentrated under reduced pressure. The residue was purified via flash eluting with a gradient CH_2Cl_2 /MeOH/ NH_4OH (0-30% MeOH/ NH_4OH) to afford (R)-2-(4-cyclopropyl-7-(1-methylpiperidin-3-yl)-6,7-dihydro-5H-pyrrolo[2,3-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol (85 mg, 71% yield over two steps). MS m/z 419.5 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 7.43 (d, J = 7.9 Hz, 1H), 7.25 – 7.18 (m, 1H), 7.14 (d, J = 1.8 Hz, 1H), 4.21 (tt, J = 11.2, 4.1 Hz, 1H), 3.75 – 3.62 (m, 2H), 3.22 – 3.12 (m, 2H), 3.12 – 3.02 (m, 1H), 2.88 (d, J = 11.9 Hz, 1H), 2.36 (s, 3H), 2.31 (d, J = 8.4 Hz, 1H), 2.07 (s, 1H), 1.97 – 1.89 (m, 1H), 1.83 (tdd, J = 14.6, 7.7, 4.7 Hz, 2H), 1.77 – 1.69 (m, 1H), 1.63 (qd, J = 12.0, 3.9 Hz, 1H), 0.69 (dt, J = 9.4, 3.1 Hz, 2H), 0.48 (td, J = 6.0, 4.3 Hz, 2H); 1H not observed (OH).

- 20 Using the procedure described for Example 1, above, additional compounds described herein may be prepared by substituting the appropriate starting material, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cmpd #	Spectral Data
I-1	See example 1. MS m/z 419.5 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 7.43 (d, J = 7.9 Hz, 1H), 7.25 – 7.18 (m, 1H), 7.14 (d, J = 1.8 Hz, 1H), 4.21 (tt, J = 11.2, 4.1 Hz, 1H), 3.75 – 3.62 (m, 2H), 3.22 – 3.12 (m, 2H), 3.12 – 3.02 (m, 1H), 2.88 (d, J = 11.9 Hz, 1H), 2.36 (s, 3H), 2.31 (d, J = 8.4 Hz, 1H), 2.07 (s, 1H), 1.97 – 1.89 (m, 1H), 1.83 (tdd, J = 14.6, 7.7, 4.7 Hz, 2H), 1.77 – 1.69 (m, 1H), 1.63 (qd, J = 12.0, 3.9 Hz, 1H), 0.69 (dt, J = 9.4, 3.1 Hz, 2H), 0.48 (td, J = 6.0, 4.3 Hz, 2H); 1H not observed (OH).

Cmpd #	Spectral Data
I-2	MS m/z 365.1 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 7.14 (s, 1H), 6.74 (d, J = 13.3 Hz, 2H), 4.21 (m, 1H), 3.67 (q, J = 8.1 Hz, 2H), 3.14 (t, J = 12.5 Hz, 3H), 2.93 (d, J = 11.4 Hz, 1H), 2.48 (m, 1H), 2.43 (s, 3H), 2.32 (s, 3H), 2.23 (m, 1H), 1.97 – 1.61 (m, 5H), 0.70 (d, J = 8.3 Hz, 2H), 0.50 (d, J = 5.6 Hz, 2H); 1H not observed (OH).
I-3	MS m/z 421.4 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 7.56 (d, J = 7.8 Hz, 1H), 7.36 (d, J = 7.4 Hz, 1H), 7.28 (s, 1H), 4.41 (s, 1H), 4.06 – 3.84 (m, 2H), 3.66 (s, 3H), 3.58 (dd, J = 16.4, 9.2 Hz, 2H), 3.09 – 3.00 (m, 1H), 2.96 (s, 3H), 2.83 (dt, J = 14.1, 7.0 Hz, 1H), 2.14 (d, J = 13.2 Hz, 2H), 1.98 (d, J = 11.0 Hz, 2H), 1.37 – 1.10 (m, 6H); 1H not observed (OH).
I-4	MS m/z 365.4 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 7.05 (d, J = 7.8 Hz, 1H), 6.66 (d, J = 7.9 Hz, 1H), 6.60 (s, 1H), 4.21 (ddt, J = 10.7, 8.3, 4.1 Hz, 1H), 3.69 (h, J = 8.9 Hz, 2H), 3.16 – 3.00 (m, 3H), 2.91 (d, J = 11.8 Hz, 1H), 2.45 (m, 1H), 2.40 (s, 3H), 2.20 (t, J = 11.5 Hz, 1H), 2.03 (s, 3H), 1.99 – 1.83 (m, 2H), 1.83 – 1.64 (m, 2H), 1.36 (d, J = 6.5 Hz, 1H), 1.03 – 0.88 (m, 2H), 0.69 (dd, J = 6.2, 4.5 Hz, 2H); 1H not observed (OH).
I-5	MS m/z 393.3 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 7.39 (d, J = 7.9 Hz, 1H), 7.23 (d, J = 7.9 Hz, 1H), 7.17 (s, 1H), 4.22 (d, J = 11.3 Hz, 1H), 3.75 (p, J = 8.5 Hz, 2H), 3.10 (t, J = 8.0 Hz, 3H), 2.91 (d, J = 11.5 Hz, 1H), 2.39 (s, 3H), 2.12 (m, 1H), 2.05 (s, 3H), 2.00 – 1.79 (m, 2H), 1.82 – 1.57 (m, 2H), 1.42 – 1.25 (m, 1H); 1H not observed (OH).
I-6	MS m/z 433.5 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 7.07 (s, 1H), 6.97 (s, 1H), 4.23 (tt, J = 11.3, 4.1 Hz, 1H), 3.73 – 3.60 (m, 2H), 3.15 (t, J = 8.2 Hz, 2H), 3.09 – 2.98 (m, 1H), 2.82 (dd, J = 9.2, 6.0 Hz, 1H), 2.31 (s, 3H), 2.09 (s, 3H), 2.01 – 1.89 (m, 2H), 1.83 (dt, J = 13.5, 3.7 Hz, 1H), 1.74 (qt, J = 12.7, 3.8 Hz, 1H), 1.69 – 1.49 (m, 3H), 0.77 (tt, J = 10.3, 5.1 Hz, 1H), 0.70 (tdd, J = 8.8, 6.1, 4.6 Hz, 1H), 0.61 (tdd, J = 9.0, 6.1, 4.5 Hz, 1H), 0.56 – 0.41 (m, 1H); 1H not observed (OH).
I-7	MS m/z 383.3 $[M+H]^+$; ^1H NMR (500 MHz, DMSO- d_6) δ : 6.69 (d, J = 10.0 Hz, 2H), 4.22 (s, 1H), 3.82 – 3.68 (m, 2H), 3.45 (s, 2H), 3.31 (t, J = 7.9 Hz, 2H), 3.17 (s, 1H), 2.89 (s, 1H), 2.83 (s, 3H), 2.32 (s, 3H), 2.08 – 1.87 (m, 2H), 1.76 (d, J = 10.3 Hz, 2H), 1.63 (p, J = 7.3 Hz, 1H), 0.75 (t, J = 6.9 Hz, 3H), 0.62 (m, 1H); 1H not observed (OH).
I-8	MS m/z 447.2 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 7.62 (d, J = 7.9 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.29 (s, 1H), 4.45 – 4.33 (m, 1H), 4.06 – 3.90 (m, 2H), 3.76 – 3.66 (m, 4H), 3.64 – 3.49 (m, 3H), 3.29 – 3.18 (m, 2H), 3.03 – 2.87 (m, 1H), 2.23 – 2.07 (m, 2H), 2.07 – 1.91 (m, 2H), 1.40 (t, J = 7.3 Hz, 3H), 1.31 (s, 3H), 0.73 (d, J = 4.7 Hz, 2H); 1H not observed (OH).
I-9	MS m/z 447.4 $[M+H]^+$; ^1H NMR (500 MHz, DMSO- d_6) δ : 10.31 (bs, 1H), 7.31 (d, J = 7.7 Hz, 1H), 7.24 – 7.08 (m, 2H), 4.08 (m, 1H), 3.67 – 3.44 (m, 3H), 3.13 (d, J = 8.4 Hz, 2H), 2.99 – 2.88 (m, 1H), 2.83 (d, J = 11.0 Hz, 1H), 2.38 (m, 2H), 2.07 (m, 1H), 1.96 (q, J = 10.1 Hz, 2H), 1.87 (m, 1H), 1.73 (tt, J = 17.3, 9.2 Hz, 4H), 1.56 (t, J = 9.7 Hz, 3H), 1.01 (t, J = 7.2 Hz, 3H); 1H not observed.
I-10	MS m/z 483.4 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 7.40 (d, J = 7.9 Hz, 1H), 7.25 (d, J = 7.8 Hz, 1H), 7.16 (s, 1H), 4.29 (s, 1H), 3.73 (hept, J = 6.4 Hz, 3H), 3.58 – 3.38 (m, 2H), 3.24 (p, J = 7.8 Hz, 4H), 2.97 (s, 2H), 2.68 – 2.57 (m, 2H), 2.51 (qd, J = 11.0, 6.9 Hz, 2H), 2.08 – 1.94 (m, 2H), 1.88 (q, J = 12.1 Hz, 2H), 1.29 (q, J = 7.2 Hz, 3H); 1H not observed (OH).

Cmpd #	Spectral Data
I-11	MS m/z 433.4 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 7.35 (s, 1H), 7.27 – 6.95 (m, 2H), 4.23 (m, 1H), 3.72 (m, 3H), 3.49 (m, 1H), 3.36 (m, 1H), 3.31 (m, 4H), 3.01 (s, 3H), 2.86 (m, 3H), 2.66 (m, 1H), 2.18 – 1.58 (m, 6H); 1H not observed (OH).
I-12	MS m/z 451.4 $[M+H]^+$; ^1H NMR (500 MHz, DMSO- d_6) δ : 10.36 (s, 1H), 7.32 (d, J = 7.7 Hz, 1H), 7.27 – 7.05 (m, 2H), 5.09 – 4.88 (m, 1H), 4.41 (m, 1H), 3.73 – 3.44 (m, 3H), 3.21 – 3.02 (m, 2H), 3.02 – 2.71 (m, 2H), 2.45 (m, 1H), 2.22 (d, J = 9.1 Hz, 4H), 2.11 – 1.83 (m, 4H), 1.83 – 1.66 (m, 2H), 1.66 – 1.48 (m, 1H); 1H not observed (OH).
I-13	MS m/z 391.4 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 7.48 – 7.05 (m, 1H), 6.93 – 6.39 (m, 2H), 4.71 – 4.40 (m, 1H), 3.84 – 3.64 (m, 2H), 3.62 – 3.47 (m, 1H), 3.29 – 3.09 (m, 3H), 3.04 – 2.83 (m, 1H), 2.68 (s, 3H), 2.13 – 1.64 (m, 6H), 1.52 – 1.22 (m, 1H), 1.12 – 0.93 (m, 2H), 0.87 – 0.69 (m, 4H), 0.68 – 0.44 (m, 2H); 1H not observed (OH).
I-14	MS m/z 381.4 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.51 (s, 1H) formic acid peak, 7.21 – 7.16 (m, 1H), 6.60 – 6.51 (m, 2H), 4.83 – 4.67 (m, 1H), 3.83 (s, 3H), 3.77 – 3.68 (m, 2H), 3.62 – 3.48 (m, 1H), 3.30 – 3.04 (m, 4H), 2.97 – 2.80 (m, 1H), 2.61 (s, 3H), 2.25 – 1.59 (m, 5H), 0.90 – 0.71 (m, 2H), 0.69 – 0.51 (m, 2H); 1H not observed (OH).
I-15	MS m/z 385.3, 387.3 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.44 (s, 1H) formic acid peak, 7.23 (s, 1H), 7.06 – 6.79 (m, 2H), 4.60 – 4.28 (m, 1H), 4.09 – 3.62 (m, 2H), 3.66 – 3.50 (m, 1H), 3.32 – 3.28 (m, 2H), 3.27 – 3.15 (m, 2H), 3.10 – 2.97 (m, 1H), 2.83 (s, 3H), 2.12 – 1.65 (m, 5H), 1.03 – 0.66 (m, 2H), 0.65 – 0.41 (m, 2H); 1H not observed (OH).
I-16	MS m/z 339.4 $[M+H]^+$.
I-17	MS m/z 393.5 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 7.70 (s, 1H), 7.23 – 7.13 (m, 1H), 7.08 (d, J = 1.6 Hz, 1H), 4.35 (d, J = 4.3 Hz, 1H), 3.94 (dq, J = 16.6, 8.4 Hz, 2H), 3.65 (d, J = 11.7 Hz, 1H), 3.55 (d, J = 12.4 Hz, 1H), 3.43 (t, J = 7.9 Hz, 2H), 3.25 (t, J = 11.5 Hz, 1H), 2.95 (m, 4H), 2.26 (s, 3H), 2.13 (d, J = 9.9 Hz, 2H), 1.98 – 1.84 (m, 2H); 1H not observed (OH).
I-18	MS m/z 379.3 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 7.71 (d, J = 10.5 Hz, 1H), 7.21 (s, 1H), 7.11 (s, 1H), 4.17 – 3.36 (m, 7H), 3.06 (s, 3H), 2.52 (s, 2H), 2.29 (s, 3H), 2.24 – 2.08 (m, 1H), 2.03 (m, 1H); 1H not observed (OH).
I-19	MS m/z 393.5 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 7.64 (d, J = 1.9 Hz, 1H), 7.18 (s, 1H), 7.08 (d, J = 1.7 Hz, 1H), 4.24 (p, J = 8.4 Hz, 1H), 3.96 (t, J = 7.9 Hz, 2H), 3.68 (d, J = 12.5 Hz, 2H), 3.42 (td, J = 7.9, 1.9 Hz, 2H), 3.21 (q, J = 9.8 Hz, 2H), 2.93 (s, 3H), 2.27 (s, 3H), 2.26 – 2.17 (m, 4H); 1H not observed (OH).
I-20	MS m/z 407.3 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 7.80 (s, 1H), 7.21 (s, 1H), 7.11 (s, 1H), 4.46 – 4.34 (m, 1H), 4.20 – 4.04 (m, 1H), 3.82 – 3.61 (m, 2H), 3.63 – 3.46 (m, 2H), 3.26 (d, J = 16.3 Hz, 1H), 3.02 (m, 1H), 2.98 (s, 3H), 2.29 (s, 3H), 2.18 (d, J = 13.2 Hz, 2H), 2.04 – 1.90 (m, 2H), 1.50 (dd, J = 7.2, 3.4 Hz, 3H); 1H not observed (OH).
I-21	MS m/z 377.3, 379.3 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 6.94 – 6.52 (m, 2H), 4.39 – 4.06 (m, 1H), 3.91 – 3.62 (m, 2H), 3.37 (d, J = 15.8 Hz, 2H), 3.28 – 2.87 (m, 4H), 2.83 – 2.51 (m, 4H), 2.24 – 1.93 (m, 4H), 1.93 – 1.63 (m, 2H); 1H not observed (OH).
I-22	MS m/z 359.3, 361.3 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 7.15 (t, J = 7.2 Hz, 1H), 6.97 – 6.81 (m, 2H), 4.19 (tt, J = 11.1, 4.2 Hz, 1H), 3.70 (dq, J = 23.2, 8.7 Hz, 2H), 3.04 (q, J = 9.7 Hz, 3H), 2.84 (d, J = 10.9 Hz, 1H), 2.32 (s, 3H), 2.26 (q, J = 9.9 Hz, 1H), 2.05–1.96 (m, 4H), 1.96 – 1.87 (m, 1H), 1.83 (dt, J = 13.7, 3.5 Hz, 1H), 1.74 (qt, J = 12.6, 3.9 Hz, 1H), 1.62 (qd, J = 12.1, 4.3 Hz, 1H); 1H not observed (OH).

Cmpd #	Spectral Data
I-23	MS m/z 407.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, methanol-d ₄) δ : 7.10 (s, 1H), 7.00 (s, 1H), 4.38 – 4.12 (m, 1H), 3.75 (t, J = 8.2 Hz, 2H), 3.25 – 3.02 (m, 3H), 3.02 – 2.77 (m, 1H), 2.66 (s, 4H), 2.07 (s, 3H), 2.03 – 1.90 (m, 6H), 1.90 – 1.79 (m, 2H); 1H not observed (OH).
I-24	MS m/z 449.3 [M+H] ⁺ ; ¹ H NMR (500 MHz, methanol-d ₄) δ : 7.44 (d, J = 7.9 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.15 (s, 1H), 4.21 (tt, J = 10.8, 4.0 Hz, 1H), 3.78 – 3.61 (m, 4H), 3.16 (t, J = 7.9 Hz, 3H), 3.06 – 2.92 (m, 1H), 2.67 (dp, J = 26.4, 6.3 Hz, 2H), 2.40 (t, J = 10.7 Hz, 1H), 2.29 – 2.14 (m, 1H), 1.98 – 1.89 (m, 1H), 1.88 – 1.62 (m, 4H), 0.78 – 0.59 (m, 2H), 0.47 (dt, J = 6.0, 3.0 Hz, 2H); 2 Hs not observed (2 OHs).
I-25	MS m/z : 406.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, methanol-d ₄) δ : 7.44 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.15 (s, 1H), 4.31 – 4.19 (m, 1H), 3.74 (t, J = 8.0 Hz, 2H), 3.19 (t, J = 8.0 Hz, 2H), 2.45 – 2.34 (m, 4H), 1.85 – 1.76 (m, 1H), 1.41 (s, 3H), 0.75 – 0.67 (m, 2H), 0.53 – 0.46 (m, 2H); 2 Hs not observed (2 OHs).
I-26	MS m/z : 406.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, methanol-d ₄) δ : 7.44 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.15 (s, 1H), 4.18 – 4.09 (m, 1H), 4.00 – 3.94 (m, 1H), 3.90 – 3.83 (m, 1H), 3.81 – 3.72 (m, 1H), 3.72 – 3.63 (m, 1H), 3.58 (t, J = 10.4 Hz, 1H), 3.49 – 3.39 (m, 1H), 3.19 – 3.13 (m, 2H), 2.06 – 1.98 (m, 1H), 1.97 – 1.88 (m, 1H), 1.84 – 1.73 (m, 3H), 0.74 – 0.66 (m, 2H), 0.50 – 0.44 (m, 2H); 1H not observed (OH).
I-27	MS m/z 423.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, methanol-d ₄) δ : 6.88 – 6.75 (m, 2H), 4.21 (ddt, J = 11.3, 8.5, 4.1 Hz, 1H), 3.76 (s, 3H), 3.70 (dd, J = 10.7, 7.0 Hz, 2H), 3.06 (t, J = 6.3 Hz, 3H), 2.86 (d, J = 11.6 Hz, 1H), 2.39 – 2.25 (m, 5H), 2.09 – 1.98 (m, 1H), 1.98 – 1.81 (m, 6H); 1H not observed (OH).
I-28	MS m/z : 392.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, methanol-d ₄) δ : 7.43 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.15 (s, 1H), 4.83 – 4.75 (m, 1H), 4.09 – 3.93 (m, 2H), 3.92 – 3.76 (m, 2H), 3.75 – 3.63 (m, 2H), 3.25 – 3.10 (m, 2H), 2.37 – 2.25 (m, 1H), 2.17 – 2.06 (m, 1H), 1.87 – 1.76 (m, 1H), 0.76 – 0.65 (m, 2H), 0.56 – 0.44 (m, 2H); 1H not observed (OH).
I-29	MS m/z : 420.5 [M+H] ⁺ ; ¹ H NMR (400 MHz, methanol-d ₄) δ : 7.45 (d, J = 7.6 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.14 (s, 1H), 3.94 – 3.86 (m, 1H), 3.80 – 3.63 (m, 3H), 3.19 (t, J = 8.0 Hz, 2H), 2.13 – 2.06 (m, 1H), 1.86 – 1.74 (m, 4H), 1.66 – 1.54 (m, 1H), 1.48 – 1.31 (m, 3H), 0.76 – 0.67 (m, 2H), 0.51 – 0.42 (m, 2H); 2Hs not observed (2 OHs).
I-30	MS m/z : 388.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, methanol-d ₄) δ : 7.48 (d, J = 7.9 Hz, 1H), 7.31 (d, J = 2.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.18 (s, 1H), 5.88 (d, J = 2.0 Hz, 1H), 4.54 – 4.42 (m, 2H), 3.62 – 3.52 (m, 2H), 2.14 – 1.97 (m, 1H), 0.85 – 0.68 (m, 2H), 0.33 – 0.18 (m, 2H); 2Hs not observed (NH and OH).
I-31	MS m/z : 442.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, methanol-d ₄) δ : 7.46 (d, J = 8.0 Hz, 1H), 7.24 – 7.09 (m, 3H), 6.88 (d, J = 8.0 Hz, 1H), 6.84 (s, 1H), 6.70 (d, J = 8.0 Hz, 1H), 5.51 (q, J = 6.8 Hz, 1H), 3.72 – 3.60 (m, 1H), 3.38 – 3.32 (m, 1H), 3.21 – 3.04 (m, 2H), 1.85 – 1.76 (m, 1H), 1.60 (d, J = 6.8 Hz, 3H), 0.77 – 0.63 (m, 2H), 0.57 – 0.37 (m, 2H); 2Hs not observed (2 OHs).
I-32	MS m/z : 420.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, methanol-d ₄) δ : 7.45 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.14 (s, 1H), 4.30 (s, 1H), 4.01 (dd, J = 16.8, 9.2 Hz, 1H), 3.97 – 3.88 (m, 1H), 3.78 (dd, J = 16.8, 9.2 Hz, 1H), 3.16 (t, J = 8.8 Hz, 2H), 2.21 – 2.01 (m, 1H), 1.94 – 1.75 (m, 3H), 1.74 – 1.57 (m, 3H), 1.56 – 1.38 (m, 2H), 0.79 – 0.61 (m, 2H), 0.54 – 0.37 (m, 2H); 2Hs not observed (2 OHs).

Cmpd #	Spectral Data
I-33	MS m/z : 420.0 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 7.45 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.15 (s, 1H), 4.13 - 4.00 (m, 1H), 3.75 - 3.62 (m, 3H), 3.17 (t, J = 8.0 Hz, 2H), 2.15 - 2.08 (m, 1H), 2.02 - 1.92 (m, 1H), 1.90 - 1.75 (m, 3H), 1.55 - 1.37 (m, 3H), 1.25 - 1.10 (m, 1H), 0.75 - 0.63 (m, 2H), 0.54 - 0.44 (m, 2H); 2Hs not observed (2 OHs).
I-34	MS m/z : 379.3 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.61 (s, 1H) (formic acid peak), 7.17 (d, J = 7.6 Hz, 1H), 6.89 - 6.83 (m, 2H), 4.96 - 4.87 (m, 1H), 3.77 - 3.66 (m, 2H), 3.60 - 3.52 (m, 1H), 3.27 - 3.05 (m, 3H), 3.05 - 2.96 (m, 1H), 2.87 - 2.78 (m, 1H), 2.81 - 2.60 (m, 2H), 2.48 (s, 3H), 2.11 - 1.67 (m, 5H), 1.28 (t, J = 7.6 Hz, 3H), 0.79 - 0.70 (m, 2H), 0.69 - 0.60 (m, 2H); 1H not observed (OH).
I-35	MS m/z : 391.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ : 10.40 (s, 1H), 7.22 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 4.08 - 4.02 (m, 1H), 3.64 - 3.50 (m, 2H), 3.07 (t, J = 8.0 Hz, 2H), 2.90 - 2.81 (m, 5H), 2.71 (d, J = 11.6 Hz, 1H), 2.20 (s, 3H), 2.07 - 1.99 (m, 3H), 1.86 - 1.70 (m, 4H), 1.62 - 1.45 (m, 2H), 0.74 - 0.69 (m, 2H), 0.48 - 0.44 (m, 2H).
I-36	MS m/z : 393.1 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 7.07 (s, 1H), 7.03 (s, 1H), 6.95 (s, 1H), 4.29 - 4.19 (m, 1H), 3.78 - 3.63 (m, 2H), 3.15 - 3.03 (m, 3H), 2.84 (d, J = 11.2 Hz, 1H), 2.37 (s, 3H), 2.33 (s, 3H), 2.26 (t, J = 10.8 Hz, 1H), 2.08 - 1.90 (m, 2H), 1.88 - 1.56 (m, 3H); 1H not observed (OH).
I-37	MS m/z : 393.1 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 7.19 (d, J = 8.0 Hz, 1H), 6.34 (d, J = 8.4 Hz, 1H), 4.59 (t, J = 8.8 Hz, 2H), 4.19 - 4.12 (m, 1H), 3.71 - 3.60 (m, 2H), 3.18 - 3.12 (m, 4H), 3.02 - 2.99 (m, 1H), 2.83 (d, J = 10.8 Hz, 1H), 2.33 (s, 3H), 2.22 (t, J = 10.8 Hz, 1H), 2.02 - 1.96 (m, 1H), 1.95 - 1.84 (m, 2H), 1.84 - 1.79 (m, 1H), 1.79 - 1.66 (m, 1H), 1.64 - 1.520 (m, 1H), 0.84 - 0.73 (m, 2H), 0.48 - 0.44 (m, 2H); 1H not observed (OH).
I-38	MS m/z : 409.1 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 7.79 (t, J = 1.6 Hz, 1H), 6.83 - 6.80 (m, 1H), 6.78 - 6.76 (m, 1H), 4.24 - 4.12 (m, 1H), 3.88 (s, 3H), 3.78 - 3.63 (m, 2H), 3.17 - 3.08 (m, 2H), 3.06 - 2.98 (m, 1H), 2.86 - 2.78 (m, 1H), 2.31 (s, 3H), 2.22 (t, J = 10.8 Hz, 1H), 2.04 - 1.96 (m, 1H), 1.95 - 1.88 (m, 1H), 1.87 - 1.79 (m, 1H), 1.79 - 1.68 (m, 1H), 1.66 - 1.54 (m, 1H); 1H not observed (OH).
I-39	MS m/z : 407.3 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.50 (brs, 1H, formic acid), 7.15-7.26 (m, 1H), 7.11 (s, 1H), 7.02 (s, 1H), 4.14-4.26 (m, 1H), 3.89-4.11 (m, 1H), 3.77-3.91 (m, 1H), 3.39-3.55 (m, 3H), 2.74-2.91 (m, 4H), 2.26-2.44 (m, 1H), 2.20 (s, 3H), 1.99-2.14 (m, 2H), 1.80-1.98 (m, 2H), 1.38-1.50 (m, 3H); 1H not observed (OH).
I-40	MS m/z : 407.3 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.52 (brs, 1H, formic acid), 7.08-7.23 (m, 2H), 6.99 (s, 1H), 4.11-4.27 (m, 1H), 3.87-4.10 (m, 1H), 3.68-3.84 (m, 1H), 3.38-3.54 (m, 2H), 3.17-3.30 (m, 2H), 2.71-2.93 (m, 4H), 2.41 (s, 3H), 2.24-2.37 (m, 1H), 1.99-2.17 (m, 2H), 1.80-1.97 (m, 1H), 1.40-1.49 (m, 3H); 1H not observed (OH).
I-41	MS m/z : 471.8 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 8.11 (s, 1H), 8.05 (d, J = 7.9 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 4.32 - 4.15 (m, 1H), 3.71 (h, J = 8.9 Hz, 2H), 3.20 (q, J = 11.2 Hz, 3H), 3.13 (s, 1H), 2.96 (d, J = 11.8 Hz, 1H), 2.44 (s, 3H), 2.32 - 2.13 (m, 1H), 1.90 (d, J = 21.9 Hz, 2H), 1.74 (dq, J = 21.2, 11.7 Hz, 2H), 1.44 (p, J = 7.3 Hz, 1H), 0.68 (dd, J = 17.3, 6.8 Hz, 4H).

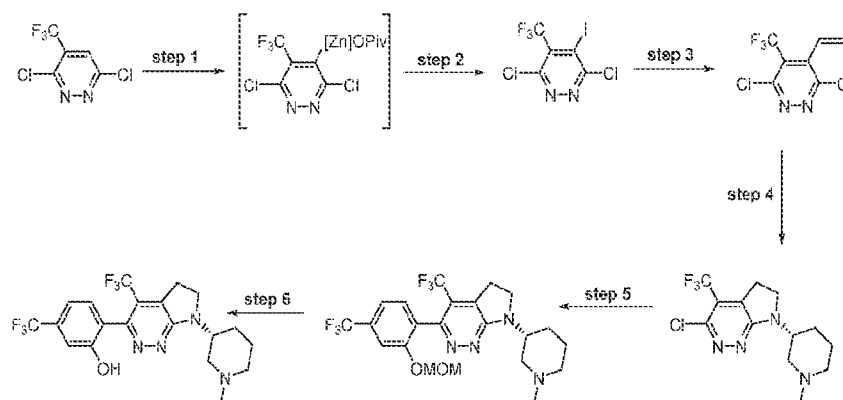
Cmpd #	Spectral Data
I-42	MS m/z 483.2 $[M+H]^+$; ^1H NMR (500 MHz, MeOD) δ 7.73 – 7.64 (m, 1H), 7.64 – 7.59 (m, 1H), 7.58 (s, 1H), 6.91 (t, J = 73.4 Hz, 1H), 4.24 (tt, J = 10.9, 4.1 Hz, 1H), 3.76 (dq, J = 19.4, 8.7 Hz, 2H), 3.28 – 3.21 (m, 2H), 3.21 – 3.10 (m, 1H), 2.97 (d, J = 11.8 Hz, 1H), 2.58 – 2.48 (m, 1H), 2.46 (s, 3H), 2.30 – 2.12 (m, 1H), 2.00 – 1.84 (m, 2H), 1.84 – 1.64 (m, 2H), 1.24 (s, 3H), 0.65 – 0.51 (m, 2H), 0.51 – 0.36 (m, 2H). NH peak not observed.
I-43	MS m/z 383.1 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ 8.48 (s, 1H), 7.69 (d, J = 2.3 Hz, 1H), 7.13 (d, J = 2.9 Hz, 2H), 7.01 (d, J = 2.1 Hz, 1H), 5.02 (d, J = 48.5 Hz, 1H), 4.58 – 4.45 (m, 1H), 3.83 – 3.61 (m, 2H), 3.32 – 3.05 (m, 3H), 2.59 – 2.48 (m, 1H), 2.45 – 2.31 (m, 4H), 2.27 – 1.97 (m, 6H). 1H not observed (OH).
I-44	MS m/z 383.2 $[M+H]^+$; ^1H NMR (500 MHz, MeOD) δ : 7.74 – 7.61 (m, 1H), 7.13 (s, 2H), 7.06 – 6.91 (m, 1H), 5.13 (d, J = 50.6 Hz, 1H), 4.45 (dd, J = 32.9, 11.3 Hz, 1H), 4.01 – 3.87 (m, 1H), 3.81 (d, J = 8.9 Hz, 1H), 3.17 – 3.04 (m, 2H), 3.00 (d, J = 8.9 Hz, 1H), 2.87 – 2.73 (m, 2H), 2.45 (s, 3H), 2.17 – 2.03 (m, 3H), 1.96 (s, 3H). OH peak not observed.
I-45	MS m/z 352.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ : 10.34 (s, 1H), 7.94 – 7.80 (m, 1H), 7.17 – 7.00 (m, 3H), 4.21 (h, J = 8.0 Hz, 1H), 3.62 (t, J = 8.2 Hz, 2H), 3.01 (t, J = 8.2 Hz, 2H), 2.29 (d, J = 9.8 Hz, 2H), 2.27 – 2.17 (m, 2H), 1.98 (s, 3H), 1.31 (s, 3H). One OH peak buried under solvent water peak.
I-46	MS m/z 409.2 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ 7.69 (d, J = 1.9 Hz, 1H), 7.24 (d, J = 8.5 Hz, 1H), 7.18 – 7.07 (m, 1H), 7.00 (d, J = 1.6 Hz, 1H), 5.04 (d, J = 47.2 Hz, 1H), 4.59 – 4.47 (m, 1H), 3.77 – 3.63 (m, 2H), 3.27 – 3.16 (m, 3H), 3.15 – 3.10 (m, 1H), 2.63 – 2.63 (m, 5H), 2.31 – 2.20 (m, 1H), 2.18 – 1.98 (m, 1H), 1.92 – 1.76 (m, 1H), 0.78 – 0.62 (m, 2H), 0.53 – 0.45 (m, 2H). 1H not observed (OH)
I-47	MS m/z 385.2 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ 6.99 (d, J = 8.1 Hz, 1H), 6.37 (d, J = 8.3 Hz, 1H), 5.00 (d, J = 46.9 Hz, 1H), 4.60 (t, J = 9.13 Hz, 2H), 4.54 – 4.43 (m, 1H), 3.79 – 3.65 (m, 2H), 3.23 – 3.05 (m, 6H), 2.53 – 2.46 (m, 1H), 2.41 (s, 3H), 2.36 – 1.92 (m, 6H). 1H not observed (OH)
I-48	MS m/z 411.2 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ 7.15 (d, J = 8.3 Hz, 1H), 6.36 (d, J = 8.3 Hz, 1H), 5.00 (d, J = 46.8 Hz, 1H), 4.60 (t, J = 8.7 Hz, 2H), 4.54 – 4.43 (m, 1H), 3.75 – 3.60 (m, 2H), 3.23 – 3.04 (m, 6H), 2.47 (t, J = 10.9 Hz, 1H), 2.39 (s, 3H), 2.35 – 1.93 (m, 3H), 1.92 – 1.82 (m, 1H), 0.83 – 0.74 (m, 2H), 0.54 – 0.43 (m, 2H). 1H not observed (OH)
I-49	MS m/z : 367.1 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 6.99 (d, J = 8.4 Hz, 1H), 6.36 (d, J = 8.4 Hz, 1H), 4.59 (t, J = 8.4 Hz, 2H), 4.25 – 4.12 (m, 1H), 3.77 – 3.62 (m, 2H), 3.17 (t, J = 8.8 Hz, 2H), 3.09 – 2.97 (m, 3H), 2.85 (d, J = 11.6 Hz, 1H), 2.34 (s, 3H), 2.29 (t, J = 10.8 Hz, 1H), 2.08 (s, 3H), 2.06 – 1.98 (m, 1H), 1.97 – 1.88 (m, 1H), 1.87 – 1.79 (m, 1H), 1.78 – 1.68 (m, 1H), 1.67 – 1.52 (m, 1H). 1H not observed (OH)
I-50	MS m/z : 365.1 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 7.68 (d, J = 2.4 Hz, 1H), 7.17 – 7.07 (m, 2H), 6.99 (d, J = 1.6 Hz, 1H), 4.28 – 4.15 (m, 1H), 3.80 – 3.65 (m, 2H), 3.20 – 3.03 (m, 3H), 2.93 (d, J = 11.2 Hz, 1H), 2.52 – 2.44 (m, 1H), 2.42 (s, 3H), 2.28 – 2.13 (m, 1H), 2.06 (s, 3H), 1.99 – 1.84 (m, 2H), 1.82 – 1.63 (m, 2H). 1H not observed (OH)

Cmpd #	Spectral Data
I-51	MS m/z 366.1 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 7.69 (d, J = 2.3 Hz, 1H), 7.19 – 7.08 (m, 2H), 7.01 (dd, J = 2.3, 0.9 Hz, 1H), 3.92 (ddd, J = 11.9, 10.0, 4.0 Hz, 1H), 3.87 – 3.66 (m, 3H), 3.16 – 3.08 (m, 2H), 2.16 – 2.09 (m, 1H), 2.08 (s, 3H), 1.87 (dd, J = 12.3, 3.7 Hz, 1H), 1.83 – 1.76 (m, 2H), 1.69 – 1.56 (m, 1H), 1.52 – 1.39 (m, 2H), 1.43 – 1.29 (m, 1H). 2 OH peaks not observed.
I-52	MS m/z 368.2 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 7.86 (d, J = 3.5 Hz, 1H), 7.70 (d, J = 2.3 Hz, 1H), 7.24 – 7.13 (m, 2H), 7.03 (dd, J = 2.3, 0.9 Hz, 1H), 6.68 (d, J = 3.5 Hz, 1H), 4.68 (td, J = 10.1, 6.1 Hz, 1H), 4.19 (dq, J = 10.0, 4.7 Hz, 1H), 2.45 (s, 3H), 2.24 – 2.12 (m, 1H), 2.12 – 2.08 (m, 2H), 1.91 – 1.84 (m, 2H), 1.55 (t, J = 8.9 Hz, 3H). 2 OH peaks not observed.
I-53	MS m/z 352.1 $[M+H]^+$; ^1H NMR (500 MHz, MeOD) δ : 7.58 (d, J = 2.3 Hz, 1H), 7.15 (t, J = 1.6 Hz, 1H), 6.97 (s, 1H), 6.92 (dd, J = 2.3, 1.0 Hz, 1H), 4.30 (p, J = 8.4 Hz, 1H), 3.75 (t, J = 8.1 Hz, 2H), 3.15 (td, J = 8.1, 1.6 Hz, 2H), 2.49 – 2.36 (m, 4H), 2.21 (s, 3H), 1.42 (s, 3H). 2 OH peaks not observed.
I-54	MS m/z 366.2 $[M+H]^+$; ^1H NMR (500 MHz, MeOD) δ : 7.58 (d, J = 2.3 Hz, 1H), 7.13 (t, J = 1.6 Hz, 1H), 6.97 (s, 1H), 6.92 (dd, J = 2.3, 1.0 Hz, 1H), 4.15 (dd, J = 11.4, 4.4 Hz, 1H), 4.06 (dd, J = 11.4, 6.3 Hz, 1H), 3.94 (ddd, J = 11.9, 10.0, 4.0 Hz, 1H), 3.78 (dtd, J = 15.3, 10.9, 5.2 Hz, 2H), 3.74 – 3.66 (m, 1H), 3.55 (dd, J = 5.6, 2.4 Hz, 1H), 3.21 – 3.10 (m, 2H), 2.22 (s, 3H), 2.16 – 2.07 (m, 1H), 1.80 (d, J = 12.0 Hz, 2H), 1.62 (ddd, J = 15.5, 9.7, 4.9 Hz, 2H). 2 OH peaks not observed.
I-55	MS m/z 378.2 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 7.67 (d, J = 2.1 Hz, 1H), 7.26 (d, J = 8.5 Hz, 1H), 7.10 (d, J = 8.4, 1H), 7.02 – 6.96 (m, 1H), 4.24 (quint, J = 8.63 Hz, 1H), 3.74 (t, J = 8.0 Hz, 2H), 3.20 (t, J = 7.7 Hz, 2H), 2.44 – 2.34 (m, 4H), 1.91 – 1.78 (m, 1H), 1.41 (s, 3H), 0.74 – 0.67 (m, 2H), 0.53 – 0.46 (m, 2H). 2 H not observed (2 OH).
I-56	MS m/z 368.2 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 7.60 (d, J = 2.3 Hz, 1H), 7.20 (s, 1H), 6.99 (s, 1H), 6.95 – 6.92 (m, 1H), 4.17 – 4.07 (m, 1H), 4.05 – 3.95 (m, 2H), 3.95 – 3.73 (m, 3H), 3.57 – 3.48 (m, 1H), 3.26 – 3.17 (m, 3H), 2.22 (s, 3H), 2.04 – 1.85 (m, 2H). 2H not observed (2 OH).
I-57	MS m/z 380.4 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 7.07 (dt, J = 11.2, 1.3 Hz, 2H), 6.96 (s, 1H), 4.36 – 4.23 (m, 1H), 3.75 (t, J = 8.2 Hz, 2H), 3.13 (td, J = 8.2, 1.6 Hz, 2H), 2.50 – 2.39 (m, 4H), 2.38 (s, 3H), 1.42 (s, 3H). OH peaks not observed.
I-58	MS m/z 310.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ : 14.42 (s, 1H), 7.97 (s, 1H), 7.70 (d, J = 7.8 Hz, 1H), 6.67 (d, J = 7.6 Hz, 1H), 4.76 (dt, J = 6.3, 4.0 Hz, 1H), 3.96 – 3.56 (m, 6H), 3.16 – 3.02 (m, 6H), 2.28 – 2.14 (m, 1H), 2.13 – 2.00 (m, 1H)
I-59	MS m/z 340.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ : 14.60 – 14.50 (m, 1H), 7.93 (s, 1H), 7.69 (d, J = 7.8 Hz, 1H), 6.67 (d, J = 7.6 Hz, 1H), 4.03 – 3.92 (m, 2H), 3.91 – 3.84 (m, 2H), 3.80 – 3.62 (m, 3H), 3.15 (t, J = 7.9 Hz, 2H), 3.45 – 3.37 (m, 1H), 3.11 – 3.02 (m, 5H), 1.91 – 1.77 (m, 1H), 1.76 – 1.67 (m, 1H)
I-60	MS m/z : 366.3 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 7.57 (d, J = 2.4 Hz, 1H), 7.16 (d, J = 1.6 Hz, 1H), 6.96 (s, 1H), 6.92 (d, J = 2.0 Hz, 1H), 4.36 – 4.23 (m, 1H), 3.91 (t, J = 9.2 Hz, 1H), 3.52 – 3.42 (m, 1H), 3.28 (s, 1H), 2.44 – 2.38 (m, 4H), 2.20 (s, 3H), 1.42 (s, 3H), 1.38 (d, J = 7.2 Hz, 3H). 2 OH peaks not observed.

Cmpd #	Spectral Data
I-61	MS m/z 410.3 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 7.14 – 7.02 (m, 2H), 6.97 (s, 1H), 4.12 (td, J = 10.8, 5.0 Hz, 1H), 3.98 (ddd, J = 20.4, 10.2, 5.1 Hz, 2H), 3.93 – 3.79 (m, 2H), 3.56 – 3.44 (m, 2H), 3.40 (dd, J = 8.7, 5.8 Hz, 1H), 3.21 (t, J = 10.5 Hz, 1H), 2.38 (s, 3H), 1.92 (qd, J = 11.4, 6.2 Hz, 2H), 1.39 (d, J = 6.9 Hz, 3H). 2 OH peaks not observed.
I-62	MS m/z 410.3 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 7.08 (d, J = 1.8 Hz, 2H), 6.97 (s, 1H), 4.12 (td, J = 10.3, 5.5 Hz, 1H), 4.05 – 3.90 (m, 3H), 3.90 – 3.79 (m, 1H), 3.61 – 3.45 (m, 2H), 3.41 (dd, J = 8.7, 5.8 Hz, 1H), 3.21 (td, J = 10.4, 3.2 Hz, 1H), 2.38 (s, 3H), 1.99 – 1.83 (m, 2H), 1.38 (dd, J = 6.9, 4.0 Hz, 3H). 2 OH peaks not observed.
I-63	MS m/z 408.8 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 7.08 (d, J = 1.5 Hz, 1H), 7.03 (dd, J = 3.4, 1.6 Hz, 1H), 6.96 (s, 1H), 3.99 – 3.83 (m, 2H), 3.79 – 3.67 (m, 1H), 3.54 – 3.33 (m, 1H), 3.26 (dd, J = 9.0, 7.1 Hz, 1H), 2.38 (s, 3H), 2.14 – 2.04 (m, 1H), 1.93 – 1.82 (m, 1H), 1.78 (dt, J = 11.8, 2.8 Hz, 2H), 1.59 (dtd, J = 24.6, 12.3, 3.1 Hz, 1H), 1.51 – 1.27 (m, 6H). 2 OH peaks not observed.
I-64	MS m/z 380.2 $[M+H]^+$. ^1H NMR (400 MHz, methanol- d_4) δ 8.52 (s, 1H, formic acid), 7.57 (d, J = 2.1 Hz, 1H), 6.95 (s, 1H), 6.91 – 6.84 (m, 2H), 5.02 – 4.98 (m, 1H), 4.94 – 4.91 (m, 1H), 3.87 – 3.76 (m, 1H), 3.53 – 3.42 (m, 1H), 2.24 – 2.13 (m, 1H), 2.11 – 2.01 (m, 4H), 1.81 – 1.71 (m, 5H), 1.49 – 1.24 (m, 5H). 2H not observed (2 OH)
I-65	MS m/z 409.3 $[M+H]^+$. ^1H NMR (500 MHz, MeOD) δ 7.76 (d, J = 2.2 Hz, 1H), 7.13 – 6.94 (m, 2H), 4.21 (ddt, J = 11.1, 7.3, 4.0 Hz, 1H), 3.69 (dtd, J = 16.7, 9.0, 7.2 Hz, 2H), 3.18 (ddd, J = 10.0, 8.2, 1.8 Hz, 2H), 3.13 – 3.02 (m, 1H), 2.91 (d, J = 11.6 Hz, 1H), 2.39 (s, 3H), 2.10 (d, J = 37.1 Hz, 2H), 2.02 – 1.91 (m, 1H), 1.87 (qd, J = 5.2, 2.7 Hz, 2H), 1.81 – 1.72 (m, 1H), 1.67 (td, J = 11.9, 3.9 Hz, 1H), 0.81 – 0.67 (m, 2H), 0.48 (td, J = 6.1, 4.3 Hz, 2H). OH peak not observed.
I-66	MS m/z 352.1 $[M+H]^+$. ^1H NMR (400 MHz, methanol- d_4) δ 7.59 (d, J = 2.2 Hz, 1H), 7.18 (s, 1H), 6.98 (s, 1H), 6.93 (d, J = 1.4 Hz, 1H), 4.40 – 4.29 (m, 1H), 4.20 – 4.09 (m, 1H), 3.87 – 3.74 (m, 1H), 3.74 – 3.63 (m, 1H), 3.23 – 3.13 (m, 2H), 2.21 (s, 3H), 2.14 – 2.01 (m, 2H), 1.93 – 1.74 (m, 3H), 1.74 – 1.61 (m, 1H). 2H not observed (2 OH)
I-67	MS m/z 354.1 $[M+H]^+$. ^1H NMR (400 MHz, methanol- d_4) δ 7.23 (s, 1H), 6.27 (s, 1H), 4.64 – 4.51 (m, 2H), 4.32 – 4.17 (m, 1H), 3.87 – 3.73 (m, 2H), 3.14 (s, 4H), 2.51 – 2.36 (m, 4H), 2.11 (s, 3H), 1.43 (s, 3H). 2H not observed (2 OH)
I-68	MS m/z 394.1 $[M+H]^+$. ^1H NMR (400 MHz, methanol- d_4) δ 7.13 (s, 1H), 7.06 (s, 1H), 6.99 (s, 1H), 4.40 (quint, J = 10.01 Hz, 1H), 3.75 (t, J = 8.1 Hz, 2H), 3.23 (s, 3H), 3.15 (t, J = 8.1 Hz, 2H), 2.47 – 2.37 (m, 2H), 2.37 – 2.28 (m, 2H), 2.18 (s, 3H), 1.42 (s, 3H). 1 H not observed (OH).
I-69	MS m/z 394.1 $[M+H]^+$. ^1H NMR (400 MHz, methanol- d_4) δ 7.08 (s, 1H), 7.06 (s, 1H), 6.96 (s, 1H), 4.41 (quint, J = 8.4 Hz, 1H), 3.74 (t, J = 8.1 Hz, 2H), 3.23 (s, 3H), 3.10 (t, J = 8.8 Hz, 2H), 2.46 – 2.29 (m, 7H), 1.42 (s, 3H). 1H not observed (OH).
I-70	MS m/z 366.1 $[M+H]^+$. ^1H NMR (400 MHz, methanol- d_4) δ 7.59 (s, 1H), 7.16 (s, 1H), 6.97 (s, 1H), 6.92 (s, 1H), 4.41 (quint, J = 8.5 Hz, 1H), 3.75 (t, J = 8.0 Hz, 2H), 3.23 (s, 3H), 3.15 (t, J = 9.0 Hz, 2H), 2.48 – 2.37 (m, 2H), 2.37 – 2.26 (m, 2H), 2.21 (s, 3H), 1.42 (s, 3H). 1H not observed (OH)

Cmpd #	Spectral Data
I-71	MS m/z 402.10 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ 7.80 (s, 1H), 7.40 (s, 1H), 7.21 (s, 1H), 7.05 (s, 1H), 6.77 (t, J = 56.0 Hz, 1H), 4.46 – 4.35 (m, 1H), 3.80 – 3.64 (m, 2H), 3.23 (s, 3H), 3.18 – 3.07 (m, 2H), 2.46 – 2.38 (m, 2H), 2.38 – 2.25 (m, 2H), 1.42 (s, 3H). 1H not observed (OH)
I-72	MS m/z 388.1 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 7.72 (s, 1H), 7.27 (s, 1H), 7.22 (s, 1H), 7.04 (s, 1H), 6.78 (t, J = 56.2 Hz, 1H), 4.36 – 4.22 (m, 1H), 3.74 (q, J = 7.6 Hz, 2H), 3.14 (t, J = 8.0 Hz, 2H), 2.41 (h, J = 9.3 Hz, 4H), 1.41 (s, 3H). OH peaks not observed.
I-73	MS m/z 338.1 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ 7.60 (s, 1H), 7.21 (s, 1H), 6.99 (s, 1H), 6.93 (s, 1H), 4.71 – 4.62 (m, 1H), 4.61 – 4.52 (m, 1H), 4.23 – 4.07 (m, 1H), 3.99 – 3.84 (m, 1H), 3.25 – 3.10 (m, 2H), 2.70 – 2.56 (m, 1H), 2.44 – 2.13 (m, 5H), 1.98 – 1.82 (m, 1H). OH peaks not observed.
I-74	MS m/z 338.0 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ 7.59 (s, 1H), 7.19 (s, 1H), 6.98 (s, 1H), 6.93 (s, 1H), 4.41 – 4.32 (m, 1H), 4.28 – 4.15 (m, 1H), 3.84 – 3.64 (m, 2H), 3.23 – 3.08 (m, 2H), 2.21 (s, 3H), 2.17 – 2.10 (m, 1H), 2.08 – 1.98 (m, 1H), 1.82 – 1.57 (m, 2H). OH peaks not observed.
I-75	MS m/z 404.1 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ 7.84 (d, J = 2.1 Hz, 1H), 7.44 (s, 1H), 7.36 (s, 1H), 7.08 (s, 1H), 6.81 (t, J = 55.7 Hz, 1H), 4.16 – 3.97 (m, 3H), 3.95 – 3.81 (m, 3H), 3.60 – 3.45 (m, 2H), 3.29 – 3.17 (m, 3H), 2.08 – 1.94 (m, 1H).
I-76	MS m/z : 352.1 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 7.03 (s, 1H), 6.52 (s, 1H), 3.96 – 3.87 (m, 1H), 3.82 – 3.65 (m, 3H), 3.18 – 3.11 (m, 2H), 3.11 – 3.05 (m, 4H), 2.13 – 2.08 (m, 1H), 2.06 (s, 3H), 1.89 – 1.82 (m, 1H), 1.82 – 1.74 (m, 2H), 1.66 – 1.56 (m, 1H), 1.44 – 1.35 (m, 2H), 1.33 (s, 1H). 2H not observed (2 OH)
I-77	MS m/z 362.9 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 7.17 (d, J = 2.0 Hz, 1H), 7.03 (s, 1H), 6.86 (s, 1H), 6.68 (t, J = 55.8 Hz, 1H), 4.28 (p, J = 8.4 Hz, 1H), 3.75 (t, J = 8.1 Hz, 2H), 3.13 (t, J = 8.0 Hz, 2H), 2.49 – 2.39 (m, 4H), 2.36 (s, 3H), 1.42 (s, 3H). 2H not observed (2 OH)
I-78	MS m/z 420.2 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 7.61 (s, 1H), 7.17 – 7.13 (m, 1H), 7.11 – 7.07 (m, 1H), 6.91 (s, 1H), 4.22 – 4.18 (m, 1H), 3.72 (t, J = 8.1 Hz, 2H), 3.47 – 3.43 (m, 2H), 3.11 – 3.06 (m, 2H), 2.34 (d, J = 6.9 Hz, 4H), 1.33 (s, 3H). 2OH peaks not observed.
I-79	MS m/z 388.2 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ 7.59 (d, J = 2.3 Hz, 1H), 7.21 – 7.14 (m, 2H), 6.99 (s, 1H), 6.95 – 6.87 (m, 3H), 6.71 (dd, J = 8.1, 1.8 Hz, 1H), 5.59 – 5.50 (m, 1H), 3.75 – 3.64 (m, 1H), 3.42 – 3.33 (m, 1H), 3.16 – 3.04 (m, 2H), 2.24 (s, 3H), 1.64 (d, J = 7.1 Hz, 3H). 2H not observed (2 OH).

Example 1A. Preparation of (R)-2-(7-(1-methylpiperidin-3-yl)-4-(trifluoromethyl)-6,7-dihydro-5H-pyrrolo[2,3-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol (IA-1)



Steps 1 and 2. A solution of 3,6-dichloro-4-(trifluoromethyl)pyridazine (1.50 g, 6.91 mmol) in dry THF (10.0 mL) under Argon atmosphere was cooled down to -40°C . A 0.81 M solution of $\text{TMPZn}(\text{OPiv})_2\text{MgClLiCl}$ (10 mL, 8.30 mmol) in THF was added then. The resulting mixture was stirred at -40°C for 1 hour after which, iodine (3.51 g, 13.8 mmol) was added into the mixture, and the solution was stirred at room temperature for 30 min. Upon completion, the reaction was quenched with saturated NH_4Cl solution, and extracted with EtOAc ($3 \times 20\text{ mL}$). The combined organic parts were washed with saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution ($2 \times 5\text{ mL}$), water, and brine, dried over Na_2SO_4 , and evaporated to dryness. The residue was purified via silica gel flash column chromatography eluting with a gradient hexanes/EtOAc (10-20% EtOAc) to afford crude product which was recrystallized from hot hexanes to yield 3,6-dichloro-4-iodo-5-(trifluoromethyl)pyridazine (1.11 g, 47% yield) as a UV-sensitive pale yellow solid. MS m/z 342.8 $[\text{M}+\text{H}]^+$.

