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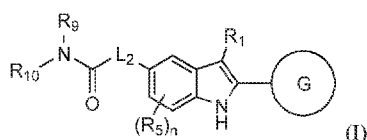
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(54) Title: AMIDE SUBSTITUTED INDOLE COMPOUNDS USEFUL AS TLR INHIBITORS



(57) Abstract: N-oxides, or salts thereof, wherein G, L₂, R₁, R₅, R₉, R₁₀, and n are defined herein. Also disclosed are methods of using such compounds as inhibitors of signaling through Toll-like receptor 7, or 8, or 9, and pharmaceutical compositions comprising such compounds. These compounds are useful in treating inflammatory and autoimmune diseases.

AMIDE SUBSTITUTED INDOLE COMPOUNDS USEFUL AS TLR INHIBITORS

CROSS REFERENCE

This application claims the benefit of U.S. Provisional Application Serial No.
5 62/607,388 filed December 19, 2017 which is incorporated herein in its entirety.

DESCRIPTION

The present invention generally relates to amide substituted indole compounds useful as inhibitors of signaling through Toll-like receptor 7, 8, or 9 (TLR7, TLR8,
10 TLR9) or combinations thereof. Provided herein are amide substituted indole 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 that are useful for the treatment of conditions related to TLR modulation, such as inflammatory and autoimmune diseases, and methods
15 of inhibiting the activity of TLRs in a mammal.

Toll/IL-1 receptor family members are important regulators of inflammation and host resistance. The Toll-like receptor family recognizes molecular patterns derived from infectious organisms including bacteria, fungi, parasites, and viruses (reviewed in Kawai, T. et al., *Nature Immunol.*, 11:373-384 (2010)). Ligand binding to the receptor induces
20 dimerization and recruitment of adaptor molecules to a conserved cytoplasmic motif in the receptor termed the Toll/IL-1 receptor (TIR) domain. With the exception of TLR3, all TLRs recruit the adaptor molecule MyD88. The IL-1 receptor family also contains a cytoplasmic TIR motif and recruits MyD88 upon ligand binding (reviewed in Sims, J.E. et al., *Nature Rev. Immunol.*, 10:89-102 (2010)).

25 Toll-like receptors (TLRs) are a family of evolutionarily conserved, transmembrane innate immune receptors that participate in the first-line defense. As pattern recognition receptors, the TLRs protect against foreign molecules, activated by pathogen associated molecular patterns (PAMPs), or from damaged tissue, activated by danger associated molecular patterns (DAMPs). A total of 13 TLR family members have
30 been identified, 10 in human, that span either the cell surface or the endosomal compartment. TLR7/8/9 are among the set that are endosomally located and respond to single-stranded RNA (TLR7 and TLR8) or unmethylated single-stranded DNA containing

cytosine-phosphate-guanine (CpG) motifs (TLR9).

Activation of TLR7/8/9 can initiate a variety of inflammatory responses (cytokine production, B cell activation and IgG production, Type I interferon response). In the case of autoimmune disorders, the aberrant sustained activation of TLR7/8/9 leads to
5 worsening of disease states. Whereas overexpression of TLR7 in mice has been shown to exacerbate autoimmune disease, knockout of TLR7 in mice was found to be protective against disease in lupus-prone MRL/lpr mice. Dual knockout of TLR7 and 9 showed further enhanced protection.

As numerous conditions may benefit by treatment involving modulation of
10 cytokines, IFN production and B cell activity, it is immediately apparent that new compounds capable of modulating TLR7 and/or TLR8 and/or TLR9 and methods of using these compounds could provide substantial therapeutic benefits to a wide variety of patients.

The present invention relates to a new class of amide substituted indole
15 compounds found to be effective inhibitors of signaling through TLR7/8/9. These compounds are provided to be useful as pharmaceuticals with desirable stability, bioavailability, therapeutic index, and toxicity values that are important to their drugability.

20 DETAILED DESCRIPTION

The present invention provides compounds of Formula (I) that are useful as inhibitors of signaling through Toll-like receptor 7, 8, or 9 and are useful for the treatment of proliferative diseases, allergic diseases, autoimmune diseases and inflammatory diseases, or stereoisomers, N-oxides, tautomers, pharmaceutically acceptable salts,
25 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.

30 The present invention also provides a method for inhibition of Toll-like receptor 7, 8, or 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 proliferative, metabolic, allergic, autoimmune and inflammatory diseases, comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the
5 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 7, 8, or 9 activity, the method comprising administering to a mammal in need thereof, at least one of the compounds of Formula (I) or salts,
10 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.

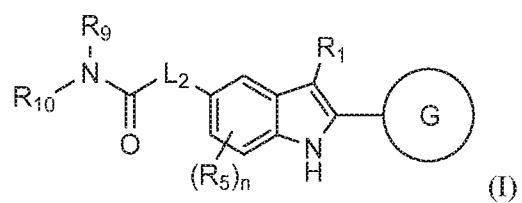
15 The present invention also provides the use of at least one of the compounds of Formula (I) or salts, solvates, and prodrugs thereof, for the manufacture of a medicament for the treatment of prophylaxis of Toll-like receptor 7, 8, or 9 related conditions, such as allergic disease, autoimmune diseases, inflammatory diseases, and proliferative diseases.

The compound of Formula (I) and compositions comprising the compounds of
20 Formula (I) may be used in treating, preventing, or curing various Toll-like receptor 7, 8, or 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 allergic disease, autoimmune diseases, inflammatory diseases, and proliferative diseases.

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

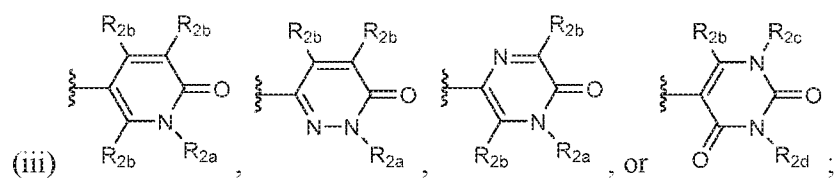
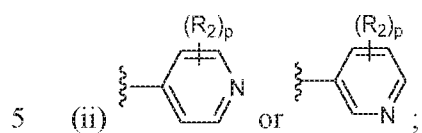
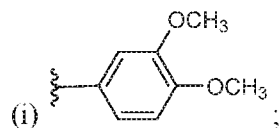
DETAILED DESCRIPTION

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

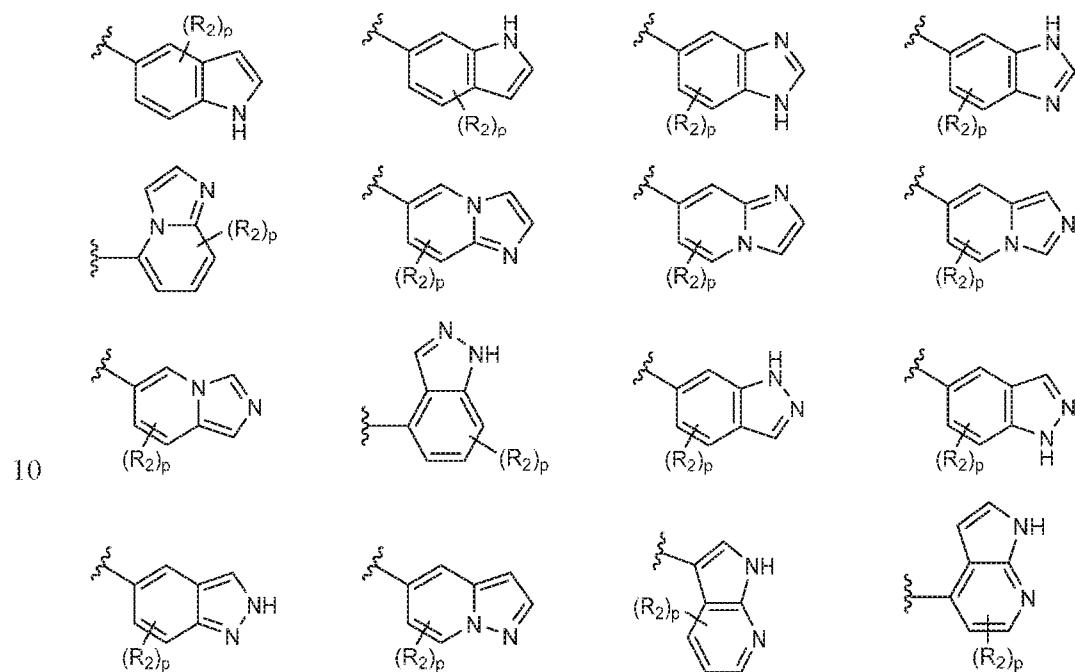


N-oxide, or a salt thereof, wherein:

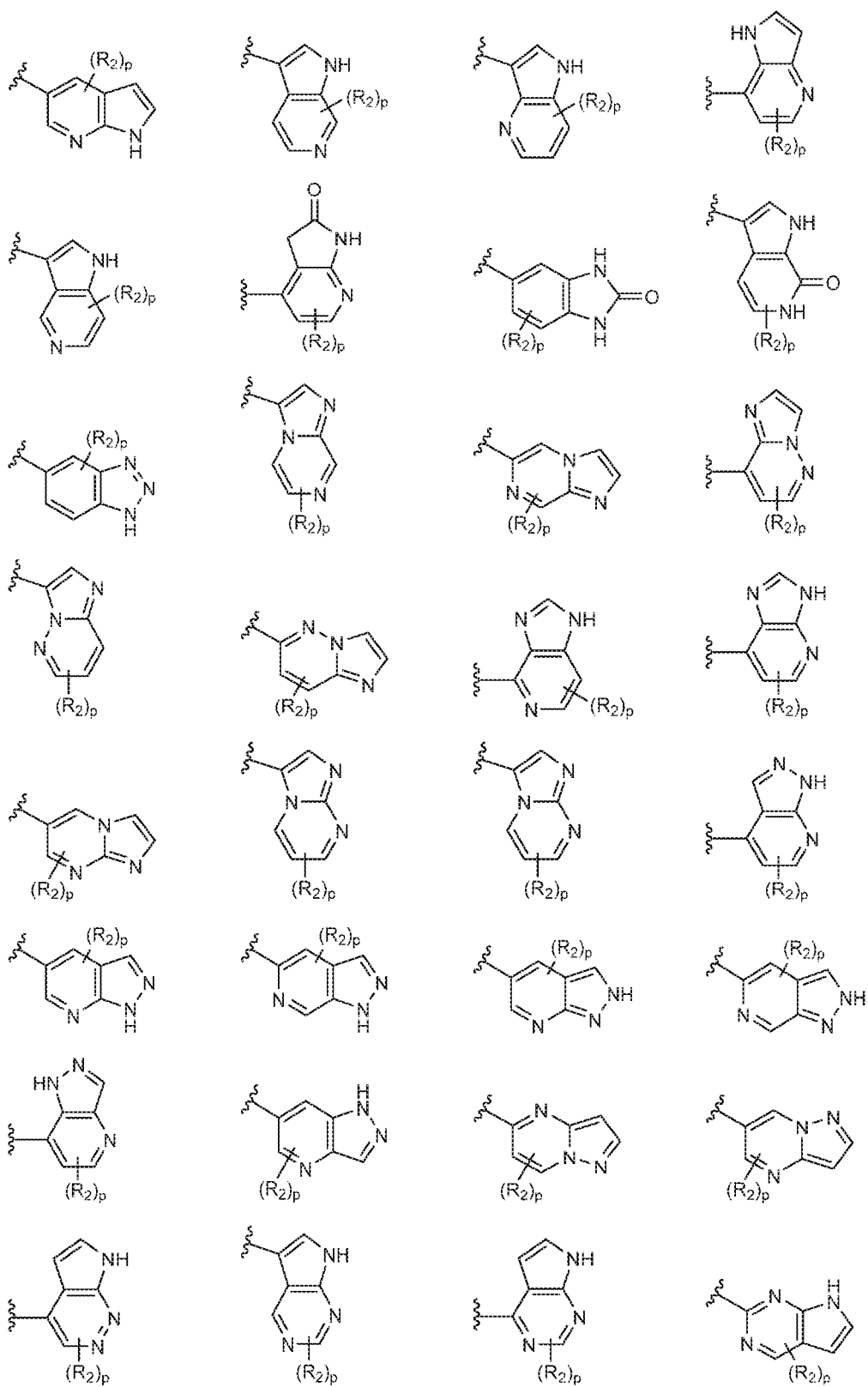
G is:



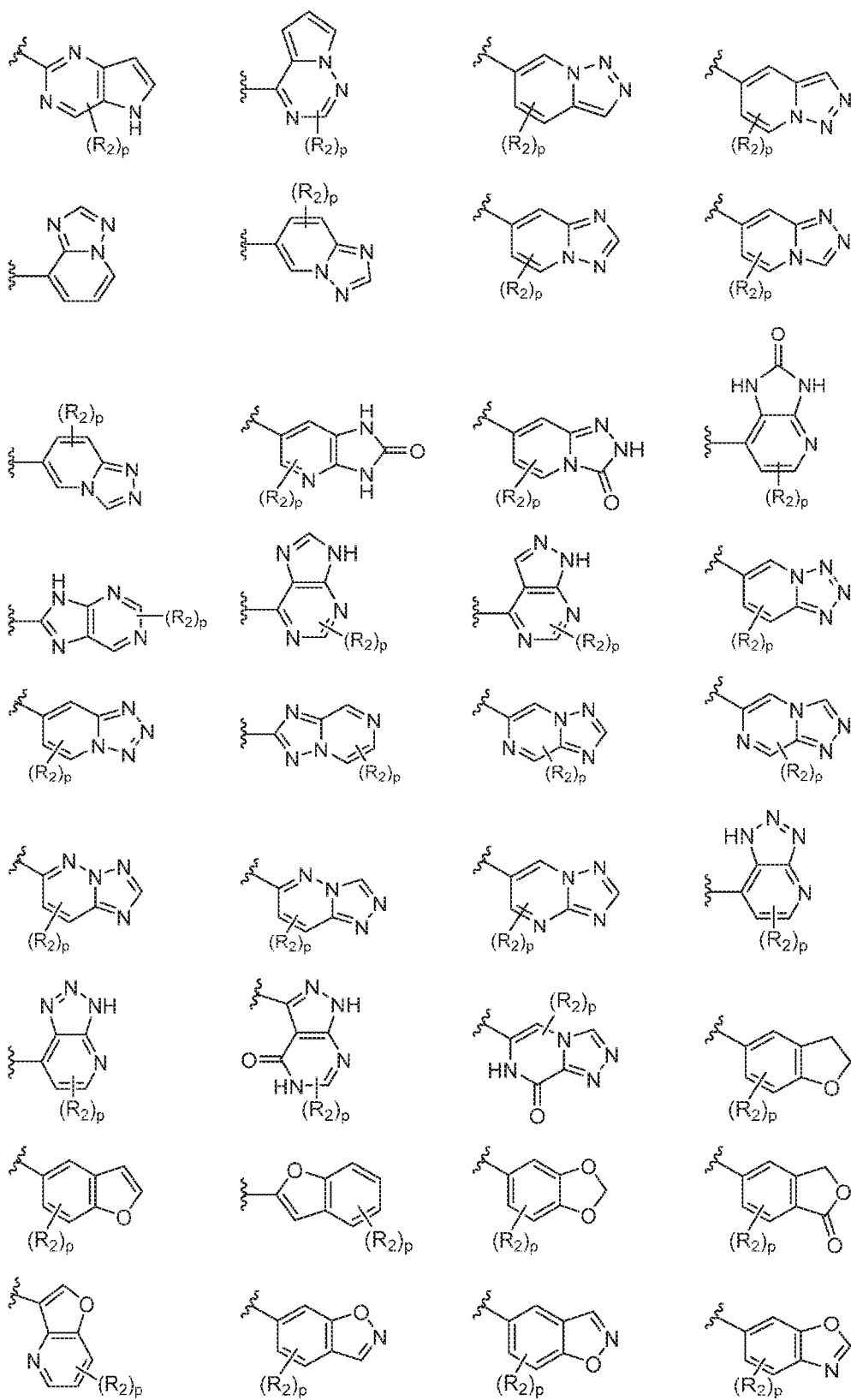
(iv) a 9-membered heterocyclic ring selected from:



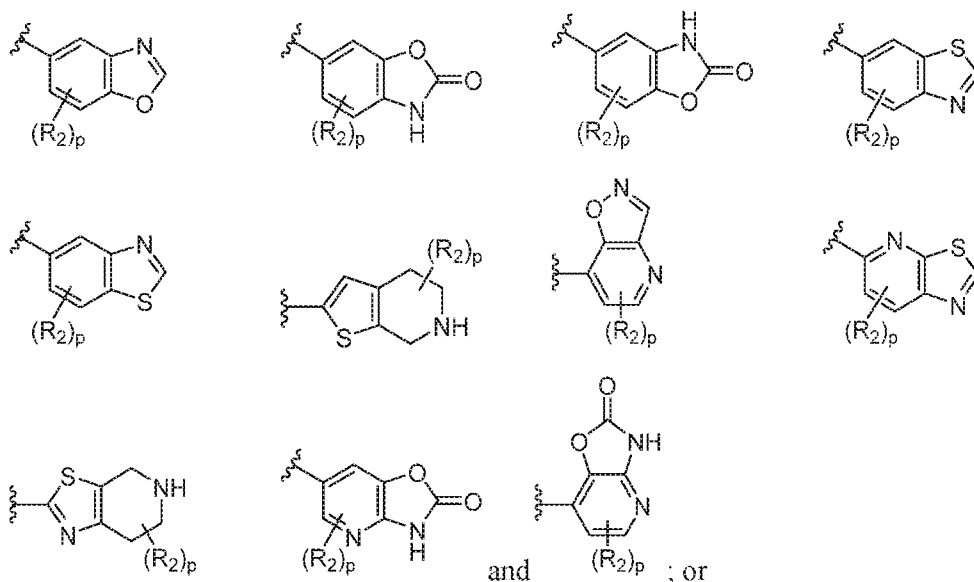
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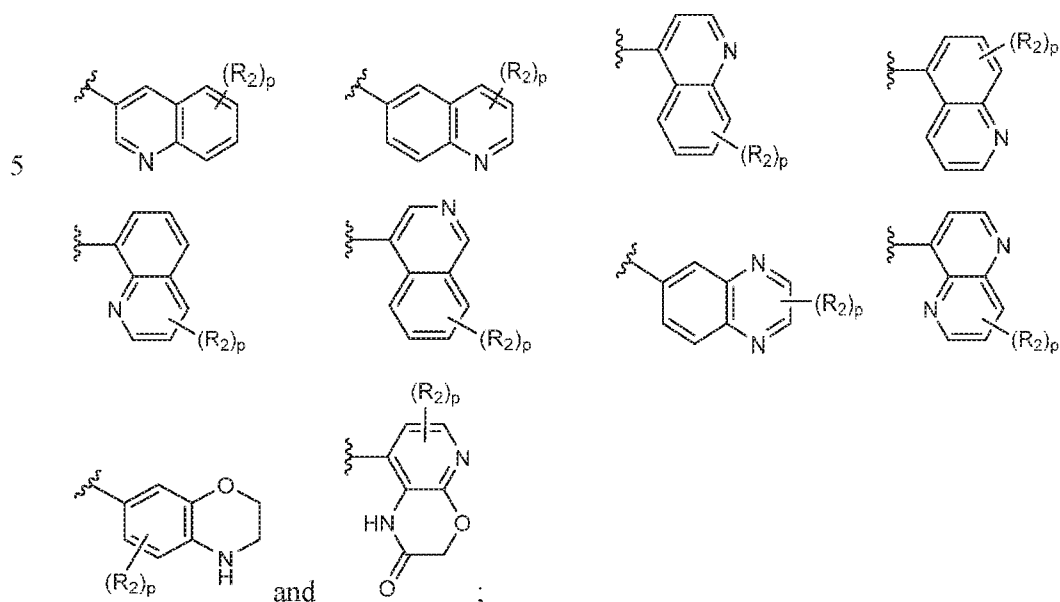
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(v) a 10-membered heterocyclic ring selected from:



L₂ is a bond or $-(CR_xR_x)_{1-3}-$;

R₁ is H, Cl, $-CN$, C₁₋₄ alkyl, C₁₋₃ fluoroalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ hydroxy-

fluoroalkyl, $-CR_v=CH_2$, C₃₋₆ cycloalkyl, $-CH_2(C_{3-6} \text{ cycloalkyl})$, $-C(O)O(C_{1-3} \text{ alkyl})$, or tetrahydropyranyl;

each R₂ is independently halo, $-CN$, $-OH$, $-NO_2$, C₁₋₄ alkyl, C₁₋₂ fluoroalkyl, C₁₋₂ cyanoalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ aminoalkyl, $-O(CH_2)_{1-2}OH$, $-(CH_2)_{0-4}O(C_{1-4} \text{ alkyl})$, C₁₋₃ fluoroalkoxy, $-(CH_2)_{1-4}O(C_{1-3} \text{ alkyl})$, $-O(CH_2)_{1-2}OC(O)(C_{1-3} \text{ alkyl})$,

- $-\text{O}(\text{CH}_2)_{1-2}\text{NR}_x\text{R}_x$, $-\text{C}(\text{O})\text{O}(\text{C}_{1-3}\text{ alkyl})$, $-(\text{CH}_2)_{0-2}\text{C}(\text{O})\text{NR}_y\text{R}_y$, $-\text{C}(\text{O})\text{NR}_x(\text{C}_{1-5}$
 hydroxyalkyl), $-\text{C}(\text{O})\text{NR}_x(\text{C}_{2-6}\text{ alkoxyalkyl})$, $-\text{C}(\text{O})\text{NR}_x(\text{C}_{3-6}\text{ cycloalkyl})$, $-\text{NR}_y\text{R}_y$,
 $-\text{NR}_y(\text{C}_{1-3}\text{ fluoroalkyl})$, $-\text{NR}_y(\text{C}_{1-4}\text{ hydroxyalkyl})$, $-\text{NR}_x\text{CH}_2(\text{phenyl})$,
 $-\text{NR}_x\text{S}(\text{O})_2(\text{C}_{3-6}\text{ cycloalkyl})$, $-\text{NR}_x\text{C}(\text{O})(\text{C}_{1-3}\text{ alkyl})$, $-\text{NR}_x\text{CH}_2(\text{C}_{3-6}\text{ cycloalkyl})$,
 5 $-\text{S}(\text{O})_2(\text{C}_{1-3}\text{ alkyl})$, $-(\text{CH}_2)_{0-2}(\text{C}_{3-6}\text{ cycloalkyl})$, $-(\text{CH}_2)_{0-2}(\text{phenyl})$, morpholinyl,
 dioxothiomorpholinyl, dimethyl pyrazolyl, methylpiperidinyl, methylpiperazinyl,
 amino-oxadiazolyl, imidazolyl, triazolyl, or $-\text{C}(\text{O})(\text{thiazolyl})$;
 R_{2a} is C_{1-6} alkyl, C_{1-3} fluoroalkyl, C_{1-6} hydroxyalkyl, C_{1-3} aminoalkyl, $-(\text{CH}_2)_{0-4}\text{O}(\text{C}_{1-3}$
 alkyl), C_{3-6} cycloalkyl, $-(\text{CH}_2)_{1-3}\text{C}(\text{O})\text{NR}_x\text{R}_x$, $-\text{CH}_2(\text{C}_{3-6}\text{ cycloalkyl})$, $-\text{CH}_2(\text{phenyl})$,
 10 tetrahydrofuranyl, tetrahydropyranyl, or phenyl;
 each R_{2b} is independently H, halo, $-\text{CN}$, $-\text{NR}_x\text{R}_x$, C_{1-6} alkyl, C_{1-3} fluoroalkyl, C_{1-3}
 hydroxyalkyl, C_{1-3} fluoroalkoxy, $-(\text{CH}_2)_{0-2}\text{O}(\text{C}_{1-3}\text{ alkyl})$, $-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{NR}_x\text{R}_x$,
 $-(\text{CH}_2)_{1-3}(\text{C}_{3-6}\text{ cycloalkyl})$, $-\text{C}(\text{O})\text{O}(\text{C}_{1-3}\text{ alkyl})$, $-\text{C}(\text{O})\text{NR}_x(\text{C}_{1-3}\text{ alkyl})$,
 $-\text{CR}_x=\text{CR}_x\text{R}_x$, or $-\text{CR}_x=\text{CH}(\text{C}_{3-6}\text{ cycloalkyl})$;
 15 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} ;
 each R_5 is independently F, Cl, $-\text{CN}$, C_{1-3} alkyl, C_{1-2} fluoroalkyl, or $-\text{OCH}_3$;
 R_9 is C_{1-6} alkyl, C_{1-6} hydroxyalkyl, C_{1-6} hydroxy fluoroalkyl, C_{1-3} aminoalkyl,
 20 $-(\text{CH}_2)_{1-2}\text{O}(\text{C}_{1-3}\text{ alkyl})$, $-(\text{CH}_2)_{1-3}\text{NR}_x\text{R}_x$, $-(\text{CH}_2)_{1-2}\text{C}(\text{O})\text{NR}_x\text{R}_x$, $-(\text{CH}_2)_{1-3}\text{S}(\text{O})_2\text{OH}$,
 $-(\text{CR}_x\text{R}_x)_{1-3}\text{NR}_x\text{S}(\text{O})_2(\text{C}_{1-2}\text{ alkyl})$, or $-(\text{CH}_2)_{0-3}\text{R}_{9a}$;
 R_{9a} is C_{3-7} cycloalkyl, furanyl, phenyl, piperazinyl, piperidinyl, pyrazolyl, pyridinyl,
 pyrrolidinyl, quinuclidinyl, thiazolyl, or octahydrocyclopenta[c]pyrrolyl, each
 substituted with zero to 3 substituents independently selected from F, Cl, $-\text{OH}$, C_{1-4}
 25 alkyl, C_{1-3} hydroxyalkyl, C_{1-3} hydroxy fluoroalkyl, C_{1-3} aminoalkyl, $-\text{NR}_y\text{R}_y$,
 oxetanyl, phenyl, piperazinyl, piperidinyl, and pyrrolidinyl;
 R_{10} is H, C_{1-4} alkyl, $-(\text{CH}_2)_{1-3}\text{O}(\text{C}_{1-2}\text{ alkyl})$, or C_{3-6} cycloalkyl;
 or R_9 and R_{10} together with the nitrogen atom to which they are attached form a
 heterocyclic ring selected from azabicyclo[3.1.1]heptanyl, azaspiro[5.5]undecanyl,
 30 diazabicyclo[2.2.1]heptanyl, diazabicyclo[3.1.1]heptanyl,

diazabicyclo[3.2.0]heptanyl, diazaspiro[3.5]nonanyl, diazaspiro[4.4]nonanyl, diazaspiro[4.5]decanyl, diazepanyl, indolynyl, morpholynyl, octahydropyrrolo[3,4-c]pyrrolyl, piperazinonyl, piperazinyl, piperidinyl, and pyrrolidinyl, each substituted with zero to 3 R_{10a} ;

- 5 each R_{10a} is independently selected from C_{1-4} alkyl, C_{1-4} hydroxyalkyl, $-(CH_2)_{1-3}O(C_{1-3}$ alkyl), $-(CH_2)_{1-3}NR_xR_x$, $-(CH_2)_{1-2}C(O)NR_xR_x$, $-(CH_2)_{1-2}(\text{methyltriazolyl})$, $-\text{CH}_2\text{CH}_2(\text{phenyl})$, $-\text{CH}_2\text{CH}_2(\text{morpholynyl})$, $-\text{C}(O)(C_{1-2} \text{ alkyl})$, $-\text{C}(O)NR_yR_y$, $-\text{C}(O)CH_2NR_yR_y$, $-\text{NR}_yR_y$, $-\text{NHC}(O)(C_{1-3} \text{ alkyl})$, $-\text{C}(O)(\text{furanyl})$, $-\text{O}(\text{piperidinyl})$, $-\text{C}(O)CH_2(\text{diethylcarbamoylpiperidinyl})$, methylpiperazinyl, piperidinyl,
- 10 methylpiperidinyl, diethylcarbamoylpiperidinyl, isopropylpiperidinyl, pyridinyl, trifluoromethylpyridinyl, pyrimidinyl, and dihydrobenzo[d]imidazolonyl;

R_v is H, C_{1-2} alkyl, or C_{1-2} fluoroalkyl;

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

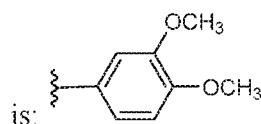
each R_y is independently H or C_{1-6} alkyl;

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

n is zero, 1, or 2; and

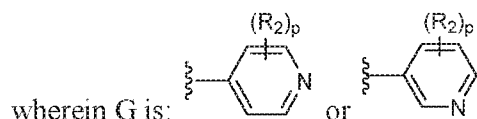
p is zero, 1, 2, 3, or 4.

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



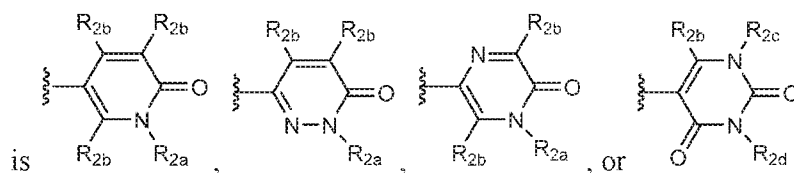
; and L_2 , R_1 , R_5 , R_9 , R_{10} , and n are defined in the first aspect.

- 20 One embodiment provides a compound of Formula (I), N-oxide, or a salt thereof



; and L_2 , R_1 , R_2 , R_5 , R_9 , R_{10} , n , and p are defined in the first aspect.

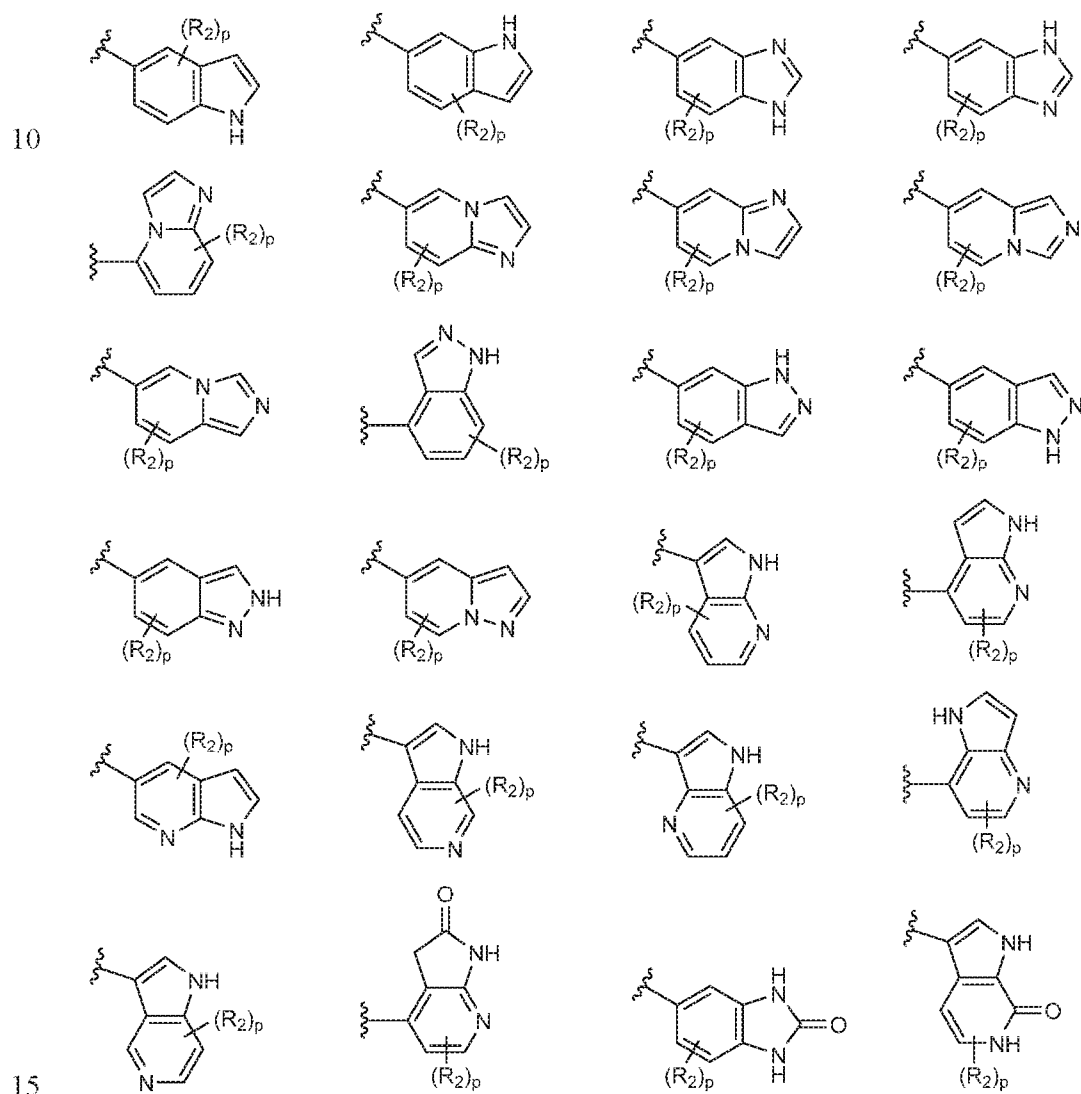
One embodiment provides a compound of Formula (I) or a salt thereof wherein G

