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(71) Applicant: BRISTOL-MYERS SQUIBB COMPANY

[US/US]; Route 206 and Province Line Road, Princeton,
New Jersey 08543 (US).

(72) Inventors: YOON, David S.; c/o Bristol-Myers Squibb Company, Route 206 and Province Line Road, Princeton, New Jersey 08543 (US). LIU, Chunjian; c/o Bristol-Myers Squibb Company, Route 206 and Province Line Road, Princeton, New Jersey 08543 (US). REGUEIRO-REN, Alicia; c/o Bristol-Myers Squibb Company, Route 206 and Province Line Road, Princeton, New Jersey 08543 (US).

(74) Agent: GREENBLATT, Gary D. et al.; Bristol-Myers Squibb Company, Route 206 and Province Line Road, Princeton, New Jersey 08543 (US).

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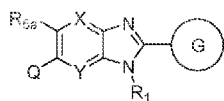
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(54) Title: SUBSTITUTED IMIDAZOPYRIDINYL COMPOUNDS USEFUL AS INHIBITORS OF TLR9



(1)

(57) Abstract: Disclosed are compounds of Formulas (I): (Formulas (I)) or a salt thereof, wherein X, Y, Q, G, R₁, and R_{5a} are defined herein. Also disclosed are methods of using such compounds as inhibitors of TLR9, and pharmaceutical compositions comprising such compounds. These compounds are useful in treating, preventing, or slowing fibrotic diseases.

SUBSTITUTED IMIDAZOPYRIDINYL COMPOUNDS USEFUL AS INHIBITORS
OF TLR9

CROSS REFERENCE

- 5 This application claims the benefit of U.S. Provisional Application Serial No. 63/311,612 filed February 18, 2022 and U.S. Provisional Application Serial No. 63/379,340 filed October 13, 2022, each of which is incorporated herein in its entirety.

DESCRIPTION

- 10 The present invention generally relates to substituted imidazopyridinyl compounds useful as inhibitors of signaling through Toll-like receptor 9 (TLR9). Provided herein are substituted imidazopyridinyl compounds, compositions comprising such compounds, and methods of their use. The invention further pertains to pharmaceutical compositions containing at least one compound according to the invention
- 15 that are useful for the treatment of conditions related to TLR9 modulation, such as fibrotic diseases, and methods of inhibiting the activity of TLR9 in a mammal.

- Toll-like receptors (TLRs) are transmembrane proteins having the ability to initiate an inflammatory response upon recognition of pattern-associated molecular patterns (PAMPs) or microbe-associated molecular patterns (MAMPs). A total of 10
- 20 human TLRs have been identified and can be located in the cell surface or, as in the case of TLR7, 8 and 9, in the endolysosomes. TLR9 recognizes unmethylated single-stranded DNA containing cytosine-phosphate-guanine (CpG) motifs that are typically found in bacterial and mitochondrial DNA (mtDNA). TLR9 may contribute to fibrogenesis by promoting inflammation via the MyD88-dependent signalling pathway that ultimately
- 25 mediates activation of IL-6, IFN- α , IL-1 β , and TNF- α among others cytokines. (Barton GM, Kagan JC (2009) *Nat. Rev. Immunol.* 9(8), 535–42; Li X, Jiang S, Tapping RI (2010) *Cytokine* 49(1), 1–9).

- TLR9 levels are higher in lung biopsies of rapid idiopathic pulmonary fibrosis (IPF) progressors than in the healthy or stable IPF progressors (Sci. Transl. Med. 2010,
- 30 2(57):57ra82). Circulating mtDNA, the ligand for TLR9 has recently been identified as a mechanism-based prognostic biomarker of IPF (Am J. Resp. and Crit. Care Med. 2017,

196(12), 1502). In addition, it has been observed that TLR9 is up-regulated in human and murine non-alcoholic steatohepatitis (NASH) (Clin. Sci. 2017, 131(16), 2145), while hepatocyte mitochondrial DNA drives NASH via activation of TLR9 (J. Clin. Inv. 2016, 126(3), 859. Accordingly, inhibitors/antagonists of TLR9 are predicted to have efficacy
5 as novel therapeutic agents to treat fibrotic diseases.

TLR9 inhibition has been recognized as a potential route to therapies for fibrotic diseases including idiopathic pulmonary fibrosis (Trujillo et al. *Sci. Transl. Med.* 2010, 2(57):57ra82; Yoshizaki et al. *Ann Rheum Dis.* 2016 Oct;75(10):1858-65), non-alcoholic steatohepatitis (Garcia-Martinez et al. *J Clin Invest* 2016, 126: 859–864; Gabele et al.
10 *Biochem Biophys Res Commun.* 2008;376:271–276), hepatic injury (Shaker et al. *Biochem Pharmacol.* 2016. 112:90-101; Hoeque et al. *J. Immun.* 2013, 190:4297-304), and scleroderma (systemic sclerosis or SSc) (Yoshizaki et al. *Ann Rheum Dis.* 2016 Oct;75(10):1858-65); as well as heart failure (Oka et al. *Nature* 485, pages251–255(2012)), and hypertension (McCarthy et al. *Cardiovascular Research*, 2015, Pages
15 119–130).

There remains a need for compounds useful as inhibitors of TLR9. Additionally, there remains a need for compounds useful as inhibitors of TLR9 that have selectivity over TLR7 or TLR8.

In view of the conditions that may benefit by treatment involving modulation of
20 Toll-like receptors, it is immediately apparent that new compounds capable of inhibiting TLR9 and methods of using these compounds could provide substantial therapeutic benefits to a wide variety of patients.

Applicants have found potent compounds that have activity as TLR9 inhibitors. Further, applicants have found compounds that have activity as TLR9 inhibitors and are
25 selective over TLR7 or TLR8. These compounds are provided to be useful as pharmaceuticals with desirable stability, bioavailability, therapeutic index, and toxicity values that are important to their drugability.

SUMMARY OF THE INVENTION

30 The present invention relates to a new class of substituted imidazopyridinyl compounds found to be effective inhibitors of signaling through TLR9. These compounds are provided to be useful as pharmaceuticals with desirable stability,

bioavailability, therapeutic index, and toxicity values that are important to their drugability.

The present invention provides compounds of Formula (I) that are useful as inhibitors of signaling through Toll-like receptor 9 and are useful for the treatment of fibrotic diseases, or stereoisomers, N-oxides, tautomers, pharmaceutically acceptable salts, solvates or prodrugs thereof.

The present invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and at least one of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof.

The present invention also provides a method for inhibition of Toll-like receptor 9 comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof.

The present invention also provides a method for treating fibrotic diseases, comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof.

The present invention also provides a method of treating a disease or disorder associated with Toll-like receptor 9 activity, the method comprising administering to a mammal in need thereof, at least one of the compounds of Formula (I) or salts, solvates, and prodrugs thereof.

The present invention also provides processes and intermediates for making the compounds of Formula (I) including salts, solvates, and prodrugs thereof.

The present invention also provides at least one of the compounds of Formula (I) or salts, solvates, and prodrugs thereof, for use in therapy.

The present invention also provides the use of at least one of the compounds of Formula (I) or salts, solvates, and prodrugs thereof, for the manufacture of a medicament for the treatment of prophylaxis of Toll-like receptor 9 related conditions, such as fibrotic diseases, autoimmune diseases, or inflammatory diseases.

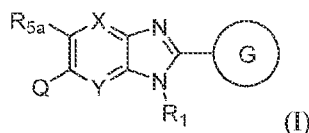
The compound of Formula (I) and compositions comprising the compounds of Formula (I) may be used in treating, preventing, or curing various Toll-like receptor 9

- related conditions. Pharmaceutical compositions comprising these compounds are useful for treating, preventing, or slowing the progression of diseases or disorders in a variety of therapeutic areas, such as fibrotic diseases including nonalcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), idiopathic pulmonary fibrosis,
- 5 primary sclerosing cholangitis (PSC), and primary biliary cirrhosis (PBC).

These and other features of the invention will be set forth in expanded form as the disclosure continues.

DETAILED DESCRIPTION

- 10 The first aspect of the present invention provides at least one compound of Formula (I):

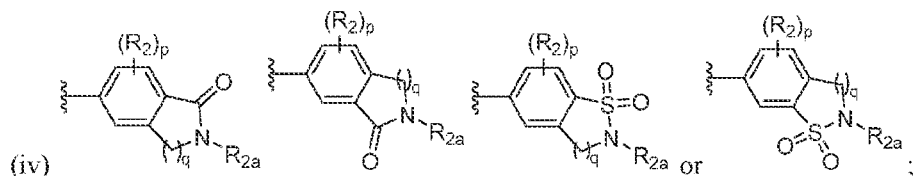
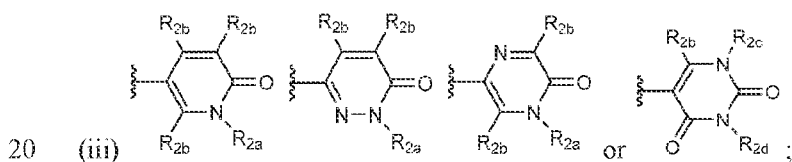
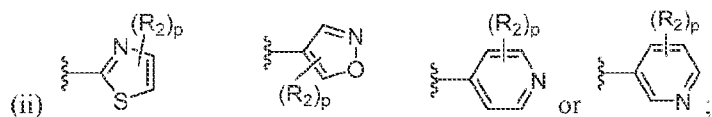


or a salt thereof, wherein:

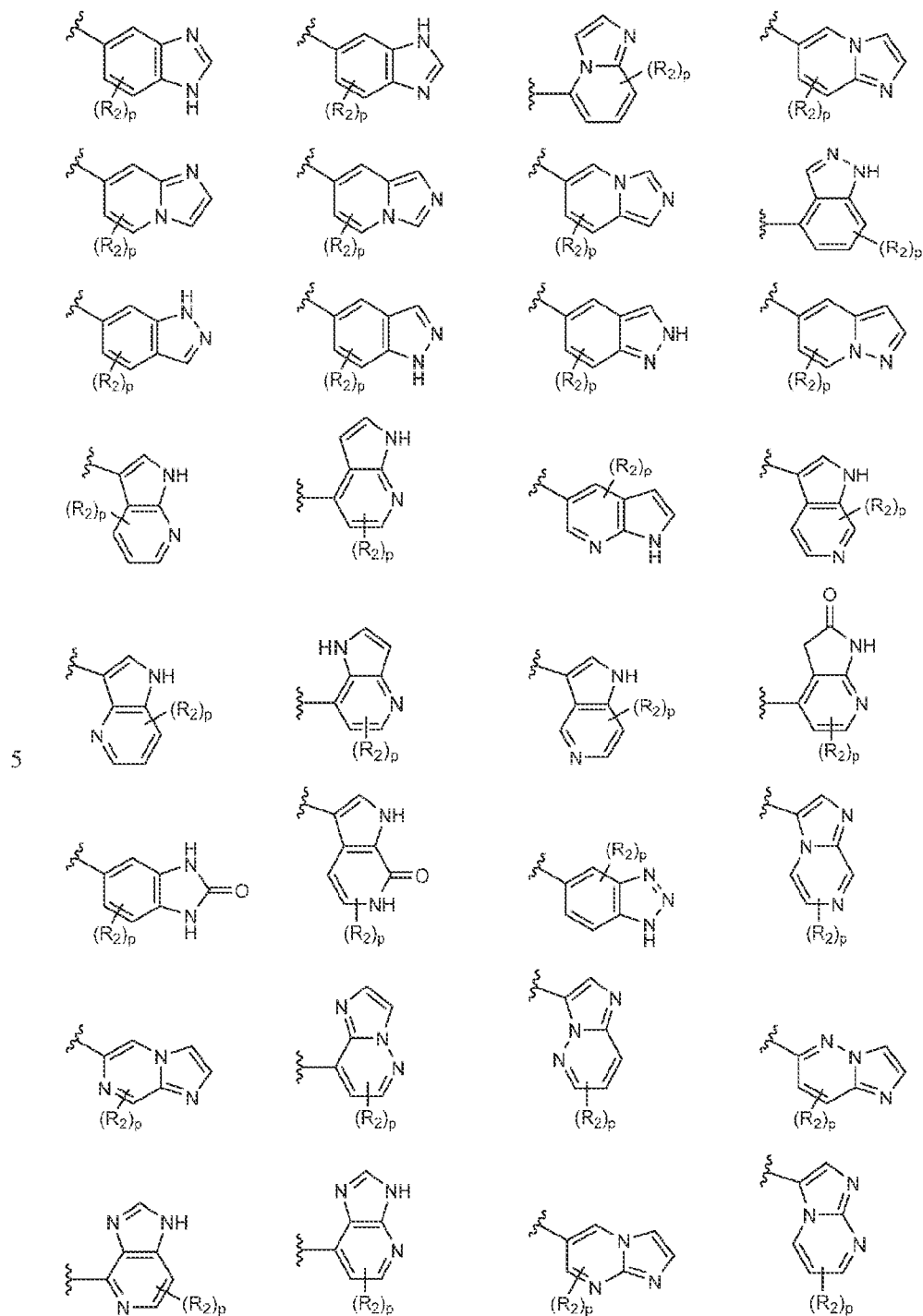
one of X and Y is N and the other of X and Y is CR_{5b};

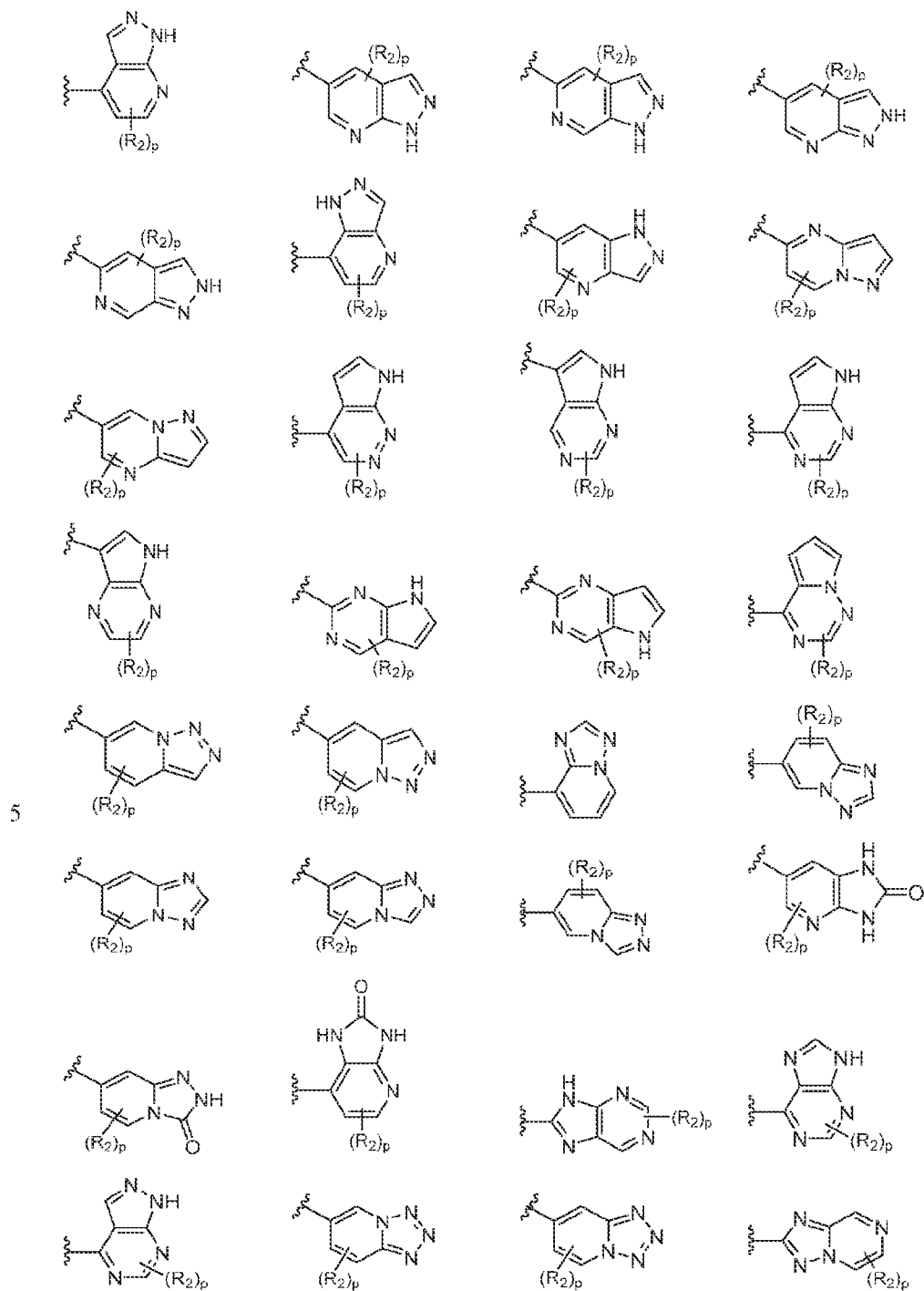
- 15 G is:

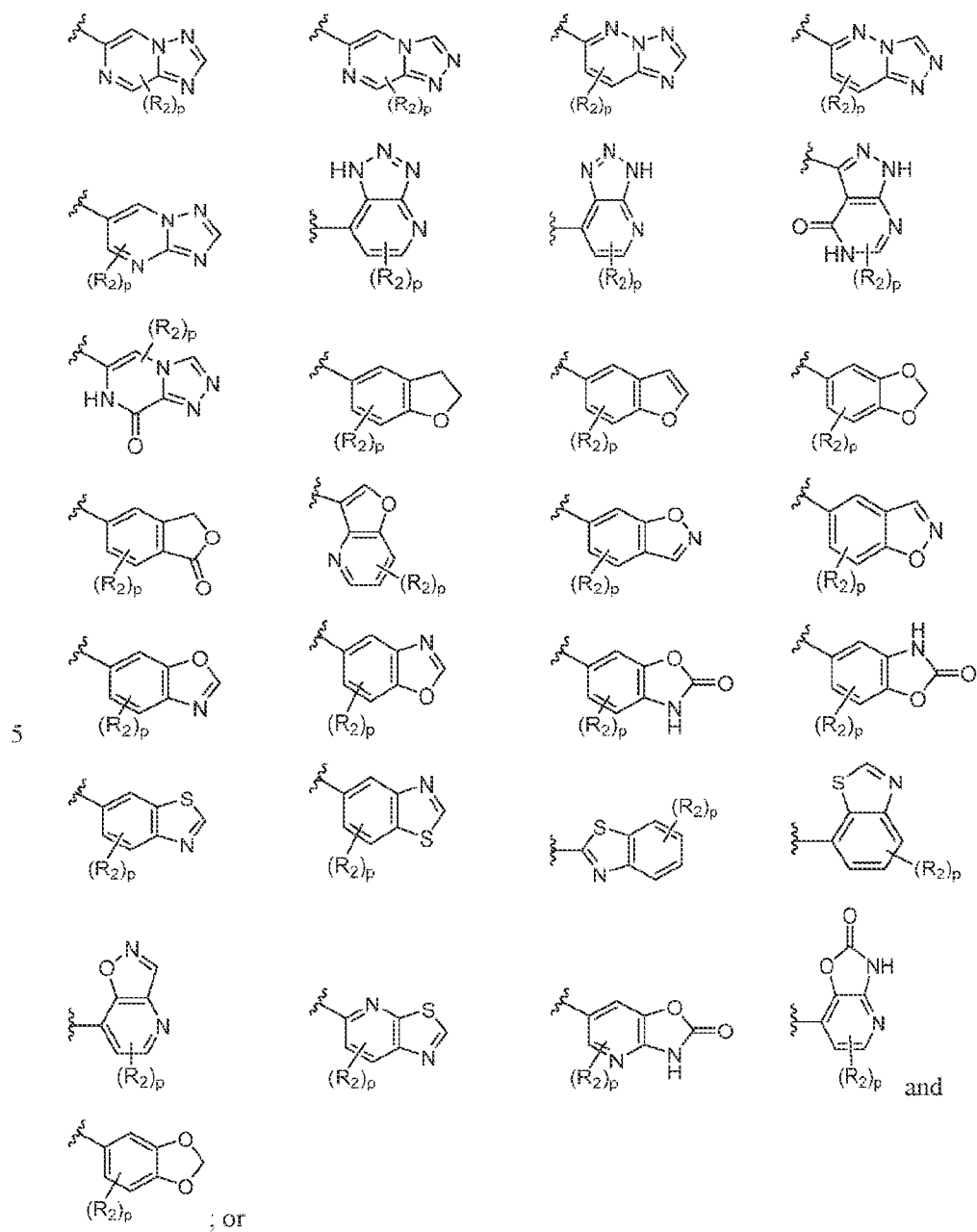
- (i) phenyl substituted with 1 to 3 substituents independently selected from F, Cl, Br, C₁₋₂ alkoxy, C₁₋₂ fluoroalkoxy, C₃₋₄ cycloalkyl, -C(O)NR_yR_y, -S(O)₂CH₃, -S(O)₂(phenyl), -S(O)₂NR_xR_x, and -S(O)(NH)NR_xR_x;



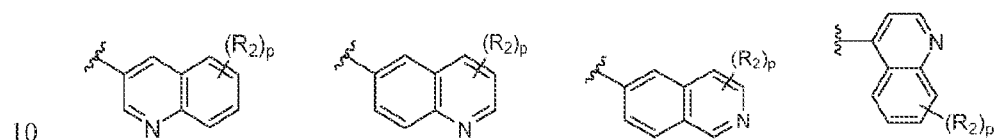
- (v) a 9-membered heterocyclic ring selected from:

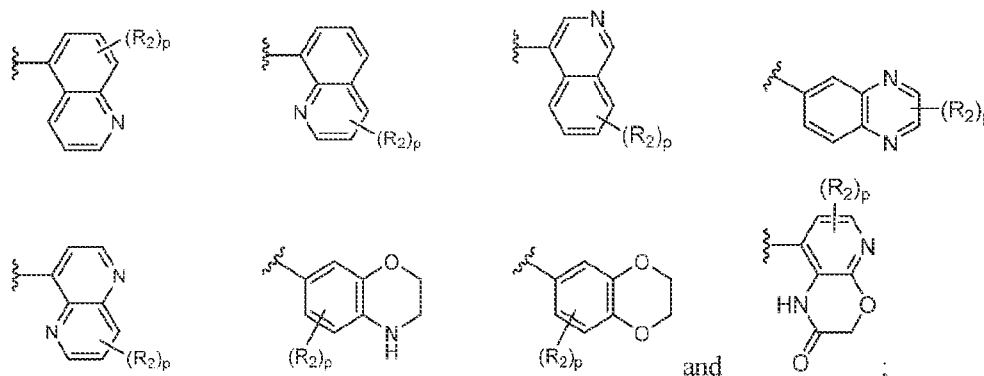






(vi) 10-membered heterocyclic ring selected from:





Q is piperidinyl, phenyl, tetrahydropyridinyl, pyridinyl, or azabicyclo[3.2.1]octanyl, each substituted with $-L-R_4$ and zero to 2 R_{4b} ;

5 L is a bond, $-(CR_xR_x)_{1-2}-$, or $-C(O)(CR_xR_x)_{0-2}-$;

R_1 is hydrogen, C_{1-3} alkyl, C_{1-2} fluoroalkyl, or C_{3-4} cycloalkyl;

each R_2 is independently halo, $-CN$, $-OH$, $-NO_2$, C_{1-4} alkyl, C_{1-2} fluoroalkyl, C_{1-2}

cyanoalkyl, C_{1-3} hydroxyalkyl, C_{1-3} aminoalkyl, $-O(CH_2)_{1-2}OH$, $-(CH_2)_{0-4}O(C_{1-4}$

alkyl), C_{1-3} fluoroalkoxy, $-O(CH_2)_{1-2}OC(O)(C_{1-3}$ alkyl), $-O(CH_2)_{1-2}NR_xR_x$,

10 $-C(O)O(C_{1-3}$ alkyl), $-(CH_2)_{0-2}C(O)NR_yR_y$, $-C(O)NR_x(C_{1-5}$ hydroxyalkyl),

$-C(O)NR_x(C_{2-6}$ alkoxyalkyl), $-C(O)NR_x(C_{3-6}$ cycloalkyl), $-NR_yR_y$, $-NR_y(C_{1-3}$

fluoroalkyl), $-NR_y(C_{1-4}$ hydroxyalkyl), $-NR_xCH_2(\text{phenyl})$, $-NR_xS(O)_2(C_{3-6}$

cycloalkyl), $-NR_xC(O)(C_{1-3}$ alkyl), $-NR_xCH_2(C_{3-6}$ cycloalkyl), $-S(O)_2(C_{1-3}$ alkyl),

$-S(O)_2N(C_{1-3}$ alkyl) $_2$, $-S(O)(NH)N(C_{1-3}$ alkyl) $_2$, $-(CH_2)_{0-2}(C_{3-6}$ cycloalkyl),

15 $-(CH_2)_{0-2}(\text{phenyl})$, morpholinyl, dioxothiomorpholinyl, dimethyl pyrazolyl,

methylpiperidinyl, methylpiperazinyl, amino-oxadiazolyl, imidazolyl, triazolyl, or

$-C(O)(\text{thiazolyl})$;

R_{2a} is C_{1-6} alkyl, C_{1-3} fluoroalkyl, C_{1-6} hydroxyalkyl, C_{1-3} aminoalkyl, $-(CH_2)_{0-4}O(C_{1-3}$

alkyl), C_{3-6} cycloalkyl, $-(CH_2)_{1-3}C(O)NR_xR_x$, $-CH_2(C_{3-6}$ cycloalkyl), $-CH_2(\text{phenyl})$,

20 tetrahydrofuranlyl, tetrahydropyranlyl, or phenyl;

each R_{2b} is independently hydrogen, halo, $-CN$, $-NR_xR_x$, C_{1-6} alkyl, C_{1-3} fluoroalkyl,

C_{1-3} hydroxyalkyl, C_{1-3} fluoroalkoxy, $-(CH_2)_{0-2}O(C_{1-3}$ alkyl), $-(CH_2)_{0-3}C(O)NR_xR_x$,

$-(CH_2)_{1-3}(C_{3-6}$ cycloalkyl), $-C(O)O(C_{1-3}$ alkyl), $-C(O)NR_x(C_{1-3}$ alkyl),

$-\text{CR}_x=\text{CR}_x\text{R}_x$, or $-\text{CR}_x=\text{CH}(\text{C}_{3-6} \text{ cycloalkyl})$;

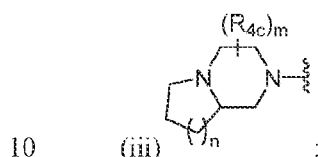
R_{2c} is R_{2a} or R_{2b} ;

R_{2d} is R_{2a} or R_{2b} ; provided that one of R_{2c} and R_{2d} is R_{2a} , and the other of R_{2c} and R_{2d} is R_{2b} ;

5 R_4 is:

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

(ii) pyrrolidinyl, piperidinyl, piperazinyl, pyridinyl, azepanyl, azaspiro[3.3]heptanyl, octahydrocyclopenta[c]pyrrolyl, diazaspiro[3.3]heptanyl, azabicyclo[3.2.1]octanyl, or hexahydropyrrolo[3,4-c]pyrrolyl, each substituted with zero to 2 R_{4a} ; or



each R_{4a} is independently C_{1-6} alkyl, C_{1-3} fluoroalkyl, C_{1-4} hydroxyalkyl, $-(\text{CH}_2)_{1-3}\text{OCH}_3$, C_{3-6} cycloalkyl, $-(\text{CH}_2)_{1-3}(\text{C}_{3-6} \text{ cycloalkyl})$, $-(\text{CH}_2)_{1-3}(\text{oxetanyl})$,

$-(\text{CH}_2)_{1-3}(\text{morpholinyl})$, $-\text{C}(\text{O})(\text{C}_{1-4} \text{ alkyl})$, $-\text{C}(\text{O})(\text{C}_{3-6} \text{ cycloalkyl})$, $-\text{C}(\text{O})(\text{phenyl})$,

$-\text{C}(\text{O})\text{CH}_2(\text{C}_{3-6} \text{ cycloalkyl})$, $-\text{C}(\text{O})\text{CH}_2(\text{phenyl})$, $-\text{C}(\text{O})\text{O}(\text{C}_{1-4} \text{ alkyl})$, $-\text{NR}_y\text{R}_y$,

15 $-\text{NR}_x(\text{C}_{3-6} \text{ cycloalkyl})$, azetidiny, oxetanyl, tetrahydropyranyl, pyrrolidinyl, phenyl, morpholinyl, or piperidinyl substituted with zero to 2 substituents selected from $-\text{OH}$ or $-\text{CH}_3$;

R_{4b} is F, Cl, $-\text{CN}$, or $-\text{CH}_3$;

each R_{4c} is independently C_{1-6} alkyl, C_{1-3} fluoroalkyl, $-\text{CH}_2(\text{C}_{3-6} \text{ cycloalkyl})$, $-\text{C}(\text{O})(\text{C}_{1-4}$
20 $\text{alkyl})$, $-\text{C}(\text{O})(\text{phenyl})$, $-\text{C}(\text{O})\text{CH}_2(\text{phenyl})$, $-\text{C}(\text{O})\text{OCH}_2\text{CH}_3$, or $\text{C}_{3-6} \text{ cycloalkyl}$;

R_{5a} is hydrogen, F, Cl, C_{1-2} alkyl, C_{1-2} fluoroalkyl, or cyclopropyl;

R_{5b} is hydrogen, F, Cl, C_{1-2} alkyl, C_{1-2} fluoroalkyl, or cyclopropyl;

each R_x is independently hydrogen or $-\text{CH}_3$;

each R_y is independently hydrogen or C_{1-6} alkyl;

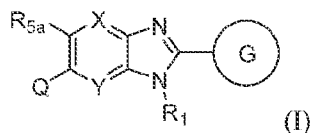
25 m is zero, 1, or 2;

n is zero, 1, or 2;

p is zero, 1, 2, 3, or 4; and

q is 1 or 2.

The second aspect of the present invention provides at least one compound of Formula (I):

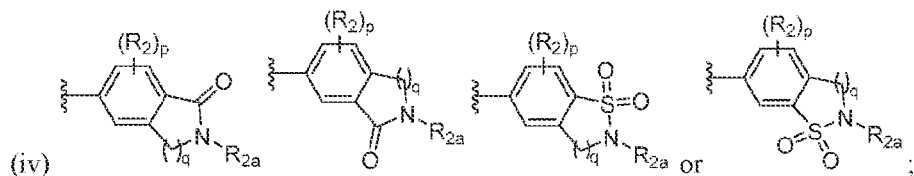
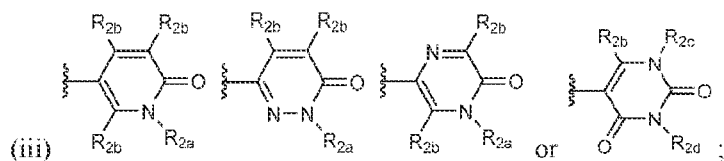
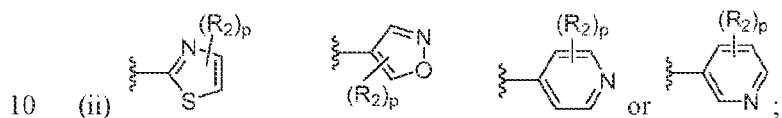


or a salt thereof, wherein:

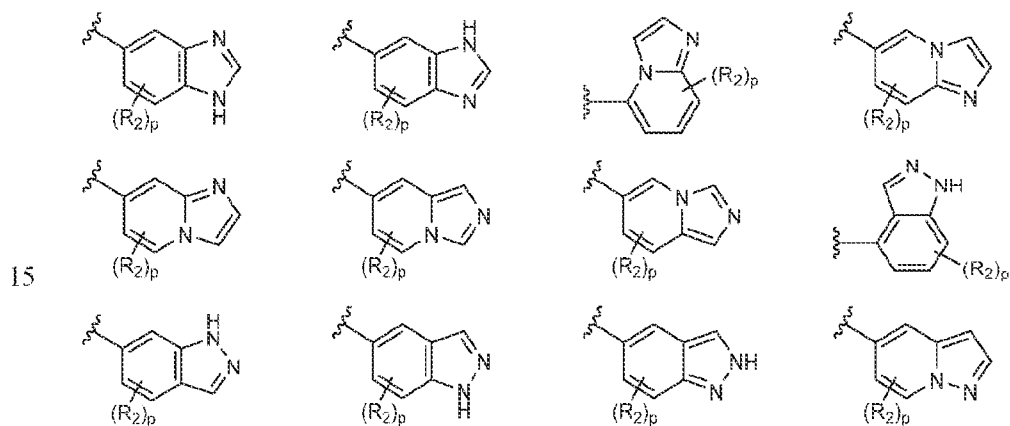
- 5 one of X and Y is N and the other of X and Y is CR_{5b};

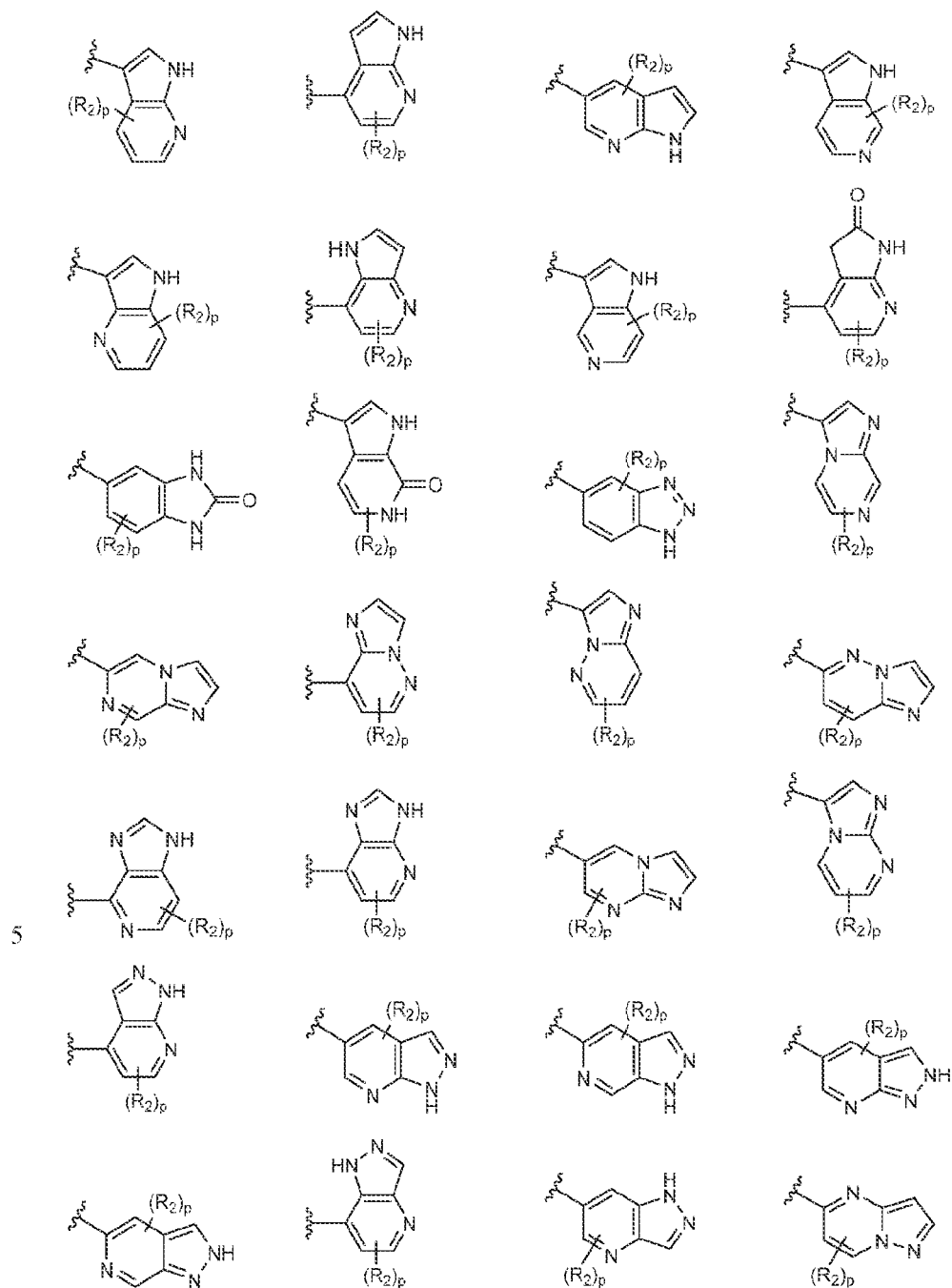
G is:

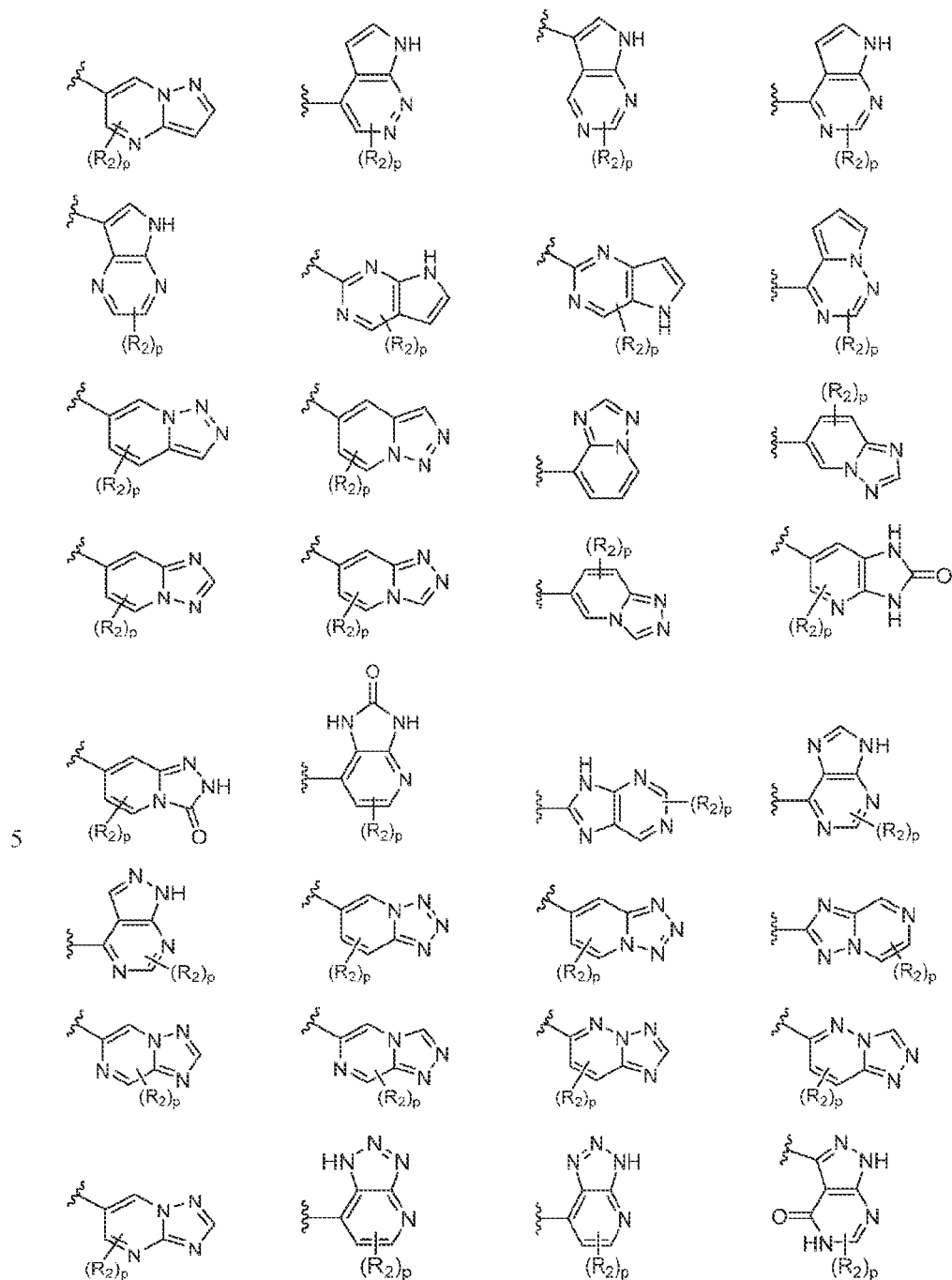
- (i) phenyl substituted with 1 to 3 substituents independently selected from F, Cl, Br, C₁₋₂ alkoxy, C₁₋₂ fluoroalkoxy, C₃₋₄ cycloalkyl, -C(O)NR_xR_y, -S(O)₂CH₃, -S(O)₂(phenyl), -S(O)₂NR_xR_x, and -S(O)(NH)NR_xR_x;