Step 3. To a dry screw-cap vial were added: 3,6-dichloro-4-iodo-5-(trifluoromethyl)pyridazine (0.100 g, 0.292 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (0.045 g, 0.05 mL, 0.29 mmol), (2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II) chloride (0.021 g, 0.029 mmol), and potassium carbonate (0.121 g, 0.875 mmol). The mixture was degassed by purging with nitrogen for 15 min before 1,4 dioxane (2.1 mL) and water (0.7 mL) were added. The reaction vessel was evacuated and backflushed with nitrogen ($3 \times$), and the mixture was heated at 60°C for 2 hours. Upon completion, the mixture was partitioned between EtOAc and water. The combined organic parts were washed with brine, dried over sodium sulfate, filtered and concentrated under pressure. The residue was purified via silica gel flash column chromatography eluting with a gradient hexanes/EtOAc (0-20% EtOAc) to afford 3,6-dichloro-4-(trifluoromethyl)-5-vinylpyridazine

(0.017 g, 24.0% yield) as brown oil. MS m/z 243.1, 245.1 $[M+H]^+$.

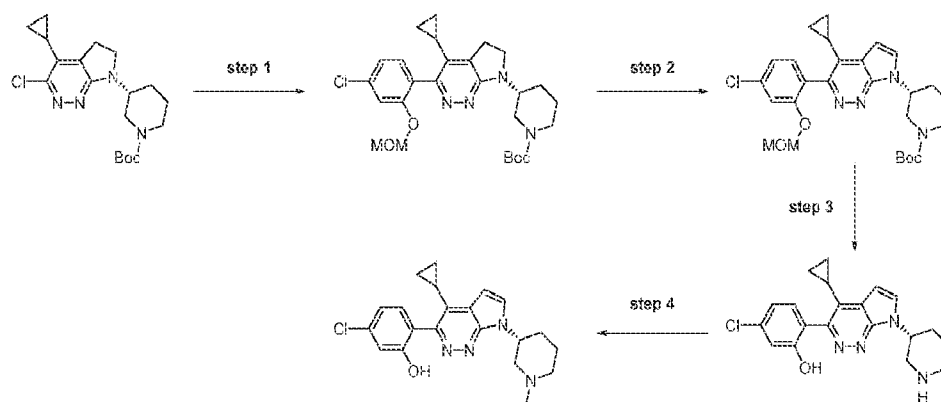
Step 4. To a solution of 3,6-dichloro-4-(trifluoromethyl)-5-vinyl-pyridazine (75.0 mg, 0.31 mmol) in anhydrous acetonitrile (1.5 mL) were added (R)-1-methylpiperidin-3-amine dihydrochloride (64.0 mg, 0.339 mmol) and N, N-diisopropylethylamine (0.160 mL, 0.926 mmol). The resulting mixture was then heated at 60 °C for 15 minutes, upon which all starting material has been consumed. The solvent was evaporated and the residue was purified by flash column chromatography eluting with a gradient $CH_2Cl_2/MeOH$ (5-20% MeOH) to afford (R)-3-chloro-7-(1-methylpiperidin-3-yl)-4-(trifluoromethyl)-6,7-dihydro-5H-pyrrolo[2,3-c]pyridazine (75.1 mg, 76% yield) as yellow oil that solidified over time. MS m/z 321.1, 323.1 $[M+H]^+$.

Step 5. To a dry screw-cap vial were added: (R)-3-chloro-7-(1-methylpiperidin-3-yl)-4-(trifluoromethyl)-6,7-dihydro-5H-pyrrolo[2,3-c]pyridazine (75.1 mg, 0.23 mmol), 2-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (156 mg, 0.47 mmol), (2-Dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (19.8 mg, 0.023 mmol), and potassium carbonate (97.1 mg, 0.70 mmol). The mixture was degassed by purging with nitrogen for 15 min before 1,4-dioxane (1.5 mL) and water (0.5 mL) were added. The reaction vessel was evacuated and backflushed with nitrogen (3 times), and the mixture was heated at 90 °C for 1 hour. Upon completion, the mixture was partitioned between EtOAc and water. The combined organic parts were washed with brine, dried over sodium sulfate, filtered and concentrated under pressure. The residue was purified via silica gel flash column chromatography eluting with a gradient $CH_2Cl_2/MeOH$ (0-20% MeOH) to afford (R)-3-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-7-(1-methylpiperidin-3-yl)-4-(trifluoromethyl)-6,7-dihydro-5H-pyrrolo[2,3-c]pyridazine (87.7 mg, 76% yield) as brown foam. MS m/z 491.2 $[M+H]^+$.

Step 6. A solution of (R)-3-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-7-(1-methylpiperidin-3-yl)-4-(trifluoromethyl)-6,7-dihydro-5H-pyrrolo[2,3-c]pyridazine (87.7 mg, 0.179 mmol) in MeOH (1.0 mL) was treated with 12 N HCl solution (1.0 mL). The mixture was stirred at room temperature for 3 hours. After all starting material has been consumed, the acidic solution was neutralized with solid $NaHCO_3$. The aqueous solution was then extracted with CH_2Cl_2 (3x 20mL). The combined organic parts were washed with water, dried over Na_2SO_4 , and evaporated to dryness. The residue was purified via silica gel flash column chromatography

eluting with a gradient CH₂Cl₂/MeOH (0-20% MeOH) to afford (R)-2-(7-(1-methylpiperidin-3-yl)-4-(trifluoromethyl)-6,7-dihydro-5H-pyrrolo[2,3-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol (53.0 mg, 66% yield) as yellow solid. MS *m/z* 447.2 [M+H]⁺; ¹H NMR (500 MHz, methanol-*d*₄) δ: 8.48 (br s, 1H, formate CH), 7.34 (d, *J* = 7.9 Hz, 1H), 7.19 (d, *J* = 7.9 Hz, 1H), 7.13 (s, 1H), 4.41 – 4.27 (m, 1H), 3.91 – 3.74 (m, 2H), 3.42 – 3.35 (m, 2H), 3.13 (d, *J* = 11.8 Hz, 1H), 2.83 – 2.68 (m, 1H), 2.60 (s, 3H), 2.55 – 2.41 (m, 1H), 2.08 – 1.93 (m, 2H), 1.90 – 1.76 (m, 2H); 2Hs not observed (OH and one CH overlaps with solvent peak).

Example 2. Preparation of (R)-5-chloro-2-(4-cyclopropyl-7-(1-methylpiperidin-3-yl)-7H-pyrrolo[2,3-c]pyridazin-3-yl)phenol (II-1)



Step 1: To a screw top vial were added: *tert*-butyl (3R)-3-(3-chloro-4-cyclopropyl-5,6-dihydropyrrolo[2,3-c]pyridazin-7-yl)piperidine-1-carboxylate (prepared according to example 1, 150 mg, 0.4 mmol), 2-[4-chloro-2-(methoxymethoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (142 mg, 0.48 mmol), Pd(dppf)Cl₂ (29 mg, 0.04 mmol) and potassium carbonate (142 mg, 1.0 mmol). The vial was purged with Ar for 15 min, followed by addition of water (0.5 mL) and 1,4-dioxane (1.3 mL). The mixture was heated at 90 °C for 2 hours. Upon completion, the reaction was concentrated and directly loaded on precolumn to purify by flash column chromatography eluting with a gradient CH₂Cl₂/MeOH/NH₄OH (0-30% MeOH/NH₄OH) to afford *tert*-butyl (3R)-3-[3-[4-chloro-2-(methoxymethoxy)phenyl]-4-cyclopropyl-5,6-dihydropyrrolo[2,3-c]pyridazin-7-yl]piperidine-1-carboxylate (110.1 mg, 54 % yield). MS *m/z* 515.4, 517.4 [M+H]⁺.

Step 2: To a screw top vial were added: *tert*-butyl (3R)-3-[3-[4-chloro-2-(methoxymethoxy)phenyl]-4-cyclopropyl-5,6-dihydropyrrolo[2,3-c]pyridazin-7-yl]piperidine-1-carboxylate (55 mg, 0.11 mmol), manganese(II) oxide (178 mg, 2.1 mmol), and toluene (0.2 mL). The suspension was heated at 110 °C for 16 h. Upon completion, the reaction was filtered through a pad of Celite and concentrated under reduced pressure to give crude *tert*-butyl (3R)-3-[3-[4-chloro-2-(methoxymethoxy)phenyl]-4-cyclopropyl-pyrrolo[2,3-c]pyridazin-7-yl]piperidine-1-carboxylate. The crude product was used directly in the next step without further purification.

Step 3: To a vial charged with *tert*-butyl (3R)-3-[3-[4-chloro-2-(methoxymethoxy)phenyl]-4-cyclopropyl-pyrrolo[2,3-c]pyridazin-7-yl]piperidine-1-carboxylate (crude from step 2) was added TFA (1.0 mL). The mixture was stirred at room temperature for 1h. Upon completion, the solvent was removed and the mixture was purified by silica flash column chromatography eluting with a gradient CH₂Cl₂/MeOH/NH₄OH (0-30% MeOH/NH₄OH) to give 5-chloro-2-[4-cyclopropyl-7-[(3R)-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]phenol (36 mg, 99% yield). MS *m/z* 369.3, 371.3 [M+H]⁺.

Step 4: A solution of 5-chloro-2-[4-cyclopropyl-7-[(3R)-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]phenol (36 mg, 0.1 mmol) in CH₂Cl₂ (1.0 mL) was cooled down to 0 °C and formaldehyde (37% in water) (0.011 mL, 0.15 mmol) was added. Then sodium triacetoxyborohydride (62 mg, 0.3 mmol) was added. The mixture was stirred for 20 min at 0 °C. Upon completion, the reaction was quenched with water, neutralized with saturated aq NaHCO₃, and extracted with EtOAc. The organic layers were combined, dried over sodium sulphate, and filtered. The solvent was removed under reduced pressure to give the crude which was purified using C18 EZ-Prep with formic acid as the modifier to give 5-chloro-2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]phenol (13.9 mg, 37% yield) as formic acid salt. MS *m/z* 383.3, 385.2 [M+H]⁺; ¹H NMR (400 MHz, methanol-*d*₄) δ: 8.35 (s, 1H, formate peak), 7.93 (d, J = 3.6 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 7.09 – 7.00 (m, 2H), 6.74 (d, J = 3.5 Hz, 1H), 5.67 – 5.46 (m, 1H), 3.93 – 3.70 (m, 1H), 3.58 – 3.45 (m, 1H), 3.45 – 3.36 (m, 1H), 3.14 – 2.93 (m, 1H), 2.79 (s, 3H), 2.40 – 2.21 (m, 2H), 2.20 – 1.88 (m, 3H), 1.20 – 0.95 (m, 4H); 1H not observed (OH).

Using the procedure described for Example 2, above, additional compounds described herein may be prepared by substituting the appropriate starting material, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

5 Table 2

Cmpd #	Characterization
II-1	MS <i>m/z</i> 383.3, 385.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, methanol- <i>d</i> ₄) δ: 8.35 (s, 1H, formate peak), 7.93 (d, J = 3.6 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 7.09 – 7.00 (m, 2H), 6.74 (d, J = 3.5 Hz, 1H), 5.67 – 5.46 (m, 1H), 3.93 – 3.70 (m, 1H), 3.58 – 3.45 (m, 1H), 3.45 – 3.36 (m, 1H), 3.14 – 2.93 (m, 1H), 2.79 (s, 3H), 2.40 – 2.21 (m, 2H), 2.20 – 1.88 (m, 3H), 1.20 – 0.95 (m, 4H); 1H not observed (OH).
II-2	MS <i>m/z</i> 389.4 [M+H] ⁺ ; ¹ H NMR (400 MHz, methanol- <i>d</i> ₄) δ: 8.05 (brs, 1H, formic acid), 7.46 – 7.16 (m, 1H), 6.91 – 6.69 (m, 3H), 6.26 – 5.86 (m, 1H), 3.89 – 3.80 (m, 1H), 3.55 – 3.39 (m, 1H), 3.27 – 3.15 (m, 1H), 3.13 – 2.84 (m, 1H), 2.56 (s, 3H), 2.44 – 1.90 (m, 7H), 1.29 – 1.12 (m, 2H), 1.13 – 1.05 (m, 4H), 0.97 – 0.72 (m, 2H); 1 H not observed (OH).
II-3	MS <i>m/z</i> 417.4 [M+H] ⁺ ; ¹ H NMR (500 MHz, methanol- <i>d</i> ₄) δ: 7.91 (s, 1H), 7.52 (s, 1H), 7.39 – 7.12 (m, 2H), 6.73 (d, J = 3.6 Hz, 1H), 5.29 (s, 1H), 3.70 (d, J = 11.4 Hz, 1H), 3.41 (d, J = 12.4 Hz, 2H), 2.98 (s, 1H), 2.83 (s, 3H), 2.27 (d, J = 8.7 Hz, 2H), 2.14 (d, J = 14.7 Hz, 1H), 2.02 (t, J = 14.2 Hz, 2H), 1.06 (d, J = 5.0 Hz, 2H), 1.01 (dd, J = 8.6, 4.3 Hz, 2H); 1 H not observed (OH).
II-4	MS <i>m/z</i> 363.4 [M+H] ⁺ .
II-5	MS <i>m/z</i> 379.3 [M+H] ⁺ ; ¹ H NMR (400 MHz, methanol- <i>d</i> ₄) δ: 7.92 (s, 1H), 7.48 – 7.04 (m, 1H), 6.93 – 6.43 (m, 3H), 5.65 – 5.30 (m, 1H), 3.84 (s, 3H), 3.58 – 3.39 (m, 1H), 3.20 – 2.86 (m, 2H), 2.59 – 2.40 (m, 4H), 2.30 – 1.70 (m, 5H), 1.18 – 0.89 (m, 4H); 1 H not observed (OH).
II-6	MS <i>m/z</i> 365.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, methanol- <i>d</i> ₄) δ: 8.23 (s, 1H), 7.32 (s, 1H), 7.00 – 6.83 (m, 1H), 6.77 – 6.51 (m, 2H), 5.43 – 5.25 (m, 1H), 3.86 (s, 3H), 3.83 – 3.70 (m, 1H), 3.66 – 3.52 (m, 1H), 3.46 – 3.38 (m, 1H), 3.19 – 2.94 (m, 1H), 2.53 – 2.27 (m, 2H), 2.27 – 2.12 (m, 2H), 2.12 – 1.90 (m, 1H), 1.24 – 0.98 (m, 4H); 2Hs not observed (NH and OH).
II-7	MS <i>m/z</i> 393.3 [M+H] ⁺ ; ¹ H NMR (400 MHz, methanol- <i>d</i> ₄) δ: 8.05 (s, 1H), 7.57 – 7.10 (m, 1H), 6.91 – 6.21 (m, 3H), 6.19 – 5.41 (m, 1H), 3.86 (s, 3H), 3.33 – 3.21 (m, 2H), 3.08 – 2.75 (m, 3H), 2.41 – 1.85 (m, 6H), 1.65 – 0.81 (m, 7H); 1H not observed (OH).
II-8	MS <i>m/z</i> 409.4 [M+H] ⁺ ; ¹ H NMR (400 MHz, methanol- <i>d</i> ₄) δ: 8.14 – 7.88 (m, 1H), 7.46 – 7.21 (m, 1H), 6.96 – 6.51 (m, 3H), 5.45 – 5.20 (m, 1H), 3.92 – 3.79 (m, 5H), 3.75 – 3.61 (m, 1H), 3.29 – 3.16 (m, 2H), 3.11 – 2.75 (m, 3H), 2.40 – 1.85 (m, 5H), 1.31 – 0.92 (m, 4H); 2Hs not observed (2 OHs).
II-9	MS <i>m/z</i> 391.3 [M+H] ⁺ ; ¹ H NMR (500 MHz, MeOD) δ: 7.96 (d, J = 3.5 Hz, 1H), 7.46 (d, J = 7.9 Hz, 1H), 7.28 (s, 1H), 7.24 (d, J = 22.1 Hz, 1H), 6.71 (d, J = 3.5 Hz, 1H), 5.15 (tt, J = 10.9, 4.1 Hz, 1H), 3.29 – 3.15 (m, 1H), 2.93 (d, J = 11.6 Hz, 1H), 2.64 (t, J = 10.8 Hz, 1H), 2.44 (s, 3H), 2.40 (s, 3H), 2.27 (td, J = 11.8, 2.9 Hz, 1H), 2.17 (dt, J = 12.9, 4.0 Hz, 1H), 2.09 (qd, J = 12.0, 4.2 Hz, 1H), 1.99 – 1.91 (m, 1H), 1.87 (tdd, J = 15.6, 9.9, 4.0 Hz, 1H). OH peak not observed.

Cmpd #	Characterization
II-10	MS m/z 357.2, 359.2 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.06 (s, 1H), 7.49 – 7.21 (m, 1H), 7.14 – 6.90 (m, 2H), 6.87 – 6.73 (m, 1H), 5.71 – 5.42 (m, 1H), 3.90 – 3.73 (m, 1H), 3.65 – 3.49 (m, 1H), 3.45 – 3.36 (m, 1H), 3.20 – 2.97 (m, 1H), 2.80 (s, 3H), 2.52 (s, 3H), 2.38 – 2.25 (m, 2H), 2.22 – 2.10 (m, 1H), 2.08 – 1.96 (m, 1H); 1H not observed (OH).
II-11	MS m/z 353.2 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.49 (s, 1H) formic acid peak, 8.06 (s, 1H), 7.22 (d, J = 8.1 Hz, 1H), 6.85 (d, J = 3.2 Hz, 1H), 6.80 – 6.54 (m, 2H), 6.28 – 5.83 (m, 1H), 3.85 (s, 3H), 3.83 – 3.81 (m, 1H), 3.46 – 3.38 (m, 1H), 3.27 – 3.13 (m, 1H), 3.05 – 2.82 (m, 1H), 2.53 (s, 3H), 2.47 (s, 3H), 2.36 – 2.18 (m, 2H), 2.17 – 1.83 (m, 2H); 1H not observed (OH).
II-12	MS m/z 363.2 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 7.94 (t, J = 2.9 Hz, 1H), 7.71 (d, J = 2.4 Hz, 1H), 7.34 – 7.10 (m, 2H), 7.03 (d, J = 2.4 Hz, 1H), 6.69 (t, J = 3.0 Hz, 1H), 5.14 (td, J = 9.3, 5.4 Hz, 1H), 3.30 – 3.14 (m, 1H), 2.90 (d, J = 11.6 Hz, 1H), 2.60 (t, J = 10.9 Hz, 1H), 2.45 (s, 3H), 2.38 (s, 3H), 2.24 (dd, J = 43.3, 32.0 Hz, 2H), 2.15 – 1.95 (m, 1H), 2.02 – 1.72 (m, 2H); 1H not observed (OH).
II-13	MS m/z 379.2 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.03 – 7.91 (m, 1H), 7.61 (dd, J = 5.7, 2.6 Hz, 1H), 7.52 (ddd, J = 13.9, 7.0, 2.7 Hz, 2H), 7.27 (dd, J = 8.1, 2.6 Hz, 1H), 6.75 – 6.62 (m, 1H), 5.15 (tt, J = 11.0, 3.9 Hz, 1H), 3.25 – 3.11 (m, 1H), 2.90 (d, J = 11.7 Hz, 1H), 2.66 – 2.55 (m, 1H), 2.48 (s, 3H), 2.37 (s, 3H), 2.28 – 2.14 (m, 2H), 2.07 (dtf, J = 15.7, 7.3, 3.8 Hz, 1H), 1.91 (tdd, J = 22.0, 10.5, 7.0 Hz, 2H); 1H not observed (OH).
II-14	MS m/z 363.3 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 7.92 (d, J = 3.4 Hz, 1H), 7.05 (dd, J = 7.8, 2.8 Hz, 1H), 6.88 (dd, J = 7.6, 2.7 Hz, 1H), 6.67 (d, J = 3.4 Hz, 1H), 5.12 (tt, J = 11.1, 4.0 Hz, 1H), 3.19 (d, J = 11.5 Hz, 1H), 2.97 (td, J = 7.4, 2.6 Hz, 2H), 2.95 – 2.80 (m, 3H), 2.58 (t, J = 10.9 Hz, 1H), 2.44 (s, 3H), 2.37 (s, 3H), 2.26 – 2.10 (m, 4H), 2.10 – 1.99 (m, 1H), 1.96 – 1.75 (m, 2H); 1H not observed (OH).
II-15	MS m/z 365.3 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 7.90 (t, J = 4.0 Hz, 1H), 7.02 (d, J = 7.8 Hz, 1H), 6.65 (t, J = 3.8 Hz, 1H), 6.42 (dd, J = 8.1, 2.7 Hz, 1H), 5.10 (tt, J = 11.1, 3.8 Hz, 1H), 4.61 (t, J = 8.6 Hz, 2H), 3.19 (q, J = 8.3 Hz, 3H), 2.89 (d, J = 11.3 Hz, 1H), 2.58 (td, J = 10.7, 6.1 Hz, 1H), 2.45 (s, 3H), 2.34 (s, 3H), 2.29 – 2.17 (m, 1H), 2.17 – 2.08 (m, 1H), 2.03 (dtd, J = 16.0, 8.2, 3.3 Hz, 1H), 1.99 – 1.75 (m, 2H); 1H not observed (OH).
II-16	MS m/z 389.3 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 7.89 (d, J = 3.6 Hz, 1H), 7.70 (d, J = 2.2 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.15 (dd, J = 8.4, 1.0 Hz, 1H), 7.02 (dd, J = 2.3, 0.9 Hz, 1H), 6.62 (d, J = 3.6 Hz, 1H), 5.14 (tt, J = 10.8, 4.1 Hz, 1H), 3.19 (dd, J = 11.6, 4.0 Hz, 1H), 2.96 – 2.83 (m, 1H), 2.57 (t, J = 10.6 Hz, 1H), 2.37 (s, 3H), 2.22 (td, J = 11.5, 3.1 Hz, 1H), 2.20 – 2.11 (m, 1H), 2.11 – 1.98 (m, 2H), 1.98 – 1.89 (m, 1H), 1.89 – 1.79 (m, 1H), 1.10 – 1.01 (m, 2H), 0.98 – 0.86 (m, 2H); 1H not observed (OH).
II-17	MS m/z 405.3, $[M+H]^+$; ^1H NMR (methanol- d_4) δ : 7.51-7.60 (m, 1H), 7.00-7.08 (m, 1H), 6.91 (s, 1H), 6.32 (s, 1H), 4.65-4.72 (m, 1H), 3.68-3.77 (m, 1H), 3.23-3.32 (m, 1H), 3.07-3.16 (m, 1H), 2.63-2.78 (m, 2H), 2.54-2.61 (m, 3H), 2.52 (s, 3H), 2.31 (s, 3H), 1.76-2.02 (m, 3H); 1H not observed (OH).
II-18	MS m/z 405.3, $[M+H]^+$; ^1H NMR (methanol- d_4) δ : 7.59 (s, 1H), 7.02 (s, 1H), 6.95 (s, 1H), 6.34 (s, 1H), 4.59-4.69 (m, 1H), 3.57-3.72 (m, 1H), 3.14-3.19 (m, 1H), 3.01-3.11 (m, 1H), 2.68-2.86 (m, 1H), 2.44-2.59 (m, 7H), 2.02 (s, 3H), 1.94 (m, 2H), 1.73-1.88 (m, 1H); 1H not observed (OH).

Cmpd #	Characterization
II-19	¹ H NMR (400 MHz, MeOD) δ 7.90 (s, 1H), 7.00 (d, J = 12 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.62 (d, J = 4.0 Hz, 1H), 5.17 – 5.09 (m, 1H), 3.19 – 3.13 (m, 1H), 2.90 – 2.88 (m, 1H), 2.57 – 2.52 (m, 1H), 2.35 (s, 3H), 2.27 (s, 3H), 2.29 – 1.83 (m, 6H), 1.07 – 1.02 (m, 2H), 1.01 – 0.95 (m, 2H). 1 OH signal not observed.
II-20	¹ H NMR (400 MHz, MeOD) δ 7.90 (d, J = 4.0 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 6.82 (t, J = 8.0 Hz, 1H), 6.62 (d, J = 4.0 Hz, 1H), 5.17 – 5.09 (m, 1H), 3.19 – 3.13 (m, 1H), 2.91 – 2.88 (m, 1H), 2.57 – 2.54 (m, 1H), 2.34 (s, 3H), 2.26 (s, 3H), 2.23 – 1.83 (m, 6H), 1.06 – 1.00 (m, 2H), 0.99 – 0.94 (m, 2H). 1 OH signal not observed.
II-21	MS <i>m/z</i> 391.3 [M+H] ⁺ ; ¹ H NMR (500 MHz, MeOD) δ: 8.00 (d, J = 3.5 Hz, 1H), 7.77 (s, 1H), 7.14 (s, 1H), 7.01 (s, 1H), 6.63 (d, J = 3.6 Hz, 1H), 5.20 (tt, J = 10.8, 4.1 Hz, 1H), 3.29 – 3.16 (m, 1H), 2.94 (d, J = 11.4 Hz, 1H), 2.66 (t, J = 10.7 Hz, 1H), 2.50 – 2.34 (m, 6H), 2.33 – 2.22 (m, 1H), 2.20 (dt, J = 13.0, 4.2 Hz, 1H), 2.10 (qd, J = 12.0, 4.3 Hz, 1H), 1.96 (dp, J = 11.4, 3.8 Hz, 1H), 1.93 – 1.77 (m, 1H). 1 OH peak not observed.
II-22	MS <i>m/z</i> 350.1 [M+H] ⁺ ; ¹ H NMR (500 MHz, MeOD) δ: 7.94 (d, J = 3.6 Hz, 1H), 7.69 (dd, J = 14.8, 2.3 Hz, 1H), 7.26 – 7.12 (m, 2H), 7.03 (dd, J = 2.3, 1.0 Hz, 1H), 6.70 (d, J = 3.6 Hz, 1H), 5.18 – 5.04 (m, 1H), 2.77 (tt, J = 7.9, 2.5 Hz, 2H), 2.70 (td, J = 9.3, 2.4 Hz, 2H), 2.45 (s, 3H), 1.51 (s, 3H). 2 OH peaks not observed.
II-23	MS <i>m/z</i> 391.3 [M+H] ⁺ ; ¹ H NMR (500 MHz, MeOD) δ: 8.03 (d, J = 3.5 Hz, 1H), 7.85 (s, 1H), 7.12 (s, 1H), 7.05 (s, 1H), 6.72 – 6.57 (m, 1H), 5.25 – 5.11 (m, 1H), 3.28 (dt, J = 10.8, 3.3 Hz, 1H), 2.96 (d, J = 11.6 Hz, 1H), 2.69 (t, J = 10.7 Hz, 1H), 2.43 (s, 3H), 2.40 – 2.25 (m, 1H), 2.19 (tt, J = 14.9, 7.4 Hz, 1H), 2.09 (s, 3H), 2.04 – 1.92 (m, 2H), 1.92 – 1.82 (m, 1H). 1 OH peak not observed.
II-24	MS <i>m/z</i> 381.2 [M+H] ⁺ ; ¹ H NMR (500 MHz, MeOD) δ: 7.97 (s, 1H), 7.72 (s, 1H), 7.20 (d, J = 12.4 Hz, 2H), 7.04 (d, J = 2.2 Hz, 1H), 6.75 (d, J = 3.7 Hz, 1H), 5.51 (dd, J = 29.8, 11.3 Hz, 1H), 5.13 (d, J = 50.6 Hz, 1H), 3.13 (dd, J = 11.1, 4.2 Hz, 1H), 3.05 (t, J = 11.2 Hz, 1H), 2.87 (d, J = 11.8 Hz, 1H), 2.60 (t, J = 11.4 Hz, 1H), 2.48 (s, 3H), 2.22 (d, J = 12.9 Hz, 1H), 2.19 – 2.03 (m, 1H), 1.99 (s, 3H). 1 OH peak not observed.
II-25	MS <i>m/z</i> 381.2 [M+H] ⁺ ; ¹ H NMR (500 MHz, MeOD) δ: 7.91 (d, J = 3.5 Hz, 1H), 7.71 (d, J = 2.2 Hz, 1H), 7.25 – 7.12 (m, 2H), 7.03 (d, J = 2.3 Hz, 1H), 6.70 (d, J = 3.6 Hz, 1H), 5.42 (dt, J = 11.4, 5.9 Hz, 1H), 5.05 (d, J = 46.6 Hz, 1H), 3.26 – 3.02 (m, 3H), 2.75 (t, J = 10.8 Hz, 1H), 2.58 – 2.42 (m, 4H), 2.39 (s, 3H), 2.29 – 2.20 (m, 1H). 1 OH peak not observed.
II-26	MS <i>m/z</i> 395.3 [M+H] ⁺ ; ¹ H NMR (500 MHz, MeOD) δ: 7.95 (s, 1H), 7.71 (d, J = 2.2 Hz, 1H), 7.22 – 7.13 (m, 2H), 7.03 (d, J = 2.3 Hz, 1H), 6.72 (d, J = 3.6 Hz, 1H), 5.55 – 5.40 (m, 1H), 5.20 – 5.02 (m, 1H), 3.15 (dd, J = 11.1, 4.5 Hz, 1H), 2.98 (d, J = 11.3 Hz, 1H), 2.95 – 2.88 (m, 1H), 2.63 (pd, J = 7.5, 4.0 Hz, 2H), 2.54 (td, J = 11.9, 3.5 Hz, 1H), 2.45 (s, 3H), 2.23 – 2.16 (m, 1H), 2.12 – 2.00 (m, 1H), 1.17 (t, J = 7.2 Hz, 3H). 1 OH peak not observed.
II-27	MS <i>m/z</i> : 349.3 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ: 7.91 (d, J = 3.6 Hz, 1H), 7.08 (d, J = 7.2 Hz, 1H), 6.71 (d, J = 7.6 Hz, 1H), 6.66 (d, J = 4.0 Hz, 1H), 5.19 – 5.04 (m, 1H), 3.23 – 3.11 (m, 5H), 2.99 – 2.84 (m, 1H), 2.64 – 2.55 (m, 1H), 2.41 (s, 3H), 2.38 (s, 3H), 2.28 – 2.20 (m, 1H), 2.20 – 2.13 (m, 1H), 2.12 – 2.01 (m, 1H), 1.99 – 1.81 (m, 2H). 1 OH peak not observed.
II-28	MS <i>m/z</i> 364.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, methanol-d ₄) δ: 8.44 (s, 2H), 7.66 – 7.56 (m, 1H), 7.10 – 7.02 (m, 1H), 6.98 – 6.89 (m, 1H), 5.02 – 4.88 (m, 1H), 2.80 – 2.69 (m, 2H), 2.69 – 2.59 (m, 2H), 2.39 (s, 3H), 2.13 (s, 3H), 1.43 (s, 3H); 2 OH peaks not observed.

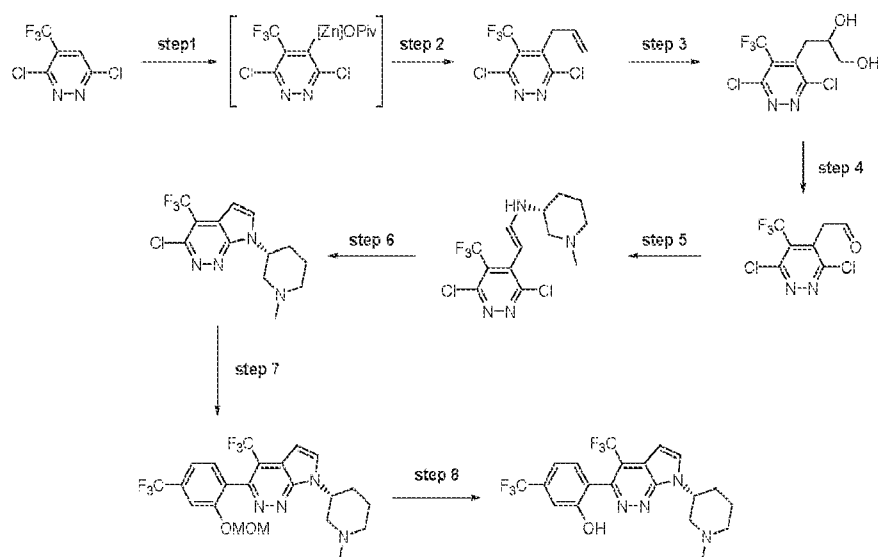
Cmpd #	Characterization
II-29	MS m/z 364.3 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 7.86 (d, J = 3.5 Hz, 1H), 7.70 (d, J = 2.3 Hz, 1H), 7.24 – 7.13 (m, 2H), 7.03 (dd, J = 2.3, 0.9 Hz, 1H), 6.68 (d, J = 3.5 Hz, 1H), 4.68 (td, J = 10.1, 6.1 Hz, 1H), 4.19 (dq, J = 10.0, 4.7 Hz, 1H), 2.45 (s, 3H), 2.24 – 2.12 (m, 1H), 2.12 – 2.08 (m, 2H), 1.91 – 1.84 (m, 2H), 1.55 (t, J = 8.9 Hz, 3H). 2 OH peaks not observed.
II-30	MS m/z 366.1 $[M+H]^+$; ^1H NMR (500 MHz, DMSO- d_6) δ : 10.09 (s, 1H), 8.03 (d, J = 3.5 Hz, 1H), 7.87 (s, 1H), 7.20 – 7.14 (m, 2H), 6.67 (d, J = 3.5 Hz, 1H), 5.13 (d, J = 6.0 Hz, 1H), 4.83 (ddd, J = 12.0, 10.0, 4.4 Hz, 1H), 4.17 (dq, J = 10.0, 5.2 Hz, 1H), 4.11 (s, 1H), 3.98 (dt, J = 10.0, 4.7 Hz, 2H), 3.53 (td, J = 12.1, 2.1 Hz, 1H), 3.22 (t, J = 10.6 Hz, 1H), 3.16 (s, 1H), 2.37 (s, 3H), 2.00 (dd, J = 13.0, 4.4 Hz, 1H).
II-31	MS m/z 378.2 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.59 – 8.50 (m, 2H), 7.08 (s, 1H), 6.65 (s, 1H), 5.15 – 5.01 (m, 1H), 2.91 – 2.81 (m, 2H), 2.81 – 2.72 (m, 2H), 2.51 (s, 3H), 2.47 (s, 3H), 2.23 (s, 3H), 1.55 (s, 3H). 2 OH peaks not observed.
II-32	MS m/z : 365.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ : 8.11 (d, J = 3.6 Hz, 1H), 7.72 (s, 1H), 6.56 (d, J = 3.2 Hz, 1H), 6.28 (s, 1H), 5.15 – 4.99 (m, 1H), 4.54 (t, J = 8.4 Hz, 2H), 3.11 (t, J = 8.4 Hz, 2H), 3.05 – 2.97 (m, 1H), 2.78 – 2.69 (m, 1H), 2.49 – 2.40 (m, 2H), 2.26 (s, 3H), 2.17 – 2.06 (m, 1H), 2.07 – 1.99 (m, 2H), 1.95 (s, 3H), 1.87 – 1.64 (m, 2H).
II-33	MS m/z : 363.2 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.01 (d, J = 3.6 Hz, 1H), 7.84 (s, 1H), 7.61 (d, J = 2.4 Hz, 1H), 7.03 (s, 1H), 6.95 (d, J = 2.0 Hz, 1H), 6.64 (d, J = 3.2 Hz, 1H), 5.21–5.17 (m, 1H), 3.26–3.25 (m, 1H), 2.97–2.94 (m, 1H), 2.71–2.68 (m, 1H), 2.42 (s, 3H), 2.30–2.29 (m, 1H), 2.21–2.13 (m, 2H), 2.12 (s, 3H), 1.97–1.95 (m, 1H), 1.90 (s, 1H). 1 OH peaks not observed.
II-34	MS m/z 350.1 $[M+H]^+$; ^1H NMR (500 MHz, MeOD) δ : 8.03 (d, J = 3.5 Hz, 1H), 7.85 (s, 1H), 7.62 (d, J = 2.3 Hz, 1H), 7.04 (s, 1H), 6.96 (d, J = 2.3 Hz, 1H), 6.68 (d, J = 3.5 Hz, 1H), 5.19 (p, J = 8.4 Hz, 1H), 2.89 – 2.76 (m, 2H), 2.78 – 2.63 (m, 2H), 2.13 (s, 3H), 1.54 (s, 3H). 2 OH peaks not observed.
II-35	MS m/z 364.2 $[M+H]^+$; ^1H NMR (500 MHz, MeOD) δ : 7.94 (d, J = 3.5 Hz, 1H), 7.84 (s, 1H), 7.61 (d, J = 2.2 Hz, 1H), 7.03 (s, 1H), 6.95 (dd, J = 2.2, 1.0 Hz, 1H), 6.64 (d, J = 3.5 Hz, 1H), 4.73 (td, J = 10.5, 5.4 Hz, 1H), 4.23 (dt, J = 10.9, 5.4 Hz, 1H), 4.15 (dd, J = 11.4, 4.4 Hz, 1H), 4.06 (dd, J = 11.4, 6.3 Hz, 1H), 3.85 – 3.77 (m, 1H), 3.59 – 3.52 (m, 1H), 2.24 – 2.18 (m, 1H), 2.14 (s, 3H), 1.92 (d, J = 17.0 Hz, 1H), 1.61 – 1.52 (m, 2H). 2 OH peaks not observed.
II-36	MS m/z : 379.2 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 7.65 (s, 1H), 7.00 (d, J = 8.0 Hz, 1H), 6.42 (d, J = 8.0 Hz, 1H), 5.12 – 5.03 (m, 1H), 4.62 (t, J = 8.4 Hz, 2H), 3.24 – 3.16 (m, 3H), 2.97 – 2.89 (m, 1H), 2.59 – 2.57 (m, 1H), 2.57 (s, 3H), 2.51 (s, 3H), 2.40 (s, 3H), 2.31 – 2.21 (m, 1H), 2.17 – 2.08 (m, 1H), 2.06 – 1.80 (m, 3H). 1 OH not observed.
II-37	MS m/z : 366.2 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 7.93 (s, 1H), 7.91 (s, 1H), 6.32 (s, 1H), 5.11 – 5.07 (m, 1H), 4.58 (t, J = 8.8 Hz, 2H), 3.15 (t, J = 8.8 Hz, 2H), 2.79 – 2.67 (m, 4H), 2.37 (s, 3H), 2.02 (s, 3H), 1.51 (s, 3H). 2 OH peaks not observed.
II-38	MS m/z 363.2 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 8.08 (s, 1H), 7.89 (d, J = 2.2 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 7.9 Hz, 1H), 7.00 (d, J = 3.6 Hz, 1H), 6.96 (d, J = 2.2 Hz, 1H), 5.47 (s, 1H), 3.88 (dd, J = 12.2, 4.2 Hz, 1H), 3.66 (s, 1H), 3.51 (d, J = 12.4 Hz, 1H), 3.19 (s, 1H), 2.88 (d, J = 13.1 Hz, 3H), 2.56 (s, 3H), 2.46 – 2.32 (m, 2H), 2.23 (d, J = 14.8 Hz, 1H), 2.10 (ddd, J = 15.7, 11.7, 4.4 Hz, 1H). OH peak not observed.

Cmpd #	Characterization
II-39	MS m/z 389.2 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 7.90 (d, J = 3.6 Hz, 1H), 7.79 (d, J = 2.2 Hz, 1H), 7.20 (q, J = 7.9 Hz, 2H), 6.88 (d, J = 2.1 Hz, 1H), 6.63 (d, J = 3.6 Hz, 1H), 5.15 (tt, J = 10.8, 4.1 Hz, 1H), 3.26 – 3.19 (m, 1H), 2.92 (d, J = 11.5 Hz, 1H), 2.62 (t, J = 10.7 Hz, 1H), 2.40 (s, 3H), 2.32 – 2.22 (m, 1H), 2.20 – 1.82 (m, 5H), 1.10 – 0.98 (m, 2H), 1.00 – 0.89 (m, 2H). OH peak not observed.
II-40	MS m/z 381.4 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 7.95 (d, J = 3.6 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.13 (dd, J = 8.4, 0.8 Hz, 1H), 6.77 (d, J = 3.6 Hz, 1H), 6.20 (dd, J = 6.5, 0.8 Hz, 1H), 5.31 – 5.19 (m, 1H), 3.60 – 3.52 (m, 1H), 3.36 – 3.16 (m, 2H), 2.78 (t, J = 11.8 Hz, 1H), 2.69 (s, 3H), 2.46 (s, 3H), 2.24 (m, 2H), 2.10 (dd, J = 14.6, 3.8 Hz, 1H), 2.03 – 1.88 (m, 1H). OH peak not observed.
II-41	MS m/z 377.4 $[M+H]^+$. ^1H NMR (500 MHz, MeOD) δ 7.95 (d, J = 3.6 Hz, 1H), 7.71 (d, J = 2.2 Hz, 1H), 7.16 (s, 2H), 7.03 (d, J = 2.3 Hz, 1H), 6.71 (d, J = 3.5 Hz, 1H), 5.16 (tt, J = 10.9, 4.1 Hz, 1H), 3.24 (ddd, J = 14.7, 11.1, 2.9 Hz, 1H), 2.95 – 2.88 (m, 1H), 2.85 (q, J = 7.6 Hz, 2H), 2.63 (t, J = 10.7 Hz, 1H), 2.39 (s, 3H), 2.25 (td, J = 11.6, 3.1 Hz, 1H), 2.18 (dt, J = 13.1, 4.3 Hz, 1H), 2.08 (qd, J = 12.0, 4.2 Hz, 1H), 2.00 – 1.89 (m, 1H), 1.89 – 1.83 (m, 1H), 1.14 (t, J = 7.6 Hz, 3H). OH peak not observed.
II-42	MS m/z : 392.2 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ : 7.80 (s, 1H), 7.73 (s, 1H), 7.14 (s, 1H), 7.01 (s, 1H), 5.21 – 5.04 (m, 1H), 2.83 – 2.72 (m, 2H), 2.71 – 2.65 (m, 2H), 2.42 (s, 3H), 2.35 (s, 3H), 1.51 (s, 3H). OH peaks not observed.
II-43	MS m/z 363.4 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 7.93 (d, J = 3.6 Hz, 1H), 7.07 (d, J = 7.3 Hz, 1H), 6.76 – 6.70 (m, 1H), 6.69 (s, 1H), 5.15 (tt, J = 10.7, 4.1 Hz, 1H), 3.20 (tp, J = 6.8, 3.4 Hz, 5H), 2.92 (d, J = 11.5 Hz, 1H), 2.85 (q, J = 7.6 Hz, 2H), 2.61 (t, J = 10.7 Hz, 1H), 2.39 (s, 3H), 2.30 – 2.15 (m, 2H), 2.08 (qd, J = 11.9, 4.2 Hz, 1H), 2.02 – 1.82 (m, 2H), 1.15 (t, J = 7.6 Hz, 3H). OH peak not observed.
II-44	MS m/z 391.4 $[M+H]^+$. ^1H NMR (400 MHz, methanol- d_4) δ 8.37 (s, Formate, 1H), 7.96 (d, J = 3.6 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 6.86 (d, J = 7.6 Hz, 1H), 6.78 (d, J = 3.6 Hz, 1H), 5.44 – 5.28 (m, 1H), 3.64 – 3.54 (m, 1H), 3.28 – 3.13 (m, 2H), 2.90 (t, J = 7.1 Hz, 2H), 2.83 – 2.72 (m, 1H), 2.64 (s, 3H), 2.47 (s, 3H), 2.31 – 2.16 (m, 2H), 2.13 – 1.89 (m, 4H), 1.31 (s, 6H). OH peak not observed.
II-45	MS m/z 408.2 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 7.81 – 7.67 (m, 2H), 7.14 (d, J = 1.5 Hz, 1H), 7.02 (s, 1H), 4.84 – 4.66 (m, 1H), 4.28 (td, J = 10.1, 5.1 Hz, 1H), 4.07 (ddt, J = 23.4, 11.6, 5.9 Hz, 2H), 3.61 (qd, J = 11.8, 2.1 Hz, 1H), 2.48 (s, 1H), 2.42 (s, 3H), 2.41 – 2.33 (m, 3H), 2.32 (d, J = 1.1 Hz, 1H), 2.16 – 2.05 (m, 1H). OH peaks not observed.
II-46	MS m/z 406.3 $[M+H]^+$. ^1H NMR (500 MHz, MeOD) δ 7.74 – 7.69 (m, 2H), 7.14 (d, J = 1.5 Hz, 1H), 7.01 (s, 1H), 4.67 (td, J = 9.8, 7.0 Hz, 1H), 4.15 (dq, J = 10.2, 5.1 Hz, 1H), 2.42 (s, 3H), 2.35 (d, J = 1.1 Hz, 3H), 2.22 – 2.15 (m, 1H), 2.13 – 2.07 (m, 2H), 1.90 – 1.85 (m, 2H), 1.61 – 1.49 (m, 3H). OH peaks not observed.
II-47	MS m/z 366.2 $[M+H]^+$. ^1H NMR (400 MHz, methanol- d_4) δ 8.06 (d, J = 3.5 Hz, 1H), 7.93 (s, 1H), 7.63 (d, J = 2.3 Hz, 1H), 7.06 (s, 1H), 6.98 – 6.98 (m, 1H), 6.72 (d, J = 3.5 Hz, 1H), 4.96 – 4.88 (m, 1H), 4.36 (td, J = 10.1, 5.1 Hz, 1H), 4.11 (ddd, J = 19.7, 11.5, 4.9 Hz, 2H), 3.65 (td, J = 12.0, 1.9 Hz, 1H), 3.39 – 3.34 (m, 1H), 2.52 (dd, J = 12.8, 4.8 Hz, 1H), 2.20 – 2.12 (m, 4H). 2H not observed (2 OH).
II-48	MS m/z : 377.3 $[M+H]^+$. ^1H NMR (400 MHz, methanol- d_4) δ : 7.74 (d, J = 2.4 Hz, 1H), 7.71 (s, 1H), 7.20 (s, 2H), 7.05 (d, J = 2.4 Hz, 1H), 5.34 (s, 1H), 3.53 (d, J = 11.2 Hz, 1H), 3.18 – 3.16 (m, 2H), 2.76 – 2.73 (m, 1H), 2.63 – 2.51 (m, 9H), 2.24 – 2.13 (m, 2H), 2.07 – 2.03 (m, 1H), 1.96 – 1.93 (m, 1H). OH not observed.

Cmpd #	Characterization
II-49	MS m/z 381.2 $[M+H]^+$. ^1H NMR (500 MHz, MeOD) δ 7.95 (d, J = 3.6 Hz, 1H), 7.80 (d, J = 2.2 Hz, 1H), 7.08 (t, J = 2.5 Hz, 1H), 7.02 (d, J = 10.9 Hz, 1H), 6.70 (d, J = 3.5 Hz, 1H), 5.14 (tt, J = 10.8, 4.1 Hz, 1H), 3.21 (dd, J = 10.9, 3.9 Hz, 1H), 2.91 (d, J = 11.5 Hz, 1H), 2.61 (t, J = 10.7 Hz, 1H), 2.46 (s, 3H), 2.38 (s, 3H), 2.30 – 2.13 (m, 2H), 2.08 (qd, J = 12.0, 4.3 Hz, 1H), 1.99 – 1.82 (m, 2H). OH peak not observed.
II-50	MS m/z 350.1 $[M+H]^+$. ^1H NMR (400 MHz, methanol- d_4) δ 7.95 (d, J = 3.5 Hz, 1H), 7.87 (s, 1H), 7.62 (d, J = 2.2 Hz, 1H), 7.04 (s, 1H), 6.96 (d, J = 2.2 Hz, 1H), 6.67 (d, J = 3.5 Hz, 1H), 5.17 – 5.02 (m, 1H), 4.76 – 4.65 (m, 1H), 2.52 – 2.37 (m, 1H), 2.33 – 2.17 (m, 2H), 2.14 (s, 3H), 2.07 – 1.95 (m, 2H), 1.88 – 1.75 (m, 1H). OH peaks not observed.
II-51	MS m/z 378.1 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ 7.81 (s, 1H), 7.73 (s, 1H), 7.61 (d, J = 2.3 Hz, 1H), 7.04 (s, 1H), 6.98 – 6.92 (m, 1H), 4.72 – 4.63 (m, 1H), 4.20 – 4.11 (m, 1H), 2.37 (s, 3H), 2.23 – 2.16 (m, 1H), 2.15 – 2.07 (m, 5H), 1.92 – 1.91 (m, 1H), 1.62 – 1.48 (m, 4H). 2H not observed (2 OH).
II-52	MS m/z 352.2 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 8.01 (d, J = 3.5 Hz, 1H), 7.80 (s, 1H), 6.65 (d, J = 3.5 Hz, 1H), 6.31 (s, 1H), 5.17 (p, J = 8.4 Hz, 1H), 4.58 (t, J = 8.6 Hz, 2H), 3.15 (t, J = 8.5 Hz, 2H), 2.85 – 2.67 (m, 4H), 2.01 (s, 3H), 1.53 (s, 3H). OH peaks not observed.
II-53	MS m/z 399.2 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 8.06 (dd, J = 13.4, 3.6 Hz, 1H), 7.91 (s, 1H), 7.83 (d, J = 2.3 Hz, 1H), 7.45 (s, 1H), 7.08 (d, J = 2.5 Hz, 1H), 6.67 (d, J = 3.5 Hz, 1H), 6.58 (t, J = 56 Hz, 1H), 5.21 (ddd, J = 14.9, 10.6, 4.1 Hz, 1H), 3.24 (d, J = 8.9 Hz, 1H), 2.92 (d, J = 11.7 Hz, 1H), 2.63 (t, J = 10.7 Hz, 1H), 2.39 (s, 3H), 2.32 – 2.17 (m, 2H), 2.10 (qd, J = 12.0, 4.6 Hz, 1H), 2.03 – 1.83 (m, 2H). OH peak not observed.
II-54	MS m/z 378.1 $[M+H]^+$. ^1H NMR (400 MHz, methanol- d_4) δ 8.05 – 7.79 (m, 2H), 7.21 – 6.99 (m, 2H), 6.77 – 6.59 (m, 1H), 5.20 – 5.01 (m, 1H), 4.77 – 4.63 (m, 1H), 2.50 – 2.37 (m, 1H), 2.32 – 2.16 (m, 2H), 2.13 (s, 3H), 2.07 – 1.96 (m, 2H), 1.88 – 1.73 (m, 1H). OH peaks not observed.
II-55	MS m/z 392.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ 10.03 (s, 1H), 8.15 (d, J = 3.1 Hz, 1H), 7.81 (s, 1H), 7.16 (s, 1H), 7.10 (s, 1H), 6.63 (d, J = 3.4 Hz, 1H), 5.23 (quint, J = 8.4 Hz, 1H), 3.20 (s, 3H), 2.75 – 2.66 (m, 2H), 2.63 – 2.54 (m, 2H), 2.06 (s, 3H), 1.46 (s, 3H)
II-56	MS m/z 392.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ 9.84 (s, 1H), 8.12 (d, J = 3.5 Hz, 1H), 7.73 (s, 1H), 7.11 (s, 1H), 7.05 (s, 1H), 6.60 (d, J = 3.4 Hz, 1H), 5.22 (quint, J = 8.4 Hz, 1H), 3.20 (s, 3H), 2.74 – 2.66 (m, 2H), 2.64 – 2.53 (m, 2H), 2.38 (s, 3H), 1.45 (s, 3H)
II-57	MS m/z 400.1 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ 8.06 (d, J = 3.5 Hz, 1H), 7.93 (s, 1H), 7.83 (d, J = 2.0 Hz, 1H), 7.46 (s, 1H), 7.08 (d, J = 1.9 Hz, 1H), 6.69 (d, J = 3.63 Hz, 1H), 6.59 (t, J = 57.53 Hz, 1H), 5.28 (quint, J = 9.38 Hz, 1H), 3.28 (s, 3H), 2.80 – 2.67 (m, 4H), 1.54 (s, 3H). 1H not observed (OH)
II-58	MS m/z 386.2 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 8.06 (d, J = 3.5 Hz, 1H), 7.93 (s, 1H), 7.83 (d, J = 2.2 Hz, 1H), 7.46 (s, 1H), 7.08 (d, J = 2.3 Hz, 1H), 6.69 (d, J = 3.5 Hz, 1H), 6.58 (t, J = 64 Hz, 1H), 5.20 (p, J = 8.3 Hz, 1H), 2.88 – 2.78 (m, 2H), 2.78 – 2.65 (m, 2H), 1.54 (s, 3H). OH peaks not observed.

Cmpd #	Characterization
II-59	MS m/z 377.5 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 8.02 (d, J = 3.6 Hz, 1H), 7.83 (s, 1H), 7.63 (d, J = 2.3 Hz, 1H), 7.06 (s, 1H), 6.95 (d, J = 2.3 Hz, 1H), 6.64 (d, J = 3.6 Hz, 1H), 5.20 (s, 1H), 3.27 – 3.19 (m, 1H), 2.92 (d, J = 11.7 Hz, 1H), 2.63 (t, J = 10.6 Hz, 1H), 2.45 (q, J = 7.5 Hz, 2H), 2.39 (s, 3H), 2.31 – 2.16 (m, 2H), 2.10 (dd, J = 12.0, 4.3 Hz, 1H), 2.02 – 1.82 (m, 2H), 1.02 (t, J = 7.5 Hz, 3H). OH peak not observed.
II-60	MS m/z 336.0 $[M+H]^+$. ^1H NMR (400 MHz, methanol- d_4) δ 8.14 (s, 1H), 7.87 (s, 1H), 7.62 (s, 1H), 7.16 – 6.86 (m, 2H), 6.77 – 6.51 (m, 1H), 5.68 (s, 1H), 4.78 – 4.62 (m, 1H), 3.04 – 2.79 (m, 1H), 2.70 – 2.52 (m, 1H), 2.52 – 2.30 (m, 1H), 2.29 – 1.95 (m, 4H). OH peaks not observed.
II-61	MS m/z 336.0 $[M+H]^+$. ^1H NMR (400 MHz, methanol- d_4) δ 8.05 (s, 1H), 7.90 (s, 1H), 7.62 (s, 1H), 7.04 (s, 1H), 6.96 (s, 1H), 6.69 (d, J = 3.2 Hz, 1H), 5.21 – 5.09 (m, 1H), 4.80 – 4.71 (m, 1H), 2.44 – 2.28 (m, 2H), 2.24 – 2.07 (m, 4H), 1.90 – 1.73 (m, 1H). OH peaks not observed.
II-62	MS m/z 380.0 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 8.07 (d, J = 3.5 Hz, 1H), 7.94 (s, 1H), 7.26 (d, J = 2.0 Hz, 1H), 7.13 (d, J = 2.0 Hz, 1H), 6.71 (s, 1H), 6.51 (t, J = 56.0 Hz, 1H), 5.20 (p, J = 8.4 Hz, 1H), 2.89 – 2.79 (m, 2H), 2.79 – 2.68 (m, 2H), 1.55 (s, 3H). OH peaks not observed.