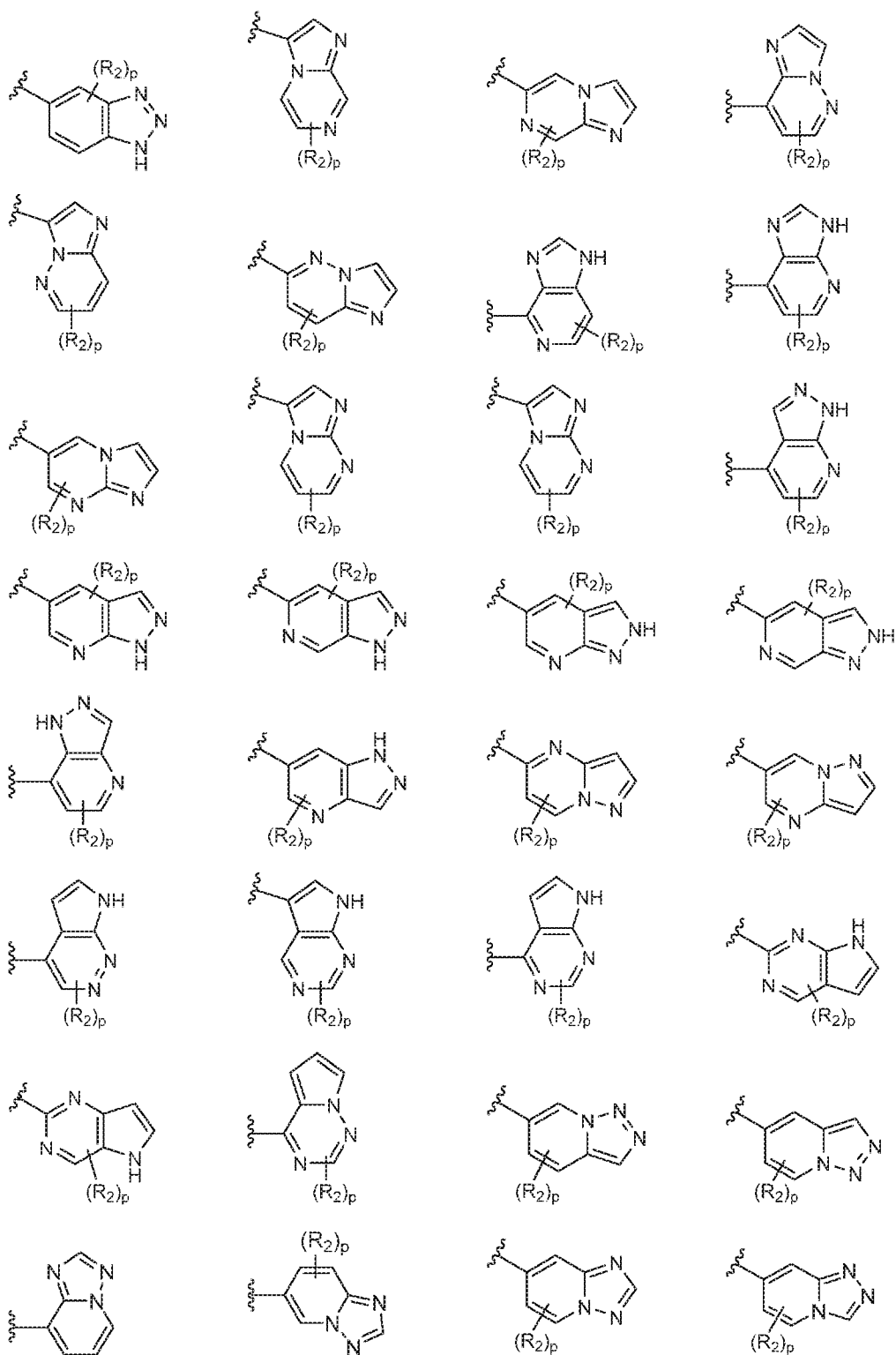


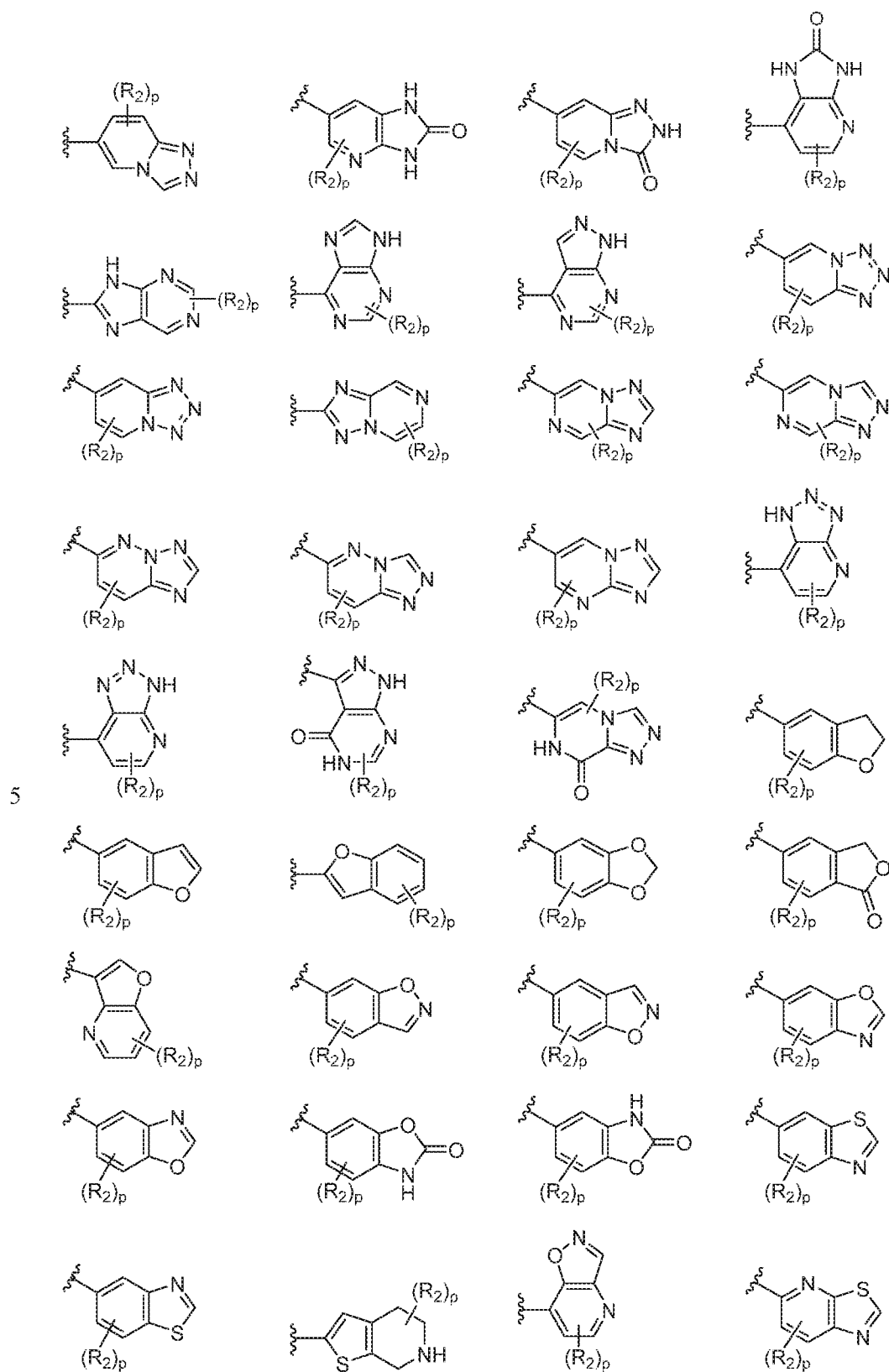
- 25 R_{2c} , R_{2d} , R_5 , R_9 , R_{10} , n , and p are defined in the first aspect. Included in this embodiment

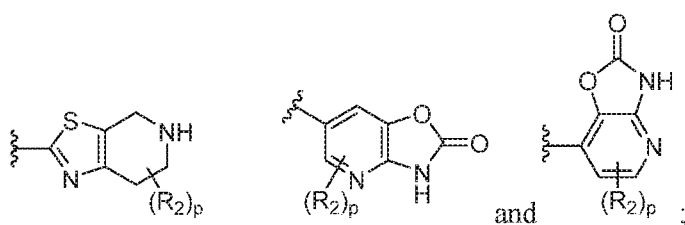
- are compounds in which R_{2a} is C_{1-4} alkyl, C_{1-2} fluoroalkyl, C_{1-4} hydroxyalkyl, $-(CH_2)_{1-3}OCH_3$, C_{3-6} cycloalkyl, $-CH_2C(O)NR_xR_x$, $-CH_2(C_{3-6}$ cycloalkyl), $-CH_2$ (phenyl), tetrahydrofuranyl, or phenyl; and each R_{2b} is independently H, F, Cl, $-CN$, $-NR_xR_x$, C_{1-6} alkyl, C_{1-2} fluoroalkyl, C_{1-3} hydroxyalkyl, $-(CH_2)_{0-2}O(C_{1-2}$ alkyl),
- 5 $-(CH_2)_{0-2}C(O)NR_xR_x$, $-(CH_2)_{1-3}$ (cyclopropyl), $-C(O)O(C_{1-2}$ alkyl), $-C(O)NR_x(C_{1-3}$ alkyl), $-CR_x=CH_2$, or $-CH=CH(C_{3-6}$ cycloalkyl). Also included in this embodiment are compounds in which R_{2a} is $-CH_3$; and each R_{2b} is independently H, Cl, or $-CH_3$.

One embodiment provides a compound of Formula (I) or a salt thereof wherein G is a 9-membered heterocyclic ring selected from:



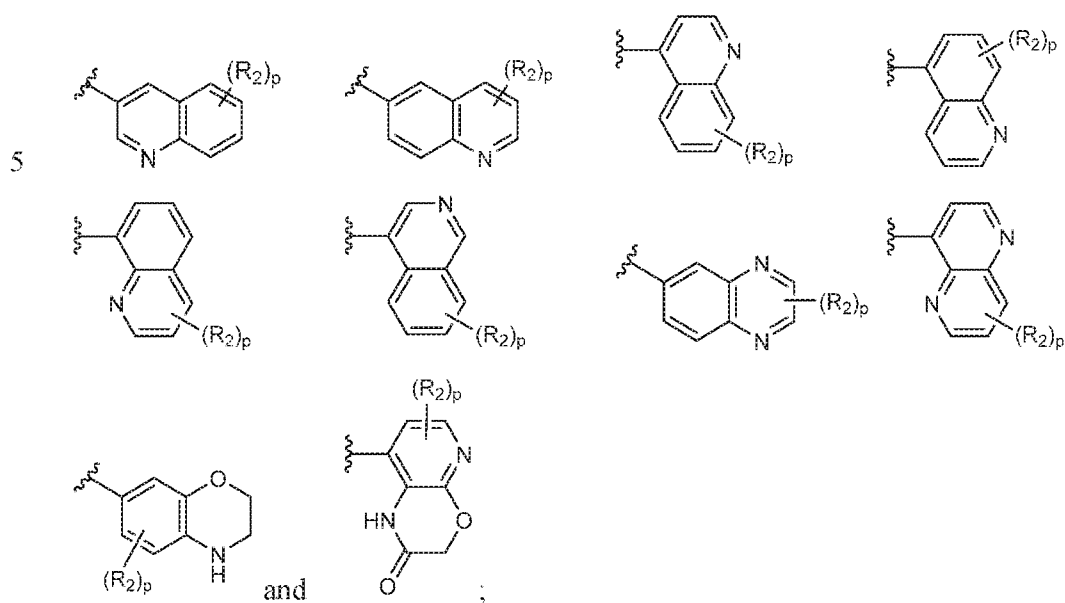






and L_2 , R_1 , R_2 , R_5 , R_9 , R_{10} , n , and p are defined in the first aspect.

One embodiment provides a compound of Formula (I) or a salt thereof wherein G is a 10-membered heterocyclic ring selected from:

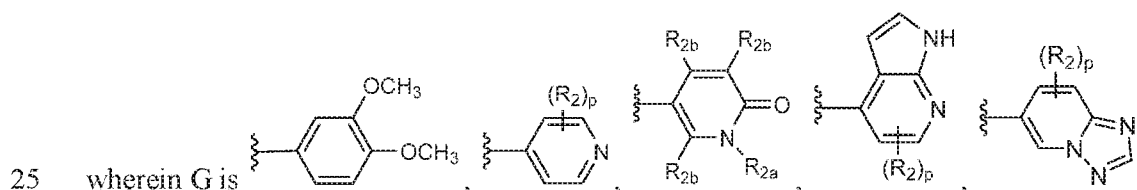


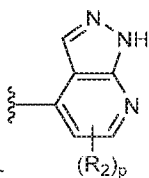
and L_2 , R_1 , R_2 , R_5 , R_9 , R_{10} , n , and p are defined in the first aspect.

One embodiment provides a compound of Formula (I), N-oxide, or a salt thereof wherein R_1 is H, Cl, $-\text{CN}$, C_{1-4} alkyl, C_{1-2} fluoroalkyl, C_{1-2} hydroxyalkyl, or $-\text{C}(\text{O})\text{O}(\text{C}_{1-2}$ alkyl); each R_2 is independently F, Cl, $-\text{CN}$, $-\text{OH}$, C_{1-3} alkyl, C_{1-2} fluoroalkyl, C_{1-2} cyanoalkyl, C_{1-3} hydroxyalkyl, C_{1-2} aminoalkyl, $-(\text{CH}_2)_{0-2}\text{O}(\text{C}_{1-3}$ alkyl), C_{3-6} cycloalkyl, $-\text{NR}_x\text{R}_x$, $-(\text{CH}_2)_{0-2}\text{C}(\text{O})\text{NR}_x\text{R}_x$, $-\text{CH}_2(\text{C}_{3-6}$ cycloalkyl), $-\text{CH}_2(\text{phenyl})$, or phenyl; R_{2a} is C_{1-4} alkyl, C_{1-2} fluoroalkyl, C_{1-4} hydroxyalkyl, $-(\text{CH}_2)_{1-3}\text{OCH}_3$, C_{3-6} cycloalkyl, $-\text{CH}_2\text{C}(\text{O})\text{NR}_x\text{R}_x$, $-\text{CH}_2(\text{C}_{3-6}$ cycloalkyl), $-\text{CH}_2(\text{phenyl})$, tetrahydrofuranyl, or phenyl; each R_{2b} is independently H, F, Cl, $-\text{CN}$, $-\text{NR}_x\text{R}_x$, C_{1-6} alkyl, C_{1-2} fluoroalkyl, C_{1-3} hydroxyalkyl, $-(\text{CH}_2)_{0-2}\text{O}(\text{C}_{1-2}$ alkyl), $-(\text{CH}_2)_{0-2}\text{C}(\text{O})\text{NR}_x\text{R}_x$, $-(\text{CH}_2)_{1-3}(\text{cyclopropyl})$, $-\text{C}(\text{O})\text{O}(\text{C}_{1-2}$ alkyl), $-\text{C}(\text{O})\text{NR}_x(\text{C}_{1-3}$ alkyl), $-\text{CR}_x=\text{CH}_2$, or

- $-\text{CH}=\text{CH}(\text{C}_{3-6} \text{ cycloalkyl})$; L_2 is a bond or $-(\text{CR}_x\text{R}_x)_{1-2}-$; R_9 is C_{1-3} alkyl, C_{1-5} hydroxyalkyl, C_{2-5} hydroxy fluoroalkyl, C_{1-2} aminoalkyl, $-(\text{CH}_2)_{1-2}\text{O}(\text{C}_{1-2} \text{ alkyl})$, $-(\text{CH}_2)_{1-3}\text{N}(\text{CH}_3)_2$, $-(\text{CH}_2)_{1-2}\text{C}(\text{O})\text{NH}_2$, $-(\text{CH}_2)_{1-2}\text{S}(\text{O})_2\text{OH}$, $-(\text{CH}_2)_{1-2}\text{CR}_x\text{R}_x\text{NHS}(\text{O})_2\text{CH}_3$, or $-(\text{CH}_2)_{0-3}\text{R}_{9a}$; R_{9a} is C_{5-7} cycloalkyl, furanyl, phenyl, piperazinyl, piperidiny, pyrazolyl, pyridinyl, pyrrolidinyl, quinuclidinyl, thiazolyl, or octahydrocyclopenta[c]pyrrolyl, each substituted with zero to 2 substituents independently selected from $-\text{OH}$, C_{1-3} alkyl, $-\text{NR}_x\text{R}_x$, oxetanyl, phenyl, piperazinyl, piperidiny, and pyrrolidinyl; R_{10} is H, C_{1-3} alkyl, $-(\text{CH}_2)_{1-2}\text{O}(\text{C}_{1-2} \text{ alkyl})$, or C_{3-6} cycloalkyl; or R_9 and R_{10} together with the nitrogen atom to which they are attached form a heterocyclic ring selected from azabicyclo[3.1.1]heptanyl, azaspiro[5.5]undecanyl, diazabicyclo[2.2.1]heptanyl, diazabicyclo[3.1.1]heptanyl, diazabicyclo[3.2.0]heptanyl, diazaspino[3.5]nonanyl, diazaspino[4.4]nonanyl, diazaspino[4.5]decanyl, diazepanyl, indolinyl, morpholinyl, octahydropyrrolo[3,4-c]pyrrolyl, piperazinonyl, piperazinyl, piperidiny, and pyrrolidinyl, each substituted with zero to 3 R_{10a} ; each R_{10a} is independently selected from C_{1-3} alkyl, C_{1-3} hydroxyalkyl, $-(\text{CH}_2)_{1-2}\text{O}(\text{C}_{1-2} \text{ alkyl})$, $-(\text{CH}_2)_{1-2}\text{NR}_x\text{R}_x$, $-\text{CH}_2\text{C}(\text{O})\text{NR}_x\text{R}_x$, $-\text{CH}_2(\text{methyltriazolyl})$, $-\text{CH}_2\text{CH}_2(\text{phenyl})$, $-\text{CH}_2\text{CH}_2(\text{morpholinyl})$, $-\text{C}(\text{O})(\text{C}_{1-2} \text{ alkyl})$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{N}(\text{C}_{1-2} \text{ alkyl})_2$, $-\text{C}(\text{O})\text{CH}_2\text{NR}_x\text{R}_x$, $-\text{NR}_x\text{R}_x$, $-\text{NHC}(\text{O})(\text{C}_{1-2} \text{ alkyl})$, $-\text{C}(\text{O})(\text{furanyl})$, $-\text{O}(\text{piperidiny})$, $-\text{C}(\text{O})\text{CH}_2(\text{diethylcarbamoylpiperidiny})$, methylpiperazinyl, piperidiny, methylpiperidiny, diethylcarbamoylpiperidiny, isopropylpiperidiny, pyridinyl, trifluoromethylpyridinyl, pyrimidinyl, and dihydrobenzo[d]imidazolonyl; each R_5 is independently F, Cl, $-\text{CN}$, C_{1-2} alkyl, or $-\text{OCH}_3$; n is zero or 1; and p is zero, 1, 2, or 3; and G and R_x are defined in the first aspect.

One embodiment provides a compound of Formula (I), N-oxide, or a salt thereof





- or $(R_2)_p$; R_1 is $-\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CHF}_2$, or $-\text{CH}_2\text{CF}_3$; each R_2 is independently $-\text{CH}_3$, $-\text{OCH}_3$, or $-\text{NH}_2$; R_{2a} is $-\text{CH}_3$; each R_{2b} is independently H, Cl, or $-\text{CH}_3$; L is a bond, $-\text{CH}(\text{CH}_3)-$, $-\text{C}(\text{CH}_3)_2-$, or $-\text{CH}_2\text{CH}_2-$; R_9 is $-\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{OH}$, $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CHFC}(\text{CH}_3)_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_2\text{OH}$, $-\text{CH}(\text{CH}_2\text{OH})_2$, $-\text{CH}_2\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{S}(\text{O})_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_2\text{NHS}(\text{O})_2\text{CH}_3$, or $-(\text{CH}_2)_{0-3}\text{R}_{9a}$; R_{9a} is cyclohexyl, cycloheptyl, furanyl, phenyl, piperazinyl, piperidiny, pyrazolyl, pyridinyl, pyrrolidinyl, quinuclidinyl, thiazolyl, or octahydrocyclopenta[c]pyrrolyl, each substituted with zero to 2 substituents independently selected from $-\text{OH}$, C_{1-3} alkyl, $-\text{NH}_2$, $-\text{N}(\text{CH}_3)_2$, oxetanyl, phenyl, piperazinyl, piperidiny, and pyrrolidinyl; R_{10} is H, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{OCH}_3$, or cyclopropyl; or R_9 and R_{10} together with the nitrogen atom to which they are attached form a heterocyclic ring selected from azabicyclo[3.1.1]heptanyl, azaspiro[5.5]undecanyl, diazabicyclo[2.2.1]heptanyl, diazabicyclo[3.1.1]heptanyl, diazabicyclo[3.2.0]heptanyl, diazaspiro[3.5]nonanyl, diazaspiro[4.4]nonanyl, diazaspiro[4.5]decanyl, diazepanyl, indolinyl, morpholinyl, octahydropyrrolo[3,4-c]pyrrolyl, piperazinonyl, piperazinyl, piperidiny, and pyrrolidinyl, each substituted with zero to 2 R_{10a} ; each R_{10a} is independently selected from $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{CH}_2\text{NH}(\text{CH}_3)$, $-\text{CH}_2\text{C}(\text{O})\text{NH}(\text{CH}_3)$, $-\text{CH}_2\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, $-\text{CH}_2(\text{methyltriazolyl})$, $-\text{CH}_2\text{CH}_2(\text{phenyl})$, $-\text{CH}_2\text{CH}_2(\text{morpholinyl})$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{N}(\text{CH}_2\text{CH}_3)_2$, $-\text{C}(\text{O})\text{CH}_2\text{NH}(\text{CH}_3)$, $-\text{C}(\text{O})\text{CH}_2\text{N}(\text{CH}_3)_2$, $-\text{NH}_2$, $-\text{N}(\text{CH}_3)_2$, $-\text{NHC}(\text{O})\text{CH}_3$, $-\text{C}(\text{O})(\text{furanyl})$, $-\text{O}(\text{piperidiny})$, $-\text{C}(\text{O})\text{CH}_2(\text{diethylcarbamoylpiperidiny})$, methylpiperazinyl, piperidiny, methylpiperidiny, diethylcarbamoylpiperidiny, isopropylpiperidiny, pyridinyl, trifluoromethylpyridinyl, pyrimidinyl, and dihydrobenzo[d]imidazolonyl; n is zero; and p is zero, 1, or 2.

One embodiment provides a compound of Formula (I), N-oxide, or a salt thereof wherein L_2 is a bond or $-(\text{CR}_x\text{R}_x)_{1-2}-$; and G, R_1 , R_5 , R_9 , R_{10} , and n are defined in the

first aspect. Included in this embodiment are compounds in which L_2 is a bond, $-CR_xR_x-$, or $-CR_xR_xCH_2-$. Also included in this embodiment are compounds in which L_2 is a bond, $-CH(CH_3)-$, $-C(CH_3)_2-$, or $-CH_2CH_2-$.

One embodiment provides a compound of Formula (I), N-oxide, or a salt thereof
 5 wherein R_1 is H, Cl, $-CN$, C_{1-4} alkyl, C_{1-3} fluoroalkyl, C_{1-3} hydroxyalkyl, C_{1-3} hydroxy-fluoroalkyl, C_{3-6} cycloalkyl, $-CH_2(C_{3-6}$ cycloalkyl), or $-C(O)O(C_{1-3}$ alkyl); and G, L_2 , R_5 , R_9 , R_{10} , and n are defined in the first aspect. Included in this embodiment are compounds in which R_1 is H, Cl, $-CN$, C_{1-4} alkyl, C_{1-2} fluoroalkyl, C_{1-2} hydroxyalkyl, or $-C(O)O(C_{1-2}$ alkyl). Also included in this embodiment are compounds in which R_1 is
 10 $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CHF_2$, or $-CH_2CF_3$.

One embodiment provides a compound of Formula (I), N-oxide, or a salt thereof wherein each R_2 is independently F, Cl, Br, $-CN$, $-OH$, 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, $-(CH_2)_{1-3}O(C_{1-3}$ alkyl), $-O(CH_2)_{1-2}OC(O)(C_{1-2}$ alkyl),
 15 $-O(CH_2)_{1-2}NR_xR_x$, $-C(O)O(C_{1-2}$ 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), $-NR_xR_y$, $-NR_y(C_{1-3}$ fluoroalkyl), $-NR_y(C_{1-4}$ hydroxyalkyl), $-NR_xCH_2(\text{phenyl})$, $-NR_xS(O)_2(C_{3-6}$ cycloalkyl), $-NR_xC(O)(C_{1-2}$ alkyl), $-NR_xCH_2(\text{cyclopropyl})$, $-S(O)_2(C_{1-2}$ alkyl), $-(CH_2)_{0-2}(C_{3-6}$ cycloalkyl), $-(CH_2)_{0-2}(\text{phenyl})$, morpholinyl, dioxothiomorpholinyl,
 20 dimethyl pyrazolyl, methylpiperidinyl, methylpiperazinyl, amino-oxadiazolyl, imidazolyl, or triazolyl; and G, L_2 , R_1 , R_5 , R_9 , R_{10} , and n are defined in the first aspect. Included in this embodiment are compounds in which each R_2 is independently F, Cl, $-CN$, $-OH$, C_{1-3} alkyl, C_{1-2} fluoroalkyl, C_{1-2} cyanoalkyl, C_{1-3} hydroxyalkyl, C_{1-2} aminoalkyl, $-(CH_2)_{0-2}O(C_{1-3}$ alkyl), C_{3-6} cycloalkyl, $-NR_xR_x$, $-(CH_2)_{0-2}C(O)NR_xR_x$, $-CH_2(C_{3-6}$ cycloalkyl), $-CH_2(\text{phenyl})$, or phenyl. Also included in this embodiment are compounds
 25 in which each R_2 is independently $-CH_3$, $-OCH_3$, or $-NH_2$.

One embodiment provides a compound of Formula (I), N-oxide, or a salt thereof wherein R_9 is C_{1-6} alkyl, C_{1-6} hydroxyalkyl, C_{1-6} hydroxy fluoroalkyl, C_{1-3} aminoalkyl, $-(CH_2)_{1-2}O(C_{1-3}$ alkyl), $-(CH_2)_{1-3}NR_xR_x$, $-(CH_2)_{1-2}C(O)NR_xR_x$, $-(CH_2)_{1-3}S(O)_2OH$,
 30 $-(CR_xR_x)_{1-3}NR_xS(O)_2(C_{1-2}$ alkyl), or $-(CH_2)_{0-3}R_{9a}$; R_{10} is H, C_{1-4} alkyl, $-(CH_2)_{1-3}O(C_{1-2}$

alkyl), or C₃₋₆ cycloalkyl; and G, L₂, R₁, R₅, R_{9a}, R_x, and n are defined in the first aspect. Included in this embodiment are compounds in which R₉ is C₁₋₃ alkyl, C₁₋₅ hydroxyalkyl, C₂₋₅ hydroxy fluoroalkyl, C₁₋₂ aminoalkyl, $-(CH_2)_{1-2}O(C_{1-2} \text{ alkyl})$, $-(CH_2)_{1-3}N(CH_3)_2$, $-(CH_2)_{1-2}C(O)NH_2$, $-(CH_2)_{1-2}S(O)_2OH$, $-(CH_2)_{1-2}CR_xR_xNHS(O)_2CH_3$, or $-(CH_2)_{0-3}R_{9a}$; and R₁₀ is H, C₁₋₃ alkyl, $-(CH_2)_{1-2}O(C_{1-2} \text{ alkyl})$, or C₃₋₆ cycloalkyl. Also included in this embodiment are compounds in which R₉ is $-CH_3$, $-CH_2CH_2OH$, $-CH_2C(CH_3)_2OH$, $-CH_2C(CH_3)_2CH_2OH$, $-CH_2CHFC(CH_3)_2OH$, $-CH_2CH_2C(CH_3)_2OH$, $-CH(CH_2OH)_2$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NH_2$, $-CH_2CH_2N(CH_3)_2$, $-CH_2CH_2CH_2N(CH_3)_2$, $-CH_2CH_2C(O)NH_2$, $-CH_2S(O)_2OH$, $-CH_2CH_2C(CH_3)_2NHS(O)_2CH_3$, or $-(CH_2)_{0-3}R_{9a}$; and R₁₀ is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2OCH_3$, or cyclopropyl.

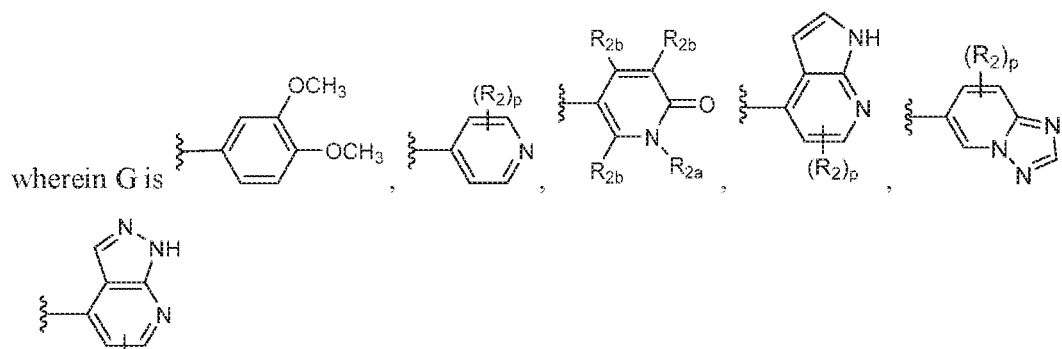
One embodiment provides a compound of Formula (I), N-oxide, or a salt thereof wherein R₉ is C₁₋₃ alkyl, C₁₋₅ hydroxyalkyl, C₂₋₅ hydroxy fluoroalkyl, C₁₋₂ aminoalkyl, $-(CH_2)_{1-2}O(C_{1-2} \text{ alkyl})$, $-(CH_2)_{1-3}N(CH_3)_2$, $-(CH_2)_{1-2}C(O)NH_2$, $-(CH_2)_{1-2}S(O)_2OH$, $-(CH_2)_{1-2}CR_xR_xNHS(O)_2CH_3$, or $-(CH_2)_{0-3}R_{9a}$; R_{9a} is C₅₋₇ cycloalkyl, furanyl, phenyl, piperazinyl, piperidinyl, pyrazolyl, pyridinyl, pyrrolidinyl, quinuclidinyl, thiazolyl, or octahydrocyclopenta[c]pyrrolyl, each substituted with zero to 2 substituents independently selected from $-OH$, C₁₋₃ alkyl, $-NR_xR_x$, oxetanyl, phenyl, piperazinyl, piperidinyl, and pyrrolidinyl; R₁₀ is H, C₁₋₃ alkyl, $-(CH_2)_{1-2}O(C_{1-2} \text{ alkyl})$, or C₃₋₆ cycloalkyl; and G, L₂, R₁, R₅, R_x, and n are defined in the first aspect.

One embodiment provides a compound of Formula (I), N-oxide, or a salt thereof wherein R₉ is $-CH_3$, $-CH_2CH_2OH$, $-CH_2C(CH_3)_2OH$, $-CH_2C(CH_3)_2CH_2OH$, $-CH_2CHFC(CH_3)_2OH$, $-CH_2CH_2C(CH_3)_2OH$, $-CH(CH_2OH)_2$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NH_2$, $-CH_2CH_2N(CH_3)_2$, $-CH_2CH_2CH_2N(CH_3)_2$, $-CH_2CH_2C(O)NH_2$, $-CH_2S(O)_2OH$, $-CH_2CH_2C(CH_3)_2NHS(O)_2CH_3$, or $-(CH_2)_{0-3}R_{9a}$; R_{9a} is cyclohexyl, cycloheptyl, furanyl, phenyl, piperazinyl, piperidinyl, pyrazolyl, pyridinyl, pyrrolidinyl, quinuclidinyl, thiazolyl, or octahydrocyclopenta[c]pyrrolyl, each substituted with zero to 2 substituents independently selected from $-OH$, C₁₋₃ alkyl, $-NH_2$, $-N(CH_3)_2$, oxetanyl, phenyl, piperazinyl, piperidinyl, and pyrrolidinyl; R₁₀ is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2OCH_3$, or cyclopropyl; and G, L₂, R₁, R₅, and n are defined in the first aspect.

One embodiment provides a compound of Formula (I), N-oxide, or a salt thereof

wherein R_9 and R_{10} together with the nitrogen atom to which they are attached form a heterocyclic ring selected from azabicyclo[3.1.1]heptanyl, azaspiro[5.5]undecanyl, diazabicyclo[2.2.1]heptanyl, diazabicyclo[3.1.1]heptanyl, diazabicyclo[3.2.0]heptanyl, diazaspiro[3.5]nonanyl, diazaspiro[4.4]nonanyl, diazaspiro[4.5]decanyl, diazepanyl, indolynyl, morpholynyl, octahydropyrrolo[3,4-c]pyrrolyl, piperazinonyl, piperazinyl, piperidinyl, and pyrrolidinyl, each substituted with zero to 3 R_{10a} ; and G , L_2 , R_1 , R_5 , R_{10a} , and n are defined in the first aspect. Included in this embodiment are compounds in which R_9 and R_{10} together with the nitrogen atom to which they are attached form a heterocyclic ring selected from azabicyclo[3.1.1]heptanyl, azaspiro[5.5]undecanyl, diazabicyclo[2.2.1]heptanyl, diazabicyclo[3.1.1]heptanyl, diazabicyclo[3.2.0]heptanyl, diazaspiro[3.5]nonanyl, diazaspiro[4.4]nonanyl, diazaspiro[4.5]decanyl, diazepanyl, indolynyl, morpholynyl, octahydropyrrolo[3,4-c]pyrrolyl, piperazinonyl, piperazinyl, piperidinyl, and pyrrolidinyl, each substituted with zero to 2 R_{10a} . Also included in this embodiment are compounds in which each R_{10a} is independently selected from $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2NH(CH_3)$, $-CH_2C(O)NH(CH_3)$, $-CH_2C(O)N(CH_3)_2$, $-CH_2(\text{methyltriazolyl})$, $-CH_2CH_2(\text{phenyl})$, $-CH_2CH_2(\text{morpholynyl})$, $-C(O)CH_3$, $-C(O)NH_2$, $-C(O)N(CH_2CH_3)_2$, $-C(O)CH_2NH(CH_3)$, $-C(O)CH_2N(CH_3)_2$, $-NH_2$, $-N(CH_3)_2$, $-NHC(O)CH_3$, $-C(O)(\text{furanyl})$, $-O(\text{piperidinyl})$, $-C(O)CH_2(\text{diethylcarbamoylpiperidinyl})$, methylpiperazinyl, piperidinyl, methylpiperidinyl, diethylcarbamoylpiperidinyl, isopropylpiperidinyl, pyridinyl, trifluoromethylpyridinyl, pyrimidinyl, and dihydrobenzo[d]imidazolonyl.

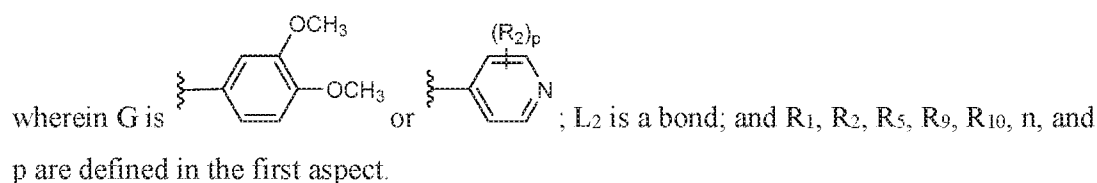
One embodiment provides a compound of Formula (I), N-oxide, or a salt thereof



25 or L_2 is a bond; and R_1 , R_2 , R_{2a} , R_{2b} , R_5 , R_9 , R_{10} , n , and p are defined in the

- first aspect. Included in this embodiment are compounds in which R₉ is –CH₃, –CH₂CH₂OH, –CH₂C(CH₃)₂OH, –CH₂C(CH₃)₂CH₂OH, –CH₂CHFC(CH₃)₂OH, –CH₂CH₂C(CH₃)₂OH, –CH(CH₂OH)₂, –CH₂CH₂OCH₃, –CH₂CH₂NH₂, –CH₂CH₂N(CH₃)₂, –CH₂CH₂CH₂N(CH₃)₂, –CH₂CH₂C(O)NH₂, –CH₂S(O)₂OH, –CH₂CH₂C(CH₃)₂NHS(O)₂CH₃, or –(CH₂)_{0–3}R_{9a}; R_{9a} is cyclohexyl, cycloheptyl, furanyl, phenyl, piperazinyl, piperidiny, pyrazolyl, pyridinyl, pyrrolidinyl, quinuclidinyl, thiazolyl, or octahydrocyclopenta[c]pyrrolyl, each substituted with zero to 2 substituents independently selected from –OH, C_{1–3} alkyl, –NH₂, –N(CH₃)₂, oxetanyl, phenyl, piperazinyl, piperidiny, and pyrrolidinyl; and R₁₀ is H, –CH₃, –CH₂CH₃, –CH₂CH₂OCH₃, or cyclopropyl. Also included in this embodiment are compounds in which or R₉ and R₁₀ together with the nitrogen atom to which they are attached form a heterocyclic ring selected from azabicyclo[3.1.1]heptanyl, azaspiro[5.5]undecanyl, diazabicyclo[2.2.1]heptanyl, diazabicyclo[3.1.1]heptanyl, diazabicyclo[3.2.0]heptanyl, diazasp[3.5]nonanyl, diazasp[4.4]nonanyl, diazasp[4.5]decanyl, diazepanyl, indolinyl, morpholinyl, octahydropyrrolo[3,4-c]pyrrolyl, piperazinonyl, piperazinyl, piperidiny, and pyrrolidinyl, each substituted with zero to 2 R_{10a}; and each R_{10a} is independently selected from –CH₃, –CH₂CH₃, –CH(CH₃)₂, –CH₂OH, –CH₂CH₂OH, –CH₂OCH₃, –CH₂CH₂OCH₃, –CH₂NH₂, –CH₂CH₂NH₂, –CH₂CH₂NH(CH₃), –CH₂C(O)NH(CH₃), –CH₂C(O)N(CH₃)₂, –CH₂(methyltriazolyl), –CH₂CH₂(phenyl), –CH₂CH₂(morpholinyl), –C(O)CH₃, –C(O)NH₂, –C(O)N(CH₂CH₃)₂, –C(O)CH₂NH(CH₃), –C(O)CH₂N(CH₃)₂, –NH₂, –N(CH₃)₂, –NHC(O)CH₃, –C(O)(furanyl), –O(piperidiny), –C(O)CH₂(diethylcarbamoylpiperidiny), methylpiperazinyl, piperidiny, methylpiperidiny, diethylcarbamoylpiperidiny, isopropylpiperidiny, pyridiny, trifluoromethylpyridiny, pyrimidinyl, and dihydrobenzo[d]imidazolonyl.

One embodiment provides a compound of Formula (I), N-oxide, or a salt thereof



One embodiment provides a compound of Formula (I), N-oxide, or a salt thereof

wherein each R_5 is independently F, Cl, $-\text{CN}$, C_{1-3} alkyl, $-\text{CF}_3$, or $-\text{OCH}_3$; n is zero, 1, or 2; and G , L_2 , R_1 , R_9 , and R_{10} are defined in the first aspect. Included in this embodiment are compounds in which each R_5 is independently F, Cl, $-\text{CN}$, C_{1-2} alkyl, or $-\text{OCH}_3$; and n is zero, 1, or 2. Also included in this embodiment are compounds in which n is zero or 1.

One embodiment provides a compound of Formula (I), N-oxide, or a salt thereof wherein n is zero or 1; p is zero, 1, 2, or 3; and G , L_2 , R_1 , R_2 , R_5 , R_9 , and R_{10} are defined in the first aspect. Included in this embodiment are compounds in which n is zero or 1; and p is zero, 1, or 2. Also included in this embodiment are compounds in which n is zero.