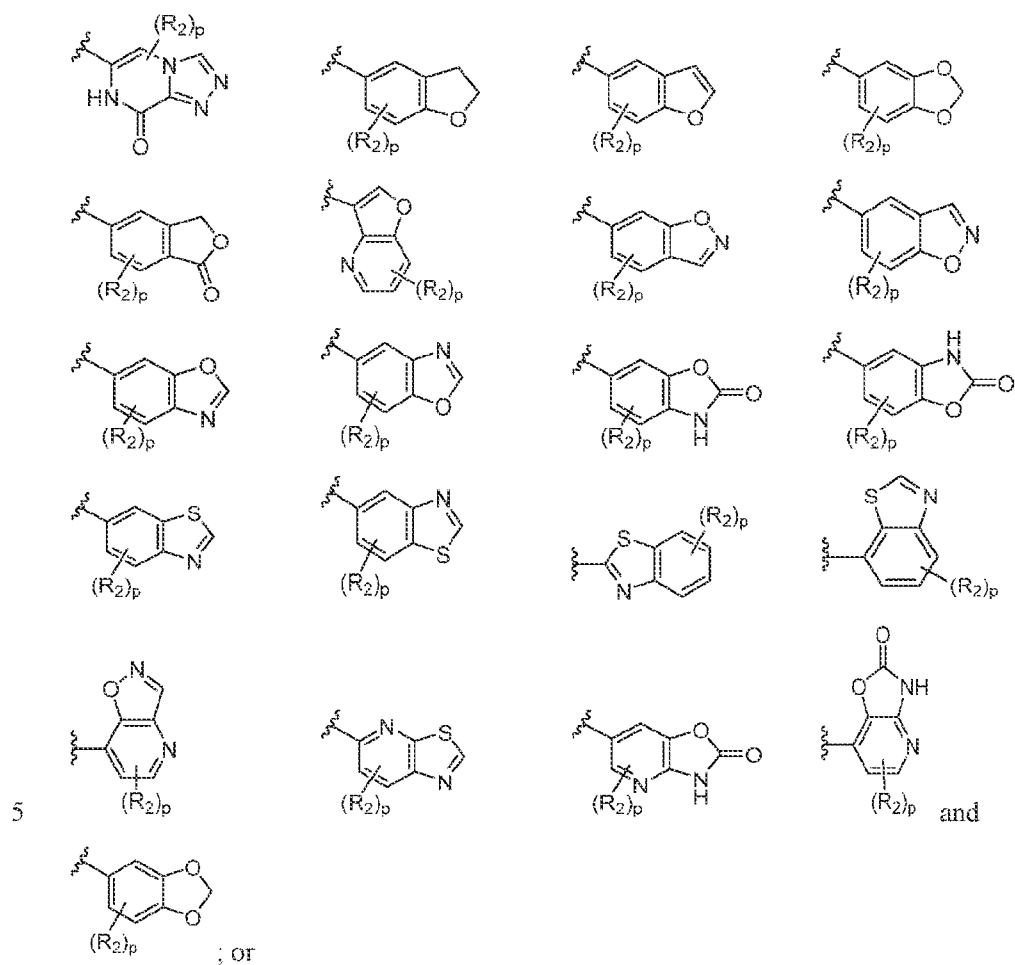


- (v) a 9-membered heterocyclic ring selected from:

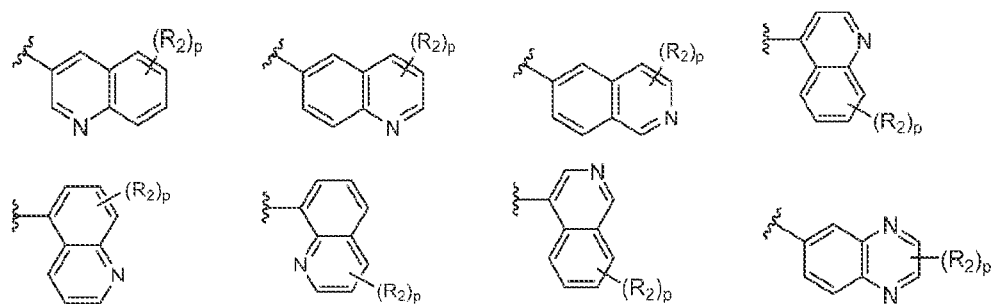


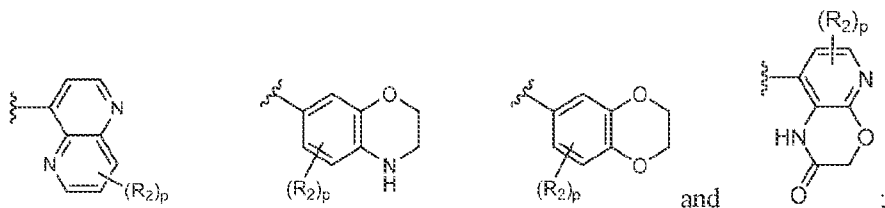






(vi) 10-membered heterocyclic ring selected from:





Q is piperidinyl, phenyl, tetrahydropyridinyl, pyridinyl, or azabicyclo[3.2.1]octanyl, each substituted with $-L-R_4$ and zero to 2 R_{4b} ;

L is a bond, $-(CR_xR_x)_{1-2}-$, or $-C(O)(CR_xR_x)_{0-2}-$;

5 R_1 is hydrogen, C_{1-3} alkyl, C_{1-2} fluoroalkyl, or C_{3-4} cycloalkyl;

each R_2 is independently halo, $-CN$, $-OH$, $-NO_2$, C_{1-4} alkyl, C_{1-2} fluoroalkyl, C_{1-2} cyanoalkyl, C_{1-3} hydroxyalkyl, C_{1-3} aminoalkyl, $-O(CH_2)_{1-2}OH$, $-(CH_2)_{0-4}O(C_{1-4}$ alkyl), C_{1-3} fluoroalkoxy, $-O(CH_2)_{1-2}OC(O)(C_{1-3}$ alkyl), $-O(CH_2)_{1-2}NR_xR_x$, $-C(O)O(C_{1-3}$ alkyl), $-(CH_2)_{0-2}C(O)NR_yR_y$, $-C(O)NR_x(C_{1-5}$ hydroxyalkyl),
 10 $-C(O)NR_x(C_{2-6}$ alkoxyalkyl), $-C(O)NR_x(C_{3-6}$ cycloalkyl), $-NR_yR_y$, $-NR_y(C_{1-3}$ fluoroalkyl), $-NR_y(C_{1-4}$ hydroxyalkyl), $-NR_xCH_2(phenyl)$, $-NR_xS(O)_2(C_{3-6}$ cycloalkyl), $-NR_xC(O)(C_{1-3}$ alkyl), $-NR_xCH_2(C_{3-6}$ cycloalkyl), $-S(O)_2(C_{1-3}$ alkyl), $-S(O)_2N(C_{1-3}$ alkyl) $_2$, $-S(O)(NH)N(C_{1-3}$ alkyl) $_2$, $-(CH_2)_{0-2}(C_{3-6}$ cycloalkyl), $-(CH_2)_{0-2}(phenyl)$, morpholinyl, dioxothiomorpholinyl, dimethyl pyrazolyl,
 15 methylpiperidinyl, methylpiperazinyl, amino-oxadiazolyl, imidazolyl, triazolyl, or $-C(O)(thiazolyl)$;

R_{2a} is C_{1-6} alkyl, C_{1-3} fluoroalkyl, C_{1-6} hydroxyalkyl, C_{1-3} aminoalkyl, $-(CH_2)_{0-4}O(C_{1-3}$ alkyl), C_{3-6} cycloalkyl, $-(CH_2)_{1-3}C(O)NR_xR_x$, $-CH_2(C_{3-6}$ cycloalkyl), $-CH_2(phenyl)$, tetrahydrofuranlyl, tetrahydropyranlyl, or phenyl;

20 each R_{2b} is independently hydrogen, halo, $-CN$, $-NR_xR_x$, C_{1-6} alkyl, C_{1-3} fluoroalkyl, C_{1-3} hydroxyalkyl, C_{1-3} fluoroalkoxy, $-(CH_2)_{0-2}O(C_{1-3}$ alkyl), $-(CH_2)_{0-3}C(O)NR_xR_x$, $-(CH_2)_{1-3}(C_{3-6}$ cycloalkyl), $-C(O)O(C_{1-3}$ alkyl), $-C(O)NR_x(C_{1-3}$ alkyl), $-CR_x=CR_xR_x$, or $-CR_x=CH(C_{3-6}$ cycloalkyl);

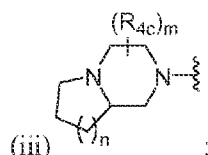
R_{2c} is R_{2a} or R_{2b} ;

25 R_{2d} is R_{2a} or R_{2b} ; provided that one of R_{2c} and R_{2d} is R_{2a} , and the other of R_{2c} and R_{2d} is R_{2b} ;

R₄ is:

(i) -N(CH₃)₂;

(ii) pyrrolidinyl, piperidinyl, piperazinyl, pyridinyl, azepanyl, azaspiro[3.3]heptanyl, octahydrocyclopenta[c]pyrrolyl, diazaspiro[3.3]heptanyl, azabicyclo[3.2.1]octanyl, or
 5 hexahydropyrrolo[3,4-c]pyrrolyl, each substituted with zero to 2 R_{4a}; or



each R_{4a} is independently C₁₋₆ alkyl, C₁₋₃ fluoroalkyl, C₃₋₆ cycloalkyl, -CH₂(C₃₋₆ cycloalkyl), -C(O)(C₁₋₄ alkyl), -C(O)(C₃₋₆ cycloalkyl), -C(O)(phenyl), -C(O)CH₂(C₃₋₆ cycloalkyl), -C(O)CH₂(phenyl), or -C(O)O(C₁₋₄ alkyl);

10 R_{4b} is F, Cl, -CN, or -CH₃;

each R_{4c} is independently C₁₋₆ alkyl, C₁₋₃ fluoroalkyl, -CH₂(C₃₋₆ cycloalkyl), -C(O)(C₁₋₄ alkyl), -C(O)(phenyl), -C(O)CH₂(phenyl), -C(O)OCH₂CH₃, or C₃₋₆ cycloalkyl;

R_{5a} is hydrogen, F, Cl, C₁₋₂ alkyl, C₁₋₂ fluoroalkyl, or cyclopropyl;

R_{5b} is hydrogen, F, Cl, C₁₋₂ alkyl, C₁₋₂ fluoroalkyl, or cyclopropyl;

15 each R_x is independently hydrogen or -CH₃;

each R_y is independently hydrogen or C₁₋₆ alkyl;

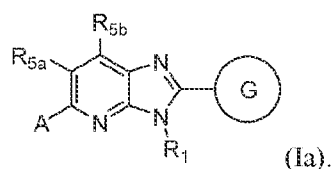
m is zero, 1, or 2;

n is zero, 1, or 2;

p is zero, 1, 2, 3, or 4; and

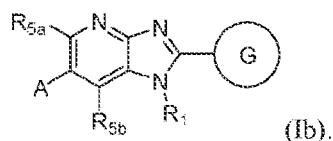
20 q is 1 or 2.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein X is CR_{5b} and Y is N. Compounds of this embodiment have the structure of Formula (Ia):

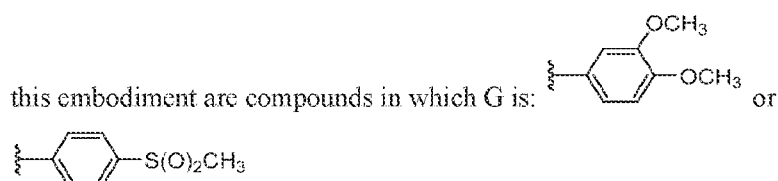


25 In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein X is N and Y is CR_{5b}. Compounds of this embodiment have the structure of

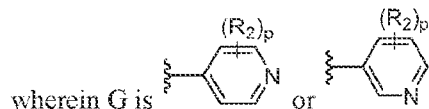
Formula (Ib):



In one embodiment, a compound of Formula (I), or a salt thereof is provided wherein G is phenyl substituted with 1 to 3 substituents independently selected from F, Cl, Br, C₁₋₂ alkoxy, C₁₋₂ fluoroalkoxy, C₃₋₄ cycloalkyl, -C(O)NR_yR_y, -S(O)₂CH₃, -S(O)₂(phenyl), -S(O)₂NR_xR_x, and -S(O)(NH)NR_xR_x. Included in this embodiment are compounds in which G is phenyl substituted with 1 to 2 substituents independently selected from F, -OCH₃, -S(O)₂CH₃, -S(O)₂N(CH₃)₂, and -S(O)(NH)N(CH₃)₂. Also included in this embodiment are compounds in which G is phenyl substituted with 1 to 2 substituents independently selected from F, -OCH₃, and -S(O)₂CH₃. Further, included in



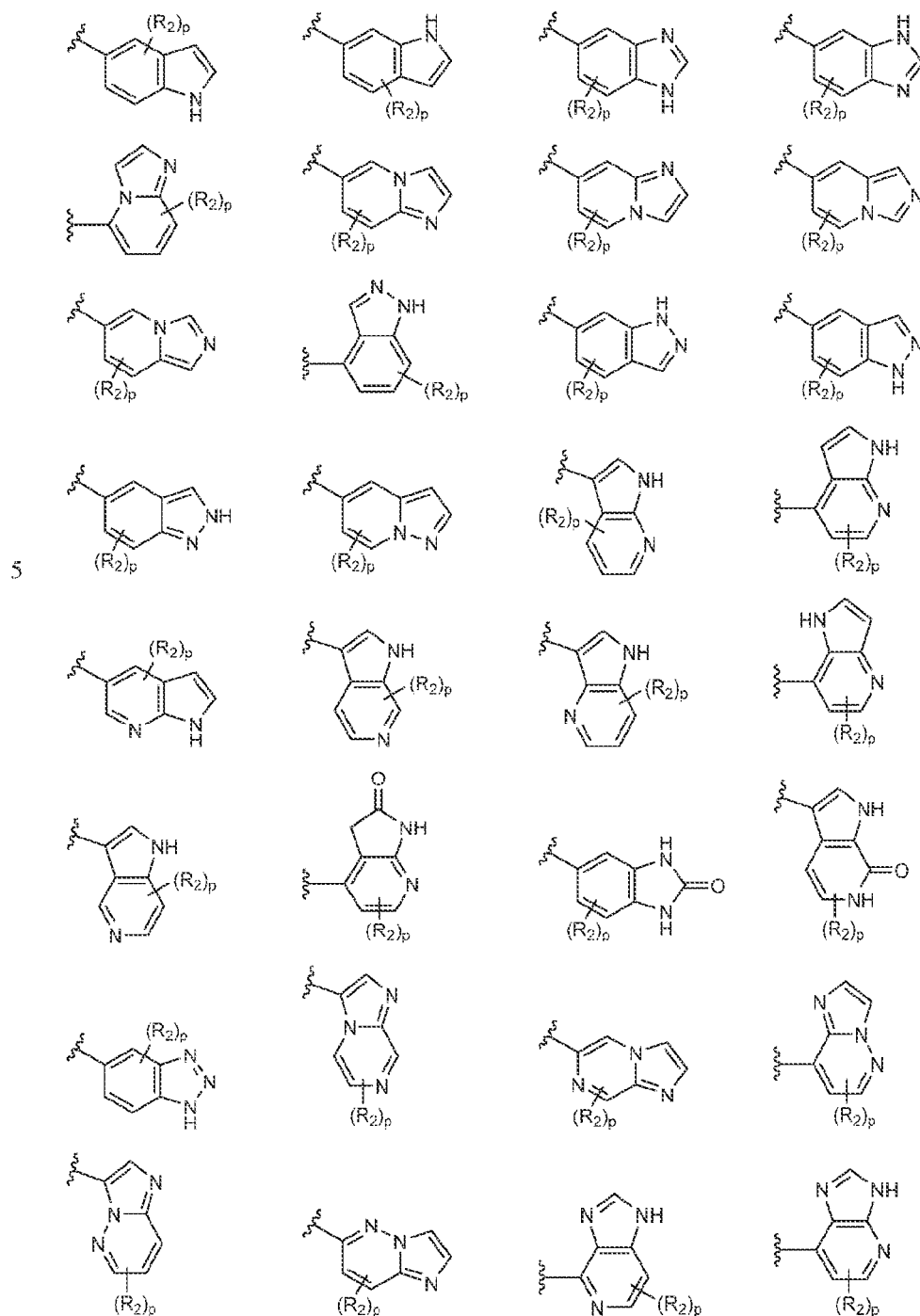
In one embodiment, a compound of Formula (I), or a salt thereof is provided

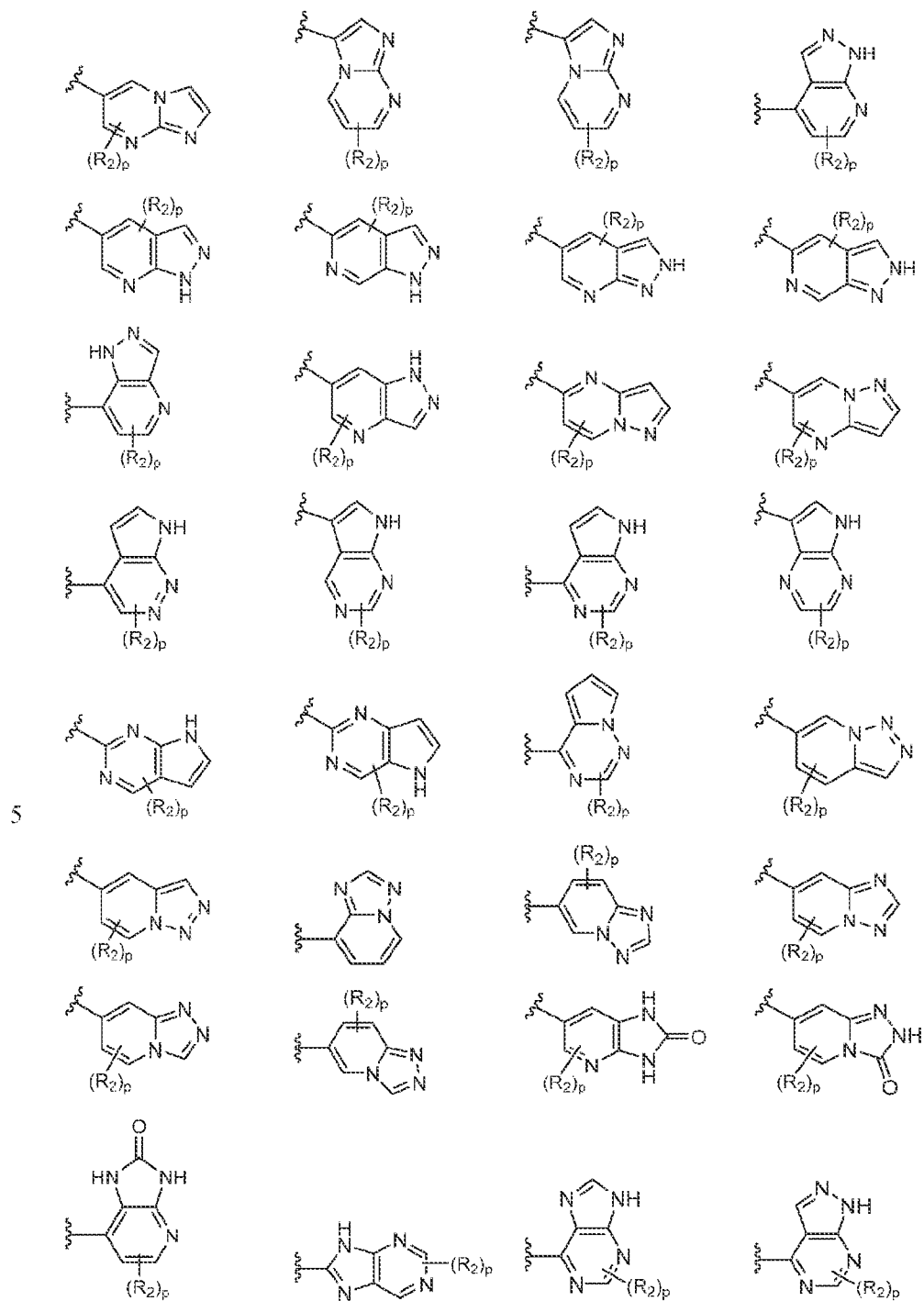


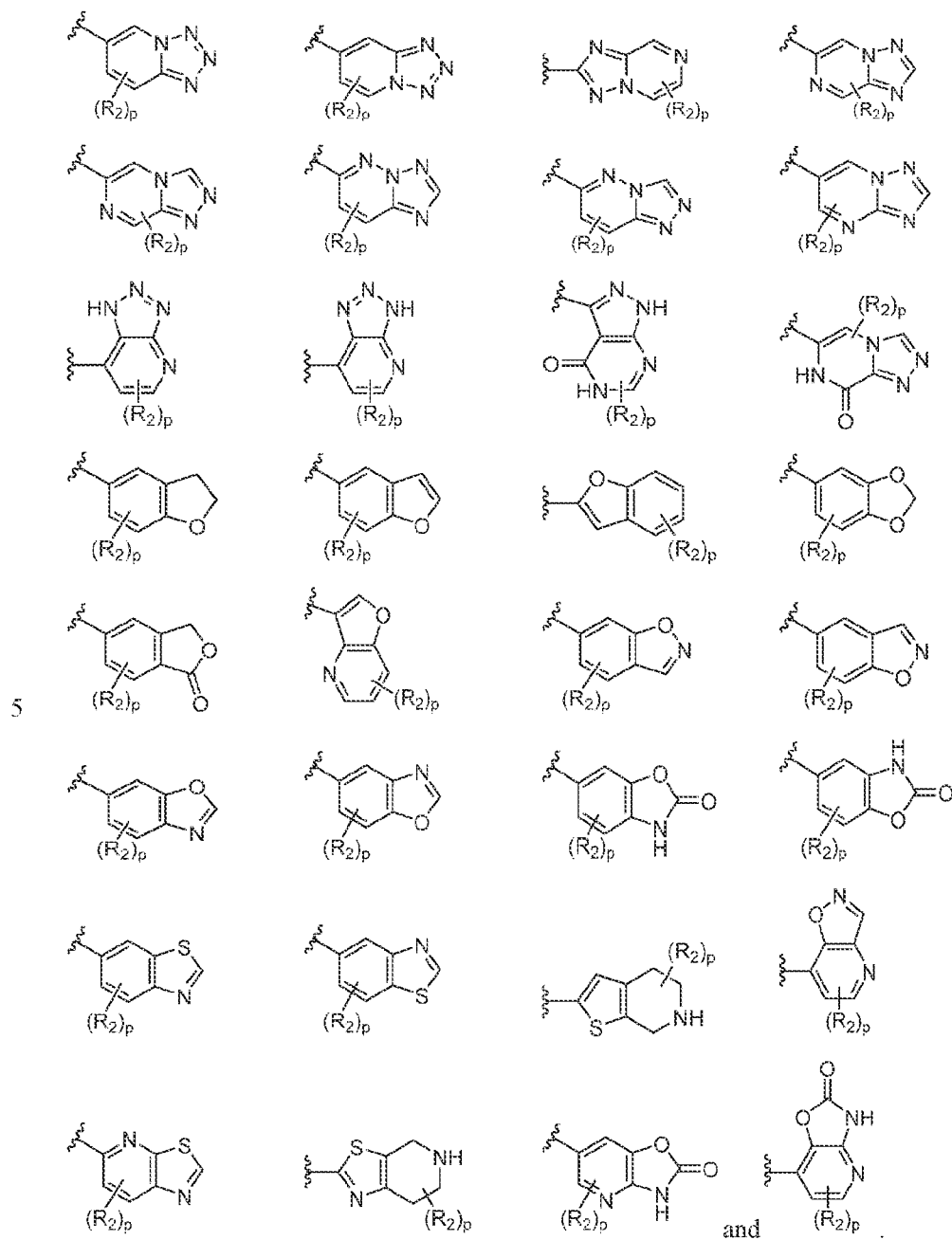
wherein G is or . Included in this embodiment are compounds in which each R₂ is independently F, Cl, Br, -CN, -OH, -CH₃, -CH₂CH₃, -CF₃, -CH₂OH, -C(CH₃)₂OH, -CH₂NH₂, -OCH₃, -OCH₂CH₃, -OCH(CH₃)₂, -OCH₂CH₂OCH₃, -OCH₂CH₂N(CH₃)₂, -OCHF₂, -C(O)OCH₃, -C(O)NH₂, -C(O)NH(CH₂CH₃), -C(O)(thiazolyl), -NH₂, -NH(CH₃), -NH(CH₂CH₃), -N(CH₃)₂, -NHC(O)CH₃, -NHC(O)C(CH₃)₃, -NH(CH₂-cyclopropyl), cyclopropyl, methylpiperidinyl, methylpiperazinyl, amino-oxadiazolyl, imidazolyl, or triazolyl. Also included in this embodiment are compounds in which each R₂ is independently F, Cl, -CN, -CH₃, -OCH₃, -NH₂, or cyclopropyl. Additionally, included in this embodiment are compounds in which p is 2; one R₂ is -CH₃; and the other R₂ is F, Cl, -CN, -CH₃, -OCH₃, -NH₂, or cyclopropyl.

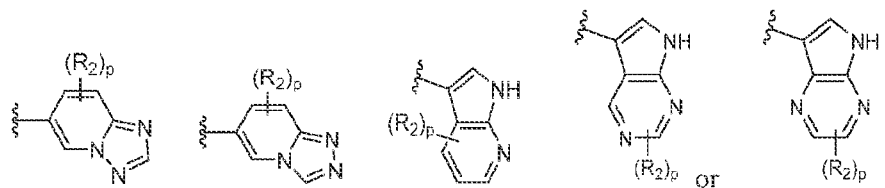
In one embodiment, a compound of Formula (I) or a salt thereof is provided

wherein G is a 9-membered heterocyclic ring selected from:

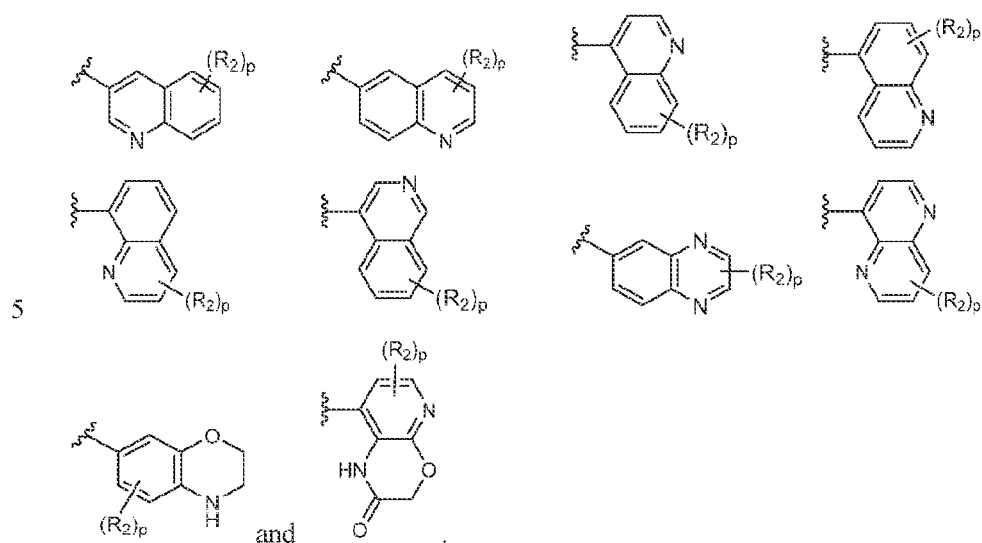




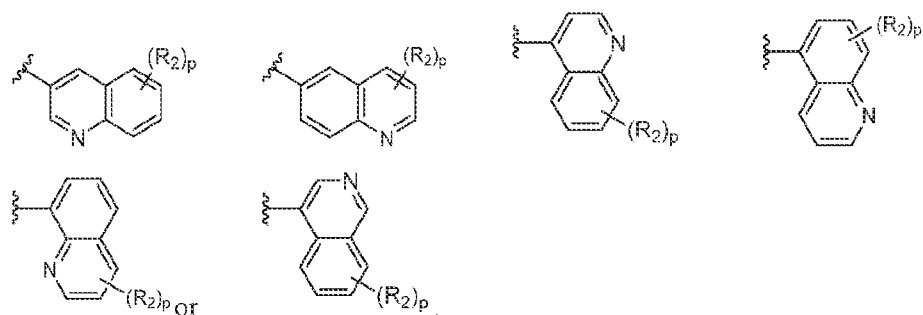




In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein G is a 10-membered heterocyclic ring selected from:

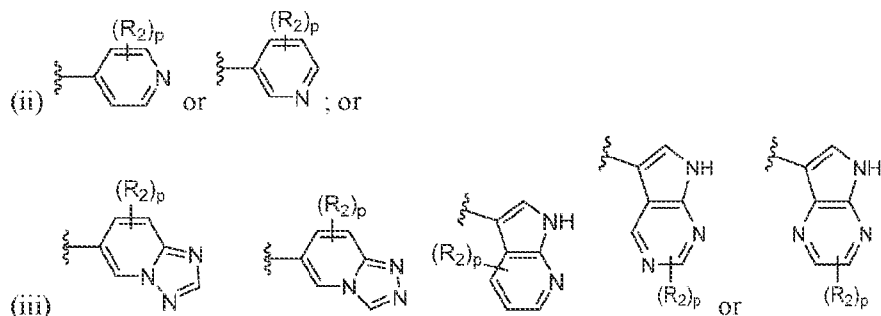


Included in this embodiment are compounds in which G is:



In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein G is:

- (i) phenyl substituted with 1 to 2 substituents independently selected from F, $-\text{OCH}_3$, $-\text{S(O)}_2\text{CH}_3$, $-\text{S(O)}_2\text{N(CH}_3)_2$, and $-\text{S(O)}(\text{NH})\text{N(CH}_3)_2$;

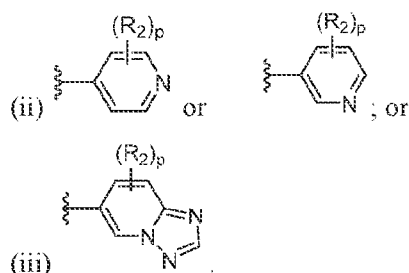


Included in this embodiment are compounds in which each R_2 is independently Cl, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CN}$, $-\text{OCH}_3$, $-\text{CH}_2\text{OCH}_3$, or

5 $-\text{CH}_2\text{CH}_2\text{S}(\text{O})_2\text{CH}_3$.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein G is:

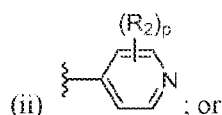
- (i) phenyl substituted with 1 to 3 substituents independently selected from F, Cl, Br, $-\text{CN}$, C_{1-2} alkoxy, C_{1-2} fluoroalkoxy, C_{3-4} cycloalkyl, $-\text{C}(\text{O})\text{NR}_y\text{R}_y$, $-\text{S}(\text{O})_2\text{CH}_3$,
 10 $-\text{S}(\text{O})_2(\text{phenyl})$, $-\text{S}(\text{O})_2(\text{cyclopropyl})$, $-\text{S}(\text{O})_2\text{NR}_x\text{R}_x$, $-\text{S}(\text{O})(\text{NH})\text{NR}_x\text{R}_x$, and $-\text{NHS}(\text{O})_2\text{CH}_3$;

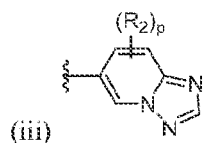


Included in this embodiment are compounds in which each R_2 is independently Cl, $-\text{CH}_3$,
 15 $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CN}$, $-\text{OCH}_3$, or $-\text{CH}_2\text{OCH}_3$.

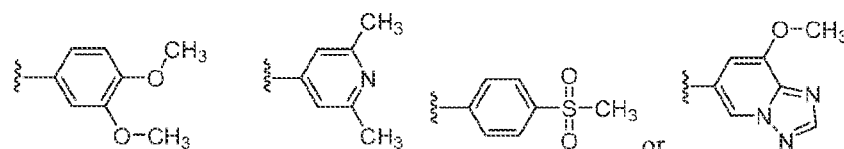
In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein G is:

- (i) phenyl substituted $-\text{S}(\text{O})_2\text{CH}_3$ or phenyl substituted with two $-\text{OCH}_3$;



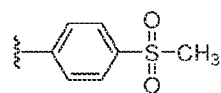


Included in this embodiment are compounds in which each R_2 is independently $-\text{CH}_3$ or $-\text{OCH}_3$. Also included in this embodiment are compounds in which G is:



- 5 In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein G is phenyl substituted $-\text{S}(\text{O})_2\text{CH}_3$ or phenyl substituted with two $-\text{OCH}_3$.

Included in this embodiment are compounds in which G is:



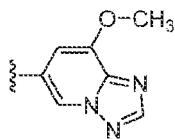
In one embodiment, a compound of Formula (I) or a salt thereof is provided

- 10 wherein G is . Included in this embodiment are compounds in which each R_2

is $-\text{CH}_3$. Also included in this embodiment are compounds in which G is

In one embodiment, a compound of Formula (I) or a salt thereof is provided

wherein G is . Included in this embodiment are compounds in which each R_2 is independently $-\text{CH}_3$ or $-\text{OCH}_3$. Also included in this embodiment are compounds



in which G is

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein Q is piperidinyl, phenyl, pyridinyl, or tetrahydropyridinyl, each substituted with $-L-R_4$ and zero to 1 R_{4b} . Included in this embodiment are compounds in which Q is piperidinyl, phenyl, or tetrahydropyridinyl, each substituted with $-L-R_4$ and zero to 1 R_{4b} .

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein Q is piperidinyl, phenyl, or pyridinyl, each substituted with $-L-R_4$ and zero to 1 R_{4b} .

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein Q is piperidinyl or phenyl, each substituted with $-L-R_4$ and zero to 1 R_{4b} . Included in this embodiment are compounds in which Q is piperidinyl or phenyl, each substituted with $-L-R_4$.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein Q is piperidinyl substituted with $-L-R_4$ and zero to 1 R_{4b} . Included in this embodiment are compounds in which Q is piperidinyl substituted with $-L-R_4$.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein Q is phenyl substituted with $-L-R_4$ and zero to 1 R_{4b} . Included in this embodiment are compounds in which Q is phenyl substituted with $-L-R_4$.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein Q is pyridinyl substituted with $-L-R_4$ and zero to 1 R_{4b} . Included in this embodiment are compounds in which Q is pyridinyl substituted with $-L-R_4$.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein Q is tetrahydropyridinyl substituted with $-L-R_4$ and zero to 1 R_{4b} . Included in this embodiment are compounds in which Q is tetrahydropyridinyl substituted with $-L-R_4$.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R_1 is hydrogen, C_{1-3} alkyl, $-CHF_2$, $-CF_3$, or C_{3-4} cycloalkyl. Included in this

embodiment are compounds in which R_1 is hydrogen, C_{1-2} alkyl, $-CHF_2$, $-CF_3$, or cyclopropyl. Also included in this embodiment are compounds in which R_1 is hydrogen, $-CH_3$, or cyclopropyl.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R_1 is hydrogen.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R_1 is C_{1-3} alkyl, C_{1-2} fluoroalkyl, or C_{3-4} cycloalkyl. Included in this embodiment are compounds in which R_1 is C_{1-3} alkyl, $-CHF_2$, $-CF_3$, or C_{3-4} cycloalkyl. Also included in this embodiment are compounds in which R_1 is $-CH_3$ or cyclopropyl. Further, included in this embodiment are compounds in which R_1 is $-CH_3$.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein p is zero, 1, 2, or 3. Included in this embodiment are compounds in which p is 1 or 2.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein L is a bond, $-(CR_xR_x)_{1-2}-$, or $-C(O)(CR_xR_x)_{0-1}-$. Included in this embodiment are compounds in which L is a bond, $-CH_2-$ or $-C(O)(CH_2)_{0-1}-$. Also included in this embodiment are compounds in which L is $-CR_xR_x-$ or $-C(O)(CR_xR_x)_{0-1}-$. Additionally, included in this embodiment are compounds in which L is $-C(O)CH_2-$.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein L is a bond or $-(CR_xR_x)_{1-2}-$. Included in this embodiment are compounds in which L is a bond or $-CR_xR_x-$.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein L is a bond or $-(CH_2)_{1-2}-$. Included in this embodiment are compounds in which L is a bond or $-CH_2-$.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein L is a bond, $-CH_2-$, or $-C(O)(CH_2)_{0-1}-$. Included in this embodiment are compounds in which L is $-CH_2-$.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein L is $-C(O)(CH_2)_{0-2}-$. Included in this embodiment are compounds in which L is $-C(O)(CH_2)_{0-1}-$. Also included in this embodiment are compounds in which L is

$-\text{C}(\text{O})(\text{CH}_2)_{1-2}-$.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein L is a bond.

In one embodiment, a compound of Formula (I) or a salt thereof is provided
 5 wherein L is $-(\text{CR}_x\text{R}_x)_{1-2}-$. Included in this embodiment are compounds in which L is $-\text{CR}_x\text{R}_x-$.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein L is $-(\text{CH}_2)_{1-2}-$. Included in this embodiment are compounds in which L is $-\text{CH}_2-$.

10 In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein L is $-\text{C}(\text{O})-$.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein L is $-\text{C}(\text{O})\text{CH}_2-$.

In one embodiment, a compound of Formula (I) or a salt thereof is provided
 15 wherein L is $-\text{C}(\text{O})\text{CH}_2\text{CH}_2-$.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R_4 is $-\text{N}(\text{CH}_3)_2$.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R_4 is pyrrolidinyl, piperidinyl, piperazinyl, pyridinyl, azepanyl,
 20 azaspiro[3.3]heptanyl, octahydrocyclopenta[c]pyrrolyl, diazaspiro[3.3]heptanyl, azabicyclo[3.2.1]octanyl, or hexahydropyrrolo[3,4-c]pyrrolyl, each substituted with zero to 2 R_{4a} . Included in this embodiment are compounds in which R_4 is pyrrolidinyl, piperidinyl, piperazinyl, pyridinyl, azepanyl, azaspiro[3.3]heptanyl, octahydrocyclopenta[c]pyrrolyl, diazaspiro[3.3]heptanyl, azabicyclo[3.2.1]octanyl, or
 25 hexahydropyrrolo[3,4-c]pyrrolyl, each substituted with zero to 1 R_{4a} .