Example 2A. Preparation of (R)-2-(7-(1-methylpiperidin-3-yl)-4-(trifluoromethyl)-7H-pyrrolo[2,3-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol (IIA-1)



- 5 Step 1 and 2. A solution of 2,2,6,6-tetramethylpiperidinylmagnesium chloride lithium chloride complex (1.0 mol/L) in THF/toluene (10.0 mL, 1:1) was cooled down to 0 °C. Dried zinc pivalate (2.9 g, 11.0 mmol) was then added in one portion to the solution under stream of nitrogen. The ice bath was removed, and the solution was stirred at room temperature for 1 h, resulting in a 0.73 M solution of TMPZn(OPiv)₂MgClLiCl as determined by titration with

diphenylacetic acid. In a separate round-bottom flask, a solution of 3,6-dichloro-4-(trifluoromethyl)pyridazine (0.500 g, 2.30 mmol) in dry THF (4.60 mL) was cooled to -20 °C. A solution of 0.73 M TMP-Zn(OPiv)₂-MgCl-LiCl (4.70 mL, 3.46 mmol) in THF/toluene (prepared as described above) was added dropwise. The reaction was stirred at -20 °C for 1 h, upon which the zincation was complete (as indicated by LCMS analysis of I₂-quenched aliquot sample). A solution of 2.1 M copper(I) cyanide di(lithium chloride) complex solution (0.11 mL, 0.230 mmol) in THF was then added to the reaction mixture followed by addition of 3-bromoprop-1-ene (0.418 g, 0.299 mL, 3.46 mmol). The mixture was gradually warmed up to 0 °C and stirred for 1 hour at this temperature. Upon completion, the reaction was quenched with aq. saturated NH₄Cl, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic parts were washed with water, brine, dried over sodium sulfate, filtered, and solvent evaporated under reduced pressure. The resulting residue was purified via silica gel flash column chromatography eluting with a gradient hexanes/EtOAc (0-10% EtOAc) to afford 4-allyl-3,6-dichloro-5-(trifluoromethyl)pyridazine (0.236 g, 40% yield over 2 steps) as pale yellow oil. MS *m/z* 257.0, 259.0, 261.0 [M+H]⁺.

Step 3. To a solution of 4-allyl-3,6-dichloro-5-(trifluoromethyl)pyridazine (0.30 g, 1.17 mmol) in THF (6.0 mL) and water (2.0 mL) were added 2,4,6-trimethylpyridine (0.283 g, 0.31 mL, 2.33 mmol), osmium tetroxide (4%) in water (0.36 mL, 0.059 mmol), and sodium periodate (1.25 g, 5.84 mmol). After the addition, the reaction mixture changed color from transparent yellow to dark to milky white. The reaction mixture was stirred for 6 hours at room temperature. Upon completion, the reaction was quenched with water (10 mL). The aqueous solution was then extracted with CH₂Cl₂ (3 × 10 mL). The combined organic parts were washed with water, brine, dried over sodium sulfate, filtered, and solvent evaporated under reduced pressure. The resulting residue was purified via silica gel flash column chromatography eluting with a gradient hexanes/EtOAc (0-10% EtOAc) to yield 3-[3,6-dichloro-5-(trifluoromethyl)pyridazin-4-yl]propane-1,2-diol (0.199 g, 59% yield) as pale brown oil. MS *m/z* 291.0, 293.0, 295.0 [M+H]⁺.

Step 4. A solution of 3-[3,6-dichloro-5-(trifluoromethyl)pyridazin-4-yl]propane-1,2-diol (0.199 g, 0.683 mmol) in MeOH (3.0 mL) was cooled down to 0 °C and a solution of sodium periodate (0.161 g, 0.751 mmol) in water (3.0 mL) was added dropwise. The mixture was stirred at room temperature for 2 hours (precipitate formation was observed), then partitioned between water and EtOAc (3 × 10 mL). The combined organic parts were washed with water, brine, dried over

sodium sulfate, filtered, and solvent evaporated under reduced pressure. The resulting residue was purified via silica gel flash column chromatography eluting with a gradient hexanes/EtOAc (10-20% EtOAc) to afford 2-(3,6-dichloro-5-(trifluoromethyl)pyridazin-4-yl)acetaldehyde (0.083 g, 47% yield) as pale yellow solid. MS m/z 257.0, 259.0, 260.9 $[M-H]^-$.

- 5 Step 5. To a solution of 2-(3,6-dichloro-5-(trifluoromethyl)pyridazin-4-yl)acetaldehyde (0.083 g, 0.321 mmol) in CH_2Cl_2 (3.0 mL) was added acetic acid (0.0386 g, 0.0368 mL, 0.642 mmol), (*R*)-1-methylpiperidin-3-amine (0.0440 g, 0.385 mmol), and sodium triacetoxymethylborohydride (0.102 g, 0.482 mmol). The mixture was stirred for 15 minutes at room temperature, upon which starting material has been consumed. The solution was then partitioned between CH_2Cl_2 and water. The combined organic parts were washed with water, brine, dried over sodium sulfate, filtered, and solvent was evaporated under reduced pressure to afford crude (*R,E*)-N-(2-(3,6-dichloro-5-(trifluoromethyl)pyridazin-4-yl)vinyl)-1-methylpiperidin-3-amine, which was used in the next step without further purification. MS m/z 355.1, 357.1, 359.1 $[M+H]^+$.

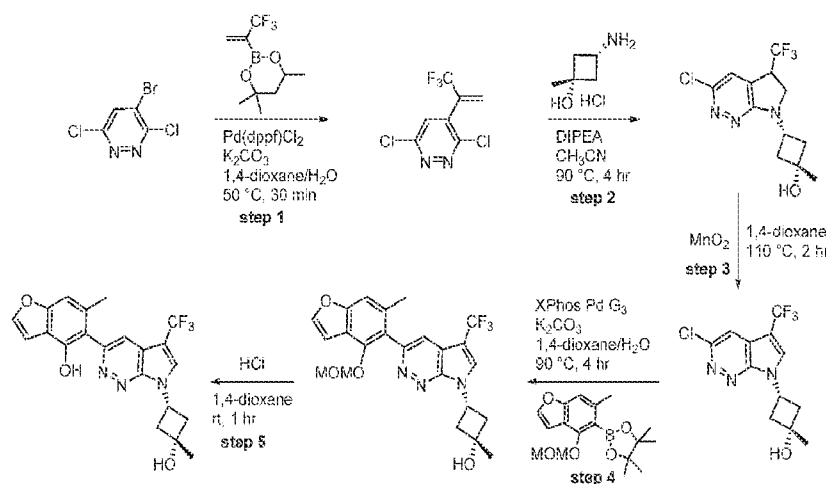
- 15 Step 6. (*R,E*)-N-(2-(3,6-dichloro-5-(trifluoromethyl)pyridazin-4-yl)vinyl)-1-methylpiperidin-3-amine from previous step was dissolved in CH_2Cl_2 (1.0 mL) and MeOH (1.0 mL). Silica gel (5.0 g) was then added to the solution. The mixture was stirred at room temperature for 48 hours, upon which LCMS showed complete consumption of the starting material. The solvent was evaporated and the residue was purified by flash column chromatography eluting with a gradient CH_2Cl_2 /MeOH (0-20% MeOH) to afford (*R*)-3-chloro-7-(1-methylpiperidin-3-yl)-4-(trifluoromethyl)-7*H*-pyrrolo[2,3-*c*]pyridazine (19.2 mg, 19% yield over 2 steps) as yellow solid. MS m/z 319.1, 321.1 $[M+H]^+$.

- 20 Step 7. To a screw top vial were added: (*R*)-3-chloro-7-(1-methylpiperidin-3-yl)-4-(trifluoromethyl)-7*H*-pyrrolo[2,3-*c*]pyridazine (19.2 mg, 0.06 mmol), 2-[2-(methoxymethoxy)-4-(trifluoromethyl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (39.6 g, 0.119 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (4.9 mg, 0.0060 mmol), and potassium carbonate (24.7 mg, 0.179 mmol). The mixture was degassed by purging with nitrogen for 15 min before 1,4 dioxane (2.1 mL) and water (0.7 mL) were added. The reaction vessel was vacuumed and backflushed with nitrogen, and the mixture was stirred at 90 °C for 16 hours. Upon completion, the mixture was partitioned between EtOAc and water.
- 30 The combined organic parts were washed with brine, dried over sodium sulfate, filtered and

concentrated under pressure to afford (R)-3-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-7-(1-methylpiperidin-3-yl)-4-(trifluoromethyl)-7H-pyrrolo[2,3-c]pyridazine as a brown oil. The crude material was taken to the next step without further purification. MS m/z 489.1 $[M+H]^+$.

Step 8. The crude product from the previous step was then dissolved in MeOH (1.0 mL) and 12.0 N HCl (few drops) was added. After 2 hours of stirring, the reaction was quenched with sat. aq. NaHCO₃ solution. The aqueous solution was then extracted with EtOAc (3×20 mL). The combined organic parts were washed with water, brine, dried over Na₂SO₄, solvents were evaporated. The residue was purified by reverse-phase column chromatography eluting with a gradient ACN (0.1% formic acid)/water(0.1% formic acid) (5-10% ACN) to yield (R)-2-(7-(1-methylpiperidin-3-yl)-4-(trifluoromethyl)-7H-pyrrolo[2,3-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol (4.6 mg, 17% yield over 2 steps) as pale yellow solid. MS m/z 445.1 $[M+H]^+$; ¹H NMR (500 MHz, methanol-*d*₄) δ : 8.31 (s, 1H), 7.43 (d, J = 7.9 Hz, 1H), 7.26 (d, J = 8.3 Hz, 1H), 7.20 (s, 1H), 6.82 (s, 1H), 5.34 – 5.22 (m, 1H), 3.01 – 2.92 (m, 1H), 2.81 – 2.68 (m, 1H), 2.45 (s, 3H), 2.40 – 2.30 (m, 1H), 2.30 – 2.08 (m, 2H), 2.05 – 1.95 (m, 1H), 1.95 – 1.82 (m, 1H); 2Hs not observed (NH and OH).

Example 2B. Preparation of 5-(7-((1*S*,3*S*)-3-hydroxy-3-methylcyclobutyl)-5-(trifluoromethyl)-7H-pyrrolo[2,3-c]pyridazin-3-yl)-6-methylbenzofuran-4-ol (IIB-1)



Step 1: To a degassed solution of 4-bromo-3,6-dichloropyridazine (115 mg, 0.50 mmol) in 1,4-dioxane (3mL) was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (Pd(dppf)Cl₂) (37 mg, 0.05 mmol), 4,4,6-trimethyl-2-(3,3,3-trifluoroprop-1-en-2-yl)-1,3,2-

dioxaborinane (168 mg, 0.76 mmol), and a 2 M aqueous solution of potassium carbonate (0.76 mL, 1.5 mmol) under nitrogen. The mixture was heated to 50 °C for 30 minutes. Upon completion, the reaction was diluted with water, extracted with DCM, dried over sodium sulfate, filtered, and evaporated under reduced pressure. Crude residue was purified via flash chromatography eluting with 0 to 100% EtOAc in hexanes to afford 3,6-dichloro-4-[1-(trifluoromethyl)vinyl]pyridazine (80 mg, 65% yield). MS m/z 243.0 $[M+H]^+$.

Step 2: To a solution of 3,6-dichloro-4-[1-(trifluoromethyl)vinyl]pyridazine (350 mg, 1.44 mmol) and *cis*-3-amino-1-methylcyclobutanol hydrochloride (238 mg, 1.73 mmol) in acetonitrile (4.80 mL) was added *N,N*-diisopropylethylamine (0.75 mL, 4.32 mmol). The mixture was stirred at 90 °C for 4 hours. Upon completion the reaction was diluted with DCM (5 mL) and washed with saturated ammonium chloride, water, and brine. Combined organics were dried over sodium sulfate, filtered and evaporated under reduced pressure. The crude residue was purified via flash chromatography eluting with 0 to 30% MeOH in DCM to afford *cis*-3-[3-chloro-5-(trifluoromethyl)-5,6-dihydropyrrolo[2,3-*c*]pyridazin-7-yl]-1-methyl-cyclobutanol (100 mg, 22% yield). MS m/z 308.0 $[M+H]^+$.

Step 3: To a solution of *cis*-3-[3-chloro-5-(trifluoromethyl)-5,6-dihydropyrrolo[2,3-*c*]pyridazin-7-yl]-1-methyl-cyclobutanol (50 mg, 0.162 mmol) in 1,4-dioxane (0.54 mL) was added manganese (IV) oxide (0.028 mL, 1.62 mmol). The reaction was stirred at 110 °C for 2 hours until TLC indicated disappearance of starting material. The reaction was then filtered over a pad of celite. The celite pad was washed with ethyl acetate and the filtrate evaporated under reduced pressure. The residue was further purified via flash chromatography eluting with 0 to 30% MeOH in DCM to afford *cis*-3-[3-chloro-5-(trifluoromethyl)pyrrolo[2,3-*c*]pyridazin-7-yl]-1-methyl-cyclobutanol (34 mg, 68% yield). MS m/z 306.0 $[M+H]^+$; ^1H NMR (500 MHz, MeOD) δ : 8.62 (d, J = 1.3 Hz, 1H), 7.99 (s, 1H), 5.10 (p, J = 8.3 Hz, 1H), 2.82 (ddt, J = 10.2, 5.2, 2.6 Hz, 2H), 2.69 (td, J = 9.3, 2.8 Hz, 2H), 1.51 (s, 3H).

Step 4: To a solution of *cis*-3-[3-chloro-5-(trifluoromethyl)pyrrolo[2,3-*c*]pyridazin-7-yl]-1-methyl-cyclobutanol (110 mg, 0.360 mmol) in dioxane was added XPhos Pd G3 (30 mg, 0.0360 mmol), 2-[4-(methoxymethoxy)-6-methyl-benzofuran-5-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (229 mg, 0.720 mmol), and aqueous 2 M potassium carbonate (0.54 mL, 1.08 mmol). The reaction stirred at 90 °C for 4 hours. Upon completion, organics were separated, and

solvent evaporated under reduced pressure. The crude residue was purified via flash chromatography eluting with 0 to 30% MeOH in DCM to afford cis-3-[3-[4-(methoxymethoxy)-6-methyl-benzofuran-5-yl]-5-(trifluoromethyl)pyrrolo[2,3-c]pyridazin-7-yl]-1-methyl-cyclobutanol (100 mg, 60% yield). MS m/z 462.2 $[M+H]^+$.

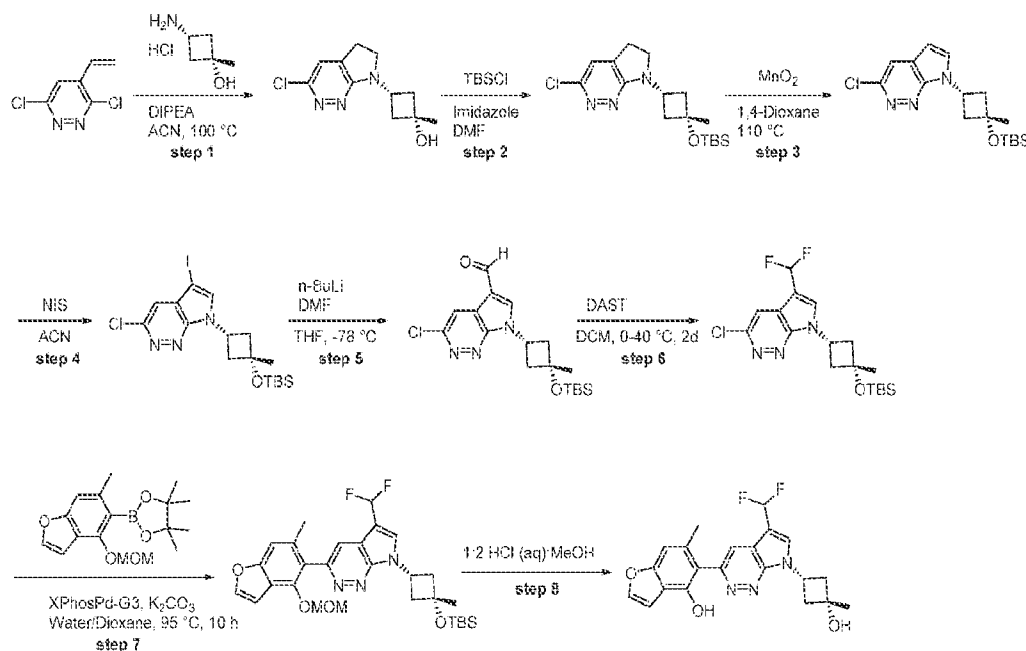
- 5 Step 5: To a solution of cis-3-[3-[4-(methoxymethoxy)-6-methyl-benzofuran-5-yl]-5-(trifluoromethyl)pyrrolo[2,3-c]pyridazin-7-yl]-1-methyl-cyclobutanol in 1,4-dioxane (1.25 mL) was added a 4 M solution of HCl in 1,4-dioxane (0.13 mL, 0.54 mmol). The reaction was stirred at room temperature for 1 hour. Upon completion, the mixture was diluted with DCM and quenched with 10% aqueous sodium bicarbonate solution. Organics were washed with water,
10 brine, dried over sodium sulfate, filtered, and evaporated under reduced pressure. The crude residue was purified via flash chromatography eluting with 0 to 30% MeOH in DCM. The product fractions were collected, evaporated under reduced pressure, and re-purified via flash chromatography eluting with 0 to 100% CH₃CN in water to afford 5-[7-(3-hydroxy-3-methyl-cyclobutyl)-5-(trifluoromethyl)pyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol (4 mg,
15 10% yield). MS m/z 418.0 $[M+H]^+$; ¹H NMR (400 MHz, MeOD) δ : 8.58 (s, 1H), 7.91 (s, 1H), 7.63 (d, J = 2.3 Hz, 1H), 7.06 (s, 1H), 7.02 – 6.89 (m, 1H), 5.22 (p, J = 8.3 Hz, 1H), 2.92-2.83 (m, 2H), 2.81 – 2.64 (m, 2H), 2.13 (s, 3H), 1.54 (s, 3H).

Using the procedure described for Example 2B, above, additional compounds described herein
20 may be prepared by substituting the appropriate starting material, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Table 2B

Cmpd #	Characterization
IIB-1	MS m/z 418.0 $[M+H]^+$. ¹ H NMR (400 MHz, MeOD) δ 8.58 (s, 1H), 7.91 (s, 1H), 7.63 (d, J = 2.3 Hz, 1H), 7.06 (s, 1H), 7.02 – 6.89 (m, 1H), 5.22 (p, J = 8.3 Hz, 1H), 2.87 (ddd, J = 10.2, 7.8, 2.7 Hz, 2H), 2.81 – 2.64 (m, 2H), 2.13 (s, 3H), 1.54 (s, 3H). OH peaks not observed.
IIB-2	MS m/z 446.2 $[M+H]^+$. ¹ H NMR (500 MHz, MeOD) δ 8.58 (d, J = 1.3 Hz, 1H), 7.83 (s, 1H), 7.16 (d, J = 1.5 Hz, 1H), 7.04 (s, 1H), 5.22 (p, J = 8.3 Hz, 1H), 2.86 (ddt, J = 10.2, 5.2, 2.6 Hz, 2H), 2.74 (td, J = 9.2, 2.8 Hz, 2H), 2.43 (s, 3H), 1.53 (s, 3H). OH peaks not observed.

Example 2C. Preparation of 5-(5-(difluoromethyl)-7-((cis)-3-hydroxy-3-methylcyclobutyl)-7H-pyrrolo[2,3-*c*]pyridazin-3-yl)-6-methylbenzofuran-4-ol (IIC-1)



- 5 **Step 1.** *N,N*-diisopropylethylamine (2.6 mL, 15.0 mmol) was added to a solution of 3,6-dichloro-4-vinyl-pyridazine (875 mg, 5.00 mmol, prepared according to the procedure in example 2B) and cis-3-amino-1-methyl-cyclobutanol hydrochloride (826 mg, 6.00 mmol) in ACN (12.5 mL) and stirred at 100 °C for 3 h. Upon reaction completion, the mixture was concentrated. The crude residue was purified by silica gel column chromatography eluting with 0:100 to
- 10 30:70 MeOH:DCM to afford cis-3-(3-chloro-5,6-dihydropyrrolo[2,3-*c*]pyridazin-7-yl)-1-methyl-cyclobutanol (1.110 g, 4.64 mmol, 93% yield). MS *m/z* 240.1 [*M*+*H*]⁺. ¹H NMR (400 MHz, methanol-*d*₄) δ 7.13 – 7.08 (m, 1H), 4.17 (p, *J* = 8.4 Hz, 1H), 3.79 – 3.69 (m, 2H), 3.14 – 3.06 (m, 2H), 2.40 – 2.31 (m, 4H), 1.39 (s, 3H).

- Step 2.** cis-3-(3-chloro-5,6-dihydropyrrolo[2,3-*c*]pyridazin-7-yl)-1-methyl-cyclobutanol (1.007 g, 4.20 mmol), *tert*-butyldimethylchlorosilane (0.950 g, 6.30 mmol), and imidazole (857.8 mg, 12.6 mmol) were dissolved in DMF (10.5 mL) and stirred at rt for 4 h. After completion, the reaction was diluted with EtOAc and NaHCO₃ (sat. aq.). The product was extracted several times with EtOAc and the combined organic extracts were dried over Na₂SO₃ and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography eluting with 0:100 to 20:80 EtOAc:DCM to afford 7-((cis)-3-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclobutyl)-3-
- 15
- 20

chloro-6,7-dihydro-5*H*-pyrrolo[2,3-*c*]pyridazine (1.281 g, 3.62 mmol, 86% yield). MS *m/z* 354.2 [M+H]⁺. ¹H NMR (400 MHz, methanol-*d*₄) δ 7.14 – 7.07 (m, 1H), 4.17 (p, *J* = 8.4 Hz, 1H), 3.79 – 3.66 (m, 2H), 3.16 – 3.03 (m, 2H), 2.46 – 2.32 (m, 4H), 1.44 (s, 3H), 0.90 (s, 9H), 0.12 (s, 6H).

Step 3. Manganese (IV) oxide (5.216 g, 60.0 mmol) was added to a solution of 7-((*cis*)-3-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclobutyl)-3-chloro-6,7-dihydro-5*H*-pyrrolo[2,3-*c*]pyridazine (1.062 g, 3.00 mmol) in 1,4-dioxane (15 mL) and heated to 110 °C for 8 h. After the reaction was cooled to ambient temperature, the crude reaction mixture was diluted with ethyl acetate and then filtered through celite. The filtrate was concentrated *in vacuo* and the crude residue was purified by silica gel column chromatography eluting with 0:100 to 40:60 EtOAc (40% DCM in hexanes) to afford 7-((*cis*)-3-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclobutyl)-3-chloro-7*H*-pyrrolo[2,3-*c*]pyridazine (640 mg, 1.81 mmol, 61% yield). MS *m/z* 352.3 [M+H]⁺. ¹H NMR (400 MHz, methanol-*d*₄) δ 7.99 (d, *J* = 3.5 Hz, 1H), 7.92 (s, 1H), 6.62 (d, *J* = 3.5 Hz, 1H), 5.02 (p, *J* = 8.4 Hz, 1H), 2.84 – 2.63 (m, 4H), 1.56 (s, 3H), 0.93 (s, 9H), 0.15 (s, 6H).

Step 4. *N*-iodosuccinimide (405 mg, 1.80 mmol) was added to a solution of 7-((*cis*)-3-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclobutyl)-3-chloro-7*H*-pyrrolo[2,3-*c*]pyridazine (528 mg, 1.50 mmol) in ACN (10 mL) at 0 °C. After 30 min, the mixture was returned to rt and stirred for 3 h. Upon reaction completion, the mixture was poured into ice cold NaHCO₃ (sat, aq) and extracted with EtOAc. The product was extracted several times with EtOAc and the combined organic extracts were dried over Na₂SO₃ and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography eluting with 5:95 to 30:70 EtOAc:hexanes to afford 7-((*cis*)-3-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclobutyl)-3-chloro-5-iodo-7*H*-pyrrolo[2,3-*c*]pyridazine (654 mg, 1.37 mmol, 91% yield). MS *m/z* 478.1 [M+H]⁺. ¹H NMR (400 MHz, methanol-*d*₄) δ 8.15 (s, 1H), 7.68 (s, 1H), 5.00 (p, *J* = 8.3 Hz, 1H), 2.87 – 2.67 (m, 4H), 1.55 (s, 3H), 0.93 (s, 9H), 0.15 (s, 6H).

Step 5. *n*-BuLi (1.25 M in hexanes/Et₂O, 0.88 mL, 1.1 mmol) was added dropwise to a solution of 7-((*cis*)-3-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclobutyl)-3-chloro-5-iodo-7*H*-pyrrolo[2,3-*c*]pyridazine (477.8 mg, 1.00 mmol) in THF (5 mL) cooled to -78 °C. After 45 min, DMF (4M in Et₂O, 0.325 mL, 1.3 mmol) was added dropwise to the reaction mixture at -78 °C. After 1 h, the cooling bath was removed, and the reaction mixture was stirred for 30 min. The reaction mixture was moved to an ice bath and quenched with water. The product was extracted several times

with EtOAc and the combined organic extracts were dried over Na₂SO₃ and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography eluting with 1:99 to 40:60 EtOAc:hexanes to afford 7-((cis)-3-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclobutyl)-3-chloro-7*H*-pyrrolo[2,3-*c*]pyridazine-5-carbaldehyde (266 mg, 0.700 mmol, 70% yield). MS *m/z* 380.1 [M+H]⁺. ¹H NMR (400 MHz, methanol-*d*₄) δ 9.98 (s, 1H), 8.87 (s, 1H), 8.35 (s, 1H), 5.11 – 4.96 (m, 1H), 2.93 – 2.72 (m, 4H), 1.59 (s, 3H), 0.94 (s, 9H), 0.17 (s, 6H).

Step 6. DAST (483.6 mg, 3.00 mmol) was added to a solution of 7-((cis)-3-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclobutyl)-3-chloro-7*H*-pyrrolo[2,3-*c*]pyridazine-5-carbaldehyde (228 mg, 0.600 mmol) in DCM (4 mL) at 0 °C. After 20 min, the ice bath was removed, and the mixture was stirred at rt for 2 h. After 2 h, the temperature was increased to 40 °C and the reaction was stirred for 24 h. Upon reaction completion, the mixture was slowly quenched with cold NaHCO₃ (sat, aq) while cooled in an ice bath. The products were extracted with DCM and the combined organic extracts were dried over Na₂SO₃ and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography eluting with 1:99 to 50:50 EtOAc:hexanes to afford 7-((cis)-3-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclobutyl)-3-chloro-5-(difluoromethyl)-7*H*-pyrrolo[2,3-*c*]pyridazine (175 mg, 0.435 mmol, 73% yield). MS *m/z* 402.1 [M+H]⁺. ¹H NMR (400 MHz, methanol-*d*₄) δ 8.34 – 8.28 (m, 1H), 8.02 (s, 1H), 7.06 (t, *J* = 55.5 Hz, 1H), 5.01 (p, *J* = 8.5 Hz, 1H), 2.87 – 2.67 (m, 4H), 1.56 (s, 3H), 0.92 (s, 9H), 0.15 (s, 6H).

Step 7. A mixture of 7-((cis)-3-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclobutyl)-3-chloro-5-(difluoromethyl)-7*H*-pyrrolo[2,3-*c*]pyridazine (60 mg, 0.150 mmol), 2-[4-(methoxymethoxy)-6-methyl-benzofuran-5-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (57 mg, 0.180 mmol), K₂CO₃ (2 M, 0.23 mL, 0.450 mmol), XPhos Pd G3 (7.6 mg, 0.009 mmol) in 1,4-Dioxane (0.75 mL) was sparged with argon and then heated to 95 °C for 2 h. After cooling to rt, the reaction was diluted with NaHCO₃ (sat, aq.) and the products were extracted several times with EtOAc. The combined organic extracts were dried over Na₂SO₃ and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography eluting with 0:100 to 100:0 EtOAc:hexanes to afford 7-((cis)-3-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclobutyl)-5-(difluoromethyl)-3-(4-(methoxymethoxy)-6-methylbenzofuran-5-yl)-7*H*-pyrrolo[2,3-*c*]pyridazine (75 mg, 0.134 mmol, 89% yield). ¹H NMR (400 MHz, methanol-*d*₄) δ 8.30 (s, 1H), 7.95 (s, 1H), 7.72 (d, *J* = 2.3 Hz,

1H), 7.29 (s, 1H), 7.10 (t, $J = 55.5$ Hz, 1H), 7.04 – 7.01 (m, 1H), 5.14 (p, $J = 7.7$ Hz, 1H), 3.13 (s, 3H), 2.94 – 2.69 (m, 4H), 2.14 (s, 3H), 1.59 (s, 3H), 0.94 (s, 9H), 0.17 (s, 6H).

Step 8. 7-((cis)-3-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclobutyl)-3-chloro-5-

(difluoromethyl)-7*H*-pyrrolo[2,3-*c*]pyridazine (72 mg, 0.129 mmol) was dissolved in 1:2 HCl

(12M, aq):MeOH and stirred at rt for 3 h. The mixture was concentrated *in vacuo* and the crude residue was purified by C18 reverse phase Prep-HPLC eluting with ACN:Water with formic acid as the modifier. After reverse phase purification, solvents were removed to afford 5-(5-

(difluoromethyl)-7-((cis)-3-hydroxy-3-methylcyclobutyl)-7*H*-pyrrolo[2,3-*c*]pyridazin-3-yl)-6-methylbenzofuran-4-ol (22 mg, 0.055 mmol, 43%). MS m/z 400.1 $[M+H]^+$. ^1H NMR (400 MHz,

methanol- d_4) δ : 8.35 (s, 1H), 7.94 (s, 1H), 7.63 (d, $J = 2.2$ Hz, 1H), 7.31 – 6.94 (m, 3H), 5.27 – 5.13 (m, 1H), 2.90 – 2.78 (m, 2H), 2.77 – 2.66 (m, 2H), 2.13 (s, 3H), 1.54 (s, 3H). OH peaks not observed.

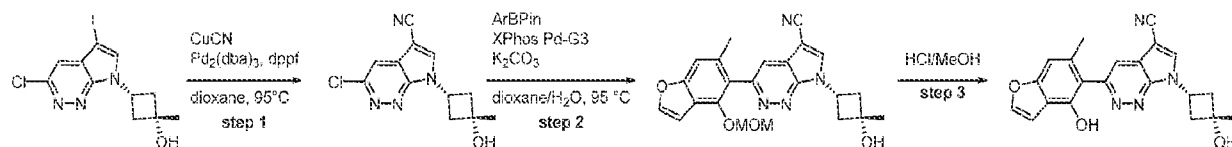
Using the procedure described for Example 2C, above, additional compounds described herein

may be prepared by substituting the appropriate starting material, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Table 2C

Cmpd#	Characterization
IIC-1	MS m/z 400.1 $[M+H]^+$. ^1H NMR (400 MHz, methanol- d_4) δ : 8.35 (s, 1H), 7.94 (s, 1H), 7.63 (d, $J = 2.2$ Hz, 1H), 7.31 – 6.94 (m, 3H), 5.27 – 5.13 (m, 1H), 2.90 – 2.78 (m, 2H), 2.77 – 2.66 (m, 2H), 2.13 (s, 3H), 1.54 (s, 3H). OH peaks not observed.
IIC-2	MS m/z 378.0 $[M+H]^+$. ^1H NMR (400 MHz, methanol- d_4) δ : 10.02 (s, 1H), 8.88 (s, 1H), 8.32 (s, 1H), 7.63 (d, $J = 2.1$ Hz, 1H), 7.06 (s, 1H), 6.98 (s, 1H), 5.19 (quint, $J = 8.2$ Hz, 1H), 2.94 – 2.84 (m, 2H), 2.81 – 2.71 (m, 2H), 2.14 (s, 3H), 1.55 (s, 3H). OH peaks not observed.
IIC-3	MS m/z 428.1 $[M+H]^+$. ^1H NMR (400 MHz, methanol- d_4) δ : 8.36 (s, 1H), 7.95 (s, 1H), 7.14 (s, 1H), 7.11 (t, $J = 55.7$ Hz, 1H), 7.07 (s, 1H), 5.19 (p, $J = 8.4$ Hz, 1H), 2.89 – 2.78 (m, 2H), 2.78 – 2.67 (m, 2H), 2.12 (s, 3H), 1.53 (s, 3H). OH peaks not observed.
IIC-4	MS m/z 402.1 $[M+H]^+$. ^1H NMR (400 MHz, methanol- d_4) δ : 8.31 (s, 1H), 7.94 (s, 1H), 7.62 (s, 1H), 7.26 – 6.90 (m, 3H), 5.73 – 5.57 (m, 1H), 3.18 – 2.88 (m, 4H), 2.13 (s, 3H), 1.65 (d, $J = 21.8$ Hz, 3H). OH peak not observed.
IIC-5	MS m/z 436.1 $[M+H]^+$. ^1H NMR (400 MHz, methanol- d_4) δ : 8.37 (s, 1H), 8.03 (s, 1H), 7.84 (d, $J = 2.0$ Hz, 1H), 7.48 (s, 1H), 7.11 (t, $J = 55.7$ Hz, 1H), 7.09 (d, $J = 1.4$ Hz, 1H), 6.63 (t, $J = 55.7$ Hz, 1H), 5.20 (p, $J = 8.0$ Hz, 1H), 2.90 – 2.80 (m, 2H), 2.78 – 2.66 (m, 2H), 1.54 (s, 3H). OH peaks not observed.

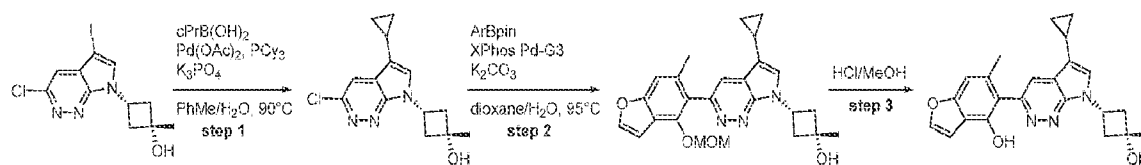
Example 2D. Preparation of 7-((1s,3s)-3-hydroxy-3-methylcyclobutyl)-3-(4-hydroxy-6-methylbenzofuran-5-yl)-7H-pyrrolo[2,3-c]pyridazine-5-carbonitrile (IID-1)



Step 1: 3-(3-Chloro-5-iodo-pyrrolo[2,3-c]pyridazin-7-yl)-1-methyl-cyclobutanol (0.150 g, 0.412 mmol), CuCN (0.110 g, 1.24 mmol), Pd₂(dba)₃ (0.037 g, 0.041 mmol), and dppf (0.091 g, 0.165 mmol) were dissolved in dioxane (4.1 mL). The reaction mixture was heated at 90 °C for 16 h, then diluted with EtOAc and washed with water and brine. The organic phase was dried (MgSO₄), filtered and concentrated. Purification by chromatography on SiO₂ (EtOAc:hexanes, 0 to 100%) gave a yellow foam (0.095 g, 87%). MS *m/z* 263.0, 264.9 [M+H]⁺.

Steps 2 and 3: 3-chloro-7-((3-hydroxy-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazine-5-carbonitrile (0.025 g, 0.091 mmol), 2-[4-(methoxymethoxy)-6-methyl-benzofuran-5-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.036 g, 0.114 mmol), XPhos Pd-G3 (0.008 g, 0.009 mmol), and K₂CO₃ (0.14 mL, 0.285 mmol, 2 M) were dissolved in dioxane (0.6 mL). The reaction was heated at 95 °C for 14 h. The reaction was diluted with EtOAc and washed with water and brine. The organic phase was dried (MgSO₄), filtered and concentrated. Purification by chromatography on SiO₂ (EtOAc:hexanes, 0 to 80%) gave a yellow film. MS *m/z* 419.1 [M+H]⁺. The material was dissolved in MeOH (1 mL), to which was added HCl (0.2 mL, 4.0M in dioxane) and the mixture was stirred at rt. Upon reaction completion, the mixture was concentrated, and the resulting residue was dissolved in DCM and washed with sat. NaHCO₃ and brine. The organic phase was dried (Na₂SO₄), filtered and concentrated. Purification by reverse-phase chromatography (1% formic acid in MeCN: 1% formic acid in water, 0 to 80%) gave a white solid (0.006 g, 17% 2 steps). MS *m/z* 375.1 [M+H]⁺; ¹H NMR (400 MHz, methanol-d₄) δ: 8.77 (s, 1H), 8.00 (s, 1H), 7.63 (d, *J* = 2.1 Hz, 1H), 7.06 (s, 1H), 7.00 – 6.96 (m, 1H), 5.20 (quint, *J* = 8.3 Hz, 1H), 2.91 – 2.83 (m, 2H), 2.82 – 2.68 (m, 2H), 2.14 (s, 3H), 1.54 (s, 3H). (2H not observed, 2 OH).

Example 2E. Preparation of 5-(5-cyclopropyl-7-((1s,3s)-3-hydroxy-3-methylcyclobutyl)-7H-pyrrolo[2,3-c]pyridazin-3-yl)-6-methylbenzofuran-4-ol (IIE-1)

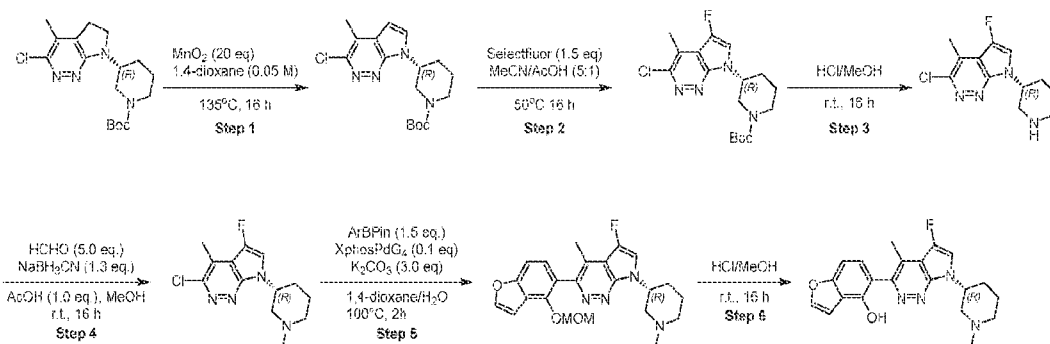


Step 1: 3-(3-Chloro-5-iodo-pyrrolo[2,3-c]pyridazin-7-yl)-1-methyl-cyclobutanol (0.60 g, 0.165 mmol), cyclopropylboronic acid (0.028 g, 0.330 mmol), Pd(OAc)_2 (0.009 g, 0.040 mmol), PCy_3 (0.018 g, 0.066 mmol), and K_3PO_4 (0.116 g, 0.545 mmol) were dissolved in $\text{PhMe/H}_2\text{O}$ (8:1, 0.9 mL). The reaction was heated at 90°C for 16 h. The reaction was diluted with EtOAc and washed with water and brine. The organic phase was dried (MgSO_4), filtered and concentrated. Purification by chromatography on SiO_2 (EtOAc:hexanes, 0 to 80%) gave a yellow solid (0.020 g, 44%). MS m/z 278.0, 279.9 $[\text{M}+\text{H}]^+$.

Step 2: 3-(3-Chloro-5-cyclopropyl-pyrrolo[2,3-c]pyridazin-7-yl)-1-methyl-cyclobutanol (0.020 g, 0.072 mmol), 2-[4-(methoxymethoxy)-6-methyl-benzofuran-5-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.027 g, 0.086 mmol), XPhos Pd-G3 (0.006 g, 0.007 mmol), and K_2CO_3 (0.11 mL, 0.216 mmol, 2 M soln) were dissolved in dioxane (0.36 mL). The reaction was heated at 95°C for 14 h, then diluted with EtOAc and washed with water and brine. The organic phase was dried over MgSO_4 , filtered and concentrated. Purification by chromatography on SiO_2 (EtOAc:hexanes, 0 to 80%) gave a yellow film. MS m/z 419.1 $[\text{M}+\text{H}]^+$.

Step 3: The material from step 2 was dissolved in MeOH (1 mL) and added HCl (0.2 mL, 4.0M in dioxane) and stirred at rt. Upon completion, the reaction was concentrated, and the resulting residue was dissolved in DCM and washed with sat. NaHCO_3 and brine. The organic phase was dried (Na_2SO_4), filtered and concentrated. Purification by reverse-phase chromatography (1% formic acid in MeCN: 1% formic acid in water, 0 to 80%) gave a white solid (0.008 g, 29% 2 steps). MS m/z 390.1 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.21 (s, 1H, formic acid), 7.99 (s, 1H), 7.86 (s, 1H), 7.63 (d, $J = 2.1$ Hz, 1H), 7.06 (s, 1H), 6.97 (d, $J = 1.9$ Hz, 1H), 5.12 (quint, $J = 8.4$ Hz, 1H), 2.80 – 2.73 (m, 2H), 2.73 – 2.65 (m, 2H), 2.15 (s, 3H), 2.06 – 1.98 (m, 1H), 1.51 (s, 3H), 1.03 – 0.93 (m, 2H), 0.79 – 0.73 (m, 2H). (2H not observed, 2 OH).

Example 2F. Preparation of (R)-5-(5-fluoro-4-methyl-7-(1-methylpiperidin-3-yl)-7H-pyrrolo[2,3-c]pyridazin-3-yl)benzofuran-4-ol (IIF-1)



Step 1. A 20 mL tube was charged with a mixture of tert-butyl (R)-3-(3-chloro-4-methyl-5,6-dihydro-7H-pyrrolo[2,3-c]pyridazin-7-yl)piperidine-1-carboxylate (100 mg, 0.283 mmol, 1.0 eq., prepared according to example 1) and MnO₂ (493 mg, 5.67 mmol, 20.0 eq.) in 1,4-dioxane (6 mL). The reaction was stirred at 135°C for 16 h. The reaction mixture was cooled to room temperature, filtered through a pad of Celite and rinsed with EtOAc (50 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with 0-50% EtOAc in hexanes to afford tert-butyl (R)-3-(3-chloro-4-methyl-7H-pyrrolo[2,3-c]pyridazin-7-yl)piperidine-1-carboxylate (35 mg, 0.998 mmol, 35.2% yield) as a pale yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 7.53 (d, J = 3.6 Hz, 1H), 6.48 (d, J = 3.6 Hz, 1H), 5.04 – 4.80 (m, 1H), 4.33 – 4.15 (m, 1H), 4.06 – 3.86 (m, 1H), 3.56 – 3.35 (m, 1H), 3.14 – 2.96 (m, 1H), 2.58 (s, 3H), 2.35 – 2.09 (m, 2H), 1.89 – 1.76 (m, 1H), 1.76 – 1.66 (m, 1H), 1.61 (s, 3H), 1.45 (s, 9H). MS m/z 351.4 [M+H]⁺.

Step 2. To a solution of tert-butyl (R)-3-(3-chloro-4-methyl-7H-pyrrolo[2,3-c]pyridazin-7-yl)piperidine-1-carboxylate (500 mg, 1.43 mmol, 1.0 eq.) and AcOH (2 mL) in MeCN (10 mL) was added Selectfluor (757 mg, 2.14 mmol, 1.5 eq.). The reaction was stirred at 50°C under N₂ atmosphere for 16 h. Upon completion, the reaction mixture was cooled to room temperature, neutralized with sat. NaHCO₃ aq. to pH = 8 and extracted with EtOAc (20 mL x 3). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by silica gel column chromatography eluting with 0-30% EtOAc in hexanes to give tert-butyl (R)-3-(3-chloro-5-fluoro-4-methyl-7H-pyrrolo[2,3-c]pyridazin-7-yl)piperidine-1-carboxylate (44 mg, 0.119 mmol, 8.37% yield) as yellow oil. MS m/z 369.4 [M+H]⁺.

Step 3. A mixture of tert-butyl (R)-3-(3-chloro-5-fluoro-4-methyl-7H-pyrrolo[2,3-c]pyridazin-7-yl)piperidine-1-carboxylate (45 mg, 0.122 mmol, 1.0 eq.) in HCl (25% w/w in MeOH, 1 mL) was stirred at rt for 16 h. The reaction mixture was concentrated under reduced pressure to afford

(R)-3-chloro-5-fluoro-4-methyl-7-(piperidin-3-yl)-7H-pyrrolo[2,3-c]pyridazine hydrochloride as a yellow solid (37 mg, 0.121 mmol, 99.4% yield), which was used directly for next step without further purification. MS m/z 269.4 $[M+H]^+$.

Step 4. To a solution of (R)-3-chloro-5-fluoro-4-methyl-7-(piperidin-3-yl)-7H-pyrrolo[2,3-c]pyridazine hydrochloride (37 mg, 0.121 mmol, 1.0 eq.) in MeOH (2 mL) were added Et_3N (12 mg, 0.121 mmol, 1 eq.), HCHO (37%w/w in H_2O) (49 mg, 0.606 mmol, 5 eq.) and AcOH (7 mg, 0.121 mmol, 1.0 eq.) in turn. The reaction was stirred at room temperature under N_2 atmosphere for 1 h and $NaBH_3CN$ (15 mg, 0.242 mmol, 2.0 eq.) was added into the mixture. The reaction was stirred at room temperature under N_2 atmosphere for 2 h. Upon completion, the reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by prep-TLC eluting with 50% EtOAc in hexanes to afford (R)-3-chloro-5-fluoro-4-methyl-7-(1-methylpiperidin-3-yl)-7H-pyrrolo[2,3-c]pyridazine (25 mg, 0.088 mmol, 72.9% yield) as a white solid. MS m/z 283.4 $[M+H]^+$.

Step 5. A 5 mL tube was charged with a mixture of (R)-3-chloro-5-fluoro-4-methyl-7-(1-methylpiperidin-3-yl)-7H-pyrrolo[2,3-c]pyridazine (25 mg, 0.088 mmol, 1.0 eq.), 2-(4-(methoxymethoxy)benzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (54 mg, 0.177 mmol, 2.0 eq.), K_2CO_3 (37 mg, 0.265 mmol, 3.0 eq.) and XPhos Pd G4 (8 mg, 0.009 mmol, 0.1 eq.) in H_2O (0.2 mL) and 1,4-dioxane (1 mL). The reaction was sealed under N_2 atmosphere and stirred at 100°C for 2 h. Upon completion, the reaction was cooled to room temperature, diluted with (10 mL) and extracted with EtOAc (10 mL x 3). The organic phase was dried over Na_2SO_4 , filtered and concentrated in vacuum. The residue was purified by prep-TLC eluting with 10% MeOH in DCM to afford (R)-5-fluoro-3-(4-(methoxymethoxy)benzofuran-5-yl)-4-methyl-7-(1-methylpiperidin-3-yl)-7H-pyrrolo[2,3-c]pyridazine (25 mg, 0.059 mmol, 66.6% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 6.65 (dd, J = 18.0, 12.0 Hz, 1H), 5.94 (dd, J = 12.0, 0.8 Hz, 1H), 5.67 (dd, J = 18.0, 0.8 Hz, 1H). MS m/z 425.1 $[M+H]^+$.

Step 6. A mixture of (R)-5-fluoro-3-(4-(methoxymethoxy)benzofuran-5-yl)-4-methyl-7-(1-methylpiperidin-3-yl)-7H-pyrrolo[2,3-c]pyridazine (25 mg, 0.058 mmol, 1.0 eq.) in HCl (25% w/w in MeOH, 1 mL) was stirred at rt for 16 h. The reaction mixture was neutralized with aq. sat. $NaHCO_3$ to pH = 8 and extracted with EtOAc (10 mL x 3). The organic phase was dried over

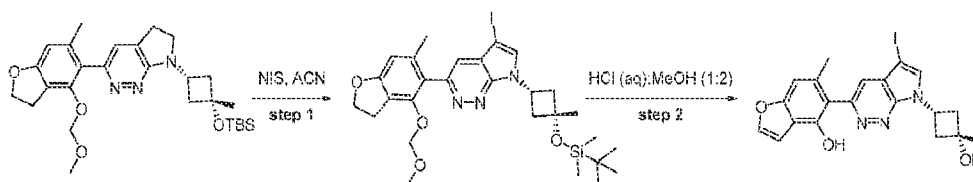
Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by prep-TLC eluting with 10% MeOH in DCM to afford (R)-5-(5-fluoro-4-methyl-7-(1-methylpiperidin-3-yl)-7H-pyrrolo[2,3-c]pyridazin-3-yl)benzofuran-4-ol (20 mg, 0.053 mmol, 91.0% yield) as a white solid. MS *m/z* 381.1 [M+H]⁺. ¹H NMR (400 MHz, MeOD) δ 7.88 (d, *J* = 2.0 Hz, 1H), 7.71 (d, *J* = 2.4 Hz, 1H), 7.22 – 7.15 (m, 2H), 7.03 (dd, *J* = 2.4, 0.8 Hz, 1H), 5.24 – 5.14 (m, 1H), 3.23 – 3.14 (m, 1H), 2.93 – 2.83 (m, 1H), 2.60 – 2.53 (m, 1H), 2.52 (s, 3H), 2.38 (s, 3H), 2.28 – 2.20 (m, 1H), 2.18 – 2.10 (m, 1H), 2.06 – 1.97 (m, 1H), 1.96 – 1.89 (m, 1H), 1.90 – 1.79 (m, 1H).

Using the procedure described for Example 2F, above, additional compounds described herein may be prepared by substituting the appropriate starting material, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Table 2F

Cmpd#	Characterization
IIF-1	MS <i>m/z</i> 381.1 [M+H] ⁺ . ¹ H NMR (400 MHz, MeOD) δ 7.88 (d, <i>J</i> = 2.0 Hz, 1H), 7.71 (d, <i>J</i> = 2.4 Hz, 1H), 7.22 – 7.15 (m, 2H), 7.03 (dd, <i>J</i> = 2.4, 0.8 Hz, 1H), 5.24 – 5.14 (m, 1H), 3.23 – 3.14 (m, 1H), 2.93 – 2.83 (m, 1H), 2.60 – 2.53 (m, 1H), 2.52 (s, 3H), 2.38 (s, 3H), 2.28 – 2.20 (m, 1H), 2.18 – 2.10 (m, 1H), 2.06 – 1.97 (m, 1H), 1.96 – 1.89 (m, 1H), 1.90 – 1.79 (m, 1H). OH peak not observed.
IIF-2	MS <i>m/z</i> : 383.5 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ: 7.85 (d, <i>J</i> = 2.0 Hz, 1H), 7.02 (d, <i>J</i> = 8.0 Hz, 1H), 6.43 (d, <i>J</i> = 8.0 Hz, 1H), 5.23 – 5.12 (m, 1H), 4.62 (t, <i>J</i> = 8.8 Hz, 2H), 3.21 (t, <i>J</i> = 8.8 Hz, 3H), 2.99 – 2.93 (m, 1H), 2.70 – 2.62 (m, 1H), 2.53 (s, 3H), 2.44 (s, 3H), 2.37 – 2.28 (m, 1H), 2.18 – 2.11 (m, 1H), 2.06 – 1.93 (m, 2H), 1.91 – 1.82 (m, 1H). OH peak not observed.
IIF-3	MS <i>m/z</i> 368.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, methanol- <i>d</i> ₄) δ 7.88 (d, <i>J</i> = 1.8 Hz, 1H), 7.72 (d, <i>J</i> = 2.3 Hz, 1H), 7.22 – 7.16 (m, 2H), 7.04 (d, <i>J</i> = 2.0 Hz, 1H), 5.19 (quint, <i>J</i> = 8.3 Hz, 1H), 2.81 – 2.72 (m, 2H), 2.70 – 2.59 (m, 2H), 2.53 (s, 3H), 1.51 (s, 3H). 2 H not observed (2 OH).