One embodiment provides a compound of Formula (I) or a salt thereof, wherein said compound is selected from 2-(3,4-dimethoxyphenyl)-5-{octahydropyrrolo[3,4-c]pyrrole-2-carbonyl}-3-(propan-2-yl)-1H-indole (1); 2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl(4-methyl-1,4-diazepan-1-yl)methanone (2); 2-(3,4-dimethoxyphenyl)-3-isopropyl-N,N-dimethyl-1H-indole-5-carboxamide (3); 2-(3,4-dimethoxyphenyl)-3-isopropyl-N-methyl-1H-indole-5-carboxamide (4); ((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl)methanone (5); 2-{5-[2-(3,4-dimethoxyphenyl)-3-(propan-2-yl)-1H-indole-5-carbonyl]-octahydropyrrolo[3,4-c]pyrrol-2-yl}-N,N-dimethylacetamide (6); 2-(5-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-methylacetamide (7); 1-(2-{5-[2-(3,4-dimethoxyphenyl)-3-(propan-2-yl)-1H-indole-5-carbonyl]-octahydropyrrolo[3,4-c]pyrrol-2-yl}-2-oxoethyl)-N,N-diethylpiperidine-3-carboxamide (8); 1-(5-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-(dimethylamino)ethan-1-one (9); 1-(2-{5-[2-(3,4-dimethoxyphenyl)-3-(propan-2-yl)-1H-indole-5-carbonyl]-octahydropyrrolo[3,4-c]pyrrol-2-yl}-2-oxoethyl)-N,N-diethylpiperidine-3-carboxamide (10-11); 3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl(5-(2-(methylamino)ethyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (12); (2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl)(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (13); (2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl)(5-isopropylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (14); (2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl)(5-(1-methylpiperidin-4-

yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (15); 1-(5-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-(methylamino)ethanone (16); 2-(3,4-dimethoxyphenyl)-N-[2-(dimethylamino)ethyl]-3-ethyl-1H-indole-5-carboxamide (17); (R)-2-(3,4-dimethoxyphenyl)-3-ethyl-N-(2-fluoro-3-hydroxy-3-methylbutyl)-1H-indole-5-carboxamide (18); 2-(3,4-dimethoxyphenyl)-N-(4-(dimethylamino)cyclohexyl)-3-ethyl-1H-indole-5-carboxamide (19); N-cycloheptyl-2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carboxamide (20); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)-1H-indole-5-carboxamide (21); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-methyl-N-(pyridin-3-ylmethyl)-1H-indole-5-carboxamide (22); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-methyl-N-((2-(piperidin-4-yl)thiazol-4-yl)methyl)-1H-indole-5-carboxamide (23); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-methyl-N-(2-(pyridin-2-yl)ethyl)-1H-indole-5-carboxamide (24); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(4-methylpiperazin-1-yl)piperidin-1-yl)methanone (25); (R)-1-(1-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carbonyl)pyrrolidin-3-yl)propan-2-one (26); (S)-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(2-(methoxymethyl)pyrrolidin-1-yl)methanone (27); (S)-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone (28); (R)-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(3-(dimethylamino)pyrrolidin-1-yl)methanone (29); (S)-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(3-(dimethylamino)pyrrolidin-1-yl)methanone (30); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(dimethylamino)piperidin-1-yl)methanone (31); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(3,3-dimethylpiperidin-1-yl)methanone (32); 1-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carbonyl)-N,N-diethylpiperidine-3-carboxamide (33); 1-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carbonyl)piperidine-4-carboxamide (34); 1-(4-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carbonyl)-1,4-diazepan-1-yl)ethan-1-one (35); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(1-methylpiperidin-4-yl)piperazin-1-yl)methanone (36); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-phenethylpiperazin-1-yl)methanone (37); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-isopropylpiperazin-1-yl)methanone (38); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-ethylpiperazin-1-yl)methanone (39); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(2-hydroxyethyl)piperazin-1-yl)methanone (40); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(2-

- methoxyethyl)piperazin-1-yl)methanone (41); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(2-morpholinoethyl)piperazin-1-yl)methanone (42); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(furan-2-ylmethyl)-1H-indole-5-carboxamide (43); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(pyridin-2-ylmethyl)-1H-indole-5-carboxamide (44); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-((2-phenylthiazol-4-yl)methyl)-1H-indole-5-carboxamide (45); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(4-(piperazin-1-yl)benzyl)-1H-indole-5-carboxamide (46); N-((1r,4r)-4-aminocyclohexyl)-2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carboxamide (47); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(2-(pyrrolidin-1-yl)ethyl)-1H-indole-5-carboxamide (48); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(2-(piperidin-1-yl)ethyl)-1H-indole-5-carboxamide (49); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(2-(pyridin-4-yl)ethyl)-1H-indole-5-carboxamide (50); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(2-(pyridin-3-yl)ethyl)-1H-indole-5-carboxamide (51); N-(4-aminobenzyl)-2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carboxamide (52); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(3-(piperidin-1-yl)propyl)-1H-indole-5-carboxamide (53); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(2-(1-methylpyrrolidin-2-yl)ethyl)-1H-indole-5-carboxamide (54); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(3-(4-methylpiperazin-1-yl)propyl)-1H-indole-5-carboxamide (55); [1,4'-bipiperidin]-1'-yl(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)methanone (56); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone (57); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(pyrazin-2-yl)piperazin-1-yl)methanone (58); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(pyridin-2-yl)piperazin-1-yl)methanone (59); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(furan-2-carbonyl)piperazin-1-yl)methanone (60); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)methanone (61); 4-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carbonyl)piperazin-2-one (62); 1-(1-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carbonyl)piperidin-4-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one (63); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(pyrimidin-2-yl)-1,4-diazepan-1-yl)methanone (64); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(pyridin-2-yl)-1,4-diazepan-1-yl)methanone (65); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(indolin-1-yl)methanone (66); N-(1,3-dihydroxypropan-2-yl)-2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carboxamide (67); N-(3-amino-3-oxopropyl)-2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carboxamide

- (68); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(2-hydroxyethyl)-1H-indole-5-carboxamide (69); 2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carboxamido)methanesulfonic acid (70); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(3-methyl-3-(methylsulfonamido)butyl)-1H-indole-5-carboxamide (71); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(3-hydroxy-2,2-dimethylpropyl)-1H-indole-5-carboxamide (72); 2-(3,4-dimethoxyphenyl)-N-(2-(dimethylamino)ethyl)-N,3-diethyl-1H-indole-5-carboxamide (73); 2-(3,4-dimethoxyphenyl)-N-(3-(dimethylamino)propyl)-3-ethyl-N-methyl-1H-indole-5-carboxamide (74); 2-(3,4-dimethoxyphenyl)-N-(3-(dimethylamino)propyl)-3-ethyl-1H-indole-5-carboxamide (75); 2-(3,4-dimethoxyphenyl)-N-(2-(dimethylamino)ethyl)-3-ethyl-N-methyl-1H-indole-5-carboxamide (76); 2-(3,4-dimethoxyphenyl)-3-ethyl-N,N-bis(2-methoxyethyl)-1H-indole-5-carboxamide (77); 2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(piperazin-1-yl)methanone hydrochloride (78); 2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (79); 2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(1-isopropylpiperidin-4-yl) piperazin-1-yl)methanone (80); 2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(5-isopropylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (81); 2-(5-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-methylacetamide (82); N-(2-(dimethylamino)ethyl)-N,3-diethyl-2-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-indole-5-carboxamide (83); N-(2-(dimethylamino)ethyl)-N,3-diethyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carboxamide (84); (3-ethyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (85); (3-ethyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)(5-isopropylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (86); 2-(2-aminopyridin-4-yl)-N-(4-(dimethylamino)cyclohexyl)-3-isopropyl-1H-indole-5-carboxamide (87); 2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indol-5-yl)(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone hydrochloride (88); 1-(5-(2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indole-5-carbonyl) hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-(dimethylamino)ethan-1-one (89); 2-(5-(2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indole-5-carbonyl) hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N,N-dimethylacetamide (90); 2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-N-(1-isopropylpiperidin-4-yl)-1H-indole-5-carboxamide (91); 2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indol-5-yl)(4-methyl-1,4-diazepan-1-yl)methanone (92); N-(2-(dimethylamino)ethyl)-2-(2,6-dimethylpyridin-

4-yl)-N-ethyl-3-isopropyl-1H-indole-5-carboxamide (93); 2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-N,N-dimethyl-1H-indole-5-carboxamide (94); N-(3-(dimethylamino)propyl)-2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indole-5-carboxamide (95); N-(2-(dimethylamino)ethyl)-2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indole-5-carboxamide (96); 2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-N-methyl-1H-indole-5-carboxamide (97); (2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indol-5-yl)(4-((1-methyl-1H-1,2,4-triazol-3-yl)methyl)piperazin-1-yl)methanone (98); N-benzyl-2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-N-methyl-1H-indole-5-carboxamide (99); 2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-N-methyl-N-(pyridin-3-ylmethyl)-1H-indole-5-carboxamide (100); 2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-N-methyl-N-(1-methylpiperidin-4-yl)-1H-indole-5-carboxamide (101); 2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-N-methyl-N-phenethyl-1H-indole-5-carboxamide (102); N-(3-aminobenzyl)-2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-N-methyl-1H-indole-5-carboxamide (103); (4-(dimethylamino)piperidin-1-yl)(2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indol-5-yl)methanone (104); 2-(2,6-dimethylpyridin-4-yl)-N-(2-hydroxyethyl)-3-isopropyl-N-methyl-1H-indole-5-carboxamide (105); 2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-N-(2-methoxyethyl)-N-methyl-1H-indole-5-carboxamide (106); (2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indol-5-yl)(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone, HCl (107); (2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indol-5-yl)(piperazin-1-yl)methanone (108); (2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indol-5-yl)(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (109); (2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indol-5-yl)(5-isopropylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (110); 2-(dimethylamino)-1-(5-(2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethanone (111); (hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)methanone, HCl (112); 3-isopropyl-N-(1-isopropylpiperidin-4-yl)-2-(2-methylpyridin-4-yl)-1H-indole-5-carboxamide (113); (3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)(4-methyl-1,4-diazepan-1-yl)methanone (114); (3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (115); (3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)(5-isopropylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (116); 2-(5-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-

N,N-dimethylacetamide (117); 2-(5-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-methylacetamide (118); 1-(5-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-(methylamino)ethanone (119); 2-(dimethylamino)-1-(5-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethan-1-one (120); (hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(3-isopropyl-2-(1H-pyrazolo[3,4-b]pyridin-4-yl)-1H-indol-5-yl)methanone, HCl (121); (3-(2,2-difluoroethyl)-2-(2,6-dimethylpyridin-4-yl)-1H-indol-5-yl)(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (122); 3-(2,2-difluoroethyl)-2-(2,6-dimethylpyridin-4-yl)-N-(1-isopropylpiperidin-4-yl)-1H-indole-5-carboxamide (123); (3-(2,2-difluoroethyl)-2-(2,6-dimethylpyridin-4-yl)-1H-indol-5-yl)(4-methyl-1,4-diazepan-1-yl)methanone (124); 3-(2,2-difluoroethyl)-N-(2-(dimethylamino)ethyl)-2-(2,6-dimethylpyridin-4-yl)-N-ethyl-1H-indole-5-carboxamide (125); (hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(3-isopropyl-2-(8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-1H-indol-5-yl)methanone (126); 3-isopropyl-N-(1-isopropylpiperidin-4-yl)-2-(8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-1H-indole-5-carboxamide (127); (3-isopropyl-2-(8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-1H-indol-5-yl)(4-methyl-1,4-diazepan-1-yl)methanone (128); N-(2-(dimethylamino)ethyl)-3-isopropyl-2-(8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-N-methyl-1H-indole-5-carboxamide (129); N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propanamide (130); N-(2-hydroxy-2-methylpropyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propanamide (131); N-(3-hydroxy-3-methylbutyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propanamide (132); (R)-N-(2-fluoro-3-hydroxy-3-methylbutyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropanamide (133); N-(2-aminoethyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropanamide (134); N-(3-hydroxy-3-methylbutyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropanamide (135); 3-(3-isopropyl-2-(1H-pyrazolo[3,4-b]pyridin-4-yl)-1H-indol-5-yl)-1-morpholinopropan-1-one (136); 3-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl)-1-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)propan-1-one (137); (S)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(pyrrolidin-3-yl)propanamide (138); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-(1-isopropylpiperidin-4-yl)-2-methylpropanamide (139); (R)-2-(3-isopropyl-2-(2-

methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(piperidin-3-yl)propanamide (140); (R)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(pyrrolidin-3-yl)propanamide (141); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(quinuclidin-3-yl)propanamide (142); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(piperidin-4-yl)propanamide (143); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(octahydrocyclopenta[c]pyrrol-4-yl)propanamide (144); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(1-(pyrrolidin-3-yl)piperidin-4-yl)propanamide (145); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(octahydrocyclopenta[c]pyrrol-4-yl)propanamide (146); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(octahydrocyclopenta[c]pyrrol-4-yl)propanamide (147); 1-(6-amino-3-azabicyclo[3.1.1]heptan-3-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropan-1-one (148); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-1-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)propan-1-one (149); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-1-(2-methyl-2,8-diazaspiro[4.5]decan-8-yl)propan-1-one (150); 1-(3-(aminomethyl)pyrrolidin-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropan-1-one (151); 1-(7-amino-2-azaspiro[5.5]undecan-2-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropan-1-one (152); 1-(4-aminopiperidin-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropan-1-one (153); 1-(3-(2-aminoethyl)piperidin-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropan-1-one (154); (S)-1-(3-aminopiperidin-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropan-1-one (155); 1-(3-(aminomethyl)piperidin-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropan-1-one (156); 1-(2-(aminomethyl)piperidin-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropan-1-one (157); 1-(4-(aminomethyl)piperidin-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropan-1-one (158); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(piperidin-2-ylmethyl)propanamide (159); (S)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(pyrrolidin-3-ylmethyl)propanamide (160); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N,2-dimethyl-N-(piperidin-3-yl)propanamide (161); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-

yl)-N,2-dimethyl-N-(quinuclidin-3-yl)propanamide (162); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(piperidin-3-ylmethyl)propanamide (163); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(piperidin-4-ylmethyl)propanamide (164); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N,2-dimethyl-N-(piperidin-4-yl)propanamide (165); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-((1R,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)propanamide (166); N-(4-aminocyclohexyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropanamide (167); N-(3-aminocyclohexyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropanamide (168); N-((1R,2R)-2-aminocyclohexyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropanamide (169); N-((1S,2R)-2-aminocyclohexyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropanamide (170); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(2-(piperidin-3-yl)ethyl)propanamide (171); N-(((1r,4r)-4-aminocyclohexyl)methyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropanamide (172); N-((4-hydroxy-1-methylpiperidin-4-yl)methyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropanamide (173); N-((3-hydroxyquinuclidin-3-yl)methyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropanamide (174); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-1-(piperazin-1-yl)propan-1-one (175); 1-(2,5-diazabicyclo[2.2.1]heptan-2-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropan-1-one (176); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-1-(4-(piperidin-4-yloxy)piperidin-1-yl)propan-1-one (177); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-1-(2,7-diazaspiro[4.4]nonan-2-yl)propan-1-one (178); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-1-(2,7-diazaspiro[3.5]nonan-2-yl)propan-1-one (179); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-1-(2,6-diazaspiro[3.5]nonan-6-yl)propan-1-one (180); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-1-(2,8-diazaspiro[4.5]decan-8-yl)propan-1-one (181); 1-([2,4'-bipiperidin]-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropan-1-one (182); 1-(hexahydroindolopyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropan-1-one (183); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-1-(2,7-diazaspiro[4.5]decan-7-yl)propan-1-one (184); 1-(3,6-diazabicyclo[3.2.0]heptan-3-yl)-2-

(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropan-1-one (185); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-(octahydrocyclopenta[c]pyrrol-4-yl)propanamide (186); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-(octahydrocyclopenta[c]pyrrol-4-yl)propanamide (187); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-((R)-pyrrolidin-3-yl)propanamide (188); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-((S)-pyrrolidin-3-yl)propanamide (189); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-((S)-pyrrolidin-3-yl)propanamide (190); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-(quinuclidin-3-yl)propanamide (191); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-(quinuclidin-3-yl)propanamide (192); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-(piperidin-4-yl)propanamide (193); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-(1-isopropylpiperidin-4-yl)propanamide (194); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-((R)-piperidin-3-yl)propanamide (195); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-((R)-piperidin-3-yl)propanamide (196); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-1-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)propan-1-one (197); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-1-(2-methyl-2,8-diazaspiro[4.5]decan-8-yl)propan-1-one (198); 1-(3-(aminomethyl)pyrrolidin-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propan-1-one (199); 1-(7-amino-2-azaspiro[5.5]undecan-2-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propan-1-one (200); 1-(7-amino-2-azaspiro[5.5]undecan-2-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propan-1-one (201); 1-(4-(aminomethyl)piperidin-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propan-1-one (202); 1-(4-aminopiperidin-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propan-1-one (203); 1-((S)-3-aminopiperidin-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propan-1-one (204); 1-(3-(aminomethyl)piperidin-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propan-1-one (205); 1-(3-(2-aminoethyl)piperidin-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propan-1-one (206); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-methyl-N-(piperidin-4-yl)propanamide (207); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-(((R)-pyrrolidin-3-yl)methyl)propanamide (208); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-methyl-N-(piperidin-3-yl)propanamide (209); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-

1H-indol-5-yl)-N-methyl-N-(piperidin-3-yl)propanamide (210); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-methyl-N-(quinuclidin-3-yl)propanamide (211); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-(((S)-pyrrolidin-3-yl)methyl)propanamide (212); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-(piperidin-3-ylmethyl)propanamide (213); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-((1R,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)propanamide (214); N-((1R,2R)-2-aminocyclohexyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propanamide (215); N-((1R,2R)-2-aminocyclohexyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propanamide (216); N-(4-aminocyclohexyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propanamide (217); N-(3-aminocyclohexyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propanamide (218); N-(3-aminocyclohexyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propanamide (219); 3-chloro-5-(3-isopropyl-5-(4-methylpiperazine-1-carbonyl)-1H-indol-2-yl)-1,4-dimethylpyridin-2(1H)-one (220); 2-(5-chloro-1,4-dimethyl-6-oxo-1,6-dihydropyridin-3-yl)-N-cyclopropyl-3-isopropyl-N-(1-propylpiperidin-4-yl)-1H-indole-5-carboxamide (221); and 2-(5-chloro-1,4-dimethyl-6-oxo-1,6-dihydropyridin-3-yl)-N-(2-(dimethylamino)ethyl)-3-isopropyl-N-methyl-1H-indole-5-carboxamide (222).

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention encompasses all combinations of the aspects and/or embodiments of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment or embodiments to describe additional embodiments. It is also to be understood that each individual element of the embodiment is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment.

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 and/or salts thereof” refers to at least one compound, at least one salt of the compounds, or a combination thereof. For example, compounds of Formula (I) and/or salts thereof includes a compound of Formula (I); two compounds of Formula (I); a salt of a compound of Formula (I); a compound of Formula (I) and one or more salts of the compound of Formula (I); and two or more salts of a compound of Formula (I).

Unless otherwise indicated, any atom 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.

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, "C₁₋₄ alkyl" denotes straight and branched chain alkyl groups with one to four 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 "aminoalkyl" includes both branched and straight-chain saturated alkyl groups substituted with one or more amine groups. For example, "aminoalkyl" includes -CH₂NH₂, -CH₂CH₂NH₂, and C₁₋₄ aminoalkyl.

The term "hydroxyalkyl" includes both branched and straight-chain saturated alkyl groups substituted with one or more hydroxyl groups. For example, "hydroxyalkyl" includes -CH₂OH, -CH₂CH₂OH, and C₁₋₄ hydroxyalkyl.

The term "hydroxy-fluoroalkyl" includes both branched and straight-chain saturated alkyl groups substituted with one or more hydroxyl groups and one or more fluorine atoms. For example, "hydroxy-fluoroalkyl" includes -CHFCH₂OH, -CH₂CHFC(CH₃)₂OH, and C₁₋₄ hydroxy-fluoroalkyl.

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 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 term “alkoxy,” as used herein, refers to an alkyl group attached to the parent molecular moiety through an oxygen atom, for example, methoxy group (-OCH₃). For example, “C₁₋₃ alkoxy” denotes alkoxy groups with one to three carbon atoms.

5 The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of 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.

10 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 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
15 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.*, 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
20 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) 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.

25 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,
30 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-phenamine, 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. Preferred salts include monohydrochloride, hydrogensulfate, methanesulfonate, phosphate or nitrate salts.

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 a solid.

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, ethanolates, methanolates, isopropanolates, 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:

a) *The Practice of Medicinal Chemistry*, Camille G. Wermuth et al., Ch 31,

(Academic Press, 1996);

b) *Design of Prodrugs*, edited by H. Bundgaard, (Elsevier, 1985);

c) *A Textbook of Drug Design and Development*, P. Krogsgaard-Larson and H. Bundgaard, eds. Ch 5, pgs 113 – 191 (Harwood Academic Publishers, 1991); and

5 d) *Hydrolysis in Drug and Prodrug Metabolism*, Bernard Testa and Joachim M. Mayer, (Wiley-VCH, 2003).

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) (“substantially pure”), which is then used
10 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
15 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 to TLR7/8/9, or effective to treat or
20 prevent autoimmune and/or inflammatory disease states, such as SLE, IBD, multiple sclerosis (MS), and Sjögren's syndrome, and rheumatoid arthritis.

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.,
25 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
30 limitation, isotopes of hydrogen include deuterium (D) and tritium (T). Isotopes of carbon include ¹³C and ¹⁴C. 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.

Compounds in accordance with Formula (I) and/or pharmaceutically acceptable salts thereof 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/or pharmaceutically acceptable salts thereof; 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 parenterally 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 croscopovidone. 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 Formula (I) and/or at least one pharmaceutically acceptable salt thereof 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 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 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 compound of Formula (I) and/or at least one salt thereof 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) and/or at least one pharmaceutically acceptable salt thereof 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 paraffin, and olive oil.

An aqueous suspension can be prepared, for example, by admixing at least one compound of Formula (I) and/or at least one pharmaceutically acceptable salt thereof with
5 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 example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, alginic acid, polyvinyl-pyrrolidone, gum tragacanth, and gum acacia; dispersing
10 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 hexitol, such
15 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 at least one sweetening
20 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) and/or at least one pharmaceutically acceptable salt thereof 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. An oily suspension can also
25 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-oxidant, such as, for
30 example, butylated hydroxyanisol, and alpha-tocopherol.

Dispersible powders and granules can, for example, be prepared by admixing at least one compound of Formula (I) and/or at least one pharmaceutically acceptable salt

thereof 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 preservatives include, but are not limited to, for example, anti-oxidants, e.g., ascorbic acid. In addition, dispersible
5 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) and/or at least one pharmaceutically acceptable salt thereof can, for example, be prepared as an oil-in-water emulsion. The oily phase of the emulsions comprising compounds of Formula (I) may be
10 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
15 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
20 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.
25 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) and/or at least one pharmaceutically acceptable
30 salt thereof 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-
5 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,
10 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
15 micellar solubilization (i.e. Tween 80).

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In
20 addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. 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
25 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 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
30 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 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 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 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 alkanolic 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 Formula (I) and/or at least one pharmaceutically acceptable salt thereof, 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.

UTILITY

The human immune system has evolved to defend the body from micro-organisms, viruses, and parasites that can cause infection, disease or death. Complex regulatory mechanisms ensure that the various cellular components of the immune system target the foreign substances or organisms, while not causing permanent or significant damage to the individual. While the initiating events are not well understood at this time, in autoimmune disease states the immune system directs its inflammatory response to target organs in the afflicted individual. Different autoimmune diseases are typically characterized by the predominate or initial target organ or tissues affected; such as the joint in the case of rheumatoid arthritis, the thyroid gland in the case of Hashimoto's

thyroiditis, the central nervous system in the case of multiple sclerosis, the pancreas in the case of type I diabetes, and the bowel in the case of inflammatory bowel disease.

The compounds of the invention inhibit signaling through Toll-like receptor 7, or 8, or 9 (TLR7, TLR8, TLR9) or combinations thereof. Accordingly, compounds of
5 Formula (I) have utility in treating conditions associated with the inhibition of signaling through one or more of TLR7, TLR8, or TLR9. Such conditions include TLR7, TLR8, or TLR9 receptor associated diseases in which cytokine levels are modulated as a consequence of intracellular signaling.

As used herein, the terms "treating" or "treatment" encompass the treatment of a
10 disease state in a mammal, particularly in a human, and include: (a) preventing or delaying the occurrence of the disease state 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) achieving a full or partial reduction of the symptoms or disease state, and/or alleviating, ameliorating,
15 lessening, or curing the disease or disorder and/or its symptoms.

In view of their activity as selective inhibitors of TLR7, TLR8, or TLR9, compounds of Formula (I) are useful in treating TLR7, TLR8, or TLR9 family receptor associated diseases, but not limited to, inflammatory diseases such as Crohn's disease, ulcerative colitis, asthma, graft versus host disease, allograft rejection, chronic obstructive
20 pulmonary disease; autoimmune diseases such as Graves' disease, rheumatoid arthritis, systemic lupus erythematosus, lupus nephritis, cutaneous lupus, psoriasis; auto-inflammatory diseases including Cryopyrin-Associated Periodic Syndromes (CAPS), TNF Receptor Associated Periodic Syndrome (TRAPS), Familial Mediterranean Fever (FMF), adult onset stills, systemic onset juvenile idiopathic arthritis, gout, gouty arthritis;
25 metabolic diseases including type 2 diabetes, atherosclerosis, myocardial infarction; destructive bone disorders such as bone resorption disease, osteoarthritis, osteoporosis, multiple myeloma-related bone disorder; proliferative disorders such as acute myelogenous leukemia, chronic myelogenous leukemia; angiogenic disorders such as angiogenic disorders including solid tumors, ocular neovascularization, and infantile
30 haemangiomas; infectious diseases such as sepsis, septic shock, and Shigellosis; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, cerebral ischemias or neurodegenerative disease caused by traumatic injury, oncologic and viral

diseases such as metastatic melanoma, Kaposi's sarcoma, multiple myeloma, and HIV infection and CMV retinitis, AIDS, respectively.

More particularly, the specific conditions or diseases that may be treated with the inventive compounds include, without limitation, pancreatitis (acute or chronic), asthma, allergies, adult respiratory distress syndrome, chronic obstructive pulmonary disease, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis, graft vs. host disease, inflammatory reaction induced by endotoxin, tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, gout, traumatic arthritis, rubella arthritis, acute synovitis, pancreatic β -cell disease; diseases characterized by massive neutrophil infiltration; rheumatoid spondylitis, gouty arthritis and other arthritic conditions, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption disease, allograft rejections, fever and myalgias due to infection, cachexia secondary to infection, keloid formation, scar tissue formation, ulcerative colitis, pyresis, influenza, osteoporosis, osteoarthritis, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, sepsis, septic shock, and Shigellosis; Alzheimer's disease, Parkinson's disease, cerebral ischemias or neurodegenerative disease caused by traumatic injury; angiogenic disorders including solid tumors, ocular neovascularization, and infantile haemangiomas; viral diseases including acute hepatitis infection (including hepatitis A, hepatitis B and hepatitis C), HIV infection and CMV retinitis, AIDS, ARC or malignancy, and herpes; stroke, myocardial ischemia, ischemia in stroke heart attacks, organ hypoxia, vascular hyperplasia, cardiac and renal reperfusion injury, thrombosis, cardiac hypertrophy, thrombin-induced platelet aggregation, endotoxemia and/or toxic shock syndrome, conditions associated with prostaglandin endoperoxidase synthase-2, and pemphigus vulgaris. Included in this embodiment are methods of treatment in which the condition is selected from lupus including lupus nephritis and systemic lupus erythematosus (SLE), Crohn's disease, ulcerative colitis, allograft rejection, rheumatoid arthritis, psoriasis, ankylosing spondylitis, psoriatic arthritis, and pemphigus vulgaris. Also included are

methods of treatment in which the condition is selected from ischemia reperfusion injury, including cerebral ischemia reperfusion injury arising from stroke and cardiac ischemia reperfusion injury arising from myocardial infarction. Another method of treatment is one in which the condition is multiple myeloma.

5 In one embodiment, the compounds of Formula (I) are useful in treating cancer, including Waldenstrom's Macroglobulinemia (WM), diffuse large B cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL), cutaneous diffuse large B cell lymphoma, and primary CNS lymphoma.

10 In addition, the TLR7, TLR8, or TLR9 inhibitors of the present invention inhibit the expression of inducible pro-inflammatory proteins such as prostaglandin endoperoxide synthase-2 (PGHS-2), also referred to as cyclooxygenase-2 (COX-2), IL-1, IL-6, IL-18, chemokines. Accordingly, additional TLR7/8/9 associated conditions include edema, analgesia, fever and pain, such as neuromuscular pain, headache, pain caused by cancer, dental pain and arthritis pain. The inventive compounds also may be
15 used to treat veterinary viral infections, such as lentivirus infections, including, but not limited to equine infectious anemia virus; or retrovirus infections, including feline immunodeficiency virus, bovine immunodeficiency virus, and canine immunodeficiency virus.

20 The present invention thus provides methods for treating such conditions, comprising administering to a subject in need thereof a therapeutically-effective amount of at least one compound of Formula (I) or a salt thereof. "Therapeutically effective amount" is intended to include an amount of a compound of the present invention that is effective when administered alone or in combination to inhibit autoimmune disease or chronic inflammatory disease.

25 The methods of treating TLR7, TLR8, or TLR9 associated conditions may comprise administering compounds of Formula (I) alone or in combination with each other and/or other suitable therapeutic agents useful in treating such conditions. Accordingly, "therapeutically effective amount" is also intended to include an amount of the combination of compounds claimed that is effective to inhibit TLR7, TLR8, or TLR9
30 and/or treat diseases associated with TLR7, TLR8, or TLR9.

Exemplary of such other therapeutic agents include corticosteroids, rolipram, calphostin, cytokine-suppressive anti-inflammatory drugs (CSAIDs), Interleukin-10,

glucocorticoids, salicylates, nitric oxide, and other immunosuppressants; nuclear translocation inhibitors, such as deoxyspergualin (DSG); non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, celecoxib and rofecoxib; steroids such as prednisone or dexamethasone; antiviral agents such as abacavir; antiproliferative agents such as methotrexate, leflunomide, FK506 (tacrolimus, PROGRAF®); anti-malarials such as hydroxychloroquine; cytotoxic drugs such as azathioprine and cyclophosphamide; TNF- α inhibitors such as tenidap, anti-TNF antibodies or soluble TNF receptor, and rapamycin (sirolimus or RAPAMUNE®) or derivatives thereof.

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 administration of the inventive compounds. The present invention also provides pharmaceutical compositions capable of treating TLR7/8/9 receptor-associated conditions, including IL-1 family receptor-mediated diseases as described above.

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 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.

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-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 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

5 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.

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
10 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
15 (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 parenterally including intravascularly, intravenously, intraperitoneally, subcutaneously, intramuscularly, and intrasternally in dosage unit
20 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
25 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
30 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 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 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 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 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 paraffin, and olive oil.

5 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 example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, alginic acid, polyvinyl-pyrrolidone, gum tragacanth, and gum
10 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
15 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
20 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.
25 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-
30 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 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
5 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 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
10 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
15 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
20 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
25 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
30 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 solution, 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 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 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 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 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 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 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.

5 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 alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and
10 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
15 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
20 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
25 stating that the pharmaceutical composition can be used for the treatment of a inflammatory disorder and/or an autoimmune disease (as defined previously). 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 an inflammatory disorder and/or an autoimmune disease. The article of manufacture can
30 further comprise: (d) a second 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. 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
5 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 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
10 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
15 outside of the second container, it is preferable that the package insert is physically 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, etc. that recites information relating to the pharmaceutical composition located within the first container. The information
20 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). In one embodiment, 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
25 therein or thereon. For example, the package insert is a printable material (*e.g.*, paper, plastic, cardboard, foil, adhesive-backed paper or plastic, etc.) on which the desired information has been formed (*e.g.*, printed or applied).

METHODS OF PREPARATION

30 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, those described below. All references cited herein are hereby incorporated in their entirety by reference.

5 The compounds of this invention may be prepared using the reactions and techniques described in this section. The reactions 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 choice of solvent, reaction
10 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
15 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
20 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 and Wuts (*Protective Groups In Organic Synthesis*, Third Edition, Wiley and Sons, 1999).

 Compounds of Formula (I) may be prepared by reference to the methods
25 illustrated in the following Schemes. As shown therein the end product is a compound having the same structural formula as Formula (I). It will be understood that any compound of Formula (I) may be produced by the schemes by the suitable selection of reagents with appropriate substitution. Solvents, temperatures, pressures, and other reaction conditions may readily be selected by one of ordinary skill in the art. Starting
30 materials are commercially available or readily prepared by one of ordinary skill in the art. Constituents of compounds are as defined herein or elsewhere in the specification.

EXAMPLES

Preparation of compounds of Formula (I), and intermediates used in the preparation of compounds of Formula (I), 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 Formula (I) can be prepared. Starting materials and reagents used in these examples, when not prepared by a 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.

ABBREVIATIONS

	Ac	acetyl
	ACN	acetonitrile
15	anhyd.	anhydrous
	aq.	aqueous
	Bn	benzyl
	Boc-anhydride	di- <i>tert</i> -butyl dicarbonate
	Bu	butyl
20	Boc	<i>tert</i> -butoxycarbonyl
	CV	Column Volumes
	DCE	dichloroethane
	DCM	dichloromethane
	DMAP	dimethylaminopyridine
25	DMF	dimethylformamide
	DMSO	dimethylsulfoxide
	EtOAc	ethyl acetate
	Et	ethyl
	Et ₃ N	triethylamine
30	H or H ₂	hydrogen
	h, hr or hrs	hour(s)
	hex	hexane

	i	iso
	HCl	hydrochloric acid
	HPLC	high pressure liquid chromatography
	LC	liquid chromatography
5	LCMS	liquid chromatography-mass spectrometry
	LiAlH ₄	lithium aluminum hydride
	M	molar
	mM	millimolar
	Me	methyl
10	MeOH	methanol
	MHz	megahertz
	min.	minute(s)
	mins	minute(s)
	M ⁺	(M+H) ⁺
15	MS	mass spectrometry
	n or N	normal
	NBS	n-bromosuccinimide
	NCS	n-chlorosuccinimide
	nm	nanometer
20	nM	nanomolar
	NMP	N-methylpyrrolidinone
	Pd/C	palladium on carbon
	PdCl ₂ (dppf)	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
	Ph	phenyl
25	Pr	propyl
	PSI	pounds per square inch
	Ret Time	retention time
	sat.	saturated
	SFC	supercritical fluid chromatography
30	TEA	triethylamine
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran

Tr Trityl: Triphenylmethyl
 Ts Tosyl: *p*-toluenesulfonyl
 XPhos Precatalyst G2 chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-
 biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II)

5

Analytical and Preparative HPLC conditions:

QC-ACN-AA-XB: Column: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7
 µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10 mM ammonium acetate;
 Mobile Phase B: 95:5 acetonitrile:water with 10 mM ammonium acetate; Temperature:
 10 50 °C; Gradient: 0-100% B over 3 minutes, then a 0.75-minute hold at 100% B; Flow: 1.0
 mL/min; Detection: UV at 220 nm.

QC-ACN-TFA-XB: Column: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7
 µm particles; Mobile Phase A: 5:95 acetonitrile:water with 0.1% trifluoroacetic acid;
 Mobile Phase B: 95:5 acetonitrile:water with 0.1% trifluoroacetic acid; Temperature: 50
 15 °C; Gradient: 0-100% B over 3 minutes, then a 0.75-minute hold at 100% B; Flow: 1.0
 mL/min; Detection: UV at 220 nm.

Method A1: L3 Acquity: Column: (LCMS) UPLC BEH C18, 2.1 x 50 mm, 1.7
 µm particles; Mobile Phase: (A) water; (B) acetonitrile; Buffer: 0.05% TFA; Gradient
 Range: 2%-98% B (0 to 1 min) 98%B (to 1.5 min) 98%-2% B (to 1.6 min); Gradient
 20 Time: 1.6 min; Flow Rate: 0.8 mL/min; Analysis Time: 2.2 min; Detection: Detector 1:
 UV at 220 nm; Detector 2: MS (ESI⁺).

Method B1: L2 Aquity; Column: (LCMS) UPLC BEH C18, 2.1 x 50 mm, 1.7 µm
 particles; Mobile Phase: (A) water; (B) acetonitrile; Buffer: 0.05% TFA; Gradient Range:
 2%-98% B (0 to 1 min), 98%-2% B (to 1.5 min); Gradient Time: 1.8 min; Flow Rate: 0.8
 25 mL/min; Analysis Time: 2.2 min; Detection: Detector 1: UV at 220 nm; Detector 2: MS
 (ESI⁺).

Method C1 SCP: Column: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7 µm
 particles; Mobile Phase A: 5:95 acetonitrile:water with 10 mM ammonium acetate;
 Mobile Phase B: 95:5 acetonitrile:water with 10 mM ammonium acetate. Temperature:
 30 50°C; Gradient: 0-100% B over 3 minutes, then a 0.75 minute hold at 100% B; Flow:
 1.11 mL/min; Detection: UV at 220 nm.

Method D1 SCP: Column: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7 µm

particles; Mobile Phase A: 5:95 acetonitrile:water with 0.1% trifluoroacetic acid; Mobile Phase B: 95:5 acetonitrile:water with 0.1% trifluoroacetic acid; Temperature: 50 °C; Gradient: 0-100% B over 3 minutes, then a 0.75-minute hold at 100% B; Flow: 1.11 mL/min; Detection: UV at 220 nm.

- 5 Method D2 SCP: Column: XBridge C18, 19 x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 10-50% B over 20 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min. Detection: UV at 220 nm.