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R_4 is piperidinyl, piperazinyl, octahydrocyclopenta[c]pyrrolyl, diazaspiro[3.3]heptanyl, or azabicyclo[3.2.1]octanyl, each substituted with zero or 1 R_{4a} . Included in this embodiment are compounds in which R_4 is piperidinyl or piperazinyl,
 30 each substituted with zero to 1 R_{4a} .

In one embodiment, a compound of Formula (I) or a salt thereof is provided

wherein R₄ is piperidinyl substituted with zero or 1 R_{4a}.

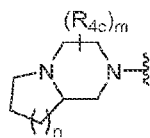
In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R₄ is piperazinyl substituted with zero or 1 R_{4a}.

In one embodiment, a compound of Formula (I) or a salt thereof is provided
5 wherein R₄ is octahydrocyclopenta[c]pyrrolyl substituted with zero or 1 R_{4a}.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R₄ is diazaspiro[3.3]heptanyl substituted with zero or 1 R_{4a}.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R₄ is azabicyclo[3.2.1]octanyl substituted with zero or 1 R_{4a}.

10 In one embodiment, a compound of Formula (I) or a salt thereof is provided



wherein R₄ is . Included in this embodiment are compounds in which n is 1 or 2. Also included in this embodiment are compounds in which n is 1. Additionally, included in this embodiment are compounds in which n is 2.

In one embodiment, a compound of Formula (I) or a salt thereof is provided
15 wherein each R_{4a} is independently -CH₃, -CH₂CH₃, -CH(CH₃)₂, -CH₂CH(CH₃)₂, -CH₂C(CH₃)₂OH, -CH₂CH₂OCH₃, -C(O)CH(CH₃)₂, cyclopropyl, cyclobutyl, -CH₂(cyclopropyl), -CH₂(cyclobutyl), -CH₂(oxetanyl), -CH₂CH₂(morpholinyl), -CH₂CH₂CH₂(morpholinyl), -N(CH₃)₂, -N(CH₃)(CH₂CH₃), -N(CH₃)(cyclopropyl), azetidiny, oxetanyl, tetrahydropyranyl, pyrrolidinyl, phenyl, morpholinyl, or piperidinyl
20 substituted with zero to 2 substituents selected from -OH or -CH₃. Included in this embodiment are compounds in which each R_{4a} is -CH₃, -CH(CH₃)₂, -CH₂CH(CH₃)₂, -CH₂C(CH₃)₂OH, -CH₂CH₂OCH₃, -CH₂(cyclopropyl), -CH₂CH₂(morpholinyl), -CH₂CH₂CH₂(morpholinyl), cyclopropyl, cyclobutyl, pyrrolidinyl, oxetanyl, tetrahydropyranyl, or morpholinyl.

25 In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein each R_{4a} is independently -CH₃, -CH₂CH₃, -CH(CH₃)₂, -CH₂CH(CH₃)₂, -CH₂C(CH₃)₂OH, -CH₂CH₂OCH₃, -C(O)CH(CH₃)₂, cyclopropyl, cyclobutyl, -CH₂(cyclopropyl), -CH₂(cyclobutyl), -CH₂(oxetanyl), -N(CH₃)₂, -N(CH₃)(CH₂CH₃),

–N(CH₃)(cyclopropyl), azetidiny, oxetanyl, tetrahydropyranyl, pyrrolidinyl, phenyl, or piperidinyl substituted with zero to 2 substituents selected from –OH or –CH₃. Included in this embodiment are compounds in which each R_{4a} is independently –CH₃, –CH(CH₃)₂, –CH₂CH(CH₃)₂, –CH₂C(CH₃)₂OH, –CH₂CH₂OCH₃, –CH₂(cyclopropyl),
 5 cyclopropyl, cyclobutyl, pyrrolidinyl, oxetanyl, or tetrahydropyranyl.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R_{4b} is F, –CN, or –CH₃. Included in this embodiment are compounds in which R_{4b} is F. Also included in this embodiment are compounds in which R_{4b} is –CH₃.

In one embodiment, a compound of Formula (I) or a salt thereof is provided
 10 wherein each R_{4c} is independently C₁₋₄ alkyl, C₁₋₂ fluoroalkyl, –CH₂(C₃₋₆ cycloalkyl), –C(O)(C₁₋₃ alkyl), –C(O)(phenyl), –C(O)CH₂(phenyl), –C(O)OCH₂CH₃, or C₃₋₆ cycloalkyl. Included in this embodiment are compounds in which each R_{4c} is independently C₁₋₃ alkyl, C₁₋₂ fluoroalkyl, –CH₂(C₃₋₄ cycloalkyl), –C(O)(C₁₋₂ alkyl), –C(O)(phenyl), –C(O)CH₂(phenyl), –C(O)OCH₂CH₃, or C₃₋₄ cycloalkyl.

15 In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein each R₂ is independently F, Cl, –CN, –OH, C₁₋₃ alkyl, C₁₋₂ fluoroalkyl, C₁₋₂ cyanoalkyl, C₁₋₃ hydroxyalkyl, C₁₋₂ aminoalkyl, –(CH₂)₀₋₂O(C₁₋₃ alkyl), C₃₋₆ cycloalkyl, –NR_xR_x, –(CH₂)₀₋₂C(O)NR_xR_x, –CH₂(C₃₋₆ cycloalkyl), –CH₂(phenyl), or phenyl. Included in this embodiment are compounds in which each R₂ is independently Cl, –CH₃,
 20 –CH₂CH₃, –CH₂OH, –CH₂CH₂OH, –CH₂CN, –OCH₃, –CH₂OCH₃, or –CH₂CH₂S(O)₂CH₃. Also, included in this embodiment are compounds in which each R₂ is independently Cl, –CH₃, –CH₂OH, or –OCH₃.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R_{2a} is C₁₋₄ alkyl, C₁₋₂ fluoroalkyl, C₁₋₄ hydroxyalkyl, –(CH₂)₁₋₃OCH₃, C₃₋₆
 25 cycloalkyl, –CH₂C(O)NR_xR_x, –CH₂(C₃₋₆ cycloalkyl), –CH₂(phenyl), tetrahydrofuranyl, or phenyl; and each R_{2b} is independently H, F, Cl, –CN, –NR_xR_x, C₁₋₆ alkyl, C₁₋₂ fluoroalkyl, C₁₋₃ hydroxyalkyl, –(CH₂)₀₋₂O(C₁₋₂ alkyl), –(CH₂)₀₋₂C(O)NR_xR_x, –(CH₂)₁₋₃(cyclopropyl), –C(O)O(C₁₋₂ alkyl), –C(O)NR_x(C₁₋₃ alkyl), –CR_x=CH₂, or –CH=CH(C₃₋₆ cycloalkyl). Also included in this embodiment are compounds in which
 30 R_{2a} is –CH₃; and each R_{2b} is independently H, Cl, or –CH₃.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R_{5a} is hydrogen, F, Cl, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, or cyclopropyl. Included in this embodiment are compounds in which R_{5a} is hydrogen, F, $-CH_3$, $-CF_3$, or cyclopropyl. Also included in this embodiment are compounds in which R_{5a} is hydrogen,
 5 $-CH_3$, or $-CF_3$.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R_{5a} is $-CH_3$.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R_{5a} is hydrogen.

10 In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R_{5b} is hydrogen, F, Cl, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, or cyclopropyl. Included in this embodiment are compounds in which R_{5b} is hydrogen, F, $-CH_3$, or $-CF_3$. Also included in this embodiment are compounds in which R_{5b} is hydrogen or $-CH_3$.

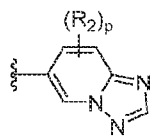
In one embodiment, a compound of Formula (I) or a salt thereof is provided
 15 wherein R_{5b} is hydrogen.

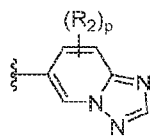
In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R_{5b} is $-CH_3$.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R_{5a} is hydrogen; and R_{5b} is hydrogen.

20 In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R_{5a} is hydrogen; and R_{5b} is hydrogen or $-CH_3$.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein G is: (i) phenyl substituted $-S(O)_2CH_3$; (ii) phenyl substituted with two $-OCH_3$;



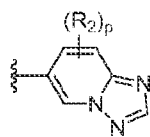
or (iii) ; Q is phenyl or piperidinyl, each substituted with $-L-R_4$; L is a
 25 bond or $-CH_2-$; R_1 is hydrogen, $-CH_3$, or cyclopropyl; R_4 is piperidinyl, piperazinyl, octahydrocyclopenta[c]pyrrolyl, diazaspiro[3.3]heptanyl, or azabicyclo[3.2.1]octanyl, each substituted with zero or 1 R_{4a} ; R_{4a} is $-CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH_2C(CH_3)_2OH$, $-CH_2CH_2OCH_3$, $-CH_2(cyclopropyl)$, $-CH_2CH_2(morpholinyl)$,

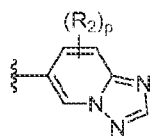
–CH₂CH₂CH₂(morpholinyl), cyclopropyl, cyclobutyl, pyrrolidinyl, oxetanyl, tetrahydropyranyl, or morpholinyl; R_{5a} is hydrogen; and R_{5b} is hydrogen or –CH₃.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein G is phenyl substituted with 1 to 3 substituents independently selected from F,
 5 Cl, Br, –CN, C₁₋₂ alkoxy, C₁₋₂ fluoroalkoxy, C₃₋₄ cycloalkyl, –C(O)NR_yR_y, –S(O)₂CH₃,
 –S(O)₂(phenyl), –S(O)₂(cyclopropyl), –S(O)₂NR_xR_x, –S(O)(NH)NR_xR_x, and
 –NHS(O)₂CH₃; L is a bond, –CH₂–, or –CH₂CH₂–; Q is piperidinyl, phenyl,
 tetrahydropyridinyl, or pyridinyl, each substituted with –L–R₄ and zero to 1 R_{4b};

R₁ is hydrogen, C₁₋₃ alkyl, –CHF₂, –CF₃, or C₃₋₄ cycloalkyl; each R₂ is
 10 independently Cl, –CH₃, –CH₂CH₃, –CH₂OH, –CH₂CH₂OH, –CH₂CN, –OCH₃, or
 –CH₂OCH₃; R₄ is pyrrolidinyl, piperidinyl, piperazinyl, pyridinyl,
 octahydrocyclopenta[c]pyrrolyl, azaspiro[3.3]heptanyl, diazaspiro[3.3]heptanyl,
 azabicyclo[3.2.1]octanyl, or hexahydropyrrolo[3,4-c]pyrrolyl, each substituted with zero
 to 1 R_{4a}; R_{4a} is –CH₃, –CH₂CH₃, –CH(CH₃)₂, –CH₂CH(CH₃)₂, –CH₂C(CH₃)₂OH,
 15 –CH₂CH₂OCH₃, –C(O)CH(CH₃)₂, cyclopropyl, cyclobutyl, –CH₂(cyclopropyl),
 –CH₂(cyclobutyl), –CH₂(oxetanyl), –N(CH₃)₂, –N(CH₃)(CH₂CH₃),
 –N(CH₃)(cyclopropyl), azetidiny, oxetanyl, tetrahydropyranyl, pyrrolidinyl, phenyl, or
 piperidinyl substituted with zero to 2 substituents selected from –OH or –CH₃; R_{4b} is F,
 –CN, or –CH₃; R_{5a} is hydrogen, –CH₃, –CF₃, or cyclopropyl; and R_{5b} is hydrogen, –CH₃,
 20 or –CF₃.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein: G is: (i) phenyl substituted –S(O)₂CH₃; (ii) phenyl substituted with two –OCH₃;



or (iii) ; Q is phenyl or piperidinyl, each substituted with –L–R₄; L is a
 bond or –CH₂–; R₁ is hydrogen, –CH₃, or cyclopropyl; R₄ is piperidinyl, piperazinyl,
 25 octahydrocyclopenta[c]pyrrolyl, diazaspiro[3.3]heptanyl, or azabicyclo[3.2.1]octanyl,
 each substituted with zero or 1 R_{4a}; R_{4a} is –CH₃, –CH(CH₃)₂, –CH₂CH(CH₃)₂,
 –CH₂C(CH₃)₂OH, –CH₂CH₂OCH₃, –CH₂(cyclopropyl), –CH₂CH₂(morpholinyl),
 –CH₂CH₂CH₂(morpholinyl), cyclopropyl, cyclobutyl, pyrrolidinyl, oxetanyl,

tetrahydropyranyl, or morpholinyl; R_{5a} is hydrogen; and R_{5b} is hydrogen or -CH₃.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein G is: (i) phenyl substituted -S(O)₂CH₃; or (ii) phenyl substituted with two -OCH₃; Q is phenyl or piperidinyl, each substituted with -L-R₄; L is a bond or -CH₂-;

- 5 R₁ is hydrogen, -CH₃, or cyclopropyl; R₄ is piperidinyl, piperazinyl, octahydrocyclopenta[c]pyrrolyl, diazaspiro[3.3]heptanyl, or azabicyclo[3.2.1]octanyl, each substituted with zero or 1 R_{4a}; R_{4a} is -CH₃, -CH(CH₃)₂, -CH₂CH(CH₃)₂, -CH₂C(CH₃)₂OH, -CH₂CH₂OCH₃, -CH₂(cyclopropyl), cyclopropyl, cyclobutyl, pyrrolidinyl, oxetanyl, or tetrahydropyranyl; R_{5a} is hydrogen; and R_{5b} is hydrogen or
10 -CH₃.

- One embodiment provides a compound of Formula (I) or a salt thereof, wherein said compound is: 5-(4-((6-cyclobutyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-3-cyclopropyl-7-methyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (1); 3-cyclopropyl-7-methyl-2-(4-(methylsulfonyl)phenyl)-5-(4-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridine (2); 3-cyclopropyl-5-(4-((6-isopropyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-7-methyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (3); 3-cyclopropyl-5-(4-((6-isobutyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-7-methyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (4); 3-cyclopropyl-7-methyl-2-(4-(methylsulfonyl)phenyl)-5-(4-((6-(tetrahydro-2H-pyran-4-yl)-2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridine (5); 3-cyclopropyl-7-methyl-2-(4-(methylsulfonyl)phenyl)-5-(4-((6-(oxetan-3-yl)-2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridine (6); 5-(4-(4-isopropylpiperazin-1-yl)phenyl)-3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (7); 5-(4-(4-isobutylpiperazin-1-yl)phenyl)-3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (8); 3-cyclopropyl-7-methyl-5-(4-(1-methylpiperidin-4-yl)phenyl)-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (9); 2-(3,4-dimethoxyphenyl)-5-(4-(4-isopropylpiperazin-1-yl)phenyl)-3,7-dimethyl-3H-imidazo[4,5-b]pyridine (10); 5-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-3-methyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (17); 5-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-3-methyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (18); 5-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-3-methyl-2-(4-(methylsulfonyl)phenyl)-

3H-imidazo[4,5-b]pyridine (19); 5-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (20); 5-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (21); 1-(4-(3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridin-5-yl)-[1,4'-bipiperidin]-1'-yl)-2-methylpropan-2-ol (22); 5-(1'-(cyclopropylmethyl)-[1,4'-bipiperidin]-4-yl)-3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (23); 5-(1'-cyclobutyl-[1,4'-bipiperidin]-4-yl)-3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (24); 3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-5-(1'-(tetrahydro-2H-pyran-4-yl)-[1,4'-bipiperidin]-4-yl)-3H-imidazo[4,5-b]pyridine (25); 5-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (26-27); 5-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (28-29); 5-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (30-31); 5-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (32-33); 3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-5-(1-(8-(tetrahydro-2H-pyran-4-yl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-3H-imidazo[4,5-b]pyridine (34-35); 2-(3,4-dimethoxyphenyl)-5-(1-(2-isopropyl-octahydrocyclopenta[c]pyrrol-5-yl)piperidin-4-yl)-3,7-dimethyl-3H-imidazo[4,5-b]pyridine (36); 2-(3,4-dimethoxyphenyl)-5-(1-(2-isobutyl-octahydrocyclopenta[c]pyrrol-5-yl)piperidin-4-yl)-3,7-dimethyl-3H-imidazo[4,5-b]pyridine (37); 5-(1-(2-(cyclopropylmethyl)-octahydrocyclopenta[c]pyrrol-5-yl)piperidin-4-yl)-2-(3,4-dimethoxyphenyl)-3,7-dimethyl-3H-imidazo[4,5-b]pyridine (38); 5-(1-(2-cyclobutyl-octahydrocyclopenta[c]pyrrol-5-yl)piperidin-4-yl)-2-(3,4-dimethoxyphenyl)-3,7-dimethyl-3H-imidazo[4,5-b]pyridine (39); 2-(3,4-dimethoxyphenyl)-3,7-dimethyl-5-(1-(2-(tetrahydro-2H-pyran-4-yl)-octahydrocyclopenta[c]pyrrol-5-yl)piperidin-4-yl)-3H-imidazo[4,5-b]pyridine (40); 2-(3,4-dimethoxyphenyl)-5-(1-((3aR,5s,6aS)-2-(2-methoxyethyl)-octahydrocyclopenta[c]pyrrol-5-yl)piperidin-4-yl)-3,7-dimethyl-3H-imidazo[4,5-b]pyridine (41); 5-(1-((3aR,5s,6aS)-2-cyclobutyl-octahydrocyclopenta[c]pyrrol-5-yl)piperidin-4-yl)-2-(8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3,7-dimethyl-3H-imidazo[4,5-b]pyridine (42); 5-(1-((3aR,5s,6aS)-2-(cyclopropylmethyl)-octahydrocyclopenta[c]pyrrol-5-yl)piperidin-4-yl)-2-(8-methoxy-[1,2,4]triazolo[1,5-a]

pyridin-6-yl)-3,7-dimethyl-3H-imidazo[4,5-b]pyridine (43); 2-(8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3,7-dimethyl-5-(1-((3aR,5s,6aS)-2-(tetrahydro-2H-pyran-4-yl)octahydrocyclopenta[c]pyrrol-5-yl)piperidin-4-yl)-3H-imidazo[4,5-b]pyridine (44); 5-(4-(4-isopropylpiperazin-1-yl)phenyl)-2-(8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3,7-dimethyl-3H-imidazo[4,5-b]pyridine (45); 2-(8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-5-(1-((3aR,5s,6aS)-2-(2-methoxyethyl) octahydrocyclopenta[c]pyrrol-5-yl)piperidin-4-yl)-3,7-dimethyl-3H-imidazo[4,5-b] pyridine (46); 4-(1-(4-(3-cyclopropyl-7-methyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridin-5-yl)benzyl)piperidin-4-yl)morpholine (47); 2-(3,4-dimethoxyphenyl)-5-(4-(4-isopropylpiperazin-1-yl)phenyl)-3-methyl-3H-imidazo[4,5-b] pyridine (52); 5-(4-(4-isopropylpiperazin-1-yl)phenyl)-3-methyl-2-(4-(methylsulfonyl) phenyl)-3H-imidazo[4,5-b]pyridine (53); 3-cyclopropyl-5-(4-(4-isopropylpiperazin-1-yl) phenyl)-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b] pyridine (54); 3-cyclopropyl-2-(3,4-dimethoxyphenyl)-5-(4-(4-isopropylpiperazin-1-yl) phenyl)-3H-imidazo[4,5-b] pyridine (55); 4-(3-(4-(4-(3-cyclopropyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridin-5-yl)phenyl)piperazin-1-yl)propyl) morpholine (56); 4-(2-(4-(4-(3-cyclopropyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridin-5-yl) phenyl)piperazin-1-yl) ethyl)morpholine (57); 2-(3,4-dimethoxyphenyl)-5-(4-(2-isopropyl-2,7-diazaspiro[3.5]nonan-7-yl)phenyl)-3,7-dimethyl-3H-imidazo[4,5-b] pyridine (58); 2-(3,4-dimethoxyphenyl)-5-(4-(6-isopropyl-2,6-diazaspiro[3.3]heptan-2-yl) phenyl)-3,7-dimethyl-3H-imidazo[4,5-b]pyridine (59); 2-(3,4-dimethoxyphenyl)-5-(4-(2-isobutyl-2,7-diazaspiro[3.5]nonan-7-yl)phenyl)-3,7-dimethyl-3H-imidazo[4,5-b]pyridine (60); 5-(4-(2-isopropyl-2,7-diazaspiro[3.5]nonan-7-yl)phenyl)-3-methyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (61); 5-(4-(2-isobutyl-2,7-diazaspiro[3.5]nonan-7-yl)phenyl)-3-methyl-2-(4-(methylsulfonyl) phenyl)-3H-imidazo[4,5-b]pyridine (62); 2-methyl-1-(7-(4-(3-methyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridin-5-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)propan-2-ol (63); 2-(3,4-dimethoxyphenyl)-5-(4-(6-isobutyl-2,6-diazaspiro[3.3]heptan-2-yl)phenyl)-3,7-dimethyl-3H-imidazo[4,5-b]pyridine (64); 5-(4-(6-isopropyl-2,6-diazaspiro[3.3]heptan-2-yl)phenyl)-3-methyl-2-(4-(methylsulfonyl) phenyl)-3H-imidazo[4,5-b]pyridine (65); or 5-(4-(6-isobutyl-2,6-diazaspiro[3.3]heptan-2-yl)phenyl)-3-methyl-2-(4-(methylsulfonyl) phenyl)-3H-imidazo[4,5-b]pyridine (66).

One embodiment provides a compound of Formula (I) or a salt thereof, wherein said

compound is 2-(3,4-dimethoxyphenyl)-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1H-imidazo[4,5-b]pyridine (11); 2-(3,4-dimethoxyphenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1H-imidazo[4,5-b]pyridine (12); 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3,4-dimethoxyphenyl)-1H-imidazo[4,5-b]pyridine (13); 6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-imidazo[4,5-b]pyridine (14); 6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-imidazo[4,5-b]pyridine (15); 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-imidazo[4,5-b]pyridine (16); 2-(3,4-dimethoxyphenyl)-6-(4-(4-isopropylpiperazin-1-yl)phenyl)-1-methyl-1H-imidazo[4,5-b]pyridine (48); 6-(4-(4-isopropylpiperazin-1-yl)phenyl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-imidazo[4,5-b]pyridine (49); 1-cyclopropyl-2-(3,4-dimethoxyphenyl)-6-(4-(4-isopropylpiperazin-1-yl)phenyl)-1H-imidazo[4,5-b]pyridine (50); or 1-cyclopropyl-6-(4-(4-isopropylpiperazin-1-yl)phenyl)-2-(4-(methylsulfonyl)phenyl)-1H-imidazo[4,5-b]pyridine (51).

One embodiment provides compounds of the Formula (I) having TLR9 IC₅₀ values of $\leq 0.6 \mu\text{M}$.

One embodiment provides compounds of the Formula (I) having TLR9 IC₅₀ values of $\leq 0.1 \mu\text{M}$.

One embodiment provides compounds of the Formula (I) having TLR9 IC₅₀ values of $\leq 0.05 \mu\text{M}$.

One embodiment provides compounds of the Formula (I) having TLR9 IC₅₀ values of $\leq 0.025 \mu\text{M}$.

One embodiment provides compounds of the Formula (I) having TLR9 IC₅₀ values of $\leq 0.015 \mu\text{M}$.

One embodiment provides compounds of the Formula (I) having TLR9 IC₅₀ values of $\leq 0.01 \mu\text{M}$.

In another embodiment, the present invention provides a composition comprising at least one of the compounds of the present invention, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or a solvate thereof.

In another embodiment, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and at least one of the

compounds of the present invention or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or a solvate thereof.

In another embodiment, the present invention provides a pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or a solvate thereof.

In another embodiment, the present invention provides a process for making a compound of the present invention.

In another embodiment, the present invention provides an intermediate for making a compound of the present invention.

In another embodiment, the present invention provides a pharmaceutical composition as defined above further comprising one or more additional therapeutic agents.

DEFINITIONS

The features and advantages of the invention may be more readily understood by those of ordinary skill in the art upon reading the following detailed description. It is to be appreciated that certain features of the invention that are, for clarity reasons, described above and below in the context of separate embodiments, may also be combined to form a single embodiment. Conversely, various features of the invention that are, for brevity reasons, described in the context of a single embodiment, may also be combined so as to form sub-combinations thereof. Embodiments identified herein as exemplary or preferred are intended to be illustrative and not limiting.

Unless specifically stated otherwise herein, references made in the singular may also include the plural. For example, "a" and "an" may refer to either one, or one or more.

As used herein, the phrase "compounds" refers to at least one compound. For example, a compound of Formula (I) includes a compound of Formula (I) and two or more compounds of Formula (I).

Unless otherwise indicated, any heteroatom with unsatisfied valences is assumed to have hydrogen atoms sufficient to satisfy the valences.

The definitions set forth herein take precedence over definitions set forth in any

patent, patent application, and/or patent application publication incorporated herein by reference.

Listed below are definitions of various terms used to describe the present invention. These definitions apply to the terms as they are used throughout the specification (unless they are otherwise limited in specific instances) either individually or as part of a larger group.

Throughout the specification, groups and substituents thereof may be chosen by one skilled in the field to provide stable moieties and compounds.

In accordance with a convention used in the art,



is used in structural formulas herein to depict the bond that is the point of attachment of the moiety or substituent to the core or backbone structure.

The terms "halo" and "halogen," as used herein, refer to F, Cl, Br, and I.

The term "cyano" refers to the group -CN.

15 The term "amino" refers to the group -NH₂.

The term "oxo" refers to the group =O.

The term "alkyl" as used herein, refers to both branched and straight-chain saturated aliphatic hydrocarbon groups containing, for example, from 1 to 12 carbon atoms, from 1 to 6 carbon atoms, and from 1 to 4 carbon atoms. Examples of alkyl groups include, but are not limited to, methyl (Me), ethyl (Et), propyl (*e.g.*, *n*-propyl and *i*-propyl), butyl (*e.g.*, *n*-butyl, *i*-butyl, *sec*-butyl, and *t*-butyl), and pentyl (*e.g.*, *n*-pentyl, isopentyl, neopentyl), *n*-hexyl, 2-methylpentyl, 2-ethylbutyl, 3-methylpentyl, and 4-methylpentyl. When numbers appear in a subscript after the symbol "C", the subscript defines with more specificity the number of carbon atoms that a particular group may contain. For example, "C₁₋₆ alkyl" denotes straight and branched chain alkyl groups with one to six carbon atoms.

The term "fluoroalkyl" as used herein is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups substituted with one or more fluorine atoms. For example, "C₁₋₄ fluoroalkyl" is intended to include C₁, C₂, C₃, and C₄ alkyl groups substituted with one or more fluorine atoms. Representative examples of fluoroalkyl groups include, but are not limited to, -CF₃ and -CH₂CF₃.

The term "cycloalkyl," as used herein, refers to a group derived from a non-aromatic monocyclic or polycyclic hydrocarbon molecule by removal of one hydrogen atom from a saturated ring carbon atom. Representative examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclopentyl, and cyclohexyl. When numbers
5 appear in a subscript after the symbol "C", the subscript defines with more specificity the number of carbon atoms that a particular cycloalkyl group may contain. For example, "C₃₋₆ cycloalkyl" denotes cycloalkyl groups with three to six carbon atoms.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of
10 sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The compounds of Formula (I) can form salts which are also within the scope of this invention. Unless otherwise indicated, reference to an inventive compound is
15 understood to include reference to one or more salts thereof. The term "salt(s)" denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. In addition, the term "salt(s)" may include zwitterions (inner salts), *e.g.*, when a compound of Formula (I) contains both a basic moiety, such as an amine or a pyridine or imidazole ring, and an acidic moiety, such as a carboxylic acid. Pharmaceutically acceptable (*i.e.*,
20 non-toxic, physiologically acceptable) salts are preferred, such as, for example, acceptable metal and amine salts in which the cation does not contribute significantly to the toxicity or biological activity of the salt. However, other salts may be useful, *e.g.*, in isolation or purification steps which may be employed during preparation, and thus, are contemplated within the scope of the invention. Salts of the compounds of the formula (I)
25 may be formed, for example, by reacting a compound of the 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. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th Edition, Mack Publishing Company, Easton, PA (1990), the disclosure of which is hereby incorporated by
30 reference.

Exemplary acid addition salts include acetates (such as those formed with acetic

acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides (formed with hydrochloric acid), hydrobromides (formed with hydrogen bromide), hydroiodides, maleates (formed with maleic acid), 2-hydroxyethanesulfonates, lactates, methanesulfonates (formed with methanesulfonic acid), 2-naphthalenesulfonates, nicotines, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates such as tosylates, undecanoates, and the like.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts; alkaline earth metal salts such as calcium and magnesium salts; barium, zinc, and aluminum salts; salts with organic bases (for example, organic amines) such as trialkylamines such as triethylamine, procaine, dibenzylamine, N-benzyl-β-phenethylamine, 1-phenethylamine, N,N'-dibenzylethylene-diamine, dehydroabietylamine, N-ethylpiperidine, benzylamine, dicyclohexylamine or similar pharmaceutically acceptable amines and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g., methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g., decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g., benzyl and phenethyl bromides), and others.

The compounds of Formula (I) can be provided as amorphous solids or crystalline solids. Lyophilization can be employed to provide the compounds of Formula (I) as amorphous solids.

It should further be understood that solvates (e.g., hydrates) of the compounds of Formula (I) are also within the scope of the present invention. The term "solvate" means a physical association of a compound of Formula (I) with one or more solvent molecules, whether organic or inorganic. This physical association includes 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. "Solvate" encompasses both solution-phase and isolable solvates. Exemplary solvates include hydrates, ethanulates, methanulates, isopropanulates, acetonitrile solvates, and ethyl acetate solvates. Methods of solvation are known in the art.

Various forms of prodrugs are well known in the art and are described in Rautio, J. et al., *Nature Review Drug Discovery*, 17, 559-587 (2018).

In addition, compounds of Formula (I), subsequent to their preparation, can be isolated and purified to obtain a composition containing an amount by weight equal to or greater than 99% of a compound of Formula (I), respectively ("substantially pure"), which is then used or formulated as described herein. Such "substantially pure" compounds of Formula (I) are also contemplated herein as part of the present invention.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. The present invention is intended to embody stable compounds.

"Therapeutically effective amount" is intended to include an amount of a compound of the present invention alone or an amount of the combination of compounds claimed or an amount of a compound of the present invention in combination with other active ingredients effective to act as an inhibitor of TLR9, or effective to treat or prevent disorders associated with a fibrotic disease or disorder, dysregulation of bile acids, such as pathological fibrosis.

As used herein, "treating" or "treatment" cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b) inhibiting the disease-state, i.e., arresting its development; and/or (c) relieving the disease-state, i.e., causing regression of the disease state.

The compounds of the present invention are intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium (D) and tritium (T). Isotopes of

carbon include ^{13}C and ^{14}C . Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed. For example, methyl (-
5 CH_3) also includes deuterated methyl groups such as $-\text{CD}_3$.

UTILITY

The compounds of the invention are useful for inhibiting the TLR9 receptor.

One embodiment provides a method for the treatment of a disease, disorder, or
10 condition associated with dysregulation of bile acids in a patient in need of such treatment, and the method comprises administering a therapeutically effective amount of a compound of the present invention, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof, to the patient.

One embodiment provides a method for the treatment of a disease, disorder, or
15 condition associated with activity of the TLR9 receptor in a patient in need of such treatment comprising administering a therapeutically effective amount of a compound of the present invention, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof, to the patient.

One embodiment provides a method for the treatment of the disease, disorder, or
20 condition comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

One embodiment provides a method for eliciting an TLR9 receptor agonizing
25 effect in a patient comprising administering a therapeutically effective amount of a compound of the present invention, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof, to the patient.

In some embodiments, the disease, disorder, or condition is associated with TLR9 dysfunction include pathological fibrosis, cancer, inflammatory disorders, metabolic, or
30 cholestatic disorders.

In some embodiments, the disease, disorder, or condition is associated with fibrosis, including liver, biliary, renal, cardiac, dermal, ocular, and pancreatic fibrosis.

In other embodiments, the disease, disorder, or condition is associated with cell-proliferative disorders, such as cancer. In some embodiments, the cancer includes solid tumor growth or neoplasia. In other embodiments, the cancer includes tumor metastasis. In some embodiments, the cancer is of the liver, gall bladder, small intestine, large
 5 intestine, kidney, prostate, bladder, blood, bone, brain, breast, central nervous system, cervix, colon, endometrium, esophagus, genitalia, genitourinary tract, head, larynx, lung, muscle tissue, neck, oral or nasal mucosa, ovary, pancreas, skin, spleen, stomach, testicle, or thyroid. In other embodiments, the cancer is a carcinoma, sarcoma, lymphoma, leukemia, melanoma, mesothelioma, multiple myeloma, or seminoma.

10 Examples of diseases, disorders, or conditions associated with the activity of TLR9 that can be prevented, modulated, or treated according to the present invention include, but are not limited to, transplant rejection, fibrotic disorders (e. g., liver fibrosis, kidney fibrosis), inflammatory disorders (e. g., acute hepatitis, chronic hepatitis, non-alcoholic steatohepatitis (NASH), irritable bowel syndrome (IBS), inflammatory bowel
 15 disease (IBD)), as well as cell-proliferative disorders (e. g., cancer, myeloma, fibroma, hepatocellular carcinoma, colorectal cancer, prostate cancer, leukemia, Kaposi's sarcoma, solid tumors).

The fibrotic disorders, inflammatory disorders, as well as cell-proliferative disorders that are suitable to be prevented or treated by the compounds of the present
 20 invention include, but are not limited to, non-alcoholic fatty liver disease (NAFLD), alcoholic or non-alcoholic steatohepatitis (NASH), acute hepatitis, chronic hepatitis, liver cirrhosis, primary biliary cirrhosis, primary sclerosing cholangitis, drug-induced hepatitis, biliary cirrhosis, portal hypertension, regenerative failure, liver hypofunction, hepatic blood flow disorder, nephropathy, irritable bowel syndrome (IBS), inflammatory bowel
 25 disease (IBD), abnormal pancreatic secretion, benign prostatic hyperplasia, neuropathic bladder disease, diabetic nephropathy, focal segmental glomerulosclerosis, IgA nephropathy, nephropathy induced by drugs or transplantation, autoimmune nephropathy, lupus nephritis, liver fibrosis, kidney fibrosis, chronic kidney disease (CKD), diabetic kidney disease (DKD), skin fibrosis, keloids, systemic sclerosis, scleroderma, virally-
 30 induced fibrosis, idiopathic pulmonary fibrosis (IPF), interstitial lung disease, non-specific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), radiation-induced fibrosis, familial pulmonary fibrosis, airway fibrosis, chronic obstructive

pulmonary disease (COPD), spinal cord tumor, hernia of intervertebral disk, spinal canal stenosis, heart failure, cardiac fibrosis, vascular fibrosis, perivascular fibrosis, foot-and-mouth disease, cancer, myeloma, fibroma, hepatocellular carcinoma, colorectal cancer, prostate cancer, leukemia, chronic lymphocytic leukemia, Kaposi's sarcoma, solid
5 tumors, cerebral infarction, cerebral hemorrhage, neuropathic pain, peripheral neuropathy, age-related macular degeneration (AMD), glaucoma, ocular fibrosis, corneal scarring, diabetic retinopathy, proliferative vitreoretinopathy (PVR), cicatricial pemphigoid glaucoma filtration surgery scarring, Crohn's disease or systemic lupus erythematosus; keloid formation resulting from abnormal wound healing; fibrosis
10 occurring after organ transplantation, myelofibrosis, and fibroids. In one embodiment, the present invention provides a method for the treatment of a fibrotic disorder, an inflammatory disorder, or a cell-proliferative disorder, comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention, alone, or, optionally, in combination with another
15 compound of the present invention and/or at least one other type of therapeutic agent.

In another embodiment, the present invention provides a compound of the present invention for use in therapy.

In another embodiment, the present invention provides a compound of the present invention for use in therapy for the treatment of a fibrotic disorder, an inflammatory
20 disorder, or a cell-proliferative disorder thereof.

In another embodiment, the present invention also provides the use of a compound of the present invention for the manufacture of a medicament for the treatment of a fibrotic disorder, an inflammatory disorder, or a cell-proliferative disorder thereof.

In another embodiment, the present invention provides a method for the treatment
25 of a fibrotic disorder, an inflammatory disorder, or a cell-proliferative disorder, comprising administering to a patient in need thereof a therapeutically effective amount of a first and second therapeutic agent, wherein the first therapeutic agent is a compound of the present invention.

In another embodiment, the present invention provides a combined preparation of
30 a compound of the present invention and additional therapeutic agent(s) for simultaneous, separate or sequential use in therapy.

In another embodiment, the present invention provides a combined preparation of

a compound of the present invention and additional therapeutic agent(s) for simultaneous, separate or sequential use in the treatment of a fibrotic disorder, an inflammatory disorder, or a cell-proliferative disorder.

The compounds of the present invention may be employed in combination with
5 additional therapeutic agent(s), such as one or more anti-fibrotic and/or anti-inflammatory therapeutic agents.

In one embodiment, additional therapeutic agent(s) used in combined pharmaceutical compositions or combined methods or combined uses, are selected from one or more, preferably one to three, of the following therapeutic agents: TGF β receptor
10 inhibitors (for example, galunisertib), inhibitors of TGF β synthesis (for example, pirfenidone), inhibitors of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) receptor kinases (for example, nintedanib), humanized anti- α v β 6 integrin monoclonal antibody (for example, 3G9), human recombinant pentraxin-2, recombinant human Serum Amyloid P, recombinant
15 human antibody against TGF β -1, -2, and -3, endothelin receptor antagonists (for example, macitentan), interferon gamma, c-Jun amino-terminal kinase (JNK) inhibitor (for example, 4-[[9-[(3S)-tetrahydro-3-furanyl]-8-[(2,4,6-trifluorophenyl)amino]-9H-purin-2-yl]amino]-trans-cyclohexanol, 3-pentylbenzeneacetic acid (PBI-4050), tetra-substituted porphyrin derivative containing manganese (III), monoclonal antibody targeting eotaxin-
20 2, interleukin-13 (IL-13) antibody (for example, lebrikizumab, tralokinumab), bispecific antibody targeting interleukin 4 (IL-4) and interleukin 13 (IL-13), NK1 tachykinin receptor agonist (for example, Sar⁹, Met(O₂)¹¹-Substance P), Cintredekin Besudotox, human recombinant DNA-derived, IgG1 kappa monoclonal antibody to connective growth factor, and fully human IgG1 kappa antibody, selective for CC-chemokine ligand
25 2 (for example, carlumab, CCX140), antioxidants (for example, N-acetylcysteine), phosphodiesterase 5 (PDE5) inhibitors (for example, sildenafil), agents for treatment of obstructive airway diseases such as muscarinic antagonists (for example, tiotropium, ipatropium bromide), adrenergic β 2 agonists (for example, salbutamol, salmeterol), corticosteroids (for example, triamcinolone, dexamethasone, fluticasone),
30 immunosuppressive agents (for example, tacrolimus, rapamycin, pimecrolimus), and therapeutic agents useful for the treatment of fibrotic conditions, such as liver, biliary, and

kidney fibrosis, Non-Alcoholic Fatty Liver Disease (NALFD), Non-Alcoholic Steato-Hepatitis (NASH), cardiac fibrosis, Idiopathic Pulmonary Fibrosis (IPF), and systemic sclerosis. The therapeutic agents useful for the treatment of such fibrotic conditions include, but are not limited to, FXR agonists (for example OCA, GS-9674, and LJN452),

5 LOXL2 inhibitors (for example simtuzumab), LPA1 antagonists (for example, BMS-986020 and SAR 100842), PPAR modulators (for example, elafibrinor, pioglitazone, and saroglitazar, IVA337), SSAO/VAP-1 inhibitors (for example, PXS-4728A and SZE5302), ASK-1 inhibitors (for example GS-4997 or selonsertib), ACC inhibitors (for example, CP-640186 and NDI-010976 or GS-0976), FGF21 mimetics (for example, LY2405319

10 and BMS-986036), caspase inhibitors (for example, emricasan), NOX4 inhibitors (for example, GKT137831), MGAT2 inhibitor (for example, BMS-963272), α V integrin inhibitors (for example, abituzumab) and bile acid/fatty acid conjugates (for example aramchol). The TLR9 inhibitors of various embodiments of the present invention may also be used in combination with one or more therapeutic agents such as CCR2/5 inhibitors

15 (for example, cenicriviroc), Galectin-3 inhibitors (for example, TD-139, GR-MD-02), leukotriene receptor antagonists (for example, tielukast, montelukast), SGLT2 inhibitors (for example, dapagliflozin, remogliflozin), GLP-1 receptor agonists (for example, liraglutide and semaglutide), FAK inhibitors (for example, GSK-2256098), CB1 inverse agonists (for example, JD-5037), CB2 agonists (for example, APD-371 and JBT-101),

20 autotaxin inhibitors (for example, GLPG1690), prolyl t-RNA synthetase inhibitors (for example, halofuginone), FPR2 agonists (for example, ZK-994), and THR agonists (for example, MGL:3196). In another embodiment, additional therapeutic agent(s) used in combined pharmaceutical compositions or combined methods or combined uses, are selected from one or more, preferably one to three, of immunoncology agents, such as

25 Alemtuzumab, Atezolizumab, Ipilimumab, Nivolumab, Ofatumumab, Pembrolizumab, and Rituximab.

When the terms "TLR9-associated condition" or "TLR9-associated disease or disorder" are used herein, each is intended to encompass all of the conditions identified above as if repeated at length, as well as any other condition that is affected by inhibition

30 of TLR9.