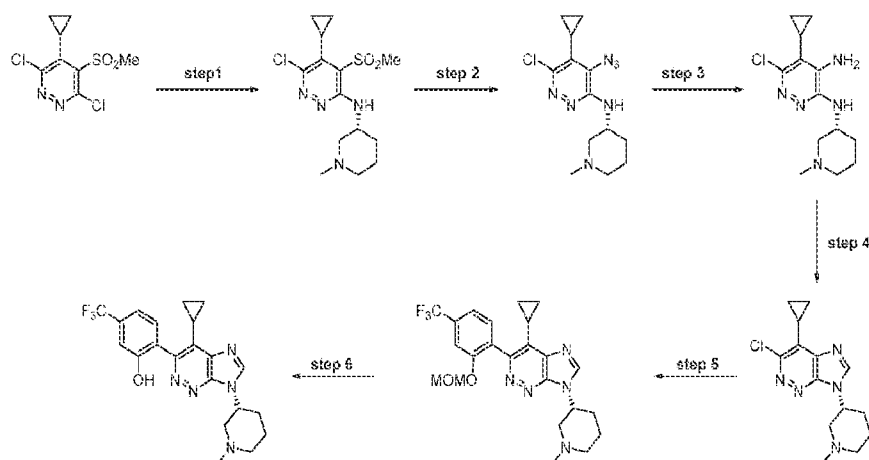
Example 2G. Preparation of 5-(7-((1*s*,3*s*)-3-hydroxy-3-methylcyclobutyl)-5-iodo-7H-pyrrolo[2,3-*c*]pyridazin-3-yl)-6-methylbenzofuran-4-ol (IIG-1)



Step 1. *N*-iodosuccinimide (27 mg, 0.12 mmol) was added to a solution of 7-((1*s*,3*s*)-3-((tert-butyl)dimethylsilyl)oxy)-3-methylcyclobutyl)-3-(4-(methoxymethoxy)-6-methyl-2,3-dihydrobenzofuran-5-yl)-6,7-dihydro-5*H*-pyrrolo[2,3-*c*]pyridazine (51.2 mg, 0.100 mmol) in ACN (10 mL) at 0°C. After 30 min, the mixture was returned to rt and stirred overnight. Upon reaction completion, the mixture was poured into ice cold NaHCO₃ (sat, aq.) and extracted with EtOAc. The product was extracted several times with EtOAc and the combined organic extracts were dried over Na₂SO₃ and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography eluting with 0:100 to 100:00 EtOAc:DCM to afford 7-((1*s*,3*s*)-3-((tert-butyl)dimethylsilyl)oxy)-3-methylcyclobutyl)-5-iodo-3-(4-(methoxymethoxy)-6-methyl-2,3-dihydrobenzofuran-5-yl)-7*H*-pyrrolo[2,3-*c*]pyridazine (11.2 mg, 0.018 mmol, 18% yield). MS *m/z* 636.4 [M+H]⁺. ¹H NMR (400 MHz, methanol-*d*₄) δ 7.89 (s, 1H), 7.29 (s, 1H), 6.33 (s, 1H), 4.90 (p, *J* = 8.7 Hz, 1H), 4.62 (s, 2H), 4.44 – 4.33 (m, 2H), 3.19 – 3.11 (m, 2H), 2.86 (s, 3H), 2.71 – 2.47 (m, 4H), 1.77 (s, 3H), 1.36 (s, 3H), 1.07 – 0.91 (m, 2H), 0.73 (s, 9H), -0.05 (s, 6H).

Step 2. 7-((1*s*,3*s*)-3-((tert-butyl)dimethylsilyl)oxy)-3-methylcyclobutyl)-5-iodo-3-(4-(methoxymethoxy)-6-methyl-2,3-dihydrobenzofuran-5-yl)-7*H*-pyrrolo[2,3-*c*]pyridazine (11.2 mg, 0.018 mmol) was dissolved in 1:2 HCl (12M, aq.):MeOH and stirred at rt for 2 h. The mixture was concentrated *in vacuo* and the crude residue was purified by C18 reverse phase Prep-HPLC eluting with ACN:water with formic acid as the modifier. After reverse phase purification, solvents were removed to afford 5-(7-((1*s*,3*s*)-3-hydroxy-3-methylcyclobutyl)-5-iodo-7*H*-pyrrolo[2,3-*c*]pyridazin-3-yl)-6-methylbenzofuran-4-ol (7.9 mg, 0.0166 mmol, 94%). MS *m/z* 478.0 [M+H]⁺. ¹H NMR (400 MHz, methanol-*d*₄) δ 8.83 (s, 1H), 8.21 (s, 1H), 6.43 (s, 1H), 5.16 – 5.01 (m, 1H), 4.72 – 4.59 (m, 2H), 3.24 – 3.15 (m, 2H), 2.91 – 2.80 (m, 2H), 2.80 – 2.71 (m, 2H), 2.10 (s, 3H), 1.52 (s, 3H). OH peaks not observed.

Example 3. Preparation of (R)-2-(4-cyclopropyl-7-(1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol (III-1)



Step 1: To a solution of 3,6-dichloro-4-cyclopropyl-5-(phenylsulfonyl)pyridazine (410 mg, 1.5 mmol) in dioxane (6.0 mL) were added (R)-1-methylpiperidin-3-amine (209 mg, 1.83 mmol) and potassium carbonate (274 mg, 2 mmol). The reaction mixture was stirred at 60°C for 2h. Upon completion the mixture was filtered, and the filtrate was diluted with water (20 mL) and extracted with ethyl acetate. The combined organic parts were washed with brine, dried over sodium sulfate, filtered and reduced under pressure to afford (R)-6-chloro-5-cyclopropyl-N-(1-methylpiperidin-3-yl)-4-(phenylsulfonyl)pyridazin-3-amine (415 mg, 80% yield) as an orange oil. The crude material was taken to the next step without further purification. MS m/z 345.0, 347.0 $[M+H]^+$.

Step 2: To a solution of (R)-6-chloro-5-cyclopropyl-N-(1-methylpiperidin-3-yl)-4-(phenylsulfonyl)pyridazin-3-amine (415 mg, 1.2 mmol) in DMSO (0.5 mL) was added sodium azide (140 mg, 2.2 mmol). The reaction was stirred at 80°C for 2 hours. Upon completion, the reaction was diluted with water (20 mL) and extracted with EtOAc. The combined organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to afford (R)-4-azido-6-chloro-5-cyclopropyl-N-(1-methylpiperidin-3-yl)pyridazin-3-amine (200 mg, 58% yield) as a brown oil. The crude material was taken to the next step without further purification. MS m/z 308.0, 310.0 $[M+H]^+$.

Step 3: To a solution of (R)-4-azido-6-chloro-5-cyclopropyl-N-(1-methylpiperidin-3-yl)pyridazin-3-amine (100 mg, 0.32 mmol) in CH_2Cl_2 (0.8 mL) and AcOH (0.2 mL) was added Zinc (60 mg, 0.92 mmol) at 0°C. The reaction stirred at this temperature for 2 h. Upon completion, the mixture was filtered over a pad of celite and the filtrate was concentrated under reduced pressure to afford (R)-4-azido-6-chloro-5-cyclopropyl-N-(1-methylpiperidin-3-

yl)pyridazin-3-amine (60 mg, 63% yield) as a yellow oil. The crude material was taken to the next step without further purification. MS m/z 282.1, 284.1 $[M+H]^+$.

Step 4: To a solution of (R)-4-azido-6-chloro-5-cyclopropyl-N-(1-methylpiperidin-3-yl)pyridazin-3-amine (60 mg, 0.21 mmol) in triethyl orthoformate (700 μ L, 4.2 mmol) was added hydrochloric acid (100 μ L, 0.02 mmol). The mixture was heated at 100 $^{\circ}$ C for 24 h. Upon completion, the reaction was diluted with dichloromethane and washed with water, brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified via flash silica gel column chromatography eluting with a gradient $CH_2Cl_2/MeOH/NH_4OH$ (0-30% $MeOH/NH_4OH$) to afford 3-chloro-4-cyclopropyl-7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazine as a yellow solid (60 mg, 95% yield). MS m/z 292.1, 294.1 $[M+H]^+$.

Step 5: To a screw top vial were added: 3-chloro-4-cyclopropyl-7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazine (30 mg, 0.1 mmol), XPhos Pd-G3 (9 mg, 0.01 mmol), 2-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (40 mg, 0.12 mmol). The mixture was degassed by purging with Ar for 15 min before 1,4 dioxane (0.5 mL) and a 2M solution of potassium carbonate (150 μ L, 0.3 mmol) were added. The mixture was stirred at 110 $^{\circ}$ C for 2 h. Upon completion the reaction was concentrated and loaded directly onto precolumn and purified via flash silica gel column chromatography eluting with a gradient $CH_2Cl_2/MeOH/NH_4OH$ (0-30% $MeOH/NH_4OH$) to afford 4-cyclopropyl-3-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazine (28 mg, 51% yield) as a yellow oil. MS m/z 462.3 $[M+H]^+$.

Step 6: 4-Cyclopropyl-3-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazine (28 mg, 0.06 mmol, 1 eq) was dissolved in trifluoroacetic acid (0.5 mL) and stirred for 2 h at room temperature. Upon completion, the reaction was diluted with dichloromethane and sodium bicarbonate was added. The solution was stirred for 10 minutes before extracting with dichloromethane. The combined organic parts were washed with water, brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified via silica gel flash column chromatography eluting with a gradient $CH_2Cl_2/MeOH/NH_4OH$ (0-30% $MeOH/NH_4OH$) to afford (R)-2-(4-cyclopropyl-7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol (12 mg, 53% yield). MS m/z 418.1 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.81 (s, 1H), 7.60 (d, J = 7.9

Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.29 (s, 1H), 5.17 (m, 1H), 3.96 (m, 1H), 3.68 (m, 2H), 3.17 (m, 1H), 3.01 (s, 3H), 2.59 – 2.35 (m, 2H), 2.27 (m, 1H), 2.07 (m, 1H), 1.87 (d, J = 4.7 Hz, 3H), 1.21 (h, J = 4.8 Hz, 2H); 1H not observed (OH).

- 5 Using the procedure described for Example 3, above, additional compounds described herein may be prepared by substituting the appropriate starting material, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Table 3

Cmpd#	Characterization
III-1	MS m/z 418.1 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.81 (s, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.29 (s, 1H), 5.17 (m, 1H), 3.96 (m, 1H), 3.68 (m, 2H), 3.17 (m, 1H), 3.01 (s, 3H), 2.59 – 2.35 (m, 2H), 2.27 (m, 1H), 2.07 (m, 1H), 1.87 (d, J = 4.7 Hz, 3H), 1.21 (h, J = 4.8 Hz, 2H); 1H not observed (OH).
III-2	MS m/z 392.9 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.12 (s, 1H), 7.17 (s, 1H), 7.08 (s, 1H), 5.20 (m, 1H), 4.03 (m, 1H), 3.88 – 3.59 (m, 2H), 3.21 (m, 2H), 3.01 (s, 3H), 2.57 (m, 1H), 2.46 (m, 1H), 2.38 – 2.20 (m, 1H), 2.15 (m, 4H); 1H not observed (OH).
III-3	MS m/z 376.1, 378.1 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.23 (s, 1H), 6.89 (s, 2H), 4.23 (m, J = 11.5 Hz, 1H), 3.83 (m, J = 11.7 Hz, 2H), 3.67 (m, 1H), 3.03 (s, 3H), 2.94 (m, 1H), 2.84 (s, 3H), 2.27 (m, 2H), 2.01 (m, 2H); 1H not observed (OH).
III-4	MS m/z 385.6, 386.6 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.88 (s, 1H), 7.41 (d, J = 8.1 Hz, 1H), 7.11 (d, J = 8.2 Hz, 1H), 7.08 (s, 1H), 5.15 (m, 1H), 3.93 (m, 1H), 3.66 (m, 2H), 3.13 (m, 1H), 3.01 (s, 3H), 2.59 – 2.36 (m, 2H), 2.26 (m, 1H), 2.06 (d, J = 14.0 Hz, 1H), 1.92 (d, J = 3.8 Hz, 3H), 1.25 (t, J = 5.6 Hz, 2H); 1H not observed (OH).
III-5	MS m/z 420.3 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.82 (s, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.28 (dd, J = 7.9, 1.7 Hz, 1H), 7.21 (d, J = 1.8 Hz, 1H), 5.01 (tt, J = 9.7, 4.3 Hz, 1H), 3.29 – 3.18 (m, 1H), 2.95 (p, J = 7.0 Hz, 1H), 2.88 (s, 2H), 2.43 (s, 3H), 2.31 – 2.15 (m, 3H), 1.95 (dt, J = 13.7, 4.1 Hz, 1H), 1.86 (ddt, J = 14.3, 8.4, 4.1 Hz, 1H), 1.50 (d, J = 6.9 Hz, 6H); 1H not observed (OH).
III-6	MS m/z 406.3 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.90 (s, 1H), 7.17 (s, 1H), 7.07 (s, 1H), 5.01 (tt, J = 9.4, 4.3 Hz, 1H), 3.29 – 3.15 (m, 1H), 2.83 (d, J = 11.2 Hz, 2H), 2.42 (s, 3H), 2.39 (d, J = 1.9 Hz, 3H), 2.38 – 2.31 (m, 1H), 2.25 (dq, J = 9.6, 5.1 Hz, 2H), 2.02 (s, 3H), 1.99 – 1.87 (m, 1H), 1.84 (tt, J = 13.6, 7.5 Hz, 1H); 1H not observed (OH).
III-7	MS m/z 432.1 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.71 (d, J = 4.9 Hz, 1H), 7.17 (s, 1H), 7.07 (d, J = 1.7 Hz, 1H), 5.07 – 4.90 (m, 1H), 3.27 – 3.15 (m, 1H), 2.79 (dd, J = 24.4, 10.0 Hz, 2H), 2.39 (s, 3H), 2.34 (d, J = 9.9 Hz, 1H), 2.21 (dq, J = 8.2, 4.7 Hz, 2H), 2.07 (s, 3H), 2.02 – 1.90 (m, 1H), 1.90 – 1.75 (m, 2H), 1.66 (dddd, J = 14.6, 11.2, 9.0, 4.8 Hz, 2H), 1.16 – 0.95 (m, 2H); 1H not observed (OH).
III-8	MS m/z 392.1 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.89 (s, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.30 (dd, J = 7.9, 1.7 Hz, 1H), 7.24 (d, J = 1.7 Hz, 1H), 5.00 (tt, J = 9.5, 4.2 Hz, 1H), 3.23 (dt, J = 11.3, 4.0 Hz, 1H), 2.83 (t, J = 10.1 Hz, 2H), 2.52 (s, 3H), 2.39 (s, 3H), 2.34 (q, J = 5.1 Hz, 1H), 2.25 (dpt, J = 11.0, 8.0, 4.5 Hz, 2H), 1.88 (dddt, J = 34.7, 14.3, 10.0, 4.8 Hz, 2H); 1H not observed (OH).

Cmpd#	Characterization
III-9	MS m/z 448.3 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.88 (s, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.29 (dd, J = 7.9, 1.7 Hz, 1H), 7.23 (d, J = 1.7 Hz, 1H), 5.01 (tt, J = 8.3, 3.9 Hz, 1H), 3.73 (t, J = 5.7 Hz, 2H), 3.29 – 3.12 (m, 1H), 2.99 (t, J = 9.8 Hz, 1H), 2.83 (s, 1H), 2.66 (t, J = 5.8 Hz, 2H), 2.56 (s, 1H), 2.25 (dp, J = 13.7, 4.7 Hz, 1H), 2.21 – 2.06 (m, 1H), 1.94 – 1.75 (m, 3H), 1.69 (dt, J = 5.1, 3.1 Hz, 2H), 1.08 (dq, J = 6.7, 4.0 Hz, 2H); 2 Hs not observed (2 OHs).
III-10	MS m/z 376.3, 378.2 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.89 (s, 1H), 6.97 – 6.63 (m, 2H), 5.12 – 4.92 (m, 1H), 3.69 – 3.42 (m, 2H), 2.92 – 2.68 (m, 2H), 2.39 (s, 2H), 2.27–2.18 (m, 2H), 2.05 – 1.75 (m, 2H), 1.31 (d, J = 14.2 Hz, 3H), 1.01 – 0.70 (m, 1H); 1H not observed (OH).
III-11	MS m/z 378.3 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.73 – 8.59 (m, 1H), 6.70 (s, 1H), 6.63 (s, 1H), 4.95 (tt, J = 10.1, 4.7 Hz, 1H), 3.26 – 3.12 (m, 1H), 2.81 (d, J = 18.8 Hz, 2H), 2.40 (s, 3H), 2.31 (s, 3H), 2.17 (dtd, J = 29.6, 9.0, 4.8 Hz, 2H), 1.95 (s, 4H), 1.88 – 1.71 (m, 3H), 1.60 (q, J = 6.1 Hz, 1H), 1.30 (dt, J = 8.7, 3.4 Hz, 1H), 1.03 (td, J = 9.5, 6.0 Hz, 2H); 1H not observed (OH).
III-12	MS m/z 354.3 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.84 (s, 1H), 7.20 (d, J = 8.4 Hz, 1H), 6.59 (dd, J = 8.4, 2.4 Hz, 1H), 6.54 (d, J = 2.4 Hz, 1H), 4.97 (tt, J = 9.5, 4.4 Hz, 1H), 3.83 (s, 3H), 3.26 – 3.11 (m, 1H), 2.82 (d, J = 10.3 Hz, 2H), 2.52 (s, 3H), 2.38 (s, 4H), 2.23 (td, J = 9.8, 4.5 Hz, 2H), 1.87 (dddt, J = 34.4, 14.3, 9.8, 4.8 Hz, 2H); 1H not observed (OH).
III-13	MS m/z 380.1 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.65 (s, 1H), 7.22 (d, J = 8.4 Hz, 1H), 6.58 (dt, J = 8.4, 2.0 Hz, 1H), 6.53 (d, J = 2.2 Hz, 1H), 4.92 (dq, J = 9.5, 4.6 Hz, 1H), 3.81 (d, J = 1.6 Hz, 3H), 3.21 – 3.10 (m, 1H), 2.78 (q, J = 11.0 Hz, 2H), 2.37 (d, J = 1.6 Hz, 3H), 2.34 – 2.25 (m, 1H), 2.18 (td, J = 9.7, 4.3 Hz, 2H), 1.97 – 1.84 (m, 2H), 1.81 (tq, J = 9.8, 5.3 Hz, 1H), 1.66 (dq, J = 6.6, 4.0 Hz, 2H), 1.06 (dt, J = 8.8, 3.2 Hz, 2H); 1H not observed (OH).
III-14	MS m/z 375.3 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.71 (s, 1H), 7.50 (d, J = 7.7 Hz, 1H), 7.36 (dd, J = 7.8, 1.7 Hz, 1H), 7.26 (d, J = 1.8 Hz, 1H), 4.96 (dp, J = 9.5, 4.2 Hz, 1H), 3.27 – 3.11 (m, 1H), 2.80 (d, J = 10.5 Hz, 2H), 2.39 (s, 3H), 2.35 (d, J = 12.3 Hz, 1H), 2.23 – 2.02 (m, 2H), 1.91 (dt, J = 13.6, 4.2 Hz, 1H), 1.81 (ddp, J = 13.8, 8.5, 5.1 Hz, 2H), 1.68 (dq, J = 6.9, 4.1 Hz, 2H), 1.08 (dt, J = 8.9, 3.3 Hz, 2H); 1H not observed (OH).
III-15	MS m/z 405.3 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.72 (s, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.05 (d, 1H), 6.99 (s, 1H), 4.88 (p, J = 8.3 Hz, 1H), 2.69 (dt, J = 27.4, 10.7 Hz, 3H), 1.87 – 1.73 (m, 1H), 1.72 – 1.48 (m, 3H), 1.40 (s, 3H), 1.07 – 0.91 (m, 2H); 2Hs not observed (2 OHs).
III-16	MS m/z 421.7 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.58 (s, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 7.9 Hz, 1H), 7.23 (s, 1H), 4.65 (td, J = 11.6, 4.4 Hz, 1H), 4.44 (td, J = 9.9, 5.1 Hz, 1H), 4.16 – 3.98 (m, 2H), 3.61 (t, J = 12.1 Hz, 1H), 2.74 (tt, J = 13.1, 6.3 Hz, 2H), 2.17 (d, J = 12.6 Hz, 1H), 1.82 (dd, J = 8.7, 5.2 Hz, 1H), 1.70 (dq, J = 6.6, 3.9 Hz, 2H), 1.08 (dd, J = 8.6, 2.7 Hz, 2H); 2Hs not observed (2 OHs).
III-17	MS m/z 419.7 $[M+H]^+$; ^1H NMR (500 MHz, DMSO- d_6) δ : 10.04 (d, J = 1.5 Hz, 1H), 8.76 (d, J = 1.5 Hz, 1H), 7.19 (s, 1H), 7.10 (s, 1H), 4.90 (t, J = 8.4 Hz, 1H), 3.26 – 3.19 (m, 2H), 2.76 (s, 1H), 2.68 (d, J = 7.4 Hz, 2H), 1.98 (s, 3H), 1.84 (t, J = 5.0 Hz, 1H), 1.60 – 1.46 (m, 2H), 1.40 (s, 3H), 1.11 – 0.92 (m, 2H).

Cmpd#	Characterization
III-18	MS m/z 434.1 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.77 (s, 1H), 7.50 (d, J = 7.7 Hz, 1H), 7.29 (d, J = 7.9 Hz, 1H), 7.23 (s, 1H), 5.20 (dd, J = 8.8, 5.4 Hz, 1H), 4.29 – 4.12 (m, 1H), 3.06 (t, J = 10.6 Hz, 1H), 2.95 (d, J = 11.9 Hz, 1H), 2.78 – 2.57 (m, 2H), 2.42 (d, J = 2.2 Hz, 3H), 2.04 (q, J = 10.4 Hz, 1H), 1.92 (td, J = 8.9, 4.1 Hz, 1H), 1.82 (tdd, J = 7.9, 5.2, 2.6 Hz, 1H), 1.69 (pd, J = 8.1, 2.7 Hz, 2H), 1.08 (dd, J = 8.6, 2.9 Hz, 2H); 2Hs not observed (2 OHs).
III-19	MS m/z 448.1 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.81 (s, 1H), 7.50 (d, J = 7.7 Hz, 1H), 7.29 (d, J = 7.9 Hz, 1H), 7.23 (s, 1H), 5.21 (tt, J = 10.6, 4.9 Hz, 1H), 4.23 (dd, J = 5.5, 2.8 Hz, 1H), 3.17 – 2.96 (m, 2H), 2.83 – 2.68 (m, 2H), 2.61 (q, J = 7.2 Hz, 2H), 2.04 (q, J = 10.3 Hz, 1H), 1.98 – 1.88 (m, 1H), 1.83 (td, J = 8.8, 4.4 Hz, 1H), 1.76 – 1.61 (m, 2H), 1.16 (td, J = 7.2, 1.9 Hz, 3H), 1.08 (dd, J = 8.5, 3.0 Hz, 2H); 2Hs not observed (2 OHs).
III-20	MS m/z 464.1 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.93 (s, 1H), 7.51 (d, J = 7.7 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.23 (s, 1H), 5.28 – 5.15 (m, 1H), 4.21 (dt, J = 6.6, 3.0 Hz, 1H), 3.72 (tt, J = 5.4, 2.5 Hz, 2H), 3.17 (t, J = 10.3 Hz, 1H), 3.01 (d, J = 12.5 Hz, 1H), 2.85 – 2.82 (m, 1H), 2.68 (q, J = 6.6 Hz, 3H), 2.02 (d, J = 11.1 Hz, 1H), 1.94 – 1.79 (m, 2H), 1.69 (ddd, J = 7.2, 5.0, 2.4 Hz, 2H), 1.08 (dd, J = 8.6, 2.8 Hz, 2H); 3Hs not observed (3 OHs).
III-21	MS m/z : 390.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ : 8.76 (s, 1H), 8.71 (br s, 1H), 7.03 (d, J = 7.6 Hz, 1H), 6.83 (d, J = 7.6 Hz, 1H), 4.89 – 4.80 (m, 1H), 3.04 – 2.97 (m, 1H), 2.95 – 2.83 (m, 4H), 2.70 – 2.65 (m, 1H), 2.63 – 2.56 (m, 1H), 2.26 (s, 3H), 2.21 – 2.00 (m, 5H), 1.83 – 1.61 (m, 5H), 1.10 – 0.95 (m, 2H).
III-22	MS m/z : 392.1 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.66 (s, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.44 (d, J = 8.4 Hz, 1H), 4.98 – 4.90 (m, 1H), 4.62 (t, J = 8.4 Hz, 2H), 3.24 – 3.12 (m, 3H), 2.85 – 2.73 (m, 2H), 2.37 (s, 3H), 2.35 – 2.26 (m, 1H), 2.25 – 2.14 (m, 2H), 2.01 – 1.78 (m, 3H), 1.71 – 1.64 (m, 2H), 1.11 – 1.03 (m, 2H); 1H not observed (OH).
III-23	MS m/z : 338.1 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.91 (s, 1H), 7.87 (s, 1H), 6.68 (s, 1H), 6.63 (s, 1H), 5.06 – 4.98 (m, 1H), 3.23 (d, J = 8.8 Hz, 1H), 2.84 (t, J = 10.4 Hz, 2H), 2.39 (s, 3H), 2.35 (s, 1H), 2.30 (s, 3H), 2.28 – 2.22 (m, 2H), 2.03 (s, 3H), 1.95 – 1.90 (m, 1H), 1.85 – 1.81 (m, 1H); 1H not observed (OH).
III-24	MS m/z : 392.1 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.94 (s, 1H), 7.87 (s, 1H), 7.16 (s, 1H), 7.03 (s, 1H), 5.09 – 4.98 (m, 1H), 3.28 – 3.20 (m, 1H), 2.90 – 2.77 (m, 2H), 2.42 (s, 3H), 2.40 (s, 3H), 2.37 – 2.30 (m, 1H), 2.29 – 2.19 (m, 2H), 1.97 – 1.78 (m, 2H); 1H not observed (OH).
III-25	MS m/z 366.2 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.87 (s, 1H), 7.07 (dd, J = 8.1, 2.3 Hz, 1H), 6.47 (dd, J = 8.2, 2.4 Hz, 1H), 5.06 – 4.91 (m, 1H), 4.65 (td, J = 8.7, 2.4 Hz, 2H), 3.29 – 3.14 (m, 3H), 2.83 (d, J = 10.0 Hz, 2H), 2.56 (s, 3H), 2.41 (s, 4H), 2.31 – 2.15 (m, 2H), 2.03 – 1.77 (m, 2H); 1H not observed (OH).
III-26	MS m/z 364.3 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.85 (s, 1H), 7.06 (dd, J = 7.6, 2.1 Hz, 1H), 6.90 (d, J = 7.4 Hz, 1H), 4.98 (tt, J = 9.5, 4.1 Hz, 1H), 3.26 – 3.08 (m, 1H), 2.99 (t, J = 7.4 Hz, 2H), 2.93 (t, J = 7.4 Hz, 2H), 2.81 (d, J = 10.2 Hz, 2H), 2.52 (s, 3H), 2.39 (s, 4H), 2.30 – 2.20 (m, 2H), 2.15 (pd, J = 7.5, 2.1 Hz, 2H), 1.88 (ddt, J = 40.6, 14.3, 3.7 Hz, 2H); 1H not observed (OH).
III-27	MS m/z : 408.0 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.94 (s, 1H), 8.21 (s, 1H), 6.91 (s, 1H), 6.90 (s, 1H), 5.06 – 4.98 (m, 1H), 3.84 (s, 3H), 3.26 – 3.20 (m, 1H), 2.84 (t, J = 10.0 Hz, 2H), 2.40 (s, 3H), 2.38 – 2.30 (m, 1H), 2.30 – 2.21 (m, 2H), 1.98 – 1.78 (m, 2H); 1H not observed (OH).

Cmpd#	Characterization
III-28	MS m/z 364.2 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.87 (s, 1H), 7.73 (d, J = 2.2 Hz, 1H), 7.29 – 7.13 (m, 2H), 7.05 (d, J = 2.3 Hz, 1H), 5.00 (tt, J = 9.6, 4.2 Hz, 1H), 3.24 (d, J = 12.1 Hz, 1H), 2.96 – 2.73 (m, 2H), 2.53 (s, 3H), 2.41 (s, 4H), 2.33 – 2.13 (m, 2H), 1.90 (ddt, J = 41.6, 14.4, 3.9 Hz, 2H); 1H not observed (OH).
III-29	MS m/z 390.2 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.68 (s, 1H), 7.71 (t, J = 1.8 Hz, 1H), 7.25 (dd, J = 8.4, 1.5 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 7.03 (d, J = 2.2 Hz, 1H), 4.96 (dq, J = 9.6, 4.7 Hz, 1H), 3.25 – 3.08 (m, 1H), 2.79 (q, J = 10.2 Hz, 2H), 2.38 (d, J = 1.5 Hz, 4H), 2.20 (dq, J = 9.8, 4.5 Hz, 2H), 1.98 – 1.84 (m, 2H), 1.84 – 1.71 (m, 1H), 1.70 (dt, J = 5.2, 3.2 Hz, 2H), 1.11 – 0.93 (m, 2H); 1H not observed (OH).
III-30	MS m/z 380.2 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.87 (s, 1H), 7.62 (d, J = 5.6 Hz, 1H), 7.59 – 7.43 (m, 2H), 7.28 (dd, J = 8.1, 1.8 Hz, 1H), 4.99 (dp, J = 9.5, 4.1 Hz, 1H), 3.23 (d, J = 10.7 Hz, 1H), 2.84 (t, J = 10.7 Hz, 2H), 2.55 (s, 3H), 2.48 – 2.30 (m, 4H), 2.32 – 2.15 (m, 2H), 1.88 (ddt, J = 40.6, 14.8, 4.1 Hz, 2H); 1H not observed (OH).
III-31	MS m/z 406.3 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.70 (d, J = 6.1 Hz, 1H), 7.64 – 7.57 (m, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.51 (d, J = 5.5 Hz, 1H), 7.32 (d, J = 8.2 Hz, 1H), 5.04 – 4.89 (m, 1H), 3.20 (d, J = 11.1 Hz, 1H), 2.81 (t, J = 10.5 Hz, 2H), 2.39 (s, 4H), 2.22 (dq, J = 22.0, 6.6 Hz, 2H), 1.92 (ddt, J = 12.6, 8.6, 3.4 Hz, 2H), 1.84 (dt, J = 9.8, 6.1 Hz, 1H), 1.80 – 1.65 (m, 2H), 1.06 (dq, J = 6.8, 3.9 Hz, 2H); 1H not observed (OH).
III-32	MS m/z 393.7 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.59 (s, 1H), 7.61 (dd, J = 5.6, 2.3 Hz, 1H), 7.59 – 7.54 (m, 1H), 7.54 – 7.39 (m, 1H), 7.32 (dd, J = 8.2, 2.3 Hz, 1H), 4.95 (qd, J = 8.2, 2.3 Hz, 1H), 3.00 – 2.68 (m, 4H), 1.94 (tt, J = 8.7, 5.4 Hz, 1H), 1.72 (dq, J = 5.7, 3.5 Hz, 2H), 1.51 (s, 3H), 1.07 (dq, J = 9.2, 3.5 Hz, 2H); 2Hs not observed (2 OH).
III-33	MS m/z 368.3 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.87 (s, 1H), 7.20 (dd, J = 8.4, 2.3 Hz, 1H), 6.60 (dd, J = 8.4, 2.7 Hz, 1H), 6.54 (d, J = 2.5 Hz, 1H), 4.99 (dq, J = 10.0, 5.1 Hz, 1H), 3.83 (d, J = 2.3 Hz, 3H), 2.91 (d, J = 10.7 Hz, 1H), 2.84 (t, J = 10.2 Hz, 1H), 2.58 (td, J = 7.3, 4.1 Hz, 2H), 2.52 (d, J = 2.3 Hz, 4H), 2.37 (t, J = 9.7 Hz, 1H), 2.25 (dq, J = 12.5, 7.7 Hz, 2H), 1.99 – 1.89 (m, 1H), 1.85 (tt, J = 10.4, 3.8 Hz, 1H), 1.15 (td, J = 7.1, 2.3 Hz, 3H); 1H not observed (OH).
III-34	MS m/z 418.9 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.54 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1H), 7.22 (s, 1H), 4.49 – 4.40 (m, 1H), 4.36 – 4.27 (m, 1H), 2.45 – 2.35 (m, 1H), 2.23 – 2.10 (m, 2H), 1.95 – 1.78 (m, 3H), 1.71 – 1.64 (m, 2H), 1.61 – 1.45 (m, 3H), 1.12 – 1.03 (m, 2H); 2Hs not observed (2 OH).
III-35	MS m/z 379.0 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.38 (s, 1H), 7.41 (d, J = 8 Hz, 1H), 7.19 (d, J = 8 Hz, 1H), 7.13 (s, 1H), 4.43 (d, J = 10.8 Hz, 1H), 4.22 – 4.17 (m, 2H), 1.76 – 1.70 (m, 1H), 1.62 – 1.58 (m, 2H), 1.17 (d, J = 5.6 Hz, 3H), 1.0 – 0.97 (m, 2H); 2Hs not observed (2 OH).
III-36	MS m/z 401.2 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.89 (dd, J = 4.2, 1.7 Hz, 1H), 8.72 (s, 1H), 8.36 (dd, J = 8.3, 1.7 Hz, 1H), 7.67 – 7.48 (m, 3H), 5.07 – 4.90 (m, 1H), 3.21 (d, J = 11.0 Hz, 1H), 2.90 – 2.72 (m, 2H), 2.39 (s, 3H), 2.34 (d, J = 5.7 Hz, 1H), 2.22 (td, J = 9.7, 4.3 Hz, 2H), 1.99 – 1.89 (m, 2H), 1.83 (ddt, J = 15.0, 10.6, 5.6 Hz, 1H), 1.75 – 1.62 (m, 2H), 1.05 (dt, J = 8.9, 3.2 Hz, 2H); 1H not observed (OH).
III-37	MS m/z : 405.0 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.63 (s, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.33 – 7.28 (m, 1H), 7.26 – 7.23 (m, 1H), 5.26 – 5.14 (m, 1H), 3.71 (d, J = 5.6 Hz, 2H), 2.82 – 2.71 (m, 2H), 2.67 – 2.57 (m, 2H), 2.57 – 2.47 (m, 1H), 1.89 – 1.80 (m, 1H), 1.74 – 1.68 (m, 2H), 1.14 – 1.05 (m, 2H); 2Hs not observed (2 OHs).

Cmpd#	Characterization
III-38	MS m/z : 379.1 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.80 (s, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.33 – 7.30 (m, 1H), 7.26 (s, 1H), 5.06 – 4.95 (m, 1H), 2.96 – 2.83 (m, 4H), 2.54 (s, 3H), 1.54 (s, 3H); 2Hs not observed (2 OHs).
III-39	MS m/z : 375.2 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.90 (d, J = 4.2 Hz, 2H), 8.36 (dq, J = 8.5, 1.7 Hz, 1H), 7.60 (dt, J = 7.6, 3.6 Hz, 1H), 7.56 (d, J = 2.6 Hz, 2H), 5.02 (tq, J = 6.8, 3.5 Hz, 1H), 3.24 (d, J = 9.4 Hz, 1H), 2.97 – 2.73 (m, 2H), 2.58 (s, 3H), 2.41 (d, J = 2.6 Hz, 4H), 2.31 – 2.17 (m, 2H), 1.94 (td, J = 9.4, 4.2 Hz, 1H), 1.91 – 1.66 (m, 1H); 1H not observed (OH).
III-40	MS m/z : 405.3 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.69 (s, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.20 (d, J = 8.2 Hz, 1H), 5.03 – 4.94 (m, 1H), 3.29 – 3.24 (m, 1H), 2.96 – 2.83 (m, 2H), 2.65 (s, 3H), 2.48 – 2.40 (m, 4H), 2.33 – 2.16 (m, 2H), 2.01 – 1.91 (m, 1H), 1.91 – 1.79 (m, 2H), 1.76 – 1.63 (m, 2H), 1.10 – 0.99 (m, 2H); 1H not observed (OH).
III-41	MS m/z : 422.3 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.87 (s, 1H), 6.98 – 6.77 (m, 2H), 5.00 (dp, J = 9.7, 4.4 Hz, 1H), 3.76 (s, 3H), 3.22 (d, J = 11.2 Hz, 1H), 2.83 (t, J = 10.7 Hz, 2H), 2.51 – 2.31 (m, 6H), 2.24 (qt, J = 10.6, 4.5 Hz, 2H), 2.02 – 1.83 (m, 2H), 1.87 – 1.71 (m, 1H); 1H not observed (OH).
III-42	MS m/z : 416.9 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.93 (s, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.23 (s, 1H), 5.12 – 5.02 (m, 1H), 3.85 – 3.73 (m, 2H), 3.25 (dd, J = 11.2, 4.0 Hz, 1H), 3.12 – 3.05 (m, 1H), 2.87 – 2.78 (m, 1H), 2.70 – 2.61 (m, 1H), 2.52 (s, 3H), 2.36 – 2.24 (m, 1H), 2.23 – 2.14 (m, 1H), 1.96 – 1.80 (m, 2H); 1H not observed (OH).
III-43	MS m/z : 389.1 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.91 (s, 1H), 7.72 (d, J = 2.0 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.19 – 7.16 (m, 1H), 7.04 (dd, J = 2.0, 0.8 Hz, 1H), 5.12 – 5.00 (m, 1H), 3.85 – 3.74 (m, 2H), 3.28 – 3.22 (m, 1H), 3.12 – 3.05 (m, 1H), 2.87 – 2.80 (m, 1H), 2.70 – 2.62 (m, 1H), 2.53 (s, 3H), 2.36 – 2.26 (m, 1H), 2.23 – 2.14 (m, 1H), 1.96 – 1.81 (m, 2H); 1H not observed (OH).
III-44	MS m/z : 443.1 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.75 (s, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.22 (s, 1H), 5.09 – 4.97 (m, 1H), 3.83 – 3.70 (m, 2H), 3.26 – 3.16 (m, 1H), 3.09 – 2.98 (m, 1H), 2.85 – 2.75 (m, 1H), 2.69 – 2.59 (m, 1H), 2.30 – 2.20 (m, 1H), 2.19 – 2.10 (m, 1H), 1.99 – 1.87 (m, 1H), 1.87 – 1.77 (m, 2H), 1.74 – 1.64 (m, 2H), 1.13 – 1.01 (m, 2H); 1H not observed (OH).
III-45	MS m/z : 421.5 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.68 (s, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.48 (d, J = 8.2 Hz, 1H), 5.07 – 4.96 (m, 1H), 3.44 – 3.35 (m, 1H), 3.12 – 2.97 (m, 2H), 2.87 (s, 3H), 2.64 – 2.51 (m, 4H), 2.35 – 2.18 (m, 2H), 2.07 – 1.95 (m, 1H), 1.95 – 1.82 (m, 2H), 1.78 – 1.67 (m, 2H), 1.15 – 1.04 (m, 2H); 1H not observed (OH).
III-46	MS m/z : 379.2 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.84 (s, 1H), 8.30 (br s, 1H, formic acid), 7.27 (d, J = 8.2 Hz, 1H), 7.21 (d, J = 7.8 Hz, 1H), 5.13 – 5.00 (m, 1H), 3.47 (d, J = 11.0 Hz, 1H), 3.22 – 3.12 (m, 1H), 3.11 – 3.04 (m, 1H), 2.70 – 2.62 (m, 4H), 2.60 (s, 3H), 2.54 (s, 3H), 2.42 – 2.24 (m, 2H), 2.09 – 2.00 (m, 1H), 1.99 – 1.86 (m, 1H); 1H not observed (OH).
III-47	MS m/z : 395.2 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.89 (s, 1H), 7.59 (d, J = 8.2 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H), 5.08 – 4.98 (m, 1H), 2.99 – 2.84 (m, 5H), 2.56 (s, 3H), 2.49 – 2.40 (m, 4H), 2.41 – 2.22 (m, 2H), 2.01 – 1.92 (m, 1H), 1.91 – 1.82 (m, 1H); 2H not observed (OH and CH overlapped with methanol- d_4 signal).

Cmpd#	Characterization
III-48	MS m/z : 424.0 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.72 (s, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 2.8 Hz, 1H), 5.03 – 4.94 (m, 1H), 3.20 (d, J = 8.8 Hz, 1H), 2.83 – 2.78 (m, 2H), 2.40 (s, 3H), 2.34 – 2.32 (m, 1H), 2.25 – 2.2 (m, 2H), 1.94 – 1.89 (m, 2H), 1.87 – 1.83 (m, 1H), 1.75 – 1.71 (m, 2H), 1.11 – 1.06 (m, 2H); 1H not observed (OH).
III-49	MS m/z : 415.1 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.76 (s, 1H), 7.73 (d, J = 2.0 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.19 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 1.6 Hz, 1H), 5.11 – 5.01 (m, 1H), 3.86 – 3.80 (m, 1H), 3.80 – 3.74 (m, 1H), 3.28 – 3.21 (m, 1H), 3.10 – 3.02 (m, 1H), 2.89 – 2.80 (m, 1H), 2.70 – 2.63 (m, 1H), 2.34 – 2.23 (m, 1H), 2.22 – 2.14 (m, 1H), 1.98 – 1.89 (m, 2H), 1.88 – 1.81 (m, 1H), 1.76 – 1.69 (m, 2H), 1.10 – 1.03 (m, 2H); 1H not observed (OH).
III-50	MS m/z : 394.2 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.93 (s, 1H), 8.80 (s, 1H), 6.76 (s, 2H), 5.09 – 4.98 (m, 1H), 3.09 – 2.88 (m, 2H), 2.57 – 2.38 (m, 5H), 2.37 – 2.21 (m, 2H), 2.05 – 1.94 (m, 1H), 1.94 – 1.80 (m, 1H); 2 Hs not observed (2 OHs).
III-51	MS m/z : 398.5 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.88 (s, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 2.4 Hz, 1H), 5.02 – 4.98 (m, 1H), 3.24 – 3.13 (m, 1H), 2.89 – 2.87 (m, 3H), 2.54 (s, 3H), 2.42 (s, 3H), 2.29 – 2.24 (m, 2H), 1.95 – 1.83 (m, 2H); 1H not observed (OH).
III-52	MS m/z : 380.2 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.88 (s, 1H), 7.63 (d, J = 5.2 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 5.6 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 4.97 – 5.02 (m, 1H), 3.23 – 3.20 (m, 1H), 2.81 – 2.86 (m, 2H), 2.57 (s, 3H), 2.40 (s, 3H), 2.37 – 2.23 (m, 3H), 1.96 – 1.77 (m, 2H); 1H not observed (OH).
III-53	MS m/z : 382.5 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ : 9.36 (s, 1H), 8.84 (s, 1H), 6.67 (d, J = 8.4 Hz, 1H), 6.52 (d, J = 8.4 Hz, 1H), 4.93 – 4.80 (m, 1H), 4.30 – 4.21 (m, 2H), 4.21 – 4.13 (m, 2H), 3.11 – 2.95 (m, 1H), 2.77 – 2.59 (m, 2H), 2.37 (s, 3H), 2.28 (s, 3H), 2.22 – 2.10 (m, 2H), 2.10 – 2.03 (m, 1H), 1.84 – 1.75 (m, 1H), 1.74 – 1.63 (m, 1H).
III-54	MS m/z : 408.2 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.85 (s, 1H), 8.45 (br s, 1H, formate CH), 6.75 (s, 2H), 5.08 – 4.98 (m, 1H), 3.02 – 2.85 (m, 2H), 2.53 – 2.36 (m, 8H), 2.33 – 2.22 (m, 2H), 2.03 – 1.93 (m, 1H), 1.93 – 1.80 (m, 1H); 2Hs not observed (2 OHs).
III-55	MS m/z : 432.8 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.98 (d, J = 3.1 Hz, 1H), 7.73 (t, J = 2.0 Hz, 1H), 7.26 – 7.10 (m, 2H), 7.05 (q, J = 3.9 Hz, 1H), 5.07 (dt, J = 8.1, 4.0 Hz, 1H), 3.30 – 3.18 (m, 3H), 2.91 (d, J = 6.3 Hz, 1H), 2.86 – 2.71 (m, 1H), 2.53 (d, J = 3.0 Hz, 3H), 2.35 – 2.21 (m, 2H), 2.19 (d, J = 22.0 Hz, 1H), 1.83 (qd, J = 7.7, 4.1 Hz, 2H); 1H not observed (OH).
III-56	MS m/z : 374.2 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.89 (s, 1H), 8.44 (br s, 1H, formic acid), 8.39 – 8.27 (m, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.62 – 7.48 (m, 3H), 7.45 – 7.35 (m, 1H), 5.03–5.02 (m, 1H), 3.29 – 3.24 (m, 1H), 2.99 – 2.79 (m, 2H), 2.62 – 2.54 (m, 3H), 2.47 – 2.37 (m, 4H), 2.34 – 2.22 (m, 2H), 2.01 – 1.91 (m, 1H), 1.91 – 1.79 (m, 1H); 1H not observed (OH).
III-57	MS m/z : 406.3 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.91 (s, 1H), 7.72 (q, J = 2.1 Hz, 1H), 7.22 (dd, J = 8.7, 3.2 Hz, 1H), 7.18 (dd, J = 8.5, 3.0 Hz, 1H), 7.05 (d, J = 2.9 Hz, 1H), 5.09 – 4.98 (m, 1H), 4.69 (ddt, J = 18.1, 15.8, 6.6 Hz, 4H), 3.65 (t, J = 6.5 Hz, 1H), 3.12 (d, J = 10.8 Hz, 1H), 2.83 – 2.67 (m, 2H), 2.54 (s, 3H), 2.35 – 2.16 (m, 3H), 2.00 – 1.88 (m, 1H), 1.88 – 1.73 (m, 1H); 1H not observed (OH).

Cmpd#	Characterization
III-58	MS m/z 460.2 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.79 (s, 1H), 7.50 (dd, J = 8.0, 2.9 Hz, 1H), 7.29 (dd, J = 8.0, 2.7 Hz, 1H), 7.23 (t, J = 2.2 Hz, 1H), 5.00 (dq, J = 8.8, 4.3 Hz, 1H), 4.76 – 4.55 (m, 4H), 3.62 (tq, J = 9.6, 4.9 Hz, 1H), 3.06 (d, J = 10.9 Hz, 1H), 2.77 – 2.61 (m, 2H), 2.23 (dt, J = 21.9, 13.4, 4.9 Hz, 3H), 1.91 (dt, J = 13.6, 4.3 Hz, 1H), 1.82 (qd, J = 8.8, 4.4 Hz, 2H), 1.70 (dq, J = 6.5, 3.9 Hz, 2H), 1.08 (dq, J = 10.2, 3.7 Hz, 2H); 1H not observed (OH).
III-59	MS m/z 408.2 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.65 (s, 1H), 6.77 (d, J = 8.4 Hz, 1H), 6.57 (d, J = 8.4 Hz, 1H), 4.98 – 4.91 (m, 1H), 4.34 – 4.27 (m, 2H), 4.25 – 4.17 (m, 2H), 3.24 – 3.15 (m, 1H), 2.89 – 2.74 (m, 2H), 2.39 (s, 3H), 2.38 – 2.29 (m, 1H), 2.24 – 2.14 (m, 2H), 1.94 – 1.81 (m, 3H), 1.75 – 1.57 (m, 2H), 1.21 – 0.94 (m, 2H); 1H not observed (OH).
III-60	MS m/z 375.3 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.92 – 8.88 (m, 1H), 8.85 – 8.82 (m, 1H), 8.81 – 8.77 (m, 1H), 8.15 – 8.13 (m, 1H formic acid), 7.74 – 7.70 (m, 2H), 7.62 – 7.55 (m, 1H), 4.09 – 4.01 (m, 1H), 3.42 – 3.36 (m, 1H), 2.97 – 2.86 (m, 1H), 2.84 – 2.75 (m, 1H), 2.64 – 2.55 (m, 3H), 2.10 – 1.95 (m, 2H), 1.84 – 1.64 (m, 1H), 1.50 – 1.37 (m, 5H); 1H not observed (OH).
III-61	MS m/z 406.0 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.88 (s, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.23 (s, 1H), 5.04 – 4.96 (m, 1H), 3.25 – 3.18 (m, 1H), 2.94 (q, J = 7.6 Hz, 2H), 2.87 – 2.78 (m, 2H), 2.39 (s, 3H), 2.37 – 2.29 (m, 1H), 2.29 – 2.20 (m, 2H), 1.97 – 1.78 (m, 2H), 1.18 (t, J = 7.6 Hz, 3H); 1H not observed (OH).
III-62	MS m/z 432.2 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 8.88 (s, 1H), 7.81 – 7.57 (m, 3H), 7.29 (ddd, J = 5.2, 3.0, 1.0 Hz, 1H), 7.17 – 7.11 (m, 1H), 7.11 – 7.06 (m, 1H), 6.95 (d, J = 2.2 Hz, 1H), 5.05 (m, 1H), 2.91 – 2.72 (m, 3H), 2.41 (s, 3H), 2.33 – 2.13 (m, 3H), 1.89 (m, 2H). 1 OH peak not observed.
III-63	MS m/z : 380.2 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 7.06 (d, J = 8.0 Hz, 1H), 6.46 (d, J = 8.8 Hz, 1H), 4.70 – 4.60 (m, 3H), 3.28 – 3.19 (m, 3H), 3.12 – 3.05 (m, 1H), 3.02 – 2.95 (m, 1H), 2.90 – 2.81 (m, 1H), 2.80 (s, 3H), 2.50 (s, 3H), 2.42 (s, 3H), 2.29 – 2.19 (m, 1H), 2.13 – 2.03 (m, 1H), 2.03 – 1.94 (m, 1H), 1.93 – 1.80 (m, 1H). OH peak not observed.
III-64	MS m/z : 378.0 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 7.74 (d, J = 2.4 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 1.6 Hz, 1H), 4.73 – 4.62 (m, 1H), 3.31 – 3.24 (m, 1H), 3.14 – 3.07 (m, 1H), 3.03 – 2.96 (m, 1H), 2.92 – 2.83 (m, 1H), 2.82 (s, 3H), 2.49 (s, 3H), 2.43 (s, 3H), 2.29 – 2.20 (m, 1H), 2.13 – 2.06 (m, 1H), 2.03 – 1.95 (m, 1H), 1.94 – 1.79 (m, 1H). OH not observed.
III-65	MS m/z : 406.2 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 8.70 (s, 1H), 7.63 – 7.58 (m, 1H), 7.54 – 7.48 (m, 1H), 7.42 – 7.38 (m, 1H), 7.38 – 7.32 (m, 1H), 5.02 – 4.92 (m, 1H), 3.23 – 3.15 (m, 1H), 2.87 – 2.73 (m, 2H), 2.38 (s, 3H), 2.36 – 2.28 (m, 1H), 2.26 – 2.15 (m, 2H), 1.99 – 1.87 (m, 2H), 1.86 – 1.76 (m, 1H), 1.76 – 1.66 (m, 2H), 1.14 – 1.01 (m, 2H). OH not observed.
III-66	MS m/z : 378.0 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 8.85 (s, 1H), 7.02 (d, J = 7.6 Hz, 1H), 6.89 (d, J = 7.6 Hz, 1H), 5.03 – 4.93 (m, 1H), 3.25 – 3.17 (m, 1H), 3.01 – 2.90 (m, 6H), 2.85 – 2.77 (m, 2H), 2.39 (s, 3H), 2.37 – 2.30 (m, 1H), 2.29 – 2.19 (m, 2H), 2.19 – 2.10 (m, 2H), 1.97 – 1.88 (m, 1H), 1.88 – 1.77 (m, 1H), 1.16 (t, J = 7.6 Hz, 3H). OH not observed.
III-67	MS m/z : 350.3 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 8.84 (s, 1H), 7.10 (d, J = 7.2 Hz, 1H), 6.73 (d, J = 7.2 Hz, 1H), 5.06 – 4.92 (m, 1H), 3.29 – 3.24 (m, 1H), 3.22 – 3.14 (m, 4H), 2.95 – 2.80 (m, 2H), 2.50 (s, 3H), 2.43 (s, 3H), 2.41 – 2.34 (m, 1H), 2.33 – 2.17 (m, 2H), 2.00 – 1.90 (m, 1H), 1.89 – 1.71 (m, 1H). OH not observed.