- Method D3 SCP: Column: XBridge C18, 19 x 200 mm, 5 µm particles; Mobile
10 Phase A: 5:95 acetonitrile: water with 0.1% trifluoroacetic acid; Mobile Phase B: 95:5 acetonitrile: water with 0.1% trifluoroacetic acid; Gradient: 6-46% B over 20 minutes, then a 4-minute hold at 100% B; Flow: 20 mL/min. Detection: UV at 220 nm.

- Method E1 iPAC: Column: Waters Xbridge C18 4.6 x 50 mm 5 µm particles;
Mobile Phase A: 5:95 acetonitrile:water with 10 mM ammonium acetate; Mobile Phase
15 B: 95:5 acetonitrile:water with 10 mM ammonium acetate. Temperature: 50 °C; Gradient: 0-100% B over 1 minute; Flow: 4 mL/min; Detection: UV at 220 nm.

- Method F1 iPAC: Column: Waters Acquity BEH C18 2.1x50 mm 1.7 µm
particles; Mobile Phase A: 5:95 acetonitrile:water with 0.1% trifluoroacetic acid; Mobile
Phase B: 95:5 acetonitrile:water with 0.1% trifluoroacetic acid; Temperature: 50 °C;
20 Gradient: 0-100% B over 2.20 minutes; Flow: 0.800 mL/min; Detection: UV at 220 nm.

(A): Column-Ascentis Express C18 (50 x 2.1 mm-2.7 µm) Mphase A: 10 mM NH₄COOH in water: ACN (98:02); Mphase B: 10 mM NH₄COOH in water: ACN (02:98), Gradient: 0-100% B over 3 minutes, Flow = 1 mL/min.

- (B): Waters Acquity BEH C18 (2.1 x 50 mm) 1.7 micron; Buffer: 5 mM
25 ammonium acetate pH 5 adjusted with HCOOH, Solvent A: Buffer:ACN (95:5), Solvent B: Buffer:ACN (5:95), Method:%B: 0 min-5%: 1.1 min -95%: 1.7 min-95%, Flow: 0.8 mL/min.

- (C): Column-Ascentis Express C18 (50 x 2.1 mm-2.7 µm) Mobile phase A: 0.1% HCOOH in water; Mobile phase B: ACN. Temperature: 50 °C; Gradient: 0-100% B over
30 3 minutes; Flow rate: 1.0 mL/min.

(D): Kinetex XB-C18 (75 x 3 mm) 2.6 micron; Solvent A: 10 mM ammonium formate in water: acetonitrile (98:02); Mobile Phase B: 10 mM ammonium formate in

water: acetonitrile (02:98); Temperature: 50 °C; Gradient: 0-100% B over 3 minutes;
Flow rate: 1.1 mL/min; Detection: UV at 220 nm.

(E): Column: Ascentis Express C18 (50 x 2.1)mm, 2.7 µm; Mobile Phase A: 5:95 acetonitrile: water with 10 mM NH₄OAc; Mobile Phase B: 95:5 acetonitrile: water with 10 mM NH₄OAc; Temperature: 50 °C; Gradient: 0-100% B over 3 minutes; Flow: 1.1 mL/min.

(F): Column: Ascentis Express C18 (50 x 2.1)mm, 2.7 µm; Mobile Phase A: 5:95 acetonitrile: water with 0.1% TFA; Mobile Phase B: 95:5 acetonitrile: water with 0.1% TFA; Temperature: 50 °C; Gradient: 0-100%B over 3 minutes; Flow: 1.1 mL/min.

(G): Column: Waters Acquity UPLC BEH C18 (2.1 x 50 mm), 1.7 micron; Solvent A = 100% water with 0.05% TFA; Solvent B = 100% acetonitrile with 0.05% TFA; gradient = 2-98% B over 1 minute, then a 0.5-minute hold at 98% B; Flow rate: 0.8 mL/min; Detection: UV at 220 nm.

(H): Column: Acentis Express C18 (50 x 2.1 mm) 1.7 µm, Acentis C8 NH₄COOH 5 min. M, Mobile Phase A: -10 mM ammonium formate: ACN (98:2), Mobile Phase B: -10 mM ammonium formate: ACN (2:98), gradient: 20%-100% B (0-4 min); 100% B (4-4.6 min); Flow: 1 mL/min

(I) Column: Sunfire C18 (4.6 x 150) mm, 3.5 µm; Mobile Phase A: 5:95 acetonitrile: water with 0.05% TFA; Mobile Phase B: 95:5 acetonitrile: water with 0.05% TFA; Temperature: 50 °C; Gradient: 10-100%B over 12 minutes; Flow: 1 mL/min.

(J) Column: Sunfire C18 (4.6 x 150)mm, 3.5 µm; Mobile Phase A: 5:95 acetonitrile: water with 0.05% TFA; Mobile Phase B: 95:5 acetonitrile: water with 0.05% TFA;

(K) Waters Acquity SDS Mobile Phase: A: water B: ACN; 5%-95%B in 1 min; Gradient Range: 50%-98% B (0-0.5 min); 98%B (0.5 min-1 min); 98%-2% B (1-1.1 min); Run time: 1.2 min; Flow Rate: 0.7 mL/min; Analysis Time: 1.7 min; Detection: Detector 1: UV at 220 nm; Detector 2: MS (ES⁺).

(L) Acquity UPLC BEH C18 (3.0 x 50 mm) 1.7 µm. Buffer: 5 mM ammonium acetate; Mobile phase A: Buffer:ACN (95:5); Mobile phase B: Buffer:ACN (5:95) Method: %B: 0 min-20%:1.1 min -90%:1.7 min-90%. Run time: 2.25 min; Flow Rate: 0.7 mL/min; Detection: Detector 1: UV at 220 nm; Detector 2: MS (ES⁺).

(M): Kinetex SBC18 (4.6 x 50 mm) 5 micron; Solvent A: 10 mM ammonium

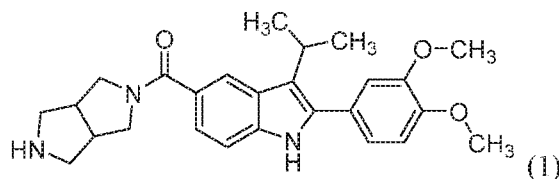
formate in water: acetonitrile (98:02); Mobile Phase B: 10 mM ammonium formate in water: acetonitrile (02:98); Temperature: 50 °C; Gradient: 30-100% B (0-4 min), 100% B (4-4.6 min), 100-30% B (4.6-4.7 min), 30% B (4.7-5.0 min); Flow rate: 1.5 mL/min; Detection: UV at 220 nm.

5 (N): Column-Ascentis Express C18 (50 x 2.1 mm-2.7 µm) Mphase A: 10 mM NH₄COOH in water: ACN (98:02); Mphase B: 10 mM NH₄COOH in water: ACN (02:98), Gradient: 0-100% B (0-1.7 minutes); 100% B (1.7-3.4 minutes). Flow = 1 mL/min.

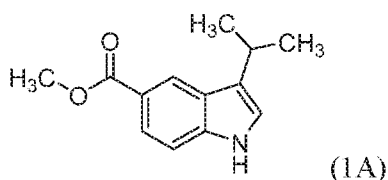
10 (O) Waters Acquity SDS Column BEH C18 (2.1 x 50 mm) 1.7 µm. Phase A: buffer in water; Mphase B: buffer in ACN, Gradient: 20-98% B (0-1.25 minutes); 98% B (1.25-1.70 minutes); 98%-2% B (1.70-1.75 minutes); Flow = 0.8 mL/min.

EXAMPLE 1

15 2-(3,4-dimethoxyphenyl)-5-{octahydropyrrolo[3,4-c]pyrrole-2-carbonyl}-3-(propan-2-yl)-1H-indole



Intermediate 1A: Methyl 3-isopropyl-1H-indole-5-carboxylate

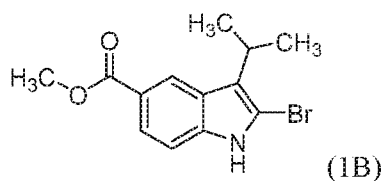


20 To a solution of 5-bromo-3-isopropyl-1H-indole (4.00 g, 16.80 mmol) in MeOH (80.00 mL) and DMF (80.00 mL) were added palladium(II) acetate (0.754 g, 1.119 mmol) and DPPF (2.79 g, 5.04 mmol). The mixture was degassed with nitrogen for 5 min. and TEA (7.02 mL, 50.4 mmol) was added. The reaction mixture was stirred in an autoclave at 100 °C with 5 kg pressure in presence of CO gas for 16 h. Crude LCMS showed formation of product and no starting material. The reaction mass was

25 concentrated and the residue was dissolved in EtOAc (50 mL). The solid was filtered and washed with EtOAc (2 X 30 mL), the combined filtrates was collected and concentrated

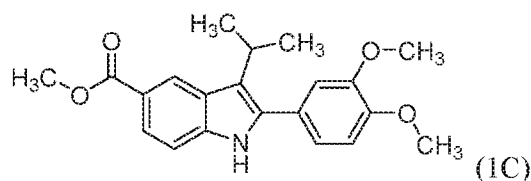
to get crude compound. The crude material was purified by column chromatography using 120 g silica column. The compound was eluted in 35% ethyl acetate in hexanes, the fractions were collected and concentrated to afford methyl 3-isopropyl-1H-indole-5-carboxylate (3.42 g, 15.74 mmol, 94 % yield) as an oil. LCMS retention time 0.96 min [G]. MS m/z : 218.6 $[M+H]^+$.

Intermediate 1B: Methyl 2-bromo-3-isopropyl-1H-indole-5-carboxylate



To a solution of methyl 3-isopropyl-1H-indole-5-carboxylate (0.790 g, 2.69 mmol) in DCE (20 mL) was added NBS (0.479 g, 2.69 mmol) at room temperature. The mixture was stirred at the same temperature for 10 min. Crude LCMS showed formation of product and no starting material. The reaction was quenched with the addition of water (5 mL). The reaction mixture was extracted with DCM (2 X 20 mL), combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated to get crude compound. The crude material was purified by column chromatography using 24 g silica column, the compound was eluted in 15% EtOAc in hexanes, the fractions were collected and concentrated to afford methyl 2-bromo-3-isopropyl-1H-indole-5-carboxylate (0.582 g, 1.965 mmol, 73.0 % yield) as pale brown solid. LCMS retention time 1.05 min [G]. MS m/z : 298 $[M+2]+H]^+$.

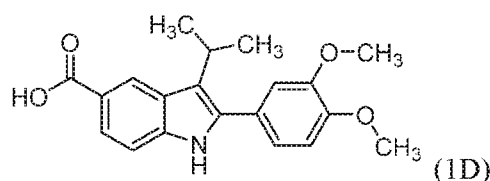
Intermediate 1C: Methyl-2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carboxylate



A solution of methyl 2-bromo-3-isopropyl-1H-indole-5-carboxylate (0.570 g, 1.925 mmol), (3,4-dimethoxyphenyl)boronic acid (0.736 g, 4.04 mmol) and cesium carbonate (1.881 g, 5.77 mmol) in dioxane (12.00 mL) and water (3.00 mL) was degassed for 30 min. Next, $\text{Pd}(\text{Ph}_3\text{P})_4$ (0.222 g, 0.192 mmol) was added and the reaction mixture

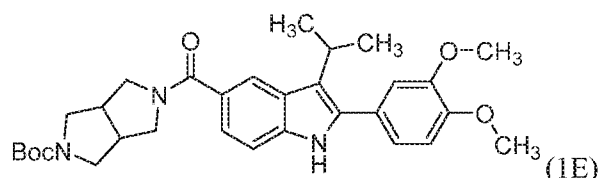
was stirred at 90 °C for 4 h. Crude LCMS showed formation of product and no starting material. The reaction was quenched with the addition of water (5 mL). The reaction mixture was extracted with EtOAc (2 X 30 mL), combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄), and concentrated to get crude compound. The crude material was purified by column chromatography, using 24g silica column, the compound was eluted in 15% EtOAc in hexane, the fractions were collected and concentrated to afford methyl 2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carboxylate (0.520 g, 1.471 mmol, 76 % yield) as pale orange solid. LCMS retention time 1.13 min [G]. MS *m/z*: 354 [M+H]⁺.

Intermediate 1D: 2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carboxylic acid



To a solution of methyl 2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carboxylate (0.325g, 0.920 mmol) in THF (8.00 mL), MeOH (4.00 mL) and water (2.000 mL) solvent mixture was added lithium hydroxide (0.110 g, 4.60 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 4 h. Crude LCMS showed starting material remained. The reaction mixture was stirred at 75 °C for 16 h. Crude LCMS showed formation of product and no starting material. The reaction mixture was concentrated and the residue/solid was added to water (20 mL), washed with EtOAc (1 X 20 mL), then the aqueous slurry was brought to acid pH with 1.5 N HCl, the solids were filtered, washed with water and dried under vacuum to afford 2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carboxylic acid (0.210 g, 0.619 mmol, 67 % yield) as a white solid. LCMS retention time 0.97 min [G]. MS *m/z*: 340.1 [M+H]⁺.

Intermediate 1E: tert-butyl 5-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carboxyl)hexahydro pyrrolo[3,4-c]pyrrole-2(1H)-carboxylate



To a solution of 2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carboxylic acid (0.095 g, 0.280 mmol) in DCM (2.00 mL) and DMF (2.00 mL) were added tert-butyl hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (0.059 g, 0.280 mmol) and EDC (0.080 g, 0.420 mmol) at room temperature. The mixture was stirred at the same temperature for 2 h. Crude LCMS showed formation of product. The reaction was quenched with the addition of water (5 mL). The reaction mixture was extracted with 10% MeOH in CH₂Cl₂ (2 x 10 mL), combined organic extracts was washed with water (10 mL), brine (5 mL), dried (Na₂SO₄) and concentrated to get crude compound. The crude material was purified by column chromatography using 12 g silica column, compound was eluted in neat ethyl acetate, the fractions were collected and concentrated to afford tert-butyl 5-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carbonyl)hexahydro pyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (0.101 g, 0.189 mmol, 67 % yield) as off white solid. LCMS retention time 1.12 min [G]. MS *m/z*: 534 [M+H]⁺.

Example 1:

To a solution of tert-butyl 5-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (0.190 g, 0.356 mmol) in dioxane (1 mL) was added 4 N HCl in dioxane (0.50 mL, 2.0 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 2 h. The reaction mixture was concentrated, the residue was triturated with diethyl ether (2 X 5 mL) to afford (2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl)(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl) methanone hydrochloride (0.161 g, 0.343 mmol, 96 % yield) as a pale yellow solid.

LCMS retention time 0.82 min [G]. MS *m/z*: 434.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.24 (s, 1 H), 9.22 (bs, 2 H), 7.88 (s, 1 H), 7.32 (dd, *J* = 8.4, 1.2 Hz, 1 H), 7.26 (dd, *J* = 8.4, 1.2 Hz, 1 H), 7.15-7.03 (m, 3 H), 3.83 (s, 3 H), 3.81 (s, 3 H), 3.78-3.72 (m, 3 H), 3.65-3.51 (m, 2 H), 3.48-3.27 (m, 3 H), 3.14-2.98 (m, 3 H), 1.45-1.42 (m, 6 H).

The examples in Table 1 were prepared according to the general procedure described for Example 1.

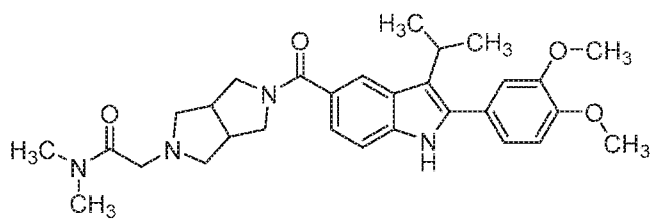
TABLE 1

Ex. No.	Structure	Mol Wt.	LCMS MH ⁺	Ret Time (min)	HPLC Method
2		435.57	436	1.398	E
3		366.46	367	1.633	F
4		352.43	353	1.478	F
5		419.53	420	1.26	E

5

EXAMPLE 6

2-{5-[2-(3,4-dimethoxyphenyl)-3-(propan-2-yl)-1H-indole-5-carbonyl]-octahydropyrrolo[3,4-c]pyrrol-2-yl}-N,N-dimethylacetamide



To a solution of (2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl) (hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone hydrochloride (0.040 g, 0.085 mmol) in THF (2.00 mL) and DMF (1.00 mL) were added TEA (0.036 mL, 0.255 mmol) and 2-chloro-N,N-dimethylacetamide (0.016 g, 0.128 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 16 h. Crude LCMS showed formation of product and no starting material. The reaction mixture was concentrated to get crude compound. The crude material was purified by reverse phase prep HPLC using method D2. The fractions containing the compound were combined and evaporated to dryness using Genevac to afford 2-(5-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N,N-dimethylacetamide (0.032 g, 0.059 mmol, 69 % yield) as a pale yellow solid. LCMS retention time 2.10 min [H], MS *m/z*: 519.2 (M+H); ¹H NMR (400 MHz, CD₃OD) δ ppm 7.91 (s, 1 H), 7.38 (d, J = 8.4 Hz, 1 H), 7.25 (dd, J = 8.4, 1.2 Hz, 1 H), 7.12-7.04 (m, 3 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.88-3.82 (m, 3 H), 3.38-3.36 (m, 3 H), 3.11 (s, 3 H), 2.98 – 2.93 (m, 5 H), 2.86 – 2.42 (m, 5 H), 1.45-1.42 (m, 6 H).

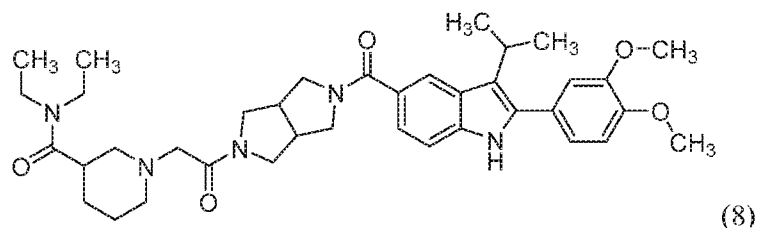
The example in Table 2 was prepared according to the general procedure described for Example 6

TABLE 2

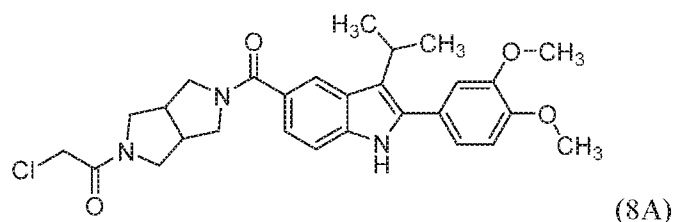
Ex. No.	Structure	Mol Wt.	LCMS MH ⁺	Ret Time (min)	HPLC Method
7		504.63	505.4	1.461	E

EXAMPLE 8

1-(2-{5-[2-(3,4-dimethoxyphenyl)-3-(propan-2-yl)-1H-indole-5-carbonyl]-
octahydropyrrolo[3,4-c]pyrrol-2-yl}-2-oxoethyl)-N,N-diethylpiperidine-3-carboxamide



Intermediate 8A: 2-chloro-1-(5-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carbonyl)hexahydro pyrrolo[3,4-c]pyrrol-2(1H)-yl)ethanone



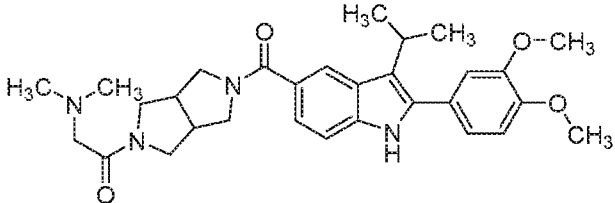
To a solution of (2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl)
(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone hydrochloride (0.160 g, 0.340
mmol) in THF (5.00 mL) (compound was not dissolved completely) was added DIPEA
(0.178 mL, 1.021 mmol) at 0 °C (compound was not dissolved completely). The reaction
mixture was stirred for 5 min, then chloroacetyl chloride (0.030 mL, 0.374 mmol) was
added at the same temperature. Stirring was continued at room temperature for 12 h.
Crude LCMS showed formation of product and 12% starting material remained. An
additional amount of chloroacetyl chloride (0.2 eq) was added and the reaction was
allowed to proceed for another 3 h. Crude LCMS showed formation of product and no
starting material. The reaction was quenched with the addition of water. The reaction
mixture was extracted with DCM (2 X 20 mL), combined organic extracts were washed
with brine (5 mL), dried (Na₂SO₄) and concentrated to afford 2-chloro-1-(5-(2-(3,4-
dimethoxyphenyl)-3-isopropyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c] pyrrol-
2(1H)-yl)ethanone (0.168 g, 0.329 mmol, 97 % yield) as a gummy solid. LCMS retention
time 1.08 min [G]. MS *m/z*: 510.1 [M+H]⁺.

Example 8:

To a solution of 2-chloro-1-(5-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethanone (0.100 g, 0.196 mmol) in THF (2.00 mL) were added TEA (0.082 mL, 0.588 mmol) and N,N-diethylnipecotamide (0.055 mL, 0.294 mmol) at room temperature. The mixture was stirred at the same temperature for 16 h and concentrated to yield crude compound. The crude sample was purified by reverse phase prep HPLC using method D2, the product containing fraction was collected, concentrated and lyophilized to afford 1-(2-(5-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-oxoethyl)-N,N-diethylpiperidine-3-carboxamide, TFA (0.072 g, 0.089 mmol, 45 % yield) as a pale yellow solid. LCMS retention time 1.08 min [G]. MS m/z : 658.4 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 11.21 (s, 1 H), 9.69-9.46 (br m, 1 H), 7.87 (s, 1 H), 7.38-7.31 (m, 1 H), 7.29-7.22 (m, 1 H), 7.15-7.04 (m, 3 H), 4.29-2.88 (m, 28 H), 1.92-1.78 (m, 4 H), 1.42-1.40 (m, 6 H), 1.17-1.11 (m, 3 H), 1.09-0.93 (m, 3 H).

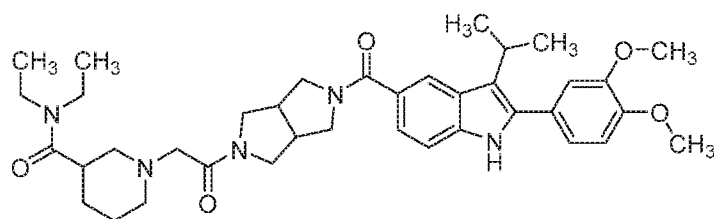
The following Examples were prepared according to the general procedure described for Example 8.

TABLE 3

Ex. No.	Structure	Mol Wt.	LCMS MH ⁺	Ret Time (min)	HPLC Method
9		518.66	519.4	1.126	F

EXAMPLES 10 AND 11

1-(2-{5-[2-(3,4-dimethoxyphenyl)-3-(propan-2-yl)-1H-indole-5-carbonyl]-octahydropyrrolo[3,4-c]pyrrol-2-yl}-2-oxoethyl)-N,N-diethylpiperidine-3-carboxamide.



(10-11)

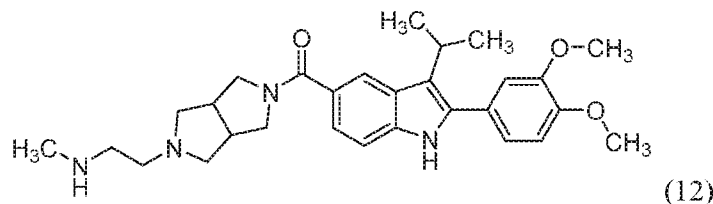
The racemic mixture of Example 8 was separated to afford the two individual enantiomers. Chiral HPLC using column: Chiralpak IA (250 X 4.6)mm, 5 micron, Run time: 25 min, Flow rate: 0.7 mL/min, mobile phase: 0.2 % DEA n-hexane:ethanol:50:50, wave length: 220 nm. After prep purification, the enantiomers were collected separately, concentrated and lyophilized to afford 1-(2-(5-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-oxoethyl)-N,N-diethyl piperidine-3-carboxamide (0.022 g, 0.032 mmol, 34.0 % yield) (Peak-1, Chiral HPLC RT-10.456) as a white solid and 1-(2-(5-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carbonyl)hexahydropyrrolo [3,4-c]pyrrol-2(1H)-yl)-2-oxoethyl)-N,N-diethylpiperidine-3-carboxamide (0.026 g, 0.039 mmol, 42 % yield) (Peak-2, Chiral HPLC RT-12.331) as a white solid.

Example 10: Enantiomer 1: LCMS retention time 1.861 min [H], MS m/z : 658.4 (M+H); ^1H NMR (400 MHz, DMSO- d_6) δ 11.21 (s, 1 H), 9.69-9.46 (br m, 1 H), 7.87 (s, 1 H), 7.38-7.31 (m, 1 H), 7.29-7.22 (m, 1 H), 7.15-7.04 (m, 3 H), 4.29-2.88 (m, 28 H), 1.92-1.78 (m, 4 H), 1.42-1.40 (m, 6 H), 1.17-1.11 (m, 3 H), 1.09-0.93 (m, 3 H).

Example 11: Enantiomer 2: LCMS retention time 1.853 min [H], MS m/z : 658.4 (M+H); ^1H NMR (400 MHz, DMSO- d_6) δ 11.21 (s, 1 H), 9.69-9.46 (br m, 1 H), 7.87 (s, 1 H), 7.38-7.31 (m, 1 H), 7.29-7.22 (m, 1 H), 7.15-7.04 (m, 3 H), 4.29-2.88 (m, 28 H), 1.92-1.78 (m, 4 H), 1.42-1.40 (m, 6 H), 1.17-1.11 (m, 3 H), 1.09-0.93 (m, 3 H).

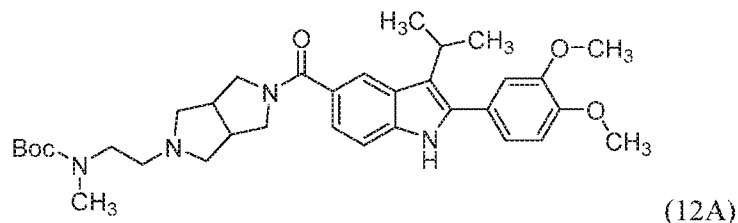
EXAMPLE 12

(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl)(5-(2-(methylamino)ethyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone



(12)

Intermediate 12A: tert-butyl (2-(5-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carbonyl)hexahydro pyrrolo [3,4-c]pyrrol-2(1H)-yl)ethyl)(methyl)carbamate



To a solution of (2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl)
 5 (hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone hydrochloride (0.050 g, 0.106 mmol) in MeOH (3 mL) were added N-Boc-(methylamino)acetaldehyde (0.028 g, 0.160 mmol) and TEA (0.030 mL, 0.213 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was cooled to 0 °C and acetic acid (0.20 mL, 3.49 mmol) was added. The reaction mixture was stirred at room temperature for 1
 10 h. Again the reaction mixture was cooled to 0 °C and sodium borohydride (0.012 g, 0.319 mmol) was added. The reaction mixture was left at room temperature overnight. Crude LCMS showed formation of product and no starting material. The reaction was quenched with water (5 mL). Methanol was removed from the mixture using rotavap, the residue was extracted with 10% MeOH in DCM (2 X 10 mL), combined organic extracts
 15 were washed with brine (2 mL), dried (Na₂SO₄) and concentrated to afford crude tert-butyl (2-(5-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c] pyrrol-2(1H)-yl)ethyl)(methyl)carbamate as gummy solid. LCMS retention time 1.10 min [H], MS *m/z*: 591.4 (M+H).

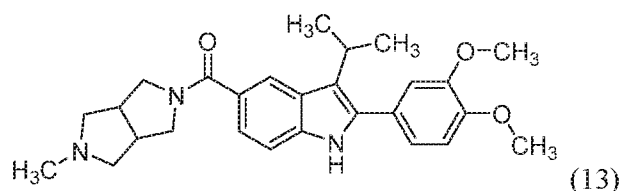
20 Example 12:

To a solution of tert-butyl (2-(5-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethyl)(methyl)carbamate (0.063 g, 0.106 mmol) in DCM (2.00 mL) was added TFA (0.5 mL, 6.49 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. Crude LCMS showed
 25 formation of product and no starting material. The reaction mass was concentrated to get crude compound. The crude material was purified by Prep LCMS using method D2, fractions containing the product were combined and dried using Genevac centrifugal evaporator to afford (2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl)(5-(2-

(methylamino)ethyl)hexahydro pyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (0.014 g, 0.028 mmol, 26 % yield) as a pale yellow solid. LCMS retention time 1.90 min [E], MS *m/z*: 491.2 (M+H); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.20 (s, 1 H), 7.82 (s, 1 H), 7.35 (d, J = 8.4 Hz, 1 H), 7.22 (dd, J = 8.4, 1.2 Hz, 1 H), 7.12-7.04 (m, 3 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.76-3.74 (m, 2 H), 3.55-3.42 (m, 3 H), 2.86-2.74 (m, 4 H), 2.66-2.52 (m, 3 H), 2.49 (s, 3 H), 2.48-2.40 (m, 3 H), 1.43 (d, J = 12.4 Hz, 6 H).

EXAMPLE 13

(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl)(5-methylhexahydro pyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone



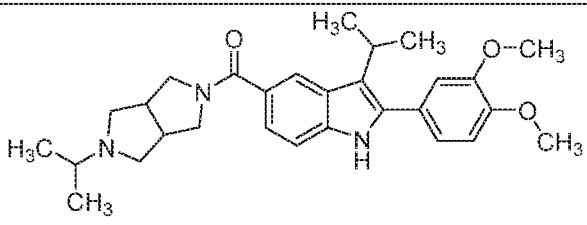
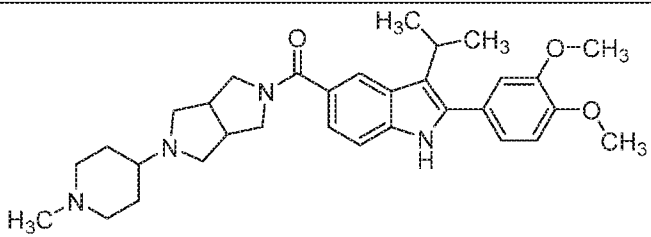
To a solution of (2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl)(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone hydrochloride (0.044 g, 0.094 mmol) in MeOH (3.00 mL) were added formaldehyde in water (0.1 mL, 1.271 mmol) and acetic acid (0.016 mL, 0.281 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. Again the reaction mixture was cooled to 0 °C and sodium borohydride (10.63 mg, 0.281 mmol) was added portion wise. The reaction mixture was stirred at room temperature for 16 h. Crude LCMS showed formation of product and no starting material. The reaction was quenched with water (5 mL). Methanol was removed from the reaction mixture using rotavap, the residue was extracted with 10% MeOH in DCM (2 X 10 mL), combined organic extracts was washed with brine (2 mL), dried (Na₂SO₄) and concentrated to get crude compound. The crude material was purified by Preparative LCMS using method D2, the fractions containing the product were combined and dried using Genevac centrifugal evaporator to afford (2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl)(5-methylhexahydro pyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (0.027 g, 0.058 mmol, 62 % yield) as a pale yellow solid. LCMS retention time 1.966 min [E], MS *m/z*: 448.2 (M+H); ¹H NMR (400 MHz, CD₃OD) δ ppm 7.93 (d, J = 0.8 Hz, 1 H), 7.39 (d, J = 8.4 Hz, 1 H), 7.26 (dd, J = 8.4, 1.2 Hz, 1 H), 7.11-7.06 (m, 3 H), 3.92 (s, 3 H), 3.90 (s, 3 H), 3.89-3.81 (m, 2 H), 3.80-3.72 (m, 2 H), 3.48-3.37 (m, 1 H), 3.09-2.95

(m, 4 H), 2.65-2.54 (m, 2 H), 2.50 (s, 3 H), 1.48 (d, J = 6.8 Hz, 6 H).

The examples in Table 4 were prepared according to the general procedure described in Example 13.

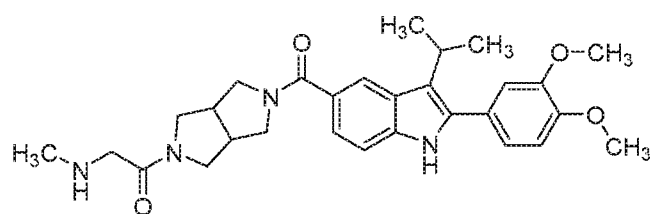
5

TABLE 4

Ex. No.	Structure	Mol Wt.	LCMS MH ⁺	Ret Time (min)	HPLC Method
14		475.63	476.4	6.564	I
15		530.71	531	1.356	E

EXAMPLE 16

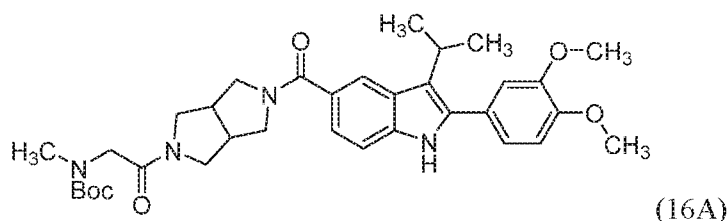
1-(5-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carbonyl)hexahydro pyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-(methylamino)ethanone



10

(16)

Intermediate 16A: tert-butyl (2-(5-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carbonyl)hexahydro pyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-oxoethyl)(methyl)carbamate



To a solution of (2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl) (hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone hydrochloride (0.030 g, 0.064 mmol) in DMF (3.00 mL) were added TEA (0.027 mL, 0.191 mmol), 2-((tert-butoxycarbonyl)(methyl)amino)acetic acid (0.018 g, 0.096 mmol), and HATU (0.049 g, 0.128 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. Crude LCMS showed formation of product and no starting material. The reaction was quenched with water (5 mL). The reaction mixture was extracted with 10% MeOH in DCM (2 X 10 mL), combined organic extracts was washed with brine (5 mL), dried (Na₂SO₄) and concentrated to afford crude tert-butyl (2-(5-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-oxoethyl) (methyl)carbamate as a gummy solid. LCMS retention time 0.92 min [G]. MS *m/z*: 505.8 [M+H-Boc]⁺.

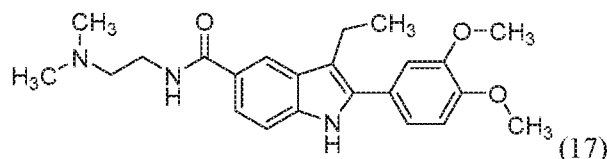
Example 16:

To a solution of tert-butyl (2-(5-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-oxoethyl)(methyl)carbamate (0.039 g, 0.064 mmol) in DCM (2.00 mL) was added TFA (0.2 mL, 2.60 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 2 h. Crude LCMS showed formation of product and no starting material. The crude material was purified by Preparative LCMS method D2, the fractions containing the product were combined and dried using Genevac centrifugal evaporator to afford 1-(5-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-(methylamino)ethanone, TFA (0.015 g, 0.024 mmol, 38 % yield) as a pale yellow solid. LCMS retention time 1.148 min [E]. MS *m/z*: 505.4 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.20 (s, 1 H), 7.86 (s, 1 H), 7.34 (d, *J* = 8.4 Hz, 1 H), 7.26 (dd, *J* = 8.4, 1.6 Hz, 1 H), 7.11-7.04 (m, 3 H), 3.84 (s, 3 H), 3.82 (s, 3 H), 3.80-3.75 (m, 2 H), 3.66-3.58 (m, 2 H), 3.46-3.31 (m, 4 H), 3.27-3.22 (m, 2 H), 3.02-2.97 (m, 1 H), 2.91-2.83

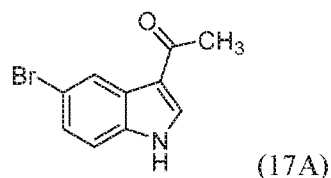
(m, 1 H), 2.26 (s, 3 H), 1.42 (d, $J = 8.8$ Hz, 6 H).

EXAMPLE 17

2-(3,4-dimethoxyphenyl)-N-[2-(dimethylamino)ethyl]-3-ethyl-1H-indole-5-carboxamide

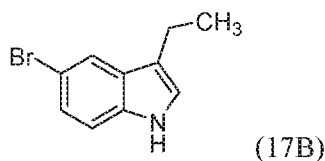


Intermediate 17A: 1-(5-bromo-1H-indol-3-yl)ethanone



To a solution of 5-bromo-1H-indole (1 g, 5.10 mmol) in toluene (10 mL) was added acetyl chloride (0.725 mL, 10.20 mmol) at 0 °C followed by the addition of tin(IV) chloride (10.20 mL, 10.20 mmol) drop wise. The reaction temperature was raised to ambient temperature and the reaction mixture was stirred at the same temperature for 4 h. LC/MS showed completion of reaction. The reaction was quenched with ice cold water. Yellow solid precipitated out and was collected by filtration. The reaction solids were air dried with vacuum filtration. The residue was washed with water and dried under vacuum for 12 h. The dried solid was further triturated with dry toluene and collected to afford 1-(5-bromo-1H-indol-3-yl)ethanone (1 g, 82 % yield) as a yellow solid. LCMS retention time 2.13 min [D]. MS m/z : 237 (M+H). ^1H NMR (300 MHz, DMSO- d_6) δ ppm 12.11 (br. s., 1 H), 8.37 (s, 1 H), 8.33-8.29 (m, 1 H), 7.43 (d, $J = 0.6$ Hz, 1 H), 7.38-7.30 (m, 1 H), 2.45 (s, 3 H).