The above other therapeutic agents, when employed in combination with the

compounds of the present invention, may be used, for example, in those amounts indicated in the *Physicians' Desk Reference* (PDR) or as otherwise determined by one of ordinary skill in the art. In the methods of the present invention, such other therapeutic agent(s) may be administered prior to, simultaneously with, or following the
5 administration of the inventive compounds. The present invention also provides pharmaceutical compositions capable of treating TLR9-associated conditions.

The inventive compositions may contain other therapeutic agents as described above and may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode
10 of desired administration (*e.g.*, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation.

Accordingly, the present invention further includes compositions comprising one or more compounds of Formula (I) and a pharmaceutically acceptable carrier.

15 A "pharmaceutically acceptable carrier" refers to media generally accepted in the art for the delivery of biologically active agents to animals, in particular, mammals. Pharmaceutically acceptable carriers are formulated according to a number of factors well within the purview of those of ordinary skill in the art. These include without limitation the type and nature of the active agent being formulated; the subject to which the agent-
20 containing composition is to be administered; the intended route of administration of the composition; and, the therapeutic indication being targeted. Pharmaceutically acceptable carriers include both aqueous and non-aqueous liquid media, as well as a variety of solid and semi-solid dosage forms. Such carriers can include a number of different ingredients and additives in addition to the active agent, such additional ingredients being included in
25 the formulation for a variety of reasons, *e.g.*, stabilization of the active agent, binders, etc., well known to those of ordinary skill in the art. Descriptions of suitable pharmaceutically acceptable carriers, and factors involved in their selection, are found in a variety of readily available sources such as, for example, *Remington's Pharmaceutical Sciences*, 17th Edition (1985), which is incorporated herein by reference in its entirety.

30 Compounds in accordance with Formula (I) can be administered by any means suitable for the condition to be treated, which can depend on the need for site-specific treatment or quantity of Formula (I) compound to be delivered.

Also embraced within this invention is a class of pharmaceutical compositions comprising a compound of Formula (I), and one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as “carrier” materials) and, if desired, other active ingredients. The compounds of Formula (I) may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and compositions of the present invention may, for example, be administered orally, mucosally, or parentally including intravascularly, intravenously, intraperitoneally, subcutaneously, intramuscularly, and intrasternally in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles. For example, the pharmaceutical carrier may contain a mixture of mannitol or lactose and microcrystalline cellulose. The mixture may contain additional components such as a lubricating agent, e.g. magnesium stearate and a disintegrating agent such as crospovidone. The carrier mixture may be filled into a gelatin capsule or compressed as a tablet. The pharmaceutical composition may be administered as an oral dosage form or an infusion, for example.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, liquid capsule, suspension, or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. For example, the pharmaceutical composition may be provided as a tablet or capsule comprising an amount of active ingredient in the range of from about 0.1 to 1000 mg, preferably from about 0.25 to 250 mg, and more preferably from about 0.5 to 100 mg. A suitable daily dose for a human or other mammal may vary widely depending on the condition of the patient and other factors, but, can be determined using routine methods.

Any pharmaceutical composition contemplated herein can, for example, be delivered orally via any acceptable and suitable oral preparations. Exemplary oral preparations, include, but are not limited to, for example, tablets, troches, lozenges, aqueous and oily suspensions, dispersible powders or granules, emulsions, hard and soft capsules, liquid capsules, syrups, and elixirs. Pharmaceutical compositions intended for oral administration can be prepared according to any methods known in the art for manufacturing pharmaceutical compositions intended for oral administration. In order to

provide pharmaceutically palatable preparations, a pharmaceutical composition in accordance with the invention can contain at least one agent selected from sweetening agents, flavoring agents, coloring agents, demulcents, antioxidants, and preserving agents.

A tablet can, for example, be prepared by admixing at least one compound of
5 Formula (I) with at least one non-toxic pharmaceutically acceptable excipient suitable for the manufacture of tablets. Exemplary excipients include, but are not limited to, for example, inert diluents, such as, for example, calcium carbonate, sodium carbonate, lactose, calcium phosphate, and sodium phosphate; granulating and disintegrating agents, such as, for example, microcrystalline cellulose, sodium crosscarmellose, corn starch, and
10 alginic acid; binding agents, such as, for example, starch, gelatin, polyvinyl-pyrrolidone, and acacia; and lubricating agents, such as, for example, magnesium stearate, stearic acid, and talc. Additionally, a tablet can either be uncoated, or coated by known techniques to either mask the bad taste of an unpleasant tasting drug, or delay disintegration and absorption of the active ingredient in the gastrointestinal tract thereby sustaining the
15 effects of the active ingredient for a longer period. Exemplary water soluble taste masking materials, include, but are not limited to, hydroxypropyl-methylcellulose and hydroxypropyl-cellulose. Exemplary time delay materials, include, but are not limited to, ethyl cellulose and cellulose acetate butyrate.

Hard gelatin capsules can, for example, be prepared by mixing at least one
20 compound of Formula (I) with at least one inert solid diluent, such as, for example, calcium carbonate; calcium phosphate; and kaolin.

Soft gelatin capsules can, for example, be prepared by mixing at least one compound of Formula (I) with at least one water soluble carrier, such as, for example, polyethylene glycol; and at least one oil medium, such as, for example, peanut oil, liquid
25 paraffin, and olive oil.

An aqueous suspension can be prepared, for example, by admixing at least one compound of Formula (I) with at least one excipient suitable for the manufacture of an aqueous suspension. Exemplary excipients suitable for the manufacture of an aqueous suspension, include, but are not limited to, for example, suspending agents, such as, for
30 example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, alginic acid, polyvinyl-pyrrolidone, gum tragacanth, and gum acacia; dispersing or wetting agents, such as, for example, a naturally-occurring

phosphatide, e.g., lecithin; condensation products of alkylene oxide with fatty acids, such as, for example, polyoxyethylene stearate; condensation products of ethylene oxide with long chain aliphatic alcohols, such as, for example heptadecaethylene-oxycetanol; condensation products of ethylene oxide with partial esters derived from fatty acids and
5 hexitol, such as, for example, polyoxyethylene sorbitol monooleate; and condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, such as, for example, polyethylene sorbitan monooleate. An aqueous suspension can also contain at least one preservative, such as, for example, ethyl and n-propyl p-hydroxybenzoate; at least one coloring agent; at least one flavoring agent; and/or
10 at least one sweetening agent, including but not limited to, for example, sucrose, saccharin, and aspartame.

Oily suspensions can, for example, be prepared by suspending at least one compound of Formula (I) in either a vegetable oil, such as, for example, arachis oil; olive oil; sesame oil; and coconut oil; or in mineral oil, such as, for example, liquid paraffin.
15 An oily suspension can also contain at least one thickening agent, such as, for example, beeswax; hard paraffin; and cetyl alcohol. In order to provide a palatable oily suspension, at least one of the sweetening agents already described hereinabove, and/or at least one flavoring agent can be added to the oily suspension. An oily suspension can further contain at least one preservative, including, but not limited to, for example, an anti-
20 oxidant, such as, for example, butylated hydroxyanisol, and alpha-tocopherol.

Dispersible powders and granules can, for example, be prepared by admixing at least one compound of Formula (I) with at least one dispersing and/or wetting agent; at least one suspending agent; and/or at least one preservative. Suitable dispersing agents, wetting agents, and suspending agents are as already described above. Exemplary
25 preservatives include, but are not limited to, for example, anti-oxidants, e.g., ascorbic acid. In addition, dispersible powders and granules can also contain at least one excipient, including, but not limited to, for example, sweetening agents; flavoring agents; and coloring agents.

An emulsion of at least one compound of Formula (I) thereof can, for example, be
30 prepared as an oil-in-water emulsion. The oily phase of the emulsions comprising compounds of Formula (I) may be constituted from known ingredients in a known manner. The oil phase can be provided by, but is not limited to, for example, a vegetable

oil, such as, for example, olive oil and arachis oil; a mineral oil, such as, for example, liquid paraffin; and mixtures thereof. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Suitable emulsifying agents include, but are not limited to, for example, naturally-occurring phosphatides, e.g., soy bean lecithin; esters or partial esters derived from fatty acids and hexitol anhydrides, such as, for example, sorbitan monooleate; and condensation products of partial esters with ethylene oxide, such as, for example, polyoxyethylene sorbitan monooleate. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. An emulsion can also contain a sweetening agent, a flavoring agent, a preservative, and/or an antioxidant. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, sodium lauryl sulfate, glyceryl distearate alone or with a wax, or other materials well known in the art.

The compounds of Formula (I) can, for example, also be delivered intravenously, subcutaneously, and/or intramuscularly via any pharmaceutically acceptable and suitable injectable form. Exemplary injectable forms include, but are not limited to, for example, sterile aqueous solutions comprising acceptable vehicles and solvents, such as, for example, water, Ringer's solution, and isotonic sodium chloride solution; sterile oil-in-water microemulsions; and aqueous or oleaginous suspensions.

Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules using one or more of the carriers or diluents mentioned for use in the formulations for oral administration or by using other suitable dispersing or wetting agents and suspending agents. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art. The active ingredient may also be administered by

injection as a composition with suitable carriers including saline, dextrose, or water, or with cyclodextrin (i.e. Captisol), cosolvent solubilization (i.e. propylene glycol) or micellar solubilization (i.e. Tween 80).

The sterile injectable preparation may also be a sterile injectable solution or
5 suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic
10 mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

A sterile injectable oil-in-water microemulsion can, for example, be prepared by 1) dissolving at least one compound of Formula (I) in an oily phase, such as, for example, a mixture of soybean oil and lecithin; 2) combining the Formula (I) containing oil phase
15 with a water and glycerol mixture; and 3) processing the combination to form a microemulsion.

A sterile aqueous or oleaginous suspension can be prepared in accordance with methods already known in the art. For example, a sterile aqueous solution or suspension can be prepared with a non-toxic parenterally-acceptable diluent or solvent, such as, for
20 example, 1,3-butane diol; and a sterile oleaginous suspension can be prepared with a sterile non-toxic acceptable solvent or suspending medium, such as, for example, sterile fixed oils, e.g., synthetic mono- or diglycerides; and fatty acids, such as, for example, oleic acid.

Pharmaceutically acceptable carriers, adjuvants, and vehicles that may be used in
25 the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d-alpha-tocopherol polyethyleneglycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens, polyethoxylated castor oil such as CREMOPHOR surfactant (BASF), or other similar polymeric delivery matrices, serum
30 proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen

phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat. Cyclodextrins such as alpha-, beta-, and gamma-cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl-cyclodextrins, or other solubilized derivatives may also be advantageously used to enhance delivery of compounds of the formulae described herein.

The pharmaceutically active compounds of this invention can be processed in accordance with conventional methods of pharmacy to produce medicinal agents for administration to patients, including humans and other mammals. The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc. Tablets and pills can additionally be prepared with enteric coatings. Such compositions may also comprise adjuvants, such as wetting, sweetening, flavoring, and perfuming agents.

The amounts of compounds that are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex, the medical condition of the subject, the type of disease, the severity of the disease, the route and frequency of administration, and the particular compound employed. Thus, the dosage regimen may vary widely, but can be determined routinely using standard methods. A daily dose of about 0.001 to 100 mg/kg body weight, preferably between about 0.0025 and about 50 mg/kg body weight and most preferably between about 0.005 to 10 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day. Other dosing schedules include one dose per week and one dose per two day cycle.

For therapeutic purposes, the active compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered orally, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alcanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or

polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose.

Pharmaceutical compositions of this invention comprise at least one compound of
5 Formula (I) and optionally an additional agent selected from any pharmaceutically acceptable carrier, adjuvant, and vehicle. Alternate compositions of this invention comprise a compound of the Formula (I) described herein, or a prodrug thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

The present invention also encompasses an article of manufacture. As used
10 herein, article of manufacture is intended to include, but not be limited to, kits and packages. The article of manufacture of the present invention, comprises: (a) a first container; (b) a pharmaceutical composition located within the first container, wherein the composition, comprises: a first therapeutic agent, comprising: a compound of the present invention or a pharmaceutically acceptable salt form thereof; and, (c) a package insert
15 stating that the pharmaceutical composition can be used for the treatment of a cardiovascular disorder, diuresis, and/or natriuresis. In another embodiment, the package insert states that the pharmaceutical composition can be used in combination (as defined previously) with a second therapeutic agent to treat cardiovascular disorder, diuresis, and/or natriuresis. The article of manufacture can further comprise: (d) a second
20 container, wherein components (a) and (b) are located within the second container and component (c) is located within or outside of the second container. Located within the first and second containers means that the respective container holds the item within its boundaries.

The first container is a receptacle used to hold a pharmaceutical composition.
25 This container can be for manufacturing, storing, shipping, and/or individual/bulk selling. First container is intended to cover a bottle, jar, vial, flask, syringe, tube (*e.g.*, for a cream preparation), or any other container used to manufacture, hold, store, or distribute a pharmaceutical product.

The second container is one used to hold the first container and, optionally, the
30 package insert. Examples of the second container include, but are not limited to, boxes (*e.g.*, cardboard or plastic), crates, cartons, bags (*e.g.*, paper or plastic bags), pouches, and sacks. The package insert can be physically attached to the outside of the first container

via tape, glue, staple, or another method of attachment, or it can rest inside the second container without any physical means of attachment to the first container. Alternatively, the package insert is located on the outside of the second container. When located on the outside of the second container, it is preferable that the package insert is physically
5 attached via tape, glue, staple, or another method of attachment. Alternatively, it can be adjacent to or touching the outside of the second container without being physically attached.

The package insert is a label, tag, marker, or other written sheet that recites information relating to the pharmaceutical composition located within the first container.
10 The information recited will usually be determined by the regulatory agency governing the area in which the article of manufacture is to be sold (*e.g.*, the United States Food and Drug Administration). Preferably, the package insert specifically recites the indications for which the pharmaceutical composition has been approved. The package insert may be made of any material on which a person can read information contained therein or
15 thereon. Preferably, the package insert is a printable material (*e.g.*, paper, plastic, cardboard, foil, adhesive-backed paper or plastic) on which the desired information has been formed (*e.g.*, printed or applied).

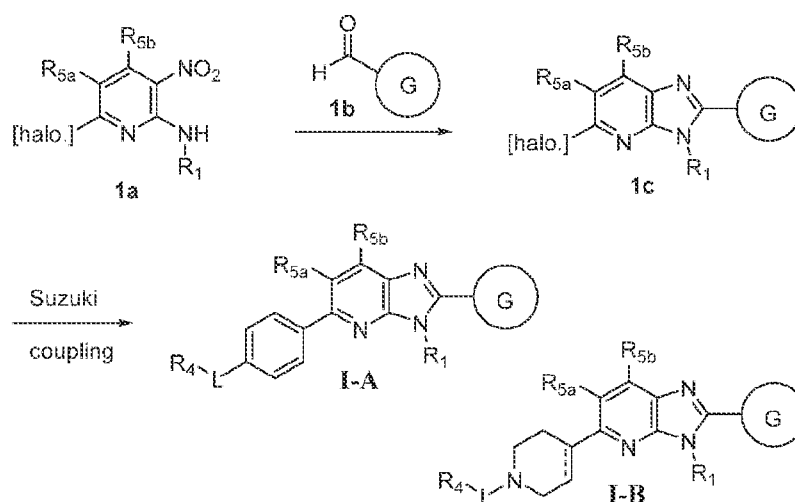
METHODS OF PREPARATION

20 The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to,
25 those described below.

The reactions and techniques described in this section are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including
30 choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and work up procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in

the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents that are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention. It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene et al. (*Protective Groups in Organic Synthesis*, Fifth Edition, Wiley and Sons (2014)).

SCHEME 1



Scheme 1 describes one potential route for the synthesis of compounds of Formula I-A and I-B, a subset of Formula I. The term “halo.” in this scheme refers to any halogen that one of ordinary skill in the art would deem proper to achieve the intended transformation. Compound 1a can be reacted with aldehyde 1b in the presence of sodium hydrosulfite, in a suitable solvent (e.g. EtOH, MeOH, DMSO, NMP), with heating, to furnish compound 1c. Contingent upon the nature of the R₁ substituent, it may be necessary to first reduce the nitro group of compound 1a. Reduction is accomplished

using a typical nitro-reducing agent (e.g. Fe powder, tin chloride dihydrate, catalytic hydrogenation), followed by cyclization with aldehyde 1b in the presence of sodium metabisulfite, in a suitable solvent (e.g. NMP, DMSO, EtOH), with heating to provide compound 1c. Compound 1c can be reacted with the appropriate boronate ester or
5 boronic acid using standard Suzuki coupling conditions to furnish compounds of Formula I-A and I-B.

EXAMPLES

Compounds of the current invention and intermediates used in the preparation of
10 compounds of the current invention can be prepared using procedures shown in the following examples and related procedures. The methods and conditions used in these examples, and the actual compounds prepared in these examples, are not meant to be limiting, but are meant to demonstrate how the compounds of the current invention can be prepared. Starting materials and reagents used in these examples, when not prepared by a
15 procedure described herein, are generally either commercially available, or are reported in the chemical literature, or may be prepared by using procedures described in the chemical literature. The invention is further defined in the following Examples. It should be understood that the Examples are given by way of illustration only. From the above discussion and the Examples, one skilled in the art can ascertain the essential
20 characteristics of the invention, and without departing from the spirit and scope thereof, can make various changes and modifications to adapt the invention to various uses and conditions. As a result, the invention is not limited by the illustrative examples set forth herein below, but rather defined by the claims appended hereto.

In the examples given, the phrase "dried and concentrated" generally refers to
25 drying of a solution in an organic solvent over either sodium sulfate or magnesium sulfate, followed by filtration and removal of the solvent from the filtrate (generally under reduced pressure and at a temperature suitable to the stability of the material being

Chemical names were determined using ChemDraw Professional, version
20.1.0.110 (PerkinElmer Informatics, Inc.). The following abbreviations are used:

30

AcOH	acetic acid
aq.	aqueous

	brine	saturated aqueous sodium chloride
	DCM	dichloromethane
	DMF	<i>N,N</i> -dimethylformamide
	DMSO	dimethyl sulfoxide
5	EtOAc	ethyl acetate
	EtOH	ethanol
	IPA	isopropyl alcohol
	MeCN	acetonitrile
	MeOH	methanol
10	NMP	<i>N</i> -methyl-2-pyrrolidone
	THF	tetrahydrofuran
	pet ether	petroleum ether
	g	gram(s)
	h	hour(s)
15	min	minute(s)
	HPLC	High Performance Liquid Chromatography
	LC/MS	Liquid Chromatography / Mass Spectroscopy
	Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium(0)
	TEA	triethylamine
20	TFA	trifluoroacetic acid
	<i>rac</i> -BINAP	(±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene, 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene
	XPhos Pd G3	2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl][2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate
25	XPhos Pd G4	methanesulfonato(2-dicyclohexylphosphino-2',4',6'-tri- <i>i</i> -propyl-1,1'-biphenyl)(2'-methylamino-1,1'-biphenyl-2-yl)palladium(II)
	Pd(dppf)Cl ₂ ·DCM	[1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane

30 PREPARATION

All reagents purchased from commercial sources were used without further purification unless otherwise noted. All reactions involving air or moisture sensitive

reagents were performed under an inert atmosphere. Proton magnetic resonance spectra were recorded primarily on a Bruker Avance 400 or 500 MHz spectrometer.

Analytical LC/MS Methods

- 5 Method 1: Column: Waters Acquity BEH C18, 2.1 x 50mm, 1.7 μ m particles; Mobile Phase A: 5:95 MeCN:water with 0.05 % TFA; Mobile Phase B: 95:5 MeCN:water with 0.05 % TFA; Temperature: 50 °C; Gradient: 0 %B to 100 %B over 3 min, then a 0.50 min hold at 100 %B; Flow: 1 mL/min; Detection: MS and UV (220, 254 nm).
- 10 Method 2: Column: XBridge C18, 2.1 mm x 50 mm, 1.7 μ m particles; Mobile Phase A: MeCN/H₂O (5:95) with 10 mM NH₄OAc; Mobile Phase B: MeCN/H₂O (95:5) with 10 mM NH₄OAc; Temperature: 50 °C; Gradient: 0-100 %B (0.0-3.0 min), 100 %B (3.0-3.5 min); Flow: 1.0 mL/min; Detection: UV (220 nm) and MS (ESI +).
- Method 3: Column: XBridge C18, 2.1 mm x 50 mm, 1.7 μ m particles; Mobile
15 Phase A: MeCN/H₂O (5:95) with 0.05 % TFA; Mobile Phase B: MeCN/H₂O (95:5) with 0.05 % TFA; Temperature: 50 °C; Gradient: 0-100 %B (0.0-3.0 min), 100 %B (3.0-3.5 min); Flow: 1.0 mL/min; Detection: UV (220 nm) and MS (ESI +).
- Method 4: Column: HALO C18, 3.0 x 30mm, 2.7 μ m particles; Mobile Phase A: water with 0.05 % TFA; Mobile Phase B: MeCN with 0.05 % TFA; Temperature: 40 °C;
20 Gradient: 5 %B to 100 %B over 1.3 min, then a 0.50 min hold at 100 %B; Flow: 1.5 mL/min; Detection: MS and UV (254/220 nm).
- Method 5: Column: HALO C18, 3.0 x 30mm, 2.7 μ m particles; Mobile Phase A: water with 0.05 % TFA; Mobile Phase B: MeCN with 0.05 % TFA; Temperature: 40 °C; Gradient: 5 %B to 50 %B over 2 min, 50 %B to 100 %B over 0.4 min, then a 0.40 min
25 hold at 100 %B; Flow: 1.5 mL/min; Detection: MS and UV (254/220 nm).
- Method 6: Column: Waters Acquity BEH C18, 2.1 x 50 mm, 1.7 μ m particles; Mobile Phase A: 5:95 MeCN:water with 10 mM NH₄OAc; Mobile Phase B: 95:5 MeCN:water with 10 mM NH₄OAc; Temperature: 50 °C; Gradient: 0 %B to 100 %B over 3 min, then a 0.50 min hold at 100 %B; Flow: 1 mL/min; Detection: MS and UV
30 (220, 254 nm).

Preparative HPLC Methods

Prep Method A: Column: XBridge C18, 200 mm x 19 mm, 5- μ m particles; Mobile Phase A: 5:95 MeCN: water with NH_4OAc ; Mobile Phase B: 95:5 MeCN: water with NH_4OAc ; Gradient: (variable; dependent on substrate) %B over 20 minutes, then a 0-minute hold at 100% B; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation.

Prep Method B: Column: XBridge C18, 200 mm x 19 mm, 5- μ m particles; Mobile Phase A: 5:95 MeCN: water with 0.05% TFA; Mobile Phase B: 95:5 MeCN: water with 0.05% TFA; Gradient: (variable; dependent on substrate) % B over 20 minutes, then a 0-minute hold at 100% B; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS signals. Fractions containing the desired product were combined and dried via centrifugal evaporation.

Prep Method C: Column: Phenomenex AXIA 5u C18, 30x100mm; Mobile Phase A: 90% H_2O /10% MeOH-10mM NH_4OAc ; Mobile Phase B: 10% H_2O /90% MeOH-10 mM NH_4OAc ; Method: Grad.Solv.System: From 100% A: 0% B to 0% A: 100% B; Detection at 220 nM; 10 min grad.

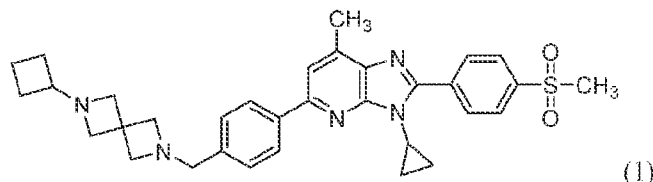
Prep Method D: Column: Phenomenex AXIA 5u C18, 30x100mm; Mobile Phase A: 90% H_2O /10% MeCN/0.1% TFA; Mobile Phase B: 10% H_2O /90% MeCN/0.1% TFA; Method: Grad.Solv.System: From 100% A: 0% B to 0% A: 100% B; Detection at 220 nM; 10 min grad.

Prep Method E: Column: Column: SunFire Prep C18 OBD Column, 19x150 mm, 5 μ m 10nm; Mobile Phase A: Water (0.05% TFA), Mobile Phase B: MeCN; Flow rate: 25 mL/min; Gradient: 5% B to 15% B in 6.8 min; Wave Length: 254 nm; Column Temperature: 25 °C. Fraction collection was triggered by MS and UV signals. The pure fractions were combined and concentrated under vacuum to remove organic solvents. The residual aqueous solution was dried by lyophilization to afford the final product.

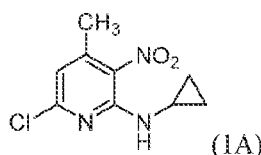
Prep Method F: Column: XBridge Prep C18 OBD Column, 19x150 mm, 5 μ m; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: MeCN; Flow rate: 20 mL/min; Gradient: 30% B to 50% B in 4.5 min; Wave Length: 254/210 nm; Column Temperature: 25 °C. Fraction collection was triggered by MS and UV signals. The pure fractions were combined and concentrated under vacuum to remove organic solvents. The residual aqueous solution was dried by lyophilization to afford the final product.

EXAMPLE 1

5-((4-(((6-cyclobutyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-3-cyclopropyl-7-methyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine

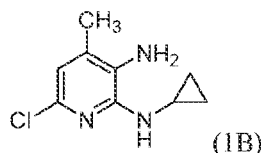


Step A. Intermediate 1A. Preparation of 6-chloro-N-cyclopropyl-4-methyl-3-nitropyridin-2-amine



To a 500 mL round bottomed flask were added 2,6-dichloro-4-methyl-3-nitropyridine (5.0 g, 24 mmol), DIEA (13 mL, 73 mmol), THF (200 mL), followed by cyclopropylamine (1.7 mL, 24 mmol). The reaction mixture was stirred under N₂. After 18 h, the solvent was concentrated and the residue was purified by flash column chromatography (120 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100%B; flow rate = 80 mL/min). The fractions corresponding to product were combined, concentrated and dried *in vacuo* to afford the title compound (2.9 g, 13 mmol, 54 % yield) as a yellow solid. Analytical LC/MS (Method 1): Observed Mass: 228.0; Retention Time: 2.037 min. ¹H NMR (500 MHz, METHANOL-d₄) δ 6.65 (s, 1H), 2.91 (s, 1H), 2.46 (s, 3H), 0.85 (dd, *J*=7.0, 1.6 Hz, 2H), 0.66-0.49 (m, 2H).

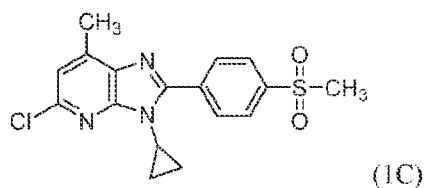
Step B. Intermediate 1B. Preparation of 6-chloro-N²-cyclopropyl-4-methylpyridine-2,3-diamine



To a 200 mL pear shaped flask were added Intermediate 1A (2.0 g, 8.8 mmol),

ammonium chloride (2.4 g, 44 mmol), iron powder (2.5 g, 44 mmol), EtOH (10 mL), and water (10 mL). The mixture was stirred at 80 °C. After 18 h, the reaction mixture was cooled, filtered, the filter cake was washed with MeOH, and the volatiles were concentrated from the filtrate. The resultant suspension was diluted with water (100 mL) and extracted with EtOAc (2x50 mL). The organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (120 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100% B; flow rate = 80 mL/min). The fractions corresponding to product were combined, concentrated and dried *in vacuo* to afford the title compound (1.0 g, 5.2 mmol, 59 % yield) as a pale yellow solid. Analytical LC/MS (Method 1): Observed Mass: 197.9; Retention Time: 1.133 min. ¹H NMR (500 MHz, METHANOL-d₄) δ 6.42 (s, 1H), 2.85-2.73 (m, 1H), 2.11 (s, 3H), 0.76 (br d, *J*=5.0 Hz, 2H), 0.57-0.47 (m, 2H).

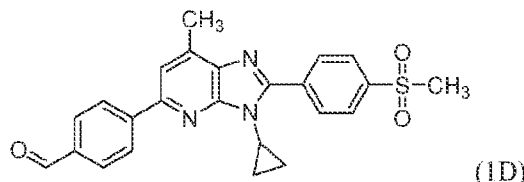
Step C. Intermediate 1C. Preparation of 5-chloro-3-cyclopropyl-7-methyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine



To a 200 mL pear shaped flask were added Intermediate 1B (1.0 g, 5.2 mmol) and NMP (60 mL). To this mixture was added sodium metabisulfite (1.5 g, 7.7 mmol), followed by 4-(methylsulfonyl)benzaldehyde (1.0 g, 5.7 mmol). The reaction mixture was stirred at 70 °C under N₂. After 18 h, the mixture was cooled, diluted with water (250 mL), and extracted with EtOAc (2x100 mL). The organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (120 g silica gel cartridge; A = DCM, B = MeOH; 30 min grad.; 0% B to 15%B; flow rate = 80 mL/min). The fractions corresponding to product were combined, concentrated and dried *in vacuo* to afford the title compound (0.85 g, 2.3 mmol, 44 % yield) as a pale yellow solid. Analytical LC/MS (Method 1): Observed Mass: 361.9; Retention Time: 1.592 min. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.32-8.26 (m, 2H), 8.21-8.17 (m, 2H), 7.29-7.21 (m, 1H), 3.77-3.67

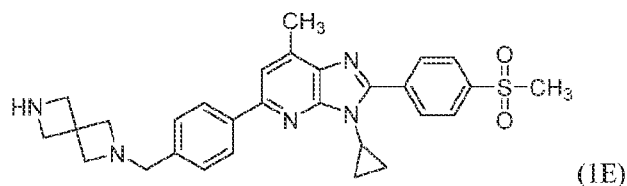
(m, 1H), 3.25 (s, 3H), 2.68 (d, $J=0.7$ Hz, 3H), 1.22-1.15 (m, 2H), 0.85-0.76 (m, 2H).

Step D. Intermediate 1D. Preparation of 4-(3-cyclopropyl-7-methyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridin-5-yl)benzaldehyde



To a 250 mL round bottomed flask were added Intermediate 1C (0.85 g, 2.3 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (0.60 g, 2.6 mmol), 1,4-dioxane (20 mL), and potassium phosphate tribasic (1.5 g, 7.1 mmol) dissolved in water (5 mL). The mixture was purged with N_2 , XPhos Pd G3 (0.099 g, 0.12 mmol) was added, the vessel was purged again, and the reaction was heated to 80 °C and stirred. After 18 h, the mixture was cooled, diluted with water (150 mL), and extracted with EtOAc (2x75 mL). The organic phase was combined, washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (80 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100% B; flow rate = 60 mL/min). The fractions corresponding to product were combined, concentrated and dried *in vacuo* to afford the title compound (0.89 g, 2.1 mmol, 88 % yield) as a pale yellow solid. Analytical LC/MS (Method 1): Observed Mass: 432.0; Retention Time: 1.677 min. (3 min. gradient) is product. 1H NMR (500 MHz, $DMSO-d_6$) δ 10.10 (s, 1H), 8.55-8.50 (m, 1H), 8.44 (d, $J=8.3$ Hz, 2H), 8.37 (s, 2H), 8.14 (d, $J=8.6$ Hz, 2H), 8.06 (d, $J=8.5$ Hz, 2H), 3.94-3.80 (m, 1H), 3.35 (s, 3H), 2.72-2.67 (m, 3H), 1.26-1.14 (m, 2H), 0.99-0.83 (m, 2H).

Step E. Intermediate 1E. Preparation of 5-(4-((2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-3-cyclopropyl-7-methyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine, 2 TFA salt



To a 40 mL vial were added Intermediate 1D (0.40 g, 0.93 mmol), tert-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate, oxalic acid salt (0.80 g, 2.8 mmol), AcOH (0.058 mL, 1.0 mmol), magnesium sulfate (1.7 g, 14 mmol), and DMF (10 mL). The reaction mixture was stirred for 20 min, then sodium triacetoxyborohydride (0.98 g, 4.6 mmol) was added. After stirring 18 h, the mixture was diluted with 10% IPA/CHCl₃ (100 mL) and filtered. The filtrate was partitioned into KOH solution (10% aqueous saturated with solid NaCl) (50 mL) and the layers were separated. The aqueous phase was extracted with 10% IPA/CHCl₃ (50 mL), the organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (80 g silica gel cartridge; A = DCM, B = MeOH; 30 min grad.; 0% B to 20 % B; flow rate = 60 mL/min). The fractions corresponding to product were combined and concentrated. The obtained intermediate was dissolved in MeOH (10 mL), TFA (1.4 mL, 19 mmol) was added and the reaction mixture was stirred at 45 °C. After 2 h, the solvent was concentrated, the residue was co-evaporated with toluene (2x), and the product was dried *in vacuo* to afford the title compound (480 mg, 0.65 mmol, 70 % yield) as a pale yellow solid. Analytical LC/MS (Method 1): Observed Mass: 514.1; Retention Time: 1.051 min. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.34-8.30 (m, 4H), 8.22 (d, *J*=8.6 Hz, 2H), 7.84-7.81 (m, 1H), 7.63-7.60 (m, 2H), 4.48-4.44 (m, 6H), 4.39-4.33 (m, 4H), 3.86-3.75 (m, 1H), 3.27 (s, 3H), 2.79-2.75 (m, 3H), 1.29-1.18 (m, 2H), 1.01-0.90 (m, 2H).

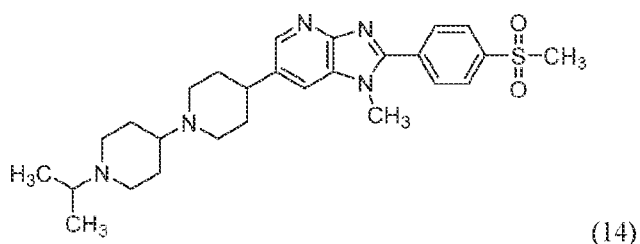
Step F. Preparation of Example 1

To a 40 mL vial were added Intermediate 1E (96 mg, 0.13 mmol), cyclobutanone (45 mg, 0.65 mmol), AcOH (8.2 μL, 0.14 mmol), magnesium sulfate (230 mg, 1.9 mmol), and DMF (2 mL). The reaction mixture was stirred for 20 min, then sodium triacetoxyborohydride (140 mg, 0.65 mmol) was added, the vial was capped and the mixture was stirred. After 18 h, the reaction was diluted with 10% IPA/CHCl₃ (40 mL)

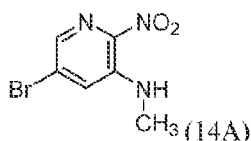
- and filtered. The filtrate was partitioned into KOH solution (10% aqueous saturated with solid NaCl) (20 mL) and the layers were separated. The aqueous phase was extracted with 10% IPA/ CHCl_3 (10 mL), the organic phase was combined, washed with brine, dried over MgSO_4 , filtered and concentrated. The crude material was purified via preparative HPLC (Method A) to afford the title compound (44 mg, 0.077 mmol, 59 % yield).
- Analytical LC/MS (Method 2): Observed Mass: 568.20; Retention Time: 1.53 min.
- Analytical LC/MS (Method 3): Observed Mass: 568.20; Retention Time: 1.14 min. ^1H NMR (500 MHz, DMSO-d_6) δ 8.36 (br d, $J=8.2$ Hz, 2H), 8.12 (br dd, $J=8.1, 4.1$ Hz, 4H), 7.77 (s, 1H), 7.38 (br d, $J=7.9$ Hz, 2H), 3.88-3.80 (m, 1H), 3.61-3.54 (m, 1H), 3.37-3.30 (m, 1H), 3.24-3.21 (m, 2H), 3.16 (s, 3H), 3.05-2.96 (m, 1H), 2.91-2.86 (m, 1H), 2.66 (s, 3H), 2.51 (br s, 3H), 1.91 (s, 2H), 1.88-1.78 (m, 2H), 1.74-1.51 (m, 4H), 1.25-1.13 (m, 2H), 0.86 (br s, 2H).

EXAMPLE 14

- 6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-imidazo[4,5-b]pyridine

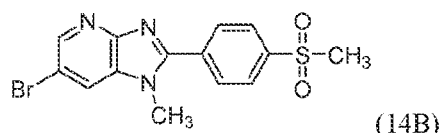


Step A. Intermediate 14A. Preparation of 5-bromo-N-methyl-2-nitro-pyridin-3-amine



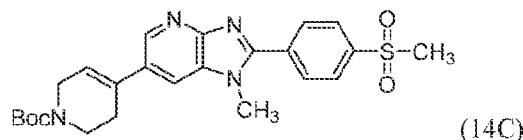
- To a solution of 5-bromo-3-fluoro-2-nitro-pyridine (5 g, 22.63 mmol) in dry THF (70 mL) was added methylamine solution (2 M in THF) (33.94 mL, 67.88 mmol). After stirring 18 h at 50 °C, the mixture was cooled, the solvent concentrated and the crude product was purified by silica gel column chromatography (hexane/EtOAc; 0-70% as eluent) to afford the title compound (5.2 g, 22.4 mmol, 99 % yield) as a yellow solid.
- Analytical LC/MS (Method 4): Observed Mass: 232.0/234.0; Retention Time: 0.836 min.