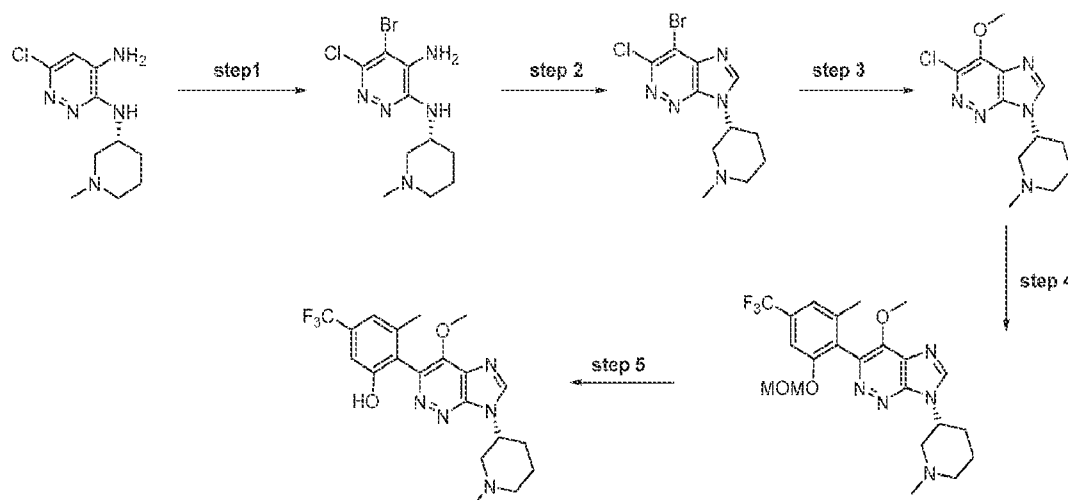
Cmpd#	Characterization
III-68	MS m/z : 394.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ : 8.87 (s, 1H), 7.63 – 7.60 (m, 1H), 7.58 – 7.52 (m, 2H), 7.24 (d, J = 8.0 Hz, 1H), 5.06 – 4.98 (m, 1H), 3.28 – 3.22 (m, 1H), 2.99 (q, J = 7.6 Hz, 2H), 2.93 – 2.81 (m, 2H), 2.45 – 2.34 (m, 4H), 2.31 – 2.20 (m, 2H), 1.99 – 1.79 (m, 2H), 1.16 (t, J = 7.6 Hz, 3H). OH not observed.
III-69	MS m/z : 382.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ : 8.63 (s, 1H), 7.00 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 5.06 – 4.96 (m, 1H), 3.54 – 3.47 (m, 1H), 3.40 – 3.23 (m, 1H), 3.19 – 3.12 (m, 1H), 2.80 – 2.75 (m, 1H), 2.68 (s, 3H), 2.34 – 2.22 (m, 5H), 2.10 – 2.00 (m, 1H), 1.96 – 1.88 (m, 2H), 1.73 – 1.69 (m, 2H), 1.12 – 1.07 (m, 2H). 1 OH signal not observed.
III-70	MS m/z : 382.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ : 8.64 (s, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.85 (t, J = 8.0 Hz, 1H), 5.08 – 4.98 (m, 1H), 3.52 – 3.45 (m, 1H), 3.24 – 3.08 (m, 2H), 2.73 – 2.63 (m, 1H), 2.63 (s, 3H), 2.30 (s, 3H), 2.29 – 2.24 (m, 2H), 2.06 – 1.98 (m, 1H), 1.96 – 1.88 (m, 2H), 1.73 – 1.69 (m, 2H), 1.11 – 1.06 (m, 2H). 1 OH signal not observed.
III-71	MS m/z : 410.2 [M+H] ⁺ ; ¹ H NMR (500 MHz, MeOD) δ : 8.87 (s, 1H), 7.90 (s, 1H), 7.17 (d, J = 1.5 Hz, 1H), 7.04 (s, 1H), 5.31 (tt, J = 10.8, 4.2 Hz, 1H), 5.18 – 4.94 (m, 1H), 3.28 (d, J = 3.9 Hz, 1H), 3.21 – 3.06 (m, 1H), 2.95 (t, J = 10.7 Hz, 1H), 2.70 (dddd, J = 38.0, 14.3, 11.6, 2.8 Hz, 1H), 2.62 – 2.54 (m, 1H), 2.51 (td, J = 13.6, 2.9 Hz, 1H), 2.43 (s, 3H), 2.43 (s, 3H). OH peak not observed.
III-72	MS m/z : 378.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ : 8.87 (s, 1H), 7.72 (d, J = 2.0 Hz, 1H), 7.18 (s, 2H), 7.04 (d, J = 2.4 Hz, 1H), 5.04 – 4.96 (m, 1H), 3.26 – 3.19 (m, 1H), 2.97 (q, J = 7.6 Hz, 2H), 2.89 – 2.76 (m, 2H), 2.42 – 2.30 (m, 4H), 2.29 – 2.19 (m, 2H), 1.98 – 1.78 (m, 2H), 1.15 (t, J = 7.6 Hz, 3H). OH not observed.
III-73	MS m/z : 380.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ : 8.84 (s, 1H), 7.00 (d, J = 8.0 Hz, 1H), 6.43 (d, J = 8.0 Hz, 1H), 5.02 – 4.93 (m, 1H), 4.66 – 4.59 (m, 2H), 3.21 (t, J = 8.8 Hz, 3H), 2.97 (q, J = 7.6 Hz, 2H), 2.86 – 2.76 (m, 2H), 2.38 (s, 3H), 2.36 – 2.16 (m, 3H), 1.96 – 1.77 (m, 2H), 1.17 (t, J = 7.6 Hz, 3H). OH not observed.
III-74	MS m/z : 404.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ : 10.67 (s, 1H), 8.89 (s, 1H), 7.10 (d, J = 8.0 Hz, 1H), 7.04 – 6.92 (m, 1H), 4.93 – 4.82 (m, 1H), 3.07 – 2.98 (m, 1H), 2.76 – 2.59 (m, 2H), 2.40 (s, 3H), 2.27 (s, 3H), 2.22 – 2.03 (m, 3H), 1.86 – 1.76 (m, 1H), 1.74 – 1.64 (m, 1H).
III-75	MS m/z : 430.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ : 10.48 (s, 1H), 8.80 (s, 1H), 7.12 (d, J = 8.4 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 4.95 – 4.77 (m, 1H), 3.06 – 2.95 (m, 1H), 2.73 – 2.56 (m, 2H), 2.26 (s, 3H), 2.22 – 2.01 (m, 3H), 1.82 – 1.74 (m, 1H), 1.74 – 1.62 (m, 4H), 1.09 – 0.98 (m, 2H).
III-76	MS m/z : 364.5 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ : 7.09 (d, J = 7.2 Hz, 1H), 6.72 (d, J = 7.2 Hz, 1H), 4.75 – 4.58 (m, 1H), 3.43 – 3.35 (m, 1H), 3.19 – 3.14 (m, 5H), 3.06 – 3.01 (m, 1H), 2.86 – 2.79 (m, 1H), 2.78 (s, 3H), 2.48 (s, 3H), 2.44 (s, 3H), 2.41 – 2.25 (m, 1H), 2.11 – 2.04 (m, 1H), 2.03 – 1.96 (m, 1H), 1.94 – 1.81 (m, 1H). OH not observed.
III-77	MS m/z : 436.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ : 8.69 (s, 1H), 8.35 (s, 1H, formic acid), 7.34 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 4.0 Hz, 1H), 5.02 (br s, 1H), 3.44 – 3.34 (m, 1H), 3.16 – 2.95 (m, 2H), 2.66 – 2.47 (m, 4H), 2.35 – 2.19 (m, 2H), 2.06 – 1.95 (m, 1H), 1.93 – 1.79 (m, 2H), 1.76 – 1.67 (m, 2H), 1.15 – 1.06 (m, 2H). 1 OH signal not observed.
III-78	MS m/z : 364.4 [M+H] ⁺ ; ¹ H NMR (400 MHz, CDCl ₃) δ : 8.85 (s, 1H), 8.07 (s, 1H), 7.52 (d, J = 2.0 Hz, 1H), 7.09 (s, 1H), 6.97 (d, J = 1.6 Hz, 1H), 5.17 (s, 1H), 3.07 (s, 2H), 2.65–2.58 (m, 2H), 2.44 (s, 3H), 2.31–2.25 (m, 3H), 2.12 (s, 1H), 2.05 (s, 1H), 1.86 (s, 2H). OH not observed.

Cmpd#	Characterization
III-79	MS <i>m/z</i> : 366.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, CDCl ₃) δ: 8.75 (s, 1H), 8.01 (s, 1H), 6.41 (s, 1H), 5.14 (s, 1H), 4.66 (t, J = 8.4 Hz, 2H), 3.26 (t, J = 8.8 Hz, 2H), 3.14 – 3.13 (m, 2H), 2.83 – 2.77 (m, 1H), 2.64 (s, 1H), 2.47 – 2.45 (m, 6H), 2.40 – 2.31 (m, 1H), 2.14 (s, 1H), 1.90 – 1.87 (m, 2H). OH not observed.
III-80	MS <i>m/z</i> : 364.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ: 8.84 (s, 1H), 7.07 (d, J = 7.2 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 5.06 – 4.94 (m, 1H), 3.29 – 3.22 (m, 1H), 3.21 – 3.14 (m, 4H), 2.95 (q, J = 7.6 Hz, 2H), 2.91 – 2.78 (m, 2H), 2.42 (s, 3H), 2.40 – 2.30 (m, 1H), 2.30 – 2.17 (m, 2H), 2.01 – 1.89 (m, 1H), 1.88 – 1.76 (m, 1H), 1.15 (t, J = 7.6 Hz, 3H). OH not observed.
III-81	MS <i>m/z</i> : 351.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ: 10.18 (s, 1H), 9.29 (s, 1H), 8.36 (s, 1H), 7.87 (d, J = 2.0 Hz, 1H), 7.21 (s, 1H), 7.14 (s, 1H), 5.00 – 4.86 (m, 1H), 2.87 – 2.80 (m, 2H), 2.74 – 2.68 (m, 2H), 2.12 (s, 3H), 1.42 (s, 3H). 1 OH not observed.
III-82	MS <i>m/z</i> : 351.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, CDCl ₃) δ: 8.29 (s, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.18 (dd, J = 8.8, 0.8 Hz, 1H), 7.05 (dd, J = 2.0, 0.8 Hz, 1H), 4.93 – 4.85 (m, 1H), 3.07 – 2.90 (m, 4H), 2.87 (s, 3H), 1.56 (s, 3H). 2OH peaks not observed.
III-83	MS <i>m/z</i> : 337.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, CDCl ₃) δ: 8.27 (s, 1H), 7.35 (d, J = 7.6 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 4.91 – 4.87 (m, 1H), 3.29 – 3.26 (m, 2H), 3.21 – 3.18 (m, 2H), 3.03 – 2.91 (m, 4H), 2.82 (s, 3H), 1.55 (s, 3H). 2OH peaks not observed.
III-84	MS <i>m/z</i> : 379.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ: 8.83 (s, 1H), 7.89 (s, 1H), 7.16 (s, 1H), 7.03 (s, 1H), 5.09 – 4.95 (m, 1H), 3.02 – 2.77 (m, 4H), 2.43 (s, 3H), 1.52 (s, 3H). 2OH peaks not observed.
III-85	MS <i>m/z</i> : 389.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ: 8.99 (s, 1H), 7.94 (s, 1H), 7.63 (d, J = 2.0 Hz, 1H), 7.05 (s, 1H), 6.97 (dd, J = 2.4, 0.8 Hz, 1H), 5.15 – 5.11 (m, 1H), 3.85 – 3.73 (m, 2H), 3.28 – 3.25 (m, 1H), 3.16 – 3.06 (m, 1H), 2.88 – 2.80 (m, 1H), 2.70 – 2.65 (m, 1H), 2.39 – 2.28 (m, 1H), 2.27 – 2.17 (m, 1H), 2.14 (s, 3H), 1.99 – 1.82 (m, 2H). OH not observed.
III-86	MS <i>m/z</i> : 432.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ: 9.04 (s, 1H), 7.94 (s, 1H), 7.63 (d, J = 2.4 Hz, 1H), 7.05 (s, 1H), 6.97 (dd, J = 2.4, 0.8 Hz, 1H), 5.16 – 5.05 (m, 1H), 3.38 – 3.32 (m, 2H), 2.25 – 3.21 (m, 2H), 2.96 – 2.79 (m, 2H), 2.36 – 2.26 (m, 1H), 2.22 – 2.16 (m, 1H), 2.14 (s, 3H), 1.91 – 1.77 (m, 2H). OH not observed.
III-87	MS <i>m/z</i> : 384.4 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ: 8.97 (s, 1H), 7.01 (d, J = 10.4 Hz, 1H), 5.21 (s, 1H), 4.77 (t, J = 8.8 Hz, 2H), 3.97 (s, 1H), 3.68 (s, 2H), 3.30 – 3.28 (m, 2H), 3.19 (s, 1H), 3.01 (s, 3H), 2.64 (s, 3H), 2.58 – 2.48 (m, 1H), 2.43 – 2.40 (m, 1H), 2.27 – 2.26 (m, 1H), 2.16 – 2.02 (m, 1H). OH not observed.
III-88	MS <i>m/z</i> : 382.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ: 9.98 (s, 1H), 9.81 (s, 1H), 8.04 (s, 1H), 7.27 (s, 1H), 7.13 (d, J = 9.2 Hz, 1H), 4.90 (s, 1H), 3.05 – 3.03 (m, 1H), 2.15 (s, 2H), 2.43 (s, 3H), 2.28 (s, 3H), 2.16 – 2.10 (m, 3H), 1.77 – 1.71 (m, 2H).
III-89	MS <i>m/z</i> : 364.4 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ: 10.05 (s, 1H), 8.88 (s, 1H), 8.07 (d, J = 2.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.01 (d, J = 2.0 Hz, 1H), 4.96 – 4.80 (m, 1H), 3.07 – 3.02 (m, 1H), 2.69 – 2.64 (m, 2H), 2.41 (s, 3H), 2.28 (s, 3H), 2.19 – 2.15 (m, 1H), 2.12 – 2.07 (m, 1H), 2.05 – 1.97 (m, 1H), 1.83 – 1.75 (m, 1H), 1.73 – 1.64 (m, 1H).
III-90	MS <i>m/z</i> : 349.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ: 8.96 (s, 1H), 7.95 (s, 1H), 7.22 (s, 1H), 7.10 (s, 1H), 5.10 – 4.98 (m, 1H), 3.27 – 3.19 (m, 1H), 2.90 – 2.76 (m, 2H), 2.40 (s, 3H), 2.38 – 2.31 (m, 1H), 2.30 – 2.20 (m, 2H), 2.11 (s, 3H), 1.98 – 1.78 (m, 2H). OH not observed.

Cmpd#	Characterization
III-91	MS m/z 394.3 $[M+H]^+$. ^1H NMR (400 MHz, methanol- d_4) δ 8.81 (s, 1H), 6.83 (d, J = 7.6 Hz, 1H), 6.74 (d, J = 7.5 Hz, 1H), 5.11 – 4.99 (m, 1H), 3.51 – 3.43 (m, 1H), 3.20 – 3.15 (m, 1H), 3.14 (s, 2H), 3.10 – 3.01 (m, 1H), 2.71 – 2.61 (m, 1H), 2.59 (s, 3H), 2.53 (s, 3H), 2.40 – 2.23 (m, 2H), 2.09 – 1.84 (m, 2H), 1.54 (s, 6H). OH not observed.
III-92	MS m/z 392.2 $[M+H]^+$. ^1H NMR (400 MHz, methanol- d_4) δ 8.82 (s, 1H), 8.30 (s, 1H, Formate), 7.12 (d, J = 7.6 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 5.10 – 4.98 (m, 1H), 3.49 – 3.40 (m, 1H), 3.22 – 3.00 (m, 2H), 2.90 (t, J = 7.1 Hz, 2H), 2.68 – 2.60 (m, 1H), 2.58 (s, 3H), 2.54 (s, 3H), 2.41 – 2.20 (m, 2H), 2.09 – 1.97 (m, 3H), 1.97 – 1.80 (m, 1H), 1.32 (s, 6H). OH peak not observed.
III-93	MS m/z : 400.2 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ : 8.91 (s, 1H), 8.06 (s, 1H), 7.85 (d, J = 2.0 Hz, 1H), 7.48 (s, 1H), 7.10 (d, J = 1.6 Hz, 1H), 6.68 (t, J = 55.6 Hz, 1H), 5.16 – 5.11 (m, 1H), 3.55 – 3.53 (m, 1H), 3.28 – 3.23 (m, 1H), 3.15 – 3.12 (m, 1H), 2.73 – 2.68 (m, 1H), 2.64 (s, 3H), 2.46 – 2.37 (m, 1H), 2.34 – 2.30 (m, 1H), 2.10 – 2.05 (m, 1H), 2.00 – 1.96 (m, 1H). OH peak not observed.
III-94	MS m/z 353.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 8.81 (s, 1H), 7.89 (s, 1H), 6.33 (s, 1H), 5.09 – 4.90 (m, 1H), 4.59 (t, J = 8.6 Hz, 2H), 3.16 (t, J = 8.8 Hz, 2H), 3.03 – 2.79 (m, 4H), 2.02 (s, 3H), 1.53 (s, 3H). OH peaks not observed.
III-95	MS m/z 379.2 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 8.85 (s, 1H), 7.97 (s, 1H), 7.15 (d, J = 1.7 Hz, 1H), 7.08 (s, 1H), 5.03 (p, J = 8.3 Hz, 1H), 2.98 – 2.83 (m, 4H), 2.14 (s, 3H), 1.54 (s, 3H). OH peaks not observed.
III-96	MS m/z : 432.4 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ : 8.95 (s, 1H), 7.98 (s, 1H), 7.75 (d, J = 2.4 Hz, 1H), 7.26 (s, 1H), 7.04 (d, J = 2.0 Hz, 1H), 5.11 – 5.00 (m, 1H), 3.55 – 3.42 (m, 3H), 2.97 – 2.83 (m, 2H), 2.44 (s, 3H), 2.43 – 2.36 (m, 1H), 2.35 – 2.22 (m, 2H), 2.02 – 1.92 (m, 1H), 1.91 – 1.82 (m, 1H). OH peak not observed.
III-97	MS m/z 387.0 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 8.84 (s, 1H), 8.05 (s, 1H), 7.85 (d, J = 2.2 Hz, 1H), 7.48 (s, 1H), 7.15 – 7.05 (m, 1H), 6.68 (t, J = 55.6 Hz, 1H), 5.10 – 4.95 (m, 1H), 3.00 – 2.86 (m, 4H), 1.54 (s, 3H). OH peaks not observed.
III-98	MS m/z : 374.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ : 9.01 (s, 1H), 8.13 (s, 1H), 7.10 (s, 1H), 6.95 (s, 1H), 6.59 (t, J = 55.6 Hz, 1H), 5.27 – 5.14 (m, 1H), 4.12 – 3.94 (m, 1H), 3.88 – 3.72 (m, 1H), 3.70 – 3.61 (m, 1H), 3.24 – 3.15 (m, 1H), 3.02 (s, 3H), 2.63 – 2.52 (m, 1H), 2.47 – 2.42 (m, 1H), 2.41 (s, 3H), 2.34 – 2.25 (m, 1H), 2.15 – 2.02 (m, 1H). OH peak not observed.
III-99	MS m/z : 394.0 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ : 8.96 (s, 1H), 8.02 (s, 1H), 7.25 (s, 1H), 7.13 (s, 1H), 6.63 (t, J = 54.8 Hz, 1H), 5.09 – 5.01 (m, 1H), 3.27 – 3.20 (m, 1H), 2.90 – 2.80 (m, 2H), 2.41 (s, 3H), 2.39 – 2.33 (m, 1H), 2.31 – 2.21 (m, 2H), 2.03 – 1.74 (m, 2H). OH peak not observed.
III-100	MS m/z : 379.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ : 8.91 (s, 1H), 7.99 (s, 1H), 7.66 (d, J = 2.0 Hz, 1H), 7.08 (s, 1H), 7.00 (s, 1H), 5.13 – 5.09 (m, 1H), 4.26 – 4.22 (m, 1H), 3.78 – 3.64 (m, 2H), 3.53 – 3.50 (m, 1H), 2.96 – 2.92 (m, 1H), 2.16 (s, 3H), 1.94 – 1.91 (m, 1H), 1.21 (s, 3H), 0.89 (s, 3H). OH peak not observed.
III-101	MS m/z : 351.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ : 8.73 (s, 1H), 7.83 (s, 1H), 6.60 (s, 1H), 4.55 – 4.44 (m, 1H), 4.42 – 4.30 (m, 1H), 3.16 – 3.10 (m, 4H), 2.56 – 2.40 (m, 1H), 2.24 – 2.16 (m, 2H), 2.00 (s, 3H), 1.96 – 1.86 (m, 2H), 1.63 – 1.48 (m, 3H). OH peaks not observed.
III-102	MS m/z : 401.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ : 8.80 (s, 1H), 8.02 (s, 1H), 7.85 (d, J = 2.0 Hz, 1H), 7.48 (s, 1H), 7.09 (s, J = 1.6 Hz, 1H), 6.66 (t, J = 55.6 Hz, 1H), 4.57 – 4.51 (m, 1H), 4.40 – 4.35 (m, 1H), 2.53 – 2.44 (m, 1H), 2.25 – 2.17 (m, 2H), 1.95 – 1.90 (m, 2H), 1.62 – 1.53 (m, 3H). OH peaks not observed.

Cmpd#	Characterization
III-103	MS m/z : 433.0 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 8.78 (s, 1H), 7.96 (s, 1H), 7.75 (d, J = 2.4 Hz, 1H), 7.26 (s, 1H), 7.04 (d, J = 1.6 Hz, 1H), 4.61 – 4.48 (m, 1H), 4.43 – 4.31 (m, 1H), 3.47 (q, J = 11.2 Hz, 2H), 2.57 – 2.41 (m, 1H), 2.30 – 2.16 (m, 2H), 1.99 – 1.87 (m, 2H), 1.63 – 1.50 (m, 3H). OH peaks not observed.
III-104	MS m/z : 365.2 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 8.84 (s, 1H), 7.95 (s, 1H), 7.64 (d, J = 2.3 Hz, 1H), 7.08 (s, 1H), 6.97 (d, J = 2.2 Hz, 1H), 5.03 (p, J = 8.3 Hz, 1H), 3.00 – 2.80 (m, 4H), 2.47 (q, J = 7.5 Hz, 2H), 1.53 (s, 3H), 1.03 (t, J = 7.5 Hz, 3H). OH peaks not observed.
III-105	MS m/z : 365.3 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 8.95 (s, 1H), 8.09 (s, 1H), 7.65 (s, 1H), 7.08 (s, 1H), 6.98 (s, 1H), 4.57 – 4.51 (m, 1H), 4.39 – 4.34 (m, 1H), 2.49 – 2.46 (m, 1H), 2.25 – 2.21 (m, 2H), 2.17 (s, 3H), 1.96 – 1.90 (m, 2H), 1.61 – 1.54 (m, 3H). OH peaks not observed.
III-106	MS m/z : 367.0 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 8.80 (s, 1H), 7.95 (s, 1H), 7.63 (d, J = 2.4 Hz, 1H), 7.05 (s, 1H), 6.97 (d, J = 2.0 Hz, 1H), 4.76 – 4.68 (m, 1H), 4.55 – 4.45 (m, 1H), 4.16 – 4.07 (m, 2H), 3.67 – 3.60 (m, 1H), 3.36 – 3.32 (m, 1H), 2.89 – 2.77 (m, 1H), 2.26 – 2.20 (m, 1H), 2.14 (s, 3H). OH peaks not observed.
III-107	MS m/z : 395.0 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 8.82 (s, 1H), 7.97 (s, 1H), 7.15 (s, 1H), 7.07 (s, 1H), 4.75 – 4.66 (m, 1H), 4.51 – 4.44 (m, 1H), 4.18 – 4.04 (m, 2H), 3.67 – 3.59 (m, 1H), 3.35 – 3.32 (m, 1H), 2.88 – 2.77 (m, 1H), 2.24 – 2.22 (m, 1H), 2.14 (s, 3H). OH peaks not observed.
III-108	MS m/z : 379.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ : 9.65 (s, 1H), 8.92 (s, 1H), 7.91 (s, 1H), 7.82 (d, J = 2.0 Hz, 1H), 7.12 (d, J = 4.0 Hz, 1H), 7.08 (s, 1H), 5.25 – 5.13 (m, 1H), 3.86 (d, J = 8.0 Hz, 2H), 2.33 – 2.22 (m, 1H), 2.19 – 2.14 (m, 1H), 2.13 – 2.10 (m, 2H), 2.07 (s, 3H), 1.37 (s, 3H), 1.27 (s, 3H).
III-109	MS m/z : 379.0 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 8.76 (s, 1H), 7.93 (s, 1H), 7.64 (d, J = 2.0 Hz, 1H), 7.08 (s, 1H), 6.97 (d, J = 1.2 Hz, 1H), 4.56 – 4.50 (m, 1H), 4.44 – 4.30 (m, 1H), 2.49 – 2.43 (m, 3H), 2.30 – 2.15 (m, 2H), 1.99 – 1.80 (m, 2H), 1.64 – 1.49 (m, 3H), 1.03 (t, J = 7.6 Hz, 3H). OH peaks not observed.
III-110	MS m/z : 378.2 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.83 (s, 1H), 7.03 (d, J = 7.8 Hz, 1H), 6.77 (d, J = 7.8 Hz, 1H), 5.13 – 4.95 (m, 1H), 3.46 – 3.34 (m, 1H), 3.15 – 2.92 (m, 2H), 2.88 – 2.77 (m, 2H), 2.76 – 2.64 (m, 2H), 2.58 – 2.48 (m, 7H), 2.41 – 2.19 (m, 2H), 2.08 – 1.75 (m, 6H). OH peak not observed.
III-111	MS m/z : 392.2 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.89 (s, 1H), 7.10 (d, J = 7.6 Hz, 1H), 6.90 (d, J = 7.6 Hz, 1H), 5.28 – 5.14 (m, 1H), 4.08 – 3.93 (m, 1H), 3.84 – 3.59 (m, 2H), 3.24 – 3.12 (m, 1H), 3.01 (s, 3H), 2.95 (t, J = 7.4 Hz, 2H), 2.61 (s, 3H), 2.59 – 2.49 (m, 1H), 2.48 – 2.24 (m, 2H), 2.18 – 2.04 (m, 1H), 1.99 (t, J = 7.4 Hz, 2H), 1.44 (s, 6H). OH peak not observed.
III-112	MS m/z : 352.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ : 8.97 (s, 1H), 8.88 (s, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 7.6 Hz, 1H), 4.91–4.88 (m, 1H), 3.09–3.07 (m, 1H), 2.76–2.74 (m, 2H), 2.50 (s, 3H), 2.43 (s, 3H), 2.33–2.31 (m, 2H), 2.29 (s, 3H), 2.17 (s, 3H), 2.12–2.09 (m, 1H), 1.80–1.73 (m, 2H).

Example 3A. Preparation of 2-(4-methoxy-7-((R)-1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)-3-methyl-5-(trifluoromethyl)phenol (IIIA-1)



Step 1: To a solution of 6-chloro-N3-[(3R)-1-methyl-3-piperidyl]pyridazine-3,4-diamine (483 mg, 2.00 mmol) in acetonitrile (2.0 mL) was added sodium acetate (246 mg, 3.0 mmol) and bromine (0.10 mL, 2.0 mmol) dropwise while stirring. The mixture was heated to 80 °C for 1 h until LCMS analysis indicated completion. The reaction was cooled down to room temperature, diluted with dichloromethane, washed with sodium bicarbonate and water. Combined organics dried with sodium sulfate, filtered and concentrated under reduced pressure. Diethyl ether (10 mL) was added to the brown oil residue and stirred until precipitation was formed. Solids were filtered and washed with diethyl ether and dried to yield (R)-5-bromo-6-chloro-N3-(1-methylpiperidin-3-yl)pyridazine-3,4-diamine as a light brown solid (123 mg, 19% yield). MS m/z 322.0, 323.9 $[M+H]^+$.

Step 2: A solution of 5-bromo-6-chloro-N3-[(3R)-1-methyl-3-piperidyl]pyridazine-3,4-diamine (123 mg, 0.384 mmol) in triethyl orthoformate (1.3 mL, 7.67 mmol) was stirred at 120 °C for 24 h. Upon completion, the reaction was cooled down to room temperature, loaded directly on to a silica gel pre-column and purified by flash column chromatography eluting with a gradient $CH_2Cl_2/MeOH$ (0 - 30% MeOH) to afford (R)-4-bromo-3-chloro-7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazine as a brown solid (35 mg, 27% yield). MS m/z 331.9, 333.9 $[M+H]^+$.

Step 3: To a solution of 4-bromo-3-chloro-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazine (34 mg, 0.1 mmol) in 1,4-dioxane was added RuPhos-Pd-G3 (1.6 mg, 0.002 mmol), sodium-tert butoxide (14 mg, 0.14 mmol), methanol (8 μ L, 0.20 mmol). The reaction was degassed by purging with Argon and heated to 60 °C for 4 hours until LCMS indicated completion. The mixture was loaded directly to solid silica pre-column and purified by flash

column chromatography eluting with a gradient CH₂Cl₂/MeOH (0 - 30% MeOH) to afford (R)-3-chloro-4-methoxy-7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazine as a light brown solid (17 mg, 58% yield). MS *m/z* 282.1, 284.0 [M+H⁺].

Step 4: To a screw cap vial were added: 3-chloro-4-methoxy-7-[(3R)-1-methyl-3-

5 piperidyl]imidazo[4,5-c]pyridazine (17 mg, 0.06 mmol), XPhos-Pd -G3 (5.1 mg, 0.006 mmol), 2-[2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (25 mg, 0.07 mmol). The vial was degassed by purging Ar for 15 min. 1,4-Dioxane (0.5 mL) and potassium carbonate (aq. 2.0 M, 0.4 mL, 0.2 mmol) were added and the mixture was heated to 90 °C for 1 h. Upon completion, the reaction was cooled down to room
10 temperature, loaded directly onto solid silica pre-column cartridge and purified via silica gel flash column chromatography eluting with a gradient CH₂Cl₂/MeOH (0-30% MeOH) to afford 4-methoxy-3-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)-7-((R)-1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazine (15 mg, 53% yield). MS *m/z* 466.7 [M+H⁺].

Step 5: To a solution of 4-methoxy-3-[2-(methoxymethoxy)-6-methyl-4-

15 (trifluoromethyl)phenyl]-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazine (15 mg, 0.032 mmol) in 1,4-dioxane (0.5 mL) was added HCl (0.081 mL, 0.32 mmol, 4.0 M in dioxane). The reaction was stirred at room temperature for 1 hour. Upon completion, the reaction was diluted with CH₂Cl₂, quenched with aq. sodium bicarbonate (10 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic parts were washed with water, brine, dried over sodium sulfate,
20 filtered, and solvent evaporated under reduced pressure. The resulting residue was purified via silica gel flash column chromatography eluting with a gradient CH₂Cl₂/MeOH (0-30% MeOH) to afford 2-(4-methoxy-7-((R)-1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)-3-methyl-5-(trifluoromethyl)phenol as a yellow solid (7 mg, 52% yield). MS *m/z* 422.3 [M+H⁺];
25 ¹H NMR (500 MHz, methanol-*d*₄) δ: 8.65 (s, 1H), 7.12 (s, 1H), 7.02 (s, 1H), 5.18 (d, J = 10.2 Hz, 1H), 4.54 (s, 3H), 3.78 – 3.70 (m, 1H), 3.58 (d, J = 14.6 Hz, 1H), 3.40 – 3.33 (m, 1H), 3.06 – 2.93 (m, 1H), 2.82 (s, 3H), 2.46 (qd, J = 11.9, 3.3 Hz, 1H), 2.40 – 2.29 (m, 1H), 2.15 (d, J = 15.1 Hz, 2H), 2.06 (s, 3H); 1H not observed (OH).

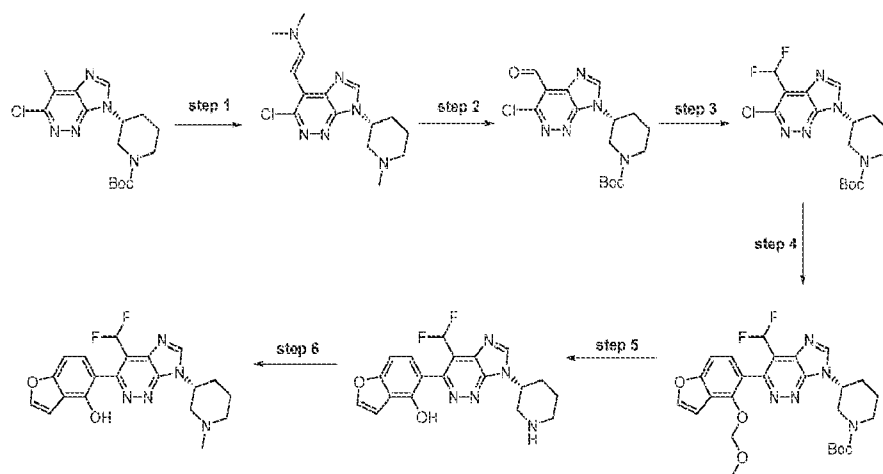
Using the procedure described for Example 3A, above, additional compounds described herein may be prepared by substituting the appropriate starting material, suitable reagents and reaction
30 conditions, obtaining compounds such as those selected from:

Table 3A

Cmpd#	Characterization
IIIA-2	MS m/z 406.1 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 8.71 (s, 1H), 7.67 (d, J = 2.3 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.13 – 7.06 (m, 1H), 6.99 (dd, J = 2.3, 0.9 Hz, 1H), 5.11 (tt, J = 6.4, 3.8 Hz, 1H), 4.98 – 4.93 (m, 1H), 3.24 – 3.16 (m, 1H), 2.82 – 2.78 (m, 2H), 2.39 (s, 3H), 2.42 – 2.30 (m, 1H), 2.20 (dp, J = 10.7, 5.1 Hz, 2H), 1.96 – 1.79 (m, 1H), 1.30 – 1.25 (m, 1H), 0.86 – 0.77 (m, 4H). OH peak not observed.
IIIA-3	MS m/z 394.2 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 8.65 (s, 1H), 7.69 (d, J = 2.2 Hz, 1H), 7.56 (d, J = 8.6 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 2.3 Hz, 1H), 5.07 (q, J = 7.0 Hz, 2H), 5.03 – 4.94 (m, 1H), 3.10 – 2.88 (m, 2H), 2.53 (s, 4H), 2.30 – 2.18 (m, 2H), 2.07 – 1.94 (m, 1H), 1.89 (dt, J = 10.0, 4.8 Hz, 1H), 1.44 (t, J = 7.0 Hz, 3H), 1.31 – 1.25 (m, 1H). OH peak not observed. One piperidine peak is buried under methyl singlet.
IIIA-4	MS m/z 380.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ : 10.33 (s, 1H), 8.81 (s, 1H), 7.89 (d, J = 2.2 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.20 – 6.97 (m, 2H), 4.87 (dt, J = 9.1, 4.8 Hz, 1H), 4.48 (s, 3H), 3.03 (d, J = 10.6 Hz, 1H), 2.62 (d, J = 10.0 Hz, 2H), 2.26 (s, 3H), 2.09 (dt, J = 15.4, 7.5 Hz, 3H), 1.85 – 1.74 (m, 1H), 1.70 (dd, J = 12.2, 7.9 Hz, 1H).
IIIA-5	MS m/z 405.3 $[M+H]^+$; ^1H NMR (500 MHz, MeOD) δ : 8.42 (s, 1H), 7.70 (d, J = 2.3 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 2.2 Hz, 1H), 4.47 (t, J = 7.6 Hz, 1H), 4.09 (d, J = 8.2 Hz, 4H), 3.19 – 3.08 (m, 1H), 2.82 – 2.65 (m, 2H), 2.38 (s, 3H), 2.34 – 2.26 (m, 1H), 2.21 (td, J = 14.2, 6.5 Hz, 2H), 2.19 – 2.04 (m, 2H), 1.95 – 1.71 (m, 2H). 1 OH peak observed.
IIIA-6	MS m/z 393.3 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 8.50 (s, 1H), 7.70 (d, J = 2.3 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.15 (dd, J = 8.5, 1.0 Hz, 1H), 7.01 (dd, J = 2.2, 1.0 Hz, 1H), 4.96 – 4.87 (m, 1H), 3.26 – 3.12 (m, 1H), 3.06 (s, 6H), 2.78 (q, J = 11.2 Hz, 2H), 2.39 (s, 3H), 2.32 (d, J = 10.9 Hz, 1H), 2.17 (td, J = 8.9, 4.7 Hz, 2H), 1.97 – 1.76 (m, 2H). 1 OH peak not observed.
IIIA-7	MS m/z 432.2 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 8.74 (s, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.24 – 7.18 (m, 1H), 7.15 (d, J = 1.7 Hz, 1H), 5.12 (p, J = 4.5 Hz, 1H), 5.02 – 4.95 (m, 1H), 3.31 – 3.20 (m, 1H), 2.87 – 2.82 (m, 2H), 2.42 (s, 3H), 2.40 – 2.36 (m, 1H), 2.23 (td, J = 8.9, 4.7 Hz, 2H), 1.98 – 1.84 (m, 1H), 1.87 – 1.82 (m, 1H), 0.81 (d, J = 4.5 Hz, 4H). 1 OH peak not observed.

Example 3B. Preparation of (R)-5-(4-(difluoromethyl)-7-(1-methylpiperidin-3-yl)-7H-

5 imidazo[4,5-c]pyridazin-3-yl)benzofuran-4-ol (IIIB-1)



Steps 1 and 2. A solution of *tert*-Butyl (*R*)-3-(3-chloro-4-methyl-7*H*-imidazo[4,5-*c*]pyridazin-7-yl)piperidine-1-carboxylate (50.0 mg, 0.142 mmol) in *N,N*-dimethylformamide dimethyl acetal (1.0 mL) was heated at 120 °C for 24 hours. Upon completion, the reaction mixture was cooled down to room temperature, partitioned between water and CH₂Cl₂. The combined organic parts were dried over Na₂SO₄ and evaporated to dryness. The resulting crude (*R,E*)-2-(3-chloro-7-(1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazin-4-yl)-*N,N*-dimethylethen-1-amine was dissolved in THF (1.0 mL) and a solution of sodium periodate (91.2 mg, 0.43 mmol) in water (1.0 mL) was then added. The reaction mixture was stirred for 2 hours at room temperature.

Upon completion, the reaction was partitioned between EtOAc and water. The organic layer was washed with water and brine, dried over Na₂SO₄, and concentrated. The residue was purified via silica gel flash column chromatography eluting with a gradient CH₂Cl₂/MeOH (0-20% MeOH) to afford *tert*-butyl (*R*)-3-(3-chloro-4-formyl-7*H*-imidazo[4,5-*c*]pyridazin-7-yl)piperidine-1-carboxylate (43.1 mg, 83% yield over 2 steps). MS *m/z* 384.2, 386.1 [*M*+H₂O]⁺.

Step 3. A solution of *tert*-butyl (*R*)-3-(3-chloro-4-formyl-7*H*-imidazo[4,5-*c*]pyridazin-7-yl)piperidine-1-carboxylate (43.1 mg, 0.118 mmol) in dichloromethane (1.2 mL) was cooled down 0 °C, and diethylaminosulfur trifluoride (47.5 mg, 0.039 mL, 0.295 mmol) was added dropwise then. The mixture was stirred at room temperature for 30 minutes. After all starting material has been consumed, the solution was loaded directly onto silica gel pre-column and purified via silica gel flash column chromatography eluting with a gradient hexanes/EtOAc (50-100% EtOAc) to afford *tert*-butyl (*R*)-3-(3-chloro-4-(difluoromethyl)-7*H*-imidazo[4,5-*c*]pyridazin-7-yl)piperidine-1-carboxylate (20.3 mg, 44% yield) as clear oil. MS *m/z* 388.1, 390.0 [*M*+H]⁺.

Step 4. To a dry crew-cap vial were added: *tert*-butyl (*R*)-3-(3-chloro-4-(difluoromethyl)-7*H*-imidazo[4,5-*c*]pyridazin-7-yl)piperidine-1-carboxylate (20.3, 0.052 mmol), 2-[4-(methoxymethoxy)benzofuran-5-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (23.5 mg, 0.077 mmol), (2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (4.4 mg, 0.0052 mmol), and potassium carbonate (21.4 mg, 0.16 mmol). The mixture was degassed by purging with nitrogen for 15 min before 1,4-dioxane (0.75 mL) and water (0.25 mL) were added. The reaction vessel was evacuated and backflushed with nitrogen (3 times), and the mixture was heated at 80°C for 16 hours. Upon completion, the mixture was partitioned between EtOAc and water. The combined organic parts were washed with brine, dried over sodium sulfate, filtered and concentrated under pressure. The residue was purified via silica gel flash column chromatography eluting with a gradient CH₂Cl₂/MeOH (0-10% MeOH) to yield *tert*-butyl (*R*)-3-(4-(difluoromethyl)-3-(4-(methoxymethoxy)benzofuran-5-yl)-7*H*-imidazo[4,5-*c*]pyridazin-7-yl)piperidine-1-carboxylate (27.0 mg, 99% yield). M/S *m/z* 530.2 [M+H]⁺.

Step 5 and 6. To a vial containing *tert*-butyl (*R*)-3-(4-(difluoromethyl)-3-(4-(methoxymethoxy)benzofuran-5-yl)-7*H*-imidazo[4,5-*c*]pyridazin-7-yl)piperidine-1-carboxylate (27.0 mg, 0.0525 mmol) was added 4 N HCl in dioxane (1.0 mL). The reaction mixture was stirred for 2h at room temperature. Upon completion, the mixture was partitioned between CH₂Cl₂ and aq. NaHCO₃. The combined organic parts were washed with brine, dried over sodium sulfate, filtered and concentrated under pressure to give crude (*R*)-5-(4-(difluoromethyl)-7-(piperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)benzofuran-4-ol as brown oil. The crude product was then dissolved in CH₂Cl₂ (1.0 mL) and MeOH (0.25 mL) and the reaction mixture was cooled to 0 °C. A solution of 37% aqueous formaldehyde (0.12 mL, 1.57 mmol) was then added. The mixture was stirred for 3 minutes before sodium triacetoxyborohydride (22.3 mg, 0.105 mmol) was added at once. The mixture was allowed to stir at room temperature for 10 minutes. Upon completion, the reaction was quenched with sat. aq. NaHCO₃ (5.0 mL). The resulting mixture was extracted with CH₂Cl₂ (3x20 mL). The organic parts were combined, dried over Na₂SO₄, and evaporated to dryness. The residue was purified via silica gel flash column chromatography eluting with a gradient CH₂Cl₂/MeOH (0-10% MeOH) to yield (*R*)-5-(4-(difluoromethyl)-7-(1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazin-3-yl)benzofuran-4-ol (6.7 mg, 32% yield over 2 steps) as pale yellow solid. MS *m/z* 400.2 [M+H]⁺; ¹H NMR (500

MHz, methanol-*d*₄) δ : 9.05 (s, 1H), 7.76 (s, 1H), 7.30 (dd, *J* = 8.5, 2.6 Hz, 1H), 7.27 – 7.21 (m, 1H), 7.07 (s, 1H), 6.86 (t, *J* = 52.8 Hz, 1H), 5.16 – 5.04 (m, 1H), 3.25 – 3.20 (m, 1H), 2.93 – 2.76 (m, 2H), 2.46 – 2.35 (m, 4H), 2.32 – 2.20 (m, 2H), 2.00 – 1.90 (m, 1H), 1.90 – 1.79 (m, 1H); 1 H not observed (OH).

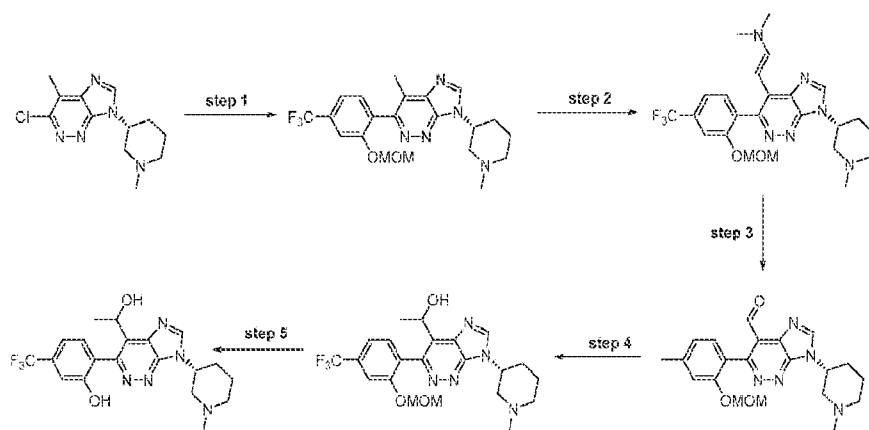
5

Using the procedure described for Example 3B, above, additional compounds described herein may be prepared by substituting the appropriate starting material, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

10 Table 3B

Cmpd#	Characterization
IIIB-2	MS <i>m/z</i> 428.2 [M+H] ⁺ ; ¹ H NMR (500 MHz, methanol- <i>d</i> ₄) δ : 9.07 (s, 1H), 7.57 (d, <i>J</i> = 7.6 Hz, 1H), 7.33 (d, <i>J</i> = 8.0 Hz, 1H), 7.26 (s, 1H), 6.92 (t, <i>J</i> = 53.0 Hz, 1H), 5.17 – 5.03 (m, 1H), 2.96 – 2.79 (m, 2H), 2.50 – 2.35 (m, 4H), 2.34 – 2.22 (m, 3H), 2.00 – 1.90 (m, 1H), 1.90 – 1.79 (m, 1H); 1H not observed (OH).

Example 3C. Preparation of 2-(4-(1-hydroxyethyl)-7-((*R*)-1-methylpiperidin-3-yl)-7H-imidazo[4,5-*c*]pyridazin-3-yl)-5-(trifluoromethyl)phenol (IIIC-1)



- 15 Step 1. To a screw-cap vial were added: 2-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (281 mg, 0.85 mmol), (*R*)-3-chloro-4-methyl-7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-*c*]pyridazine (150 mg, 0.56 mmol), XPhos Pd G3 (48 mg, 0.056 mmol), and potassium carbonate (234 mg, 1.7 mmol). The vial was evacuated and backfilled with Argon 3 times. 1,4-dioxane (3.0 mL) and water (1.0 mL) were added, and the
- 20 reaction mixture was heated at 80 °C for 1 h. The mixture was cooled to room temperature and partitioned between water and EtOAc. The combined organic parts were washed with brine,

dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified via silica gel flash column chromatography eluting with a gradient CH₂Cl₂/MeOH (0-20% MeOH) to afford (*R*)-3-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-4-methyl-7-(1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazine (229 mg, 93% yield) as pale brown foam.

5 MS *m/z* 436.2 [M+H]⁺.

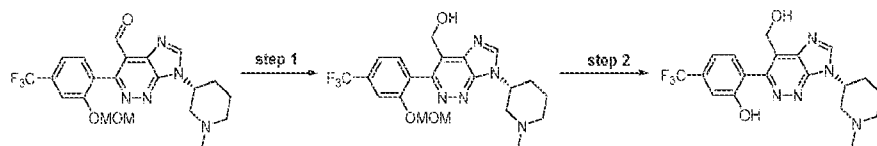
Step 2. A solution of (*R*)-3-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-4-methyl-7-(1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazine (229 mg, 0.53 mmol) in *N,N*-dimethylformamide (DMF) (0.50 mL) and *N,N*-dimethylformamide dimethyl acetal (0.35 mL, 2.63 mmol) was heated at 135 °C for 48 hours. Upon completion solvents were evaporated. The residue was partitioned between water and EtOAc. The combined organic parts were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give crude (*R,E*)-2-(3-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-7-(1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazin-4-yl)-*N,N*-dimethylethen-1-amine which was used in the next step without further purification.

15 Step 3. The crude product from step 2 was dissolved in MeOH (2.0 mL) and water (1.0 mL). Sodium periodate (338 mg, 1.58 mmol) was added, and the solution was stirred at room temperature for 5 h, upon which precipitate formation was observed. The solution was diluted with water and the resulting aqueous solution was extracted with CH₂Cl₂ (3×20 mL). The combined organic parts were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified via silica gel flash column chromatography eluting with a gradient CH₂Cl₂/MeOH (0-20% MeOH) to afford (*R*)-3-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-7-(1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazine-4-carbaldehyde (104 mg, 44% yield) as brown solid. MS *m/z* 482.2 [M+CH₃OH+H]⁺.

25 Steps 4 and 5. A solution of (*R*)-3-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-7-(1-methylpiperidin-3-yl)-7*H*-imidazo[4,5-*c*]pyridazine-4-carbaldehyde (15.0 mg, 0.0334 mmol) in anhydrous tetrahydrofuran (0.33 mL) was stirred at -78 °C under nitrogen atmosphere. A solution of 3.0 M methylmagnesium bromide (0.012 mL, 0.0367 mmol) in diethyl ether was then added dropwise. The mixture was allowed to stir at room temperature for 30 min. After all starting material had been consumed, a solution of 12 N aqueous HCl (1.0 mL, 12.0 mmol) was added. The mixture was stirred for another 30 minutes before water was added to dilute the

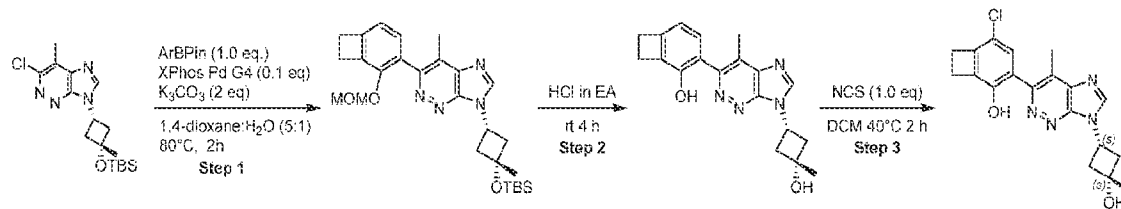
mixture. The resulting aqueous solution was neutralized with solid NaHCO_3 followed by extraction with CH_2Cl_2 (3×15 mL). Combined organic layers were dried over Na_2SO_4 , and evaporated to dryness under reduced pressure. The residue was purified via silica gel flash column chromatography eluting with a gradient $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (0-20% MeOH) to give 2-(4-(1-hydroxyethyl)-7-((R)-1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol (8 mg, 56% yield) as pale brown solid. MS m/z 422.2 $[\text{M}+\text{H}]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.91 (s, 1H), 7.49 (d, $J = 8.0$ Hz, 1H), 7.31 (d, $J = 7.9$ Hz, 1H), 7.25 (s, 1H), 5.10 – 5.00 (m, 1H), 4.94 (q, $J = 6.9$ Hz, 1H), 3.24 (s, 1H), 2.93 – 2.79 (m, 2H), 2.49 – 2.35 (m, 4H), 2.32 – 2.20 (m, 2H), 2.02 – 1.92 (m, 1H), 1.92 – 1.81 (m, 1H), 1.69 (d, $J = 6.6$ Hz, 3H); 2 Hs not observed (2 OHs).

Example 3D. Preparation of (R)-2-(4-(hydroxymethyl)-7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol (IIID-1)



Steps 1 and 2. To a solution of (R)-3-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazine-4-carbaldehyde (9.0 mg, 0.0200 mmol, prepared according to example 3c) in MeOH (1.0 mL) was added sodium borohydride (0.76 mg, 0.02 mmol). The mixture was stirred for 30 min before a 12 N solution of hydrochloric acid (1.0 mL) was added. After another 30 min of stirring, the aqueous solution was neutralized with saturated NaHCO_3 solution. The resulting solution was extracted with CH_2Cl_2 (3×15 mL). Combined organic parts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified via silica gel flash column chromatography eluting with a gradient $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (0-20% MeOH) to afford (R)-2-(4-(hydroxymethyl)-7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol (4.5 mg, 55% yield) as pale brown solid. MS m/z 408.2 $[\text{M}+\text{H}]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.85 (s, 1H), 7.57 (d, $J = 7.9$ Hz, 1H), 7.32 (d, $J = 7.9$ Hz, 1H), 7.24 (s, 1H), 5.20 – 5.08 (m, 1H), 4.94 (s, 2H), 3.82 – 3.58 (m, 1H), 2.79 (s, 3H), 2.56 – 2.41 (m, 1H), 2.41 – 2.31 (m, 1H), 2.22 – 2.07 (m, 1H), 2.06 – 1.91 (m, 1H); 5Hs not observed (3 CH signals that overlap with solvent peak and 2 OHs).

Example 3E. Preparation of 5-chloro-3-(7-((1s,3s)-3-hydroxy-3-methylcyclobutyl)-4-methyl-7H-imidazo[4,5-c]pyridazin-3-yl)bicyclo[4.2.0]octa-1(6),2,4-trien-2-ol (IIIE-1)



- 5 Step 1. To a solution of 2-(2-(methoxymethoxy)bicyclo[4.2.0]octa-1,3,5-trien-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (166.0 mg, 0.572 mmol, 1.5 eq) in 1, 4-dioxane and H₂O at rt were added (R)-3-chloro-4-methyl-7-(1-methylpiperidin-3-yl)-7H-imidazo[4,5-c] pyridazine (140.0 mg, 0.381 mmol, 1.0 eq), XPhos Pd G4 (32.83 mg, 0.038 mmol, 0.1 eq) and K₂CO₃ (158.2 mg, 1.14 mmol, 1.0 eq). N₂ was bubbled into the mixture. The sealed vial was irradiated
- 10 in the microwave at 80°C for 2 h. Upon completion, the reaction was cooled to room temperature, filtered through a pad of Celite and rinsed with EtOAc. The filtrate was concentrated in vacuo. The residue was purified by flash chromatography on silica gel (PE: EA = 1:0 ~ 20:1) to afford 7-((1s,3s)-3-((tert-butyldimethylsilyl)oxy)-3-methylcyclobutyl)-3-(2-(methoxymethoxy)bicyclo[4.2.0]octa-1(6),2,4-trien-3-yl)-4-methyl-7H-imidazo[4,5-c]pyridazine
- 15 (170 mg, 0.344 mmol, 90.07% yield) as colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 8.17 (s, 1H), 7.06 (d, J = 7.2 Hz, 1H), 6.73 (d, J = 7.2 Hz, 1H), 4.94 (s, 2H), 4.85 (t, J = 8.4 Hz, 1H), 3.25 (d, J = 3.6 Hz, 2H), 3.17 (s, 3H), 3.10 (t, J = 4.0 Hz, 2H), 2.81 – 2.75 (m, 2H), 2.56 (d, J = 8.8 Hz, 3H), 2.39 (s, 3H), 1.43 (s, 3H), 0.78 (s, 9H), 0.00 (s, 6H).

- Step 2. A solution of 7-((1s,3s)-3-((tert-butyldimethylsilyl)oxy)-3-methylcyclobutyl)-3-(2-(methoxymethoxy)bicyclo[4.2.0]octa-1(6),2,4-trien-3-yl)-4-methyl-7H-imidazo[4,5-c]pyridazine
- 20 (180 mg, 0.363 mmol, 1.0 eq) in 2 N HCl in EtOAc was stirred at rt for 1 h. Upon completion, the resulting precipitate was filtered out and rinsed with EtOAc (5 mL). The solid was dried in vacuo to afford 3-(7-((1s,3s)-3-hydroxy-3-methylcyclobutyl)-4-methyl-7H-imidazo[4,5-c]pyridazin-3-yl)bicyclo[4.2.0]octa-1(6),2,4-trien-2-ol (120 mg, 0.356 mmol, 98.07% yield) as
- 25 white solid. ¹H NMR (400 MHz, CDCl₃) δ 14.33 (s, 1H), 13.57 (s, 1H), 11.81 (d, J = 7.2 Hz, 1H), 11.45 (d, J = 7.2 Hz, 1H), 10.11 (s, 1H), 7.87 (d, J = 8.0 Hz, 4H), 7.48 (dd, J = 22.0, 9.6 Hz, 4H), 6.17 (s, 3H), 5.82 (s, 1H), 5.60 (d, J = 4.8 Hz, 2H).