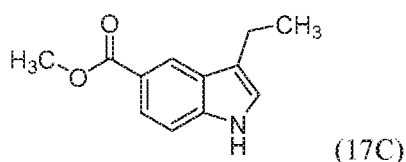
Intermediate 17B: 5-bromo-3-ethyl-1H-indole



To a solution of 1-(5-bromo-1H-indol-3-yl)ethanone (3 g, 12.60 mmol) in THF (30 mL) was added LAH (6.30 mL, 12.60 mmol) at ambient temperature. The reaction

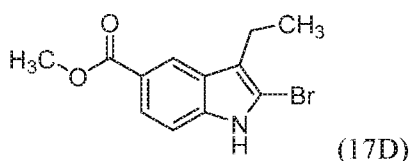
mixture was heated to 55 °C. The reaction mixture was stirred at same temperature for 1 h. LC/MS showed completion of reaction. The reaction was slowly quenched with ice cold water. White residue precipitated out. The reaction mass was diluted with ethyl acetate and filtered through a pad of celite. The organic layer was concentrated and purified by column chromatography on a 24 g silica column using petroleum ether:ethyl acetate as eluent (8:2). The fractions were collected and concentrated to afford 5-bromo-3-ethyl-1H-indole (1.8 g, 64 % yield) as a yellow solid. LCMS retention time 2.35 min [D]. MS m/z : 224 (M+H).

10 Intermediate 17C: Methyl 3-ethyl-1H-indole-5-carboxylate



To a solution of 5-bromo-3-ethyl-1H-indole (2g, 8.92 mmol) in methanol (20 mL) and DMSO (20 mL) were added DPPF (0.990 g, 1.785 mmol), Pd(OAc)₂ (0.200 g, 0.892 mmol). The solution was degassed for 10 min using argon. The reaction mass was saturated with CO gas, followed by the addition of TEA (3.11 mL, 22.31 mmol). The reaction mass was then heated to 80 °C in the presence of CO for 12 h. LC/MS showed formation of the product. The reaction mass was diluted with ethyl acetate and washed with water, followed by brine, organic layer was separated and dried over sodium sulphate and concentrated to get crude ester, which was further purified by column chromatography using 40 g silica column. The compound was eluted in petroleum ether:ethyl acetate (6:4), the fractions were collected and concentrated to methyl 3-ethyl-1H-indole-5-carboxylate (0.75 g, 41 % yield) as a pale yellow solid. LCMS retention time 2.21 min [D]. MS m/z : 204.2 (M+H).

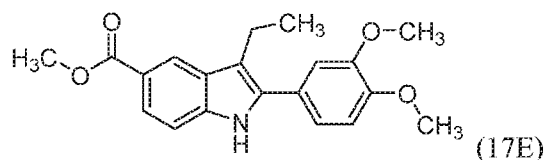
25 Intermediate 17D: Methyl 2-bromo-3-ethyl-1H-indole-5-carboxylate



To a solution of methyl 3-ethyl-1H-indole-5-carboxylate (0.75 g, 3.69 mmol) in

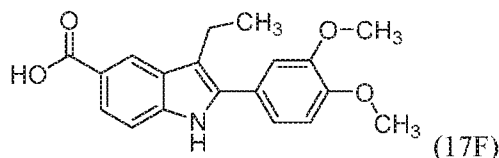
DCE (40 mL) was added NBS (0.657 g, 3.69 mmol) in DCE (40 mL) at ambient temperature. The reaction mixture was stirred for 3 h. LC/MS showed completion of the reaction. The reaction was quenched with 5 mL of sodium sulfite solution. The volatiles were removed. The residue was taken up in DCM (15 mL), filtered and loaded onto a 40g silica gel column, which was eluted using 0-50% ethyl acetate/hexane. The fractions were collected and concentrated to afford methyl 2-bromo-3-ethyl-1H-indole-5-carboxylate (0.56 g, 53 % yield) as a white foam. LCMS retention time 2.36 min [D]. MS m/z : 282 (M+H).

10 Intermediate 17E: Methyl 2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carboxylate



Methyl 2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carboxylate (0.45 g, 83 % yield) was prepared as described in preparation of Intermediate 1C, using methyl 2-bromo-3-ethyl-1H-indole-5-carboxylate (560 mg, 1.985 mmol) as the starting intermediate. LCMS retention time 2.1 min [D]. MS m/z : 340.2 (M+H).

Intermediate 17F: 2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carboxylic acid



2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carboxylic acid carboxylate (0.35 g, 81 % yield) was prepared according to the general preparation described in Intermediate 1D, using methyl 2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carboxylate (0.45 g, 1.326 mmol) as the starting intermediate. LCMS retention time 2.1 min [D]. MS m/z : 326.2 (M+H).

25 Example 17:

To a vial containing 2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carboxylic acid (10 mg, 0.031 mmol), HATU (14.02 mg, 0.037 mmol) and the corresponding amine

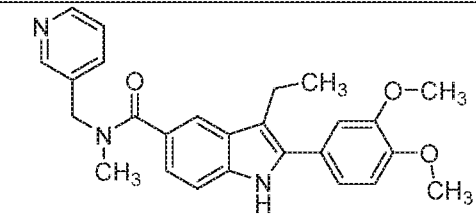
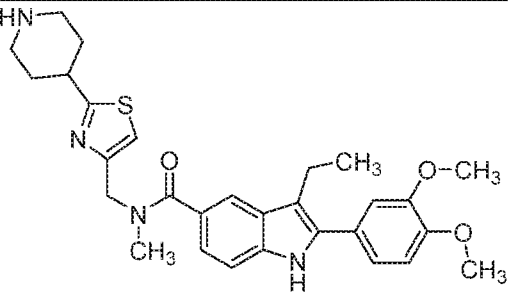
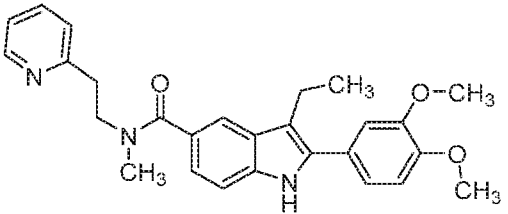
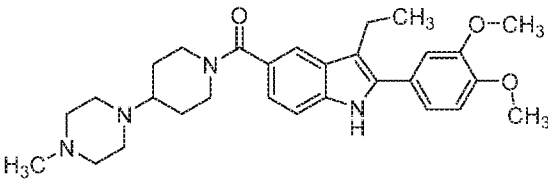
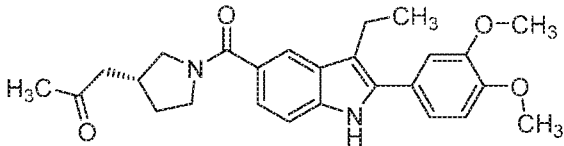
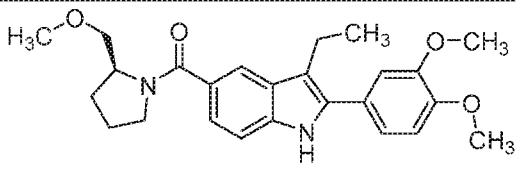
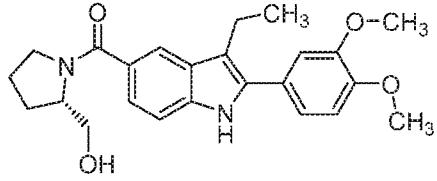
(0.037 mmol), were added DMF (0.5 mL) and DIPEA (0.016 mL, 0.092 mmol). The reaction mixture was stirred for 3 h at room temperature. The crude samples was purified by reverse phase prep HPLC using method D2. The fractions containing the compound were combined and evaporated to dryness using Genevac to afford 2-(3,4-

- 5 dimethoxyphenyl)-N-(2-(dimethylamino)ethyl)-3-ethyl-1H-indole-5-carboxamide (6.1 mg, 0.015 mmol, 50 % yield) as a pale solid. LCMS retention time 1.037 min [E]. MS m/z ; 396.2 (M+H); ^1H NMR (400 MHz, DMSO- d_6) δ ppm 11.25 (s, 1 H), 8.25 (t, J = 1.6 Hz, 1 H), 8.12 (s, 1 H), 7.63 (dd, J = 7.2, 1.6 Hz, 1 H), 7.35 (d, J = 8.8 Hz, 1 H), 7.20-7.10 (m, 3 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.42-3.36 (m, 2 H), 2.92 – 2.86 (m, 2 H), 2.46 –
- 10 2.42 (m, 2 H), 2.21 (s, 6 H), 1.30 (t, J = 7.2 Hz, 3 H).

The examples in Table 5 were prepared according to the general procedure described in Example 17.

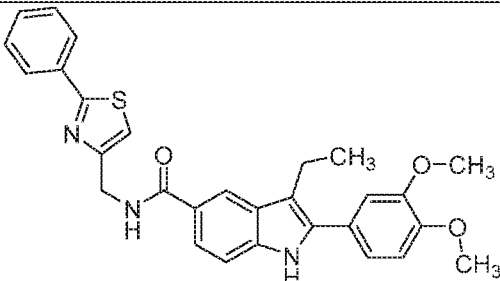
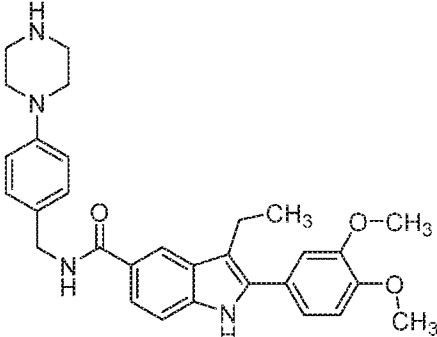
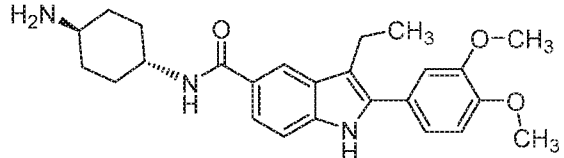
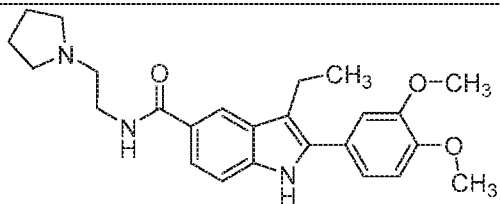
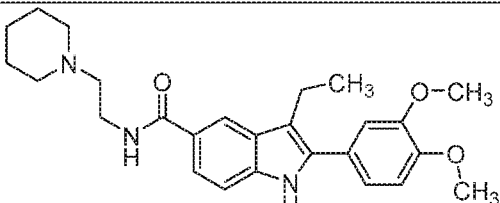
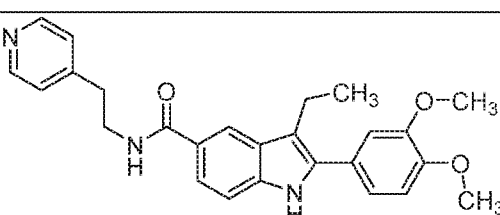
TABLE 5

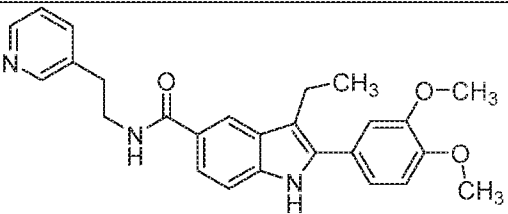
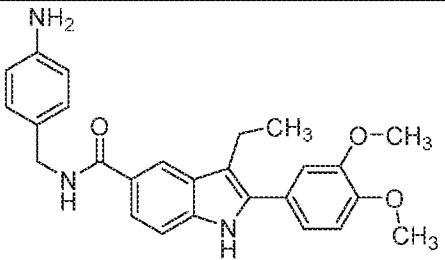
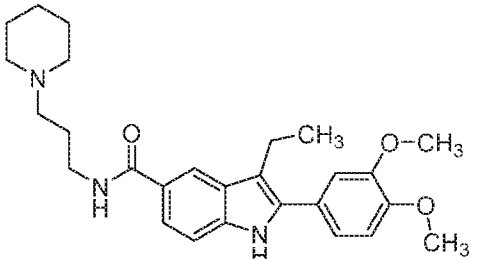
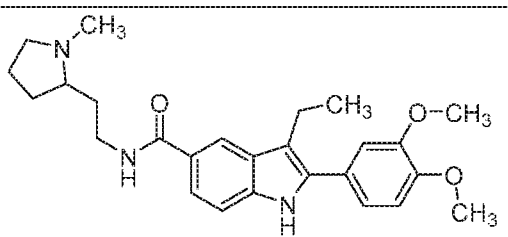
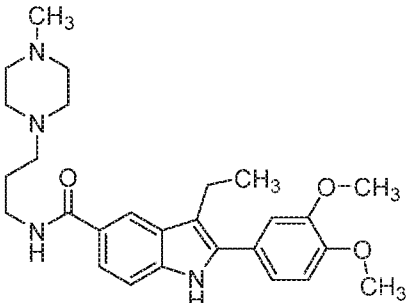
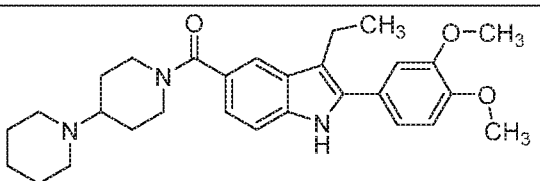
Ex. No.	Structure	Mol Wt.	LCMS MH ⁺	Ret Time (min)	HPLC Method
18		428.5	429	1.48	E
19		449.6	450.2	1.054	E
20		420.55	421.2	3.012	E
21		446.51	447	1.42	E

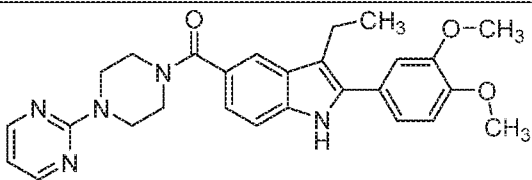
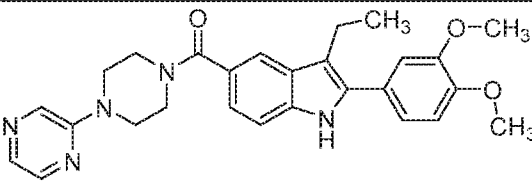
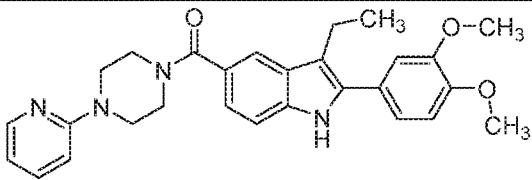
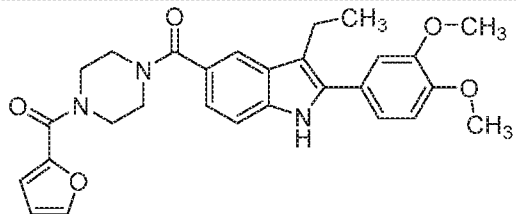
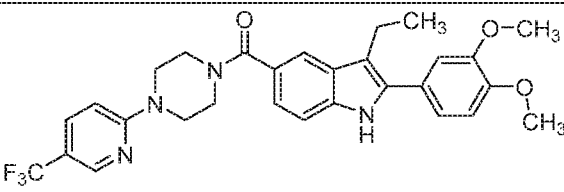
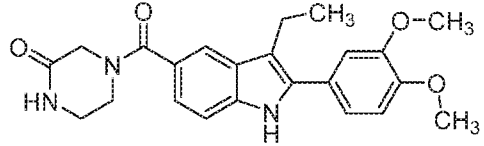
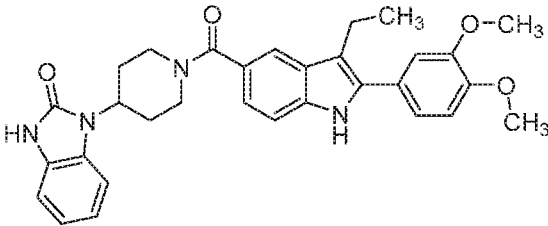
22		429.52	430.2	2.463	E
23		518.68	519.4	1.201	E
24		443.55	444	1.58	E
25		490.65	491.2	1.133	E
26		435.52	436.2	2.181	E
27		422.53	423.2	2.642	E
28		408.5	409.2	2.369	E

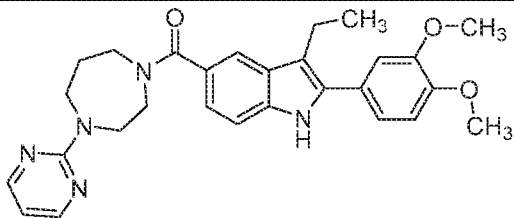
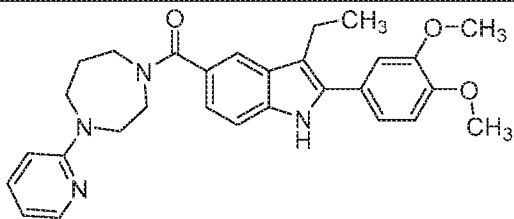
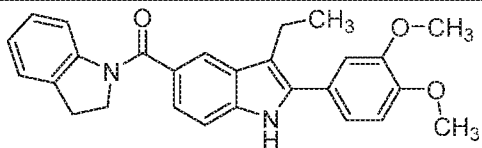
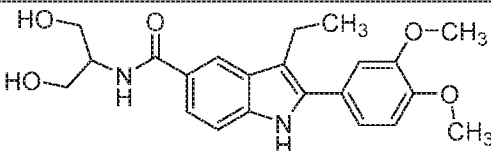
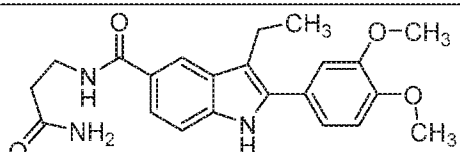
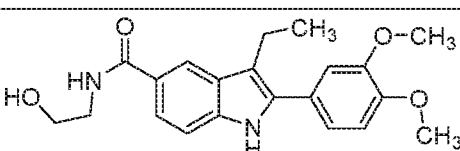
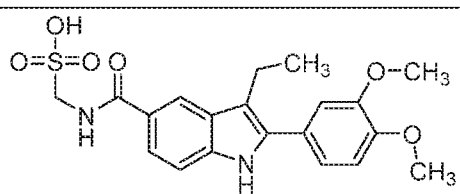
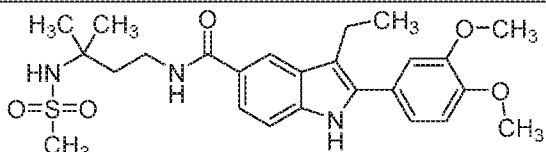
29		421.54	422.3	1.373	E
30		421.54	422.3	1.374	E
31		435.57	436.2	1.077	E
32		420.55	421.3	2.070	E
33		491.63	492.2	2.578	E
34		435.52	436.2	2.124	E
35		449.55	450.2	2.229	E
36		490.65	491.2	2.181	E

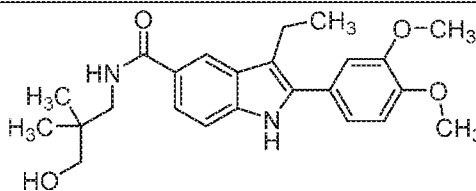
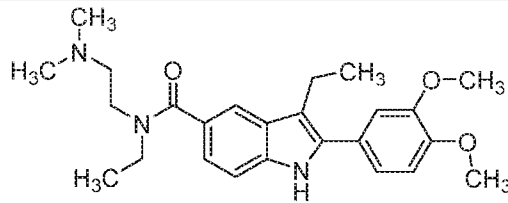
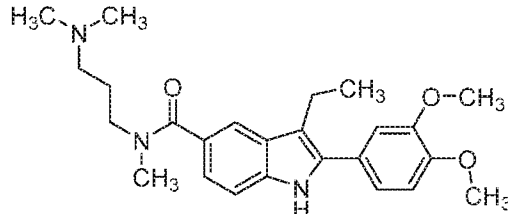
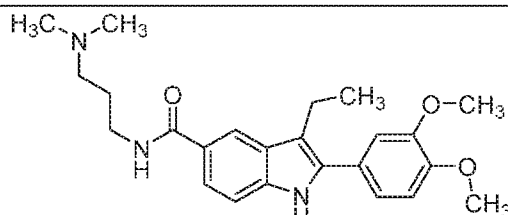
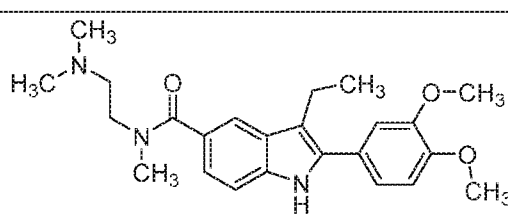
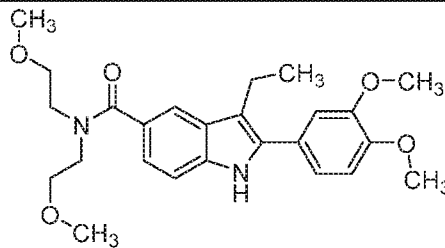
37		497.64	498.2	2.924	E
38		435.57	436.2	1.499	E
39		421.54	422.3	1.493	E
40		437.54	438.2	2.130	E
41		451.57	452.3	1.481	E
42		506.65	507.4	1.353	E
43		404.47	405.3	1.681	E
44		415.49	416.2	2.416	E

45		497.61	498.2	2.940	E
46		498.63	499.4	1.262	E
47		421.54	422.2	0.997	E
48		421.54	422.2	1.054	E
49		435.57	436.2	1.203	E
50		429.52	430	1.366	E

51		429.52	430	1.383	E
52		429.52	430.3	1.505	E
53		449.6	450.4	1.238	E
54		435.57	436.2	1.086	E
55		464.61	465.2	1.088	E
56		475.63	476.2	1.204	E

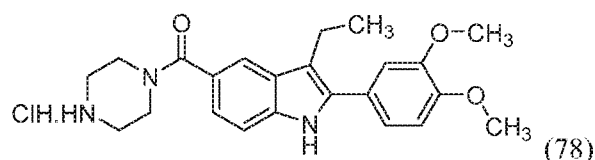
57		471.56	472	1.642	E
58		471.56	472	1.508	E
59		470.57	471	1.711	E
60		487.56	488.3	1.538	E
61		538.57	539.2	3.103	E
62		407.47	408.2	2.091	E
63		524.62	525.2	2.511	E

64		485.59	486.3	1.703	E
65		484.6	485.3	1.792	E
66		426.52	427.3	2.057	E
67		398.46	399.2	2.070	E
68		395.46	396	1.092	E
69		368.43	369.3	1.213	E
70		418.46	417	1.905	E
71		487.62	488	1.51	E

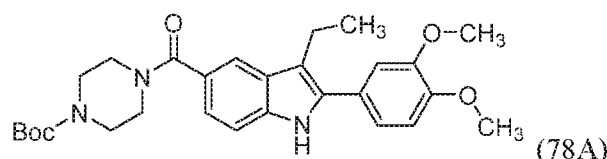
72		410.51	411.3	1.570	E
73		423.56	424.2	1.263	E
74		423.56	424.2	1.092	E
75		409.53	410.2	2.040	E
76		409.53	410.2	1.173	E
77		440.54	441.2	2.539	E

EXAMPLE 78

(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(piperazin-1-yl)methanone
hydrochloride



Intermediate 78A: tert-butyl 4-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carbonyl) piperazine-1-carboxylate



5 tert-Butyl 4-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carbonyl)piperazine-1-carboxylate (0.025 g, 0.048 mmol, 95 % yield) was prepared according to the procedure described in preparation of Intermediate 1E using 2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carboxylic acid (0.03 g, 0.092 mmol) and tert-butyl piperazine-1-carboxylate (0.021 g, 0.111 mmol) as a starting materials. LCMS retention time 2.1 min [G]. MS *m/z*:
10 494 [M+H]⁺.

Example 78:

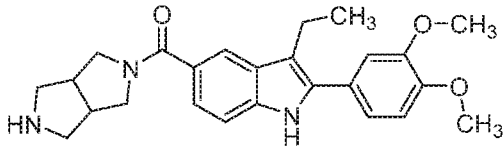
(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(piperazin-1-yl)methanone hydrochloride (0.035 g, 99 % yield) was prepared according to the general procedure
15 described in Example 1 using tert-butyl 4-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carbonyl)piperazine-1-carboxylate (40 mg, 0.081 mmol) as a starting intermediate. LCMS retention time 2.1 min [G]. MS *m/z*: 430 [M+H]⁺; (400 MHz, DMSO-d₆): δ ppm 11.25 (s, 1H), 7.56 (s, 1H), 7.36 (d, J = 11.20 Hz, 1H), 7.10-7.13 (m, 4H), 3.84 (d, J = 12.80 Hz, 6H), 3.51-3.75 (m, 4H), 2.85-2.87 (m, 4H), 2.72-2.77 (m, 2H), 2.60-2.62 (m,
20 4H), 1.82-1.89 (m, 5H), 1.80 (d, J = 8.00 Hz, 2H), 1.35-1.39 (m, 3H), 0.99 (d, J = 5.60 Hz, 6H).

The example in Table 6 was prepared according to the general procedure described in Example 78.

25

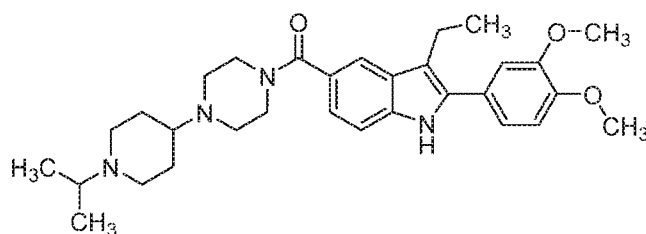
TABLE 6

Ex. No.	Structure	Mol Wt.	LCMS MH ⁺	Ret	HPLC Method
---------	-----------	---------	----------------------	-----	-------------

				Time (min)	
79		419.53	420	1.02	E

EXAMPLE 80

(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(1-isopropylpiperidin-4-yl)piperazin-1-yl)methanone

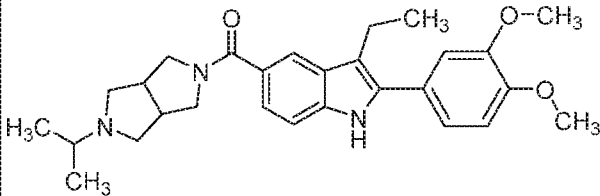


(80)

To a solution of (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(piperazin-1-yl)methanone (35mg, 0.089 mmol) in methanol (2 mL) were added 1-isopropylpiperidin-4-one (12.56 mg, 0.089 mmol), TEA (0.031 mL, 0.222 mmol) and acetic acid (5.09 μ L, 0.089 mmol) at room temperature. The mixture was stirred for 45 min, then sodium triacetoxyborohydride (18.85 mg, 0.089 mmol) was added and the mixture was stirred for another 12 h. Crude LC/MS showed formation of the product. The reaction mass was diluted with ethyl acetate, washed with water, followed by brine. The organic layer was separated and dried over sodium sulphate and concentrated to get crude compound. The crude material was purified by Preparative LCMS using method D2, the fractions containing the product were combined and dried using Genevac centrifugal evaporator to afford (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(1-isopropylpiperidin-4-yl)piperazin-1-yl)methanone (0.0027 g, 5.15 % yield) as a pale yellow solid. LCMS retention time 1.72 min [E], MS m/z : 519.2 (M+H); ^{1} H NMR (400 MHz, DMSO- d_6) δ ppm 11.25 (s, 1H), 7.69 (s, 1H), 7.14-7.18 (m, 4H), 3.86 (d, J = 7.20 Hz, 6H), 3.77-3.81 (m, 4H), 2.76-2.86 (m, 4H), 2.51-2.64 (m, 4H), 2.49 (d, J = 1.60 Hz, 3H), 1.26 (d, J = 7.60 Hz, 6H), 0.99-1.13 (m, 6H).

The example in Table 7 was prepared according to the general procedure for Example 80.

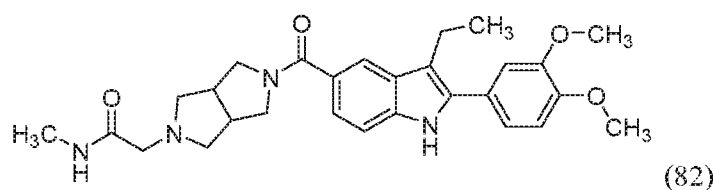
TABLE 7

Ex. No.	Structure	Mol Wt.	LCMS MH ⁺	Ret Time (min)	HPLC Method
81		461.61	462	1.28	E

5

EXAMPLE 82

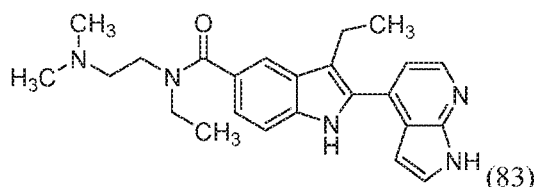
2-(5-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-methylacetamide



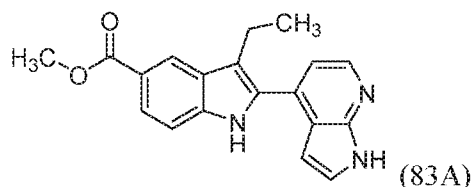
2-(5-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-methylacetamide (0.006 g, 25.4 % yield) was prepared according to the general procedure described in Example 6 using (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl) methanone (20 mg, 0.048 mmol) as the starting intermediate. LCMS retention time 1.02 min [E], MS *m/z*: 491 (M+H); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.25 (s, 1H), 7.69 (s, 1H), 7.61 (d, *J* = 4.80 Hz, 1H), 7.36 (d, *J* = 8.40 Hz, 1H), 7.25-7.28 (m, 1H), 7.14-7.18 (m, 3H), 3.86 (d, *J* = 7.20 Hz, 6H), 3.77-3.81 (m, 3H), 2.76-2.86 (m, 2H), 2.51-2.64 (m, 2H), 2.49 (d, *J* = 1.60 Hz, 3H), 1.27 (t, *J* = 7.60 Hz, 3H).

EXAMPLE 83

N-(2-(dimethylamino)ethyl)-N,3-diethyl-2-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-indole-5-carboxamide



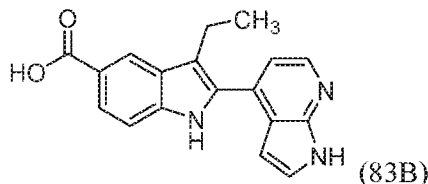
Intermediate 83A: Methyl 3-ethyl-2-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-indole-5-carboxylate



5 Methyl 3-ethyl-2-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-indole-5-carboxylate (0.18 g, 79 % yield) was prepared according to the general procedure described in preparation of Intermediate 1C using methyl 2-bromo-3-ethyl-1H-indole-5-carboxylate (0.2 g, 0.709 mmol) as a starting intermediate. LCMS retention time 2.34 min [D]. MS m/z : 320.2 (M+H).

10

Intermediate 83B: 3-ethyl-2-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-indole-5-carboxylic acid



3-ethyl-2-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-indole-5-carboxylic acid (0.12 g, 60 % yield) was prepared according to the general procedure described in the preparation of Intermediate 1D using methyl 3-ethyl-2-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-indole-5-carboxylate (0.18 g, 0.564 mmol) as the starting intermediate. LCMS retention time 1.61 min [D]. MS m/z : 306.2 (M+H).

Example 83:

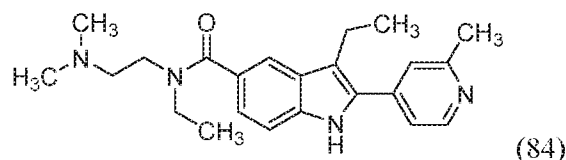
20 N-(2-(dimethylamino)ethyl)-N,3-diethyl-2-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-indole-5-carboxamide (0.006 g, 0.048 mmol, 30 % yield) was prepared according to the general procedure described in Example 17 using 3-ethyl-2-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-indole-5-carboxylic acid (15 mg, 0.049 mmol) as the starting intermediate. LCMS

retention time 1.06 min [G]. MS m/z : 404 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 11.83 (s, 1H), 11.37 (s, 1H), 8.32 (d, $J = 8.00$ Hz, 1H), 7.57 (d, $J = 4.00$ Hz, 1H), 7.44 (d, $J = 8.00$ Hz, 1H), 7.17 (d, $J = 8.00$ Hz, 2H), 6.53 (s, 1H), 1.13 (t, $J=7.03$ Hz, 3 H) 1.28 (t, $J=7.50$ Hz, 3 H) 2.57 (s, 3 H) 2.65-2.69 (m, 1 H) 2.95 (q, $J=7.53$ Hz, 2 H).

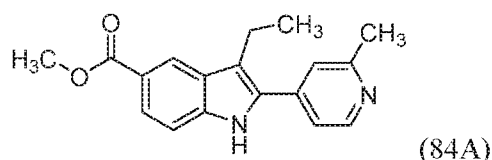
5

Example 84

N-(2-(dimethylamino)ethyl)-N,3-diethyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carboxamide



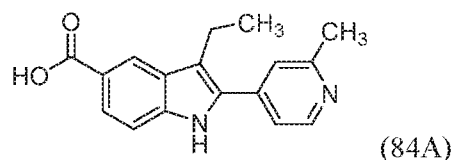
10 Intermediate 84A: methyl 3-ethyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carboxylate



Methyl 3-ethyl-2-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-indole-5-carboxylate (0.12 g, 62 % yield) was prepared according to the general procedure described in preparation of Intermediate 1C using methyl 2-bromo-3-ethyl-1H-indole-5-carboxylate (0.15 g, 0.532 mmol) as the starting intermediate. LCMS retention time 2.38 min [D]. MS m/z : 295.2 (M+H).

15

Intermediate 84B: 3-ethyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carboxylic acid



20 3-ethyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carboxylic acid (0.1 g, 62 % yield) was prepared according to the general procedure described in the preparation of Intermediate 1D using methyl 3-ethyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carboxylate (0.15g, 0.510 mmol) as the starting intermediate. LCMS retention time 1.61 min [D]. MS m/z : 281.2 (M+H).

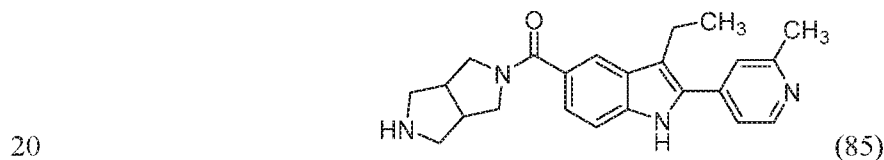
25

Example 84:

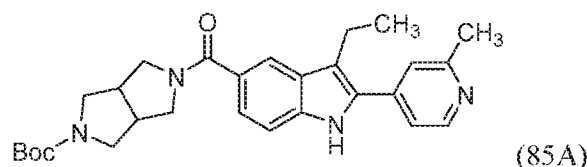
To a solution of 3-ethyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carboxylic acid (15 mg, 0.054 mmol) in DMF (2 mL) were added N1-ethyl-N2,N2-dimethylethane-1,2-diamine (12.44 mg, 0.107 mmol), DIPEA (0.028 mL, 0.161 mmol) and HATU (30.5 mg, 0.080 mmol) at room temperature. The mixture was stirred at same temperature for 12 h. Crude LCMS showed formation of product. The reaction was quenched with water (5 mL). White solid precipitated from the reaction mixture. The solids were filtered and dried to get crude product. The crude material was purified by Preparative LCMS using method D2, the fractions containing the product were combined and dried using Genevac centrifugal evaporator to afford N-(2-(dimethylamino)ethyl)-N,3-diethyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carboxamide (0.006 g, 0.007 mmol, 35 % yield) as an off white solid. LCMS retention time 1.78 min [E]. MS m/z : 379 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.56 (s, 1 H), 8.56 (d, J =5.27 Hz, 1 H), 7.66 (s, 1 H), 7.50 (s, 1 H), 7.42-7.46 (m, 2 H), 7.18-7.23 (m, 1 H), 2.95 (q, J =7.53 Hz, 2 H), 2.65-2.69 (m, 1 H), 2.57 (s, 3 H), 1.28 (t, J =7.50 Hz, 3 H), 1.13 (t, J =7.03 Hz, 3 H).

EXAMPLE 85

(3-ethyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone



Intermediate 85A: tert-butyl 5-(3-ethyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate



tert-Butyl 5-(3-ethyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate was prepared according to the general procedure described in preparation of Example 84 using 3-ethyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carboxylic acid (0.1 g, 62 % yield) as the starting intermediate. LCMS

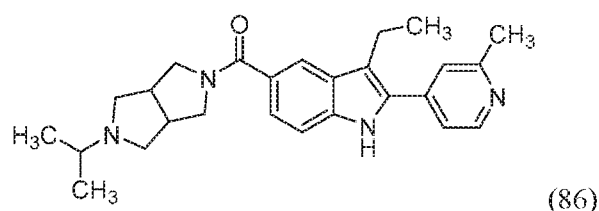
retention time 1.91 min [E]. MS m/z : 476 (M+H).