Step B. Intermediate 14B. Preparation of 6-bromo-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-imidazo[4,5-b]pyridine



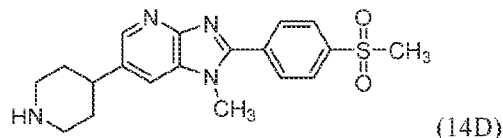
5 A mixture of Intermediate 14A (2 g, 8.62 mmol), 4-methylsulfonylbenzaldehyde (3.2 g, 17.24 mmol), Na₂S₂O₄ (4.5 g, 25.86 mmol) in ethanol (30 mL) and water (15 mL) was stirred under N₂ at 90 °C. After 36 h, the reaction mixture was cooled, the mixture was diluted with water (500 mL) and extracted with EtOAc (3x300 mL). The combined organic layer was dried over Na₂SO₄, filtered, concentrated and the residue purified by
10 silica gel column chromatography (hexane/EtOAc; 0-100% as eluent), to afford the title compound (850 mg, 2.32 mmol, 27 % yield) as a yellow solid. Analytical LC/MS (Method 4): Observed Mass: 366.2/368.2; Retention Time: 0.654 min.

Step C. Intermediate 14C. Preparation of tert-butyl 4-(1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-imidazo[4,5-b]pyridin-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate



 A mixture of Intermediate 14B (830 mg, 2.27 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (1.05 g, 3.4 mmol), K₂CO₃ (625 mg, 4.53 mmol) and Pd(PPh₃)₄ (200 mg, 0.24 mmol) in 1,4-dioxane
20 (10 mL) and water (2 mL) was degassed with nitrogen (3x) and stirred at 90 °C. After 18 h, the reaction mixture was cooled, diluted with water (100 mL) and extracted with EtOAc (3x80 mL). The combined organic layer was dried over Na₂SO₄, filtered, concentrated and the residue purified by silica gel column chromatography (hexane/EtOAc; 0-100% as eluent) to afford the title compound (850 mg, 1.81 mmol, 80
25 % yield) as a yellow solid. Analytical LC/MS (Method 4): Observed Mass: 469.2; Retention Time: 0.910 min.

Step D. Intermediate 14D. Preparation of 1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(piperidin-4-yl)-1H-imidazo[4,5-b]pyridine, HCl salt



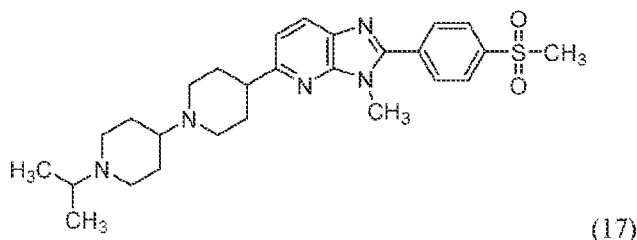
To a solution of Intermediate 14C (830 mg, 1.77 mmol) in DMF (50 mL) and DCM (10 mL) was added AcOH (1 mL). The solution was evacuated and flushed with nitrogen (3x). To the solution was added Pd/C (0.2 g), the mixture was evacuated and purged with nitrogen, and the reaction mixture was stirred under hydrogen. After 3 days, the catalyst was filtered and the filtrate was concentrated. The residue was dissolved in DCM (10 mL), HCl solution (2 M in EtOAc) (5 mL) was added and the suspension was stirred. After 2 h, the resulting precipitate was collected by vacuum filtration and washed with DCM. The product was dried *in vacuo* to afford the title compound (330 mg crude) as a light yellow solid. Analytical LC/MS (Method 4): Observed Mass: 371.2; Retention Time: 0.551 min.

Step F. Preparation of Example 14

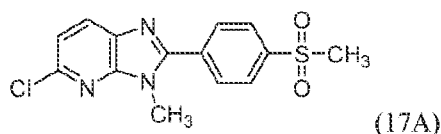
To a solution of Intermediate 14D (60 mg, 0.15 mmol) in methanol (1 mL) were added TEA (0.06 mL, 0.44 mmol), NaBH₃CN (31 mg, 0.49 mmol), ZnCl₂ solution (2 M in THF) (0.09 mL, 0.18 mmol) and 1-isopropylpiperidin-4-one (69 mg, 0.49 mmol). The resulting suspension was stirred at 60 °C. After 20 h, the reaction mixture was cooled, the solution was concentrated, and the crude product was purified by preparative HPLC (Method E) to afford the title compound (14.6 mg, 0.029 mmol, 20 % yield) as a white solid. Analytical LC/MS (Method 5): Purity: 99.3%; Observed Mass: 496.2; Retention Time: 0.553 min. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.22 (s, 1H), 9.65 (s, 1H), 8.46 (s, 1H), 8.23–8.13 (m, 4H), 8.07–8.01 (m, 1H), 3.98 (s, 3H), 3.70–3.47 (m, 6H), 3.34 (s, 3H), 3.28–3.01 (m, 5H), 2.41–2.33 (m, 2H), 2.25–1.96 (m, 6H), 1.33–1.24 (m, 6H).

EXAMPLE 17

5-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-3-methyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine



Step A. Preparation of 5-chloro-3-methyl-2-(4-methylsulfonylphenyl)imidazo[4,5-b]pyridine



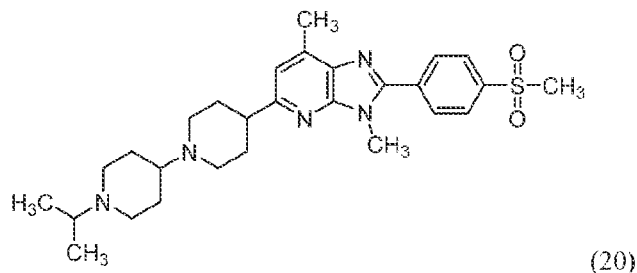
- 5 To a 40 mL vial were added 6-chloro-N-methyl-3-nitro-pyridin-2-amine (0.5 g, 2.67 mmol), 4-(methylsulfonyl)benzaldehyde (0.491 g, 2.67 mmol), sodium hydrosulfite (0.928 g, 5.33 mmol), followed by the addition of DMSO (15 mL). The reaction mixture was stirred at 80 °C. After 24 h, the mixture was cooled, diluted with water (200 mL), and extracted with EtOAc (2x100 mL). The organic phase was combined, washed with
- 10 brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (120 g silica gel cartridge; A = DCM, B = MeOH; 30 min grad.; 0% B to 20% B; flow rate = 85 mL/min). The fractions corresponding to product were combined, concentrated and dried *in vacuo* to afford the title compound (0.73 g, 2.269 mmol, 85 % yield) as a tan solid. Analytical LC/MS (Method 1): Observed Mass: 321.8;
- 15 Retention Time: 1.366 min. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.24-8.20 (m, 2H), 8.19-8.14 (m, 2H), 8.13-8.09 (m, 1H), 7.46-7.38 (m, 1H), 4.02-3.99 (m, 3H), 3.26-3.23 (m, 3H).

Step B. Preparation of Example 17

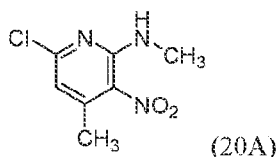
- 20 Example 17 was prepared according to general methods described elsewhere herein using appropriate starting materials, reagents and conditions. Analytical LC/MS (Method 5): Purity: 98.8%; Observed Mass: 496.1; Retention Time: 0.584 min. ¹H NMR (300 MHz, DMSO-d₆) δ 8.26-8.01 (m, 5H), 7.26 (d, *J* = 8.4 Hz, 1H), 3.96 (s, 3H), 3.32 (s, 3H), 3.04-2.94 (m, 2H), 2.87-2.59 (m, 4H), 2.38-2.00 (m, 5H), 1.96-1.66 (m, 6H), 1.51-
- 25 1.33 (m, 2H), 0.95 (d, *J* = 6.5 Hz, 6H).

EXAMPLE 20

5-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine

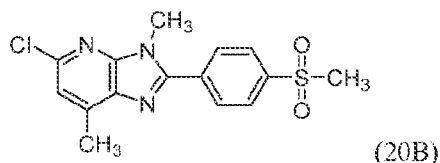


Step A. Intermediate 20A. Preparation of 6-chloro-N,4-dimethyl-3-nitro-pyridin-2-amine



To a solution of 2,6-dichloro-4-methyl-3-nitro-pyridine (1 g, 4.83 mmol) in THF (1 mL) were added methylamine solution (2 M in THF) (4.8 mL, 9.66 mmol) and DIEA (1.87 g, 14.49 mmol). After stirring 18 h, the mixture was concentrated, and the crude product was purified by silica gel chromatography (pet ether:DCM; 2:1 as eluent) to afford the title compound (450 mg, 46 % yield) as a yellow solid. Analytical LC/MS (Method 4): Observed Mass: 202/204; Retention Time: 1.072 min. ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.95 (d, *J* = 5.0 Hz, 1H), 6.72 (s, 1H), 2.89 (d, *J* = 4.6 Hz, 3H), 2.38 (s, 3H).

Step B. Intermediate 20B. Preparation of 5-chloro-3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine

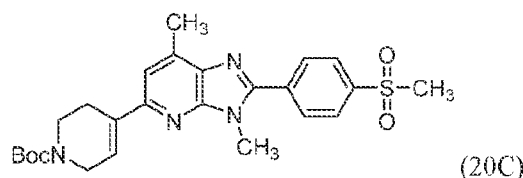


To a stirred solution of Intermediate 20A (440 mg, 2.18 mmol) in ethanol (5 mL) and water (2.5 mL) were added 4-methylsulfonylbenzaldehyde (804.1 mg, 4.36 mmol)

and Na₂S₂O₄ (759.5 mg, 4.36 mmol). After stirring at 90 °C for 18 h, the mixture was cooled to room temperature, diluted with water (100 mL) and extracted with ethyl acetate (2x50 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude was purified by silica gel

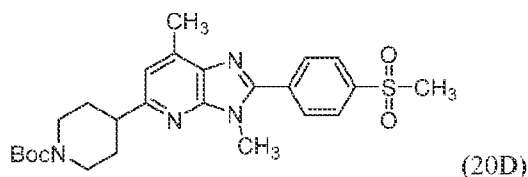
- 5 chromatography (pet ether:ethyl acetate; 1:1 as eluent) to afford the title compound (470 mg, 64 % yield) as a yellow solid. Analytical LC/MS (Method 4): Observed Mass: 336.1/338.1; Retention Time: 0.919 min. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.27-8.08 (m, 4H), 7.31 (s, 1H), 3.92 (s, 3H), 2.63 (s, 3H), 2.53 (s, 3H).

- 10 Step C. Intermediate 20C. Preparation of tert-butyl 4-(3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate



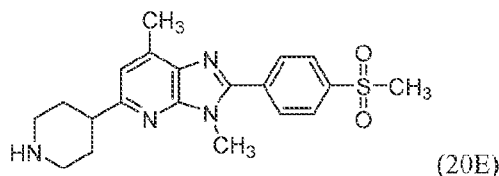
- To a solution of Intermediate 20B (460 mg, 1.37 mmol) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (847.1 mg, 2.74 mmol) in 1,4-dioxane (5 mL) and water (1 mL) were added K₃PO₄ (872.3 mg, 4.11 mmol) and Pd(dppf)Cl₂ (100.1 mg, 0.14 mmol). The resulting solution was degassed with nitrogen (3x) and stirred at 90 °C. After 18 h, the mixture was cooled to room temperature, diluted with water (100 mL) and extracted with ethyl acetate (2 x 50 mL).
- 20 The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (ethyl acetate as eluent) to afford the title compound (480 mg, 73% yield) as a white solid. Analytical LC/MS (Method 4): Observed Mass: 483.1; Retention Time: 1.051 min. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.23 (d, *J* = 8.3 Hz, 2H), 8.13 (d, *J* = 8.2 Hz, 2H), 7.43 (s, 1H), 6.74 (s, 1H), 4.10 (s, 2H), 3.97 (s, 3H), 3.59 (t, *J* = 5.5 Hz, 2H), 2.70 (s, 2H), 2.63 (s, 3H), 2.53 (s, 3H), 1.45 (s, 9H).
- 25

Step D. Intermediate 20D. Preparation of tert-butyl 4-(3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridin-5-yl)piperidine-1-carboxylate



A solution of Intermediate 20C (470 mg, 0.97 mmol) in methanol (3 mL) and DCM (1 mL) was degassed with nitrogen (3x). To this mixture was added Pd/C (100 mg), the reaction vessel was evacuated and back-filled with nitrogen (3x), then back-filled with hydrogen (1 atm). After stirring 3 h, the mixture was filtered and the filtrate was concentrated under reduced pressure. The crude material was purified by silica gel chromatography (ethyl acetate as eluent) to afford the title compound (400 mg, 85% yield) as a white solid. Analytical LC/MS (Method 4): Observed Mass: 485.3; Retention Time: 1.005 min. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.21 (d, *J* = 8.3 Hz, 2H), 8.13 (d, *J* = 8.2 Hz, 2H), 7.12 (s, 1H), 4.19-3.99 (m, 2H), 3.94 (s, 3H), 3.06-2.72 (m, 3H), 2.60 (s, 3H), 2.51 (s, 3H), 1.95-1.81 (m, 2H), 1.78-1.59 (m, 2H), 1.44 (s, 9H).

Step E. Preparation of 3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-5-(piperidin-4-yl)-3H-imidazo[4,5-b]pyridine



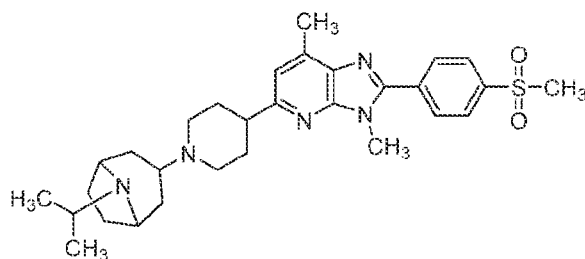
To a 200 mL pear shaped flask were added Intermediate 20D (1.9 g, 3.92 mmol), MeOH (20 mL), and HCl solution (4 M in dioxane) (20 mL). The reaction mixture was stirred. After 15 min, the solvent was concentrated, the residue was dissolved in MeOH (100 mL) and to the solution was added Dowex 550A anion exchange resin (30 g, pre-washed alternately with DCM and MeOH). The resin was filtered after 5 min and the filtrate was concentrated. The product was dried *in vacuo* to afford the title compound (1.37 g, 3.56 mmol, 91 % yield) as a tan solid. Analytical LC/MS (Method 1): Observed Mass: 385.1; Retention Time: 0.923 min. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 8.21 (s, 2H), 8.19-8.10 (m, 2H), 7.15 (s, 1H), 4.02-3.98 (m, 3H), 3.50-3.43 (m, 1H), 2.87-2.84 (m, 3H), 2.72-2.68 (m, 3H), 2.44-2.33 (m, 2H), 2.10-2.03 (m, 2H), 2.02-1.88 (m, 4H).

Step F. Preparation of Example 20

To a stirred solution of Intermediate 20E (80 mg, 0.21 mmol) in DCM (5 mL) were added 1-isopropylpiperidin-4-one (146.9 mg, 1.04 mmol) and acetic acid (0.1 mL). After stirring 20 min, NaBH(OAc)₃ (308.8 mg, 1.46 mmol) was added and the reaction mixture was stirred. After 20 h, the mixture was concentrated, diluted with water (100 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over Na₂SO₄, concentrated, and the crude product was purified by preparative HPLC (Method F) to afford the title compound (47.5 mg, 0.0945 mmol, 45 % yield) as a white solid. Analytical LC/MS (Method 5): Purity: 99.5%; Observed Mass: 510.4; Retention Time: 0.635 min. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.21 (d, *J* = 8.4 Hz, 2H), 8.13 (d, *J* = 8.8 Hz, 2H), 7.14 (s, 1H), 3.98 (s, 3H), 3.24 (s, 3H), 3.16 (d, *J* = 11.4 Hz, 2H), 3.05 (d, *J* = 11.4 Hz, 2H), 2.91-2.80 (m, 1H), 2.80-2.69 (m, 1H), 2.68 (s, 3H), 2.50-2.34 (m, 3H), 2.30-2.19 (m, 2H), 2.11-1.94 (m, 6H), 1.74-1.57 (m, 2H), 1.11 (d, *J* = 6.5 Hz, 6H).

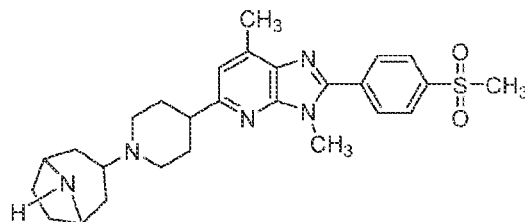
EXAMPLE 26 AND 27

5-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine



(26, 27)

Step A. Intermediate 26A. Preparation of 5-(1-(8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine, 2 HCl salt



(26A)

To a 250 mL round bottomed flask were added Intermediate 20E (1 g, 2.60

mmol), DCE (10 mL), 1,4-dioxane (10 mL), and tert-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (2.344 g, 10.40 mmol), followed by titanium(IV) isopropoxide (3.85 mL, 13.00 mmol). The reaction mixture was stirred at 40 °C under N₂. After 18 h, the mixture was cooled to room temperature, then sodium triacetoxyborohydride (2.205 g, 10.40 mmol) was added. After stirring 1.5 h, the reaction mixture was filtered, partitioned into KOH solution (10% aqueous saturated with solid NaCl) (150 mL) and 10% IPA/chloroform (150 mL). The layers were separated, the aqueous phase was extracted with 10% IPA/chloroform (75 mL), the organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (120 g silica gel cartridge; A = DCM, B = MeOH; 30 min grad.; 0% B to 30%B; flow rate = 80mL/min). Fractions containing product were combined and concentrated. The resultant residue was dissolved in MeOH (20 mL) and HCl solution (4 M in dioxane) (20 mL) and stirred. After 30 min, the solvent was concentrated, the residue was co-evaporated with toluene (2x) and the product was dried *in vacuo* to afford the title compound (1 g, 1.765 mmol, 68 % yield) (mixture of isomers) as a pale yellow solid. Analytical LC/MS (Method 1): Observed Mass: 494.1; Retention Time: 0.888. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.39-8.35 (m, 2H), 8.28-8.24 (m, 2H), 7.61-7.58 (m, 1H), 4.31-4.27 (m, 1H), 4.26-4.18 (m, 2H), 4.15 (s, 3H), 3.90-3.80 (m, 3H), 3.40-3.34 (m, 2H), 3.29 (s, 4H), 2.99-2.91 (m, 1H), 2.79 (s, 3H), 2.49-2.32 (m, 6H), 2.27-2.06 (m, 4H).

Step B. Examples 26 and 27

To a 40 mL vial were added Intermediate 26A (200 mg, 0.353 mmol), propan-2-one (103 mg, 1.765 mmol), AcOH (0.022 mL, 0.388 mmol), magnesium sulfate (637 mg, 5.29 mmol), and DMF (2 mL). The reaction mixture was stirred for 20 min, then sodium triacetoxyborohydride (374 mg, 1.765 mmol) was added. After stirring 18 h, the mixture was diluted with 10% IPA/CHCl₃ (40 mL) and filtered. The filtrate was partitioned into KOH solution (10% aqueous saturated with solid NaCl) (20 mL) and the layers were separated. The aqueous phase was extracted with 10% IPA/CHCl₃ (10 mL), the organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The crude material was purified via preparative LC/MS using the following conditions: Column: XBridge C18, 200 mm x 19 mm, 5-μm particles; Mobile Phase A: 5:95

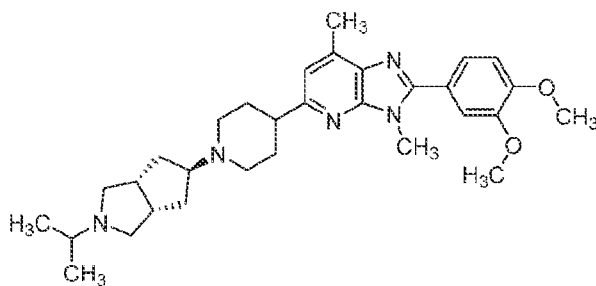
acetonitrile: water with NH_4OAc ; Mobile Phase B: 95:5 acetonitrile: water with NH_4OAc ; Gradient: a 0-minute hold at 7% B, 7-52% B over 23 minutes, then a 0-minute hold at 100% B; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS and UV signals. Fractions containing the respective desired product were combined and dried via centrifugal evaporation.

Example 26 (86 mg, 0.16 mmol, 46 % yield) was isolated as the 1st eluting isomer. Analytical LC/MS (Method 2): Purity: 100 %; Observed Mass: 536.40; Retention Time: 1.13 min. (Method 3): Purity: 100 %; Observed Mass: 536.20; Retention Time: 1.0 min. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.22-8.17 (m, 2H), 8.15-8.08 (m, 2H), 7.09 (s, 1H), 3.95-3.91 (m, 2H), 3.33-3.28 (m, 2H), 3.04-2.98 (m, 2H), 2.84-2.76 (m, 1H), 2.76-2.69 (m, 1H), 2.69-2.61 (m, 1H), 2.60-2.58 (m, 2H), 2.57-2.54 (m, 3H), 2.25-2.15 (m, 2H), 1.92-1.75 (m, 8H), 1.73-1.63 (m, 2H), 1.60-1.53 (m, 2H), 1.52-1.45 (m, 2H), 1.07-0.98 (m, 6H).

Example 27 (73 mg, 0.136 mmol, 39 % yield) was isolated as the 2nd eluting isomer. Analytical LC/MS (Method 2): Purity: 100 %; Observed Mass: 536.40; Retention Time: 1.34 min. (Method 3): Purity: 100 %; Observed Mass: 536.20; Retention Time: 0.99 min. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.24-8.17 (m, 2H), 8.13-8.12 (m, 2H), 7.11 (s, 1H), 3.94 (s, 3H), 3.69-3.60 (m, 1H), 3.58-3.42 (m, 2H), 3.31 (s, 3H), 2.92-2.69 (m, 3H), 2.61-2.58 (m, 3H), 2.41-2.31 (m, 2H), 2.07-1.92 (m, 7H), 1.88-1.78 (m, 6H), 1.11 (br d, $J = 6.1$ Hz, 6H).

EXAMPLE 36

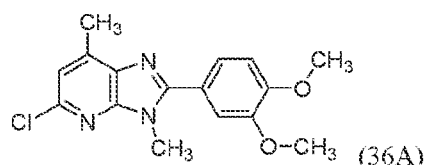
2-(3,4-dimethoxyphenyl)-5-(1-((3aR,5s,6aS)-2-isopropyloctahydrocyclopenta[c]pyrrol-5-yl)piperidin-4-yl)-3,7-dimethyl-3H-imidazo[4,5-b]pyridine



(36)

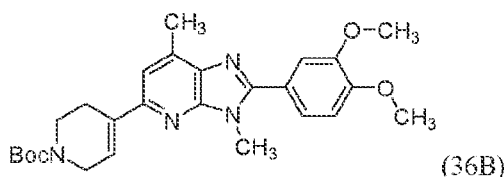
Step A. Intermediate 36A. Preparation of 5-chloro-2-(3,4-dimethoxyphenyl)-3,7-

dimethyl-3H-imidazo[4,5-b]pyridine



To a 100 mL pear shaped flask were added Intermediate 20A (1.4 g, 6.94 mmol), EtOH (27.8 mL), sodium hydrosulfite (3.63 g, 20.83 mmol), followed by 3,4-dimethoxybenzaldehyde (1.154 g, 6.94 mmol). The reaction mixture was stirred at 70 °C. After 18 h, the mixture was cooled to room temperature, the precipitated product was collected by vacuum filtration, washed with ether, and dried *in vacuo* to afford the title compound (2.08 g, 6.55 mmol, 94 % yield) as a pale yellow solid. Analytical LC/MS (Method 1): Observed Mass: 317.9; Retention Time: 1.380 min. ¹H NMR (500 MHz, DMSO-d₆) δ 7.49-7.42 (m, 2H), 7.25-7.23 (m, 1H), 7.19-7.15 (m, 1H), 3.89-3.86 (m, 9H), 2.62-2.60 (m, 3H).

Step B. Intermediate 36B. Preparation of tert-butyl 4-(2-(3,4-dimethoxyphenyl)-3,7-dimethyl-3H-imidazo[4,5-b]pyridin-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate

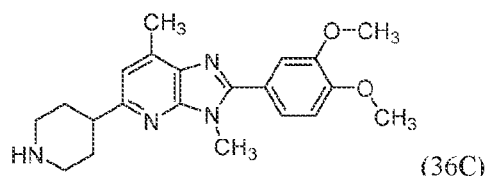


To a 250 mL round bottomed flask were added Intermediate 36A (1.48 g, 4.66 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.584 g, 5.12 mmol), Pd(dppf)Cl₂·DCM (0.190 g, 0.233 mmol), followed by potassium phosphate tribasic (3.46 g, 16.30 mmol) dissolved in water (8 mL). The vessel was flushed with N₂ and the reaction mixture was stirred at 85 °C. After 18 h, the mixture was cooled, diluted with water (200 mL) and extracted with EtOAc (2x100 mL). The organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (120 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100%B; flow rate = 80 mL/min). The fractions corresponding to product were combined, concentrated and dried *in vacuo* to afford the title compound (0.67 g, 1.442 mmol, 31 % yield) as a pale

yellow solid. Analytical LC/MS (Method 1): Observed Mass: 465.2; Retention Time: 1.662 min. ^1H NMR (500 MHz, METHANOL- d_4) δ 7.47 (s, 1H), 7.45-7.42 (m, 1H), 7.38 (s, 1H), 7.20 (s, 1H), 6.73-6.61 (m, 1H), 4.20-4.13 (m, 2H), 3.98-3.94 (m, 9H), 3.75-3.66 (m, 2H), 2.83-2.76 (m, 2H), 2.70-2.66 (m, 3H), 1.53 (s, 9H).

5

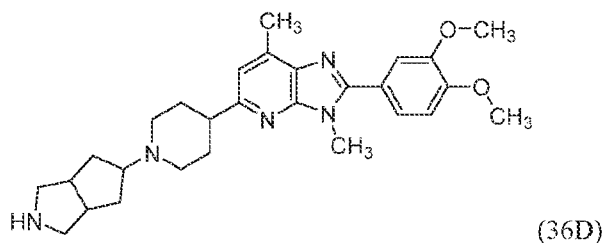
Step C. Intermediate 36C. Preparation of 2-(3,4-dimethoxyphenyl)-3,7-dimethyl-5-(piperidin-4-yl)-3H-imidazo[4,5-b]pyridine, HCl salt



To a 250 mL round bottomed flask were added Intermediate 36B (0.67 g, 1.442 mmol), DCM (7 mL), MeOH (7 mL), and Pd-C (5% wt. on carbon, wet type) (0.307 g, 0.144 mmol). The vessel was evacuated and purged with N_2 , equipped with a hydrogen balloon and stirred. After 18 h, the catalyst was filtered, and to the filtrate was added HCl solution (4 M in dioxane) (15 mL). After stirring 2 h, the solvent was concentrated, the residue was co-evaporated with toluene, and the product was dried *in vacuo* to afford the title compound (0.6 g, 1.489 mmol, 100 % yield) as a pale yellow solid. Analytical LC/MS (Method 1): Observed Mass: 367.0; Retention Time: 0.945 min. ^1H NMR (500 MHz, METHANOL- d_4) δ 7.63-7.58 (m, 1H), 7.55-7.52 (m, 1H), 7.49 (s, 1H), 7.33 (d, J = 8.5 Hz, 1H), 4.16-4.11 (m, 3H), 4.03-3.98 (m, 6H), 3.71-3.66 (m, 1H), 3.62-3.57 (m, 2H), 3.28-3.19 (m, 2H), 2.76 (s, 3H), 2.32-2.16 (m, 4H).

20

Step D. Intermediate 36D. Preparation of 2-(3,4-dimethoxyphenyl)-3,7-dimethyl-5-(1-(octahydrocyclopenta[c]pyrrol-5-yl)piperidin-4-yl)-3H-imidazo[4,5-b]pyridine, 2 HCl salt



To a 40 mL vial were added Intermediate 36C (0.6 g, 1.489 mmol), tert-butyl 5-oxohexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate (1.006 g, 4.47 mmol), AcOH (0.094 mL, 1.638 mmol), magnesium sulfate (2.69 g, 22.34 mmol), and DMF (30 mL). The reaction mixture was stirred for 20 min, then sodium triacetoxyborohydride (1.578 g, 7.45 mmol) was added. After stirring 18 h, the mixture was diluted with 10% IPA/CHCl₃ (150 mL) and filtered. The filtrate was partitioned into KOH solution (10% aqueous saturated with solid NaCl) (75 mL) and the layers were separated. The aqueous phase was extracted with 10% IPA/CHCl₃ (50 mL), the organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (80 g silica gel cartridge; A = DCM, B = MeOH; 30 min grad.; 0% B to 20% B; flow rate = 60 mL/min). The fractions corresponding to product were combined and concentrated. The resultant residue was dissolved in MeOH (10 mL) and HCl solution (4 M in dioxane) (10 mL). After stirring 1 h, the solvent was concentrated, the residue was co-evaporated with toluene, and the product was dried *in vacuo* to afford the title compound (0.65 g, 1.185 mmol, 80 % yield) as an off-white solid. Analytical LC/MS (Method 1): Observed Mass: 476.2; Retention Time: 0.908 min. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.63-7.60 (m, 1H), 7.57-7.51 (m, 2H), 7.35-7.33 (m, 1H), 4.16 (s, 3H), 4.00 (d, *J* = 6.2 Hz, 6H), 3.87-3.78 (m, 2H), 3.49-3.38 (m, 4H), 3.29-3.20 (m, 2H), 3.07-3.02 (m, 2H), 2.76 (s, 3H), 2.73-2.71 (m, 2H), 2.66-2.58 (m, 2H), 2.50-2.38 (m, 2H), 2.34-2.26 (m, 2H), 1.98-1.87 (m, 2H).

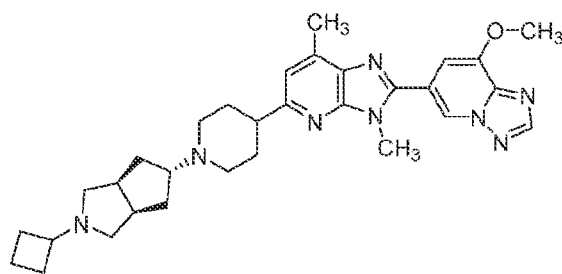
Step E. Preparation of Example 36

To a 40 mL vial were added Intermediate 36D (80 mg, 0.146 mmol), propan-2-one (42.4 mg, 0.729 mmol), AcOH (9.18 μL, 0.160 mmol), magnesium sulfate (263 mg, 2.188 mmol), and DMF (2 mL). The reaction mixture was stirred for 20 min, then sodium triacetoxyborohydride (155 mg, 0.729 mmol) was added. After stirring 18 h, the mixture was diluted with 10% IPA/CHCl₃ (40 mL) and filtered. The filtrate was partitioned into KOH solution (10% aqueous saturated with solid NaCl) (20 mL) and the layers were separated. The aqueous phase was extracted with 10% IPA/CHCl₃ (10 mL), the organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The crude product was purified by preparative HPLC (Method A) to afford the title compound (50.6 mg, 0.0978 mmol, 67 % yield). Analytical LC/MS (Method 2):

Purity: 100 %; Observed Mass: 518.5; Retention Time: 1.53 min. (Method 3): Purity: 100 %; Observed Mass: 518.4; Retention Time: 1.09 min. ¹H NMR (500 MHz, DMSO-d₆) δ 7.29-7.19 (m, 2H), 6.98-6.92 (m, 1H), 6.86-6.79 (m, 1H), 3.70-3.68 (m, 2H), 3.67-3.64 (m, 3H), 2.96-2.86 (m, 1H), 2.56-2.41 (m, 3H), 2.39-2.33 (m, 6H), 2.28-2.19 (m, 3H),
 5 2.18-2.10 (m, 1H), 2.08-1.99 (m, 2H), 1.97-1.81 (m, 4H), 1.73-1.69 (m, 2H), 1.68-1.61 (m, 4H), 1.11-0.98 (m, 2H), 0.88-0.80 (m, 6H).

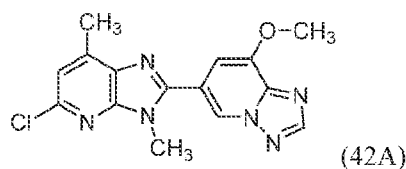
EXAMPLE 42

5-(1-((3aR,5s,6aS)-2-cyclobutyl-octahydrocyclopenta[c]pyrrol-5-yl)piperidin-4-yl)-2-(8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3,7-dimethyl-3H-imidazo[4,5-b]pyridine



(42)

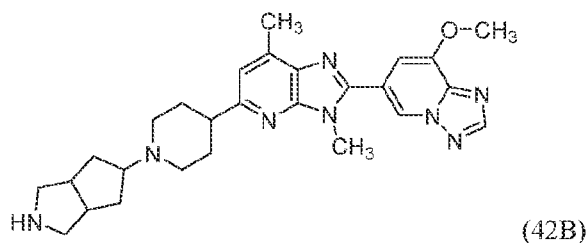
Step A. Intermediate 42A. Preparation of 5-chloro-2-(8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3,7-dimethyl-3H-imidazo[4,5-b]pyridine



(42A)

15 To a 100 mL pear shaped flask were added Intermediate 20A (1.75 g, 8.68 mmol), EtOH (34.7 mL), sodium hydrosulfite (4.53 g, 26.0 mmol), followed by 8-methoxy-[1,2,4]triazolo[1,5-a]pyridine-6-carbaldehyde (1.538 g, 8.68 mmol). The reaction mixture was stirred at 70 °C. After 18 h, the mixture was cooled to room temperature, the precipitated product was collected by vacuum filtration, washed with ether, and dried *in vacuo* to afford the title compound (2.84 g, 8.64 mmol, 100 % yield) as a pale yellow
 20 solid. Analytical LC/MS (Method 1): Observed Mass: 328.9; Retention Time: 1.385 min. ¹H NMR (500 MHz, DMSO-d₆) δ 9.15-9.11 (m, 1H), 8.62-8.58 (m, 1H), 7.51-7.47 (m, 1H), 7.36-7.29 (m, 1H), 4.10 (s, 3H), 3.96 (s, 3H), 2.67-2.64 (m, 3H).

Step B. Intermediate 42B. Preparation of 2-(8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3,7-dimethyl-5-(1-(octahydrocyclopenta[c]pyrrol-5-yl)piperidin-4-yl)-3H-imidazo[4,5-b]pyridine, 2 HCl salt



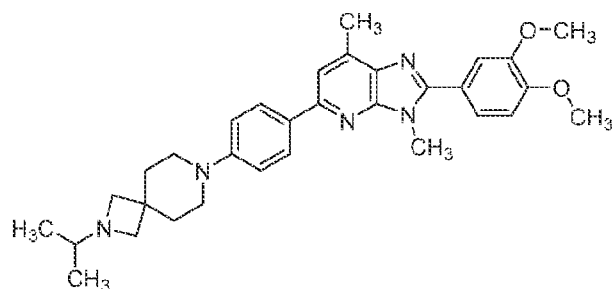
5 Intermediate 42B was prepared according to general methods described elsewhere herein using appropriate starting materials, reagents and conditions. Analytical LC/MS (Method 1): Observed Mass: 487.2; Retention Time: 0.920 min. ¹H NMR (500 MHz, METHANOL-d₄) δ 9.20-9.16 (m, 1H), 8.63 (s, 1H), 7.60-7.52 (m, 2H), 4.24-4.22 (m, 3H), 4.20-4.18 (m, 3H), 3.86-3.80 (m, 2H), 3.48-3.35 (m, 5H), 3.31-3.22 (m, 2H), 3.11-
10 2.96 (m, 3H), 2.82-2.76 (m, 3H), 2.68-2.58 (m, 2H), 2.50-2.40 (m, 2H), 2.36-2.28 (m, 2H), 1.99-1.89 (m, 2H).

Step C. Preparation of Example 42

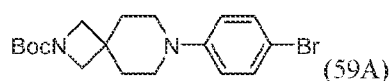
Example 42 was prepared according to general methods described elsewhere
15 herein using appropriate starting materials, reagents and conditions. Analytical LC/MS (Method 2): Purity: 98.3%; Observed Mass: 541.4; Retention Time: 1.34 min. (Method 3): Purity: 100%; Observed Mass: 541.2; Retention Time: 0.99 min. ¹H NMR (500 MHz, DMSO-d₆) δ 9.15-9.08 (m, 1H), 8.59 (s, 1H), 7.53-7.46 (m, 1H), 7.13-7.08 (m, 1H), 4.10 (s, 3H), 3.98 (s, 3H), 2.65-2.60 (m, 4H), 2.55-2.52 (m, 9H), 2.21-2.08 (m, 4H), 2.07-1.80
20 (m, 10H), 1.78-1.61 (m, 3H).

EXAMPLE 59

2-(3,4-dimethoxyphenyl)-5-(4-(2-isopropyl-2,7-diazaspiro[3.5]nonan-7-yl)phenyl)-3,7-dimethyl-3H-imidazo[4,5-b]pyridine



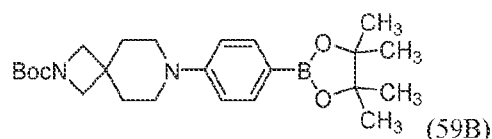
Step A. Intermediate 59A. Preparation of tert-butyl 7-(4-bromophenyl)-2,7-diazaspiro[3.5]nonane-2-carboxylate



To a 250 mL round bottomed flask were added tert-butyl 2,7-diazaspiro[3.5]nonane-2-carboxylate (4 g, 17.67 mmol), 1,4-dibromobenzene (6.25 g, 26.5 mmol), *rac*-BINAP (1.101 g, 1.767 mmol), sodium tert-butoxide (2.72 g, 28.3 mmol), followed by toluene (100 mL). The mixture was purged and evacuated with N₂, then Pd₂(dba)₃ (0.809 g, 0.884 mmol) was added. The vessel was purged with N₂ and stirred at 100 °C. After 18 h, the reaction mixture was cooled, diluted with water (200 mL), and extracted with EtOAc (2 x 100 mL). The organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (220 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100% B; flow rate = 100 mL/min). The fractions corresponding to product were combined, concentrated and dried *in vacuo* to afford the title compound (5.7 g, 14.95 mmol, 85 % yield) as a tan solid. Analytical LC/MS (Method 1): Observed Mass: 383.0; Retention Time: 1.826 min. ¹H NMR (400 MHz, METHANOL-d₄) δ 7.39-7.24 (m, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 3.77-3.63 (m, 4H), 3.21-3.08 (m, 4H), 1.95-1.80 (m, 4H), 1.46 (s, 9H).

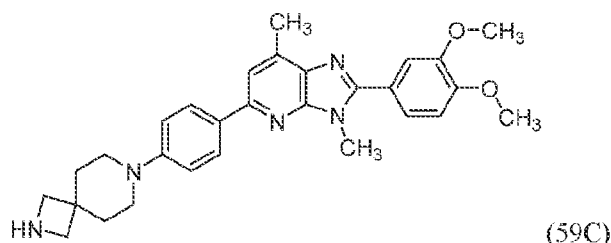
20

Step B. Intermediate 59B. Preparation of tert-butyl 7-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2,7-diazaspiro[3.5]nonane-2-carboxylate



To a 250 mL round bottomed flask were added Intermediate 59A (5.7 g, 14.95 mmol), potassium acetate (2.93 g, 29.9 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (7.59 g, 29.9 mmol), and 1,4-dioxane (150 mL). The vessel was evacuated and purged with N₂, Pd(dppf)Cl₂·DCM (1.221 g, 1.495 mmol) was added, the vessel was purged again, and the reaction mixture was stirred at 100 °C. After 18 h, the mixture was cooled, diluted with water (200 mL) and extracted with EtOAc (2 x 100 mL). The organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (120 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100% B; flow rate = 85 mL/min). The fractions corresponding to product were combined, concentrated and dried *in vacuo* to afford the title compound (4.1 g, 9.57 mmol, 64 % yield) as a tan solid. Analytical LC/MS (Method 1): Observed Mass: 429.1; Retention Time: 1.968 min. ¹H NMR (400 MHz, METHANOL-d₄) δ 7.61 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 3.75-3.63 (m, 4H), 3.29-3.20 (m, 4H), 1.97-1.83 (m, 4H), 1.50-1.46 (m, 9H), 1.34 (s, 12H).