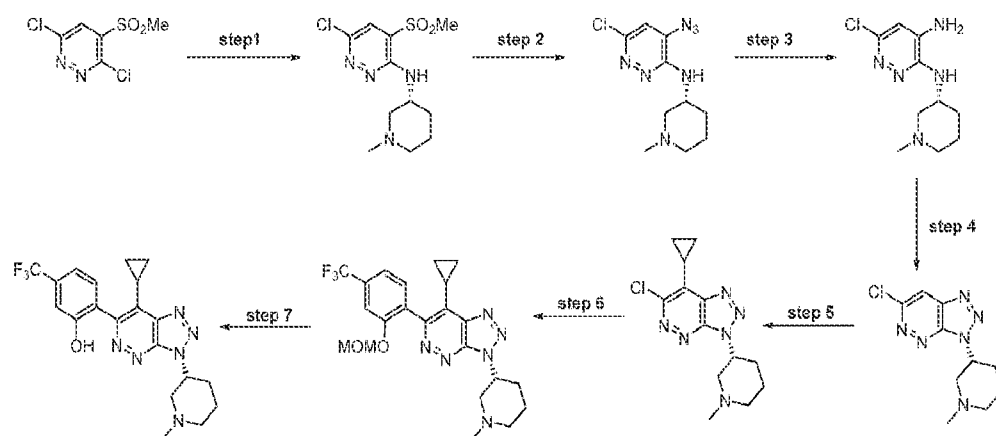
Step 3. To a solution of 3-(7-((1s,3s)-3-hydroxy-3-methylcyclobutyl)-4-methyl-7H-imidazo[4,5-c] pyridazin-3-yl) bicycle [4.2.0] octa-1(6),2,4-trien-2-ol (70 mg, 0.28 mmol, 1.0 eq) in DCM was added NCS (28 mg, 0.21 mmol, 1.0 eq). The mixture was stirred at rt for 30 min, then quenched with H₂O, extracted with DCM. The organic layer was washed with brine (50 mL x 2), dried with Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography on silica gel eluted with (PE/EA = 100:0~20:1) to give 5-chloro-3-(7-((1s,3s)-3-hydroxy-3-methylcyclobutyl)-4-methyl-7H-imidazo[4,5-c] pyridazin-3-yl) bicycle [4.2.0] octa-1(6),2,4-trien-2-ol (5.0 mg, 0.013 mmol, 6.8 % yield) as white solid. ¹H NMR (400 MHz, MeOD) δ 8.79 (s, 1H), 7.08 (s, 1H), 4.97 – 4.95 (m, 1H), 3.17 (s, 4H), 2.89 – 2.84 (m, 4H), 2.52 (s, 3H), 1.51 (s, 3H).

Using the procedure described for Example 3E, above, additional compounds described herein may be prepared by substituting the appropriate starting material, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Table 3E.

Cmpd#	Characterization
III E-2	MS <i>m/z</i> : 385.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ: 8.76 (s, 1H), 7.81 (s, 1H), 7.25 (s, 1H), 7.11 (d, J = 2.0 Hz, 1H), 5.00 – 4.96 (m, 1H), 2.97 – 2.78 (m, 4H), 2.55 (s, 3H), 1.52 (s, 3H). OH peaks not observed.
III E-3	MS <i>m/z</i> : 398.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ: 8.88 (s, 1H), 7.84 (d, J = 2.4 Hz, 1H), 7.26 (s, 1H), 7.12 (d, J = 2.0 Hz, 1H), 5.04 – 4.96 (m, 1H), 3.28 – 3.17 (m, 1H), 2.92 – 2.75 (m, 2H), 2.54 (s, 3H), 2.40 (s, 3H), 2.38 – 2.30 (m, 1H), 2.30 – 2.17 (m, 2H), 1.98 – 1.77 (m, 2H). OH peak not observed.

Example 4. Preparation of (R)-2-(3-(1-methylpiperidin-3-yl)-3H-[1,2,3]triazolo[4,5-c]pyridazin-6-yl)-5-(trifluoromethyl)phenol (IV-1)



Step 1: To a solution of 3,6-dichloro-4-(methylsulfonyl)pyridazine (700 mg, 3.0 mmol) in THF (6 mL) were added tert-butyl (3R)-1-methylpiperidin-3-amine (451 mg, 3.95 mmol) and potassium carbonate (592 mg, 9.1 mmol). The reaction mixture was stirred at 50 °C for 2 h. Upon completion, it was filtered and the filtrate was diluted with water (50 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with a gradient CH₂Cl₂/MeOH (0-30% MeOH) to afford (R)-6-chloro-N-(1-methylpiperidin-3-yl)-4-(methylsulfonyl)pyridazin-3-amine (734 mg, 80% yield) as a yellow oil. MS *m/z* 305.3, 307.1 [M+H]⁺.

Step 2: To a solution of (R)-6-chloro-N-(1-methylpiperidin-3-yl)-4-(methylsulfonyl)pyridazin-3-amine (734 mg, 2.4 mmol) in dimethyl sulfoxide (5 mL) was added sodium azide (250 mg, 3.8 mmol). The reaction mixture was stirred at 80 °C for 2 h. The mixture was filtered, and the filtrate was diluted with water (20 mL) and extracted with ethyl acetate. The combined organic parts were washed with brine, dried over sodium sulfate, filtered and evaporated to under reduced pressure to afford (R)-4-azido-6-chloro-N-(1-methylpiperidin-3-yl)pyridazin-3-amine (290 mg, 42% yield) as a yellow oil. The crude material was taken to the next step without further purification. MS *m/z* 268.3, 270.3 [M+H]⁺.

Step 3: To a solution of (R)-4-azido-6-chloro-N-(1-methylpiperidin-3-yl)pyridazin-3-amine (250 mg, 0.93 mmol) in CH₂Cl₂ (3 mL) and AcOH (1 mL) was added Zinc (195 mg, 3 mmol) at 0 °C. The reaction stirred at this temperature for 2 h. Upon completion, the mixture was filtered over a pad of Celite and the filtrate was concentrated under reduced pressure to afford (R)-6-chloro-N3-(1-methylpiperidin-3-yl)pyridazine-3,4-diamine (120 mg, 55% yield) as a yellow oil. The crude material was taken to the next step without further purification. MS *m/z* 242.2, 244.2 [M+H]⁺.

Step 4: To a solution of (R)-6-chloro-N3-(1-methylpiperidin-3-yl)pyridazine-3,4-diamine (170 mg, 0.7 mmol) in acetic acid (0.5 mL) and water (1 mL) was added sodium nitrite (68 mg, 1 mmol, 1.5 eq) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 2 hours. Upon completion, the reaction was quenched with sodium bicarbonate and extracted with dichloromethane. The combined organic parts were washed with water, brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified via flash chromatography eluting with a gradient CH₂Cl₂/MeOH/NH₄OH (0-30% MeOH/NH₄OH) to afford (R)-6-chloro-3-(1-methylpiperidin-3-yl)-3H-[1,2,3]triazolo[4,5-c]pyridazine (60 mg, 34% yield) as a yellow solid. MS *m/z* 253.2, 255.2 [M+H]⁺.

Step 5: To a solution of (R)-6-chloro-3-(1-methylpiperidin-3-yl)-3H-[1,2,3]triazolo[4,5-c]pyridazine (170 mg, 0.76 mmol) in acetonitrile (1.5 mL) is added silver nitrate (60 mg, 0.35 mmol), cyclopropane carboxylic acid (301 µL, 3.8 mmol), and sulfuric acid (176 µL, 2 mmol). The resulting mixture was heated to 70 °C and then an aqueous solution of ammonium persulfate (638 mg, 2.8 mmol) in water (5 mL) was added dropwise over 5 minutes. The reaction was cooled to room temperature and stirred for 1 hour. Upon completion the reaction was diluted with water and sodium bicarbonate was added dropwise until a pH of 7 was achieved. The aqueous solution was extracted with ethyl acetate (3 x 20 mL) and the combined organic parts were washed with water, brine, dried over sodium sulfate, filtered, concentrated and purified via silica gel flash column chromatography eluting with a gradient CH₂Cl₂/MeOH/NH₄OH (0-30% MeOH/NH₄OH) to afford (R)-6-chloro-7-cyclopropyl-3-(1-methylpiperidin-3-yl)-3H-[1,2,3]triazolo[4,5-c]pyridazine (80 mg, 40% yield) as a yellow oil. MS *m/z* 293.2, 295.2 [M+H]⁺.

Step 6: To a screw cap vial were added: (R)-6-chloro-7-cyclopropyl-3-(1-methylpiperidin-3-yl)-3H-[1,2,3]triazolo[4,5-c]pyridazine (80 mg, 0.26 mmol), XPhos Pd G3 (25 mg, 0.028 mmol), 2-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (107 mg, 0.32 mmol). The vial was degassed by purging Ar for 15 min. 1,4 dioxane (1 mL) and potassium carbonate (2.0 M aqueous, 0.4 mL, 0.2 mmol) were added and the mixture was heated at 90 °C for 4 hours. Upon completion, the reaction was loaded directly onto precolumn and purified via silica gel flash column chromatography eluting with a gradient CH₂Cl₂/MeOH (0-30% MeOH) to afford (R)-7-cyclopropyl-6-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-3-

(1-methylpiperidin-3-yl)-3H-[1,2,3]triazolo[4,5-c]pyridazine (62 mg, 48% yield) as a yellow oil. MS m/z 463.6 $[M+H]^+$.

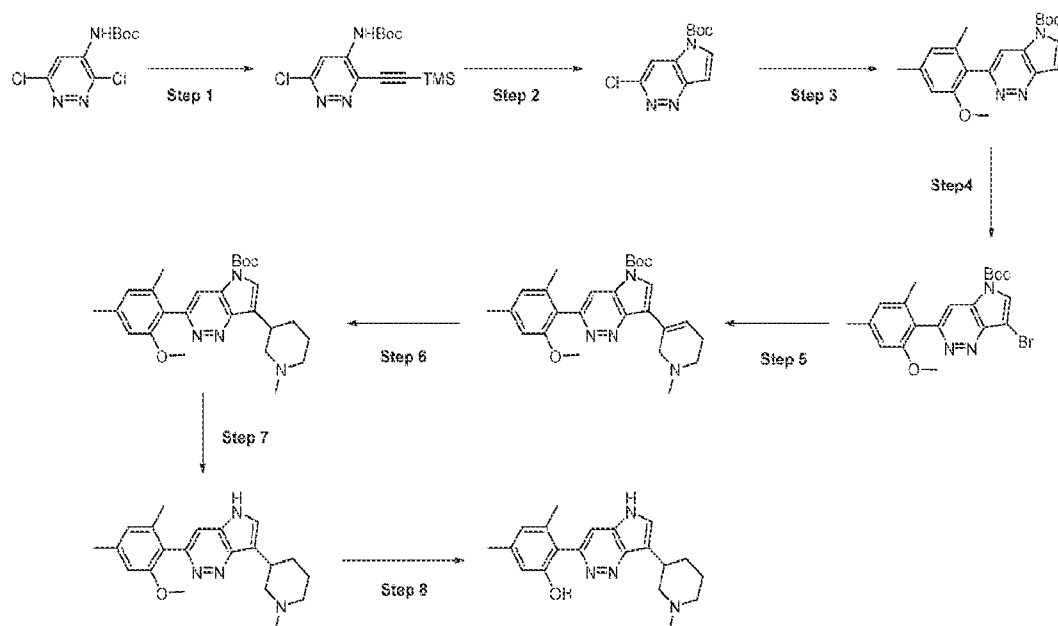
Step 7: A solution (R)-6-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-3-(1-methylpiperidin-3-yl)-3H-[1,2,3]triazolo[4,5-c]pyridazine (62 mg, 0.13 mmol) in trifluoroacetic acid (0.5 mL) was stirred for 1 hour at room temperature. Upon completion, the reaction was diluted with dichloromethane and sodium bicarbonate (10 mL) was added and the resulting mixture was allowed to stir for 10 minutes before extracting the aqueous layer with dichloromethane. The combined organic parts were washed with water, brine, dried over sodium sulfate, filtered, and evaporated under reduced pressure. The residue was purified via silica gel flash column chromatography eluting with a gradient $CH_2Cl_2/MeOH$ (0-30% MeOH) to afford (R)-2-(3-(1-methylpiperidin-3-yl)-3H-[1,2,3]triazolo[4,5-c]pyridazin-6-yl)-5-(trifluoromethyl)phenol (25 mg, 50 % yield) as a white solid. MS m/z 419.2 $[M+H]^+$; ^1H NMR (500 MHz, $DMSO-d_6$) δ : 7.57 (dd, J = 11.4, 7.7 Hz, 1H), 7.33 (dd, J = 8.0, 1.8 Hz, 1H), 7.30 (d, J = 2.0 Hz, 1H), 5.24 (tt, J = 10.5, 4.2 Hz, 1H), 3.24 – 3.15 (m, 1H), 3.17 – 3.06 (m, 1H), 2.81 (d, J = 10.8 Hz, 1H), 2.66 (t, J = 10.4 Hz, 1H), 2.27 (d, J = 7.0 Hz, 4H), 2.21 (dd, J = 9.9, 5.6 Hz, 1H), 2.09 (td, J = 11.3, 2.9 Hz, 1H), 1.92 (dq, J = 13.9, 3.7 Hz, 1H), 1.84 – 1.69 (m, 3H), 1.36 – 1.22 (m, 2H).

Using the procedure described for Example 4, above, additional compounds described herein may be prepared by substituting the appropriate starting material, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Table 4.

Cmpd#	Characterization
IV-1	MS m/z 419.2 $[M+H]^+$; ^1H NMR (500 MHz, $DMSO-d_6$) δ : 7.57 (dd, J = 11.4, 7.7 Hz, 1H), 7.33 (dd, J = 8.0, 1.8 Hz, 1H), 7.30 (d, J = 2.0 Hz, 1H), 5.24 (tt, J = 10.5, 4.2 Hz, 1H), 3.24 – 3.15 (m, 1H), 3.17 – 3.06 (m, 1H), 2.81 (d, J = 10.8 Hz, 1H), 2.66 (t, J = 10.4 Hz, 1H), 2.27 (d, J = 7.0 Hz, 4H), 2.21 (dd, J = 9.9, 5.6 Hz, 1H), 2.09 (td, J = 11.3, 2.9 Hz, 1H), 1.92 (dq, J = 13.9, 3.7 Hz, 1H), 1.84 – 1.69 (m, 3H), 1.36 – 1.22 (m, 2H).
IV-2	MS m/z : 363.5 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.71 (s, 1H), 6.90 (s, 2H), 5.92 – 5.57 (m, 1H), 4.53 (m, 1H), 4.11 (t, J = 7.1 Hz, 1H), 3.91 (m, 1H), 3.80 – 3.54 (m, 1H), 3.06 (s, 3H), 2.64 (d, J = 14.8 Hz, 1H), 2.33 (m, 1H), 2.25 – 1.96 (m, 2H). OH peak not observed.
IV-3	MS m/z : 393.3 $[M+H]^+$; ^1H NMR (500 MHz, $DMSO-d_6$) δ : 8.59 (s, 1H), 7.29 – 7.08 (m, 2H), 5.34 (tt, J = 10.5, 4.2 Hz, 1H), 3.29 (dd, J = 10.9, 3.8 Hz, 1H), 2.83 (d, J = 11.6 Hz, 2H), 2.73 (t, J = 10.5 Hz, 1H), 2.40 – 2.21 (m, 5H), 2.08 (s, 3H), 1.94 (dt, J = 10.6, 3.7 Hz, 1H), 1.89 – 1.76 (m, 1H). OH peak not observed.

Example 5. Preparation of 3,5-dimethyl-2-(7-(1-methylpiperidin-3-yl)-5H-pyrrolo[3,2-c]pyridazin-3-yl)phenol (V-1)



Step 1: To a screw cap vial were added: tert-butyl (3,6-dichloropyridazin-4-yl)carbamate (5.0 g, 18.9 mmol), CuI (180 mg, 0.94 mmol) and tetrakis(triphenylphosphine)palladium(0) (1.8 g, 1.51 mmol). The reaction was degassed by purging Ar for 15 min. Et₃N (25 mL) and THF (75 mL) were added followed by addition of trimethylsilylacetylene (5.5 ml, 37.8 mmol). The reaction was stirred for 1.5 h at room temperature. Upon completion, it was concentrated, dissolved in EtOAc and washed with water, brine. Combined organic parts were dried over sodium sulfate, concentrated and purified by flash column chromatography eluting with a gradient EtOAc/hexanes (0 - 30% EtOAc) to afford tert-butyl N-[6-chloro-3-(2-trimethylsilylethynyl)pyridazin-4-yl]carbamate (3.4 g, 55% yield). MS m/z 326.2, 328.2 [M+H]⁺.

Step 2: To a solution of tert-butyl N-[6-chloro-3-(2-trimethylsilylethynyl)pyridazin-4-yl]carbamate (3.95 g, 12.1 mmol) in DMF (30 ml) was added potassium carbonate (3.35 g, 24.2 mmol) and the mixture stirred at 60 °C for 45 min. Upon completion, the reaction was quenched by brine and extracted by EtOAc. The combined organic parts were washed with brine, dried over sodium sulfate, concentrated and purified by flash column chromatography eluting with a

gradient EtOAc/hexanes (0 - 30% EtOAc) to afford tert-butyl 3-chloropyrrolo[3,2-c]pyridazine-5-carboxylate (990 mg, 32.2% yield). MS m/z 254.1, 256.1 $[M+H]^+$.

Step 3: To a screw top vial were added tert-butyl 3-chloropyrrolo[3,2-c]pyridazine-5-carboxylate (0.99 g, 3.9 mmol), (2-methoxy-4,6-dimethyl-phenyl)boronic acid (0.91 g, 5.1 mmol), K_2CO_3 (1.61 g, 11.7 mmol) and XPhos Pd G3 (0.33 g, 0.39 mmol). The reaction was degassed by purging Ar for 15 min and dioxane (10 mL) and water (2 mL) were added. The reaction mixture was stirred for 6 h at 90 °C. Upon completion, the reaction was cooled down to room temperature, partitioned between EtOAc and brine. The combined organic parts were washed with brine, dried over sodium sulfate, concentrated and purified by flash column chromatography eluting with a gradient EtOAc/hexanes (0 - 100% EtOAc) to afford tert-butyl 3-(2-methoxy-4,6-dimethyl-phenyl)pyrrolo[3,2-c]pyridazine-5-carboxylate (1.11 g, 80.5% yield). MS m/z 354.4 $[M+H]^+$.

Step 4: To a solution of tert-butyl 3-(2-methoxy-4,6-dimethyl-phenyl)pyrrolo[3,2-c]pyridazine-5-carboxylate (1.11 g, 3.14 mmol) in CH_2Cl_2 (2 mL) was added 4.0 M HCl in dioxane (31.4 mL) and the resulting mixture was stirred for 4 h at 50 °C. The crude material was dissolved in MeOH and $NaHCO_3$ was added to neutralize the mixture to pH~7. Solids were filtered, and the filtrate was concentrated under reduced pressure. Resulting crude 3-(2-methoxy-4,6-dimethyl-phenyl)-5H-pyrrolo[3,2-c]pyridazine (790 mg, 3.1 mmol) was dissolved in DMF (15 mL) and the solution was cooled down to 0°C. NBS (0.61 g, 3.43 mmol) was added portion-wise and the resulting mixture was stirred at for 10 min. DIPEA (5.4 mL, 31.0 mmol), and tert-butoxycarbonyl tert-butyl carbonate (2.70 g, 12.4 mmol) were added then. The resulting mixture was stirred for 30 min at 0°C. Upon completion, the reaction mixture was partitioned between EtOAc and brine. The combined organic parts were washed with brine, dried over sodium sulfate, concentrated and purified by flash column chromatography eluting with a gradient EtOAc/hexanes (0 - 100% EtOAc) to afford tert-butyl 7-bromo-3-(2-methoxy-4,6-dimethyl-phenyl)pyrrolo[3,2-c]pyridazine-5-carboxylate (185 mg, 13.8% yield). MS m/z 432.1, 434.1 $[M+H]^+$.

Step 5: To a screw cap vial were added: tert-butyl 7-bromo-3-(2-methoxy-4,6-dimethyl-phenyl)pyrrolo[3,2-c]pyridazine-5-carboxylate (240 mg, 0.55 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine (0.16 g, 0.72 mmol), K_2CO_3 (0.23

g, 1.66 mmol) XPhos Pd G3 (47 mg, 0.055 mmol). The reaction was degassed by purging Ar for 15 min and dioxane (4 mL) and water (1 mL) were added. The reaction mixture was stirred for 6 h at 90 °C. Upon completion, the reaction was cooled down to room temperature, partitioned between EtOAc and brine. The combined organic parts were washed with brine, dried over sodium sulfate, concentrated and purified by flash column chromatography eluting with a gradient CH₂Cl₂/MeOH (0-20% MeOH) to afford tert-butyl 3-(2-methoxy-4,6-dimethyl-phenyl)-7-(1-methyl-3,6-dihydro-2H-pyridin-5-yl)pyrrolo[3,2-c]pyridazine-5-carboxylate (220 mg, 88% yield). MS *m/z* 449.4 [M+H]⁺.

Step 6: To a solution of tert-butyl 3-(2-methoxy-4,6-dimethyl-phenyl)-7-(1-methyl-3,6-dihydro-2H-pyridin-5-yl)pyrrolo[3,2-c]pyridazine-5-carboxylate (240 mg, 0.53 mmol) in methanol (11 mL) and EtOAc (1.0 mL) were added Pd/C (0.056 g, 0.053 mmol) and Pd(OH)₂/C (0.038 g, 0.053 mmol). The resulting mixture was subjected to 1 atm of H₂ (balloon) and stirred at 55 °C for 5 h. Upon completion, the solids were filtered through celite and rinsed with EtOAc and MeOH. Solvents were removed under reduced pressure to afford crude tert-butyl 3-(2-methoxy-4,6-dimethylphenyl)-7-(1-methylpiperidin-3-yl)-5H-pyrrolo[3,2-c]pyridazine-5-carboxylate (240 mg, 100% yield) as an orange oil. The crude material was taken to the next step without further purification. MS *m/z* 451.3 [M+H]⁺.

Step 7: Tert-butyl 3-(2-methoxy-4,6-dimethyl-phenyl)-7-(1-methyl-3-piperidyl)pyrrolo[3,2-c]pyridazine-5-carboxylate (240 mg, 0.53 mmol,) was dissolved in TFA (5.0 mL) and the mixture was heated at 40 °C for 20 min. Solvent was removed under reduced pressure to afford crude 3-(2-methoxy-4,6-dimethylphenyl)-7-(1-methylpiperidin-3-yl)-5H-pyrrolo[3,2-c]pyridazine (180 mg, 97% yield). The crude material was taken to the next step without further purification. MS *m/z* 351.4 [M+H]⁺.

Step 8: A mixture of 3-(2-methoxy-4,6-dimethyl-phenyl)-7-(1-methyl-3-piperidyl)-5H-pyrrolo[3,2-c]pyridazine (180 mg, 0.52 mmol), ethanethiol sodium salt (0.39 g, 4.19 mmol) and DMF (1.1 mL) was stirred for 4 h at 130 °C. Upon completion, the reaction was cooled down to room temperature, concentrated and purified via flash eluting with a gradient CH₂Cl₂/MeOH/NH₄OH (0-30% MeOH/NH₄OH) to afford 3,5-dimethyl-2-[7-(1-methyl-3-piperidyl)-5H-pyrrolo[3,2-c]pyridazin-3-yl]phenol (110 mg, 55% yield). MS *m/z* 337.1 [M+H]⁺; ¹H NMR (methanol-*d*₄) δ: 8.48 (s, 1H, formic acid), 7.54-7.67 (m, 1H), 7.49 (s, 1H), 6.59 (s,

1H), 6.54 (s, 1H), 3.46-3.70 (m, 2H), 2.92-3.07 (m, 1H), 2.72-2.84 (m, 1H), 2.65 (s, 3H), 2.50-2.56 (m, 3H), 2.10-2.20 (m, 1H), 1.95 (s, 3H), 1.80-1.90 (m, 2H); 4Hs not observed (NH, OH and 2CHs overlap with solvent peak).

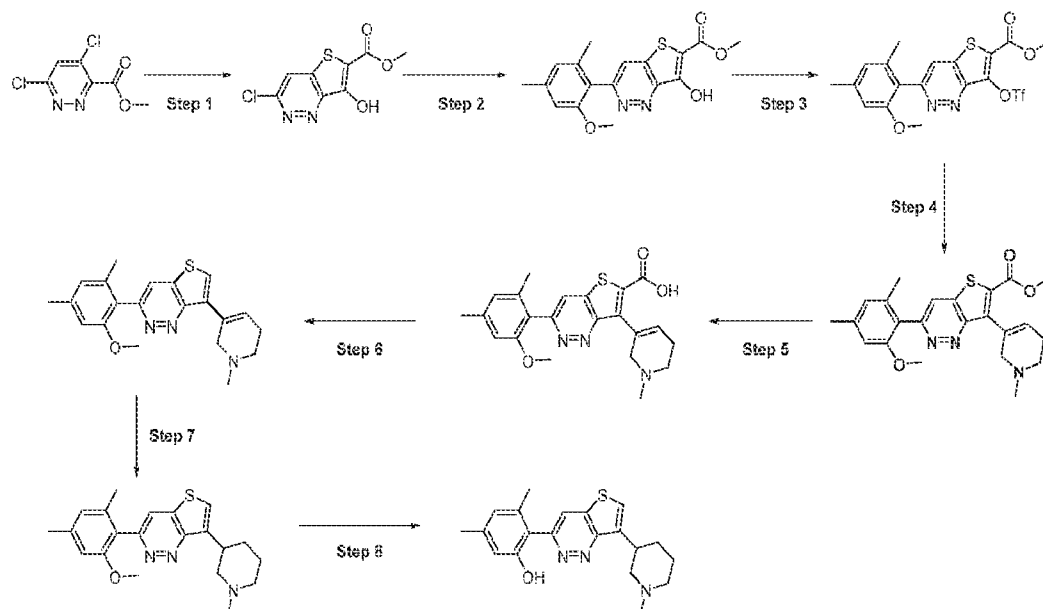
- 5 Using the procedure described for Example 5, above, additional compounds described herein may be prepared by substituting the appropriate starting material, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Table 5.

Cmpd#	Characterization
V-1	MS m/z 337.1 $[M+H]^+$; ^1H NMR (methanol- d_4) δ : 8.48 (s, 1H, formic acid), 7.54-7.67 (m, 1H), 7.49 (s, 1H), 6.59 (s, 1H), 6.54 (s, 1H), 3.46-3.70 (m, 2H), 2.92-3.07 (m, 1H), 2.72-2.84 (m, 1H), 2.65 (s, 3H), 2.50-2.56 (m, 3H), 2.10-2.20 (m, 1H), 1.95 (s, 3H), 1.80-1.90 (m, 2H); 4Hs not observed (NH, OH and 2CHs overlap with solvent peak).
V-2	MS m/z : 389.2 $[M+H]^+$; ^1H NMR (500 MHz, DMSO- d_6) δ : 8.14 (s, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 3.90 – 3.87 (m, 1H), 3.65-3.61 (m, 2H), 3.10-3.05 (m, 1H), 3.03-3.01 (m, 2H), 2.98-2.94 (m, 2H), 2.96 (s, 3H), 2.30-2.24 (m, 2H), 2.22-2.16 (m, 3H), 2.03-2.01 (m, 2H), 1.33-1.29 (m, 1H), 1.03-0.99 (m, 2H), 0.70-0.66 (m, 2H); 2Hs not observed (NH and OH).
V-3	MS m/z : 417.2 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 8.14 (s, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.34 (s, 1H), 3.91-3.88 (m, 1H), 3.65-3.63 (m, 2H), 3.34-3.30 (m, 1H), 3.11-3.09 (m, 1H), 2.96 (s, 3H), 2.33-2.29 (m, 1H), 2.27-2.17 (m, 2H), 2.02-1.99 (m, 2H), 1.04-0.99 (m, 2H), 0.68-0.64 (m, 2H). 2Hs not observed (NH and OH).

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Example 6. Preparation of 3,5-dimethyl-2-(7-(1-methylpiperidin-3-yl)thieno[3,2-c]pyridazin-3-yl)phenol (VI-1)



Step 1: To a solution of methyl 4,6-dichloropyridazine-3-carboxylate (10 g, 48.3 mmol) in ACN (96 mL) was added a solution of methyl 2-sulfanylacetate (5.2 g, 49.2 mmol) in ACN (96 mL) dropwise at 0 °C, followed by slow addition of Et₃N (6.73 mL, 48.3 mmol) at the same temperature. Reaction was stirred at 0 °C for 15 min. Additional amount of Et₃N (6.73 mL, 48.3 mmol) was added and mixture was allowed to warm up to room temperature and stirred for 3 h at rt. Upon completion, the reaction was quenched with water and ACN was evaporated under reduced pressure. The mixture was acidified with 1.0 M HCl to pH~2. During pH adjustment bright yellow solution turned colorless and white precipitate was formed. Precipitate was collected by filtration, washed with water, dried to afford methyl 3-chloro-7-hydroxy-thieno[3,2-c]pyridazine-6-carboxylate (11.6 g, 98% yield). The crude material was taken to the next step without further purification. MS *m/z* 245.0, 247.0 [M+H]⁺.

Step 2: To a dry round bottom flask were added: methyl 3-chloro-7-hydroxy-thieno[3,2-c]pyridazine-6-carboxylate (2.0 g, 8.17 mmol), (2-methoxy-4,6-dimethyl-phenyl)boronic acid (1.76 g, 9.80 mmol), K₂CO₃ (3.38 g, 24.5 mmol) and Pd(dppf)Cl₂ (0.63 g, 0.81 mmol). The reaction mixture was degassed by purging Ar for 15 min, then dioxane (60 mL) and water (15 mL) were added. The mixture was heated at 90 °C for 16h. Upon completion, the reaction was cooled down to room temperature, partitioned between EtOAc and brine. The aqueous part was extracted with EtOAc (3 times). Combined organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography eluting with a gradient EtOAc/hexanes (0 - 100% EtOAc) to afford

methyl 7-hydroxy-3-(2-methoxy-4,6-dimethyl-phenyl)thieno[3,2-c]pyridazine-6-carboxylate (1.1 g, 39% yield). MS m/z 345.4 $[M+H]^+$.

Step 3: A solution of methyl 7-hydroxy-3-(2-methoxy-4,6-dimethyl-phenyl)thieno[3,2-c]pyridazine-6-carboxylate (500 mg, 1.45 mmol) and DIPEA (0.50 mL, 2.90 mmol) in CH_2Cl_2 (14.5 mL) was cooled down to 0°C and Tf_2O (11.74 mL, 1.0 M in CH_2Cl_2 , 1.74 mmol) was added dropwise. The reaction mixture was stirred for 20 min at 0°C, then warmed up to room temperature and then partitioned between CH_2Cl_2 and brine. The aqueous part was extracted with CH_2Cl_2 (3 times). Combined organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure to give crude methyl 3-(2-methoxy-4,6-dimethylphenyl)-7-(((trifluoromethyl)sulfonyl)oxy)thieno[3,2-c]pyridazine-6-carboxylate (680 mg, 98% yield). The crude material was taken to the next step without further purification. MS m/z 477.5 $[M+H]^+$.

Step 4: To dry crew cap vial were added methyl 3-(2-methoxy-4,6-dimethyl-phenyl)-7-(trifluoromethylsulfonyloxy)thieno[3,2-c]pyridazine-6-carboxylate (680 mg, 1.42 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine (0.35 g, 1.59 mmol), K_2CO_3 (0.60 g, 4.34 mmol) and Pd XPhos G3 (0.12 g, 0.14 mmol). The reaction mixture was degassed by purging Ar for 15 min, then dioxane (10 mL) and water (2.5 mL) were added. The mixture was heated at 90 °C for 16h. Upon completion, the reaction was cooled down to room temperature, partitioned between EtOAc and brine. The aqueous part was extracted with EtOAc (3 times). Combined organic phases were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography eluting with a gradient EtOAc/hexanes (0 - 100% EtOAc) to afford methyl 3-(2-methoxy-4,6-dimethyl-phenyl)-7-(1-methyl-3,6-dihydro-2H-pyridin-5-yl)thieno[3,2-c]pyridazine-6-carboxylate (500 mg, 81.5% yield). MS m/z 424.5 $[M+H]^+$.

Step 5: To a solution of methyl 3-(2-methoxy-4,6-dimethyl-phenyl)-7-(1-methyl-3,6-dihydro-2H-pyridin-5-yl)thieno[3,2-c]pyridazine-6-carboxylate (311 mg, 0.73 mmol) in THF (12 mL) and water (1.5 mL) was added LiOH (0.35 g, 14.6 mmol) and the resulting mixture was stirred for 72 h at rt. THF was evaporated under reduced pressure, the aqueous part was extracted with CH_2Cl_2 (3 times). Combined organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography eluting with a gradient CH_2Cl_2 /MeOH (0 - 30% MeOH) to afford 3-(2-

methoxy-4,6-dimethyl-phenyl)-7-(1-methyl-3,6-dihydro-2H-pyridin-5-yl)thieno[3,2-c]pyridazine-6-carboxylic acid (130 mg, 43% yield). MS m/z 410.2 $[M+H]^+$.

Step 6: To a solution of 3-(2-methoxy-4,6-dimethyl-phenyl)-7-(1-methyl-3,6-dihydro-2H-pyridin-5-yl)thieno[3,2-c]pyridazine-6-carboxylic acid (130 mg, 0.31 mmol) in DMSO (1.5 mL) were added Ag_2CO_3 (0.018 g, 0.063 mmol) and 2 drops of AcOH. The reaction was heated at 120 °C for 4 h, then cooled down to room temperature, directly loaded on pre-column and purified by silica gel flash column chromatography eluting with a gradient $CH_2Cl_2/MeOH$ (0 – 30 % MeOH) to afford 3-(2-methoxy-4,6-dimethyl-phenyl)-7-(1-methyl-3,6-dihydro-2H-pyridin-5-yl)thieno[3,2-c]pyridazine (110 mg, 96% yield). MS m/z 366.6 $[M+H]^+$.

Step 7: To a solution of 3-(2-methoxy-4,6-dimethyl-phenyl)-7-(1-methyl-3,6-dihydro-2H-pyridin-5-yl)thieno[3,2-c]pyridazine (110 mg, 0.30 mmol) in methanol (8.0 mL) and EtOAc (1.0 mL) were added Pd/C (0.043 g, 0.041 mmol) and $Pd(OH)_2/C$ (0.028 g, 0.041 mmol). The resulting mixture was subjected to 55 psi of H_2 (Parr shaker) and stirred for 72 h. Upon completion, the solids were filtered through celite and rinsed with EtOAc and MeOH. Solvents were removed under reduced pressure to afford crude 3-(2-methoxy-4,6-dimethylphenyl)-7-(1-methylpiperidin-3-yl)thieno[3,2-c]pyridazine (100 mg, 90% yield). The crude material was taken to the next step without further purification. MS m/z 368.5 $[M+H]^+$.

Step 8: To a solution of 3-(2-methoxy-4,6-dimethyl-phenyl)-7-(1-methyl-3-piperidyl)thieno[3,2-c]pyridazine (100 mg, 0.27 mmol) in DMF (2.7 mL) was added ethanethiol sodium salt (0.38 g, 4.08 mmol) and the resulting mixture was stirred for 4 h at 130 °C. Upon completion, the reaction was cooled down to room temperature and the crude material was directly loaded on pre-column and purified by silica gel flash column chromatography eluting with a gradient $CH_2Cl_2/MeOH$ (0 – 30 % MeOH) to afford 3,5-dimethyl-2-[7-(1-methyl-3-piperidyl)thieno[3,2-c]pyridazin-3-yl]phenol (45 mg, 47% yield) as a tan solid. MS m/z 354.1 $[M+H]^+$; ^1H NMR (methanol- d_4) δ : 8.56 (br s, 1H, formic acid), 8.44 (s, 1H), 7.82 (s, 1H), 6.60 (s, 1H), 6.55 (s, 1H), 3.64-3.79 (m, 1H), 3.44-3.59 (m, 1H), 3.09-3.16 (m, 1H), 2.60-2.76 (m, 2H), 2.51 (s, 3H), 2.25-2.21 (m, 1H), 2.21 (s, 3H), 1.96 (s, 3H), 1.87-1.93 (m, 1H), 1.71-1.86 (m, 2H), 1H not observed (OH).

Using the procedure described for Example 6, above, additional compounds described herein may be prepared by substituting the appropriate starting material, suitable reagents and reaction conditions, obtaining compounds such as those selected from.

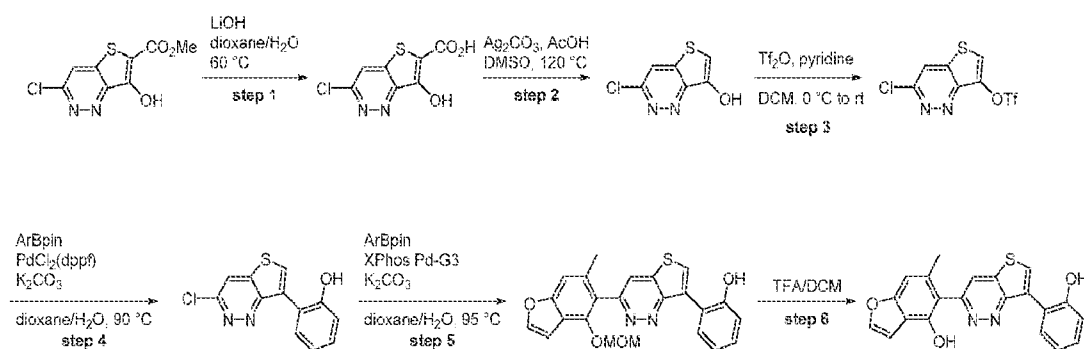
5 Table 6

Cmpd#	Characterization
VI-1	MS m/z 354.1 $[M+H]^+$; ^1H NMR (methanol- d_4) δ : 8.56 (br s, 1H, formic acid), 8.44 (s, 1H), 7.82 (s, 1H), 6.60 (s, 1H), 6.55 (s, 1H), 3.64-3.79 (m, 1H), 3.44-3.59 (m, 1H), 3.09-3.16 (m, 1H), 2.60-2.76 (m, 2H), 2.51 (s, 3H), 2.25-2.21 (m, 1H), 2.21 (s, 3H), 1.96 (s, 3H), 1.87-1.93 (m, 1H), 1.71-1.86 (m, 2H); 1H not observed (OH).
VI-2	MS m/z : 352.1 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.52 (brs, 1H, formic acid), 8.43 (s, 1H), 7.88 (s, 1H), 7.17-7.35 (m, 1H), 6.60 (s, 1H), 6.55 (s, 1H), 3.69-3.81 (m, 2H), 2.75-2.76 (m, 2H), 2.43-2.61 (m, 5H), 2.21 (s, 3H), 1.97 (s, 3H); 1H not observed (OH).
VI-3	MS m/z : 408.1 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 7.77 (s, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.14 (s, 1H), 3.68 - 3.56 (m, 1H), 3.27 (d, J = 11.6 Hz, 1H), 2.88 (d, J = 11.2 Hz, 1H), 2.40 (s, 3H), 2.33 - 2.22 (m, 4H), 2.20 - 2.01 (m, 2H), 1.87 - 1.72 (m, 2H), 1.70 - 1.55 (m, 1H); 1H not observed (OH).
VI-4	MS m/z : 408.1 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 7.77 (s, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.15 (s, 1H), 3.71 - 3.56 (m, 1H), 3.29 (d, J = 11.2 Hz, 1H), 2.90 (d, J = 11.6 Hz, 1H), 2.40 (s, 3H), 2.36 - 2.23 (m, 4H), 2.19 - 2.06 (m, 2H), 1.86 - 1.73 (m, 2H), 1.72 - 1.55 (m, 1H); 1H not observed (OH).
VI-5	MS m/z : 408.2 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.35 (s, 1H), 7.93 (d, J = 0.8 Hz, 1H), 7.17 (s, 1H), 7.09 (s, 1H), 3.82 - 3.76 (m, 1H), 3.40 (d, J = 11.6 Hz, 1H), 3.01 (d, J = 11.2 Hz, 1H), 2.43 - 2.37 (m, 4H), 2.29 - 2.19 (m, 2H), 2.18 (s, 3H), 1.94 - 1.85 (m, 2H), 1.82 - 1.70 (m, 1H); 1 H not observed (OH).
VI-6	MS m/z : 408.0 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.34 (s, 1H), 7.92 (d, J = 0.8 Hz, 1H), 7.16 (s, 1H), 7.09 (s, 1H), 3.82 - 3.75 (m, 1H), 3.40 (d, J = 10.4 Hz, 1H), 3.00 (d, J = 11.6 Hz, 1H), 2.42 - 2.36 (m, 4H), 2.29 - 2.20 (m, 2H), 2.17 (s, 3H), 1.94 - 1.87 (m, 2H), 1.82 - 1.71 (m, 1H); 1 H not observed (OH).
VI-7	MS m/z : 406.1 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.42 (s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.27 (s, 1H), 4.33 (s, 2H), 3.40 (t, J = 5.2 Hz, 2H), 3.00 (s, 3H), 2.75 (s, 2H), 2.53 (s, 3H); 1 H not observed (OH).
VI-8	MS m/z : 434.2 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 7.84 (s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.23 (s, 1H), 3.78 - 3.65 (m, 1H), 3.44 - 3.32 (m, 2H), 2.97 (d, J = 10.8 Hz, 1H), 2.40 - 2.35 (m, 3H), 2.31 - 2.25 (m, 1H), 2.25 - 2.12 (m, 2H), 1.93 - 1.85 (m, 2H), 1.78 - 1.66 (m, 1H), 0.96 - 0.87 (m, 2H), 0.84 - 0.73 (m, 2H); 1 H not observed (OH).
VI-9	MS m/z : 422.1 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 7.86 (s, 1H), 7.16 (s, 1H), 7.06 (s, 1H), 3.78 - 3.66 (m, 1H), 3.40 - 3.33 (m, 1H), 2.96 (d, J = 11.6 Hz, 1H), 2.39 (s, 3H), 2.37 - 2.31 (m, 4H), 2.27 - 2.20 (m, 1H), 2.18 - 2.10 (m, 1H), 2.03 (s, 3H), 1.92 - 1.83 (m, 2H), 1.79 - 1.66 (m, 1H); 1 H not observed (OH).

Cmpd#	Characterization
VI-10	MS <i>m/z</i> : 382.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ : 7.87 (s, 1H), 7.11 (d, J = 8.0 Hz, 1H), 6.47 (d, J = 8.0 Hz, 1H), 4.64 (t, J = 8.8 Hz, 2H), 3.77 (m, 1H), 3.59 (d, J = 12.0 Hz, 1H), 3.22 (t, J = 8.8 Hz, 3H), 2.76 (t, J = 12.0 Hz, 1H), 2.59 (s, 3H), 2.58 – 2.54 (m, 1H), 2.53 (s, 3H), 2.26 (d, J = 12.8 Hz, 1H), 2.04 – 1.83 (m, 3H). OH peak not observed.
VI-11	MS <i>m/z</i> : 382.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ : 7.82 (s, 1H), 7.11 (d, J = 8.4 Hz, 1H), 6.46 (d, J = 8.4 Hz, 1H), 4.64 (t, J = 8.8 Hz, 2H), 4.58 (s, 1H), 3.72 (m, 1H), 3.42 (d, J = 11.2 Hz, 1H), 3.22 (t, J = 8.8 Hz, 2H), 3.04 (d, J = 11.6 Hz, 1H), 2.52 (s, 3H), 2.43 (s, 3H), 2.28 – 2.22 (m, 2H), 1.95 – 1.70 (m, 3H). OH peak not observed.
VI-12	MS <i>m/z</i> : 382.3 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ : 7.94 (s, 1H), 7.11 (d, J = 8.4 Hz, 1H), 6.47 (d, J = 8.4 Hz, 1H), 4.64 (t, J = 8.4 Hz, 2H), 3.81 (t, J = 12.0 Hz, 2H), 3.43 (d, J = 11.6 Hz, 1H), 3.22 (t, J = 8.8 Hz, 2H), 3.12 (t, J = 11.2 Hz, 1H), 2.89 (t, J = 10.4 Hz, 1H), 2.80 (s, 3H), 2.53 (s, 3H), 2.30 (t, J = 10.0 Hz, 1H), 2.13 – 1.94 (m, 3H). OH peak not observed.
VI-13	MS <i>m/z</i> : 382.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, CDCl ₃) δ : 8.10 (s, 1H), 7.60 (s, 1H), 6.40 (s, 1H), 4.67 (t, J = 8.8 Hz, 2H), 3.83-3.78 (m, 1H), 3.28-3.21 (m, 3H), 2.90 (s, 1H), 2.61 (s, 1H), 2.46 (s, 3H), 2.41 (s, 3H), 2.29 (s, 1H), 2.19 (s, 1H), 2.02-2.01 (m, 1H), 1.88 – 1.84 (m, 1H), 1.66 – 1.61 (m, 1H). OH peak not observed.
VI-14	MS <i>m/z</i> : 380.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ : 7.85 (s, 1H), 7.12 (d, J = 7.6 Hz, 1H), 6.92 (d, J = 7.6 Hz, 1H), 3.73 (d, J = 11.4 Hz, 1H), 3.47 (s, 1H), 3.10 (d, J = 15.2 Hz, 1H), 2.96 (dt, J = 22.3, 7.4 Hz, 4H), 2.54-2.56 (m, 1H), 2.47-2.52 (m, 4H), 2.48 (s, 3H), 2.33 (t, J = 7.4 Hz, 1H), 2.16 (dd, J = 14.8, 7.4 Hz, 2H), 1.99 – 1.74 (m, 3H). OH peak not observed.
VI-15	MS <i>m/z</i> : 380.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ : 7.82 (s, 1H), 7.12 (d, J = 7.6 Hz, 1H), 6.92 (d, J = 7.6 Hz, 1H), 3.78 – 3.65 (m, 1H), 3.41 – 3.35 (m, 1H), 3.04 – 2.88 (m, 5H), 2.50 (s, 3H), 2.45 – 2.38 (m, 1H), 2.38 (s, 3H), 2.28 – 2.10 (m, 4H), 1.94 – 1.82 (m, 2H), 1.78 – 1.66 (m, 1H). OH peak not observed.
VI-16	MS <i>m/z</i> : 366.3 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ : 8.54 (s, 1H, formate), 7.90 (s, 1H), 7.16 (d, J = 7.2 Hz, 1H), 6.76 (d, J = 7.6 Hz, 1H), 3.84 – 3.78 (m, 1H), 3.70 (d, J = 10.4 Hz, 1H), 3.33 (s, 1H), 3.19 (d, J = 4.8 Hz, 4H), 2.94 (t, J = 11.6 Hz, 1H), 2.74 – 2.41 (m, 1H), 2.69 (s, 3H), 2.49 (s, 3H), 2.29 – 2.26 (m, 1H), 2.06 – 2.01 (m, 1H), 1.99 – 1.88 (m, 2H). OH peak not observed.
VI-17	MS <i>m/z</i> : 380.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, CDCl ₃) δ : 8.18 (s, 1H), 7.63 (s, 1H), 7.52 (d, J = 2.0 Hz, 1H), 7.07 (s, 1H), 6.98 (d, J = 1.2 Hz, 1H), 3.85 – 3.80 (m, 1H), 3.24 (d, J = 8.4 Hz, 1H), 2.92 (s, 1H), 2.61 (s, 1H), 2.58 (s, 3H), 2.42 (s, 3H), 2.33 – 2.28 (m, 1H), 2.24 – 2.18 (m, 1H), 2.02 – 1.98 (m, 1H), 1.95 – 1.92 (m, 1H), 1.65 – 1.61 (m, 1H). OH peak not observed.
VI-18	MS <i>m/z</i> : 380.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ : 8.50 (s, 1H, formate), 7.95 (s, 1H), 7.12 (d, J = 7.6 Hz, 1H), 6.93 (d, J = 7.6 Hz, 1H), 3.93 – 3.81 (m, 2H), 3.47 (d, J = 11.2 Hz, 1H), 3.21 (t, J = 12.8 Hz, 1H), 3.06 – 2.89 (m, 5H), 2.84 (s, 3H), 2.52 (s, 3H), 2.35 – 2.25 (m, 1H), 2.23 – 2.09 (m, 3H), 2.05 – 1.94 (m, 2H).
VI-19	MS <i>m/z</i> : 380.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ : 8.33 (s, 1H), 7.92 (s, 1H), 7.64 (d, J = 2.0 Hz, 1H), 7.07 (s, 1H), 6.98 (d, J = 1.2 Hz, 1H), 3.84 – 3.79 (m, 1H), 3.57 – 3.54 (m, 1H), 3.18 – 3.15 (m, 1H), 2.69 – 2.64 (m, 1H), 2.54 (s, 3H), 2.48 – 2.43 (m, 1H), 2.30 – 2.27 (m, 1H), 2.17 (s, 3H), 2.05 – 1.95 (m, 2H), 1.92 – 1.86 (m, 1H). OH peaks not observed.

Cmpd#	Characterization
VI-20	MS m/z : 380.1 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 8.31 (s, 1H), 7.88 (s, 1H), 7.63 (d, $J = 2.4$ Hz, 1H), 7.06 (s, 1H), 6.98 (d, $J = 1.6$ Hz, 1H), 3.81 – 3.74 (m, 1H), 3.43 – 3.40 (m, 1H), 3.02 – 2.99 (m, 1H), 2.44 – 2.41 (m, 1H), 2.39 (s, 3H), 2.28 – 2.24 (m, 1H), 2.21 – 2.20 (m, 1H), 2.17 (s, 3H), 1.92 – 1.87 (m, 2H), 1.81 – 1.74 (m, 1H). OH peak not observed.

Example 6A: Preparation of 5-(7-(2-hydroxyphenyl)thieno[3,2-c]pyridazin-3-yl)-6-methylbenzofuran-4-ol (VIA-1)



- 5 Step 1: To a solution of methyl 3-chloro-7-hydroxy-thieno[3,2-c]pyridazine-6-carboxylate (11.84 g, 48.39 mmol, prepared according to example 6) in dioxane/ H_2O (5:1, 95 mL) was added LiOH- H_2O (12.18 g, 290.37 mmol). The mixture was stirred at 60°C for 30 h, then concentrated and the resulting red mixture was acidified with 3 M HCl to give a tan slurry. The mixture was filtered and the filtrate was extracted with EtOAc (3x). The combined organic extracts were
- 10 dried ($MgSO_4$), filtered and combined with the filter-cake. The mixture was concentrated to give a pale yellow solid. MS m/z 230.9, 232.8 $[M+H]^+$.

- Step 2: To a solution of 3-chloro-7-hydroxy-thieno[3,2-c]pyridazine-6-carboxylic acid (10.15 g, 44.01 mmol) in DMSO (88 mL) was added Ag_2CO_3 (2.43 g, 8.80 mmol) and acetic acid (12.6 mL, 220.1 mmol). The reaction was heated to 120°C for 50 min. After cooling to rt, the reaction
- 15 was poured onto EtOAc/water (4:1), and the mixture was stirred for 10 min and filtered through Celite. The layers of the filtrate were separated, and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated. The red oil was azeotroped with PhMe to remove AcOH. Purification by chromatography on SiO_2 (EtOAc:hexanes, 5 to 80%) gave a yellow solid (3.8 g, 46%, 3 steps).
- 20 MS m/z 186.9, 188.8 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ : 10.92 (s, 1H), 8.59 (s, 1H), 7.02 (s, 1H).

Step 3: 3-Chlorothieno[3,2-c]pyridazin-7-ol (2.0 g, 10.72 mmol) in DCM (48 mL) was cooled to 0 °C and added DIPEA (3.71 mL, 21.44 mmol) followed by dropwise addition of trifluoromethylsulfonyl trifluoromethanesulfonate (11.48 mL, 16.08 mmol, 1.4 M in DCM). The reaction was stirred at 0 °C for 1 h. The reaction was diluted with DCM and washed with cold water and brine. The organic phase was dried (Na₂SO₄), filtered and concentrated. Purification by chromatography on SiO₂ (EtOAc:hexanes, 5 to 50%) gave a grey solid (2.11 g, 62%). MS *m/z* 318.8, 320.7 [M+H]⁺.

Step 4: 3-Chlorothieno[3,2-c]pyridazin-7-yl) trifluoromethanesulfonate (0.15 g, 0.471 mmol), (2-hydroxyphenyl)boronic acid (78 mg, 0.565 mmol), Pd(dppf)Cl₂ (34 mg, 0.0471 mmol), and K₂CO₃ (163 mg, 1.18 mmol) were dissolved in dioxane/H₂O (5:1, 2.4 mL). The reaction was heated at 90 °C for 1 h, then diluted with EtOAc and washed with water and brine. The organic phase was dried (MgSO₄), filtered and concentrated. Purification by chromatography on SiO₂ (EtOAc:hexanes, 0 to 55%) gave a yellow solid (0.048 g, 39%). MS *m/z* 262.9, 264.9 [M+H]⁺.