Example 85:

(3-Ethyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (0.003 g, 11 % yield) was prepared according to the general procedure described in Example 78 using tert-butyl 4-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carbonyl)piperazine-1-carboxylate (40 mg, 0.081 mmol) as the starting intermediate. LCMS retention time 1.54 min [G]. MS m/z : 375 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.55 (d, *J* = 5.20 Hz, 1H), 7.75 (s, 1H), 7.43 (t, *J* = 4.40 Hz, 1H), 7.40 -7.42 (m, 2H), 7.30 (q, *J* = 1.60 Hz, 1H), 4.11 (s, 2H), 3.87-3.99 (m, 3H), 3.10-3.28 (m, 3H), 2.83-2.86 (m, 2H), 2.65 (s, 3H), 2.31-2.49 (m, 2H), 1.91 (s, 2H), 1.27 (t, *J* = 7.60 Hz, 3H).

EXAMPLE 86

(3-ethyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)(5-isopropylhexahydropyrrolo[3,4c]pyrrol-2(1H)-yl)methanone

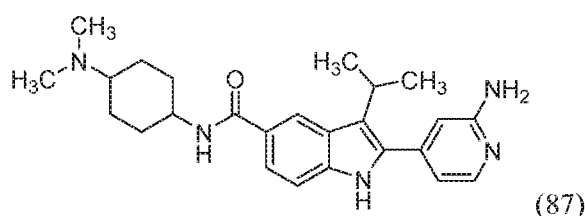


To a solution of (3-ethyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone hydrochloride (20 mg, 0.049 mmol) in methanol (5 mL) were added propan-2-one (7.07 mg, 0.122 mmol), titanium(IV) isopropoxide (0.036 mL, 0.122 mmol), and TEA (0.014 mL, 0.097 mmol) at room temperature. The reaction mixture was stirred at same temperature for 12 h. The reaction mass was cooled to ambient temperature, followed by the addition of sodium cyanoborohydride (7.65 mg, 0.122 mmol) and further stirred at room temperature for 5 h. The reaction mass was diluted with ethyl acetate and filtered through celite, and the filtrate was concentrated to get crude product. The crude material was purified by Preparative LCMS using method D2, the fractions containing the product were combined and dried using Genevac centrifugal evaporator to afford N-(2-(dimethylamino)ethyl)-N,3-diethyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carboxamide (0.007 g, 33% yield) as

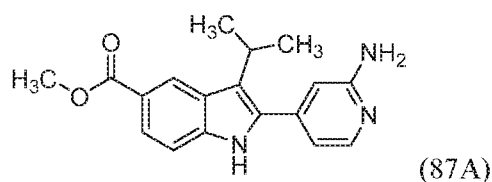
an off-white solid. LCMS retention time 1.93 min [G]. MS m/z : 417 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 8.55 (d, J = 5.20 Hz, 1H), 7.75 (s, 1H), 7.43 (t, J = 4.40 Hz, 1H), 7.40-7.42 (m, 2H), 7.30 (q, J = 1.60 Hz, 1H), 4.11 (s, 2H), 3.87-3.99 (m, 3H), 3.10-3.28 (m, 3H), 2.83-2.86 (m, 2H), 2.65 (s, 3H), 2.31-2.49 (m, 2H), 1.89 (s, 2H), 1.21 (t, J = 7.60 Hz, 3H), 1.02 (d, J = 7.20 Hz, 6H).

EXAMPLE 87

2-(2-aminopyridin-4-yl)-N-(4-(dimethylamino)cyclohexyl)-3-isopropyl-1H-indole-5-carboxamide

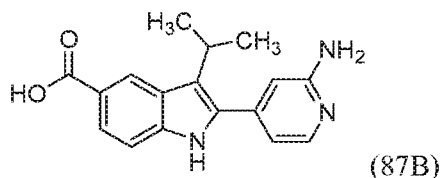


Intermediate 87A: Methyl 2-(2-aminopyridin-4-yl)-3-isopropyl-1H-indole-5-carboxylate



Methyl 2-(2-aminopyridin-4-yl)-3-isopropyl-1H-indole-5-carboxylate (350 mg, 67 % yield) was prepared according to the general procedure described in Intermediate 1C using methyl 2-bromo-3-isopropyl-1H-indole-5-carboxylate (500 mg, 1.688 mmol) as the starting intermediate. LCMS retention time 1.25 min [D]. MS m/z : 310.2 (M+H).

Intermediate 87B: 2-(2-aminopyridin-4-yl)-3-isopropyl-1H-indole-5-carboxylic acid



2-(2-aminopyridin-4-yl)-3-isopropyl-1H-indole-5-carboxylic acid (250 mg, 0.846 mmol, 82 % yield) was prepared according to the general procedure described in Intermediate 1D using methyl 2-(2-aminopyridin-4-yl)-3-isopropyl-1H-indole-5-carboxylate (320 mg, 1.034 mmol) as the starting intermediate. LCMS retention time

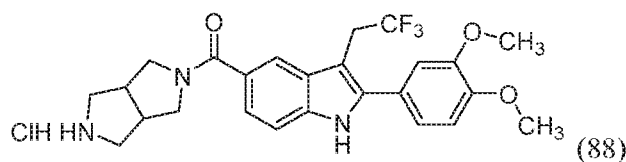
0.61 min [D]. MS m/z : 296.3 (M+H).

Example 87:

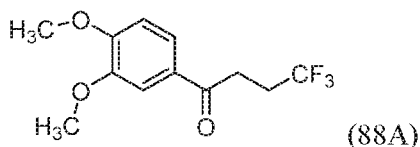
2-(2-Aminopyridin-4-yl)-N-(4-(dimethylamino)cyclohexyl)-3-isopropyl-1H-indole-5-carboxamide (4.7 mg, 0.011 mmol, 11% yield) was prepared according to the general procedure described in Example 17 using 2-(2-aminopyridin-4-yl)-3-isopropyl-1H-indole-5-carboxylic acid (30 mg, 0.102 mmol) as the starting intermediate. LCMS retention time 0.84 min [G]. MS m/z : 420 [M+H]⁺; ¹H NMR (400 MHz, DMSO- d_6) δ ppm 11.30 (s, 1H), 8.26 (s, 1H), 8.11 (d, $J=7.5$ Hz, 1H), 8.01 (d, $J=5.0$ Hz, 1H), 7.66 (dd, $J=8.5, 1.5$ Hz, 1H), 7.34 (d, $J=8.5$ Hz, 1H), 6.66-6.55 (m, 2H), 6.06 (s, 2H), 2.81 (d, $J=11.0$ Hz, 2H), 2.73-2.62 (m, 1H), 2.25-2.10 (m, 2H), 1.85 (s, 6H), 1.65-1.57 (m, 2H), 1.45 (d, $J=7.0$ Hz, 4H), 0.98 (d, $J=6.5$ Hz, 6H).

EXAMPLE 88

(2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indol-5-yl)(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone hydrochloride



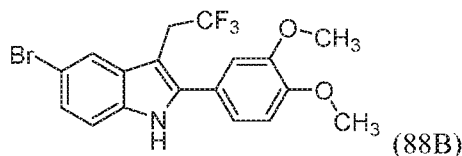
Intermediate 88A: 1-(3,4-dimethoxyphenyl)-4,4,4-trifluorobutan-1-one



To a solution of 4,4,4-trifluorobutanoic acid (10 g, 70.4 mmol) in toluene (100 mL) at 0 °C was added 1,2-dimethoxybenzene (9.00 mL, 70.4 mmol) portion wise. The suspension was stirred for 10 min at 0 °C, then polyphosphoric acid (141 mmol) was added. The reaction mixture was heated at 75 °C for 16 h. The reaction was quenched with water (50 mL). The reaction mixture extracted with ethyl acetate (3 x 100 mL), the combined organic extracts was dried with sodium sulfate and concentrated under reduced pressure to afford the crude compound (15.2 g) a colorless liquid. The crude material was purified with flash chromatography, using 120 g silica column, compound was eluted in

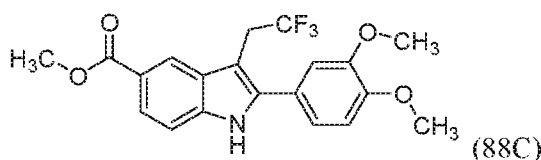
15% ethyl acetate/petroleum ether, the fractions were collected and concentrated to afford 1-(3,4-dimethoxyphenyl)-4,4,4-trifluorobutan-1-one (8 g, 30.5 mmol, 43.3 % yield) as an oil. LCMS retention time 2.305 min [D]. MS m/z: 263.2 (M+H).

- 5 Intermediate 88B: 5-bromo-2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indole



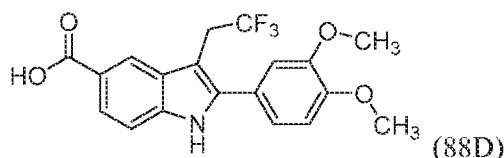
- To a mixture of (4-bromophenyl)hydrazine (1.070 g, 5.72 mmol), 1-(3,4-dimethoxyphenyl)-4,4,4-trifluorobutan-1-one (1.5 g, 5.72 mmol) and (4-bromophenyl)hydrazine (1.070 g, 5.72 mmol) at room temperature was added polyphosphoric acid (3.40 mL, 5.72 mmol) portion wise. The suspension was stirred for 10 minutes at room temperature, then stirred at 155 °C for 10-20 min. Next, the reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts was dried with sodium sulfate and concentrated under reduced pressure to get crude compound (15.2 g). The crude material was purified by flash chromatography using a 40 g silica column, compound was eluted in 20-25% ethyl acetate/Pet-Ether, the fractions were collected and concentrated to afford 5-bromo-2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indole (900 mg, 2.173 mmol, 38.0% yield) as a brown solid. LC retention time 2.62 min [D]. MS m/z: 413.0 (M-H).

- 20 Intermediate 88C: Methyl 2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indole-5-carboxylate



- Methyl 2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indole-5-carboxylate (650 mg, 1.652 mmol, 86 % yield) was prepared according to the general procedure described in Intermediate 1A using 5-bromo-2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indole (800 mg, 1.931 mmol) as the starting intermediate. LCMS retention time 1.0 min [D]. MS m/z: 394.1 (M+H).

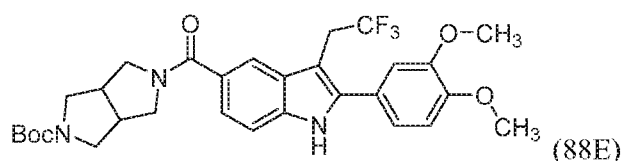
Intermediate 88D: 2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indole-5-carboxylic acid



2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indole-5-carboxylic acid (160 mg, 0.422 mmol, 83 % yield) was prepared according to the general procedure described in Intermediate 1D using 5-bromo-methyl 2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indole-5-carboxylate (200 mg, 0.508 mmol) as the starting intermediate. LCMS retention time 0.86 min [D]. MS m/z: 378.0 (M-H).

10

Intermediate 88E: tert-Butyl 5-(2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indole-5-carbonyl) hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate



Tert-butyl 5-(2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (162 mg, 0.282 mmol, 63.0 % yield) was prepared according to the general procedure described in Intermediate 1E, using 2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indole-5-carboxylic acid (170 mg, 0.448 mmol) as the starting intermediate. LCMS retention time 0.99 min [D]. MS /z: 574.3 (M+H).

20

Example 88:

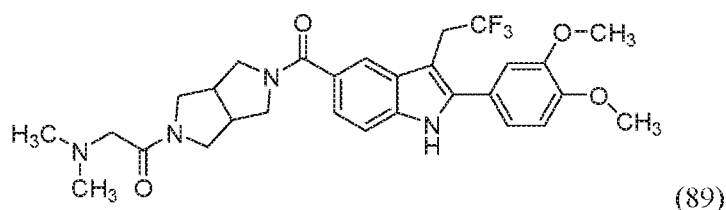
(2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indol-5-yl) (hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone hydrochloride (110 mg, 0.216 mmol, 74 % yield) was prepared according to the general procedure described in Example 1, using tert-butyl 5-(2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (168 mg, 0.293 mmol) as the starting intermediate. LCMS retention time 0.71 min [F]. MS m/z: 474.3 (M+H); ¹H

NMR (400 MHz, Methanol- d_4) δ ppm 7.85 (s, 1 H), 7.49 (dd, J = 8.4, 0.4 Hz, 1 H), 7.40 (d, J = 8.4 Hz, 1 H), 7.23-7.21 (m, 2H), 7.13 (d, J = 8.4 Hz, 1 H), 3.98-3.95 (m, 2 H), 3.93 (s, 6 H), 3.80-3.65 (m, 4 H), 3.62-3.51 (m, 2 H), 3.24-3.15 (m, 4 H).

5

EXAMPLE 89

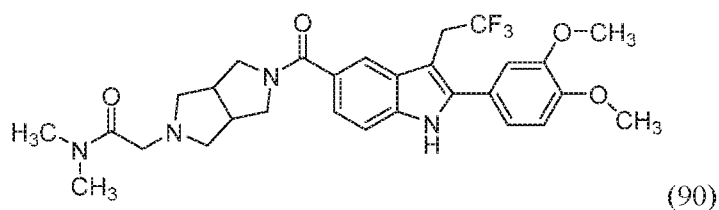
1-(5-(2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indole-5-carbonyl)
hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-(dimethylamino)ethan-1-one



1-(5-(2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indole-5-carbonyl)
10 hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-(dimethylamino)ethan-1-one (15 mg) was
prepared according to the general procedure described in Example 17, using (2-(3,4-
dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indol-5-yl)(hexahydro pyrrolo[3,4-c]
pyrrol-2(1H)-yl)methanone hydrochloride (20 mg, 0.039 mmol) as the starting
intermediate. LCMS retention time 0.83 min [E]. MS m/z : 559.3 (M+H). ^1H NMR (400
15 MHz, DMSO- d_6) δ ppm 11.65 (s, 1H), 7.80 (s, 1 H), 7.42 (d, J = 8.4 Hz, 1 H), 7.33 (d, J =
8.4 Hz 1 H), 7.21-7.13 (m, 3 H), 3.85 (s, 6 H), 3.78-3.74 (m, 2 H), 3.65-3.51 (m, 2 H),
3.10-2.91 (m, 4 H), 2.25-2.18 (m, 6 H).

EXAMPLE 90

20 2-(5-(2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indole-5-carbonyl)
hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N,N-dimethylacetamide



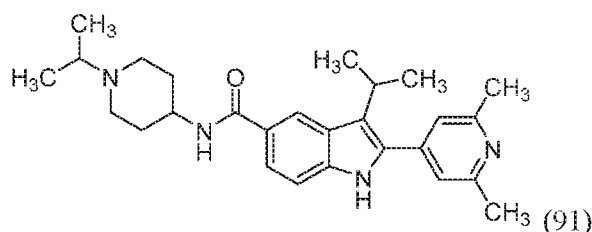
2-(5-(2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indole-5-
carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N,N-dimethylacetamide (15 mg) was
25 prepared according to the procedure described in Example 6 using (2-(3,4-

dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indol-5-yl)(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone hydrochloride (20 mg, 0.039 mmol) as the starting intermediate.

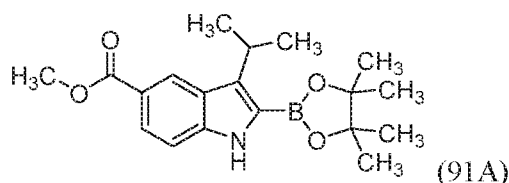
LCMS retention time 1.467 min [E]. MS m/z : 559.4 (M+H); ^1H NMR (400 MHz, DMSO- d_6) δ ppm 11.63 (s, 1H), 7.74-7.77 (m, 1 H) 7.40-7.44 (m, 1 H) 7.26-7.30 (m, 1 H) 7.18-7.22 (m, 2 H) 7.16 (s, 1 H) 3.85 (d, $J=3.70$ Hz, 8 H) 3.71-3.80 (m, 2H) 3.21-3.24 (m, 2 H) 3.02 (s, 3 H) 2.81 (s, 5 H).

EXAMPLE 91

2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-N-(1-isopropylpiperidin-4-yl)-1H-indole-5-carboxamide



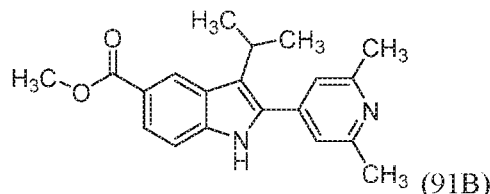
Intermediate 91A: Methyl 3-isopropyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-5-carboxylate



TEA (2.131 mL, 15.19 mmol) and pinacolborane (3.95 mL, 25.3 mmol) were added to a degassed solution of methyl 2-bromo-3-isopropyl-1H-indole-5-carboxylate (1.5 g, 5.06 mmol), bis(benzonitrile)palladium(II) chloride (0.194 g, 0.506 mmol) and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (0.208 g, 0.506 mmol) in dioxane (25 mL). The resulting mixture was stirred at 80 °C for 1 h in a sealed tube. The reaction mixture was quenched with ice cold water and diluted with ethyl acetate, filtered and washed with excess ethyl acetate. Combined organic layers were washed with water, brine, dried over sodium sulphate and evaporated to get crude compound. The crude material was purified by column chromatography using 40 g silica column, the compound was eluted with 25% ethyl acetate in petroleum ether, the fraction was collected and concentrated to afford methyl 3-isopropyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

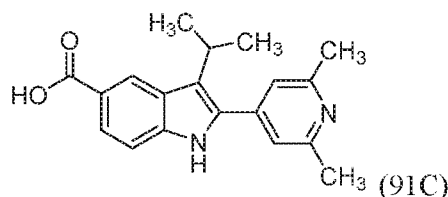
yl)-1H-indole-5-carboxylate (1.0 g, 2.91 mmol, 57.5 % yield) as an off-white solid.
LCMS retention time 1.44 min. MS m/z : 344.3 (M+H).

Intermediate 91B: Methyl 2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indole-5-
5 carboxylate



A stirred solution of methyl 3-isopropyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-5-carboxylate (1.00 g, 2.91 mmol), 4-bromo-2,6-dimethylpyridine (1.084 g, 5.83 mmol) and potassium phosphate tribasic (1.855 g, 8.74
10 mmol) in dioxane (15.00 mL) and water (5.00 mL) was degassed with nitrogen for 10 min. Next, PdCl₂(dppf)-CH₂Cl₂ adduct (0.238 g, 0.291 mmol) was added and the reaction mixture was stirred at 90 °C for 2 h. Crude LCMS showed formation of product and no starting material. The reaction mixture was diluted with water (10 mL) and DCM (30 mL). Both the layers were separated and the aqueous layer was extracted with DCM
15 (2 X 30 mL), the combined organic extracts was washed with brine (10 mL), dried (Na₂SO₄) and concentrated to get crude compound. The crude material was purified by column chromatography using 24 g silica column, compound was eluted in 80 % ethyl acetate in hexane, the fractions were collected and concentrated to afford methyl 2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indole-5-carboxylate (0.860 g, 2.67 mmol, 92 %
20 yield) as a off-white solid. LCMS retention time 1.27 min [G]. MS m/z : 323.6 (M+H).

Intermediate 91C: 2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indole-5-carboxylic acid



To a solution of methyl 2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indole-5-
25 carboxylate (0.250 g, 0.775 mmol) in THF (4.00 mL), MeOH (2.000 mL) and water (1.000 mL) was added lithium hydroxide (0.093 g, 3.88 mmol) at room temperature. The

mixture was stirred at 75 °C for 16 h. Crude LCMS showed formation of product and no starting material. The reaction mass was concentrated to remove THF and MeOH, the residue was diluted with water (2 mL), then brought to neutral pH using 0.1 M HCl. The precipitated solid was filtered and washed with water, dried under vacuum to afford 2-
 5 (2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indole-5-carboxylic acid (0.204 g, 0.662 mmol, 85 % yield) as an off-white solid. LCMS retention time 0.69 min [G]. MS m/z: 309.3 (M+H).

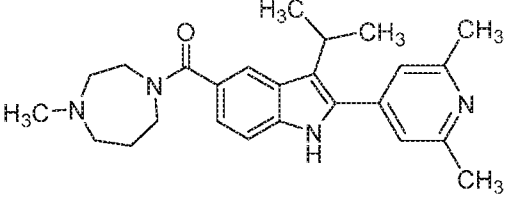
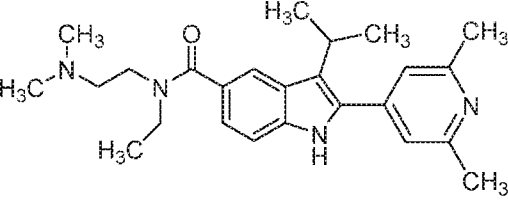
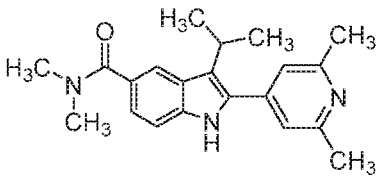
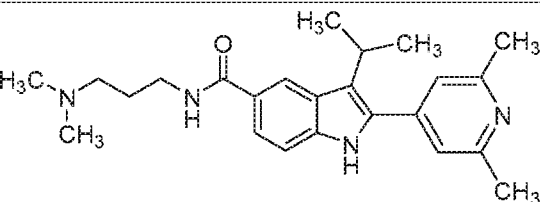
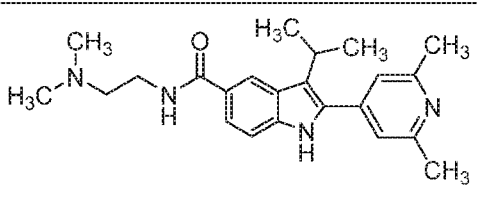
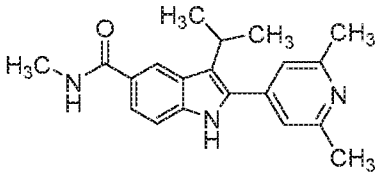
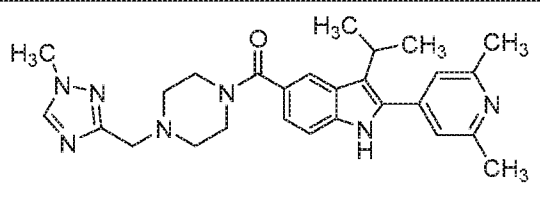
Example 91:

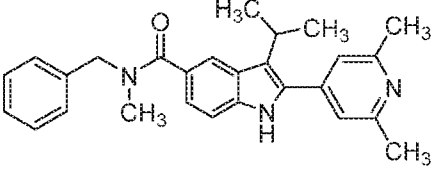
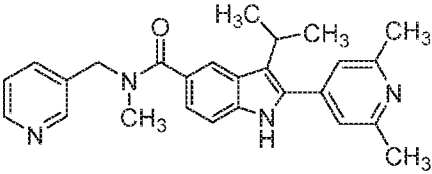
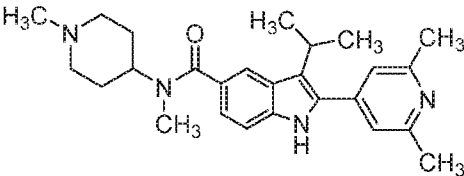
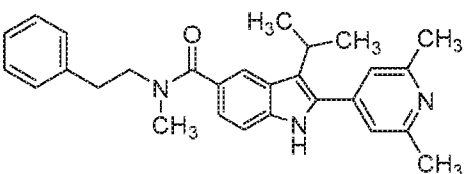
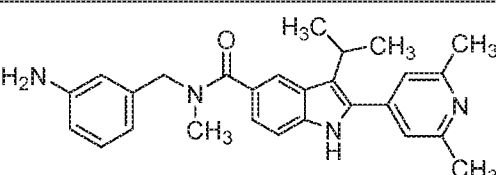
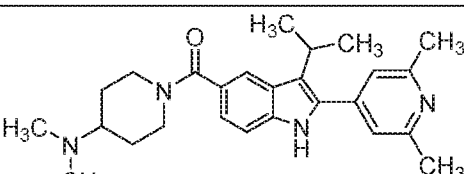
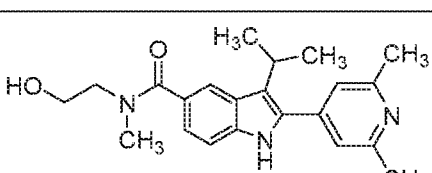
10 To a solution of 2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indole-5-carboxylic acid, HCl (0.050 g, 0.145 mmol) in DMF (1.500 mL) were added 1-isopropylpiperidin-4-amine (0.031 g, 0.217 mmol), TEA (0.2 mL, 1.435 mmol) and HATU (0.110 g, 0.290 mmol) at room temperature. The mixture was stirred at the same temperature for 3 h. Crude LCMS showed formation of product and no starting material. The reaction mass
 15 was concentrated to get crude material. The crude material was purified by Preparative LCMS purification using method D2, fractions containing the product were combined and dried using Genevac centrifugal evaporator to afford 2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-N-(1-isopropylpiperidin-4-yl)-1H-indole-5-carboxamide (0.055 g, 0.123 mmol, 85 % yield) as a pale solid. LCMS retention time 1.425 min [E]. MS m/z: 433.3 (M+H);
 20 ¹H NMR (400 MHz, CD₃OD) δ ppm 8.37 (d, J = 0.4 Hz, 1 H), 7.66 (dd, J = 8.4, 1.6 Hz, 1 H), 7.42 (dd, 8.8, 0.4 Hz, 1 H), 7.25 (s, 2 H), 4.17-4.11 (m, 1 H), 3.48-3.34 (m, 4 H), 3.16-2.98 (m, 2 H), 2.58 (s, 6 H), 2.28 -2.20 (m, 2 H), 1.98-1.88 (m, 2 H), 1.53 (d, J = 7.2 Hz, 6 H), 1.33 (d, J = 6.4 Hz, 6 H).

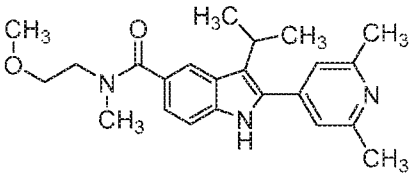
25 The examples in Table 8 were prepared according to the general procedure described in Example 91.

TABLE 8

Ex. No.	Structure	Mol Wt.	LCMS MH ⁺	Ret Time (min)	HPLC Method
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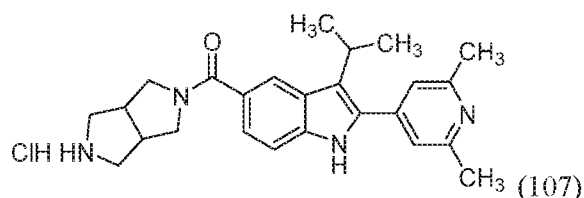
92		404.56	405.2	0.942	F
93		406.57	407.3	1.56	E
94		335.45	336.2	1.725	E
95		392.55	393.2	1.34	E
96		378.52	379.2	1.38	E
97		321.42	322.2	1.569	E
98		471.61	472.4	1.36	QC- ACN- AA-XB

99		411.55	412.2	2.1	QC- ACN- AA-XB
100		412.54	413.1	0.95	QC- ACN- TFA-XB
101		418.59	419.2	0.95	QC- ACN- TFA-XB
102		425.58	426.2	1.58	QC- ACN- TFA-XB
103		426.56	427.4	1.03	QC- ACN- TFA-XB
104		418.59	419.3	0.92	QC- ACN- TFA-XB
105		365.48	366.2	1.47	QC- ACN- AA-XB

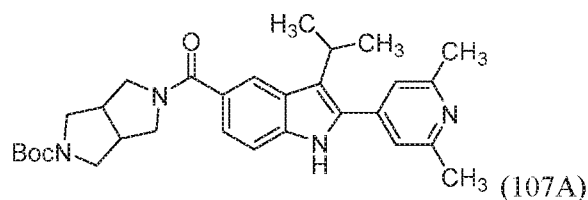
106		379.5	380.2	1.72	QC- ACN- AA-XB
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EXAMPLE 107

(2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indol-5-yl)(hexahydropyrrolo[3,4-c]pyrrole-2(1H)-yl)methanone, HCl



Intermediate 107A: tert-butyl 5-(2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indole-5-carbonyl)hexahydro pyrrolo[3,4-c]pyrrole-2(1H)-carboxylate



To a solution of 2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indole-5-carboxylic acid, HCl (0.060 g, 0.174 mmol) in DMF (2.00 mL) were added tert-butyl hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (0.055 g, 0.261 mmol), TEA (0.2 mL, 1.435 mmol) and HATU (0.132 g, 0.348 mmol) at room temperature. The reaction mixture was stirred at same temperature for 3 h. Crude LCMS showed formation of product and no starting material. The reaction was quenched with water (5 mL). The reaction mixture was extracted with DCM (2 X 10 mL), the combined organic extracts were dried (Na₂SO₄) and concentrated to afford crude tert-butyl 5-(2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate as a gummy solid. LCMS retention time 0.78 min [G]. MS *m/z*: 503.2 [M+H]⁺.

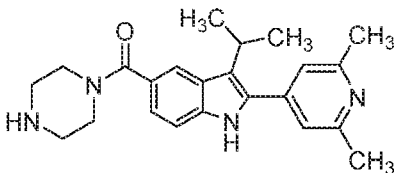
Example 107:

To a solution of tert-butyl 5-(2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indole-

5-carbonyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (0.087 g, 0.174 mmol) in dioxane (1.0 mL) was added 4 M HCl in dioxane (1 mL) at room temperature. The mixture was stirred at the same temperature for 2 h. Crude LCMS showed formation of product. The reaction mass was concentrated to get crude compound. The crude material was purified by Prep HPLC method D2, fractions containing the product were combined and dried using Genevac centrifugal evaporator to afford (2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indol-5-yl)(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone, 2 HCl (0.065 g, 0.137 mmol, 78 % yield) as a pale solid. LCMS retention time 1.323 min [E]. MS *m/z*: 403.2 [M+H]⁺; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.13 (d, *J* = 0.4 Hz, 1 H), 7.75 (s, 2 H), 7.56-7.53 (m, 1 H), 7.49-7.47 (m, 1 H), 4.00-4.93 (m, 2 H), 3.76-3.52 (m, 6 H), 3.28-3.17 (m, 3 H), 2.80 (s, 6 H), 1.58 (d, *J* = 6.8 Hz, 6 H).

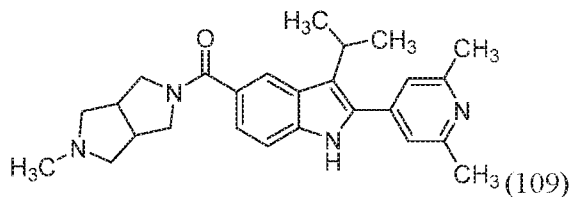
The example in Table 9 was prepared according to the general procedure described in Example 107.

TABLE 9

Ex. No.	Structure	Mol Wt.	LCMS MH ⁺	Ret Time (min)	HPLC Method
108		376.5	377.1	1.12	QC-ACN-AA-XB

EXAMPLE 109

(2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indol-5-yl)(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone

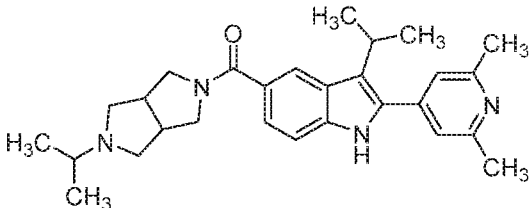


To a solution of (2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indol-5-yl)(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone, 2 HCl (0.048 g, 0.101 mmol) in

MeOH (3.00 mL) was added formaldehyde in water (0.5 mL, 7.26 mmol). The reaction mixture was cooled to 0 °C and acetic acid (0.20 mL, 3.49 mmol) was added. The reaction mixture was stirred at room temperature for 3 h. Again the reaction mixture was cooled to 0 °C and sodium cyanoborohydride (0.032 g, 0.505 mmol) was added. The reaction was allowed to sit at room temperature for 16 h. Crude LCMS showing no starting material and formation of product. The reaction was quenched with water (5 mL). The reaction mixture was concentrated to remove methanol, extracted with 10% MeOH in DCM (2 X 10 mL), the combined organic extracts was dried (Na₂SO₄) and concentrated to get crude compound. The crude material was purified by Prep HPLC method D2, fractions containing the product were combined and dried using Genevac centrifugal evaporator to afford (2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indol-5-yl) (5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (0.0181 g, 0.043 mmol, 42.5 % yield) as a pale solid. LCMS retention time 1.371 min [E]. MS *m/z*: 417.2 [M+H]⁺; ¹H NMR (400 MHz, CD₃OD) δ ppm 7.99 (d, J = 1.2 Hz, 1 H), 7.44 (d, J = 8.4 Hz, 1 H), 7.33 (dd, J = 8.8, 1.6 Hz, 1 H), 7.24 (s, 2 H), 3.88-3.81 (m, 2 H), 3.78-3.55 (m, 2 H), 3.48-3.40 (m, 1 H), 3.14-2.92 (m, 4 H), 2.58-2.52 (m, 8 H), 2.49 (s, 3 H), 1.51 (d, J = 7.2 Hz, 6 H).

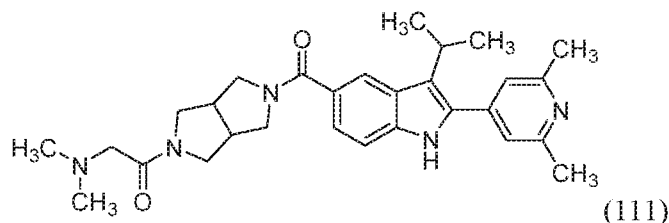
The example in Table 10 was prepared according to the general procedure described in Example 109

TABLE 10

Ex. No.	Structure	Mol Wt.	LCMS MH ⁺	Ret Time (min)	HPLC Method
110		444.62	445.3	1.463	E

EXAMPLE 111

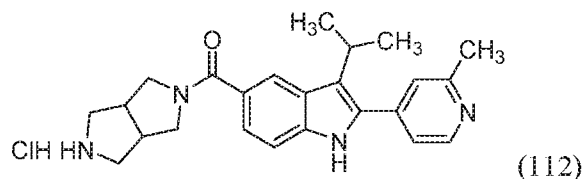
2-(dimethylamino)-1-(5-(2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethanone



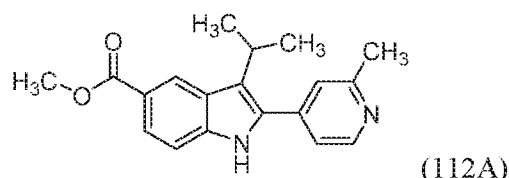
To a solution of (2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indol-5-yl)
 5 (hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone, 2 HCl (0.025 g, 0.053 mmol) and
 2-(dimethylamino)acetic acid (8.13 mg, 0.079 mmol) in DMF (2.00 mL) were added TEA
 (0.1 mL, 0.717 mmol) and HATU (0.040 g, 0.105 mmol) at room temperature. The
 reaction mixture was stirred at same temperature for 2 h. Crude LCMS showed formation
 of product and no starting material. The crude material was purified by Prep HPLC
 10 method D2, fractions containing the product were combined and dried using Genevac
 centrifugal evaporator to afford 2-(dimethylamino)-1-(5-(2-(2,6-dimethylpyridin-4-yl)-3-
 isopropyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethanone
 (0.0138 g, 0.027 mmol, 52 % yield) as a pale solid. LCMS retention time 1.393 min [E].
 MS *m/z*: 488.3 [M+H]⁺; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.02 (s, 1 H), 7.44 (d, J =
 15 8.4 Hz, 1 H), 7.35 (dd, J = 8.8, 1.6 Hz, 1 H), 7.24 (s, 2 H), 3.98 – 3.90 (m, 2 H), 3.89-3.51
 (m, 8 H), 3.49-3.40 (m, 3 H), 2.57 (s, 6 H), 2.53 (bs, 6 H), 1.94 (s, 6 H), 1.50 (d, J = 7.2
 Hz, 6 H).

EXAMPLE 112

20 (hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(3-isopropyl-2-(2-methyl pyridin-4-yl)-1H-
 indol-5-yl)methanone, HCl

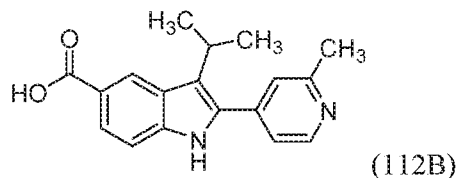


Intermediate 112A: Methyl 3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carboxylate



A solution of methyl 2-bromo-3-isopropyl-1H-indole-5-carboxylate (0.400 g, 1.351 mmol), 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.621 g, 2.84 mmol) and cesium carbonate (1.320 g, 4.05 mmol) in dioxane (10.00 mL) and water (2.500 mL) was degassed for 30 min. Next, Pd(Ph₃P)₄ (0.312 g, 0.270 mmol) was added and the reaction mixture was stirred at 90 °C for 16 h. Crude LCMS showed formation of product and no starting material. The reaction was quenched with water (5 mL). The reaction mixture was extracted with DCM (2 X 40 mL), the combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄) and concentrated to get crude compound. The crude material was purified by column chromatography using 40 g silica column, compound was eluted in ethyl acetate, the fractions were collected and concentrated to afford methyl 3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carboxylate (0.550 g, 0.856 mmol, 63 % yield) as a gummy solid. LCMS retention time 0.76 min [G]. MS m/z: 309.6 (M+H);

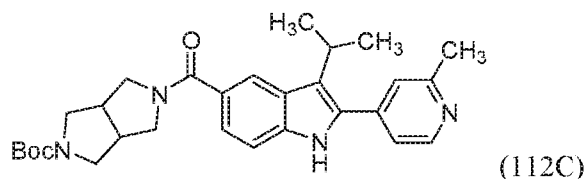
Intermediate 112B: 3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carboxylic acid



To a solution of methyl 3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carboxylate (0.552 g, 0.859 mmol) in THF (8.00 mL), MeOH (4.00 mL) and water (2.000 mL) was added lithium hydroxide (0.103 g, 4.30 mmol) at room temperature. The reaction mixture was stirred at 75 °C for 16 h. Crude LCMS showed formation of product and no starting material. The reaction mass was concentrated. The slurry was dissolved in water (10 mL) and the aqueous layer was washed with EtOAc (20 mL). The aqueous layer was acidified with 1.5 N HCl at 0 °C. The resulting precipitated solid was filtered, washed with water, then dried under vacuum to afford 3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carboxylic acid (0.216 g, 0.734 mmol, 85 % yield) as a

yellow solid. LCMS retention time 0.60 min [G]. MS m/z : 295.1 (M+H).