Step C. Intermediate 59C. Preparation of 5-(4-(2,7-diazaspiro[3.5]nonan-7-yl)phenyl)-2-(3,4-dimethoxyphenyl)-3,7-dimethyl-3H-imidazo[4,5-b]pyridine, 2 HCl salt



To a 40 mL vial were added Intermediate 36A (0.26 g, 0.818 mmol), Intermediate 59B (0.456 g, 1.064 mmol), potassium phosphate tribasic (0.347 g, 1.636 mmol), 1,4-dioxane (10 mL), and water (2 mL). The vessel was flushed with N₂, then XPhos Pd G3 (0.021 g, 0.025 mmol) was added, the vessel was flushed again, and the reaction mixture was stirred at 85 °C. After 18 h, the mixture was cooled, diluted with water (100 mL) and extracted with EtOAc (2x50 mL). The organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (80 g silica gel cartridge; A = DCM, B = MeOH; 30 min grad.; 0% B to

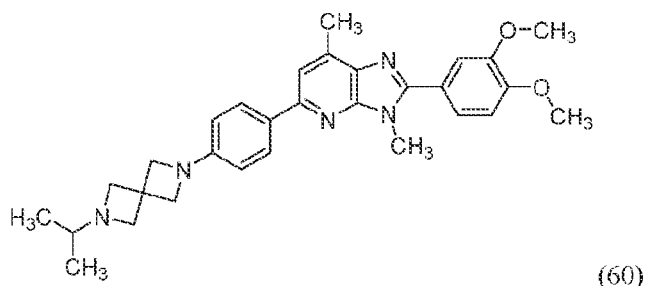
20% B; flow rate = 60 mL/min). The fractions corresponding to product were combined, and concentrated. The obtained residue was dissolved in MeOH (10 mL), and HCl solution (4 M in dioxane) (10 mL). After stirring 2 h, the solvent was concentrated, the residue was co-evaporated with toluene (2x) and the product was dried *in vacuo* to afford the title compound (140 mg, 0.252 mmol, 31 % yield) as a tan solid. Analytical LC/MS (Method 1): Observed Mass: 484.2; Retention Time: 1.052 min.

Step D. Preparation of Example 59

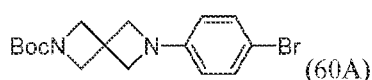
To a 40 mL vial were added Intermediate 59C (70 mg, 0.126 mmol), MgSO₄ (76 mg, 0.629 mmol), DMF (5 mL), AcOH (7.20 μ L, 0.126 mmol), followed by propan-2-one (36.5 mg, 0.629 mmol). After stirring for 10 min, sodium triacetoxyborohydride (133 mg, 0.629 mmol) was added, the vial was capped and the reaction mixture was stirred. After 18 h, the mixture was diluted with 10% IPA/CHCl₃ (40 mL), filtered, and the filtrate was concentrated. The residue was purified by preparative HPLC (Method D). The pure fractions were combined and concentrated. The resultant residue was partitioned in 10% IPA/CHCl₃ (20 mL), and KOH solution (10% aqueous saturated with solid NaCl) (20 mL). The layers were separated, the aqueous phase was extracted with 10% IPA/CHCl₃ (10 mL), the organic phase was combined, washed with brine, dried over MgSO₄, filtered, and concentrated. The product was dried *in vacuo* to afford the title compound (35.13 mg, 0.066 mmol, 53 % yield) as an off-white solid. Analytical LC/MS (Method 1): Purity: 99%; Observed Mass: 526.2; Retention Time: 1.123 min. (Method 6): Purity 99%; Observed Mass: 526.2; Retention Time: 1.459 min. ¹H NMR (500 MHz, DMSO-d₆) δ 8.07-7.98 (m, 2H), 7.64-7.61 (m, 1H), 7.48 (s, 2H), 7.19-7.14 (m, 1H), 7.06-6.99 (m, 2H), 3.98-3.93 (m, 3H), 3.91-3.84 (m, 6H), 3.25-3.18 (m, 4H), 3.08-2.87 (m, 3H), 2.66-2.62 (m, 3H), 1.83-1.70 (m, 4H), 0.97-0.79 (m, 6H) (two protons obscured).

EXAMPLE 60

2-(3,4-dimethoxyphenyl)-5-(4-(6-isopropyl-2,6-diazaspiro[3.3]heptan-2-yl)phenyl)-3,7-dimethyl-3H-imidazo[4,5-b]pyridine



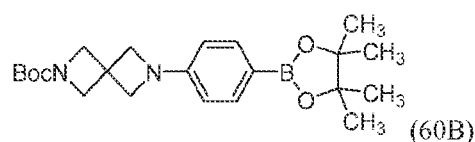
Step A. Intermediate 60A. Preparation of tert-butyl 6-(4-bromophenyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate



- 5 To a 500 mL round bottomed flask were added tert-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate, oxalic acid salt (6 g, 20.81 mmol), 1,4-dibromobenzene (7.36 g, 31.2 mmol), *rac*-BINAP (1.296 g, 2.081 mmol), sodium tert-butoxide (5.20 g, 54.1 mmol), followed by the addition of toluene (100 mL). The mixture was purged and evacuated with N₂, then Pd₂(dba)₃ (0.953 g, 1.041 mmol) was added.
- 10 The vessel was purged with N₂ and stirred at 100 °C. After 18 h, the reaction mixture was cooled, diluted with water (300 mL) and extracted with EtOAc (2x150 mL). The organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (220 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100% B; flow rate = 100
- 15 mL/min). The fractions corresponding to product were combined, concentrated and dried *in vacuo* to afford the title compound (5.0 g, 14.15 mmol, 68 % yield) as a tan solid. Analytical LC/MS (Method 1): Observed Mass: 352.9; Retention Time: 2.180 min. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.32-7.24 (m, 2H), 6.41 (d, *J* = 8.9 Hz, 2H), 4.85 (s, 4H), 3.99-3.91 (m, 4H), 1.46 (s, 9H).

20

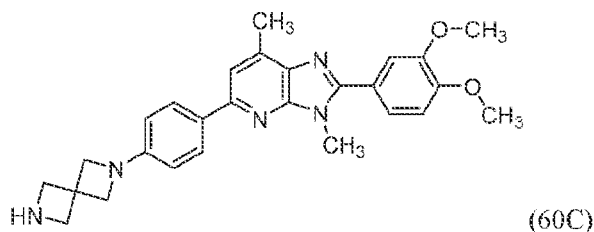
Step B. Intermediate 60B. Preparation of tert-butyl 6-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate



To a 500 mL round bottomed flask were added Intermediate 60A (5.0 g, 14.15 mmol), potassium acetate (2.78 g, 28.3 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (7.19 g, 28.3 mmol), and 1,4-dioxane (200 mL). The vessel was evacuated and purged with N₂, Pd(dppf)Cl₂·DCM (1.156 g, 1.415 mmol) was added, the vessel was purged again, and the reaction mixture was stirred at 100 °C. After 18 h, the mixture was cooled, diluted with water (200 mL), and extracted with EtOAc (2x100 mL). The organic phase was combined, washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was purified by flash column chromatography (120 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100% B; flow rate = 80 mL/min). The fractions corresponding to product were combined, concentrated and dried *in vacuo* to afford the title compound (4.06 g, 10.14 mmol, 72 % yield) as a tan solid. Analytical LC/MS (Method 1): Observed Mass: 401.0; Retention Time: 2.297 min. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.63-7.52 (m, 2H), 6.50-6.42 (m, 2H), 4.24-4.09 (m, 4H), 4.00 (s, 4H), 1.48-1.43 (m, 9H), 1.36-1.31 (m, 12H).

15

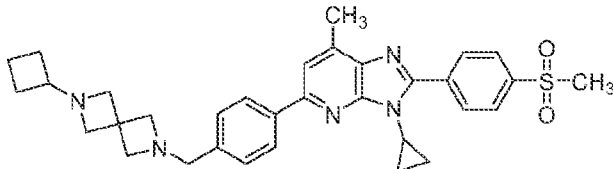
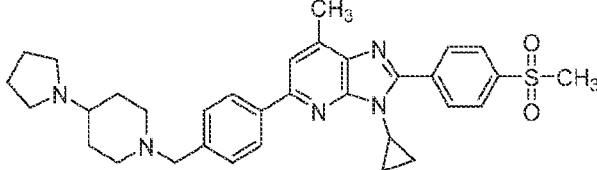
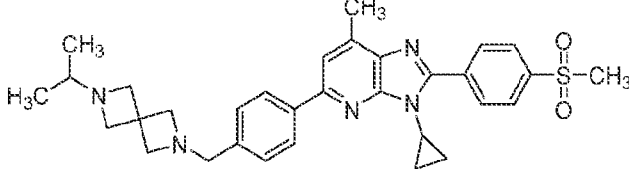
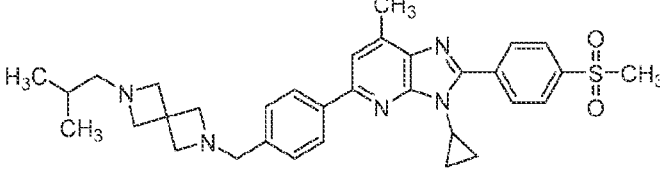
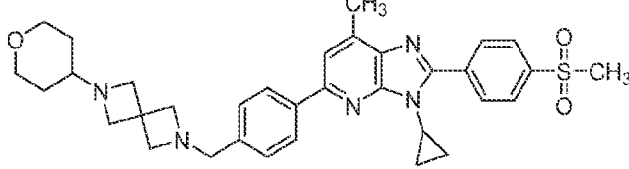
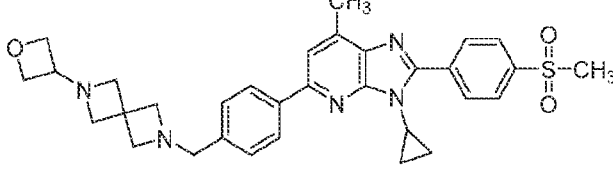
Step C. Intermediate 60C. Preparation of 5-(4-(2,6-diazaspiro[3.3]heptan-2-yl)phenyl)-2-(3,4-dimethoxyphenyl)-3,7-dimethyl-3H-imidazo[4,5-b]pyridine, 2 TFA salt

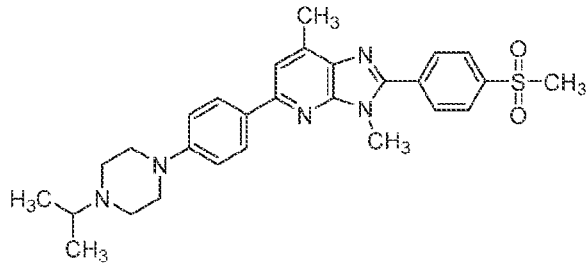
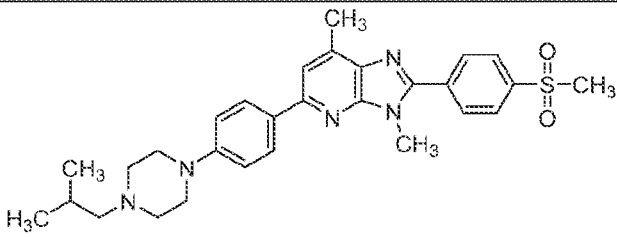
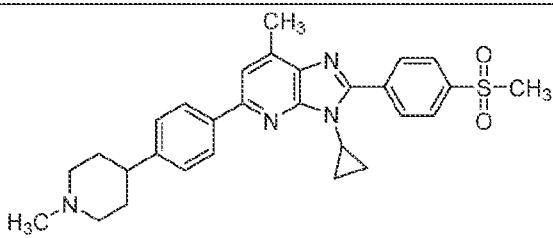
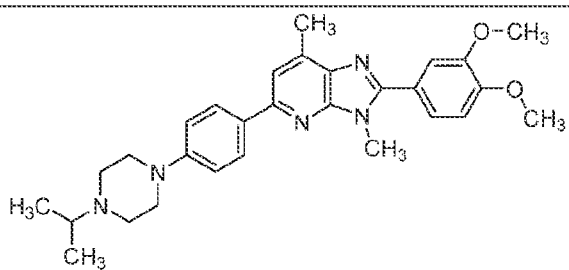
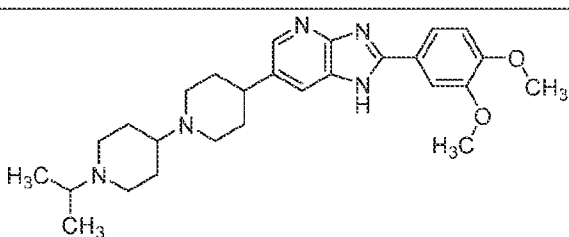


To a 40 mL vial were added Intermediate 36A (0.26 g, 0.818 mmol), Intermediate 60B (0.491 g, 1.227 mmol), potassium phosphate tribasic (0.347 g, 1.636 mmol), 1,4-dioxane (10 mL), and water (2 mL). The vessel was flushed with N₂, then XPhos Pd G3 (0.021 g, 0.025 mmol) was added, the vessel was flushed again, and the reaction mixture was stirred at 85 °C. After 18 h, the mixture was cooled, diluted with water (100 mL) and extracted with EtOAc (2 x 50 mL). The organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The crude mixture was purified by flash column chromatography (80 g silica gel cartridge; A = DCM, B = MeOH; 30 min grad.; 0% B to 20% B; flow rate = 60 mL/min). The fractions corresponding to product were

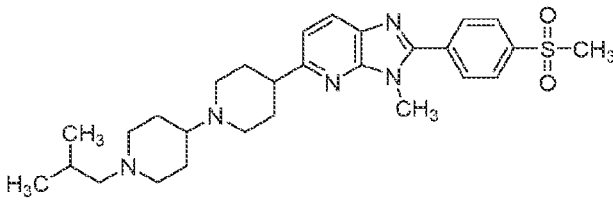
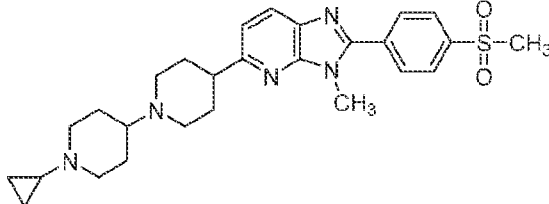
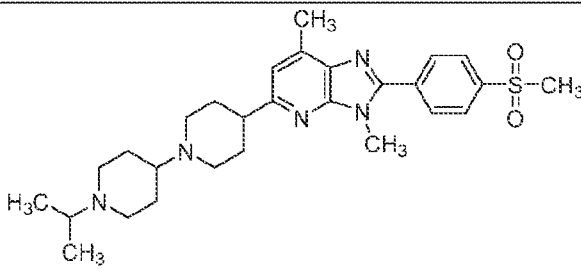
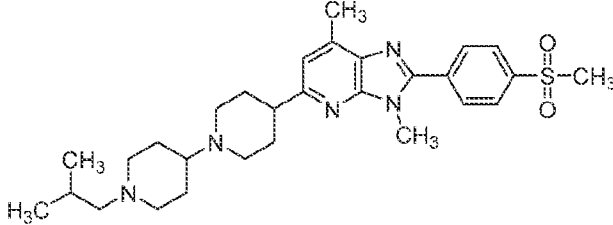
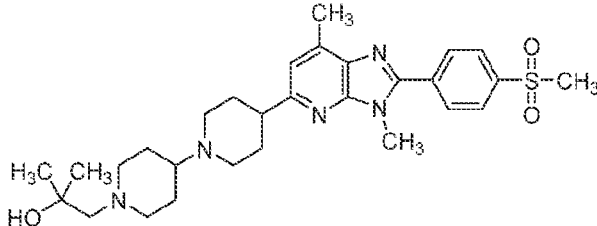
25

- combined, and concentrated. The obtained residue was dissolved in MeOH (10 mL), and HCl solution (4 M in dioxane) (10 mL). After stirring 2 h, the solvent was concentrated, the residue was co-evaporated with toluene (2x) and the product was dried *in vacuo* to afford the title compound (90 mg, 0.132 mmol, 16 % yield) as a tan solid. Analytical
- 5 LC/MS (Method 1): Observed Mass: 456.1; Retention Time: 1.067 min. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.16-8.06 (m, 2H), 7.94-7.87 (m, 1H), 7.64-7.57 (m, 1H), 7.56-7.51 (m, 1H), 7.37-7.29 (m, 1H), 6.69-6.59 (m, 2H), 4.39-4.32 (m, 4H), 4.17 (s, 7H), 4.03-3.98 (m, 6H), 2.82-2.73 (m, 3H).
- 10 Step D. Preparation of Example 60
- To a 40 mL vial were added Intermediate 60C (45 mg, 0.066 mmol), MgSO₄ (39.6 mg, 0.329 mmol), DMF (5 mL), AcOH (3.77 μL, 0.066 mmol), followed by propan-2-one (19.12 mg, 0.329 mmol). After stirring for 10 min, sodium triacetoxyborohydride (69.8 mg, 0.329 mmol) was added, the vial was capped and the reaction mixture was
- 15 stirred. After 18 h, the mixture was diluted with 10% IPA/CHCl₃ (40 mL), filtered, and the filtrate was concentrated. The residue was purified by preparative HPLC (Method D), and the fractions corresponding to product were combined. The volatiles were evaporated, and the resultant aqueous solution was partitioned in 10% IPA/CHCl₃ (20 mL), and KOH solution (10% aqueous saturated with solid NaCl) (20 mL). The layers
- 20 were separated, the aqueous phase was extracted with 10% IPA/CHCl₃ (10 mL), the organic phase was combined, washed with brine, dried over MgSO₄, filtered, and concentrated. The product was dried *in vacuo* to afford the title compound (21.57 mg, 0.043 mmol, 65 % yield) as a light tan solid. Analytical LC/MS (Method 1): Purity: 99%; Observed Mass: 498.2; Retention Time: 1.138 min. (Method 6): Purity 99%, Observed
- 25 Mass: 498.2; Retention Time: 1.432 min. ¹H NMR (500 MHz, DMSO-d₆) δ 8.06-7.99 (m, 2H), 7.62-7.58 (m, 1H), 7.48 (s, 2H), 7.20-7.13 (m, 1H), 6.52 (d, *J* = 8.7 Hz, 2H), 3.97-3.91 (m, 7H), 3.88 (d, *J* = 2.6 Hz, 6H), 3.30-3.28 (m, 1H), 3.26-3.22 (m, 4H), 2.67-2.60 (m, 3H), 0.88-0.82 (m, 6H).
- 30 The following Examples were prepared according to general methods described elsewhere herein using appropriate starting materials, reagents and conditions.

Ex. No.	Structure
1	
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Ex. No.	Structure
7	 <chem>CC1=NC2=C(N1)N(C)C(=C2C3=CC=CC=C3S(=O)(=O)C)C4=CC=C(C=C4)N5CCN(CC5C(C)C)C6=CC=CC=C6</chem>
8	 <chem>CC1=NC2=C(N1)N(C)C(=C2C3=CC=CC=C3S(=O)(=O)C)C4=CC=C(C=C4)N5CCN(CC5CC(C)C)C6=CC=CC=C6</chem>
9	 <chem>CC1=NC2=C(N1)N(C)C(=C2C3=CC=CC=C3S(=O)(=O)C)C4=CC=C(C=C4)N5CCN(CC5)C6=CC=CC=C6</chem>
10	 <chem>CC1=NC2=C(N1)N(C)C(=C2C3=CC(OC)=C(OC)C=C3)C4=CC=C(C=C4)N5CCN(CC5C(C)C)C6=CC=CC=C6</chem>
11	 <chem>CC1=NC2=C(N1)N(C)C(=C2C3=CC(OC)=C(OC)C=C3)C4=CC=C(C=C4)N5CCN(CC5C(C)C)C6=CC=CC=C6</chem>

Ex. No.	Structure
12	 <chem>CC(C)CN1CCN(CC1)C2CCN(CC2)c3cc4nc5c(n3)ccc(OC)c5OC4</chem>
13	 <chem>C1CCN(CC1)C2CCN(CC2)c3cc4nc5c(n3)ccc(OC)c5OC4C6CC7CC7N6</chem>
14	 <chem>CC(C)CN1CCN(CC1)C2CCN(CC2)c3cc4nc5c(n3)ccc(CS(=O)(=O)C)5</chem>
15	 <chem>CC(C)CN1CCN(CC1)C2CCN(CC2)c3cc4nc5c(n3)ccc(CS(=O)(=O)C)5</chem>
16	 <chem>C1CCN(CC1)C2CCN(CC2)c3cc4nc5c(n3)ccc(CS(=O)(=O)C)5C6CC7CC7N6</chem>
17	 <chem>CC(C)CN1CCN(CC1)C2CCN(CC2)c3cc4nc5c(n3)ccc(CS(=O)(=O)C)5</chem>

Ex. No.	Structure
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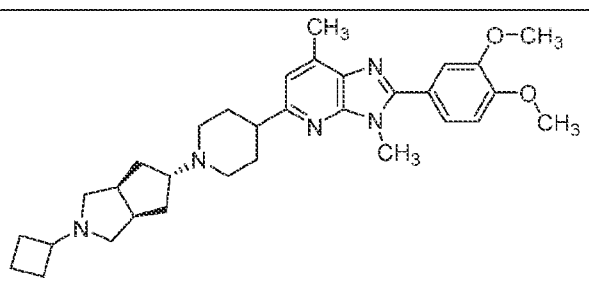
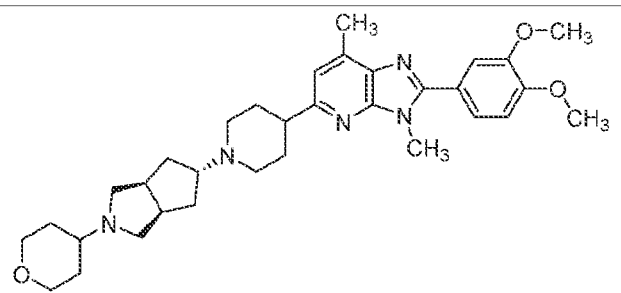
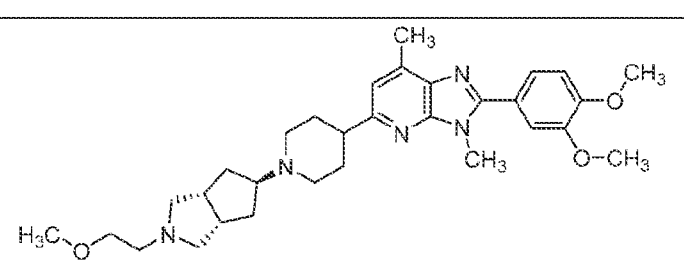
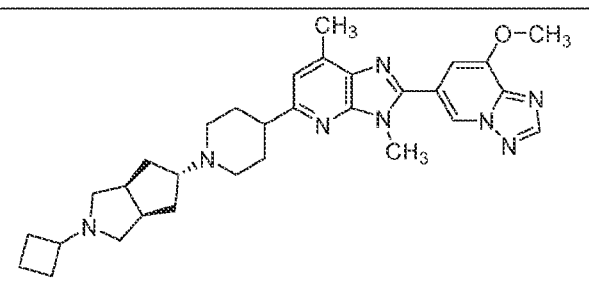
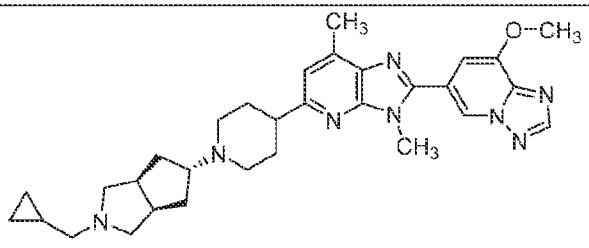
Ex. No.	Structure
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1st eluting isomer

Ex. No.	Structure
27	2nd eluting isomer
28	1st eluting isomer
29	2nd eluting isomer
30	1st eluting isomer

Ex. No.	Structure
31	2nd eluting isomer
32	1st eluting isomer
33	2nd eluting isomer
34	1st eluting isomer

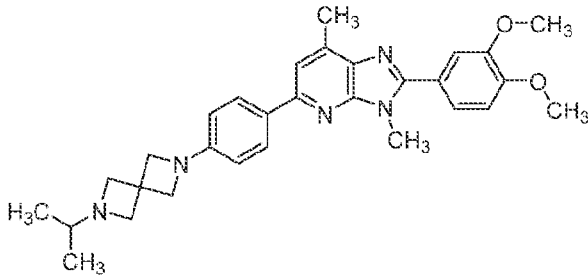
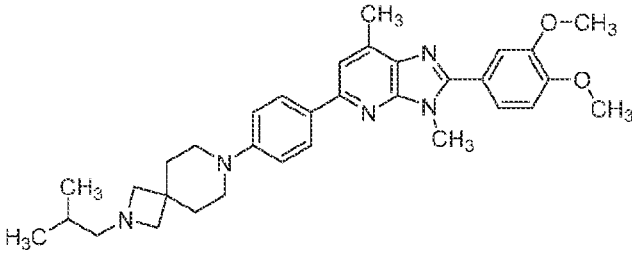
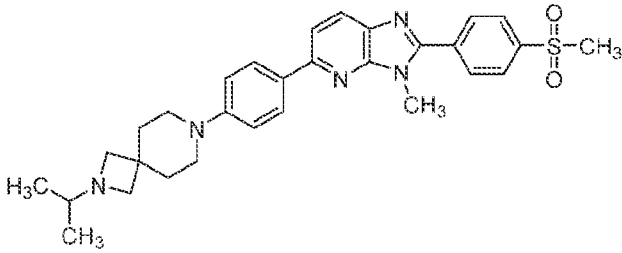
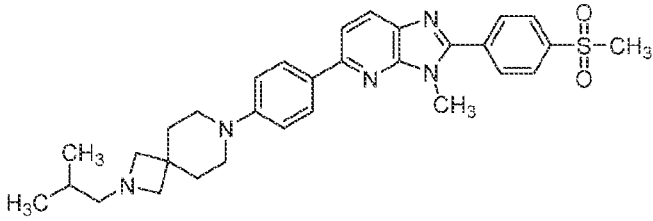
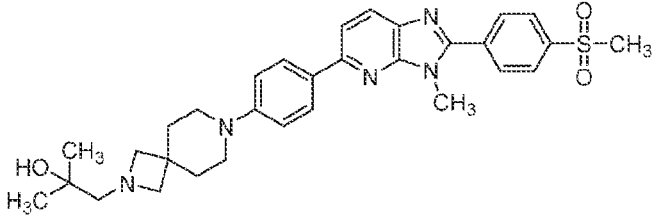
Ex. No.	Structure
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36	2nd eluting isomer
37	2nd eluting isomer
38	2nd eluting isomer

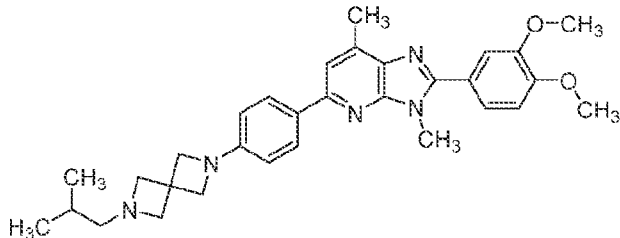
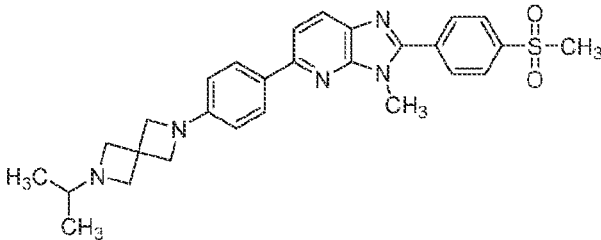
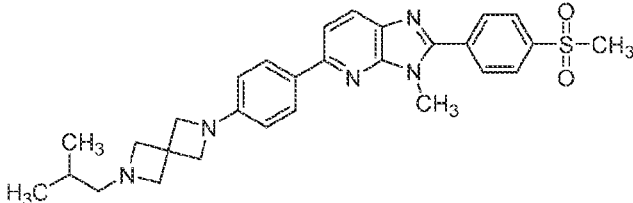
Ex. No.	Structure
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Ex. No.	Structure
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Ex. No.	Structure
49	 <chem>CC(C)N1CCN(CC1)c2ccc(cc2)-c3cc4nc5ccc(cc5n3C)cc4S(=O)(=O)C</chem>
50	 <chem>CC(C)N1CCN(CC1)c2ccc(cc2)-c3cc4nc5ccc(cc5n3C1CC1)cc4OC</chem>
51	 <chem>CC(C)N1CCN(CC1)c2ccc(cc2)-c3cc4nc5ccc(cc5n3C1CC1)cc4S(=O)(=O)C</chem>
52	 <chem>CC(C)N1CCN(CC1)c2ccc(cc2)-c3cc4nc5ccc(cc5n3C)cc4OC</chem>
53	 <chem>CC(C)N1CCN(CC1)c2ccc(cc2)-c3cc4nc5ccc(cc5n3C)cc4S(=O)(=O)C</chem>

Ex. No.	Structure
54	 <chem>CC(C)N1CCN(CC1)c2ccc(cc2)-c3nc4c(nc3n4)C5=CC=C(C=C5)S(=O)(=O)C</chem>
55	 <chem>COc1cc(OC)c(cc1)-c2nc3c(nc2n3)C4=CC=C(C=C4)N5CCN(CC5)c6ccc(cc6)N7CCN(CC7)C(C)C</chem>
56	 <chem>COc1ccc(cc1)-c2nc3c(nc2n3)C4=CC=C(C=C4)S(=O)(=O)C</chem>
57	 <chem>COc1ccc(cc1)-c2nc3c(nc2n3)C4=CC=C(C=C4)S(=O)(=O)C</chem>
58	 <chem>CC1=CC=C(C=C1)-c2nc3c(nc2n3)C4=CC=C(C=C4)OC</chem>

Ex. No.	Structure
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Ex. No.	Structure
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Ex. No.	Analytical LC/MS, ¹ H NMR
1	Analytical LC/MS (Method 2): Observed Mass: 568.20; Retention Time: 1.53 min. Analytical LC/MS (Method 3): Observed Mass: 568.20; Retention Time: 1.14 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.36 (br d, <i>J</i> =8.2 Hz, 2H), 8.12 (br dd, <i>J</i> =8.1, 4.1 Hz, 4H), 7.77 (s, 1H), 7.38 (br d, <i>J</i> =7.9 Hz, 2H), 3.88-3.80 (m, 1H), 3.61-3.54 (m, 1H), 3.37-3.30 (m, 1H), 3.24-3.21 (m, 2H), 3.16 (s, 3H), 3.05-2.96 (m, 1H), 2.91-2.86 (m, 1H), 2.66 (s, 3H), 2.51 (br s, 3H), 1.91 (s, 2H), 1.88-1.78 (m, 2H), 1.74-1.51 (m, 4H), 1.25-1.13 (m, 2H), 0.86 (br s, 2H).

2	Analytical LC/MS (Method 2): Purity: 95.6 %; Observed Mass: 570.20; Retention Time: 1.46 min. (Method 3): Purity: 94.4 %; Observed Mass: 570.3; Retention Time: 1.08 min. ¹H NMR (500 MHz, DMSO-d₆) δ 8.35 (br d, <i>J</i>=8.2 Hz, 2H), 8.12 (br d, <i>J</i>=7.3 Hz, 4H), 7.80-7.75 (m, 1H), 7.46-7.39 (m, 2H), 3.90-3.77 (m, 1H), 3.63-3.43 (m, 3H), 3.32 (s, 3H), 2.86-2.76 (m, 2H), 2.68-2.63 (m, 3H), 2.57-2.54 (m, 3H), 2.08-1.92 (m, 4H), 1.86-1.76 (m, 2H), 1.71-1.62 (m, 3H), 1.49-1.38 (m, 2H), 1.23-1.12 (m, 2H), 0.90-0.79 (m, 2H)
3	Analytical LC/MS (Method 2): Purity: 100 %; Observed Mass: 556.20; Retention Time: 1.39 min. (Method 3): Purity: 100 %; Observed Mass: 556.20; Retention Time: 1.10 min. ¹H NMR (500 MHz, DMSO-d₆) δ 8.38-8.32 (m, 2H), 8.12 (br dd, <i>J</i> = 8.1, 4.1 Hz, 4H), 7.79-7.75 (m, 1H), 7.43-7.33 (m, 2H), 3.88-3.78 (m, 1H), 3.64-3.50 (m, 1H), 3.33 (s, 2H), 2.95-2.86 (m, 1H), 2.78-2.71 (m, 1H), 2.66 (s, 3H), 2.51 (br s, 7H), 2.34-2.25 (m, 1H), 1.91 (s, 3H), 1.22-1.12 (m, 2H), 0.84 (br d, <i>J</i> = 6.1 Hz, 6H)
4	Analytical LC/MS (Method 2): Purity: 100 %; Observed Mass: 570.20; Retention Time: 1.50 min. (Method 3): Purity: 100 %; Observed Mass: 570.20; Retention Time: 1.14 min. ¹H NMR (500 MHz, DMSO-d₆) δ 8.35 (br d, <i>J</i> = 8.2 Hz, 2H), 8.12 (br dd, <i>J</i> = 7.9, 4.9 Hz, 4H), 7.77 (s, 1H), 7.38 (br d, <i>J</i> = 7.9 Hz, 2H), 3.90-3.80 (m, 1H), 3.60-3.54 (m, 1H), 3.52-3.41 (m, 1H), 3.33 (s, 1H), 3.22 (s, 2H), 2.66 (s, 3H), 2.51 (br s, 8H), 2.19-2.07 (m, 2H), 1.57-1.40 (m, 1H), 1.24-1.12 (m, 2H), 0.90-0.85 (m, 2H), 0.81 (d, <i>J</i> = 6.7 Hz, 6H)
5	Analytical LC/MS (Method 2): Purity: 100 %; Observed Mass: 598.2; Retention Time: 1.39 min. (Method 3): Purity: 100 %; Observed Mass: 598.2; Retention Time: 1.10 min. ¹H NMR (500 MHz, DMSO-d₆) δ 8.31 (s, 2H), 8.10 (br t, <i>J</i> = 7.8 Hz, 4H), 7.75 (s, 1H), 7.40 (s, 2H), 3.78 (br s, 5H), 3.64-3.54 (m, 1H), 3.26 (s, 6H), 2.65 (s, 3H), 2.55 (s, 5H), 2.26-2.16 (m, 1H), 1.92-1.84 (m, 1H), 1.60-1.49 (m, 2H), 1.20-1.02 (m, 4H), 0.88-0.77 (m, 2H)

6	Analytical LC/MS (Method 2): Purity: 96.5 %; Observed Mass: 570.20; Retention Time: 1.09 min. (Method 3): Purity: 96.5 %; Observed Mass: 570.20; Retention Time: 1.09 min. ^1H NMR (500 MHz, DMSO- d_6) δ 8.35 (d, J = 8.4 Hz, 2H), 8.12 (br d, J = 6.9 Hz, 4H), 7.77 (s, 1H), 7.39 (d, J = 8.2 Hz, 2H), 4.51 (s, 2H), 4.29 (s, 2H), 3.87-3.79 (m, 1H), 3.69-3.57 (m, 1H), 3.35-3.31 (m, 2H), 3.28-3.27 (m, 2H), 2.66 (s, 3H), 2.55 (s, 6H), 1.91 (s, 3H), 1.22-1.12 (m, 2H), 0.91-0.81 (m, 2H)
7	Analytical LC/MS (Method 5): Purity: 98.2%; Observed Mass: 504.3; Retention Time: 1.333 min. ^1H NMR (400 MHz, DMSO- d_6) δ 8.24 (d, J = 8.1 Hz, 2H), 8.14-8.08 (m, 4H), 7.72 (s, 1H), 7.05 (d, J = 8.4 Hz, 2H), 4.02 (s, 3H), 3.34 (s, 3H), 3.24 (s, 4H) 2.70-2.58 (m, 8H), 1.03 (d, J = 6.4 Hz, 6H)
8	Analytical LC/MS (Method 5): Purity: 99.1%; Observed Mass: 518.2; Retention Time: 0.799 min. ^1H NMR (400 MHz, DMSO- d_6) δ 8.24 (d, J = 8.4 Hz, 2H), 8.14 (d, J = 8.4 Hz, 2H), 8.88 (d, J = 8.8 Hz, 2H), 7.72 (s, 1H), 7.05 (d, J = 8.8 Hz, 2H), 4.02 (s, 3H), 3.33 (s, 3H), 3.28-3.20 (m, 4H), 2.66 (s, 3H), 2.49 (s, 4H), 2.11 (d, J = 3.6 Hz, 2H), 1.90-1.75 (m, 1H), 0.90 (d, J = 6.8 Hz, 6H)
9	Analytical LC/MS (Method 2): Purity: 100 %; Observed Mass: 501.40; Retention Time: 1.46 min. (Method 3): Purity: 100 %; Observed Mass: 501.10; Retention Time: 1.38 min. ^1H NMR (500 MHz, DMSO- d_6) δ 8.37 (d, J = 8.2 Hz, 2H), 8.13 (dd, J = 7.9, 5.5 Hz, 4H), 7.77 (s, 1H), 7.40 (br d, J = 8.2 Hz, 2H), 3.91-3.80 (m, 1H), 2.97-2.84 (m, 2H), 2.67 (s, 3H), 2.52 (br s, 4H), 2.22 (s, 3H), 2.06-1.96 (m, 2H), 1.85-1.67 (m, 4H), 1.25-1.13 (m, 2H), 0.88 (br s, 2H)
10	Analytical LC/MS (Method 2): Purity: 95.9 %; Observed Mass: 486.0; Retention Time: 1.81 min. (Method 3): Purity: 97.2 %; Observed Mass: 486.2; Retention Time: 1.17 min. ^1H NMR (500 MHz, DMSO- d_6) δ 8.13 (d, J = 8.8 Hz, 2H), 7.78 (s, 1H), 7.51 (s, 2H), 7.24-7.13 (m, 3H), 4.00 (s, 4H), 3.88 (s, 5H), 3.15-2.99 (m, 1H), 2.70-2.65 (m, 3H), 2.55 (s, 3H), 2.53-2.49 (m, 5H), 1.32 (d, J = 6.6 Hz, 6H)