Steps 5 and 6: 2-(3-Chlorothieno[3,2-c]pyridazin-7-yl)phenol (0.045 g, 0.171 mmol), 2-[4-(methoxymethoxy)-6-methyl-benzofuran-5-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.082 g, 0.257 mmol), XPhos Pd-G3 (0.015 g, 0.017 mmol), and K₂CO₃ (0.21 mL, 0.428 mmol, 2 M soln) were dissolved in dioxane (0.85 mL). The reaction was heated at 90 °C for 1 h. The reaction was diluted with EtOAc and washed with water and brine. The organic phase was dried (MgSO₄), filtered and concentrated. Purification by chromatography on SiO₂ (EtOAc:hexanes, 0 to 50%) gave a yellow film. MS *m/z* 419.1 [M+H]⁺. The material was dissolved in DCM (1 mL) and added TFA (0.2 mL) and stirred at rt. Upon completion, the reaction was concentrated, and the resulting residue was dissolved in DCM and washed with sat. NaHCO₃ and brine. The organic phase was dried (Na₂SO₄), filtered and concentrated. Purification by chromatography on SiO₂ (EtOAc:hexanes, 0 to 55%) gave a white solid (0.031 g, 48%). MS *m/z* 375.0 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.91 (s, 1H), 9.80 (s, 1H), 8.48 (s, 1H), 8.40 (s, 1H), 7.93 (d, *J* = 7.5 Hz, 1H), 7.84 (d, *J* = 2.0 Hz, 1H), 7.30 – 7.24 (m, 1H), 7.14 – 7.08 (m, 2H), 7.04 (d, *J* = 8.13 Hz, 1H), 6.97 (t, *J* = 7.44 Hz, 1H), 2.11 (s, 3H).

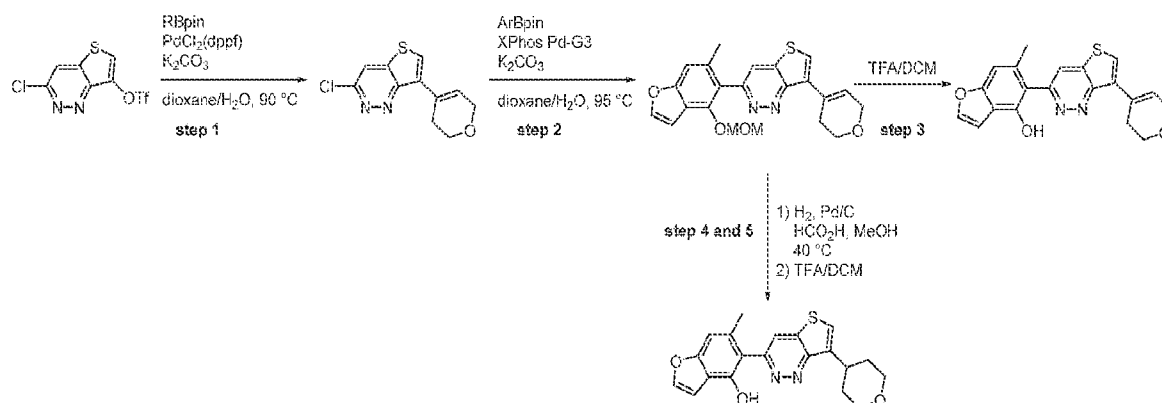
Using the procedure described for Example 6A, above, additional compounds described herein may be prepared by substituting the appropriate starting material, suitable reagents and reaction conditions, obtaining compounds such as those selected from.

Table 6A

Cmpd#	Characterization
VIA-2	MS m/z 377.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ : 9.80 (s, 1H), 8.52 (s, 1H), 8.47 (s, 1H), 8.10 – 8.04 (m, 1H), 7.84 (d, J = 2.0 Hz, 1H), 7.54 (s, 1H), 7.46 – 7.39 (m, 2H), 7.14 – 7.10 (m, 2H), 2.11 (s, 3H).
VIA-3	MS m/z 443.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ : 9.81 (s, 1H), 8.52 (s, 1H), 8.41 (s, 1H), 7.95 – 7.90 (m, 1H), 7.84 (d, J = 2.1 Hz, 1H), 7.67 – 7.56 (m, 3H), 7.14 – 7.09 (m, 2H), 2.09 (s, 3H).
VIA-4	MS m/z 427.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ : 9.82 (s, 1H), 8.51 (s, 1H), 8.28 (s, 1H), 7.96 (d, J = 7.9 Hz, 1H), 7.86 – 7.81 (m, 2H), 7.81 – 7.71 (m, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.15 – 7.09 (m, 2H), 2.08 (s, 3H).
VIA-5	MS m/z 373.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ : 9.79 (s, 1H), 8.50 (s, 1H), 8.23 (s, 1H), 7.84 (d, J = 2.1 Hz, 1H), 7.47 (d, J = 7.3 Hz, 1H), 7.40 (d, J = 4.3 Hz, 2H), 7.38 – 7.32 (m, 1H), 7.14 – 7.09 (m, 2H), 2.26 (s, 3H), 2.10 (s, 3H).
VIA-6	MS m/z 393.0, 394.9 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ 9.81 (s, 1H), 8.51 (s, 1H), 8.39 (s, 1H), 7.84 (d, J = 1.9 Hz, 1H), 7.73 – 7.65 (m, 2H), 7.57 – 7.49 (m, 2H), 7.15 – 7.09 (m, 2H), 2.10 (s, 3H)

5

Example 6B: Preparation of 5-(7-(3,6-dihydro-2H-pyran-4-yl)thieno[3,2-c]pyridazin-3-yl)-6-methylbenzofuran-4-ol (VIB-1) and 6-methyl-5-(7-(tetrahydro-2H-pyran-4-yl)thieno[3,2-c]pyridazin-3-yl)benzofuran-4-ol (VIB-2)



10 Step 1: 3-Chlorothieno[3,2-c]pyridazin-7-yl) trifluoromethanesulfonate (0.35 g, 1.09 mmol), 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.276 g, 1.31 mmol), Pd(dppf)Cl₂ (0.080 g, 0.110 mmol), and K₂CO₃ (0.379 g, 2.74 mmol) were dissolved in

dioxane/H₂O (5:1, 5.5 mL). The reaction was heated at 90 °C for 1 h. The reaction was diluted with EtOAc and washed with water and brine. The organic phase was dried (MgSO₄), filtered and concentrated. Purification by chromatography on SiO₂ (EtOAc:hexanes, 0 to 60%) gave a yellow solid (0.217 g, 78%). MS *m/z* 253.0, 254.9 [M+H]⁺.

- 5 Steps 2 and 3: 2-(3-Chlorothieno[3,2-*c*]pyridazin-7-yl)phenol (0.051 g, 0.201 mmol), 2-[4-(methoxymethoxy)-6-methyl-benzofuran-5-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.080 g, 0.252 mmol), XPhos Pd-G3 (0.017 g, 0.020 mmol), and K₂CO₃ (0.25 mL, 0.505 mmol, 2 M soln) were dissolved in dioxane (1.0 mL). The reaction was heated at 90 °C for 1 h. The reaction was diluted with EtOAc and washed with water and brine. The organic phase was dried
- 10 (MgSO₄), filtered and concentrated. Purification by chromatography on SiO₂ (EtOAc:hexanes, 0 to 50%) gave a yellow film. MS *m/z* 409.6 [M+H]⁺. The material was dissolved in DCM (1 mL) and added TFA (0.2 mL) and stirred at rt. Upon completion, the reaction was concentrated, and the resulting residue was dissolved in DCM and washed with sat. NaHCO₃ and brine. The organic phase was dried (Na₂SO₄), filtered and concentrated. Purification by chromatography on
- 15 SiO₂ (EtOAc:hexanes, 0 to 55%) gave a white solid (0.008 g, 52% 2 steps). MS *m/z* 365.0 [M+H]⁺; ¹H NMR (400 MHz, methanol-*d*₄) δ: 8.34 (s, 1H), 7.99 (s, 1H), 7.64 (s, 1H), 7.62 – 7.59 (m, 1H), 7.07 (s, 1H), 6.98 (s, 1H), 4.45 – 4.41 (m, 2H), 4.03 (t, *J* = 5.5 Hz, 2H), 2.79 – 2.72 (m, 2H), 2.18 (s, 3H). (1H not observed, OH).

- Steps 4 and 5: 7-(3,6-dihydro-2H-pyran-4-yl)-3-[4-(methoxymethoxy)-6-methyl-benzofuran-5-yl]thieno[3,2-*c*]pyridazine (0.045 g, 0.110 mmol) and Pd/C (0.012 g, 0.0110 mmol) was
- 20 evacuated and backfilled with Ar. The mixture was dissolved in MeOH (1.0 mL) and formic acid (10 μL) was added, and the solution was sparged with H₂ for 5 min before being stirred under an H₂ atmosphere (balloon, 1 atm) at 40 °C. The reaction was stirred for 48 h and then filtered through a pad of Celite. The filtrate was concentrated to give a yellow residue. The material was
- 25 dissolved in DCM (1 mL) and added TFA (0.2 mL) and stirred at rt. Upon completion, the reaction was concentrated, and the resulting residue was dissolved in DCM and washed with sat. NaHCO₃ and brine. The organic phase was dried (Na₂SO₄), filtered and concentrated. Purification by chromatography on SiO₂ (EtOAc:hexanes, 0 to 55%) gave a white solid (0.007 g, 41% 2 steps). MS *m/z* 367.4 [M+H]⁺; ¹H NMR (400 MHz, methanol-*d*₄) δ: 8.33 (s, 1H), 7.85 (s,

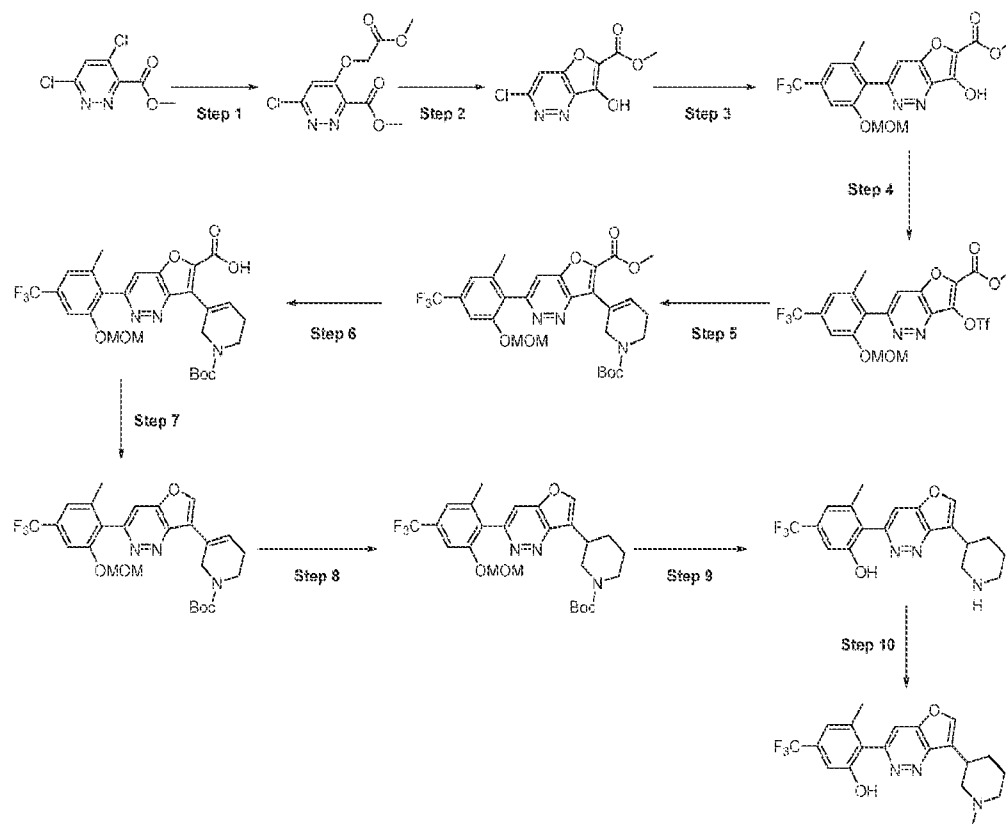
1H), 7.64 (d, $J = 2.0$ Hz, 1H), 7.07 (s, 1H), 6.98 (s, 1H), 4.11 (dd, $J = 11.2, 4.1$ Hz, 2H), 3.77 – 3.66 (m, 3H), 2.21 – 2.14 (m, 5H), 2.01 (qd, $J = 12.5, 4.1$ Hz, 2H). (1H not observed, OH).

Using the procedure described for Example 6B, above, additional compounds described herein may be prepared by substituting the appropriate starting material, suitable reagents and reaction conditions, obtaining compounds such as those selected from.

Table 6B

Cmpd#	Characterization
VIB-3	MS m/z 395.5 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.27 (s, 1H), 7.94 (s, 1H), 7.17 (s, 1H), 7.04 (s, 1H), 4.29 (d, $J = 7.5$ Hz, 1H), 3.99 (d, $J = 11.3$ Hz, 1H), 3.81 – 3.57 (m, 3H), 2.43 (s, 3H), 2.40 – 2.21 (m, 1H), 2.16 – 2.02 (m, 1H), 1.93 – 1.73 (m, 2H). (1H not observed, OH).
VIB-4	MZ m/z 353.0 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.35 (s, 1H), 7.94 – 7.93 (m, 1H), 7.64 (d, $J = 2.3$ Hz, 1H), 7.07 (s, 1H), 6.99 (d, $J = 1.4$ Hz, 1H), 4.38 – 4.33 (m, 1H), 4.25 – 4.18 (m, 1H), 4.16 – 4.09 (m, 1H), 4.06 – 3.96 (m, 2H), 2.64 – 2.53 (m, 1H), 2.42 – 2.29 (m, 1H), 2.18 (s, 3H). (1H not observed, OH).
VIB-5	MZ m/z 351.0 $[M+H]^+$; ^1H NMR (500 MHz, methanol- d_4) δ : 8.56 (s, 1H), 8.05 (s, 1H), 7.67 (d, $J = 2.3$ Hz, 1H), 7.45 – 7.42 (m, 1H), 7.11 (s, 1H), 7.01 (d, $J = 1.4$ Hz, 1H), 5.20 – 5.15 (m, 2H), 4.96 – 4.92 (m, 2H), 2.22 (s, 3H). (1H not observed, OH).
VIB-6	MS m/z 367.1 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.35 (s, 1H), 7.94 (s, 1H), 7.64 (s, 1H), 7.07 (s, 1H), 6.98 (s, 1H), 4.34 – 4.26 (m, 1H), 4.03 – 3.95 (m, 1H), 3.81 – 3.68 (m, 2H), 3.64 (td, $J = 10.7, 3.1$ Hz, 1H), 2.36 – 2.25 (m, 1H), 2.18 (s, 3H), 2.15 – 2.03 (m, 1H), 1.93 – 1.68 (m, 2H). (1H not observed, OH).

Example 7. Preparation of 3-methyl-2-(7-(1-methylpiperidin-3-yl)furo[3,2-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol (VII-2)



Step 1: A solution of 2-hydroxyacetate (4.8 g, 53.1 mmol in THF (150 mL) was cooled down to 0 °C and NaH (2.2g, 53.1 mmol, 60% w/w in oil) was added to the solution portion-wise (intense bubbling observed). After 30 min, the solution was added dropwise to another flask containing methyl 4,6-dichloropyridazine-3-carboxylate (10 g, 48.3 mmol) in 100 ml of THF at 0 °C. The reaction was stirred for 40 min before quenching the with ammonium chloride. The aqueous part was extracted with EtOAc (6 times). Combined organic parts were dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford crude methyl 6-chloro-4-(2-methoxy-2-oxo-ethoxy)pyridazine-3-carboxylate (8.9 g, 71% yield), which was used in the next step without further purification. MS *m/z* 261.0, 263.0 [M+H]⁺.

Step 2: To a solution of 6-chloro-4-(2-methoxy-2-oxo-ethoxy)pyridazine-3-carboxylate (8.9 g, 34 mmol) in ACN (35 mL) was added DBU (25.3 mL, 170 mmol) and the reaction mixture was stirred for 30 min at rt. Upon completion, ACN was evaporated under the reduced pressure and the residue was partitioned between water and EtOAc. The aqueous layer was acidified with aq. HCl to pH~6 and extracted with EtOAc (6 times). Combined organic parts were dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford methyl 3-chloro-7-

hydroxy-furo[3,2-c]pyridazine-6-carboxylate (5.9 g, 76% yield). The crude material was taken to the next step without further purification. MS m/z 229.0, 231.0 $[M+H]^+$.

Step 3: To a dry round bottom flask were added: methyl 3-chloro-7-hydroxy-furo[3,2-c]pyridazine-6-carboxylate (1.0 g, 4.37 mmol), 2-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.27 g, 6.56 mmol), K_2CO_3 (1.81 g, 13.12 mmol) and XphosPdG4 (376 mg, 0.44 mmol). The reaction was degassed by purging Ar for 15 min and dioxane (20 mL) and water (5 mL) were added. The reaction mixture was stirred for 2 h at 90 °C. Upon completion, the reaction was cooled down to room temperature, partitioned between EtOAc and brine. The combined organic parts were washed with brine, dried over sodium sulfate, concentrated to give crude methyl 7-hydroxy-3-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)furo[3,2-c]pyridazine-6-carboxylate. Which was used in the next step without further purification. MS m/z 413.9 $[M+H]^+$.

Step 4: To a solution of crude methyl 7-hydroxy-3-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)furo[3,2-c]pyridazine-6-carboxylate (1.2 g, 2.91 mmol) in pyridine (20 mL) was added Tf_2O (1.64 g, 5.82 mmol) at 0°C. The reaction mixture was stirred at rt for 4h. Upon completion, the reaction was diluted with water (100 mL) and extracted with EtOAc (3x100 mL). The organic layers were dried over sodium sulfate, concentrated and purified by flash column chromatography eluting with a gradient EtOAc/hexanes (0 - 10% EtOAc) to afford methyl 3-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)-7-(((trifluoromethyl)sulfonyl)oxy)furo [3,2-c]pyridazine-6-carboxylate (700 mg, 44% yield). MS m/z 545.0 $[M+H]^+$.

Step 5: To a dry round bottom flask were added: methyl 3-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)-7-(((trifluoromethyl)sulfonyl)oxy)furo [3,2-c]pyridazine-6-carboxylate (700 mg, 1.29 mmol), tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (596 mg, 1.93 mmol), K_2CO_3 (533 mg, 3.86 mmol) and XphosPdG3 (109 mg, 0.13 mmol). The reaction was degassed by purging Ar for 15 min and dioxane (12 mL) and water (3 mL) were added. The reaction mixture was stirred for 3 h at 90 °C. Upon completion, the reaction was cooled down to room temperature, partitioned between EtOAc and brine. The combined organic parts were washed with brine, dried over sodium sulfate, concentrated to give crude methyl 7-(1-(tert-butoxycarbonyl)-1,2,5,6-tetrahydropyridin-

3-yl)-3-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)furo[3,2-c]pyridazine-6-carboxylate (602 mg, 81% yield). The crude material was taken to the next step without further purification. MS m/z 578.2 $[M+H]^+$.

Step 6: To a solution of methyl 7-(1-(tert-butoxycarbonyl)-1,2,5,6-tetrahydropyridin-3-yl)-3-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)furo[3,2-c]pyridazine-6-carboxylate (602 mg, 1.04 mmol) in THF (10 mL) and water (2 mL) was added LiOH (875 mg, 20.85 mmol). The reaction mixture was stirred at rt for 2h. Upon completion, the pH of the reaction mixture was adjusted to 5-6 with 2N HCl. The resulting mixture was extracted with EtOAc (3x30 mL). The combined organic parts were dried over Na₂SO₄, filtered and concentrated to afford 7-(1-(tert-butoxycarbonyl)-1,2,5,6-tetrahydropyridin-3-yl)-3-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)furo[3,2-c]pyridazine-6-carboxylic acid (450 mg, 77% yield) as a yellow solid. The crude material was taken to the next step without further purification. MS m/z 564.2 $[M+H]^+$.

Step 7: To a solution of 7-(1-(tert-butoxycarbonyl)-1,2,5,6-tetrahydropyridin-3-yl)-3-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)furo[3,2-c]pyridazine-6-carboxylic acid (92 mg, 0.16 mmol) in DMSO (2 mL) were Ag₂CO₃ (9 mg, 0.033 mmol) and AcOH (49 mg, 0.82 mmol). The reaction mixture was stirred at 120°C for 2h. Upon completion, the reaction was cooled to rt and partitioned between water (30 mL) and EtOAc (3x30mL). The combined organic parts were washed with water (30 mL) and brine (30 mL), dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography eluting with a gradient EtOAc/hexanes (0 - 20% EtOAc) to afford tert-butyl 5-(3-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)furo[3,2-c]pyridazin-7-yl)-3,6-dihydropyridine-1(2H)-carboxylate (80 mg, 94% yield) as a yellow solid. MS m/z 520.2 $[M+H]^+$.

Step 8: To a solution of tert-butyl 5-(3-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)furo[3,2-c]pyridazin-7-yl)-3,6-dihydropyridine-1(2H)-carboxylate (130 mg, 0.25 mmol) in THF (5 mL) was added PtO₂ (13 mg, 10% wt). The reaction was stirred at rt under 1 atm H₂ for 8 h. The reaction mixture was filtered through a celite pad, washed with EtOAc. The filtrate was concentrated and purified by flash column chromatography eluting with a gradient EtOAc/hexanes (0 - 70% EtOAc) to afford tert-butyl 3-(3-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)furo[3,2-c]pyridazin-7-yl)piperidine-1-carboxylate (75 mg,

57% yield). MS m/z 522.2 $[M+H]^+$.

Step 9: To a solution of tert-butyl 3-(3-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)furo[3,2-c]pyridazin-7-yl)piperidine-1-carboxylate in CH_2Cl_2 (2 mL) was added 4N HCl in 1,4-dioxane (2 mL, 0.5 mmol). The reaction was stirred at rt for 2 h. Upon completion, solvents were evaporated to yield crude 3-methyl-2-(7-(piperidin-3-yl)furo[3,2-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol (54 mg, 99% yield) as an off-white solid. The crude material was taken to the next step without further purification. MS m/z 378.2 $[M+H]^+$.

Step 10: To a solution of 3-methyl-2-(7-(piperidin-3-yl)furo[3,2-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol (54 mg, 0.14 mmol) in CH_2Cl_2 (1 mL) and MeOH (0.25 mL) were added Et₃N (43 mg, 0.43 mmol) and formaldehyde (35 μ L, 0.43 mmol) at 0°C. The reaction mixture was stirred at 0°C for 1h. Then, NaBH(OAc)₃ (91 mg, 0.43 mmol) was added at 0°C. The reaction mixture was stirred at 0°C for 3h. The reaction mixture was diluted with water (30 mL) and extracted with CH_2Cl_2 (3x30mL). The combined organic parts were dried over Na₂SO₄, filtered, concentrated and purified by reversed phase flash chromatography eluting with a gradient ACN/water (0-30% ACN) to afford 3-methyl-2-(7-(1-methylpiperidin-3-yl)furo[3,2-c]pyridazin-3-yl)-5-(trifluoromethyl)phenol formate (42 mg, 75% yield) as a white solid. MS m/z 392.4 $[M+H]^+$; ¹H NMR (400 MHz, methanol-*d*₄) δ : 8.22 (d, *J* = 0.8 Hz, 1H), 7.91 (s, 1H), 7.15 (s, 1H), 7.08 (s, 1H), 3.86 – 3.74 (m, 1H), 3.64 – 3.53 (m, 1H), 3.46 – 3.38 (m, 1H), 3.28 – 3.15 (m, 1H), 2.98 – 2.86 (m, 1H), 2.82 (s, 3H), 2.36 – 2.26 (m, 1H), 2.15 (s, 3H), 2.12 – 2.05 (m, 1H), 2.05 – 1.95 (m, 2H).

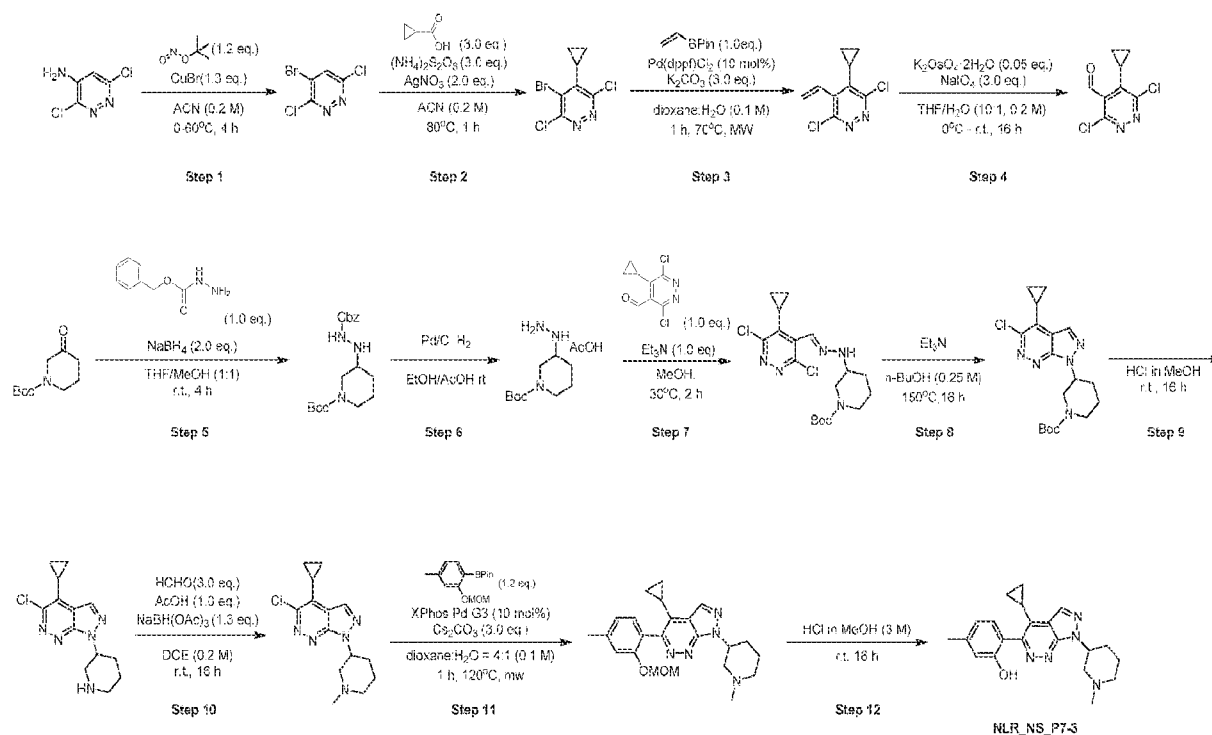
Using the procedure described for Example 7, above, additional compounds described herein may be prepared by substituting the appropriate starting material, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Table 7

Cmpd#	Characterization
VII-1	MS m/z : 390.0 $[M+H]^+$; ¹ H NMR (methanol- <i>d</i> ₄) δ : 8.54 (s, 1H), 8.91 (s, 1H), 7.46-7.59 (m, 1H), 7.18 (s, 1H), 3.53-3.59 (m, 2H), 2.83-2.92 (m, 1H), 2.58-2.63 (m, 1H), 2.59 (s, 3H), 2.18 (s, 3H), 1.60-1.76 (m, 1H), 1.33-1.46 (m, 1H), 1.05 (t, <i>J</i> =7.3 Hz, 1H); 1 H not observed (OH)

Cmpd#	Characterization
VII-2	MS m/z 392.4 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.22 (d, J = 0.8 Hz, 1H), 7.91 (s, 1H), 7.15 (s, 1H), 7.08 (s, 1H), 3.86 – 3.74 (m, 1H), 3.64 – 3.53 (m, 1H), 3.46 – 3.38 (m, 1H), 3.28 – 3.15 (m, 1H), 2.98 – 2.86 (m, 1H), 2.82 (s, 3H), 2.36 – 2.26 (m, 1H), 2.15 (s, 3H), 2.12 – 2.05 (m, 1H), 2.05 – 1.95 (m, 2H).
VII-3	MS m/z : 392.2 $[M+H]^+$; ^1H NMR (400 MHz, methanol- d_4) δ : 8.06 (s, 1H), 7.47 (d, J = 7.2 Hz, 1H), 7.21 – 7.19 (m, 2H), 3.38 – 3.33 (m, 2H), 2.94 – 2.91 (m, 1H), 2.42 (s, 3H), 2.39 – 2.38 (m, 1H), 2.35 (s, 3H), 2.26 – 2.12 (m, 2H), 1.89 – 1.81 (m, 2H), 1.79 – 1.69 (m, 1H); 1H not observed (OH).
VII-4	MS m/z : 364.2 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 8.03 (s, 1H), 7.10 (d, J = 7.6 Hz, 1H), 6.90 (d, J = 7.2 Hz, 1H), 3.40 – 3.34 (m, 2H), 3.00 – 2.91 (m, 5H), 2.47 – 2.43 (m, 1H), 2.42 (s, 3H), 2.37 (s, 3H), 2.24 – 2.10 (m, 4H), 1.91 – 1.68 (m, 3H). 1H not observed (OH).
VII-5	MS m/z : 366.1 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 8.03 (s, 1H), 7.10 (d, J = 8.4 Hz, 1H), 6.45 (d, J = 8.4 Hz, 1H), 4.63 (t, J = 8.8 Hz, 2H), 3.36 – 3.33 (m, 2H), 3.21 (t, J = 8.4 Hz, 2H), 2.95 – 2.92 (m, 1H), 2.45 (s, 3H), 2.42 – 2.39 (m, 1H), 2.36 (s, 3H), 2.21 – 2.18 (m, 2H), 1.92 – 1.67 (m, 3H). 1H not observed (OH).
VII-6	MS m/z : 406.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ : 8.29 (s, 1H), 7.20 (s, 1H), 7.13 (s, 1H), 3.28-3.24 (m, 1H), 3.20-3.16 (m, 1H), 2.82-2.80 (m, 1H), 2.32-2.30 (m, 1H), 2.27 (d, J = 2.4 Hz, 3H), 2.21 (s, 3H), 2.10-2.08 (m, 2H), 1.97 (s, 3H), 1.76-1.74 (m, 1H), 1.72-1.68 (m, 2H). 1H not observed (OH).
VII-7	MS m/z : 392.2 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 8.07 (s, 1H), 7.81 (s, 1H), 6.98 (s, 1H), 6.95 (s, 1H), 3.41 – 3.32 (m, 2H), 2.98 – 2.87 (m, 1H), 2.48 – 2.38 (m, 1H), 2.36 (s, 3H), 2.26 – 2.12 (m, 2H), 2.10 (s, 3H), 1.89 – 1.70 (m, 3H). 1H not observed (OH).
VII-8	MS m/z : 392.2 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 8.08 (s, 1H), 7.81 (s, 1H), 6.99 (s, 1H), 6.98 (s, 1H), 3.42 – 3.33 (m, 2H), 2.97 – 2.89 (m, 1H), 2.46 – 2.38 (m, 1H), 2.36 (s, 3H), 2.27 – 2.15 (m, 2H), 2.11 (s, 3H), 1.90 – 1.74 (m, 3H). 1H not observed (OH).
VII-9	MS m/z : 364.1 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 8.08 (s, 1H), 7.73 (d, J = 2.4 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.19 (dd, J = 8.4, 0.4 Hz, 1H), 7.05 (dd, J = 2.4 Hz, 0.8 Hz, 1H), 3.48 – 3.36 (m, 2H), 3.05 (d, J = 11.6 Hz, 1H), 2.66 – 2.56 (m, 1H), 2.47 (s, 3H), 2.44 (s, 3H), 2.39 – 2.30 (m, 1H), 2.28 – 2.21 (m, 1H), 1.95 – 1.76 (m, 3H). 1H not observed (OH).
VII-10	MS m/z : 366.1 $[M+H]^+$; ^1H NMR (400 MHz, MeOD- d_4) δ : 7.97 (s, 1H), 7.65 (s, 1H), 6.22 (s, 1H), 4.48 (t, J = 8.8 Hz, 2H), 3.31 – 3.23 (m, 2H), 3.05 (t, J = 8.8 Hz, 2H), 2.89 – 2.86 (m, 1H), 2.45 – 2.35 (m, 1H), 2.30 (s, 3H), 2.17 – 2.10 (m, 2H), 1.94 (s, 3H), 1.85 – 1.61 (m, 3H). 1H not observed (OH).
VII-11	MS m/z : 364.1 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 8.09 (s, 1H), 7.82 (s, 1H), 7.63 (d, J = 2.4 Hz, 1H), 7.05 (s, 1H), 6.97 (d, J = 1.2 Hz, 1H), 3.45 – 3.35 (m, 2H), 3.01 – 2.93 (m, 1H), 2.56 – 2.46 (m, 1H), 2.41 (s, 3H), 2.26 – 2.23 (m, 2H), 2.16 (s, 3H), 1.90 – 1.81 (m, 3H). 1H not observed (OH).

Example 8. Preparation of 2-(4-cyclopropyl-1-(1-methylpiperidin-3-yl)-1H-pyrazolo[3,4-c]pyridazin-5-yl)-5-methylphenol (VIII-1)



NLR_NS_P7-3

- 5 **Step 1.** To a solution of 3,6-dichloropyridazin-4-amine (70.0 g, 426.7 mmol, 1.0 eq.) in ACN (700 mL, 0.6 M) was added CuBr (79.6 g, 554.9 mmol, 1.3 eq.), tert-butyl nitrite (60.9 mL, 512.2 mmol, 1.2 eq.) at 0 °C. The reaction mixture was stirred at 60 °C for 4 h. Upon completion, the reaction mixture was cooled to room temperature and filtered, the organic layer was concentrated under reduced pressure. The concentrated residue was purified by silica gel column chromatography eluting with 0-10% EtOAc in hexanes to give 4-bromo-3,6-dichloropyridazine (45.0 g, 197.5 mmol, 46% yield) as a white solid. MS m/z 228.8 $[M+H]^+$.
- 10

- Step 2.** To a solution of 4-bromo-3,6-dichloropyridazine (30.0 g, 131.6 mmol, 1.0 eq.) in ACN (600 mL) was added cyclopropanecarboxylic acid (34.0 g, 395.0 mmol, 3.0 eq.) and AgNO₃ (44.7 g, 263.3 mmol, 2.0 eq.). (NH₄)₂S₂O₈ (150.2 g, 658.3 mmol, 5.0 eq.) was added to the mixture at 80 °C and the reaction mixture was stirred at this temperature for 1 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with water (100 mL) and extracted with EtOAc (600 mL x 3). The organic layer was dried over Na₂SO₄, filtered and concentrated in vacuum and concentrated under reduced pressure. The concentrated residue was purified by silica gel column chromatography eluting with 0-5% EtOAc in hexanes to give 4-
- 15

bromo-3,6-dichloro-5-cyclopropylpyridazine (15 g, 56.0 mmol, 43% yield) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.12 – 1.81 (m, 1H), 1.50 – 1.17 (m, 2H), 1.07 – 0.79 (m, 2H).

Step 3. To a solution of 4-bromo-3,6-dichloro-5-cyclopropylpyridazine (10.0 g, 37.3 mmol, 1.0 eq.) in water (10 mL) and dioxane (50 mL) was added 4,4,5,5-tetramethyl-2-vinyl-1,3,2-

dioxaborolane (6.3 g, 41.1 mmol, 1.1 eq.), K₂CO₃ (15.5 g, 112.0 mmol, 3.0 eq.) and Pd(dppf)Cl₂ (2.7 g, 3.7 mmol, 0.1 eq.). The reaction mixture was stirred for 1 h at 70°C under N₂ by microwave. Upon the completion of the reaction, the reaction mixture was washed with water (20 mL) and extracted with EtOAc (50 mL) twice. The organic layer was dried over Na₂SO₄, filtered and diluted concentrated under reduced pressure. The concentrated residue was purified by silica gel column chromatography eluting with 0-10% EtOAc in hexanes to give 3,6-dichloro-4-cyclopropyl-5-vinylpyridazine (4.7 g, 21.6 mmol, 58% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 6.79 – 6.71 (m, 1H), 5.98 – 5.94 (m, 1H), 5.83 – 5.79 (m, 1H), 2.00 – 1.65 (m, 1H), 1.41 – 1.17 (m, 2H), 0.80 – 0.60 (m, 2H).

Step 4. To a solution of 3,6-dichloro-4-cyclopropyl-5-vinylpyridazine (4.7 g, 21.6 mmol, 1.0 eq.)

in THF (40 mL) and H₂O (4 mL) was added NaIO₄ (14.0 g, 65.6 mmol, 3.0 eq.) and K₂OsO₄•H₂O (976 mg, 2.2 mmol, 0.1 eq.) at 0°C. The reaction was stirred at room temperature for 16 h. Upon completion, the reaction mixture was diluted with water (30 mL) and extracted with EtOAc (30 mL x 3). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with 0-3% EtOAc in hexanes to afford 3,6-dichloro-5-cyclopropylpyridazine-4-carbaldehyde (3.4 g, 15.7 mmol, 71% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.42 (s, 1H), 2.10 – 1.99 (m, 1H), 1.17 – 1.13 (m, 2H), 0.74 – 0.66 (m, 2H).

Step 5. To a solution of *tert*-butyl 3-oxopiperidine-1-carboxylate (10.0 g, 50.2 mmol, 1.0 eq.) in

THF (80 mL) and MeOH (80 mL) was added benzyl hydrazinecarboxylate (8.3 g, 50.2 mmol, 1.0 eq.). The resulting mixture was stirred at rt for 30 min, then NaBH₄ (3.8 g, 100.4 mmol, 2.0 eq.) was added. The resulting mixture was stirred at rt for 2 h. The solvent was removed under reduced pressure. The resulting residue was added with water (150 mL), then extracted with dichloromethane (3 x 100 mL). The organic phase was washed with brine (100 mL), dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (40% ethyl acetate in petroleum ether) to afford *tert*-butyl 3-(2-

((benzyloxy)carbonyl)hydrazineyl)piperidine-1-carboxylate (12.0 g, 34.3 mmol, 68.4% yield) as a white solid.

Step 6. To a solution of *tert*-butyl 3-(2-((benzyloxy)carbonyl)hydrazineyl)piperidine-1-carboxylate (4.0 g, 11.5 mmol, 1.0 eq.) in EtOH (50 mL) was added AcOH (687.4 mg, 11.5 mmol, 1.0 eq.) and Pd/C (0.4 g, 50% w.t.). The above mixture was stirred for 2 h at rt under H₂ (15 psi). The reaction mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to afford *tert*-butyl 3-hydrazinylpiperidine-1-carboxylate acetate (2.3 g, 8.4 mmol, 73.0% yield) as a black solid, which was directly used in the next step without further purification.

Step 7. To a solution of *tert*-butyl 3-hydrazinylpiperidine-1-carboxylate acetate (2.3 g, 8.4 mmol, 1.0 eq.) in MeOH (30 mL) was added Et₃N (845.3 mg, 8.4 mmol, 1.0 eq.). The resulting mixture was stirred at rt for 10 min, then 3,6-dichloro-5-cyclopropylpyridazine-4-carbaldehyde (1.8 g, 8.4 mmol, 1.0 eq.) was added. The resulting mixture was stirred at rt for another 1 h. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (20% ethyl acetate in petroleum ether) to afford *tert*-butyl (*L*)-3-(2-((3,6-dichloro-5-cyclopropylpyridazin-4-yl)methylene)hydrazinyl)piperidine-1-carboxylate (1.4 g, 3.4 mmol, 40.5% yield) as a white solid.

Step 8. To a solution of *tert*-butyl (*L*)-3-(2-((3,6-dichloro-5-cyclopropylpyridazin-4-yl)methylene)hydrazinyl)piperidine-1-carboxylate (1 g, 2.4 mmol, 1.0 eq.) in DMF (15 mL) was added KOH (270.8 mg, 4.8 mmol, 2.0 eq.). The above mixture was stirred at 120 °C for 0.5 h under microwave. The reaction mixture was added water (20 mL), then extracted with dichloromethane (3 x 20 mL). The organic phase was washed with brine (20 mL), dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% ethyl acetate in petroleum ether) to afford *tert*-butyl 3-(5-chloro-4-cyclopropyl-1H-pyrazolo[3,4-*c*]pyridazin-1-yl)piperidine-1-carboxylate (600 mg, 1.6 mmol, 65.8% yield) as a white solid. LCMS: [M+H]⁺ = 377.9.

Step 9. To a solution of *tert*-butyl 3-(5-chloro-4-cyclopropyl-1H-pyrazolo[3,4-*c*]pyridazin-1-yl)piperidine-1-carboxylate (500 mg, 1.3 mmol, 1.0 eq.) in DCM (5 mL) was added TFA (0.5 mL). The resulting mixture was stirred for 2 h at rt. The pH was adjusted to 7~8 by addition of Et₃N. The solvent was removed under reduced pressure to afford crude 5-chloro-4-cyclopropyl-

1-(piperidin-3-yl)-1H-pyrazolo[3,4-c]pyridazine (300 mg, 1.1 mmol, 81.6% yield) as a yellow oil, which was used in the next step without further purification.

Step 10. To a solution of 5-chloro-4-cyclopropyl-1-(piperidin-3-yl)-*1H*-pyrazolo[3,4-c]pyridazine (300 mg, 1.1 mmol, 1.0 eq.) in MeOH (8 mL) was added HCHO (97.3 mg, 3.3 mmol, 3.0 eq.) and AcOH (64.9 mg, 1.1 mmol, 1.0 eq.). The resulting solution was stirred at rt for 30 min, then NaBH(OAc)₃ (297.6 mg, 1.4 mmol, 1.3 eq.) was added. The resulting mixture was stirred for another 1 h at rt. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (10% methanol in dichloromethane) to afford 5-chloro-4-cyclopropyl-1-(1-methylpiperidin-3-yl)-*1H*-pyrazolo[3,4-c]pyridazine (300 mg, 1.0 mmol, 95.2 % yield). LCMS: $[M+H]^+ = 292.2$.

Step 11. To a mixture of 5-chloro-4-cyclopropyl-1-(1-methylpiperidin-3-yl)-*1H*-pyrazolo[3,4-c]pyridazine (150 mg, 0.51 mmol, 1.0 eq.) in dioxane (5 mL) and H₂O (1 mL) was added 2-(2-(methoxymethoxy)-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (171.6 mg, 0.62 mmol, 1.2 eq.), XPhos Pd G₃ (43.5 mg, 0.05 mmol, 0.1 eq.) and Cs₂CO₃ (502.5 mg, 1.54 mmol, 3.0 eq.). The above mixture was stirred under N₂ at 120°C for 1 h under microwave. The resulting solution was diluted with H₂O (30 mL) and extracted with ethyl acetate (3 x 30 mL). The organic layers were combined, washed with brine, dried and concentrated under reduced pressure. The residue was purified by flash chromatography (8% methanol in DCM) to give 4-cyclopropyl-5-(2-(methoxymethoxy)-4-methylphenyl)-1-(1-methylpiperidin-3-yl)-*1H*-pyrazolo[3,4-c]pyridazine (177.0 mg, 0.43 mmol, 84.5% yield) as a yellow oil. LCMS: $[M+H]^+ = 408.2$.

Step 12. 4-cyclopropyl-5-(2-(methoxymethoxy)-4-methylphenyl)-1-(1-methylpiperidin-3-yl)-*1H*-pyrazolo[3,4-c]pyridazine (170.0 mg, 0.42 mmol, 1.0 eq.) was dissolved in 4M HCl MeOH solution (5 mL). The resulting mixture was stirred for 16 h at rt. The resulting solution was neutralized with NH₃ in MeOH. The solvent was removed under reduced pressure. The residue was purified by prep. HPLC to afford 2-(4-cyclopropyl-1-(1-methylpiperidin-3-yl)-*1H*-pyrazolo[3,4-c]pyridazin-5-yl)-5-methyl-phenol (71.0 mg, 0.19 mmol, 46.9 % yield) as a white solid. LCMS: $[M+H]^+ = 364.2$. ¹H NMR (400 MHz, MeOD) δ 8.18 (s, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 6.80 (s, 1H), 5.34 – 5.19 (m, 1H), 3.21 – 3.14 (m, 1H), 3.00 – 2.87

(m, 1H), 2.74 – 2.61 (m, 1H), 2.36 (s, 6H), 2.22 – 2.05 (m, 4H), 2.01 – 1.92 (m, 1H), 1.92 – 1.80 (m, 1H), 1.36 – 1.24 (m, 2H), 1.24 – 1.15 (m, 2H). 1H not observed (OH).

Using the procedure described for Example 8, above, additional compounds described herein may be prepared by substituting the appropriate starting material, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Table 8.

Cmpd#	Characterization
VIII-2	MS <i>m/z</i> : 376.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ : 8.24 (s, 1H), 7.15 (d, J = 7.2 Hz, 1H), 6.75 (d, J = 7.2 Hz, 1H), 5.47 – 5.40 (m, 1H), 3.51 – 3.47 (m, 1H), 3.2 – 3.18 (m, 5H), 2.66 (s, 3H), 2.36 – 2.20 (m, 2H), 2.12 – 2.03 (m, 2H), 1.99 – 1.92 (m, 1H), 1.35 – 1.29 (m, 4H), 1.26 – 1.21 (m, 2H). 1H not observed (OH).
VIII-3	MS <i>m/z</i> : 390.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ : 8.27 (s, 1H), 7.73 (s, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.05 (s, 1H), 5.57 – 5.41 (m, 1H), 3.50 – 3.47 (m, 1H), 3.21 (s, 1H), 3.17 – 3.14 (m, 1H), 2.70 – 2.67 (m, 1H), 2.62 (s, 3H), 2.32 – 2.17 (m, 2H), 2.15 – 2.01 (m, 2H), 2.00 – 1.88 (m, 1H), 1.37 – 1.30 (m, 2H), 1.27 – 1.18 (m, 2H). 1H not observed (OH).
VIII-4	MS <i>m/z</i> : 418.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD) δ : 8.26 (s, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.24 (s, 1H), 5.39 – 5.31 (m, 1H), 3.34 – 3.32 (m, 1H), 3.07 – 3.04 (m, 1H), 2.95 – 2.90 (m, 1H), 2.50 (s, 3H), 2.42 – 2.37 (m, 1H), 2.27 – 2.18 (m, 2H), 2.25 – 2.19 (m, 2H), 1.96 – 1.84 (m, 1H), 1.37 – 1.28 (m, 2H), 1.27 – 1.19 (m, 2H).

10 BIOLOGICAL ASSAYS

IL-1 β Secretion Assay:

Monocytic THP-1 cells (ATCC: TIB-202) were maintained in growth media consisting of RPMI 1640 medium (ThermoFisher, Cat# 11875-085), 10% FBS (ThermoFisher) and 0.05mM β -mercaptoethanol (ThermoFisher, Cat# 21985-023), according to the provider's instructions. The cell concentration was adjusted to 7.5×10^5 cells/mL and plated in complete growth media with a final concentration of 100ng/mL phorbol 12-myristate 13-acetate (PMA, Sigma #P8139). Cells were seeded at 100 μ L/well into a 96-well cell culture plate (ThermoFisher Cat#165305) and allowed to differentiate for 24 h in a cell culture incubator at 37°C with 5% CO₂. Cells were washed 1x with 100ul PBS and replaced with fresh RPMI + 5% FBS.

Compounds were serially diluted in DMSO with 3-fold dilution for a total of 7 concentrations. Diluted compounds were added to the cells at a ratio of 1:200 and incubated for 20 h. The NLRP3 inflammasome was activated with the addition of 2.5 μ M Nigericin (Sigma: Cat# SML1779-1ml), for 3 h. After incubation, 15 μ L of conditioned media was removed and assayed for levels of IL-1 β using the HTRF IL-1 β assay kit (Cisbio: Cat# 62HIL1BPEH) as per the manufacturer's instructions.

TABLE I depicts examples of compounds according to generic Formula (I). Data which is < 1nM is listed as *****; data 1-10 nM is listed as *****; data 10-100 nM is listed as ***; data 100-300 nM is listed as **, and data >300 nM is listed as *.

10 Table I

Cmpd #	IC ₅₀ IL-1 β Inhibition	Cmpd #	IC ₅₀ IL-1 β Inhibition	Cmpd #	IC ₅₀ IL-1 β Inhibition	Cmpd #	IC ₅₀ IL-1 β Inhibition
I-1	*****	II-5	*****	III-13	*****	III-97	*****
I-2	*****	II-6	*****	III-14	*****	III-98	*****
I-3	*****	II-7	*****	III-15	*****	III-99	*****
I-4	*****	II-8	*****	III-16	*****	III-100	*****
I-5	*****	II-9	*****	III-17	*****	III-101	*****
I-6	*****	II-10	*****	III-18	*****	III-102	*****
I-7	*****	II-11	*****	III-19	*****	III-103	*****
I-8	*****	II-12	*****	III-20	*****	III-104	*****
I-9	*****	II-13	*****	III-21	*****	III-105	*****
I-10	*****	II-14	*****	III-22	*****	III-106	*****
I-11	*****	II-15	*****	III-23	*****	III-107	*****
I-12	*****	II-16	*****	III-24	*****	III-108	*****
I-13	*****	II-17	*****	III-25	*****	III-109	*****
I-14	*****	II-18	*****	III-26	*****	III-110	*****
I-15	*****	II-19	*****	III-27	*****	III-111	*****
I-16	*****	II-20	*****	III-28	*****	III-112	*****
I-17	*****	II-21	*****	III-29	*****	IIIA-1	*****
I-18	*****	II-22	*****	III-30	*****	IIIA-2	*****
I-19	*****	II-23	*****	III-31	*****	IIIA-3	*****
I-20	*****	II-24	*****	III-32	*****	IIIA-4	*****
I-21	*****	II-25	*****	III-33	*****	IIIA-5	*****
I-22	*****	II-26	*****	III-34	*****	IIIA-6	*****
I-23	*****	II-27	*****	III-35	*****	IIIB-1	*****
I-24	*****	II-28	*****	III-36	*****	IIIB-2	*****
I-25	*****	II-29	*****	III-37	*****	IIIC-1	*****
I-26	*****	II-30	*****	III-38	*****	IIID-1	*****
I-27	*****	II-31	*****	III-39	*****	IIIE-1	*****
I-28	*****	II-32	*****	III-40	*****	IIIE-2	*****
I-29	*****	II-33	*****	III-41	*****	IIIE-3	*****
I-30	*****	II-34	*****	III-42	*****	IV-1	*****
I-31	*****	II-35	*****	III-43	*****	IV-2	*****
I-32	*****	II-36	*****	III-44	*****	IV-3	*****

Cmpd #	IC ₅₀ IL-1 β Inhibition	Cmpd #	IC ₅₀ IL-1 β Inhibition	Cmpd	IC ₅₀ IL-1 β Inhibition	Cmpd #	IC ₅₀ IL-1 β Inhibition
I-33	***	II-37	*****	III-45	***	V-1	***
I-34	****	II-38	***	III-46	*	V-2	***
I-35	****	II-39	***	III-47	***	V-3	***
I-36	*****	II-40	****	III-48	****	VI-1	****
I-37	****	II-41	****	III-49	****	VI-2	***
I-38	***	II-42	***	III-50	***	VI-3	****
I-39	***	II-43	***	III-51	****	VI-4	***
I-40	***	II-44	**	III-52	****	VI-5	****
I-41	***	II-45	***	III-53	*	VI-6	**
I-42	**	II-46	****	III-54	****	VI-7	***
I-43	****	II-47	*****	III-55	****	VI-8	****
I-44	****	II-48	****	III-56	**	VI-9	****
I-45	****	II-49	****	III-57	****	VI-10	**
I-46	****	II-50	****	III-58	**	VI-11	****
I-47	****	II-51	****	III-59	*	VI-12	***
I-48	****	II-52	****	III-60	*	VI-13	****
I-49	****	II-53	*****	III-61	***	VI-14	****
I-50	*****	II-54	***	III-62	***	VI-15	**
I-51	****	II-55	***	III-63	***	VI-16	****
I-52	****	II-56	***	III-64	***	VI-17	*****
I-53	****	II-57	****	III-65	*****	VI-18	****
I-54	****	II-58	*****	III-66	***	VI-19	*****
I-55	***	II-59	*****	III-67	*****	VI-20	***
I-56	****	II-60	****	III-68	****	VIA-1	***
I-57	***	II-61	****	III-69	***	VIA-2	***
I-58	***	II-62	****	III-70	***	VIA-3	***
I-59	***	IIA-1	***	III-71	***	VIA-4	***
I-60	***	IIB-1	****	III-72	*****	VIA-5	***
I-61	***	IIB-2	****	III-73	****	VIA-6	***
I-62	***	IIC-1	*****	III-74	***	VIB-1	****
I-63	***	IIC-2	*****	III-75	****	VIB-2	****
I-64	***	IIC-3	****	III-76	****	VIB-3	**
I-65	****	IIC-4	****	III-77	****	VIB-4	***
I-66	****	IIC-5	*****	III-78	*****	VIB-5	****
I-67	****	IID-1	*****	III-79	****	VIB-6	***
I-68	***	IIE-1	****	III-80	****	VII-1	***
I-69	***	IIF-1	****	III-81	*****	VII-2	***
I-70	***	IIF-2	****	III-82	****	VII-3	***
I-71	****	IIF-3	****	III-83	****	VII-4	****
I-72	****	IIG-1	****	III-84	*****	VII-5	****
I-73	***	III-1	*****	III-85	*****	VII-6	***
I-74	****	III-2	****	III-86	***	VII-7	*
I-75	****	III-3	***	III-87	***	VII-8	***
I-76	***	III-4	****	III-88	****	VII-9	****
I-77	***	III-5	***	III-89	****	VII-10	****
I-78	*****	III-6	***	III-90	***	VII-11	****
I-79	****	III-7	****	III-91	*	VIII-1	***
IA-1	****	III-8	****	III-92	***	VIII-2	****
II-1	***	III-9	****	III-93	*****	VIII-3	****
II-2	***	III-10	****	III-94	****	VIII-4	***

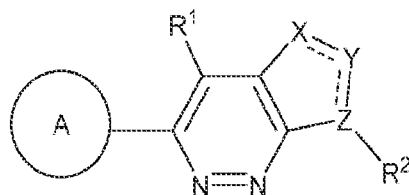
Cmpd #	IC ₅₀ IL-1 β Inhibition	Cmpd #	IC ₅₀ IL-1 β Inhibition	Cmpd	IC ₅₀ IL-1 β Inhibition	Cmpd #	IC ₅₀ IL-1 β Inhibition
II-3	****	III-11	****	III-95	***		
II-4	***	III-12	****	III-96	****		

Without regard to whether a document cited herein was specifically and individually indicated as being incorporated by reference, all documents referred to herein are incorporated by reference into the present application for any and all purposes to the same extent as if each individual reference was fully set forth herein.