Intermediate 112C: tert-butyl 5-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carbonyl)hexahydropyrrolo [3,4-c]pyrrole-2(1H)-carboxylate



To a solution of 3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carboxylic acid (0.200 g, 0.679 mmol) and tert-butyl hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (0.144 g, 0.679 mmol) in DCM (4.00 mL) and DMF (4.00 mL) was added EDC (0.130 g, 0.679 mmol) at room temperature. The reaction mixture was stirred at same temperature for 4 h. Crude LCMS showed formation of product. The reaction was quenched with water (5 mL). The reaction mixture was extracted with 10% MeOH in DCM (2 x 20 mL). The combined organic extracts was dried (Na₂SO₄) and concentrated to get crude compound. The crude material was purified by column chromatography using 12 g silica column. The compound was eluted in ethyl acetate, the fraction was collected and concentrated to afford tert-butyl 5-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (0.201 g, 0.411 mmol, 60.5 % yield) as a white solid. LCMS retention time 0.88 min [G]. MS m/z : 489.3 (M+H).

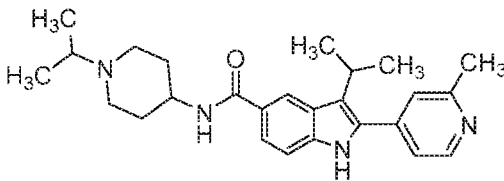
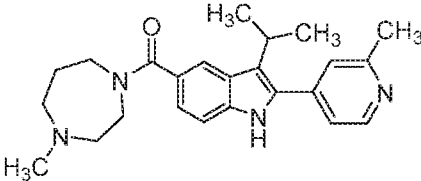
20 Example 112:

To a solution of tert-butyl 5-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (0.200 g, 0.409 mmol) in dioxane (2 mL) was added 4N HCl in dioxane (1.00 mL, 4.00 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. Crude LCMS showed formation of product and no starting material. The reaction mass was concentrated and the residue was triturated with diethyl ether (2 X 5 mL) to afford (hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)methanone, HCl (0.162 g, 0.357 mmol, 87 % yield) as a yellow color solid. LCMS retention time 1.74 min [E]. MS m/z : 389.2 [M+H]⁺; ¹H NMR (400 MHz, CD₃OD) δ ppm 11.52 (s, 0.4 H,

exchanged with CD₃OD), 8.69 (d, J = 6.8 Hz, 1 H), 8.14 (s, 1 H), 8.00-7.97 (m, 2 H), 7.56-7.48 (m, 2 H), 3.98-3.91 (m, 2 H), 3.78-3.51 (m, 5 H), 3.34-3.16 (m, 4 H), 2.85 (s, 3 H), 1.58 (d, J = 7.2 Hz, 6 H).

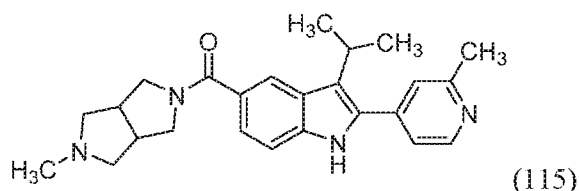
- 5 The examples in Table 11 were prepared according to the general procedure described for Example 112.

TABLE 11

Ex. No.	Structure	Mol Wt.	LCMS MH ⁺	Ret Time (min)	HPLC Method
113		418.59	419	1	E
114		390.53	391.3	0.536	F

EXAMPLE 115

- 10 (3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone



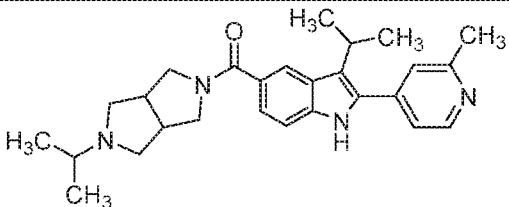
- 15 To a solution of (hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)methanone hydrochloride (0.021 g, 0.049 mmol) in MeOH (2.50 mL) were added formaldehyde in water (0.1 mL, 1.271 mmol) and acetic acid (0.1 mL, 1.747 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 6 h. Again the reaction mixture was cooled to 0 °C and sodium borohydride (5.61 mg, 0.148 mmol) was added portion wise. The reaction mixture was stirred at room

temperature for 16 h. Crude LCMS showed formation of product and no starting material. The reaction mass was concentrated to get crude compound. The crude material was purified by Prep HPLC method D2, fractions containing the product were combined and dried using Genevac centrifugal evaporator to afford (3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl) methanone (0.009 g, 0.022 mmol, 45% yield) as a pale solid. LCMS retention time 1.039 min [E]. MS m/z : 403.3 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.49 (d, J = 5.6 Hz, 1 H), 8.00 (d, J = 0.8 Hz, 1 H), 7.46-7.44 (m, 2 H), 7.40 (dd, J = 5.2, 1.2 Hz, 1 H), 7.34 (dd, J = 8.2, 1.2 Hz, 1 H), 3.88-3.78 (m, 2 H), 3.75-3.54 (m, 2 H), 3.50-3.41 (m, 2 H), 3.13-2.87 (m, 4 H), 2.62 (s, 3 H), 2.60-2.51 (m, 1 H), 2.47 (s, 3 H), 1.51 (d, J = 7.2 Hz, 6 H).

The following Example was prepared in a similar manner to the product of Example 115

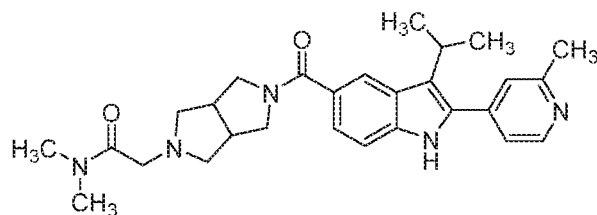
15

TABLE 12

Ex. No.	Structure	Mol Wt.	LCMS MH^+	Ret Time (min)	HPLC Method
116		430.6	431	1.12	E

EXAMPLE 117

2-(5-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N,N-dimethylacetamide



(117)

20

To a solution of (hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(3-isopropyl-2-(2-

methylpyridin-4-yl)-1H-indol-5-yl)methanone hydrochloride (0.021 g, 0.049 mmol) in THF (2.00 mL) and DMF (0.500 mL) solvent mixture was added TEA (0.1 mL, 0.717 mmol) at room temperature. The reaction mixture was stirred for 5 min. and then 2-chloro-N,N-dimethylacetamide (9.01 mg, 0.074 mmol) was added. Stirring was continued at same temperature for 16 h. Crude LCMS showed formation of product and no starting material. The reaction mass was concentrated to get crude compound. The crude material was purified by Prep HPLC method D2, fractions containing the product were combined and dried using Genevac centrifugal evaporator to afford 2-(5-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N,N-dimethylacetamide (0.009 g, 0.018 mmol, 37% yield) as a pale solid. LCMS retention time 1.172 min [E]. MS m/z : 474.4 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ ppm 11.46 (s, 1 H), 8.55 (d, $J = 7.2$ Hz, 1 H), 7.86 (s, 1 H), 7.41-7.38 (m, 2 H), 7.31 (dd, 6.0, 1.2 Hz, 1 H), 7.26 (dd, 8.4, 1.6 Hz, 1 H), 3.74-3.69 (m, 2 H), 3.53-3.45 (m, 2 H), 3.25 (s, 2 H), 3.00 (s, 3 H), 2.80 (s, 3 H), 2.79-2.72 (m, 2 H), 2.60-2.51 (m, 8 H), 1.43 (d, $J = 7.2$ Hz, 6 H).

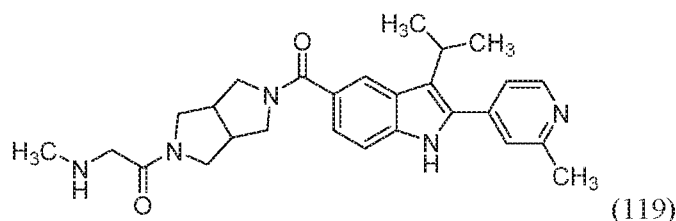
The example in Table 13 was prepared according to the general procedure described in Example 117.

TABLE 13

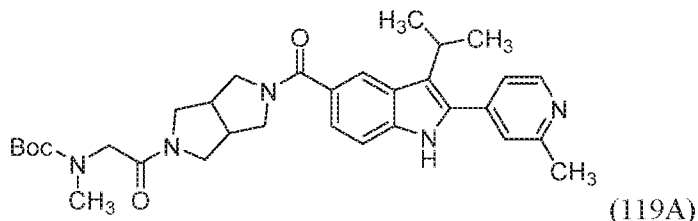
Ex. No.	Structure	Mol Wt.	LCMS MH^+	Ret Time (min)	HPLC Method
118		459.59	460	1.2	E

EXAMPLE 119

1-(5-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-(methylamino)ethanone



Intermediate 119A: 2-(5-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N,N-dimethylacetamide



- 5 To a solution of (hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)methanone hydrochloride (0.023 g, 0.054 mmol) in DMF (2.00 mL) were added TEA (0.023 mL, 0.162 mmol), 2-((tert-butoxycarbonyl)(methyl)amino)acetic acid (0.015 g, 0.081 mmol) and HATU (0.041 g, 0.108 mmol) at room temperature. The mixture was stirred at the same temperature for 16 h. Crude
- 10 LCMS showed formation of product and no starting material. The reaction was quenched with water, extracted with 10% MeOH in DCM (2 X 10 mL), combined organic extracts was washed with brine (5 mL), dried (Na₂SO₄) and concentrated to afford crude tert-butyl (2-(5-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-oxoethyl)(methyl)carbamate (0.039 g, 0.054 mmol, 99 % yield)
- 15 as gummy solid. LCMS retention time 0.71 min [E]. MS *m/z*: 560.8 [M+H]⁺.

Example 119:

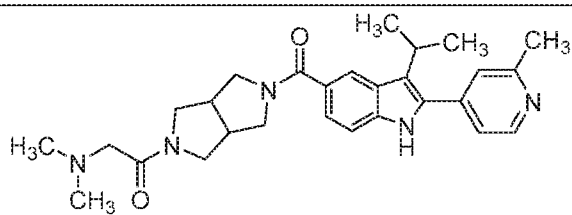
- To a solution of tert-butyl (2-(5-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-oxoethyl)(methyl)carbamate
- 20 (0.030 g, 0.054 mmol) in DCM (2.00 mL) was added TFA (0.15 mL, 1.947 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h. Crude LCMS showed formation of product and no starting material. The reaction mass was concentrated to get crude compound. The crude material was purified by Prep HPLC method D2, fractions containing the product were combined and dried using Genevac centrifugal evaporator to
- 25 afford 1-(5-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carbonyl)

hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-(methylamino)ethanone, TFA (0.001 g, 1.692 μ mol, 3% yield) as a pale solid. LCMS retention time 0.91 min [E]. MS m/z : 460.4 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ ppm 11.45 (s, 1 H), 8.55 (d, J = 7.2 Hz, 1 H), 7.92 (s, 1 H), 7.43-7.38 (m, 2 H), 7.33-7.27 (m, 2 H), 3.79-3.71 (m, 4 H), 3.43-3.34 (m, 3 H), 3.32-3.17 (m, 3 H), 3.03-2.84 (m, 3 H), 2.55 (s, 3 H), 2.29 (s, 3 H), 1.43 (d, J = 7.2 Hz, 6 H).

The example in Table 14 was prepared according to the general procedure for Example 119.

10

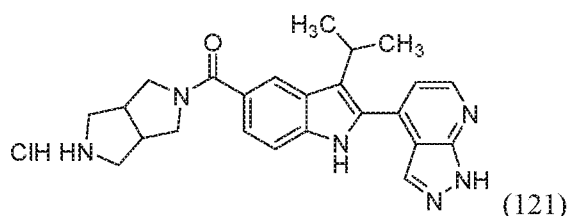
TABLE 14

Ex. No.	Structure	Mol Wt.	LCMS MH^+	Ret Time (min)	HPLC Method
120		473.62	474	0.99	E

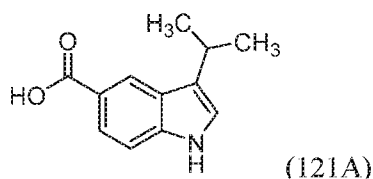
EXAMPLE 121

(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(3-isopropyl-2-(1H-pyrazolo[3,4-b]pyridin-4-yl)-1H-indol-5-yl)methanone, HCl

15



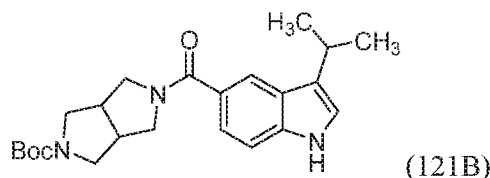
Intermediate 121A: 3-isopropyl-1H-indole-5-carboxylic acid



To a solution of methyl 3-isopropyl-1H-indole-5-carboxylate (1.350 g, 6.21

mmol) in a solvent mixture of THF (12.00 mL), MeOH (6.00 mL) and THF (12.00 mL) was added LiOH (0.744 g, 31.1 mmol) at room temperature. The reaction mixture was stirred at 75 °C for 5 h. Crude LCMS showed formation of product and no starting material. The reaction mass was concentrated, the residue was dissolved in water (5 mL),
 5 brought to acidic pH with 1.5 N HCl, then the precipitated solid was filtered, washed with water and dried under vacuum to afford 3-isopropyl-1H-indole-5-carboxylic acid (1.015 g, 4.99 mmol, 80 % yield) as white solid. LCMS retention time 0.81 min [G]. MS m/z : 204.5 $[M+H]^+$

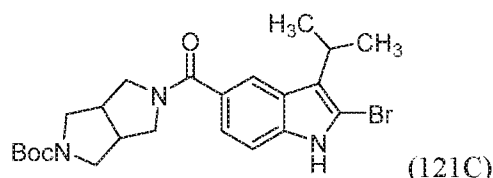
10 Intermediate 121B: tert-butyl 5-(3-isopropyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate



To a solution of 3-isopropyl-1H-indole-5-carboxylic acid (0.500 g, 2.460 mmol) and tert-butyl hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (0.574 g, 2.71 mmol) in
 15 DCM (10.00 mL) and DMF (10.00 mL) solvent was added EDC (0.707 g, 3.69 mmol) at room temperature. The mixture was stirred at the same temperature for 16 h. Crude LCMS showed formation of product and no starting material. The reaction was quenched with water (10 mL), extracted with DCM (2 X 20 mL), combined organic extracts was washed with brine (5 mL), dried (Na_2SO_4) and concentrated to get crude compound. The
 20 crude material was purified by column chromatography using 24g silica column, compound was eluted in ethyl acetate, the fractions were collected and concentrated to afford tert-butyl 5-(3-isopropyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (0.866 g, 2.179 mmol, 89 % yield) as a gummy material. LCMS retention time 0.95 min [G]. MS m/z : 342.6 $[M+H-t\text{Bu}]^+$.

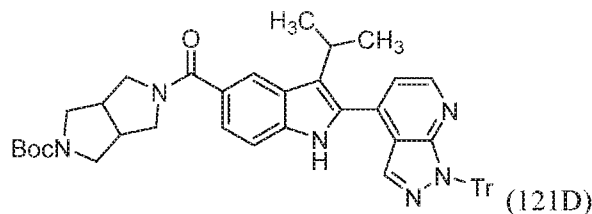
25

Intermediate 121C: tert-butyl 5-(2-bromo-3-isopropyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate



To a solution of tert-butyl 5-(3-isopropyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (0.510 g, 1.283 mmol) in DCE (25.00 mL) was added dropwise NBS (0.206 g, 1.155 mmol) in DCE (20 mL) at 0 °C. The mixture was stirred at room temperature for 15 min. Crude LCMS showed formation of product. The reaction was quenched with water (20 mL). The two layers were separated. The aqueous layer was extracted with DCM (30 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated to get crude compound. The crude material was purified by ISCO using 24 g silica column, compound was eluted in 90% ethyl acetate in hexanes, the fractions were collected and concentrated to afford tert-butyl 5-(2-bromo-3-isopropyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (0.164 g, 0.344 mmol, 27 % yield) as a white solid. LCMS retention time 1.10 min [G]. MS *m/z*: 422.1 [M+2]+H-tBu]⁺.

Intermediate 121D: tert-butyl 5-(3-isopropyl-2-(1-trityl-1H-pyrazolo[3,4-b]pyridin-4-yl)-1H-indole-5-carbonyl) hexahydropyrrolo[3,4-c] pyrrole-2(1H)-carboxylate



To a solution of tert-butyl 5-(2-bromo-3-isopropyl-1H-indole-5-carbonyl) hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (0.075 g, 0.157 mmol), potassium phosphate tribasic (0.050 g, 0.236 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-trityl-1H-pyrazolo[3,4-b]pyridine (0.092 g, 0.189 mmol) in dioxane (4.00 mL) and water (1.000 mL) was degassed with nitrogen for 20 min. Next, PdCl₂(dppf)-CH₂Cl₂ adduct (6.43 mg, 7.87 μmol) was added and the reaction mixture was stirred at 80 °C for 18 h. Crude LCMS showed no further change in the reaction mass. The reaction mixture was diluted with DCM (20 mL) and water (1 mL) and the two layers were separated. The aqueous layer was extracted with DCM (20 mL). The combined organic extracts was

dried (Na_2SO_4) and concentrated to get crude compound. The crude material was purified by column chromatography using 12 g Silica column, compound was eluted in 80% ethyl acetate in hexane, the fractions were collected and concentrated to afford tert-butyl 5-(3-isopropyl-2-(1-trityl-1H-pyrazolo[3,4-b]pyridin-4-yl)-1H-indole-5-

5 carbonyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (0.060 g, 0.079 mmol, 50 % yield) as a gummy solid. LCMS retention time 1.10 min [G]. MS m/z : 757.5 $[\text{M}+\text{H}]^+$:

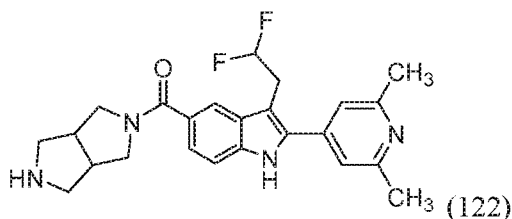
Example 121:

To a solution of tert-butyl 5-(3-isopropyl-2-(1-trityl-1H-pyrazolo[3,4-b]pyridin-4-yl)-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (0.032 g, 0.042 mmol) in dioxane (2.00 mL) was added hydrochloric acid 4M in dioxane (1.00 mL, 32.9 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 4 h. Crude LCMS showed formation of product and no starting material. The reaction mass was concentrated and triturated with diethyl ether (2 X 2 mL) to get crude compound. The crude material was purified by Prep HPLC method D2, fractions containing the product were combined and dried using Genevac centrifugal evaporator to afford (hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(3-isopropyl-2-(1H-pyrazolo[3,4-b]pyridin-4-yl)-1H-indol-5-yl)methanone, HCl (0.002 g, 4.43 μmol , 10 % yield) as a pale solid. LCMS retention time 1.10 min [E]. MS m/z : 415.3 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.61 (d, J = 4.8 Hz, 1 H), 8.16 (s, 1 H), 8.08 (d, J = 0.8 Hz, 1 H), 7.53 (dd, J = 8.8, 0.4 Hz, 1 H), 7.741 (dd, J = 8.4, 1.6 Hz, 1 H), 7.31 (d, J = 4.8 Hz, 1 H), 3.98-3.91 (m, 2 H), 3.78-3.46 (m, 2 H), 3.49-3.38 (m, 3 H), 3.18-2.96 (m, 4 H), 1.52 (d, J = 7.2 Hz, 6 H).

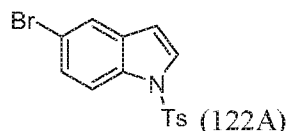
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EXAMPLE 122

(3-(2,2-difluoroethyl)-2-(2,6-dimethylpyridin-4-yl)-1H-indol-5-yl)(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone

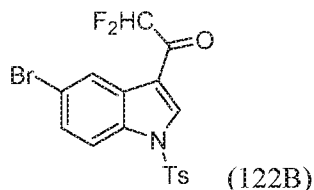


Intermediate 122A: 5-bromo-1-tosyl-1H-indole



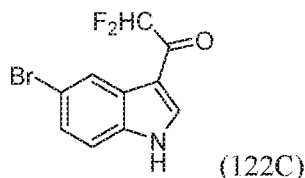
To a stirred solution of 5-bromo-1H-indole (5.0 g, 25.5 mmol), TsCl (6.03 g, 31.6 mmol) and tetrabutylammonium hydrogen sulfate (0.63 g, 1.855 mmol) in toluene (100 mL) was added NaOH (50% solution in water, 10.20 g, 255 mmol) dropwise. The reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with water (20 mL). The resulting two layers were separated, the aqueous layer was extracted with EtOAc (2 X 50 mL), the combined organic extracts was dried (Na₂SO₄) and concentrated to get crude material. The crude material was purified by ISCO using 40 g silica column, compound was eluted in 4% ethyl acetate in hexanes, the fractions were collected and concentrated to afford 5-bromo-1-tosyl-1H-indole (7.1 g, 20.27 mmol) as white solid. LCMS retention time = 2.230 min [A]. MS *m/z*: 393.3 (M-H).

Intermediate 122B: 1-(5-bromo-1-tosyl-1H-indol-3-yl)-2,2-difluoroethan-1-one



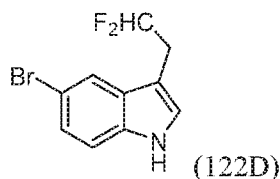
Difluoroacetic anhydride (4.47 g, 25.7 mmol) was added to a suspension of AlCl₃ (6.85 g, 51.4 mmol) in DCM (50 mL). The reaction mixture was stirred for 15 min, then a solution of 5-bromo-1-tosyl-1H-indole (3 g, 8.57 mmol) in DCM (30 mL) was added. The reaction mixture was stirred for 1 h at ambient temperature. The reaction was quenched with ice-water. The reaction mixture was extracted with DCM (2 X 50 mL), combined extracts was washed with aqueous NaHCO₃, brine, dried over MgSO₄, filtered and concentrated to get crude material. The crude material was purified by column chromatography using silica column, compound was eluted in 10% EtOAc in hexane, the fraction was collected and concentrated to afford 1-(5-bromo-1-tosyl-1H-indol-3-yl)-2,2-difluoroethanone (2.21 g, 4.1 mmol) as a crystalline solid. LCMS retention time = 2.732 min [A]. MS *m/z*: 428.0 (M+H).

Intermediate 122C: 1-(5-bromo-1H-indol-3-yl)-2,2-difluoroethan-1-one



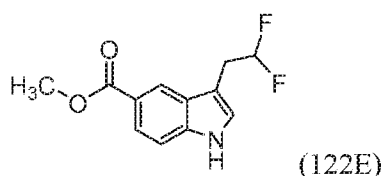
To a solution of 1-(5-bromo-1-tosyl-1H-indol-3-yl)-2,2-difluoroethanone (0.2 g, 0.467 mmol) in THF (4 mL) and MeOH (4.00 mL) was added Cs₂CO₃ (0.45 g, 1.381 mmol) at room temperature. The reaction mixture was stirred at same temperature for 12 h. The reaction mixture was concentrated, the residue was diluted with minimum amount of water and undissolved solids was filtered and dried under vacuum to afford 1-(5-bromo-1H-indol-3-yl)-2,2-difluoroethanone (105 mg, 0.244 mmol) as a white solid. LC retention time = 2.233 min [A]. MS *m/z*: 276 (M+2)+H).

Intermediate 122D: 5-bromo-3-(2,2-difluoroethyl)-1H-indole



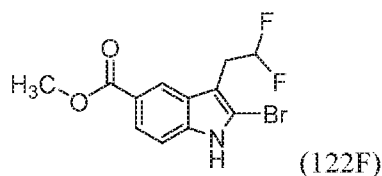
To the stirred solution of 1-(5-bromo-1H-indol-3-yl)-2,2-difluoroethanone (0.25 g, 0.912 mmol) in THF (10 mL) was added BH₃DMS (1.368 mL, 2.74 mmol) at 0 °C under nitrogen. The mixture was stirred at 80 °C for 20 h. The reaction mixture was quenched with water (2 mL) at 0 °C, diluted with ethyl acetate (100 mL), washed with sodium bicarbonate (2 x 25 mL) and water (2 x 25 mL). The combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated to get crude compound. The crude material was purified by column chromatography using 24 g silica gel column, compound was eluted at 8% ethyl acetate/hexane, the fractions were collected and concentrated to afford 5-bromo-3-(2,2-difluoroethyl)-1H-indole (120 mg, 0.438 mmol) as an oil. LCMS retention time = 2.802 min [D]. MS *m/z*: 260 (M+H).

Intermediate 122E: Methyl 3-(2,2-difluoroethyl)-1H-indole-5-carboxylate:



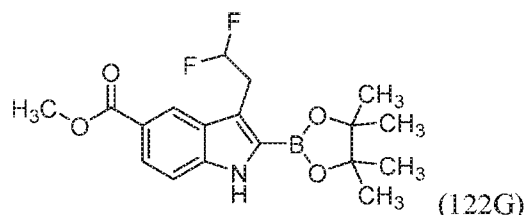
To a solution of 5-bromo-3-(2,2-difluoroethyl)-1H-indole (3.0 g, 11.53 mmol) in methanol (100 mL) and DMF (100 mL) were added TEA (3.22 mL, 23.07 mmol), Pd(OAc)₂ (0.518 g, 2.307 mmol) and DPPF (1.918 g, 3.46 mmol). The mixture was degassed for 10 min with nitrogen and stirred at 90 °C under carbon monoxide atmosphere (80 psi) for 24h. The reaction mixture was cooled to room temperature, volatiles was evaporated to get residue. The residue was dissolved in ethyl acetate, filtered and washed with ethyl acetate, combined organic layers were washed with water, brine, dried over sodium sulphate and evaporated to get crude compound. The crude material was purified by column chromatography using silica column 80 g, compound was eluted with 20% ethyl acetate in petroleum ether, the fractions were collected and concentrated to afford methyl 3-(2,2-difluoroethyl)-1H-indole-5-carboxylate (2.4 g, 10.03 mmol, 87 % yield) as a light brown liquid. LCMS retention time 0.99 min [D] MS *m/z*: 240.2 (M+H).

Intermediate 122F: methyl 2-bromo-3-(2,2-difluoroethyl)-1H-indole-5-carboxylate:



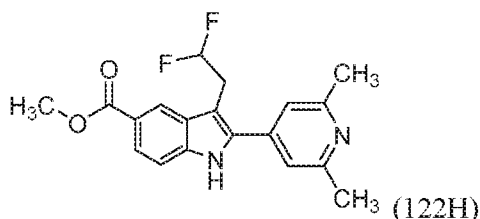
A solution of NBS (1.607 g, 9.03 mmol) in DCE (120 mL) was added to a cooled solution of methyl 3-(2,2-difluoroethyl)-1H-indole-5-carboxylate (2.4 g, 10.03 mmol) in DCE (120 mL) at 0 °C. The reaction mixture was stirred at the same temperature for 1.5 h. The reaction was quenched with cold water. The mixture was stirred for 15 min, the organic layer was separated, dried over sodium sulphate and concentrated to get crude material. The crude material was purified by ISCO using silica column 40 g, compound was eluted with 25% ethyl acetate in petroleum ether, the fractions were collected and concentrated to afford methyl 2-bromo-3-(2,2-difluoroethyl)-1H-indole-5-carboxylate (1.8 g, 5.66 mmol, 56 % yield) as an off-white solid. LCMS retention time 1.05 min, [D] MS *m/z*: 320.0 ((M+2)+H).

Intermediate 122G: methyl 3-(2,2-difluoroethyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-5-carboxylate



- 5 To a solution of methyl 2-bromo-3-(2,2-difluoroethyl)-1H-indole-5-carboxylate (1.6 g, 5.03 mmol), bis(benzonitrile)palladium(II) chloride (0.411 g, 0.503 mmol) and SPhos (0.206 g, 0.503 mmol) in dioxane (25 mL) were added TEA (2.117 mL, 15.09 mmol) and pinacolborane (6.51 mL, 25.1 mmol) at room temperature. The mixture was degassed with nitrogen for 5 min. The reaction mixture was stirred at 80 °C for 1 h in a sealed tube. The reaction was quenched with cold water. The reaction mixture was
- 10 diluted with ethyl acetate, filtered and washed with excess ethyl acetate. The combined organic layers were washed with water, brine, dried over sodium sulphate and evaporated to afford crude compound. The crude material was purified by column chromatography using silica column 40 g, compound was eluted with 25% ethyl acetate in petroleum
- 15 ether, the fractions were collected and concentrated to afford methyl 3-(2,2-difluoroethyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-5-carboxylate (1.3 g, 3.56 mmol, 71 % yield) as an off-white solid. LCMS retention time 1.32 min [G], MS *m/z*: 366.3 (M+H).

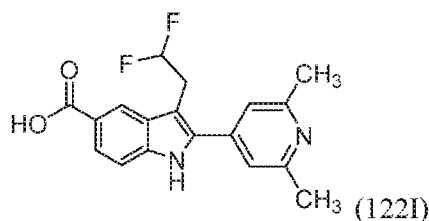
- 20 Intermediate 122H: Methyl 3-(2,2-difluoroethyl)-2-(2,6-dimethylpyridin-4-yl)-1H-indole-5-carboxylate:



- To a degassed solution of methyl 3-(2,2-difluoroethyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-5-carboxylate (1.2 g, 3.29 mmol) and 4-bromo-2,6-
- 25 dimethylpyridine (0.734 g, 3.94 mmol) in dioxane (30.0 mL) and water (5.0 mL) were

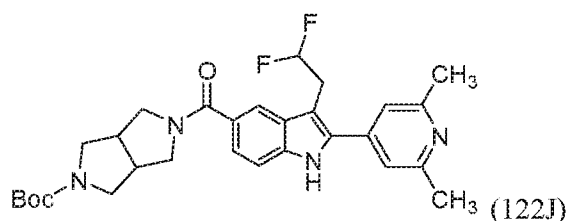
added PdCl₂ (dppf)-CH₂Cl₂ adduct (0.268 g, 0.329 mmol) and tripotassium phosphate (2.093 g, 9.86 mmol). The resulting reaction mixture was stirred at 95 °C for 5 h in a sealed tube. The reaction mixture was diluted with ethyl acetate, filtered and washed with excess ethyl acetate, combined organic layers were washed with water, brine, dried over sodium sulphate and evaporated to get crude compound. The crude material was purified by column chromatography using silica column 40 g, compound was eluted with 55-65% ethyl acetate in petroleum ether, the fractions were collected and concentrated to afford methyl 3-(2,2-difluoroethyl)-2-(2,6-dimethylpyridin-4-yl)-1H-indole-5-carboxylate (0.850 g, 2.468 mmol, 75 % yield) as a off white solid. LCMS retention time 1.07 min [D]. MS *m/z*: 345.2 (M+H);

Intermediate 122I: 3-(2,2-difluoroethyl)-2-(2,6-dimethylpyridin-4-yl)-1H-indole-5-carboxylic acid



A solution of lithium hydroxide (0.087 g, 3.63 mmol) in water (2.0 mL) was added to a solution of methyl 3-(2,2-difluoroethyl)-2-(2,6-dimethylpyridin-4-yl)-1H-indole-5-carboxylate (0.250 g, 0.726 mmol) in THF (5.0 mL) and MeOH (5.0 mL). The reaction mixture was stirred at 70 °C for 16 h. The reaction mixture was cooled to room temperature, volatiles was evaporated, the residue was diluted with water (10 mL), neutralized with 10% HCl, stirred for 30 min, the resulting solid compound was filtered, washed with minimum amount of water and petroleum ether to afford 3-(2,2-difluoroethyl)-2-(2,6-dimethylpyridin-4-yl)-1H-indole-5-carboxylic acid (0.200 g, 0.605 mmol, 83 % yield) as an off-white solid. LCMS retention time 0.55 min [G], MS *m/z*: 331.2 (M+H).

Intermediate 122J: tert-butyl 5-(3-(2,2-difluoroethyl)-2-(2,6-dimethylpyridin-4-yl)-1H-indole-5-carboxyl) hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate:



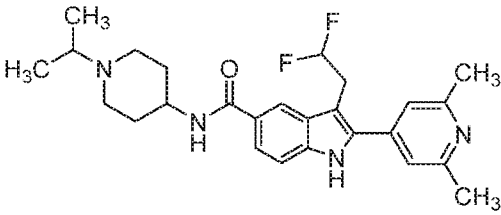
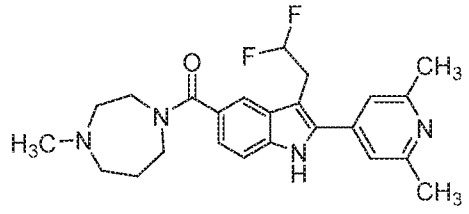
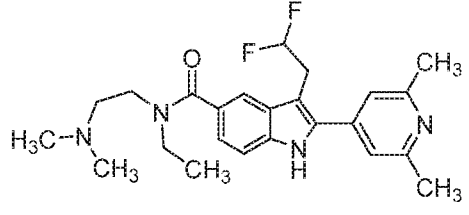
To a solution of 3-(2,2-difluoroethyl)-2-(2,6-dimethylpyridin-4-yl)-1H-indole-5-carboxylic acid (0.040 g, 0.121 mmol) and tert-butyl hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (0.039 g, 0.182 mmol) in DMF (4.0 mL) at 0 °C, were added TEA (0.051 mL, 0.363 mmol) and HATU (0.055 g, 0.145 mmol). The mixture was stirred at room temperature for 16 h. Volatiles was evaporated, the residue was dissolved with excess DCM, and washed with water and brine. The organic layer was dried over sodium sulphate and concentrated to afford tert-butyl 5-(3-(2,2-difluoroethyl)-2-(2,6-dimethylpyridin-4-yl)-1H-indole-5-carboxyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (0.055 g, 0.105 mmol, 87 % yield). LCMS retention time 1.09 min [G]. MS m/z : 525.3 (M+H).

Example 122:

To a solution of tert-butyl 5-(3-(2,2-difluoroethyl)-2-(2,6-dimethylpyridin-4-yl)-1H-indole-5-carboxyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (0.055 g, 0.105 mmol) in dioxane (3.0 mL) was added 4 M dioxane-HCl (0.655 mL, 2.62 mmol) at room temperature. The mixture was stirred at same temperature for 4 h. The reaction mass was concentrated to get crude product. The crude material was purified by Prep HPLC method D2, fractions containing the product were combined and dried using Genevac centrifugal evaporator to afford (3-(2,2-difluoroethyl)-2-(2,6-dimethylpyridin-4-yl)-1H-indol-5-yl)(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (2.0 mg, 5%) as a pale yellow solid. LCMS retention time 1.08 min [E]. MS m/z : 425.2 (M+H); ^1H NMR (400 MHz, CD_3OD) δ ppm 7.96 (s, 1H), 7.77 (br. s., 2H), 7.60-7.48 (m, 2H), 6.43-6.07 (m, 1H), 3.94 (dd, $J=12.1, 7.2$ Hz, 2H), 3.64 (td, $J=17.7, 3.9$ Hz, 8H), 3.35 (s, 2H), 3.24-3.10 (m, 3H), 2.75 (s, 8H), 2.04 (s, 1H), 1.29 (br. s., 2H).

The examples in Table 15 were prepared according to the general procedure for Example 122.