11	Analytical LC/MS (Method 2): Purity: 96.3 %; Observed Mass: 463.95; Retention Time: 1.12 min. (Method 3): Purity: 72.9 %; Observed Mass: 463.93; Retention Time: 0.97 min. ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.23-8.17 (m, 1H), 7.78 (s, 3H), 7.17-7.09 (m, 1H), 3.90-3.85 (m, 2H), 3.03-2.98 (m, 3H), 2.92-2.88 (m, 3H), 2.77-2.72 (m, 5H), 2.35-2.27 (m, 6H), 2.21-2.15 (m, 4H), 1.76-1.72 (m, 3H), 1.53-1.48 (m, 4H), 1.44-1.41 (m, 2H)
12	Analytical LC/MS (Method 2): Purity: 86.2 %; Observed Mass: 477.96; Retention Time: 1.27 min. (Method 3): Purity: 75 %; Observed Mass: 477.93; Retention Time: 1.12 min. ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.27-8.17 (m, 1H), 7.94-7.68 (m, 3H), 7.18-7.09 (m, 1H), 3.20-3.08 (m, 2H), 3.00-2.95 (m, 2H), 2.82-2.70 (m, 2H), 2.57-2.55 (m, 3H), 2.21-2.09 (m, 3H), 2.08-1.95 (m, 3H), 1.93-1.68 (m, 7H), 1.63-1.52 (m, 2H), 0.88 (br d, <i>J</i> = 6.4 Hz, 10H)
13	Analytical LC/MS (Method 2): Purity: 72.7 %; Observed Mass: 461.96; Retention Time: 1.20 min. (Method 3): Purity: 74.9 %; Observed Mass: 462.18; Retention Time: 0.94 min. ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.45-8.40 (m, 1H), 7.81 (br s, 3H), 7.19-7.12 (m, 1H), 3.03-2.94 (m, 3H), 2.68-2.59 (m, 2H), 2.33-2.23 (m, 3H), 2.19-2.07 (m, 3H), 1.94-1.88 (m, 2H), 1.85-1.78 (m, 2H), 1.77-1.65 (m, 4H), 1.60-1.51 (m, 2H), 1.45-1.33 (m, 3H), 1.29-1.20 (m, 2H), 0.43-0.36 (m, 2H), 0.30-0.24 (m, 2H)
14	Analytical LC/MS (Method 5): Purity: 99.3%; Observed Mass: 496.2; Retention Time: 0.553 min. ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.22 (s, 1H), 9.65 (s, 1H), 8.46 (s, 1H), 8.23-8.13 (m, 4H), 8.07-8.01 (m, 1H), 3.98 (s, 3H), 3.70-3.47 (m, 5H), 3.34 (s, 3H), 3.28-3.01 (m, 5H), 2.41-2.33 (m, 2H), 2.25-1.96 (m, 5H), 1.33-1.24 (m, 6H)
15	Analytical LC/MS (Method 5): Purity: 96.5%; Observed Mass: 510.2; Retention Time: 0.588 min. ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.34-10.30 (m, 1H), 9.53-9.48 (m, 1H), 8.49-8.44 (m, 1H), 8.23-8.12 (m, 4H), 8.06-8.02 (m, 1H), 3.98 (s, 3H), 3.77-3.46 (m, 5H), 3.34 (s, 3H), 3.26-3.10 (m, 3H), 3.06-2.91 (m, 3H), 2.36-2.29 (m, 2H), 2.24-2.00 (m, 6H), 1.01-0.95 (m, 6H)

16	Analytical LC/MS (Method 5): Purity: 98.0%; Observed Mass: 494.2; Retention Time: 0.558 min. ¹ H NMR (400 MHz, Trifluoroacetic acid-d) δ 7.66–7.62 (m, 2H), 7.23 (d, <i>J</i> = 8.4 Hz, 2H), 7.01 (d, <i>J</i> = 8.4 Hz, 2H), 3.07 (s, 3H), 2.89–2.85 (m, 4H), 2.85–2.82 (m, 1H), 2.32–2.29 (m, 5H), 2.20 (s, 3H), 1.69–1.60 (m, 1H), 1.53–1.50 (m, 2H), 1.37–1.27 (m, 6H), 0.10–0.02 (m, 4H)
17	Analytical LC/MS (Method 5): Purity: 98.8%; Observed Mass: 496.1; Retention Time: 0.584 min. ¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 8.26–8.01 (m, 5H), 7.26 (d, <i>J</i> = 8.4 Hz, 1H), 3.96 (s, 3H), 3.32 (s, 3H), 3.04–2.94 (m, 2H), 2.87–2.59 (m, 4H), 2.38–2.00 (m, 5H), 1.96–1.66 (m, 6H), 1.51–1.33 (m, 2H), 0.95 (d, <i>J</i> = 6.5 Hz, 6H)
18	Analytical LC/MS (Method 5): Purity: 98.1%; Observed Mass: 510.2; Retention Time: 0.606 min. ¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 8.27–8.00 (m, 5H), 7.26 (d, <i>J</i> = 8.4 Hz, 1H), 3.97 (s, 3H), 3.32 (s, 3H), 3.05–2.95 (m, 2H), 2.91–2.76 (m, 3H), 2.35–2.21 (m, 3H), 2.07–1.94 (m, 2H), 1.93–1.63 (m, 9H), 1.55–1.38 (m, 2H), 0.85 (d, <i>J</i> = 6.8 Hz, 6H)
19	Analytical LC/MS (Method 5): Purity: 98.4%; Observed Mass: 494.2; Retention Time: 0.593 min. ¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 8.29–7.98 (m, 5H), 7.26 (d, <i>J</i> = 8.4 Hz, 1H), 3.96 (s, 3H), 3.32 (s, 3H), 3.03–2.93 (m, 4H), 2.85–2.72 (m, 1H), 2.35–2.25 (m, 3H), 2.20–2.07 (m, 2H), 1.98–1.65 (m, 6H), 1.61–1.26 (m, 3H), 0.46–0.23 (m, 4H)
20	Analytical LC/MS (Method 5): Purity: 99.5%; Observed Mass: 510.4; Retention Time: 0.635 min. ¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 8.21 (d, <i>J</i> = 8.4 Hz, 2H), 8.13 (d, <i>J</i> = 8.8 Hz, 2H), 7.14 (s, 1H), 3.98 (s, 3H), 3.24 (s, 3H), 3.16 (d, <i>J</i> = 11.4 Hz, 2H), 3.05 (d, <i>J</i> = 11.4 Hz, 2H), 2.91–2.80 (m, 1H), 2.80–2.69 (m, 1H), 2.68 (s, 3H), 2.50–2.34 (m, 3H), 2.30–2.19 (m, 2H), 2.11–1.94 (m, 6H), 1.74–1.57 (m, 2H), 1.11 (d, <i>J</i> = 6.5 Hz, 6H)

21	Analytical LC/MS (Method 5): Purity: 99.8%; Observed Mass: 524.3; Retention Time: 0.653 min. ¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.21 (d, <i>J</i> = 8.4 Hz, 2H), 8.13 (d, <i>J</i> = 8.8 Hz, 2H), 7.15 (s, 1H), 3.99 (s, 3H), 3.27-3.18 (m, 5H), 3.06 (d, <i>J</i> = 11.5 Hz, 2H), 2.96-2.83 (m, 1H), 2.68 (s, 3H), 2.56-2.40 (m, 3H), 2.17 (d, <i>J</i> = 7.2 Hz, 2H), 2.09-1.92 (m, 8H), 1.90-1.79 (m, 1H), 1.77-1.64 (m, 2H), 0.96 (s, 3H), 0.94 (s, 3H)
22	Analytical LC/MS (Method 5): Purity: 99.7%; Observed Mass: 540.3; Retention Time: 0.606 min. ¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 8.21 (d, <i>J</i> = 6.4 Hz, 2H), 8.13 (d, <i>J</i> = 6.8 Hz, 2H), 7.10 (s, 1H), 4.03 (s, 1H), 3.94 (s, 3H), 3.33 (s, 3H), 3.05-2.91 (m, 4H), 2.78-2.66 (m, 1H), 2.59 (s, 3H), 2.31-2.13 (m, 5H), 2.13-2.03 (m, 2H), 1.91-1.74 (m, 4H), 1.70-1.61 (m, 2H), 1.56-1.43 (m, 2H), 1.08 (s, 6H)
23	Analytical LC/MS (Method 2): Purity: 100 %; Observed Mass: 522.1; Retention Time: 1.248 min. (Method 3): Purity: 100 %; Observed Mass: 522.2; Retention Time: 1.020 min. ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.20 (s, 2H), 8.13 (s, 2H), 7.10 (s, 1H), 3.95 (s, 3H), 3.36-3.34 (m, 3H), 3.07-2.98 (m, 4H), 2.78-2.70 (m, 1H), 2.62-2.57 (m, 3H), 2.35-2.22 (m, 3H), 2.21-2.14 (m, 2H), 2.01-1.81 (m, 6H), 1.80-1.72 (m, 2H), 1.58-1.40 (m, 2H), 0.90-0.78 (m, 1H), 0.53-0.38 (m, 2H), 0.12-0.04 (m, 2H)
24	Analytical LC/MS (Method 2): Purity: 98.7 %; Observed Mass: 522.20; Retention Time: 1.29 min. (Method 3): Purity: 100 %; Observed Mass: 522.20; Retention Time: 0.99 min. ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.18 (s, 2H), 8.15-8.09 (m, 2H), 7.10 (s, 1H), 3.99-3.91 (m, 3H), 3.34-3.27 (m, 2H), 3.07-2.99 (m, 2H), 2.90-2.82 (m, 2H), 2.80-2.63 (m, 2H), 2.59 (s, 3H), 2.40-2.26 (m, 3H), 2.01-1.92 (m, 2H), 1.92-1.67 (m, 10H), 1.66-1.55 (m, 2H), 1.53-1.41 (m, 2H) (one proton obscured)
25	Analytical LC/MS (Method 2): Purity: 100 %; Observed Mass: 552.2; Retention Time: 1.192 min. (Method 3): Purity: 100 %; Observed Mass: 552.20; Retention Time: 0.977 min. ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.25-8.18 (m, 2H), 8.13 (d, <i>J</i> = 8.7 Hz, 2H), 7.10 (s, 1H), 3.95 (s, 3H), 3.91-3.84 (m, 2H), 3.30-3.23 (m, 4H), 3.06-2.90 (m, 4H), 2.81-2.68 (m, 1H), 2.59 (s, 3H), 2.47-2.21 (m, 4H), 2.18-2.04 (m, 2H), 1.94-1.72 (m, 7H), 1.71-1.60 (m, 2H), 1.53-1.32 (m, 4H)

26	Analytical LC/MS (Method 2): Purity: 100 %; Observed Mass: 536.40; Retention Time: 1.13 min. (Method 3): Purity: 100 %; Observed Mass: 536.20; Retention Time: 1.0 min. ¹H NMR (500 MHz, DMSO-d₆) δ 8.22-8.17 (m, 2H), 8.15-8.08 (m, 2H), 7.09 (s, 1H), 3.95-3.91 (m, 2H), 3.33-3.28 (m, 2H), 3.04-2.98 (m, 2H), 2.84-2.76 (m, 1H), 2.76-2.69 (m, 1H), 2.69-2.61 (m, 1H), 2.60-2.58 (m, 2H), 2.57-2.54 (m, 3H), 2.25-2.15 (m, 2H), 1.92-1.75 (m, 8H), 1.73-1.63 (m, 2H), 1.60-1.53 (m, 2H), 1.52-1.45 (m, 2H), 1.07-0.98 (m, 6H)
27	Analytical LC/MS (Method 2): Purity: 100 %; Observed Mass: 536.40; Retention Time: 1.34 min. (Method 3): Purity: 100 %; Observed Mass: 536.20; Retention Time: 0.99 min. ¹H NMR (500 MHz, DMSO-d₆) δ 8.24-8.17 (m, 2H), 8.13-8.12 (m, 2H), 7.11 (s, 1H), 3.94 (s, 3H), 3.69-3.60 (m, 1H), 3.58-3.42 (m, 2H), 3.31 (s, 3H), 2.92-2.69 (m, 3H), 2.61-2.58 (m, 3H), 2.41-2.31 (m, 2H), 2.07-1.92 (m, 7H), 1.88-1.78 (m, 6H), 1.11 (br d, <i>J</i> = 6.1 Hz, 6H)
28	Analytical LC/MS (Method 2): Purity: 100 %; Observed Mass: 550.30; Retention Time: 1.34 min. (Method 3): Purity: 100 %; Observed Mass: 550.30; Retention Time: 1.04 min. ¹H NMR (500 MHz, DMSO-d₆) δ 8.17 (s, 2H), 8.12 (s, 2H), 7.09 (s, 1H), 3.92 (s, 2H), 3.69-3.52 (m, 1H), 3.29 (s, 2H), 3.25-3.17 (m, 2H), 3.09-3.00 (m, 2H), 2.81-2.68 (m, 1H), 2.60-2.57 (m, 3H), 2.27-2.19 (m, 2H), 2.18-2.11 (m, 2H), 1.91-1.75 (m, 8H), 1.69-1.47 (m, 7H), 0.88 (d, <i>J</i> = 6.4 Hz, 6H)
29	Analytical LC/MS (Method 2): Purity: 98.4 %; Observed Mass: 550.30; Retention Time: 1.54 min. (Method 3): Purity: 100 %; Observed Mass: 550.30; Retention Time: 1.05 min. ¹H NMR (500 MHz, DMSO-d₆) δ 8.20-8.15 (m, 2H), 8.14-8.08 (m, 2H), 7.09 (s, 1H), 3.92 (s, 2H), 3.74-3.56 (m, 1H), 3.29 (s, 2H), 3.26-3.14 (m, 3H), 2.80-2.69 (m, 1H), 2.60-2.57 (m, 3H), 2.46-2.36 (m, 1H), 2.11-2.06 (m, 2H), 2.04-1.96 (m, 2H), 1.86 (br s, 12H), 1.73-1.59 (m, 3H), 0.87 (d, <i>J</i> = 6.7 Hz, 6H)

30	Analytical LC/MS (Method 2): Purity: 95.3 %; Observed Mass: 548.30; Retention Time: 1.40 min. (Method 3): Purity: 98.8 %; Observed Mass: 548.20; Retention Time: 1.03 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.08 (d, <i>J</i> = 8.2 Hz, 2H), 8.04-7.96 (m, 2H), 6.98 (s, 1H), 3.82 (s, 3H), 3.26-3.15 (m, 1H), 2.92-2.85 (m, 2H), 2.66-2.57 (m, 1H), 2.55-2.45 (m, 4H), 2.25-2.16 (m, 2H), 2.15-2.04 (m, 2H), 1.79 (s, 9H), 1.58-1.50 (m, 2H), 1.48-1.38 (m, 4H), 0.81-0.66 (m, 1H), 0.40-0.29 (m, 2H), 0.06--0.05 (m, 2H) (one proton obscured)
31	Analytical LC/MS (Method 2): Purity: 99.2 %; Observed Mass: 548.60; Retention Time: 1.39 min. (Method 3): Purity: 98.8 %; Observed Mass: 548.30; Retention Time: 1.04 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.15-8.07 (m, 2H), 8.03 (d, <i>J</i> = 8.2 Hz, 2H), 7.00 (s, 1H), 3.84 (s, 3H), 3.22 (s, 3H), 2.70-2.58 (m, 1H), 2.52-2.47 (m, 3H), 2.45 (s, 3H), 2.33-2.22 (m, 1H), 2.13 (br d, <i>J</i> = 6.4 Hz, 2H), 1.90-1.77 (m, 6H), 1.76-1.64 (m, 9H), 0.84-0.66 (m, 1H), 0.42-0.26 (m, 2H), 0.06--0.06 (m, 2H)
32	Analytical LC/MS (Method 2): Purity: 100 %; Observed Mass: 548.30; Retention Time: 1.29 min. (Method 3): Purity: 99 %; Observed Mass: 548.30; Retention Time: 0.95 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.24-8.17 (m, 2H), 8.13 (d, <i>J</i> = 8.5 Hz, 2H), 7.10 (s, 1H), 3.95 (s, 2H), 3.24-3.16 (m, 1H), 3.09-2.95 (m, 2H), 2.77-2.66 (m, 1H), 2.59 (s, 3H), 2.55 (s, 3H), 2.26-2.16 (m, 2H), 2.04-1.95 (m, 2H), 1.91 (s, 3H), 1.88-1.77 (m, 5H), 1.77-1.60 (m, 4H), 1.59-1.47 (m, 5H) (three protons obscured)
33	Analytical LC/MS (Method 2): Purity: 93 %; Observed Mass: 548.30; Retention Time: 1.44 min. (Method 3): Purity: 100 %; Observed Mass: 548.30; Retention Time: 1.03 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.23-8.17 (m, 2H), 8.13 (d, <i>J</i> = 8.2 Hz, 2H), 7.10 (s, 1H), 3.94 (s, 2H), 3.34-3.30 (m, 2H), 3.29-3.20 (m, 1H), 3.19-3.12 (m, 1H), 3.05-2.95 (m, 1H), 2.78-2.67 (m, 1H), 2.59 (s, 3H), 2.53-2.49 (m, 2H), 2.42-2.33 (m, 1H), 2.02-1.72 (m, 18H), 1.70-1.50 (m, 3H) (one proton obscured)

34	Analytical LC/MS (Method 2): Purity: 100 %; Observed Mass: 578.30; Retention Time: 1.15 min. (Method 3): Purity: 100 %; Observed Mass: 578.30; Retention Time: 1.03 min. ¹H NMR (500 MHz, DMSO-d₆) δ 8.25-8.18 (m, 2H), 8.16-8.08 (m, 2H), 7.14-7.07 (m, 1H), 4.00-3.93 (m, 2H), 3.89-3.83 (m, 2H), 3.36-3.28 (m, 2H), 3.10-3.03 (m, 1H), 2.80-2.63 (m, 3H), 2.63-2.59 (m, 3H), 2.58-2.54 (m, 3H), 2.28-2.17 (m, 2H), 1.93-1.76 (m, 10H), 1.71-1.60 (m, 2H), 1.59-1.46 (m, 4H), 1.36-1.20 (m, 2H) (two protons obscured)
35	Analytical LC/MS (Method 2): Purity: 99.2 %; Observed Mass: 578.50; Retention Time: 1.29 min. (Method 3): Purity: 100 %; Observed Mass: 578.40; Retention Time: 1.03 min. ¹H NMR (500 MHz, DMSO-d₆) δ 8.24-8.18 (m, 2H), 8.17-8.09 (m, 2H), 7.14-7.09 (m, 1H), 3.99-3.93 (m, 2H), 3.92-3.83 (m, 2H), 3.51-3.37 (m, 2H), 3.35-3.27 (m, 2H), 2.86-2.69 (m, 2H), 2.60 (s, 2H), 2.57-2.54 (m, 2H), 2.51-2.45 (m, 5H), 2.44-2.32 (m, 2H), 2.01-1.78 (m, 13H), 1.43-1.27 (m, 3H) (one proton obscured)
36	Analytical LC/MS (Method 2): Purity: 100 %; Observed Mass: 518.5; Retention Time: 1.53 min. (Method 3): Purity: 100 %; Observed Mass: 518.4; Retention Time: 1.09 min. ¹H NMR (500 MHz, DMSO-d₆) δ 7.29-7.19 (m, 2H), 6.98-6.92 (m, 1H), 6.86-6.79 (m, 1H), 3.70-3.68 (m, 2H), 3.67-3.64 (m, 3H), 2.96-2.86 (m, 1H), 2.56-2.41 (m, 3H), 2.39-2.33 (m, 6H), 2.28-2.19 (m, 3H), 2.18-2.10 (m, 1H), 2.08-1.99 (m, 2H), 1.97-1.81 (m, 4H), 1.73-1.69 (m, 2H), 1.68-1.61 (m, 4H), 1.11-0.98 (m, 2H), 0.88-0.80 (m, 6H)
37	Analytical LC/MS (Method 2): Purity: 99.1 %; Observed Mass: 532.6; Retention Time: 1.46 min. (Method 3): Purity: 98.7 %; Observed Mass: 532.6; Retention Time: 0.97 min. ¹H NMR (500 MHz, DMSO-d₆) δ 7.45 (s, 2H), 7.17-7.14 (m, 1H), 7.07-7.02 (m, 1H), 3.86 (s, 8H), 3.64-3.52 (m, 1H), 3.46-3.39 (m, 1H), 3.21-2.96 (m, 2H), 2.95-2.68 (m, 2H), 2.62-2.57 (m, 3H), 2.55 (s, 6H), 2.44-2.31 (m, 2H), 2.22-2.04 (m, 4H), 2.04-1.90 (m, 1H), 1.89-1.67 (m, 2H), 0.97 (br d, <i>J</i> = 6.5 Hz, 6H) (three protons obscured)

38	Analytical LC/MS (Method 2): Purity: 97.5 %; Observed Mass: 530.6; Retention Time: 1.4 min. (Method 3): Purity: 100 %; Observed Mass: 530.6; Retention Time: 0.96 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.45 (s, 2H), 7.18-7.14 (m, 1H), 7.08-7.04 (m, 1H), 3.93-3.82 (m, 8H), 3.69-3.50 (m, 5H), 3.18-3.02 (m, 3H), 2.98-2.74 (m, 2H), 2.61-2.58 (m, 3H), 2.52-2.49 (m, 5H), 2.46-2.32 (m, 2H), 2.22-2.05 (m, 3H), 1.84-1.67 (m, 2H), 1.16-0.98 (m, 1H), 0.65-0.57 (m, 2H), 0.41-0.32 (m, 2H) (one proton obscured)
39	Analytical LC/MS (Method 2): Purity: 98.9 %; Observed Mass: 530.3; Retention Time: 1.64 min. (Method 3): Purity: 100 %; Observed Mass: 530.4; Retention Time: 1.11 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.44 (s, 2H), 7.15 (d, <i>J</i> = 8.7 Hz, 1H), 7.02 (s, 1H), 3.86 (s, 8H), 3.22-3.05 (m, 1H), 2.96-2.70 (m, 1H), 2.59-2.54 (m, 7H), 2.50-2.38 (m, 3H), 2.21-2.04 (m, 5H), 2.00-1.80 (m, 8H), 1.76-1.61 (m, 2H), 1.38-1.19 (m, 2H) (two protons obscured)
40	Analytical LC/MS (Method 2): Purity: 100 %; Observed Mass: 560.4; Retention Time: 1.43 min. (Method 3): Purity: 100 %; Observed Mass: 560.4; Retention Time: 1.07 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.45 (s, 2H), 7.19-7.13 (m, 1H), 7.07-7.01 (m, 1H), 3.93-3.83 (m, 10H), 3.40-3.26 (m, 1H), 3.02-2.77 (m, 1H), 2.58 (s, 3H), 2.55-2.51 (m, 9H), 2.40-2.14 (m, 4H), 2.10-1.88 (m, 4H), 1.87-1.75 (m, 2H), 1.57-1.35 (m, 3H) (four protons obscured)
41	Analytical LC/MS (Method 2): Purity: 99.4 %; Observed Mass: 534.2; Retention Time: 1.39 min. (Method 3): Purity: 100 %; Observed Mass: 534.2; Retention Time: 0.95 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.44 (s, 2H), 7.17-7.12 (m, 1H), 7.02 (s, 1H), 3.92-3.83 (m, 9H), 3.25 (s, 2H), 3.12-3.03 (m, 1H), 2.76-2.65 (m, 1H), 2.55 (s, 11H), 2.46-2.35 (m, 3H), 2.21-2.00 (m, 6H), 1.89-1.78 (m, 4H), 1.28-1.14 (m, 2H)
42	Analytical LC/MS (Method 2): Purity: 98.3%; Observed Mass: 541.4; Retention Time: 1.34 min. (Method 3): Purity: 100%; Observed Mass: 541.2; Retention Time: 0.99 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 9.15-9.08 (m, 1H), 8.59 (s, 1H), 7.53-7.46 (m, 1H), 7.13-7.08 (m, 1H), 4.10 (s, 3H), 3.98 (s, 3H), 2.65-2.60 (m, 4H), 2.55-2.52 (m, 9H), 2.21-2.08 (m, 4H), 2.07-1.80 (m, 10H), 1.78-1.61 (m, 3H).

43	Analytical LC/MS (Method 2): Purity: 99.5%; Observed Mass: 541.5; Retention Time: 1.44 min. (Method 3): Purity: 98.8%; Observed Mass: 541.2; Retention Time: 0.95 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 9.02 (s, 1H), 8.51 (s, 1H), 7.42 (s, 1H), 7.02 (s, 1H), 4.02 (s, 3H), 3.90 (s, 3H), 3.38-3.31 (m, 1H), 3.04-2.97 (m, 1H), 2.74-2.62 (m, 1H), 2.59-2.50 (m, 4H), 2.49-2.44 (m, 2H), 2.40-2.27 (m, 3H), 2.22-1.94 (m, 7H), 1.84-1.74 (m, 4H), 1.25-1.07 (m, 2H), 0.83-0.73 (m, 1H), 0.45-0.34 (m, 2H), 0.07--0.05 (m, 2H)
44	Analytical LC/MS (Method 2): Purity: 95.1%; Observed Mass: 571.2; Retention Time: 1.21 min. (Method 3): Purity: 100%; Observed Mass: 571.2; Retention Time: 0.96 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 9.10 (s, 1H), 8.59 (s, 1H), 7.50 (s, 1H), 7.10 (s, 1H), 4.10 (s, 3H), 3.98 (s, 3H), 3.91-3.79 (m, 2H), 2.83-2.71 (m, 1H), 2.70-2.63 (m, 2H), 2.61 (s, 3H), 2.55 (s, 5H), 2.49-2.40 (m, 2H), 2.29-2.00 (m, 6H), 1.94-1.84 (m, 4H), 1.82-1.70 (m, 2H), 1.45-1.34 (m, 2H), 1.32-1.17 (m, 2H) (one proton obscured)
45	Analytical LC/MS (Method 2): Purity: 99.3%; Observed Mass: 497.6; Retention Time: 1.54 min. (Method 3): Purity: 98.3%; Observed Mass: 497.2; Retention Time: 1.16 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 9.17-9.13 (m, 1H), 8.60 (s, 1H), 8.18-8.06 (m, 2H), 7.80-7.67 (m, 1H), 7.57-7.50 (m, 1H), 7.18-7.12 (m, 2H), 4.11 (s, 3H), 4.06 (s, 3H), 4.04-3.98 (m, 1H), 3.62-3.52 (m, 1H), 3.26-3.15 (m, 1H), 3.14-3.03 (m, 1H), 2.68 (s, 3H), 2.55 (s, 4H), 1.34-1.30 (m, 6H) (one proton obscured)
46	Analytical LC/MS (Method 2): Purity: 95%; Observed Mass: 545.2; Retention Time: 1.27 min. (Method 3): Purity: 95.2%; Observed Mass: 545.2; Retention Time: 0.94 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 9.11 (s, 1H), 8.59 (s, 1H), 7.50 (s, 1H), 7.10 (s, 1H), 4.10 (s, 3H), 3.98 (s, 3H), 3.30-3.22 (m, 1H), 2.86-2.73 (m, 1H), 2.55 (s, 11H), 2.50-2.38 (m, 3H), 2.32-2.00 (m, 5H), 1.99-1.75 (m, 4H), 1.43-1.09 (m, 2H) (three protons obscured)

47	Analytical LC/MS (Method 2): Purity: 98.5%; Observed Mass: 586.2; Retention Time: 1.54 min. (Method 3): Purity: 100%; Observed Mass: 586.6; Retention Time: 1.07 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.37 (d, <i>J</i> = 8.3 Hz, 2H), 8.30 (br d, <i>J</i> = 8.2 Hz, 2H), 8.14 (br d, <i>J</i> = 8.5 Hz, 2H), 7.88 (s, 1H), 7.65 (br s, 2H), 5.23-5.13 (m, 1H), 4.47-4.34 (m, 2H), 3.93-3.83 (m, 1H), 3.35 (s, 3H), 3.08-2.94 (m, 1H), 2.76-2.71 (m, 1H), 2.69 (s, 3H), 2.55 (s, 5H), 2.52-2.49 (m, 5H), 2.38-2.25 (m, 2H), 2.01-1.81 (m, 2H), 1.19 (br d, <i>J</i> = 6.7 Hz, 2H), 0.89 (br s, 2H)
48	Analytical LC/MS (Method 2): Purity: 100%; Observed Mass: 472.4; Retention Time: 1.36 min. (Method 3): Purity: 99.4%; Observed Mass: 472.4; Retention Time: 1.12 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.81-8.75 (m, 1H), 8.47-8.41 (m, 1H), 7.78 (d, <i>J</i> = 8.8 Hz, 2H), 7.50 (s, 2H), 7.18 (br d, <i>J</i> = 9.0 Hz, 3H), 4.03 (s, 4H), 3.89 (s, 6H), 3.67-3.53 (m, 1H), 3.13-3.00 (m, 1H), 2.55 (s, 5H), 1.32 (d, <i>J</i> = 6.6 Hz, 6H) (one proton obscured)
49	Analytical LC/MS (Method 2): Purity: 95.6%; Observed Mass: 490.0; Retention Time: 1.3 min. (Method 3): Purity: 100%; Observed Mass: 490.0; Retention Time: 1.03 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.81-8.78 (m, 1H), 8.40-8.35 (m, 1H), 8.24-8.20 (m, 2H), 8.18-8.13 (m, 2H), 7.81-7.76 (m, 2H), 7.21-7.12 (m, 2H), 4.03 (s, 4H), 3.65-3.49 (m, 1H), 3.38-3.26 (m, 1H), 3.20-2.94 (m, 1H), 2.51 (br d, <i>J</i> = 1.8 Hz, 4H), 1.32 (d, <i>J</i> = 6.6 Hz, 7H) (three protons obscured)
50	Analytical LC/MS (Method 2): Purity: 100%; Observed Mass: 498.5; Retention Time: 1.48 min. (Method 3): Purity: 98.8%; Observed Mass: 498.2; Retention Time: 1.21 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.73 (d, <i>J</i> = 1.2 Hz, 1H), 8.23 (d, <i>J</i> = 1.4 Hz, 1H), 7.75 (d, <i>J</i> = 8.5 Hz, 2H), 7.72-7.68 (m, 1H), 7.65 (s, 1H), 7.18 (dd, <i>J</i> = 8.6, 2.7 Hz, 3H), 3.88 (s, 8H), 3.61-3.47 (m, 1H), 3.27-2.98 (m, 1H), 2.55 (s, 3H), 1.32 (d, <i>J</i> = 6.6 Hz, 7H), 1.21 (br d, <i>J</i> = 6.1 Hz, 2H), 0.77 (br s, 2H) (two protons obscured)

51	Analytical LC/MS (Method 2): Purity: 91.7%; Observed Mass: 516.1; Retention Time: 1.37 min. (Method 3): Purity: 91.5%; Observed Mass: 516; Retention Time: 1.11 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.81-8.71 (m, 1H), 8.41-8.32 (m, 2H), 8.26-8.19 (m, 1H), 8.15 (s, 2H), 7.79-7.73 (m, 2H), 7.21-7.17 (m, 2H), 4.09-3.82 (m, 2H), 3.64-3.48 (m, 1H), 3.33-3.14 (m, 1H), 3.12-3.01 (m, 1H), 2.55 (s, 6H), 1.33 (d, <i>J</i> = 6.6 Hz, 6H), 1.25-1.08 (m, 2H), 0.83-0.71 (m, 2H) (two protons obscured)
52	Analytical LC/MS (Method 2): Purity: 100%; Observed Mass: 472.4; Retention Time: 1.7 min. (Method 3): Purity: 100%; Observed Mass: 472.1; Retention Time: 1.1 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.06 (s, 3H), 7.85-7.75 (m, 1H), 7.53 (s, 2H), 7.21-7.10 (m, 1H), 7.08-7.00 (m, 2H), 4.00 (s, 3H), 3.87 (s, 6H), 3.29-3.18 (m, 4H), 2.77-2.54 (m, 5H), 1.11-0.96 (m, 6H)
53	Analytical LC/MS (Method 2): Purity: 96.2%; Observed Mass: 490.1; Retention Time: 1.54 min. (Method 3): Purity: 97.6%; Observed Mass: 490.5; Retention Time: 1.07 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.25 (d, <i>J</i> = 8.3 Hz, 2H), 8.14 (d, <i>J</i> = 8.5 Hz, 3H), 8.09 (s, 2H), 7.91-7.82 (m, 1H), 7.13-7.02 (m, 2H), 4.04 (s, 3H), 3.46-3.35 (m, 2H), 3.35-3.30 (m, 1H), 3.20-3.15 (m, 1H), 2.83-2.55 (m, 2H), 1.06 (br d, <i>J</i> = 5.1 Hz, 6H) (six protons obscured)
54	Analytical LC/MS (Method 2): Purity: 100%; Observed Mass: 516.6; Retention Time: 1.59 min. (Method 3): Purity: 100%; Observed Mass: 516.1; Retention Time: 1.27 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.40-8.32 (m, 2H), 8.20-8.06 (m, 5H), 7.91-7.83 (m, 1H), 7.20-7.12 (m, 2H), 4.12-3.94 (m, 1H), 3.93-3.78 (m, 1H), 3.62-3.51 (m, 1H), 3.50-3.39 (m, 1H), 3.33 (s, 2H), 3.26-2.97 (m, 1H), 2.53-2.49 (m, 5H), 1.36-1.28 (m, 6H), 1.25-1.14 (m, 2H), 0.92-0.84 (m, 2H) (one proton obscured)

55	Analytical LC/MS (Method 2): Purity: 96.2%; Observed Mass: 498.2; Retention Time: 1.84 min. (Method 3): Purity: 97.3%; Observed Mass: 498.2; Retention Time: 1.25 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.09-8.04 (m, 2H), 8.03-7.98 (m, 1H), 7.79-7.74 (m, 1H), 7.71-7.67 (m, 1H), 7.66-7.63 (m, 1H), 7.17-7.12 (m, 1H), 7.09-7.00 (m, 2H), 3.91-3.84 (m, 7H), 3.83-3.77 (m, 1H), 3.26-3.22 (m, 4H), 2.64-2.57 (m, 4H), 1.21-1.16 (m, 2H), 1.09-0.98 (m, 6H), 0.95-0.85 (m, 2H)
56	Analytical LC/MS (Method 2): Purity: 100%; Observed Mass: 601; Retention Time: 1.54 min. (Method 3): Purity: 100%; Observed Mass: 601.1; Retention Time: 1.11 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.36 (d, <i>J</i> = 8.2 Hz, 2H), 8.10 (dd, <i>J</i> = 19.5, 8.9 Hz, 5H), 7.87-7.80 (m, 1H), 7.06 (s, 2H), 3.92-3.79 (m, 1H), 3.60-3.55 (m, 5H), 3.27-3.23 (m, 4H), 2.57-2.53 (m, 4H), 2.40-2.28 (m, 10H), 1.69-1.58 (m, 2H), 1.23-1.11 (m, 2H), 0.93-0.84 (m, 2H)
57	Analytical LC/MS (Method 2): Purity: 99%; Observed Mass: 587.3; Retention Time: 1.42 min. (Method 3): Purity: 100%; Observed Mass: 587.3; Retention Time: 1.23 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.35 (d, <i>J</i> = 8.4 Hz, 2H), 8.11 (dt, <i>J</i> = 8.1, 6.4 Hz, 5H), 7.89-7.81 (m, 1H), 7.10 (br d, <i>J</i> = 8.8 Hz, 2H), 3.89-3.79 (m, 1H), 3.72-3.62 (m, 1H), 3.56-3.41 (m, 2H), 3.33 (s, 4H), 2.96-2.59 (m, 10H), 2.55-2.50 (m, 6H), 1.18 (br d, <i>J</i> = 6.2 Hz, 2H), 0.87 (br s, 2H)
58	Analytical LC/MS (Method 1): Purity: 99%; Observed Mass: 526.2; Retention Time: 1.123 min. (Method 6): Purity 99%; Observed Mass: 526.2; Retention Time: 1.459 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.07-7.98 (m, 2H), 7.64-7.61 (m, 1H), 7.48 (s, 2H), 7.19-7.14 (m, 1H), 7.06-6.99 (m, 2H), 3.98-3.93 (m, 3H), 3.91-3.84 (m, 6H), 3.25-3.18 (m, 4H), 3.08-2.87 (m, 3H), 2.66-2.62 (m, 3H), 1.83-1.70 (m, 4H), 0.97-0.79 (m, 6H) (two protons obscured)
59	Analytical LC/MS (Method 1): Purity: 99%; Observed Mass: 498.2; Retention Time: 1.138 min. (Method 6): Purity 99%; Observed Mass: 498.2; Retention Time: 1.432 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.06-7.99 (m, 2H), 7.62-7.58 (m, 1H), 7.48 (s, 2H), 7.20-7.13 (m, 1H), 6.52 (d, <i>J</i> = 8.7 Hz, 2H), 3.97-3.91 (m, 7H), 3.88 (d, <i>J</i> = 2.6 Hz, 6H), 3.30-3.28 (m, 1H), 3.26-3.22 (m, 4H), 2.67-2.60 (m, 3H), 0.88-0.82 (m, 6H).

60	Analytical LC/MS (Method 1): Purity: 99%; Observed Mass: 540.3; Retention Time: 1.181 min. (Method 6): Purity 95.3%, Observed Mass: 540.6; Retention Time: 1.630 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.06-7.96 (m, 2H), 7.65-7.60 (m, 1H), 7.52-7.45 (m, 2H), 7.21-7.11 (m, 1H), 7.08-6.97 (m, 2H), 3.99-3.95 (m, 3H), 3.90-3.86 (m, 6H), 3.38-3.27 (m, 2H), 3.25-3.15 (m, 4H), 3.09-2.83 (m, 3H), 2.67-2.62 (m, 3H), 2.34-2.09 (m, 1H), 1.91-1.73 (m, 4H), 1.06-1.02 (m, 1H), 0.92-0.80 (m, 6H)
61	Analytical LC/MS (Method 1): Purity: 96.2%; Observed Mass: 530.3; Retention Time: 1.101 min. (Method 6): Observed Mass: 530.2; Retention Time: 1.356 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.28-8.23 (m, 2H), 8.19-8.12 (m, 3H), 8.10-8.04 (m, 2H), 7.87-7.81 (m, 1H), 7.09-7.03 (m, 2H), 4.04 (s, 3H), 3.33 (d, <i>J</i> = 10.5 Hz, 5H), 3.28-3.18 (m, 4H), 3.05-2.82 (m, 3H), 1.85-1.66 (m, 4H), 1.02-0.79 (m, 6H)
62	Analytical LC/MS (Method 1): Purity: 99%; Observed Mass: 544.2; Retention Time: 1.163 min. (Method 6): Observed Mass: 544.2; Retention Time: 1.417 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.29-8.22 (m, 2H), 8.20-8.12 (m, 3H), 8.11-8.03 (m, 2H), 7.89-7.79 (m, 1H), 7.11-7.02 (m, 2H), 4.04 (s, 3H), 3.35-3.33 (m, 3H), 3.26-3.19 (m, 4H), 3.06-2.87 (m, 3H), 2.33-2.12 (m, 2H), 1.89-1.71 (m, 4H), 1.66-1.46 (m, 1H), 0.92-0.80 (m, 7H)
63	Analytical LC/MS (Method 1): Purity: 99%; Observed Mass: 560.2; Retention Time: 1.071 min. (Method 6): Purity: 95%; Observed Mass: 560.2; Retention Time: 1.253 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.29-8.22 (m, 2H), 8.18-8.11 (m, 3H), 8.10-8.05 (m, 2H), 7.88-7.79 (m, 1H), 7.09-7.02 (m, 2H), 4.09-3.97 (m, 4H), 3.35-3.33 (m, 3H), 3.27-3.19 (m, 4H), 3.15-3.03 (m, 4H), 2.44-2.26 (m, 2H), 1.86-1.67 (m, 4H), 1.05 (s, 6H)
64	Analytical LC/MS (Method 1): Purity: 97.6%; Observed Mass: 512.2; Retention Time: 1.188 min. (Method 6): Purity: 95.6%; Observed Mass: 512.5; Retention Time: 1.650 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.10-8.01 (m, 2H), 7.63-7.60 (m, 1H), 7.48 (s, 2H), 7.20-7.13 (m, 1H), 6.60-6.52 (m, 2H), 3.96 (s, 7H), 3.88 (d, <i>J</i> = 2.6 Hz, 6H), 2.63 (s, 3H), 1.16-1.11 (m, 2H), 0.92-0.84 (m, 11H)

65	Analytical LC/MS (Method 1): Purity: 99%; Observed Mass: 502.1; Retention Time: 1.121 min. (Method 6): Purity: 99%; Observed Mass: 502.1; Retention Time: 1.271 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.28-8.22 (m, 2H), 8.17-8.10 (m, 3H), 8.10-8.03 (m, 2H), 7.87-7.78 (m, 1H), 6.56-6.51 (m, 2H), 4.10-4.03 (m, 3H), 3.98-3.91 (m, 4H), 3.37-3.35 (m, 2H), 3.26-3.22 (m, 5H), 2.27-2.17 (m, 1H), 0.88-0.82 (m, 6H)
66	Analytical LC/MS (Method 1): Purity: 99%; Observed Mass: 516.2; Retention Time: 1.190 min. (Method 6): Purity: 99%; Observed Mass: 516.2; Retention Time: 1.427 min. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.26-8.22 (m, 2H), 8.16-8.10 (m, 3H), 8.09-8.03 (m, 2H), 7.86-7.79 (m, 1H), 6.57-6.51 (m, 2H), 4.04 (s, 3H), 3.96 (s, 4H), 3.28 (s, 7H), 2.20-2.13 (m, 2H), 1.58-1.44 (m, 1H), 0.85 (d, <i>J</i> = 6.7 Hz, 6H)

BIOLOGICAL ASSAYS

The pharmacological properties of the compounds of this invention may be confirmed by a number of biological assays. The exemplified biological assays, which follow, have been carried out with compounds of the invention.