Having now fully described the subject matter of the claims, it will be understood by those having ordinary skill in the art that the same can be performed within a wide range of equivalents without affecting the scope of the subject matter or particular aspects described herein. It is intended that the appended claims be interpreted to include all such equivalents.

WHAT IS CLAIMED IS:

1. A compound having the structure of Formula (I):



(I)

wherein:

X and Y are independently selected from CR', C(R')(R'), N, NR'', O and S;

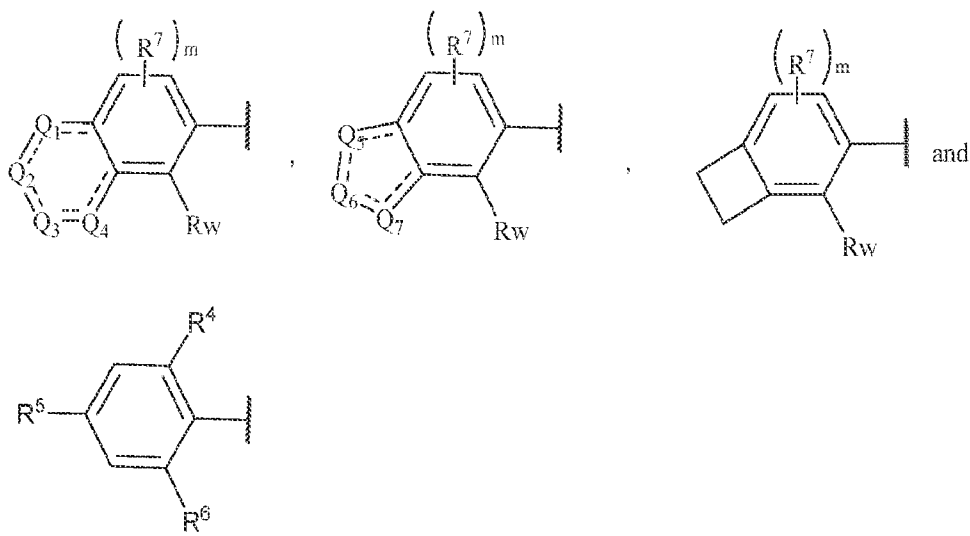
Z is selected from N, C and CH;

--- is a single or double bond;

R' is independently selected from H, halogen, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, OH, C₃₋₆cycloalkyl, C₁₋₄alkoxy, C₃₋₆cycloalkoxy, halo-C₁₋₄alkoxy, C₁₋₄alkyl-thio, SH and halo-C₁₋₄alkyl;

R'' is independently selected from H, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, C₃₋₆cycloalkyl, and halo-C₁₋₄alkyl;

Ring A is selected from the group consisting of:



Q₁, Q₂, Q₃, Q₄, Q₅, Q₆, and Q₇ are independently selected from CR⁸, C(R⁸) (R⁸), O, N, NR⁹, and S;

R_w is selected from OH, C₁₋₄alkyl, halo-C₁₋₄alkyl, C₃₋₆cycloalkyl, C₁₋₄alkoxy and halo-C₁₋₄alkoxy;

5 R¹ is selected from H, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, C₁₋₄alkyl-C₃₋₆cycloalkyl, C₁₋₄alkyl-C₃₋₆heterocycle, C₃₋₆cycloalkyl optionally substituted with halogen or R³, C₃₋₆heterocycle optionally substituted with halogen, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, halo-C₁₋₄alkyl, C₁₋₄alkyl-thio, C₁₋₄alkoxy, C₃₋₆cycloalkoxy, and halo-C₁₋₄alkoxy;

10 R² is independently selected from C₃₋₇ cycloalkyl, C₁₋₄alkyl-aryl, C₁₋₄alkyl-C₃₋₇cycloalkyl, C₁₋₄alkyl-C₃₋₇heterocycle, C₃₋₇ heterocycle and aryl, wherein said C₃₋₇ heterocycle is a saturated or partially unsaturated 4 to 8 membered monocyclic ring system having 1, 2, 3 heteroatom ring members independently selected from N, O and S, wherein said R² is optionally substituted with R³;

15 R³ is independently selected from C₁₋₄alkyl, deuterio-C₁₋₄alkyl, halogen, OH, halo-C₁₋₄alkyl, CN, C₃₋₆ cycloalkyl, C₁₋₄alkoxy, C₃₋₆cycloalkoxy, halo- C₁₋₄alkoxy, and hydroxy-C₁₋₄alkyl;

20 R⁴, R⁵ and R⁶ are independently selected from H, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, OH, C₁₋₄alkoxy, halo-C₁₋₄alkyl, halo-C₁₋₄alkoxy, halogen, C₁₋₄alkyl-thio, C₃₋₆cycloalkyl, C₃₋₆cycloalkoxy, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, and CN, wherein R⁴ is not H when R¹ is H;

R⁷ is independently selected from H, C₁₋₄alkyl, halo-C₁₋₄alkyl, C₃₋₆cycloalkyl, C₁₋₄alkoxy, halo-C₁₋₄alkoxy, halogen and CN;

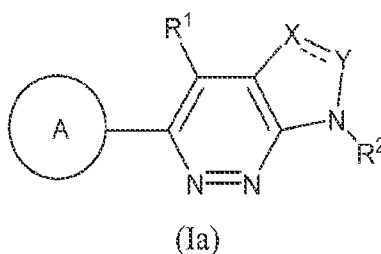
R⁸ is selected from H, C₁₋₄ alkyl, halogen and halo-C₁₋₄alkyl, C₁₋₄alkoxy and halo-C₁₋₄alkoxy;

25 R⁹ is selected from H, C₁₋₄ alkyl, halo-C₁₋₄alkyl, C₃₋₆cycloalkyl; and
m is 0, 1 or 2;

wherein a form of the compound may be selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

30

2. The compound of claim 1, wherein the compound is a compound of Formula (Ia)



or a form thereof, wherein:

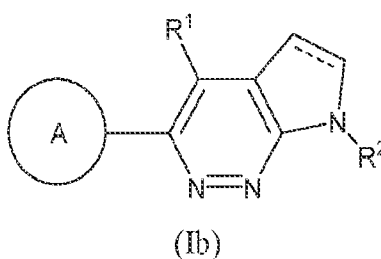
X and Y are independently selected from CR', C(R')(R');

R' is independently selected from H, halogen, C₁₋₄alkyl, OH, C₃₋₆cycloalkyl, C₁₋₄alkoxy, C₁₋₄alkyl-thio, CN, SH and halo-C₁₋₄alkyl; and

R¹ is selected from H, CH₃, CH₃CH₂, cyclopropyl, cyclobutyl, isopropyl, tertbutyl, CF₃,

NHCH₃, CHF₂, SCH₃, OCH₃ and .

3. The compound of claim 1, wherein the compound is a compound of Formula (Ib)

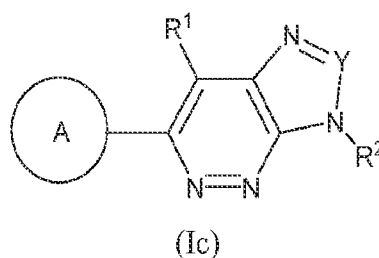


or a form thereof, wherein:

R¹ is selected from H, CH₃, CH₃CH₂, cyclopropyl, cyclobutyl, isopropyl, tertbutyl, CF₃,

NHCH₃, CHF₂, SCH₃, OCH₃ and .

4. The compound of claim 1, wherein the compound is a compound of Formula (Ic)

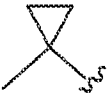


or a form thereof, wherein:

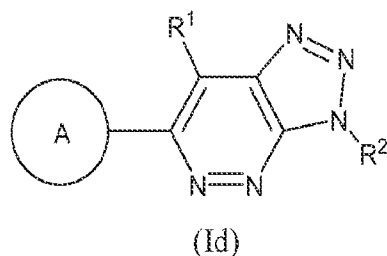
Y is selected from CR';

R' is independently selected from H, C₁₋₄alkyl, and halo-C₁₋₄alkyl; and

R¹ is selected from H, CH₃, CH₃CH₂, cyclopropyl, cyclobutyl, isopropyl, tertbutyl, CF₃,

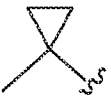
NHCH₃, CHF₂, SCH₃, OCH₃ and .

5. The compound of claim 1, wherein the compound is a compound of Formula (Id)

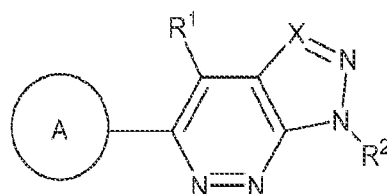


or form thereof, wherein:

R¹ is selected from H, CH₃, CH₃CH₂, cyclopropyl, cyclobutyl, isopropyl, tertbutyl, CF₃,

NHCH₃, CHF₂, SCH₃, OCH₃ and .

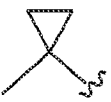
6. The compound of claim 1, wherein the compound is a compound of Formula (Ie)



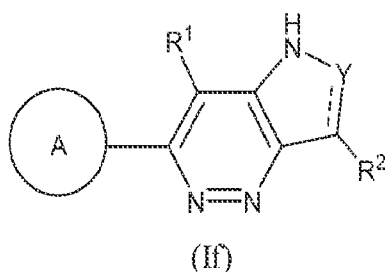
(Ie)

or form thereof, wherein:

X is CR';

R' is selected from H and CH₃; and5 R¹ is selected from H, CH₃, CH₃CH₂, cyclopropyl, cyclobutyl, isopropyl, tertbutyl, CF₃,NHCH₃, CHF₂, SCH₃, OCH₃ and .

7. The compound of claim 1, wherein the compound is a compound of Formula (If)



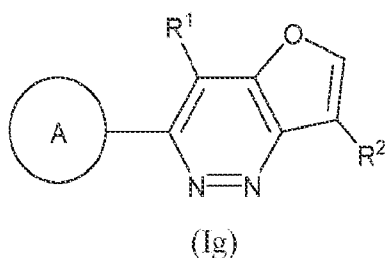
or form thereof, wherein:

Y is selected from CH and CH₂;

--- is a single or double bond; and

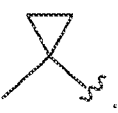
R¹ is selected from H, CH₃, CH₃CH₂, cyclopropyl, cyclobutyl, isopropyl, tertbutyl, CF₃,15 NHCH₃, CHF₂, SCH₃, OCH₃ and .

8. The compound of claim 1, wherein the compound is a compound of Formula (Ig)

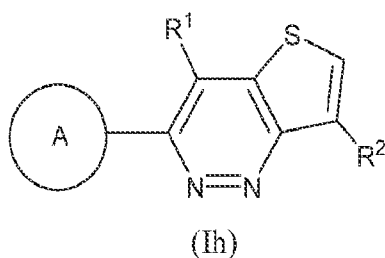


or form thereof, wherein:

R^1 is selected from H, CH_3 , CH_3CH_2 , cyclopropyl, cyclobutyl, isopropyl, tertbutyl, CF_3 ,

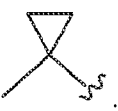
$NHCH_3$, CHF_2 , SCH_3 , OCH_3 and .

9. The compound of claim 1, wherein the compound is a compound of Formula (Ih)

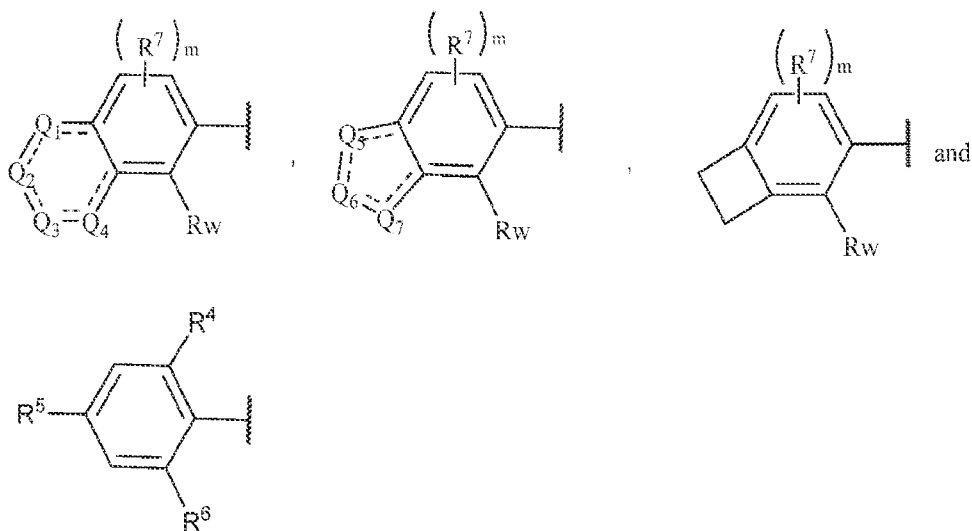


or form thereof, wherein:

R^1 is selected from H, CH_3 , CH_3CH_2 , cyclopropyl, cyclobutyl, isopropyl, tertbutyl, CF_3 ,

$NHCH_3$, CHF_2 , SCH_3 , OCH_3 and .

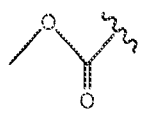
10. The compound according to claim 1, wherein Ring A is selected from:



Q_1 , Q_2 , Q_3 , Q_4 , Q_5 , Q_6 , and Q_7 are independently selected from CR^8 , $C(R^8)$ (R^8), O, N, NR^9 and S;

R_w is selected from OH, $C_{1-4}alkyl$, halo- $C_{1-4}alkyl$, $C_{3-6}cycloalkyl$, $C_{1-4}alkoxy$ and halo- $C_{1-4}alkoxy$;

R^4 , R^5 and R^6 are independently selected from H, CH_3 , CH_2CH_3 , OH, OCH_3 , CF_3 , OCF_3 ,

CH_2CF_3 , $OCHF_2$, F, Cl, Br, cyclopropyl, isopropyl, SCH_3 , $N(CH_3)_2$, CN and  ;

R^7 is independently selected from H, OH, C_{1-4} alkyl, halo- C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{1-4} alkoxy and halo- C_{1-4} alkoxy, halogen and CN;

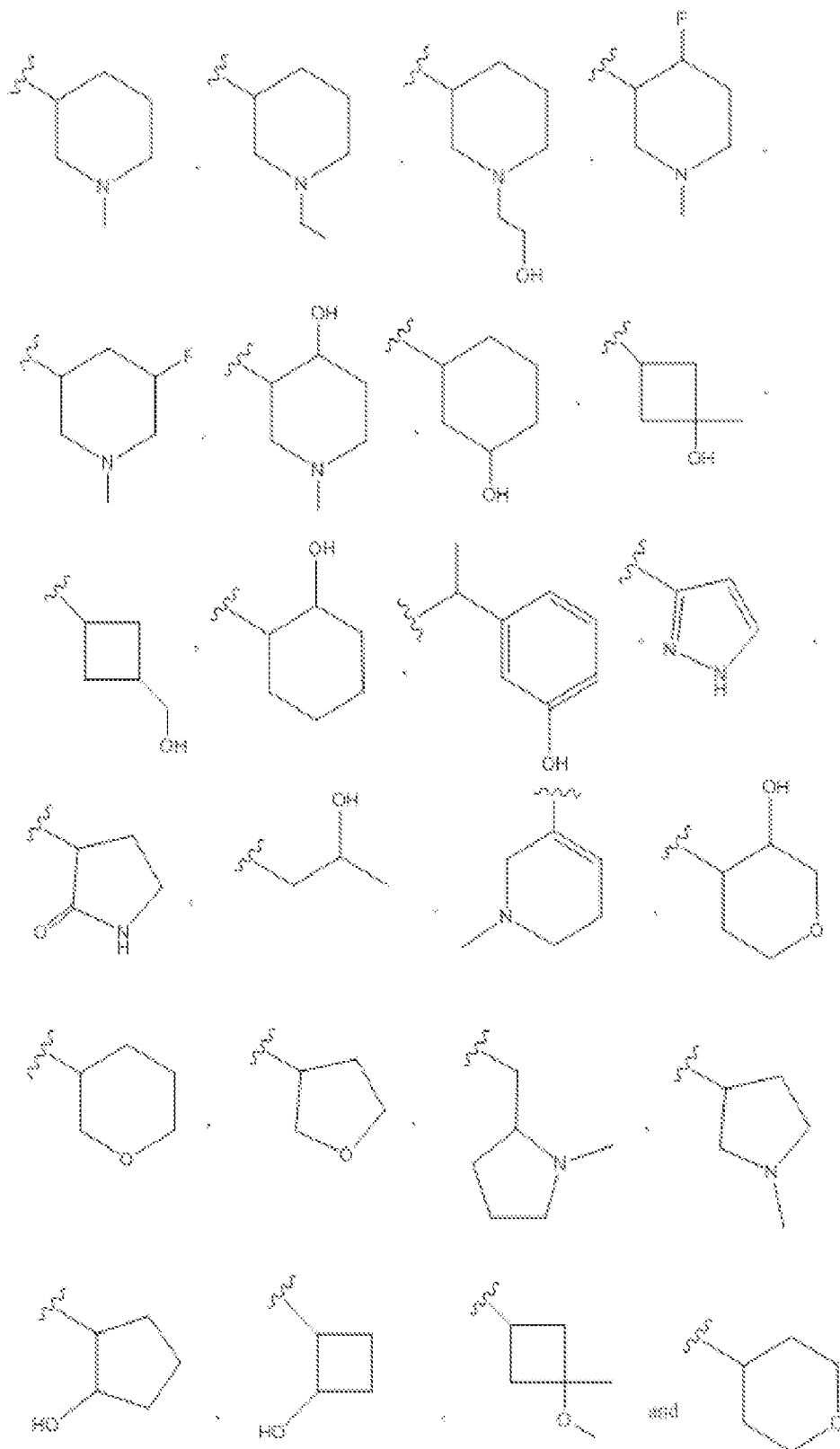
5 R^8 is selected from H, C_{1-4} alkyl, halogen and halo- C_{1-4} alkyl, C_{1-4} alkoxy, halo- C_{1-4} alkoxy;

R^9 is selected from H, C_{1-4} alkyl, halo- C_{1-4} alkyl, C_{3-6} cycloalkyl; and

m is 0, 1 or 2.

11. The compound according to claim 1, wherein R^2 is selected from:

10



wherein a form of the compound may be selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

5

12. A compound or form thereof, selected from the group consisting of:

2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

10

2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-methyl-phenol;

2-[4-isopropyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

15

5-cyclopropyl-2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]phenol;

2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

20

2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-3-fluoro-5-methyl-phenol;

2-[7-[(3R)-1-ethyl-3-piperidyl]-4-(1-methylcyclopropyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

25

2-[4-cyclobutyl-7-[(3R)-1-ethyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

2-[4-(3,3-difluorocyclobutyl)-7-[(3R)-1-ethyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

2-[4-cyclobutyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

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2-[4-cyclobutyl-7-[(3R,5R)-5-fluoro-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

5-cyclopropyl-2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]phenol;

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2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-methoxy-phenol;

- 5-chloro-2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]phenol;
- 3,5-dimethyl-2-[7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]phenol;
- 5 3-methyl-2-[7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 3-methyl-2-[7-[(3R)-1-methylpyrrolidin-3-yl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 10 3-methyl-2-[7-(1-methyl-4-piperidyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 3-methyl-2-[5-methyl-7-[rac-(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 5-chloro-3-fluoro-2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]phenol;
- 15 5-chloro-2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]phenol;
- 3-methyl-2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 20 2-[4-cyclopropyl-7-[(3R)-1-(2-hydroxyethyl)-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 2-[4-cyclopropyl-7-(3-hydroxy-3-methyl-cyclobutyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 2-[(7R)-4-cyclopropyl-7-tetrahydropyran-3-yl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 25 3-methoxy-2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 2-(4-cyclopropyl-7-tetrahydrofuran-3-yl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 30 2-[4-cyclopropyl-7-[(1R,2R)-2-hydroxycyclohexyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 2-[4-cyclopropyl-7-(1H-pyrazol-3-yl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 2-[4-cyclopropyl-7-[1-(3-hydroxyphenyl)ethyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 35 2-[(7R)-4-cyclopropyl-7-[(2S)-2-hydroxycyclohexyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

- 2-[4-cyclopropyl-7-[(1R,3S)-3-hydroxycyclohexyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-ethyl-phenol;
- 5 5-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]indan-4-ol;
- 5-methyl-2-[7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-3-(trifluoromethyl)phenol;
- 10 5-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol;
- 3-methoxy-2-[7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 3-methyl-2-[6-methyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 15 5-methyl-2-[6-methyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-3-(trifluoromethyl)phenol;
- 3-[2,4-bis(trifluoromethyl)phenyl]-4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazine;
- 20 3-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-4-(1-methylcyclopropyl)-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazine;
- 5-[7-[(3R,5R)-5-fluoro-1-methyl-3-piperidyl]-4-methyl-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 5-[7-[(3S,4R)-4-fluoro-1-methyl-3-piperidyl]-4-methyl-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 25 5-[7-(3-hydroxy-3-methyl-cyclobutyl)-4-methyl-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 5-[4-cyclopropyl-7-[(3R,5R)-5-fluoro-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 30 5-[7-[(3R,5R)-5-fluoro-1-methyl-3-piperidyl]-4-methyl-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol;
- 5-[4-cyclopropyl-7-[(3R,5R)-5-fluoro-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol;
- 5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol;
- 35 5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;

- 5-[7-[(1R,2R)-2-hydroxycyclohexyl]-4-methyl-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 5-[7-[(3S,4R)-3-hydroxytetrahydropyran-4-yl]-4-methyl-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 5 [5-[7-(3-hydroxy-3-methyl-cyclobutyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- 5-[7-[(1R,2R)-2-hydroxycyclohexyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- 10 5-[4-cyclopropyl-7-(3-hydroxy-3-methyl-cyclobutyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 5-[7-[(3S,4R)-3-hydroxytetrahydropyran-4-yl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- 2-[7-(3-hydroxy-3-methyl-cyclobutyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-methyl-3-(trifluoromethyl)phenol;
- 15 3-[(7R)-7-tetrahydrofuran-3-yl-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]bicyclo[4.2.0]octa-1,3,5-trien-2-ol;
- (3S,4R)-4-[3-(2-hydroxy-3-bicyclo[4.2.0]octa-1,3,5-trienyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-7-yl]tetrahydropyran-3-ol;
- 20 5-[7-(3-hydroxy-3-methyl-cyclobutyl)-5-methyl-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- (3S,4R)-4-[(5R)-3-[2-hydroxy-4-methyl-6-(trifluoromethyl)phenyl]-5-methyl-5,6-dihydropyrrolo[2,3-c]pyridazin-7-yl]tetrahydropyran-3-ol;
- (3S,4R)-4-[(5S)-3-[2-hydroxy-4-methyl-6-(trifluoromethyl)phenyl]-5-methyl-5,6-dihydropyrrolo[2,3-c]pyridazin-7-yl]tetrahydropyran-3-ol;
- 25 2-[7-[(1R,2R)-2-hydroxycyclohexyl]-5-methyl-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-methyl-3-(trifluoromethyl)phenol;
- 5-[7-[(1R,2R)-2-hydroxycyclohexyl]-5-methyl-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- 30 5-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-7-fluoro-benzofuran-4-ol;
- 5-[7-[(1R,2R)-2-hydroxycyclopentyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- 5-[7-(3-hydroxy-3-methyl-cyclobutyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-2,3-dihydrobenzofuran-4-ol;
- 35 2-[7-(3-methoxy-3-methyl-cyclobutyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;

- 2-[7-(3-methoxy-3-methyl-cyclobutyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-methyl-3-(trifluoromethyl)phenol;
- 5-[7-(3-methoxy-3-methyl-cyclobutyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- 5 6-(difluoromethyl)-5-[7-(3-methoxy-3-methyl-cyclobutyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 6-(difluoromethyl)-5-[7-(3-hydroxy-3-methyl-cyclobutyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 10 6-methyl-5-[7-[rac-(1R,2S)-2-hydroxycyclobutyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 6-methyl-5-[7-[rac-(1R,2R)-2-hydroxycyclobutyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 6-(difluoromethyl)-5-[7-[(3S,4R)-3-hydroxytetrahydropyran-4-yl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 15 3-[7-[(1R,2R)-2-hydroxycyclohexyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-4-methyl-bicyclo[4.2.0]octa-1,3,5-trien-2-ol;
- 3-(difluoromethyl)-2-[7-(3-hydroxy-3-methyl-cyclobutyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-methyl-phenol;
- 20 5-[7-(3-hydroxy-3-methyl-cyclobutyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-6-(2,2,2-trifluoroethyl)benzofuran-4-ol;
- 5-[7-[1-(3-hydroxyphenyl)ethyl]-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- 2-[7-[(3R)-1-methyl-3-piperidyl]-4-(trifluoromethyl)-5,6-dihydropyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 25 5-chloro-2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]phenol;
- 5-cyclopropyl-2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]phenol;
- 30 2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-5-methyl-phenol;
- 2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-5-methoxy-phenol;
- 35 2-[4-cyclopropyl-7-[(3R)-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-5-methoxy-phenol;

- 2-[4-cyclopropyl-7-[(3R)-1-ethyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-5-methoxy-phenol;
- 2-[4-cyclopropyl-7-[(3R)-1-(2-hydroxyethyl)-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-5-methoxy-phenol;
- 5 2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 5-chloro-2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]phenol;
- 5-methoxy-2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]phenol;
- 10 5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]benzothiophen-4-ol;
- 5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]indan-4-ol;
- 5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol;
- 15 5-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 3-methyl-2-[6-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 20 5-methyl-2-[6-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-3-(trifluoromethyl)phenol;
- 2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-4-fluoro-5-methyl-phenol;
- 6-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-2-fluoro-3-methyl-phenol;
- 25 5-methyl-2-[7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-3-(trifluoromethyl)phenol;
- 5-[7-(3-hydroxy-3-methyl-cyclobutyl)-4-methyl-pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 30 3-methyl-2-[7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 5-[7-[(3S,4R)-4-fluoro-1-methyl-3-piperidyl]-4-methyl-pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 5-[7-[(3R,5R)-5-fluoro-1-methyl-3-piperidyl]-4-methyl-pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 35

- 5-[7-[(3S,4R)-1-ethyl-4-fluoro-3-piperidyl]-4-methyl-pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 3-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]bicyclo[4.2.0]octa-1(6),2,4-trien-2-ol;
- 5 [5-[7-(3-hydroxy-3-methyl-cyclobutyl)-5-methyl-pyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- 5-[7-[(1R,2R)-2-hydroxycyclohexyl]-4-methyl-pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 10 5-[7-[(3S,4R)-3-hydroxytetrahydropyran-4-yl]-4-methyl-pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 5-[7-(3-hydroxy-3-methyl-cyclobutyl)-5-methyl-pyrrolo[2,3-c]pyridazin-3-yl]-2,6-dimethyl-benzofuran-4-ol;
- 6-methyl-5-[7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol;
- 15 6-methyl-5-[7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 5-[7-(3-hydroxy-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- 5-[7-[(1R,2R)-2-hydroxycyclohexyl]pyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- 20 5-[4,5-dimethyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol;
- 5-[7-(3-hydroxy-3-methyl-cyclobutyl)-5-methyl-pyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-2,3-dihydrobenzofuran-4-ol;
- 6-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-7-ol;
- 25 6-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-7-ol;
- 2-fluoro-5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 5-[4-ethyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 30 2-[7-(3-hydroxy-3-methyl-cyclobutyl)-5-methyl-pyrrolo[2,3-c]pyridazin-3-yl]-5-methyl-3-(trifluoromethyl)phenol;
- 3-[4-ethyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]bicyclo[4.2.0]octa-1,3,5-trien-2-ol;
- 1,1-dimethyl-5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]indan-4-ol;
- 35

- (3S,4R)-4-[3-[2-hydroxy-4-methyl-6-(trifluoromethyl)phenyl]-5-methyl-pyrrolo[2,3-c]pyridazin-7-yl]tetrahydropyran-3-ol;
- 2-[7-[(1R,2R)-2-hydroxycyclohexyl]-5-methyl-pyrrolo[2,3-c]pyridazin-3-yl]-5-methyl-3-(trifluoromethyl)phenol;
- 5 5-[7-[(3S,4R)-3-hydroxytetrahydropyran-4-yl]pyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- 5-[4,5-dimethyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 10 7-fluoro-5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 5-[7-[(1R,2R)-2-hydroxycyclopentyl]pyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- 5-[7-[(1R,2R)-2-hydroxycyclohexyl]-5-methyl-pyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- 15 5-[7-(3-hydroxy-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-2,3-dihydrobenzofuran-4-ol;
- 6-(difluoromethyl)-5-[7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 20 2-[7-[(1R,2R)-2-hydroxycyclopentyl]pyrrolo[2,3-c]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;
- 2-[7-(3-methoxy-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;
- 2-[7-(3-methoxy-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazin-3-yl]-5-methyl-3-(trifluoromethyl)phenol;
- 25 6-(difluoromethyl)-5-[7-(3-methoxy-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 6-(difluoromethyl)-5-[7-(3-hydroxy-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 6-ethyl-5-[7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 30 6-methyl-5-[7-[rac-(1R,2S)-2-hydroxycyclobutyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 6-methyl-5-[7-[rac-(1R,2R)-2-hydroxycyclobutyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 35 5-chloro-3-(difluoromethyl)-2-[7-(3-hydroxy-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazin-3-yl]phenol;

- 2-[7-[(3R)-1-methyl-3-piperidyl]-4-(trifluoromethyl)pyrrolo[2,3-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 5- [7-(3-hydroxy-3-methyl-cyclobutyl)-5-(trifluoromethyl)pyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- 5 2-[7-(3-hydroxy-3-methyl-cyclobutyl)-5-(trifluoromethyl)pyrrolo[2,3-c]pyridazin-3-yl]-5-methyl-3-(trifluoromethyl)phenol;
- 5-[5-(difluoromethyl)-7-(3-hydroxy-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- 10 3-(4-hydroxy-6-methyl-benzofuran-5-yl)-7-(3-hydroxy-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazine-5-carbaldehyde;
- 2-[5-(difluoromethyl)-7-(3-hydroxy-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;
- 5-[5-(difluoromethyl)-7-(3-fluoro-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- 15 6-(difluoromethyl)-5-[5-(difluoromethyl)-7-(3-hydroxy-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 3-(4-hydroxy-6-methyl-benzofuran-5-yl)-7-(3-hydroxy-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazine-5-carbonitrile;
- 20 5-[5-cyclopropyl-7-(3-hydroxy-3-methyl-cyclobutyl)pyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- 5-[5-fluoro-4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 5-[5-fluoro-4-methyl-7-[(3R)-1-methyl-3-piperidyl]pyrrolo[2,3-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol;
- 25 5-[5-fluoro-7-(3-hydroxy-3-methyl-cyclobutyl)-4-methyl-pyrrolo[2,3-c]pyridazin-3-yl]benzofuran-4-ol;
- 5-[7-(3-hydroxy-3-methyl-cyclobutyl)-5-iodo-pyrrolo[2,3-c]pyridazin-3-yl]-6-methyl-2,3-dihydrobenzofuran-4-ol;
- 30 2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 3-methyl-2-[7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 5-chloro-3-fluoro-2-[6-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]phenol;
- 35 5-chloro-2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]phenol;

- 2-[4-isopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 3-methyl-2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 5 2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;
- 2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 10 2-[4-cyclopropyl-7-[(3R)-1-(2-hydroxyethyl)-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 5-chloro-3-fluoro-2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]phenol;
- 2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-3,5-dimethyl-phenol;
- 15 5-methoxy-2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]phenol;
- 2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-methoxy-phenol;
- 20 4-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-3-hydroxy-benzonitrile;
- 2-[4-cyclopropyl-7-(3-hydroxy-3-methyl-cyclobutyl)imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- (3S,4R)-4-[4-cyclopropyl-3-[2-hydroxy-4-(trifluoromethyl)phenyl]imidazo[4,5-c]pyridazin-7-yl]tetrahydropyran-3-ol;
- 25 2-[4-cyclopropyl-7-(3-hydroxy-3-methyl-cyclobutyl)imidazo[4,5-c]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;
- (3S,4R)-3-[4-cyclopropyl-3-[2-hydroxy-4-(trifluoromethyl)phenyl]imidazo[4,5-c]pyridazin-7-yl]-1-methyl-piperidin-4-ol;
- 30 (3S,4R)-3-[4-cyclopropyl-3-[2-hydroxy-4-(trifluoromethyl)phenyl]imidazo[4,5-c]pyridazin-7-yl]-1-ethyl-piperidin-4-ol;
- (3S,4R)-3-[4-cyclopropyl-3-[2-hydroxy-4-(trifluoromethyl)phenyl]imidazo[4,5-c]pyridazin-7-yl]-1-(2-hydroxyethyl)piperidin-4-ol;
- 5-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]indan-4-ol;
- 5-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol;
- 35 3,5-dimethyl-2-[7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]phenol;

- 5-methyl-2-[7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-3-(trifluoromethyl)phenol;
- 5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol;
- 5 [5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]indan-4-ol;
- 3-methoxy-2-[7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol;
- 10 5-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol;
- 5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzothiophen-4-ol;
- 5-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzothiophen-4-ol;
- 15 5-[4-cyclopropyl-7-(3-hydroxy-3-methyl-cyclobutyl)imidazo[4,5-c]pyridazin-3-yl]benzothiophen-4-ol;
- 2-[7-[(3R)-1-ethyl-3-piperidyl]-4-methyl-imidazo[4,5-c]pyridazin-3-yl]-5-methoxyphenol;
- 2-[4-cyclopropyl-7-[(1R,2R)-2-hydroxycyclohexyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 20 2-[4-cyclopropyl-7-[(2R)-2-hydroxypropyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 7-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]quinolin-8-ol;
- 25 2-[4-cyclopropyl-7-[3-(hydroxymethyl)cyclobutyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 2-[7-(3-hydroxy-3-methyl-cyclobutyl)-4-methyl-imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 7-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]quinolin-8-ol;
- 30 5-[4-cyclopropyl-7-[rac-(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-2-methyl-1,3-benzoxazol-4-ol;
- 3-methoxy-2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 2-[(3R)-3-[3-[2-hydroxy-4-(trifluoromethyl)phenyl]-4-methyl-imidazo[4,5-c]pyridazin-7-yl]-1-piperidyl]acetonitrile;
- 35

- 2-[(3R)-3-[3-(4-hydroxybenzofuran-5-yl)-4-methyl-imidazo[4,5-c]pyridazin-7-yl]-1-piperidyl]acetonitrile;
- 2-[(3R)-3-[4-cyclopropyl-3-[2-hydroxy-4-(trifluoromethyl)phenyl]imidazo[4,5-c]pyridazin-7-yl]-1-piperidyl]acetonitrile;
- 5 5-[4-cyclopropyl-7-[rac-(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-2-methyl-1,3-benzothiazol-4-ol;
- 2-methyl-5-[4-methyl-7-[rac-(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-1,3-benzoxazol-4-ol;
- 10 2-methyl-5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-1,3-benzothiazol-4-ol;
- 5-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-2-fluorobenzothiophen-4-ol;
- 2-[(3R)-3-[4-cyclopropyl-3-(4-hydroxybenzofuran-5-yl)imidazo[4,5-c]pyridazin-7-yl]-1-piperidyl]acetonitrile;
- 15 2-[7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)benzene-1,3-diol;
- 2-fluoro-5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzothiophen-4-ol;
- 20 6-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzothiophen-7-ol;
- 6-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-2,3-dihydro-1,4-benzodioxin-5-ol;
- 2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)benzene-1,3-diol;
- 25 5-[4-methyl-7-[(3R)-1-(2,2,2-trifluoroethyl)-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol;
- 2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]naphthalen-1-ol;
- 5-[4-methyl-7-[(3R)-1-(oxetan-3-yl)-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol;
- 30 2-[4-cyclopropyl-7-[(3R)-1-(oxetan-3-yl)-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 6-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-2,3-dihydro-1,4-benzodioxin-5-ol;
- 6-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]quinolin-5-ol;
- 35 2-[4-ethyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

- 5-[7-[(3R)-1-methyl-3-piperidyl]-4-(3-thienyl)imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol;
- 5-[4,6-dimethyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol;
- 5 5-[4,6-dimethyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol;
- 6-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzothiophen-7-ol;
- 5-[4-ethyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]indan-4-ol;
- 10 3-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]bicyclo[4.2.0]octa-1(6),2,4-trien-2-ol;
- 5-[4-ethyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzothiophen-4-ol;
- 15 2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-4-fluoro-5-methyl-phenol;
- 6-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-2-fluoro-3-methyl-phenol;
- 2-[7-[(3R,5R)-5-fluoro-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-methyl-3-(trifluoromethyl)phenol;
- 20 5-[4-ethyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol;
- 5-[4-ethyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol;
- 2,2-difluoro-5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-1,3-benzodioxol-4-ol;
- 25 5-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-2,2-difluoro-1,3-benzodioxol-4-ol;
- 3-[4,6-dimethyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]bicyclo[4.2.0]octa-1,3,5-trien-2-ol;
- 2-[4-cyclopropyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-4-fluoro-5-(trifluoromethyl)phenol;
- 30 6-methyl-5-[7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol;
- 6-methyl-5-[7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol;
- 35 3-[4-ethyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]bicyclo[4.2.0]octa-1(6),2,4-trien-2-ol;

- 5-[7-(3-hydroxy-3-methyl-cyclobutyl)imidazo[4,5-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- 5-[7-(3-hydroxy-3-methyl-cyclobutyl)-4-methyl-imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol;
- 5 3-[7-(3-hydroxy-3-methyl-cyclobutyl)-4-methyl-imidazo[4,5-c]pyridazin-3-yl]bicyclo[4.2.0]octa-1(6),2,4-trien-2-ol;
- 2-[7-(3-hydroxy-3-methyl-cyclobutyl)imidazo[4,5-c]pyridazin-3-yl]-5-methyl-3-(trifluoromethyl)phenol;
- 10 2-[(3R)-3-[3-(4-hydroxy-6-methyl-benzofuran-5-yl)imidazo[4,5-c]pyridazin-7-yl]-1-piperidyl]acetonitrile;
- 6-methyl-5-[7-[(3R)-1-(2,2,2-trifluoroethyl)-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol;
- 7-fluoro-5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol;
- 15 7-fluoro-5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol;
- 6-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-7-ol;
- 3-hydroxy-5-methyl-4-[7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzonitrile;
- 20 2,2-dimethyl-6-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-3H-benzofuran-7-ol
- 1,1-dimethyl-5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]indan-4-ol
- 25 6-(difluoromethyl)-5-[7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol
- 5-[7-(3-hydroxy-3-methyl-cyclobutyl)imidazo[4,5-c]pyridazin-3-yl]-6-methyl-2,3-dihydrobenzofuran-4-ol;
- 2-[7-(3-hydroxy-3-methyl-cyclobutyl)imidazo[4,5-c]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;
- 30 5-[7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-6-(2,2,2-trifluoroethyl)benzofuran-4-ol;
- 6-(difluoromethyl)-5-[7-(3-hydroxy-3-methyl-cyclobutyl)imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol;
- 35 3-(difluoromethyl)-5-methyl-2-[7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]phenol;

- 5-chloro-3-(difluoromethyl)-2-[7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]phenol;
- 5-[7-(3,3-dimethyltetrahydropyran-4-yl)imidazo[4,5-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- 5 3-[7-[(1R,2R)-2-hydroxycyclohexyl]imidazo[4,5-c]pyridazin-3-yl]-4-methyl-bicyclo[4.2.0]octa-1,3,5-trien-2-ol;
- 6-(difluoromethyl)-5-[7-[(1R,2R)-2-hydroxycyclohexyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol;
- 10 5-[7-[(1R,2R)-2-hydroxycyclohexyl]imidazo[4,5-c]pyridazin-3-yl]-6-(2,2,2-trifluoroethyl)benzofuran-4-ol;
- 6-ethyl-5-[7-(3-hydroxy-3-methyl-cyclobutyl)imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol;
- 5-[7-[(1R,2R)-2-hydroxycyclohexyl]imidazo[4,5-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- 15 5-[7-[(3S,4R)-3-hydroxytetrahydropyran-4-yl]imidazo[4,5-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- (3S,4R)-4-[3-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]imidazo[4,5-c]pyridazin-7-yl]tetrahydropyran-3-ol;
- 20 5-[7-(2,2-dimethyltetrahydropyran-4-yl)imidazo[4,5-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- 6-ethyl-5-[7-[(1R,2R)-2-hydroxycyclohexyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol;
- 6-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]tetralin-5-ol;
- 25 3,3-dimethyl-5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]indan-4-ol;
- 2,3-dimethyl-6-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]phenol;
- 2-[4-methoxy-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-3-methyl-5-(trifluoromethyl)phenol;
- 30 5-[4-(cyclopropoxy)-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol;
- 5-[4-ethoxy-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol;
- 5-[4-methoxy-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol;
- 35 5-[4-(azetidin-1-yl)-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol;

- 5-[4-(dimethylamino)-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol;
- 5-[4-(difluoromethyl)-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol;
- 5 2-[4-(difluoromethyl)-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 2-[4-(1-hydroxyethyl)-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 10 2-[4-(hydroxymethyl)-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 5-chloro-3-[7-(3-hydroxy-3-methyl-cyclobutyl)-4-methyl-imidazo[4,5-c]pyridazin-3-yl]bicyclo[4.2.0]octa-1(6),2,4-trien-2-ol;
- 7-chloro-5-[7-(3-hydroxy-3-methyl-cyclobutyl)-4-methyl-imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol;
- 15 7-chloro-5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]imidazo[4,5-c]pyridazin-3-yl]benzofuran-4-ol;
- 2-[7-cyclopropyl-3-[(3R)-1-methyl-3-piperidyl]triazolo[4,5-c]pyridazin-6-yl]-5-(trifluoromethyl)phenol;
- 5-chloro-3-fluoro-2-[3-[(3R)-1-methyl-3-piperidyl]triazolo[4,5-c]pyridazin-6-yl]phenol;
- 20 3-methyl-2-[3-[(3R)-1-methyl-3-piperidyl]triazolo[4,5-c]pyridazin-6-yl]-5-(trifluoromethyl)phenol;
- 3,5-dimethyl-2-[7-(1-methyl-3-piperidyl)-5H-pyrrolo[3,2-c]pyridazin-3-yl]phenol;
- 5-[4-cyclopropyl-7-(1-methyl-3-piperidyl)-5H-pyrrolo[3,2-c]pyridazin-3-yl]indan-4-ol;
- 2-[4-cyclopropyl-7-(1-methyl-3-piperidyl)-5H-pyrrolo[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 25 3,5-dimethyl-2-[7-(1-methyl-3-piperidyl)thieno[3,2-c]pyridazin-3-yl]phenol;
- 3,5-dimethyl-2-[7-(1-methyl-3,6-dihydro-2H-pyridin-5-yl)thieno[3,2-c]pyridazin-3-yl]phenol;
- 2-[4-methyl-7-[(3S)-1-methyl-3-piperidyl]thieno[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 30 2-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]thieno[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 3-methyl-2-[7-[(3S)-1-methyl-3-piperidyl]thieno[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;

- 3-methyl-2-[7-[(3R)-1-methyl-3-piperidyl]thieno[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 2-[4-methyl-7-(1-methyl-3,6-dihydro-2H-pyridin-5-yl)thieno[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 5 2-[4-cyclopropyl-7-(1-methyl-3-piperidyl)thieno[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 3-methyl-2-[4-methyl-7-(1-methyl-3-piperidyl)thieno[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 10 5-[4-methyl-7-[(3S)-1-methyl-3-piperidyl]thieno[3,2-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol;
- 5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]thieno[3,2-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol;
- 5-[4-methyl-7-(1-methyl-3-piperidyl)thieno[3,2-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol;
- 15 6-methyl-5-[7-(1-methyl-3-piperidyl)thieno[3,2-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol;
- 5-[4-methyl-7-[(3R)-1-methyl-3-piperidyl]thieno[3,2-c]pyridazin-3-yl]indan-4-ol;
- 5-[4-methyl-7-[(3S)-1-methyl-3-piperidyl]thieno[3,2-c]pyridazin-3-yl]indan-4-ol;
- 20 3-[4-methyl-7-(1-methyl-3-piperidyl)thieno[3,2-c]pyridazin-3-yl]bicyclo[4.2.0]octa-1(6),2,4-trien-2-ol;
- 6-methyl-5-[7-(1-methyl-3-piperidyl)thieno[3,2-c]pyridazin-3-yl]benzofuran-4-ol;
- 5-[4-methyl-7-(1-methyl-3-piperidyl)thieno[3,2-c]pyridazin-3-yl]indan-4-ol;
- 6-methyl-5-[7-[(3S)-1-methyl-3-piperidyl]thieno[3,2-c]pyridazin-3-yl]benzofuran-4-ol;
- 6-methyl-5-[7-[(3R)-1-methyl-3-piperidyl]thieno[3,2-c]pyridazin-3-yl]benzofuran-4-ol;
- 25 5-[7-(2-hydroxyphenyl)thieno[3,2-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- 5-[7-(2-fluorophenyl)thieno[3,2-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- 6-methyl-5-[7-[2-(trifluoromethoxy)phenyl]thieno[3,2-c]pyridazin-3-yl]benzofuran-4-ol;
- 6-methyl-5-[7-[2-(trifluoromethyl)phenyl]thieno[3,2-c]pyridazin-3-yl]benzofuran-4-ol;
- 6-methyl-5-[7-(o-tolyl)thieno[3,2-c]pyridazin-3-yl]benzofuran-4-ol;
- 30 5-[7-(2-chlorophenyl)thieno[3,2-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- 5-[7-(3,6-dihydro-2H-pyran-4-yl)thieno[3,2-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- 6-methyl-5-(7-tetrahydropyran-4-ylthieno[3,2-c]pyridazin-3-yl)benzofuran-4-ol;

- 5-methyl-2-(7-tetrahydropyran-3-ylthieno[3,2-c]pyridazin-3-yl)-3-(trifluoromethyl)phenol;
- 6-methyl-5-(7-tetrahydrofuran-3-ylthieno[3,2-c]pyridazin-3-yl)benzofuran-4-ol;
- 5-[7-(2,5-dihydrofuran-3-yl)thieno[3,2-c]pyridazin-3-yl]-6-methyl-benzofuran-4-ol;
- 5 6-methyl-5-(7-tetrahydropyran-3-ylthieno[3,2-c]pyridazin-3-yl)benzofuran-4-ol;
- 3-methyl-2-[7-(1-methyl-3,6-dihydro-2H-pyridin-5-yl)furo[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 3-methyl-2-[7-(1-methyl-3-piperidyl)furo[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 10 2-[4-methyl-7-(1-methyl-3-piperidyl)furo[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 5-[4-methyl-7-(1-methyl-3-piperidyl)furo[3,2-c]pyridazin-3-yl]indan-4-ol;
- 5-[4-methyl-7-(1-methyl-3-piperidyl)furo[3,2-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol;
- 15 3-methyl-2-[4-methyl-7-(1-methyl-3-piperidyl)furo[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 3-methyl-2-[7-[(3R)-1-methyl-3-piperidyl]furo[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 20 3-methyl-2-[7-[(3S)-1-methyl-3-piperidyl]furo[3,2-c]pyridazin-3-yl]-5-(trifluoromethyl)phenol;
- 5-[4-methyl-7-(1-methyl-3-piperidyl)furo[3,2-c]pyridazin-3-yl]benzofuran-4-ol;
- 6-methyl-5-[7-(1-methyl-3-piperidyl)furo[3,2-c]pyridazin-3-yl]-2,3-dihydrobenzofuran-4-ol;
- 6-methyl-5-[7-(1-methyl-3-piperidyl)furo[3,2-c]pyridazin-3-yl]benzofuran-4-ol;
- 25 2-[4-cyclopropyl-1-(1-methyl-3-piperidyl)pyrazolo[3,4-c]pyridazin-5-yl]-5-methyl-phenol;
- 3-[4-cyclopropyl-1-(1-methyl-3-piperidyl)pyrazolo[3,4-c]pyridazin-5-yl]bicyclo[4.2.0]octa-1,3,5-trien-2-ol;
- 5-[4-cyclopropyl-1-(1-methyl-3-piperidyl)pyrazolo[3,4-c]pyridazin-5-yl]benzofuran-4-ol;
- 30 and
- 2-[4-cyclopropyl-1-(1-methyl-3-piperidyl)pyrazolo[3,4-c]pyridazin-5-yl]-5-(trifluoromethyl)phenol

wherein a form of the compound may be selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

5 13. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1 or claim 12 wherein said compounds comprise a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers.

10 14. A method for treating or ameliorating a disease modulated by NLRP3 in a subject in need thereof comprising, administering to the subject an effective amount of the compound according to claim 1 or claim 12.

15 15. A method of treating or ameliorating a disease modulated by NLRP3 according to claim 14 wherein said disease is selected from Alzheimer disease, Frontotemporal dementia (FTD), Huntington's disease, Parkinson's disease, Perioperative neurocognitive disorders, Post-cardiac arrest cognitive impairment, Poststroke cognitive impairment, Sepsis, Sepsis associated encephalopathy, Subarachnoid hemorrhage, Macular Degeneration, Retinal neovascularization, Uveitis, Colitis, Endothelial dysfunction, Gout, Pseudogout, Graft-versus-host-disease (GvHD), Systemic lupus erythematosus-lupus nephritis, Cryopyrin-associated periodic syndromes
20 (CAPS), Cystic fibrosis, Sickle-cell disease, VCP-associated disease, Liver fibrosis, Nonalcoholic fatty liver disease (NASH), muscle atrophy, inherited and acquired myopathies, Duchenne Muscular Dystrophy (DMD), Hyperalgesia, Multiple sclerosis-associated neuropathic pain, Acute Kidney Injury, Chronic crystal nephropathy, Chronic Kidney Disease, asthma and allergic airway inflammation Diabetes-associated atherosclerosis, Diabetic encephalopathy,
25 Diabetic kidney disease, Islet transplantation rejection, Obesity-associated renal disease, Oxalate-induced nephropathy, Renal fibrosis, Renal hypertension, Type I diabetes, Type II diabetes, Psoriasis, Hidradenitis suppurativa, Atherosclerosis and Cytokine Release Syndrome (CRS).

30 16. The method of claim 14, wherein the effective amount of the compound is in a range of from about 0.001 mg/kg/day to about 500 mg/kg/day.

17. A compound according to claim 1 or claim 12, wherein said pharmaceutically acceptable salt thereof, for use in treating or ameliorating a disease modulated by NLRP3 is selected from Alzheimer disease, Frontotemporal dementia (FTD), Huntington's disease, Parkinson's disease,
5 Perioperative neurocognitive disorders, Post-cardiac arrest cognitive impairment, Poststroke cognitive impairment, Sepsis, Sepsis associated encephalopathy, Subarachnoid hemorrhage, Macular Degeneration, Retinal neovascularization, Uveitis, Colitis, Endothelial dysfunction, Gout, Pseudogout, Graft-versus-host-disease (GvHD), Systemic lupus erythematosus-lupus nephritis, Cryopyrin-associated periodic syndromes (CAPS), Cystic fibrosis, Sickle-cell disease, VCP-associated disease, Liver fibrosis,
10 Nonalcoholic fatty liver disease (NASH), muscle atrophy, inherited and acquired myopathies, Hyperalgesia, Multiple sclerosis-associated neuropathic pain, Acute Kidney Injury, Chronic crystal nephropathy, Chronic Kidney Disease, asthma and allergic airway inflammation Diabetes-associated atherosclerosis, Diabetic encephalopathy, Diabetic kidney disease, Islet transplantation rejection, Obesity-associated renal disease, Oxalate-induced nephropathy, Renal fibrosis, Renal hypertension, Type I
15 diabetes, Type II diabetes, Psoriasis, Hidradenitis suppurativa, Atherosclerosis and Cytokine Release Syndrome (CRS).

18. Use of a compound according to claim 17, wherein the effective amount of the compound is in a range of from about 0.001 mg/kg/day to about 500 mg/kg/day.

19. Use of a compound according to claim 1 or claim 12 in the preparation of a pharmaceutical composition for treating or ameliorating a disease modulated by NLRP3 in a subject in need thereof comprising, administering to the subject an effective amount of the compound or a form thereof in admixture with one or more of the pharmaceutically acceptable
25 excipients.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/086506

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D487/04 C07D491/04 C07D495/04 A61K31/4985 A61P25/00 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61P C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2021/209539 A1 (JANSSEN PHARMACEUTICA NV [BE]) 21 October 2021 (2021-10-21) page 1, line 20 claims 1-2,16 -----	1-19
A	WO 2022/253326 A1 (TRANSTHERA SCIENCES NANJING INC [CN]) 8 December 2022 (2022-12-08) page 1, paragraph 1 claims 1,19-21 -----	1-19
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 3 April 2024		Date of mailing of the international search report 11/04/2024
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Fanni, Stefano

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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