TLR7/8/9 Inhibition Reporter Assays

HEK-Blue™-cells (Invivogen) overexpressing human TLR7, TLR8 or TLR9 receptors were used for screening inhibitors of these receptors using an inducible SEAP (secreted embryonic alkaline phosphatase) reporter gene under the control of the IFN-β minimal promoter fused to five NF-κB and AP-1-binding sites. Cells are seeded into Greiner 384 well plates (15000 cells per well) that are pre dispensed (by ECHO) with testing compounds in DMSO to yield a final dose response concentration range of 0.85 nM-50 μM. After a 60 minute compound pre-treatment in 37 degree incubator, the cells are then stimulated with a TLR7 ligand (gardiquimod at a final concentration of 2.5 μM), TLR8 ligand (R848 at a final concentration of 14.25 μM) or TLR9 ligand (ODN2006 at a final concentration of 200 nM) to activate NF-κB and AP-1 which induce the production of SEAP. After a 22 hour incubation at 37 °C, 5% CO₂, SEAP levels are determined with the addition of HEK-Blue™ Detection reagent (Invivogen), a cell culture medium that

allows for detection of SEAP, according to manufacturer's specifications. The percent inhibition is determined as the % reduction in the HEK-Blue signal present in wells treated with agonist plus DMSO alone compared to wells treated with a known inhibitor.

Ex. No.	TLR9 IC ₅₀ (nM)	TLR7 IC ₅₀ (nM)	TLR8 IC ₅₀ (nM)
1	130	8100	27000
2	100	7200	31000
3	190	710	>50000
4	71	2600	n.d.
5	320	200	260
6	730	15000	n.d.
7	1200	29000	>50000
8	1700	>50000	>50000
9	1700	13000	>50000
10	750	1900	17000
11	n.d.	n.d.	n.d.
12	74	n.d.	n.d.
13	1200	>25000	>25000
14	3100	>50000	>50000
15	160	6400	>25000
16	1400	>25000	>25000
17	71	18000	>50000
18	780	2800	>25000
19	870	18000	>25000
20	25	1400	>50000
21	24	4400	>50000
22	26	1300	>25000
23	61	1900	>50000
24	240	5400	>50000
25	42	4100	>50000
26	58	10000	>50000

Ex. No.	TLR9 IC ₅₀ (nM)	TLR7 IC ₅₀ (nM)	TLR8 IC ₅₀ (nM)
27	300	3700	24000
28	79	1400	>50000
29	550	n.d.	n.d.
30	60	2900	>50000
31	240	7200	19000
32	42	1600	>50000
33	69	1500	19000
34	37	5700	>50000
35	340	7400	>50000
36	140	1000	>50000
37	100	1200	>50000
38	80	740	>50000
39	130	310	24000
40	220	1300	>50000
41	73	480	>50000
42	84	17000	>50000
43	52	250	>50000
44	180	4500	>50000
45	140	5800	n.d.
46	27	360	>50000
47	290	15000	>50000
48	280	1500	18000
49	350	4200	2700
50	320	n.d.	3400
51	340	2700	4200
52	640	1200	>50000
53	930	>50000	>50000
54	760	>50000	>50000
55	1400	40000	>50000

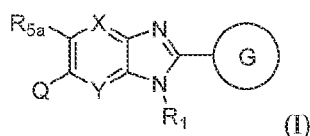
Ex. No.	TLR9 IC ₅₀ (nM)	TLR7 IC ₅₀ (nM)	TLR8 IC ₅₀ (nM)
56	280	>50000	n.d.
57	3200	>50000	>50000
58	540	1600	15000
59	860	1100	n.d.
60	1100	2500	3600
61	560	16000	18000
62	590	15000	6100
63	550	4200	44000
64	1400	6300	9800
65	740	>50000	3000
66	570	>50000	>25000

n.d. = no data available

CLAIMS

What is claimed is:

- 5 1. A compound of Formula (I):

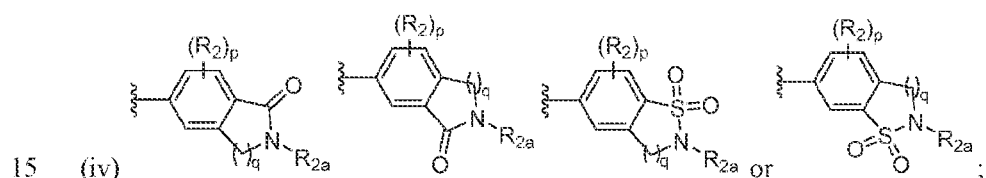
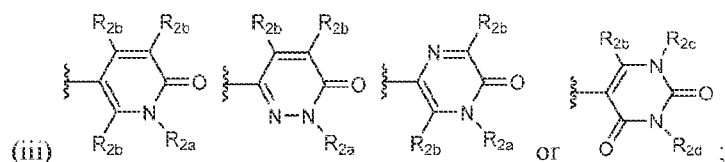
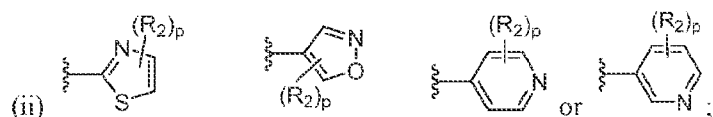


or a salt thereof, wherein:

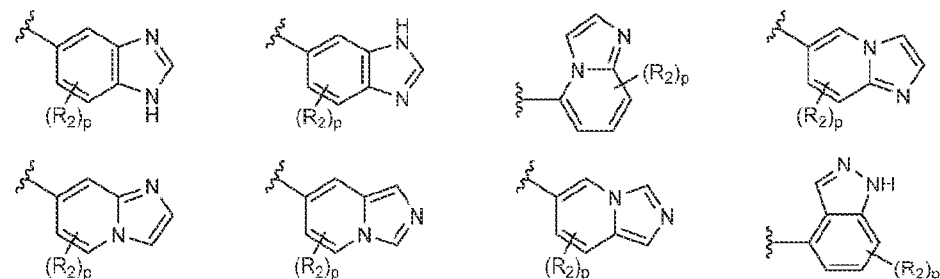
one of X and Y is N and the other of X and Y is CR_{5b};

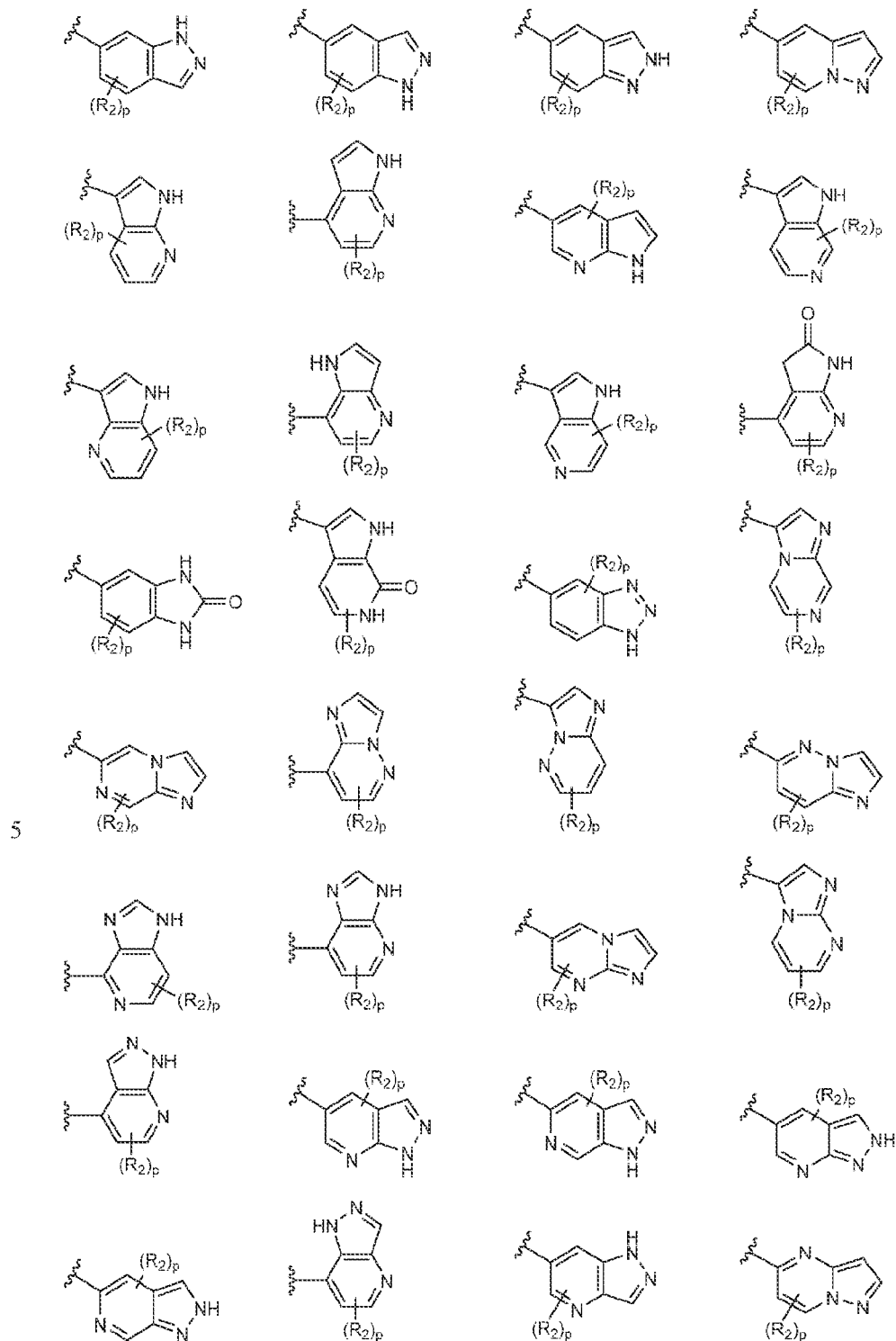
G is:

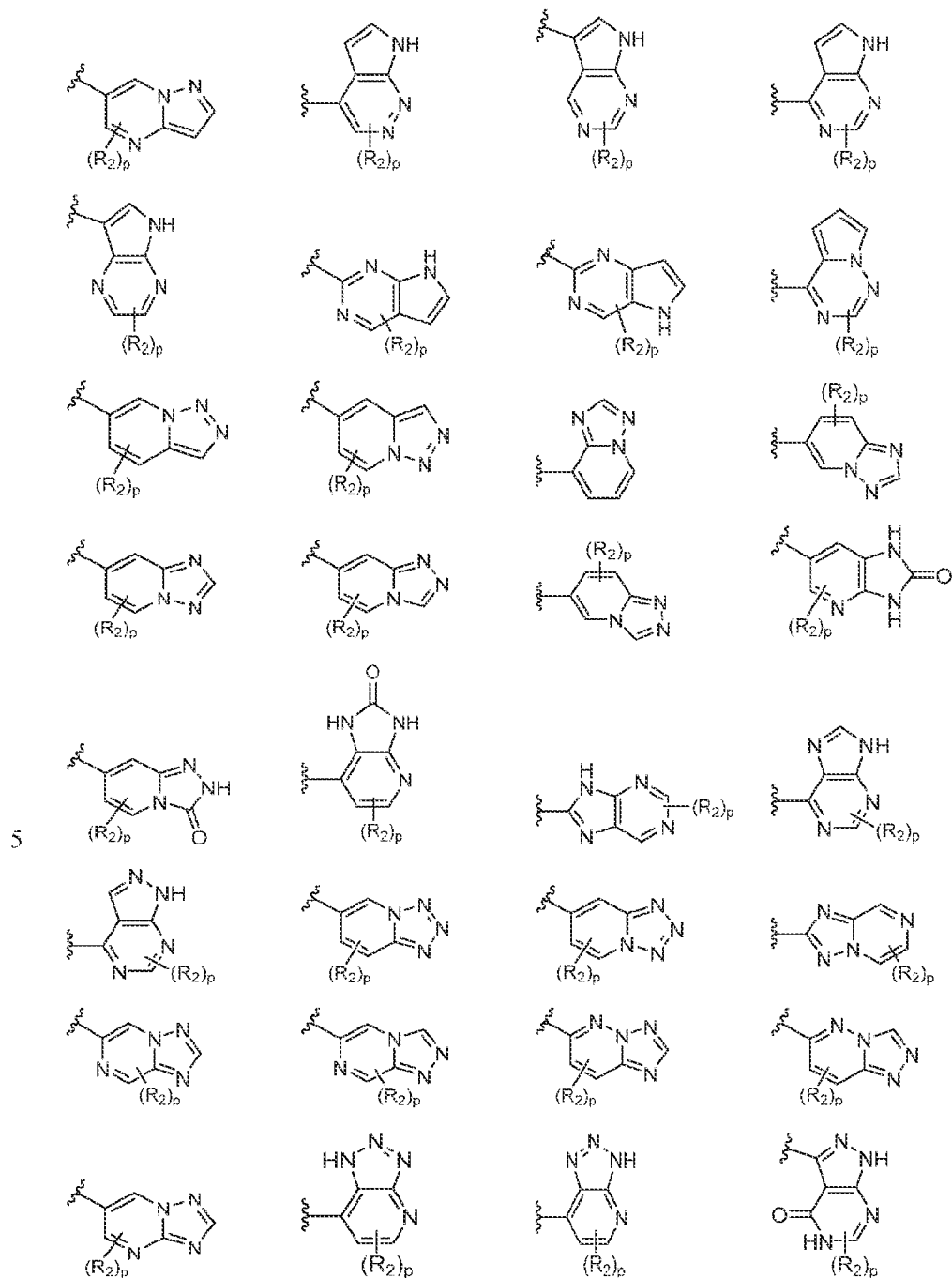
- 10 (i) phenyl substituted with 1 to 3 substituents independently selected from F, Cl, Br, C₁₋₂ alkoxy, C₁₋₂ fluoroalkoxy, C₃₋₄ cycloalkyl, -C(O)NR_xR_y, -S(O)₂CH₃, -S(O)₂(phenyl), -S(O)₂NR_xR_x, and -S(O)(NH)NR_xR_x;

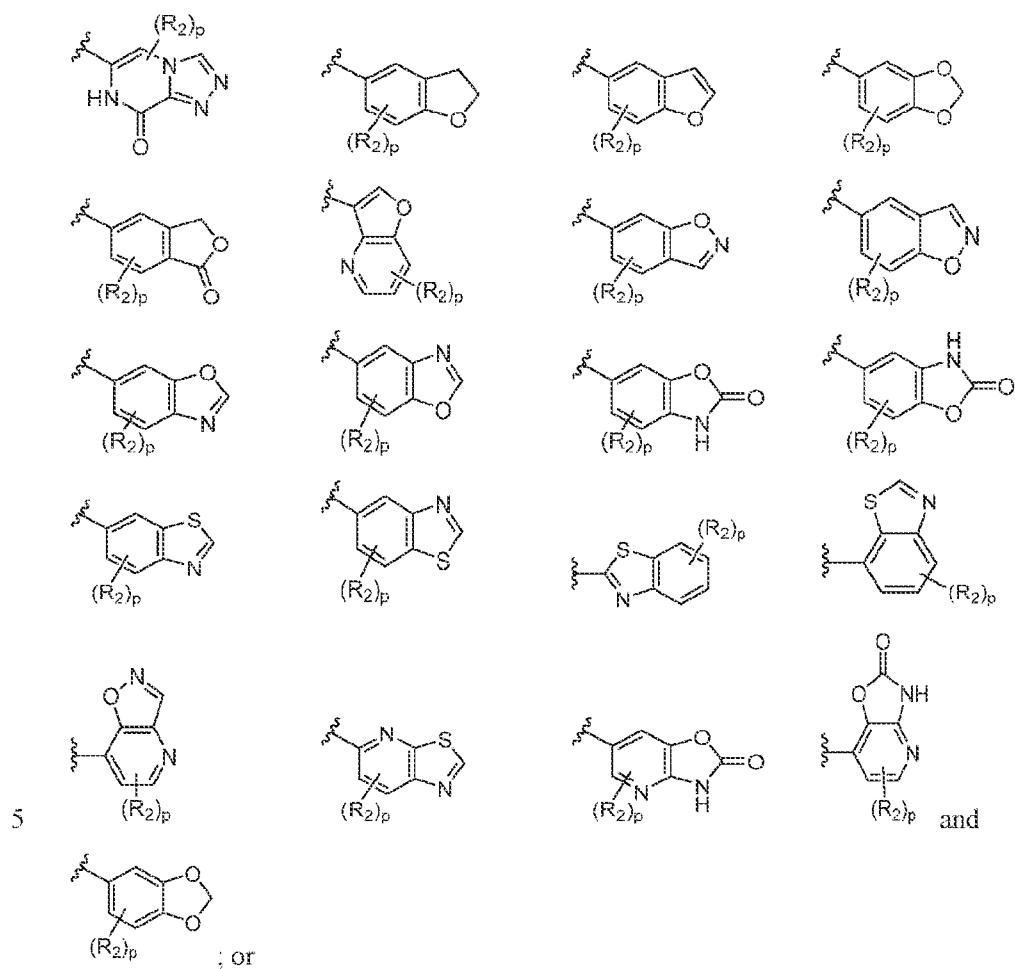


- (v) a 9-membered heterocyclic ring selected from:

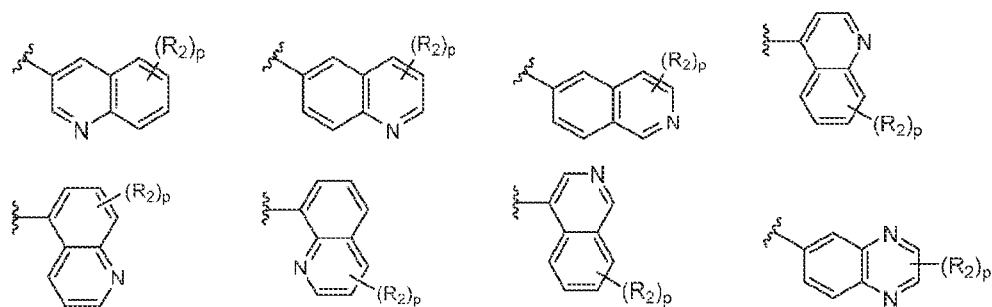


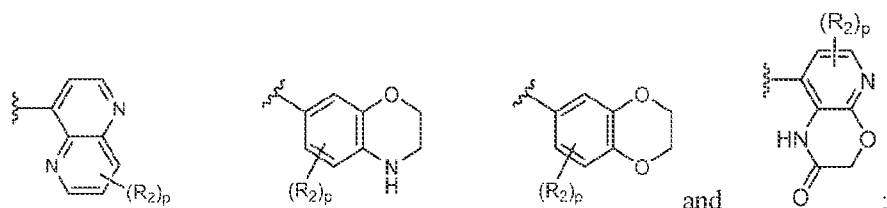






(vi) 10-membered heterocyclic ring selected from:





Q is piperidinyl, phenyl, tetrahydropyridinyl, pyridinyl, or azabicyclo[3.2.1]octanyl, each substituted with $-L-R_4$ and zero to 2 R_{4b} ;

L is a bond, $-(CR_xR_x)_{1-2}-$, or $-C(O)(CR_xR_x)_{0-2}-$;

5 R_1 is hydrogen, C_{1-3} alkyl, C_{1-2} fluoroalkyl, or C_{3-4} cycloalkyl;

each R_2 is independently halo, $-CN$, $-OH$, $-NO_2$, C_{1-4} alkyl, C_{1-2} fluoroalkyl, C_{1-2} cyanoalkyl, C_{1-3} hydroxyalkyl, C_{1-3} aminoalkyl, $-O(CH_2)_{1-2}OH$, $-(CH_2)_{0-4}O(C_{1-4}$ alkyl), C_{1-3} fluoroalkoxy, $-O(CH_2)_{1-2}OC(O)(C_{1-3}$ alkyl), $-O(CH_2)_{1-2}NR_xR_x$, $-C(O)O(C_{1-3}$ alkyl), $-(CH_2)_{0-2}C(O)NR_yR_y$, $-C(O)NR_x(C_{1-5}$ hydroxyalkyl),
 10 $-C(O)NR_x(C_{2-6}$ alkoxyalkyl), $-C(O)NR_x(C_{3-6}$ cycloalkyl), $-NR_yR_y$, $-NR_y(C_{1-3}$ fluoroalkyl), $-NR_y(C_{1-4}$ hydroxyalkyl), $-NR_xCH_2(\text{phenyl})$, $-NR_xS(O)_2(C_{3-6}$ cycloalkyl), $-NR_xC(O)(C_{1-3}$ alkyl), $-NR_xCH_2(C_{3-6}$ cycloalkyl), $-S(O)_2(C_{1-3}$ alkyl), $-S(O)_2N(C_{1-3}$ alkyl) $_2$, $-S(O)(NH)N(C_{1-3}$ alkyl) $_2$, $-(CH_2)_{0-2}(C_{3-6}$ cycloalkyl), $-(CH_2)_{0-2}(\text{phenyl})$, morpholinyl, dioxothiomorpholinyl, dimethyl pyrazolyl,
 15 methylpiperidinyl, methylpiperazinyl, amino-oxadiazolyl, imidazolyl, triazolyl, or $-C(O)(\text{thiazolyl})$;

R_{2a} is C_{1-6} alkyl, C_{1-3} fluoroalkyl, C_{1-6} hydroxyalkyl, C_{1-3} aminoalkyl, $-(CH_2)_{0-4}O(C_{1-3}$ alkyl), C_{3-6} cycloalkyl, $-(CH_2)_{1-3}C(O)NR_xR_x$, $-CH_2(C_{3-6}$ cycloalkyl), $-CH_2(\text{phenyl})$, tetrahydrofuranyl, tetrahydropyranyl, or phenyl;

20 each R_{2b} is independently hydrogen, halo, $-CN$, $-NR_xR_x$, C_{1-6} alkyl, C_{1-3} fluoroalkyl, C_{1-3} hydroxyalkyl, C_{1-3} fluoroalkoxy, $-(CH_2)_{0-2}O(C_{1-3}$ alkyl), $-(CH_2)_{0-3}C(O)NR_xR_x$, $-(CH_2)_{1-3}(C_{3-6}$ cycloalkyl), $-C(O)O(C_{1-3}$ alkyl), $-C(O)NR_x(C_{1-3}$ alkyl), $-CR_x=CR_xR_x$, or $-CR_x=CH(C_{3-6}$ cycloalkyl);

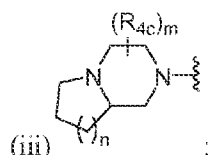
R_{2c} is R_{2a} or R_{2b} ;

25 R_{2d} is R_{2a} or R_{2b} ; provided that one of R_{2c} and R_{2d} is R_{2a} , and the other of R_{2c} and R_{2d} is R_{2b} ;

R₄ is:

(i) $-N(CH_3)_2$;

(ii) pyrrolidinyl, piperidinyl, piperazinyl, pyridinyl, azepanyl, azaspiro[3.3]heptanyl, octahydrocyclopenta[c]pyrrolyl, diazaspiro[3.3]heptanyl, azabicyclo[3.2.1]octanyl, or
 5 hexahydropyrrolo[3,4-c]pyrrolyl, each substituted with zero to 2 R_{4a}; or



each R_{4a} is independently C₁₋₆ alkyl, C₁₋₃ fluoroalkyl, C₁₋₄ hydroxyalkyl, $-(CH_2)_{1-3}OCH_3$,
 C₃₋₆ cycloalkyl, $-(CH_2)_{1-3}(C_{3-6} \text{ cycloalkyl})$, $-(CH_2)_{1-3}(\text{oxetanyl})$,
 $-(CH_2)_{1-3}(\text{morpholinyl})$, $-C(O)(C_{1-4} \text{ alkyl})$, $-C(O)(C_{3-6} \text{ cycloalkyl})$, $-C(O)(\text{phenyl})$,
 10 $-C(O)CH_2(C_{3-6} \text{ cycloalkyl})$, $-C(O)CH_2(\text{phenyl})$, $-C(O)O(C_{1-4} \text{ alkyl})$, $-NR_xR_y$,
 $-NR_x(C_{3-6} \text{ cycloalkyl})$, azetidiny, oxetanyl, tetrahydropyranyl, pyrrolidinyl, phenyl,
 morpholinyl, or piperidinyl substituted with zero to 2 substituents selected from $-OH$
 or $-CH_3$;

R_{4b} is F, Cl, $-CN$, or $-CH_3$;

15 each R_{4c} is independently C₁₋₆ alkyl, C₁₋₃ fluoroalkyl, $-CH_2(C_{3-6} \text{ cycloalkyl})$, $-C(O)(C_{1-4} \text{ alkyl})$, $-C(O)(\text{phenyl})$, $-C(O)CH_2(\text{phenyl})$, $-C(O)OCH_2CH_3$, or C₃₋₆ cycloalkyl;

R_{5a} is hydrogen, F, Cl, C₁₋₂ alkyl, C₁₋₂ fluoroalkyl, or cyclopropyl;

R_{5b} is hydrogen, F, Cl, C₁₋₂ alkyl, C₁₋₂ fluoroalkyl, or cyclopropyl;

each R_x is independently hydrogen or $-CH_3$;

20 each R_y is independently hydrogen or C₁₋₆ alkyl;

m is zero, 1, or 2;

n is zero, 1, or 2;

p is zero, 1, 2, 3, or 4; and

q is 1 or 2.

25

2. The compound according to claim 1 having the structure of Formula (I) or a salt thereof, wherein:

G is phenyl substituted with 1 to 3 substituents independently selected from F, Cl, Br,

–CN, C₁₋₂ alkoxy, C₁₋₂ fluoroalkoxy, C₃₋₄ cycloalkyl, –C(O)NR_yR_y, –S(O)₂CH₃,
 –S(O)₂(phenyl), –S(O)₂(cyclopropyl), –S(O)₂NR_xR_x, –S(O)(NH)NR_xR_x, and
 –NHS(O)₂CH₃;

L is a bond, –CH₂–, or –CH₂CH₂–;

- 5 Q is piperidinyl, phenyl, tetrahydropyridinyl, or pyridinyl, each substituted with –L–R₄
 and zero to 1 R_{4b};

R₁ is hydrogen, C₁₋₃ alkyl, –CHF₂, –CF₃, or C₃₋₄ cycloalkyl;

each R₂ is independently Cl, –CH₃, –CH₂CH₃, –CH₂OH, –CH₂CH₂OH, –CH₂CN,
 –OCH₃, or –CH₂OCH₃;

- 10 R₄ is pyrrolidinyl, piperidinyl, piperazinyl, pyridinyl, azaspiro[3.3]heptanyl,
 octahydrocyclopenta[c]pyrrolyl, diazaspiro[3.3]heptanyl, azabicyclo[3.2.1]octanyl, or
 hexahydropyrrolo[3,4-c]pyrrolyl, each substituted with zero to 1 R_{4a};

R_{4a} is –CH₃, –CH₂CH₃, –CH(CH₃)₂, –CH₂CH(CH₃)₂, –CH₂C(CH₃)₂OH, –CH₂CH₂OCH₃,
 –C(O)CH(CH₃)₂, cyclopropyl, cyclobutyl, –CH₂(cyclopropyl), –CH₂(cyclobutyl),

- 15 –CH₂(oxetanyl), –CH₂CH₂(morpholinyl), –CH₂CH₂CH₂(morpholinyl), –N(CH₃)₂,
 –N(CH₃)(CH₂CH₃), –N(CH₃)(cyclopropyl), azetidiny, oxetanyl, tetrahydropyranyl,
 pyrrolidinyl, phenyl, morpholinyl, or piperidinyl substituted with zero to 2
 substituents selected from –OH or –CH₃;

R_{4b} is F, –CN, or –CH₃;

- 20 R_{5a} is hydrogen, –CH₃, –CF₃, or cyclopropyl; and

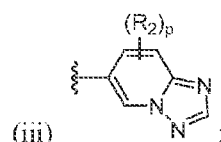
R_{5b} is hydrogen, –CH₃, or –CF₃.

3. The compound according to claim 1 having the structure of Formula (I) or a salt thereof, wherein:

- 25 G is:

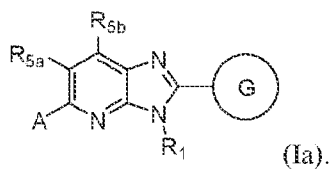
(i) phenyl substituted –S(O)₂CH₃;

(ii) phenyl substituted with two –OCH₃; or



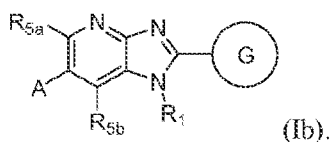
- Q is phenyl or piperidinyl, each substituted with $-L-R_4$;
 L is a bond or $-\text{CH}_2-$;
 R_1 is hydrogen, $-\text{CH}_3$, or cyclopropyl;
 R_4 is piperidinyl, piperazinyl, octahydrocyclopenta[c]pyrrolyl, diazaspiro[3.3]heptanyl, or
 5 azabicyclo[3.2.1]octanyl, each substituted with zero or 1 R_{4a} ;
 R_{4a} is $-\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{OCH}_3$,
 $-\text{CH}_2(\text{cyclopropyl})$, $-\text{CH}_2\text{CH}_2(\text{morpholinyl})$, $-\text{CH}_2\text{CH}_2\text{CH}_2(\text{morpholinyl})$,
 cyclopropyl, cyclobutyl, pyrrolidinyl, oxetanyl, tetrahydropyranyl, or morpholinyl;
 R_{5a} is hydrogen; and
 10 R_{5b} is hydrogen or $-\text{CH}_3$.

4. The compound according to claim 1 having the structure of Formula (I) or a salt thereof, having the structure of Formula (Ia):

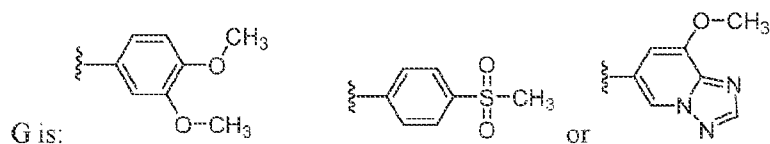


15

5. The compound according to claim 1 having the structure of Formula (I) or a salt thereof, having the structure of Formula (Ib):



- 20 6. The compound according to claim 1 having the structure of Formula (I) or a salt thereof, wherein:



7. The compound according to claim 1 having the structure of Formula (I) or a salt

thereof, wherein L is a bond.

8. The compound according to claim 1 having the structure of Formula (I) or a salt thereof, wherein L is $-(CR_xR_x)_{1-2}-$.

5

9. The compound according to claim 1 or a salt thereof, wherein said compound is:

5-(4-((6-cyclobutyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-3-cyclopropyl-7-methyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (1);

3-cyclopropyl-7-methyl-2-(4-(methylsulfonyl)phenyl)-5-(4-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridine (2);

3-cyclopropyl-5-(4-((6-isopropyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-7-methyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (3);

3-cyclopropyl-5-(4-((6-isobutyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-7-methyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (4);

3-cyclopropyl-7-methyl-2-(4-(methylsulfonyl)phenyl)-5-(4-((6-(tetrahydro-2H-pyran-4-yl)-2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridine (5);

3-cyclopropyl-7-methyl-2-(4-(methylsulfonyl)phenyl)-5-(4-((6-(oxetan-3-yl)-2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-3H-imidazo[4,5-b]pyridine (6);

5-(4-(4-isopropylpiperazin-1-yl)phenyl)-3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (7);

5-(4-(4-isobutylpiperazin-1-yl)phenyl)-3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (8);

3-cyclopropyl-7-methyl-5-(4-(1-methylpiperidin-4-yl)phenyl)-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (9);

2-(3,4-dimethoxyphenyl)-5-(4-(4-isopropylpiperazin-1-yl)phenyl)-3,7-dimethyl-3H-imidazo[4,5-b]pyridine (10);

2-(3,4-dimethoxyphenyl)-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1H-imidazo[4,5-b]pyridine (11);

2-(3,4-dimethoxyphenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1H-imidazo[4,5-b]pyridine (12);

6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3,4-dimethoxyphenyl)-1H-imidazo[4,5-

- b]pyridine (13);
- 6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-imidazo[4,5-b]pyridine (14);
- 6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-imidazo[4,5-b]pyridine (15);
- 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-imidazo[4,5-b]pyridine (16);
- 5-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-3-methyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (17);
- 5-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-3-methyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (18);
- 5-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-3-methyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (19);
- 5-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (20);
- 5-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (21);
- 1-(4-(3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridin-5-yl)-[1,4'-bipiperidin]-1'-yl)-2-methylpropan-2-ol (22);
- 5-(1'-(cyclopropylmethyl)-[1,4'-bipiperidin]-4-yl)-3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (23);
- 5-(1'-cyclobutyl-[1,4'-bipiperidin]-4-yl)-3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (24);
- 3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-5-(1'-(tetrahydro-2H-pyran-4-yl)-[1,4'-bipiperidin]-4-yl)-3H-imidazo[4,5-b]pyridine (25);
- 5-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (26-27);
- 5-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (28-29);
- 5-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (30-31);
- 5-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-3,7-dimethyl-2-(4-

- (methylsulfonyl)phenyl)-3H-imidazo[4,5-b]pyridine (32-33);
 3,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-5-(1-(8-(tetrahydro-2H-pyran-4-yl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-3H-imidazo[4,5-b]pyridine (34-35);
 2-(3,4-dimethoxyphenyl)-5-(1-(2-isopropyloctahydrocyclopenta[c]pyrrol-5-yl)piperidin-4-yl)-3,7-dimethyl-3H-imidazo[4,5-b]pyridine (36);
 2-(3,4-dimethoxyphenyl)-5-(1-(2-isobutyloctahydrocyclopenta[c]pyrrol-5-yl)piperidin-4-yl)-3,7-dimethyl-3H-imidazo[4,5-b]pyridine (37);
 5-(1-(2-(cyclopropylmethyl)octahydrocyclopenta[c]pyrrol-5-yl)piperidin-4-yl)-2-(3,4-dimethoxyphenyl)-3,7-dimethyl-3H-imidazo[4,5-b]pyridine (38);
 5-(1-(2-(cyclobutyloctahydrocyclopenta[c]pyrrol-5-yl)piperidin-4-yl)-2-(3,4-dimethoxyphenyl)-3,7-dimethyl-3H-imidazo[4,5-b]pyridine (39);
 2-(3,4-dimethoxyphenyl)-3,7-dimethyl-5-(1-(2-(tetrahydro-2H-pyran-4-yl)octahydrocyclopenta[c]pyrrol-5-yl)piperidin-4-yl)-3H-imidazo[4,5-b]pyridine (40); or
 2-(3,4-dimethoxyphenyl)-5-(1-((3aR,5s,6aS)-2-(2-methoxyethyl)octahydrocyclopenta[c]pyrrol-5-yl)piperidin-4-yl)-3,7-dimethyl-3H-imidazo[4,5-b]pyridine (41).

10. A pharmaceutical composition comprising one or more compounds according to any one of claims 1 to 9 and a pharmaceutically acceptable carrier or diluent.
11. A compound according to any one of claims 1 to 9 or salt thereof or composition according to claim 10 for use in therapy.
12. A compound according to any one of claims 1 to 9 or salt thereof or composition according to claim 10 in the treatment of inflammatory disease, autoimmune disease, or cancer.
13. A compound according to any one of claims 1 to 9 or salt thereof or composition according to claim 10 for use in therapy.
14. A compound according to any one of claims 1 to 9 or pharmaceutical salt thereof, for use in treating pathological fibrosis.

15. The compound for use according to claim 14, wherein the pathological fibrosis is liver fibrosis, renal fibrosis, biliary fibrosis, or pancreatic fibrosis.
- 5 16. A compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt thereof, for use in treating nonalcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), chronic kidney disease, diabetic kidney disease, primary sclerosing cholangitis (PSC), or primary biliary cirrhosis (PBC).
- 10 17. A compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt thereof, for use in treating idiopathic pulmonary fibrosis (IPF).

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/062780

A. CLASSIFICATION OF SUBJECT MATTER INV. A61P29/00 A61P35/00 A61P37/00 C07D471/04 C07D519/00 A61K31/437 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, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/150416 A1 (PFIZER [US]) 10 October 2013 (2013-10-10) Whole document, particularly claims 1 and 20, examples 1, 2, 4, 7, 8, 11, 14, 16, 17, 19, 21, 33-37, 40-44, 60, 100, 113, 114, 127, 140, 179-181, 183. -----	1-4, 10-13, 16
A	WO 2006/113458 A1 (BRISTOL MYERS SQUIBB CO [US]; PURANDARE ASHOK VINAYAK [US] ET AL.) 26 October 2006 (2006-10-26) claims and examples 83 and 141 -----	1-17
A	WO 2019/126083 A1 (BRISTOL MYERS SQUIBB CO [US]) 27 June 2019 (2019-06-27) Whole document, particularly claim 1 and tests in pages 102-103 ----- -/--	1-17
☒ 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 11 May 2023		Date of mailing of the international search report 22/05/2023
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 Sahagún Krause, H

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/062780

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2019/126113 A1 (BRISTOL MYERS SQUIBB CO [US]) 27 June 2019 (2019-06-27) Whole document, particularly claim 1 and tests in pages 230-241 -----	1-17
Y,P	WO 2022/040267 A1 (BRISTOL MYERS SQUIBB CO [US]) 24 February 2022 (2022-02-24) Whole document, particularly claim 1 and tests in pages 156-160 -----	1-17
Y,P	WO 2022/040293 A1 (BRISTOL MYERS SQUIBB CO [US]) 24 February 2022 (2022-02-24) Whole document, particularly claim 1 and tests in pages 89-91 -----	1-17
Y,P	WO 2022/040260 A1 (BRISTOL MYERS SQUIBB CO [US]) 24 February 2022 (2022-02-24) Whole document, particularly claim 1 and tests in pages 365-380 -----	1-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

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Information on patent family members

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