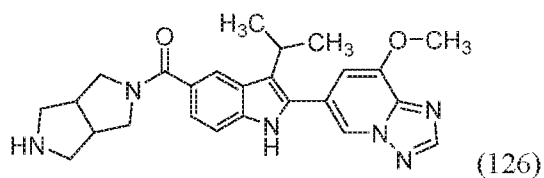
TABLE 15

Ex. No.	Structure	Mol Wt.	LCMS MH ⁺	Ret Time (min)	HPLC Method
123		454.57	455.2	1.247	E
124		426.51	427.2	1.299	E
125		428.53	429.2	1.248	E

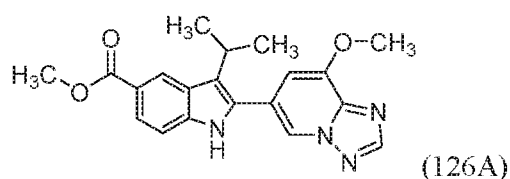
EXAMPLE 126

(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(3-isopropyl-2-(8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-1H-indol-5-yl)methanone

5



Intermediate 126A: Methyl 3-isopropyl-2-(8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-1H-indole-5-carboxylate:

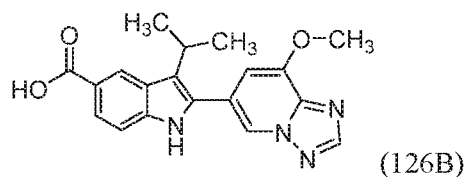


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To a degassed solution of methyl 2-bromo-3-isopropyl-1H-indole-5-carboxylate

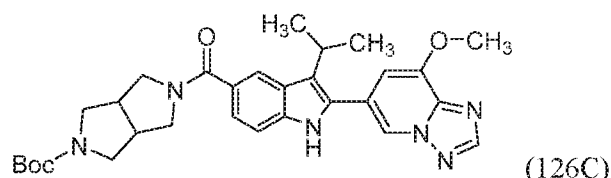
(1.0 g, 3.38 mmol) and 8-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (1.393 g, 5.06 mmol) in dioxane (20.0 mL) and water (5.0 mL) were added PdCl₂(dppf)-CH₂Cl₂ adduct (0.276 g, 0.338 mmol) and potassium phosphate (1.764 g, 10.13 mmol) at room temperature. The resulting reaction mixture was stirred at 95 °C for 4 h in a sealed tube. The reaction mixture was diluted with ethyl acetate, filtered and washed with excess ethyl acetate, combined organic layers were washed with water, brine, dried over sodium sulphate and evaporated to get crude material. The crude material was purified by ISCO using silica column 40 g, compound was eluted with 65% ethyl acetate in petroleum ether, the fractions were collected and concentrated to afford methyl 3-isopropyl-2-(8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-1H-indole-5-carboxylate (0.8 g, 2.195 mmol, 65 % yield) as a light yellow solid. LCMS retention time 1.21 min [L]. MS *m/z*: 365.5 (M+H).

Intermediate 126B: 3-isopropyl-2-(8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-1H-indole-5-carboxylic acid:



To a solution of methyl 3-isopropyl-2-(8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-1H-indole-5-carboxylate (0.620 g, 1.701 mmol) in a solvent mixture of THF (5.0 mL), MeOH (5.0 mL), and water (2.0 mL) was added sodium hydroxide (0.340 g, 8.51 mmol). The resulting mixture was stirred at 65 °C for 2 h, the reaction mixture was cooled to room temperature, volatiles were evaporated, the residue was diluted with water, and brought to acidic pH with 1 N HCl solution. The precipitated solids were filtered and dried under vacuum afford 3-isopropyl-2-(8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-1H-indole-5-carboxylic acid (0.410 g, 1.170 mmol, 69 % yield) as a white solid. LCMS retention time 0.59 min [L]. MS *m/z*: 351.4 (M+H).

Intermediate 126C: tert-butyl 5-(3-isopropyl-2-(8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate:



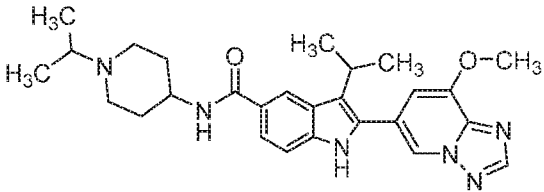
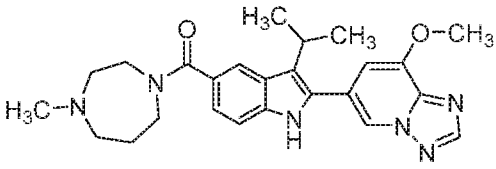
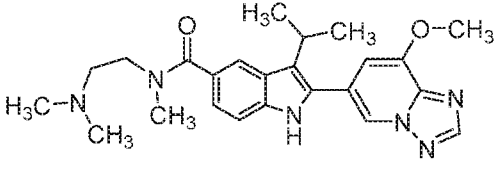
HATU (0.043 g, 0.114 mmol) was added to a solution of 3-isopropyl-2-(8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-1H-indole-5-carboxylic acid (0.040 g, 0.114 mmol), tert-butyl hexahydropyrrolo[3,4-c] pyrrole-2(1H)-carboxylate (0.032 g, 0.148 mmol), TEA (0.080 mL, 0.571 mmol) in DMF (3.0 mL) at 0 °C. The resulting mixture was stirred at room temperature for 16 h. The volatiles was evaporated, residue was dissolved with excess DCM, washed with water, brine, dried over sodium sulphate and concentrated to afford crude tert-butyl 5-(3-isopropyl-2-(8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (0.065 g, 0.119 mmol, 105 % yield) as a brown color semisolid. LCMS retention time 1.20 min. (L), MS *m/z*: 543.5 (M-H).

Example 126:

To a solution of tert-butyl 5-(3-isopropyl-2-(8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (0.060 g, 0.110 mmol) in dioxane (2.0 mL) was added 4 M HCl in dioxane (0.551 mL, 2.203 mmol) at 10°C. The reaction mixture was stirred at the same temperature for 4 h. The reaction mass was concentrated to get crude product. The crude material was purified by Prep HPLC method D2, fractions containing the product were combined and dried using Genevac centrifugal evaporator to afford (hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(3-isopropyl-2-(8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-1H-indol-5-yl) methanone (32.0 mg, 62.7%) as a pale yellow solid. LCMS retention time 1.05 min [E]. MS *m/z*: 445.1 (M+H); ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 8.56-8.45 (m, 2H), 8.08 (s, 1H), 7.52 (d, *J*=8.3 Hz, 1H), 7.42 (d, *J*=8.6 Hz, 1H), 7.26 (s, 1H), 4.18 (s, 3H), 3.99 (dd, *J*=12.2, 7.1 Hz, 2H), 3.86-3.70 (m, 5H), 3.63 (br. s., 2H), 3.48-3.37 (m, 1H), 3.25 (br. s., 4H), 1.62-1.39 (m, 6H).

The examples in Table 16 were prepared according to the general procedure described in Example 126.

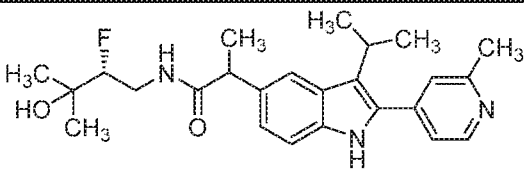
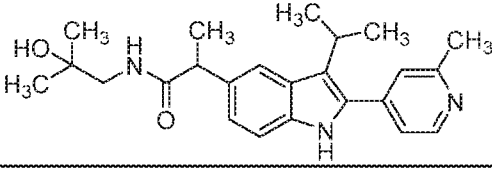
TABLE 16

Ex. No.	Structure	Mol Wt.	LCMS MH ⁺	Ret Time (min)	HPLC Method
127		474.61	475.2	1.217	E
128		446.56	447.2	1.27	E
129		434.54	435.2	1.27	E

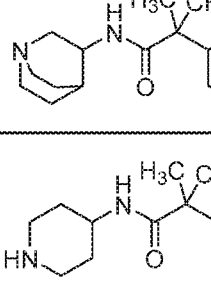
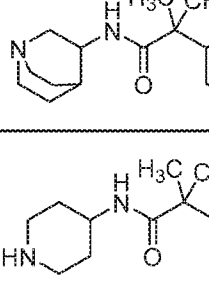
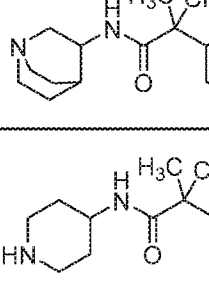
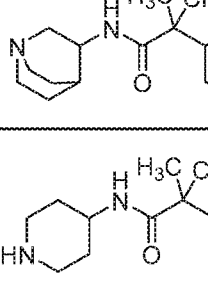
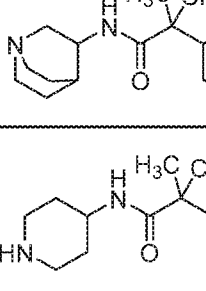
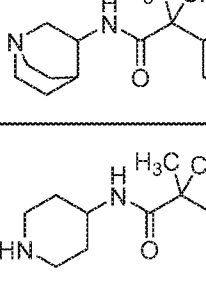
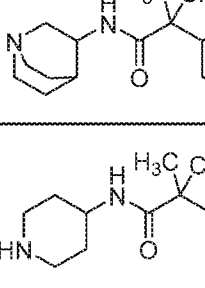
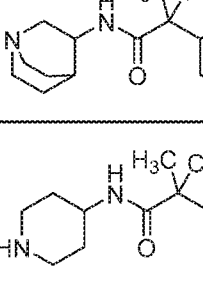
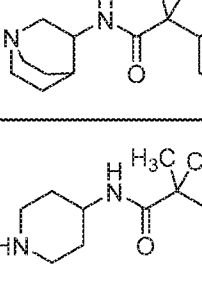
The examples in Table 17 were prepared according to the general procedure for the above examples.

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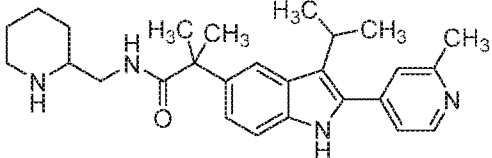
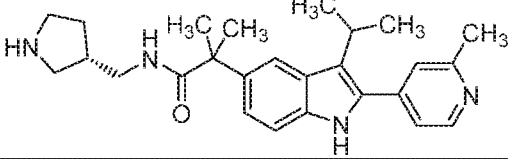
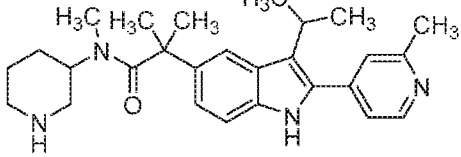
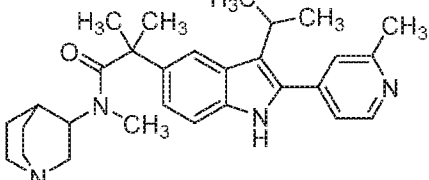
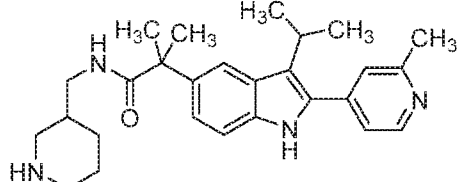
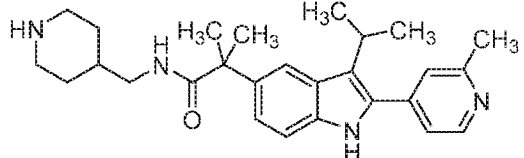
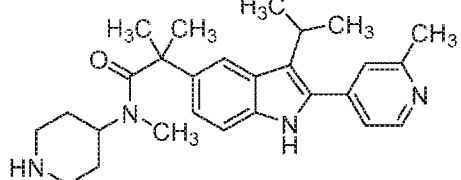
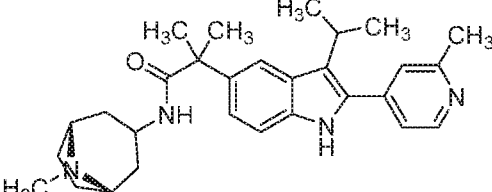
TABLE 17

Ex. No.	Structure	Mol Wt.	LCMS MH ⁺	Ret Time (min)	HPLC Method
130		425.55	426	1.52	QC-ACN-AA-XB
131		393.53	394.1	1.06	QC-ACN-TFA-XB

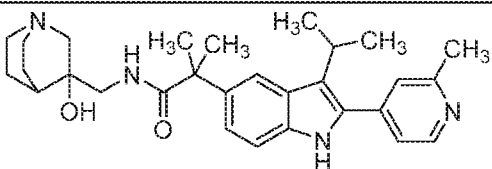
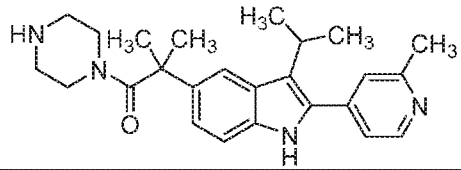
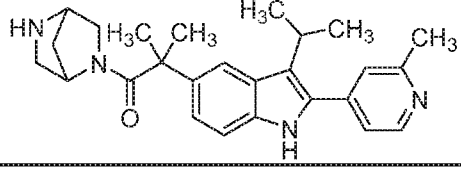
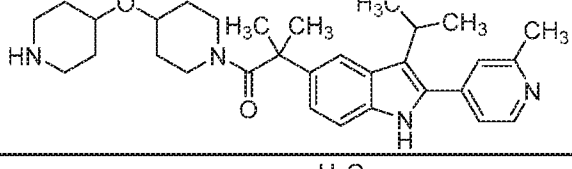
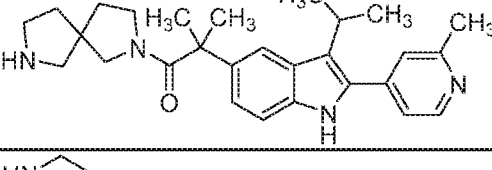
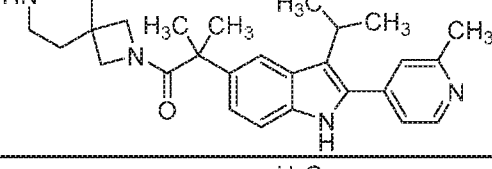
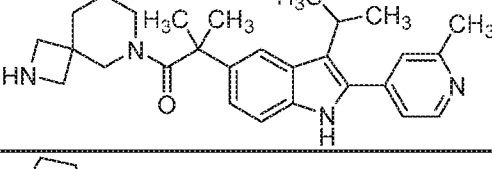
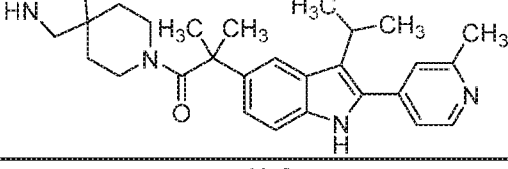
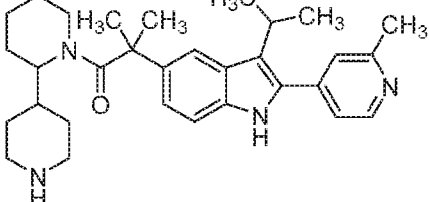
132		407.56	408.1	1.1	QC-ACN-TFA-XB
133		439.58	439.9	1.38	QC-ACN-TFA-XB
134		378.52	379.2	1.55	QC-ACN-TFA-XB
135		421.59	422.3	1.72	QC-ACN-AA-XB
136		417.513	418.2	1.32	QC-ACN-AA-XB
137		461.606	462	1.2	QC-ACN-AA-XB
138		404.558	405.3	0.9	QC-ACN-AA-XB
139		460.666	461.1	1.33	QC-ACN-AA-XB
140		418.585	419.2	1.21	QC-ACN-TFA-XB

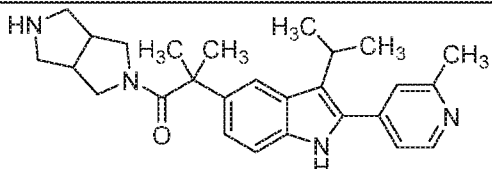
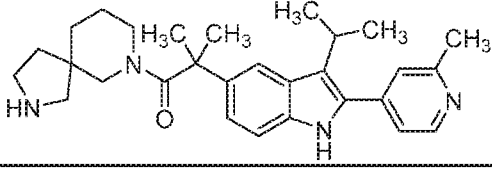
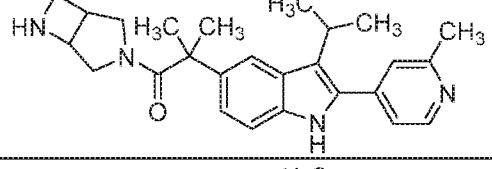
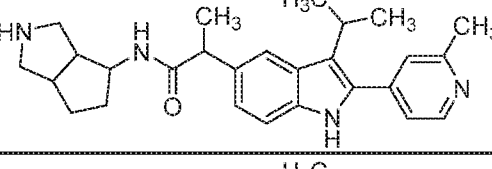
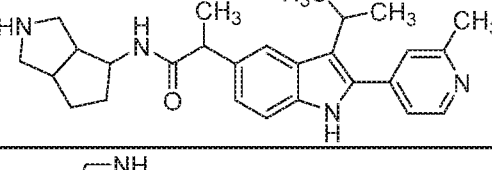
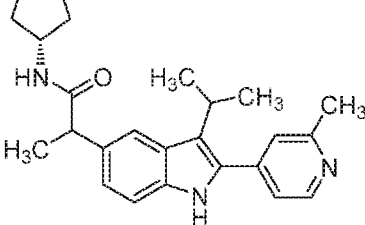
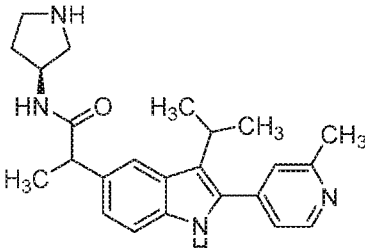
141		404.558	404.9	1.14	QC-ACN-TFA-XB
142		444.623	445.3	1.67	QC-ACN-TFA-XB
143		418.585	419.1	0.94	QC-ACN-TFA-XB
144		444.623	445.2	1.32	QC-ACN-AA-XB
145		487.69	488.4	0.92	QC-ACN-TFA-XB
146		444.62	445.5	0.67	B1
147		444.62	445.5	0.67	B1
148		430.6	431.3	1.34	QC-ACN-AA-XB
149		444.623	445.2	1.33	QC-ACN-AA-XB

150		472.677	473.2	0.97	QC- ACN- TFA- XB
151		418.585	419.3	0.89	QC- ACN- TFA- XB
152		486.704	487	1.3	QC- ACN- TFA- XB
153		418.585	419.2	0.9	QC- ACN- AA- XB
154		446.639	447.4	1.65	QC- ACN- TFA- XB
155		418.585	419.3	1.63	QC- ACN- TFA- XB
156		432.612	433.3	0.94	QC- ACN- TFA- XB
157		432.612	433.2	1.36	QC- ACN- AA- XB
158		432.612	433.2	0.94	QC- ACN- TFA- XB

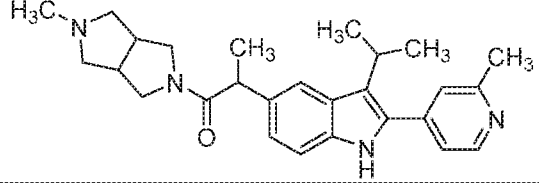
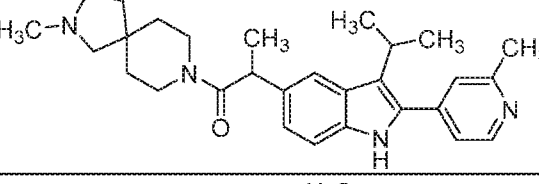
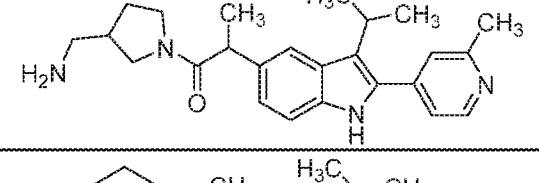
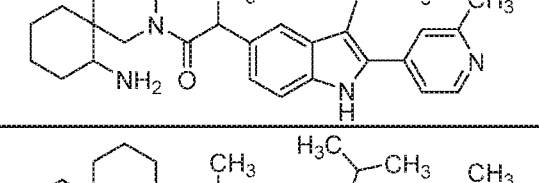
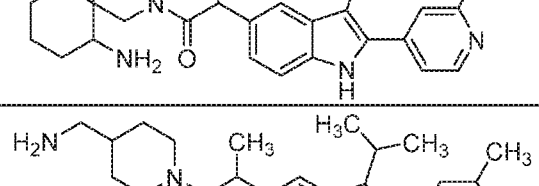
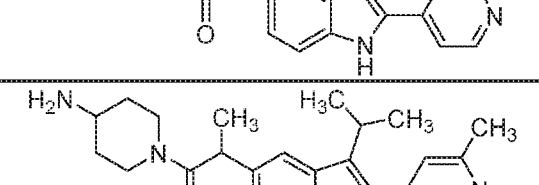
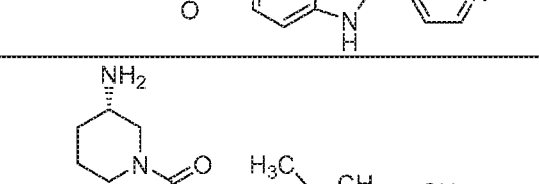
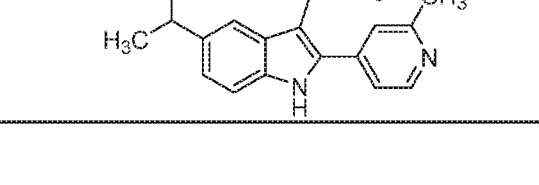
159		432.612	433.3	0.95	QC- ACN- AA- XB
160		418.585	419.3	1.61	QC- ACN- TFA- XB
161		432.612	433.2	1.25	QC- ACN- AA- XB
162		458.65	459.3	1	QC- ACN- AA- XB
163		432.612	433	1.17	QC- ACN- TFA- XB
164		432.612	433	1.54	QC- ACN- AA- XB
165		432.612	433.2	0.93	QC- ACN- TFA- XB
166		458.65	459.4	0.99	QC- ACN- AA- XB

167		432.612	433.4	1.62	QC- ACN- TFA- XB
168		432.612	433.2	1.26	QC- ACN- AA- XB
169		432.612	433.1	1.29	QC- ACN- AA- XB
170		432.612	433.2	1.4	QC- ACN- AA- XB
171		446.639	447.2	1.34	QC- ACN- AA- XB
172		446.639	447.3	1.34	QC- ACN- AA- XB
173		462.638	463.3	1.18	QC- ACN- TFA- XB

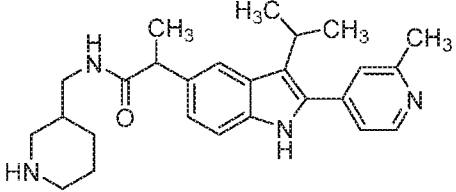
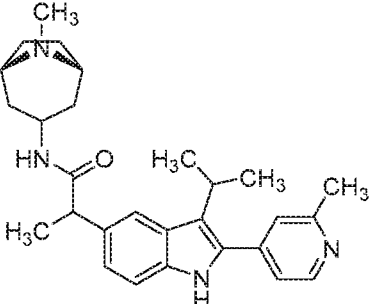
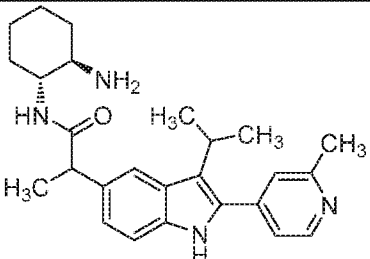
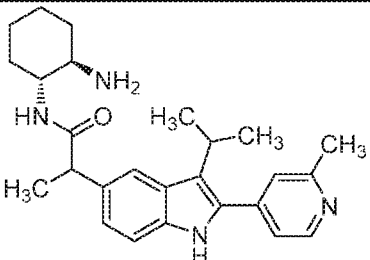
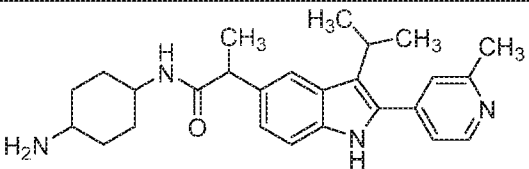
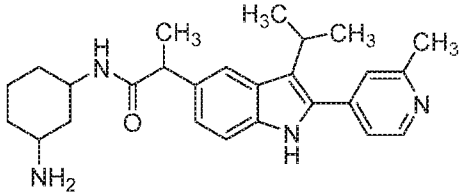
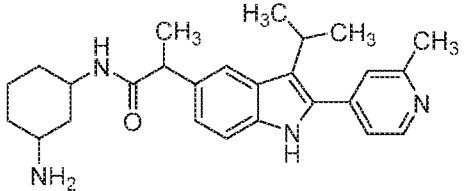
174		474.649	475.2	1.31	QC- ACN- AA- XB
175		404.558	405.2	0.89	QC- ACN- AA- XB
176		416.569	417.1	1.16	QC- ACN- TFA- XB
177		502.703	503.3	1	QC- ACN- TFA- XB
178		444.623	445.2	0.92	QC- ACN- TFA- XB
179		444.623	445.3	1.26	QC- ACN- AA- XB
180		444.623	445.2	0.96	QC- ACN- TFA- XB
181		458.65	459.3	0.95	QC- ACN- TFA- XB
182		486.704	487.2	1.39	QC- ACN- AA- XB

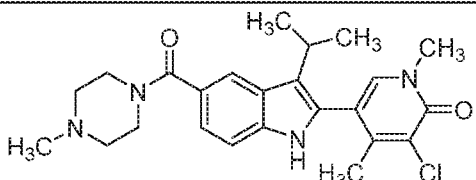
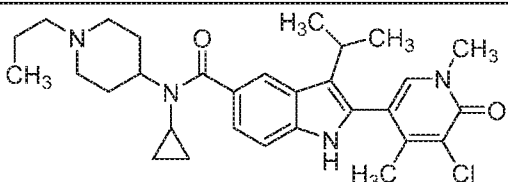
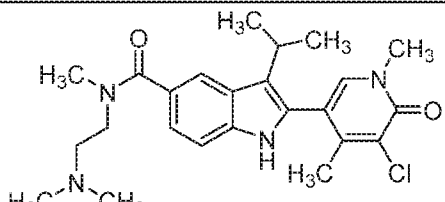
183		430.596	431.2	1.25	QC- ACN- AA- XB
184		458.65	459.4	1.77	QC- ACN- AA- XB
185		416.57	417.1	0.97	QC- ACN- TFA- XB
186		430.6	431.1	1.11	QC- ACN- AA- XB
187		430.6	431.1	1.18	QC- ACN- AA- XB
188		390.53	391.3	0.84	QC- ACN- TFA- XB
189		390.53	391.3	0.84	QC- ACN- TFA- XB

190		390.53	391.3	1.51	QC- ACN- AA- XB
191		430.6	431.3	1.53	QC- ACN- AA- XB
192		430.6	431.1	1.18	QC- ACN- AA- XB
193		404.558	405.3	0.83	QC- ACN- TFA- XB
194		446.639	447.2	0.89	QC- ACN- TFA- XB
195		404.56	405.4	1.51	QC- ACN- AA- XB
196		404.56	405.3	0.91	QC- ACN- TFA- XB

197		430.6	431.1	1.17	QC- ACN- AA- XB
198		458.65	459.1	1.21	QC- ACN- AA- XB
199		404.558	405	0.84	QC- ACN- TFA- XB
200		472.677	473.4	1.01	QC- ACN- TFA- XB
201		472.677	473.4	1.81	QC- ACN- AA- XB
202		418.585	419.4	1.48	QC- ACN- AA- XB
203		404.56	405.3	1.12	QC- ACN- AA- XB
204		404.56	405.3	0.89	QC- ACN- TFA- XB

205		418.585	419.1	1.25	QC- ACN- AA- XB
206		432.61	433.1	0.95	QC- ACN- TFA- XB
207		418.585	419.3	0.87	QC- ACN- TFA- XB
208		404.56	405.3	1.46	QC- ACN- AA- XB
209		418.59	419.1	1.22	QC- ACN- AA- XB
210		418.59	419.1	0.88	QC- ACN- TFA- XB
211		444.62	445.23	0.96	QC- ACN- TFA- XB
212		404.56	405.3	1.47	QC- ACN- AA- XB

213		418.585	419.3	1.39	QC- ACN- AA- XB
214		444.62	445.1	0.91	QC- ACN- TFA- XB
215		418.59	419.3	1.61	QC- ACN- AA- XB
216		418.59	419.3	0.98	QC- ACN- TFA- XB
217		418.59	419.1	0.9	QC- ACN- TFA- XB
218		418.59	419.3	1.54	QC- ACN- AA- XB
219		418.59	419.1	1.18	QC- ACN- AA- XB

220		440.97	441	1.17	QC- ACN- AA- XB
221		523.12	523.4	1.21	QC- ACN- TFA- XB
222		442.99	443.3	1.06	QC- ACN- AA- XB

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. Briefly, cells are seeded into Greiner 384 well plates (15000 cells per well for TLR7, 20,000 for TLR8 and 25,000 for TLR9) and then treated with test compounds in DMSO to yield a final dose response concentration range of 0.05 nM – 50 μM. After a 30 minute compound pre-treatment at room temperature, the cells are then stimulated with a TLR7 ligand (gardiquimod at a final concentration of 7.5 μM), TLR8 ligand (R848 at a final concentration of 15.9 μM) or TLR9 ligand (ODN2006 at a final concentration of 5 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.

Table 18

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TLR7/8/9 Reporter Assay Data

(Ranges: A = <100 nM; B = 100 to 1000 nM; C = >1000 to 50000 nM;

NA-1 = >3125 nM; NA-2 = > 50000 nM; NT = not tested)

Ex. No.	TLR7 IC ₅₀ (nM)	TLR8 IC ₅₀ (nM)	TLR9 IC ₅₀ (nM)	Ex. No.	TLR7 IC ₅₀ (nM)	TLR8 IC ₅₀ (nM)	TLR9 IC ₅₀ (nM)
1	30	49	375	112	335	36	334
2	45	4.0	3011	113	50	0.8	1269
3	153	79	>50000	114	135	2.4	3626
4	145	27	30483	115	147	3.5	1579
5	43	43	1381	116	117	3.6	985
6	180	180	5227	117	730	20	3696
7	343	267	4016	118	4046	165	22744
8	129	126	7519	119	2608	226	2227
9	76	54	5348	120	870	47	752
10	111	114	7630	121	1596	122	3333
11	606	645	36012	122	2264	5654	1460
12	274	175	1216	123	83	25	231
13	61	61	2160	124	128	36	1117
14	40	26	1186	125	19	23	727
15	99	54	429	126	29	233	2411
16	280	194	3937	127	2.5	1.7	916
17	115	7.9	2506	128	3.8	2.6	1399
18	1659	260	13832	129	1.8	2.3	3347
19	104	NT	1392	130	748	818	>50000
20	2312	858	>50000	131	657	979	>50000

21	764	132	37377		132	947	964	NT
22	356	264	37579		133	284	399	>50000
23	362	43	885		134	63	110	1087
24	1791	581	31404		135	202	551	>50000
25	186	14	3710		136	1760	411	>50000
26	1612	931	>50000		137	109	32	840
27	1738	782	>50000		138	52	64	1168
28	1351	220	>50000		139	25	154	1144
29	188	34	6176		140	40	32	1215
30	632	191	4161		141	58	68	895
31	296	NT	4927		142	16	120	790
32	1975	545	5100		143	35	147	562
33	1116	897	16753		144	26	64	672
34	1184	218	>50000		145	554	783	4495
35	595	190	>50000		146	160	122	979
36	138	NT	1934		147	109	92	1212
37	1303	14	9942		148	88	79	2640
38	299	1.2	5266		149	17	277	3051
39	367	2.2	4407		150	22	141	1488
40	545	5.7	8699		151	72	125	2094
41	1141	12	26730		152	31	46	2638
42	751	15	9667		153	159	91	566
43	2495	572	>50000		154	58	256	NT
44	1941	412	44839		155	113	143	2037
45	2238	1037	>50000		156	53	52	922
46	391	60	931		157	6.3	28	997
47	150	NT	2794		158	79	500	3026
48	144	4.8	2696		159	139	18	855
49	144	NT	2409		160	164	1028	5091
50	382	NT	19866		161	42	31	1738

51	705	NT	>50000		162	24	135	3516
52	2384	243	>50000		163	238	676	1877
53	258	8.1	2002		164	331	617	2530
54	206	12	1814		165	61	63	908
55	954	16	2092		166	22	135	8234
56	112	13	2194		167	63	36	2902
57	577	218	>50000		168	96	44	2674
58	194	110	NT		169	16	7.1	899
59	1141	NT	>50000		170	11	51	1663
60	206	115	>50000		171	67	602	5218
61	4124	1623	10209		172	58	325	1804
62	493	381	>50000		173	57	150	691
63	801	464	13592		174	54	550	2055
64	1278	2187	16637		175	167	36	1014
65	1210	1630	7245		176	260	211	8394
66	3936	1170	>50000		177	128	58	1465
67	1770	412	>50000		178	61	859	1659
68	1707	277	>50000		179	35	1127	4931
69	968	274	>50000		180	147	306	1000
70	441	243	>50000		181	76	1243	1947
71	1630	439	>50000		182	15	81	716
72	579	408	>50000		183	30	103	387
73	25	4.0	4336		184	91	139	533
74	156	16	5884		185	71	554	11855
75	124	7.6	250		186	146	100	599
76	56	3.9	4888		187	223	496	1350
77	714	480	40270		188	458	387	2621
79	296	124	1054		189	268	246	1677
80	177	2.9	836		190	137	211	957
81	418	87	1922		191	175	209	1292

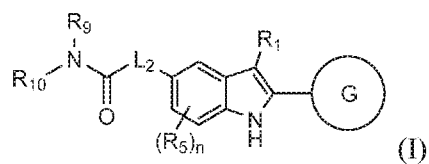
82	515	446	21907		192	71	142	1533
83	16	0.5	2348		193	203	147	3372
84	49	2.1	2521		194	152	106	3891
85	776	160	386		195	273	75	912
86	469	28	1569		196	51	88	866
87	1049	27	438		197	200	130	3289
88	401	278	593		198	46	72	1308
89	914	217	5865		199	443	303	1207
90	866	344	4052		200	12	69	690
91	9.2	2.1	670		201	74	70	1869
92	32	3.2	2473		202	174	534	1348
93	2.9	1.4	594		203	296	365	746
94	18	23	>50000		204	74	119	939
95	50	3.6	516		205	277	341	2461
96	75	7.3	1501		206	517	126	686
97	45	30	>50000		207	172	156	396
98	82	45	>50000		208	1287	2571	7309
99	201	481	1833		209	103	96	685
100	46	320	>50000		210	280	210	718
101	1.9	0.34	776		211	50	51	472
102	185	418	5062		212	821	1473	4998
103	54	192	27053		213	466	241	2643
104	14	12	373		214	107	167	4624
105	33	59	20807		215	148	174	1368
106	51	105	>50000		216	131	159	1057
107	73	58	264		217	167	316	999
108	7.3	1.5	247		218	803	1077	1401
109	18	2.3	116		219	256	182	1751
110	49	11	410		220	141	2.1	NT
111	171	74	668		221	5.2	0.7	2941

					222	22	10	6920
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CLAIMS

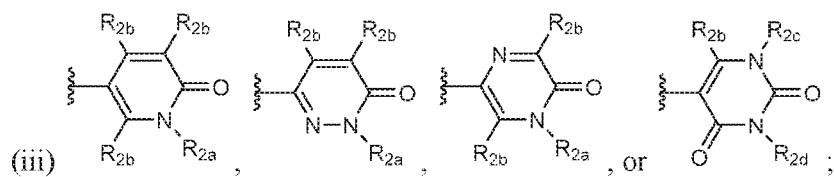
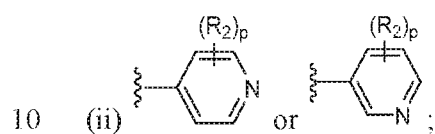
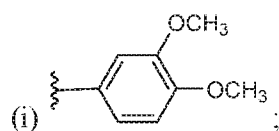
What is claimed is:

- 5 1. A compound of Formula (I)

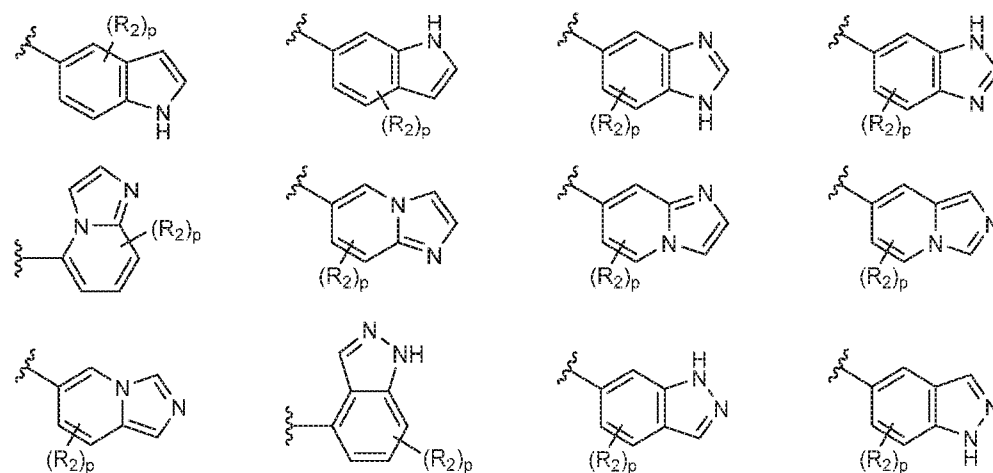


N-oxide, or a salt thereof, wherein:

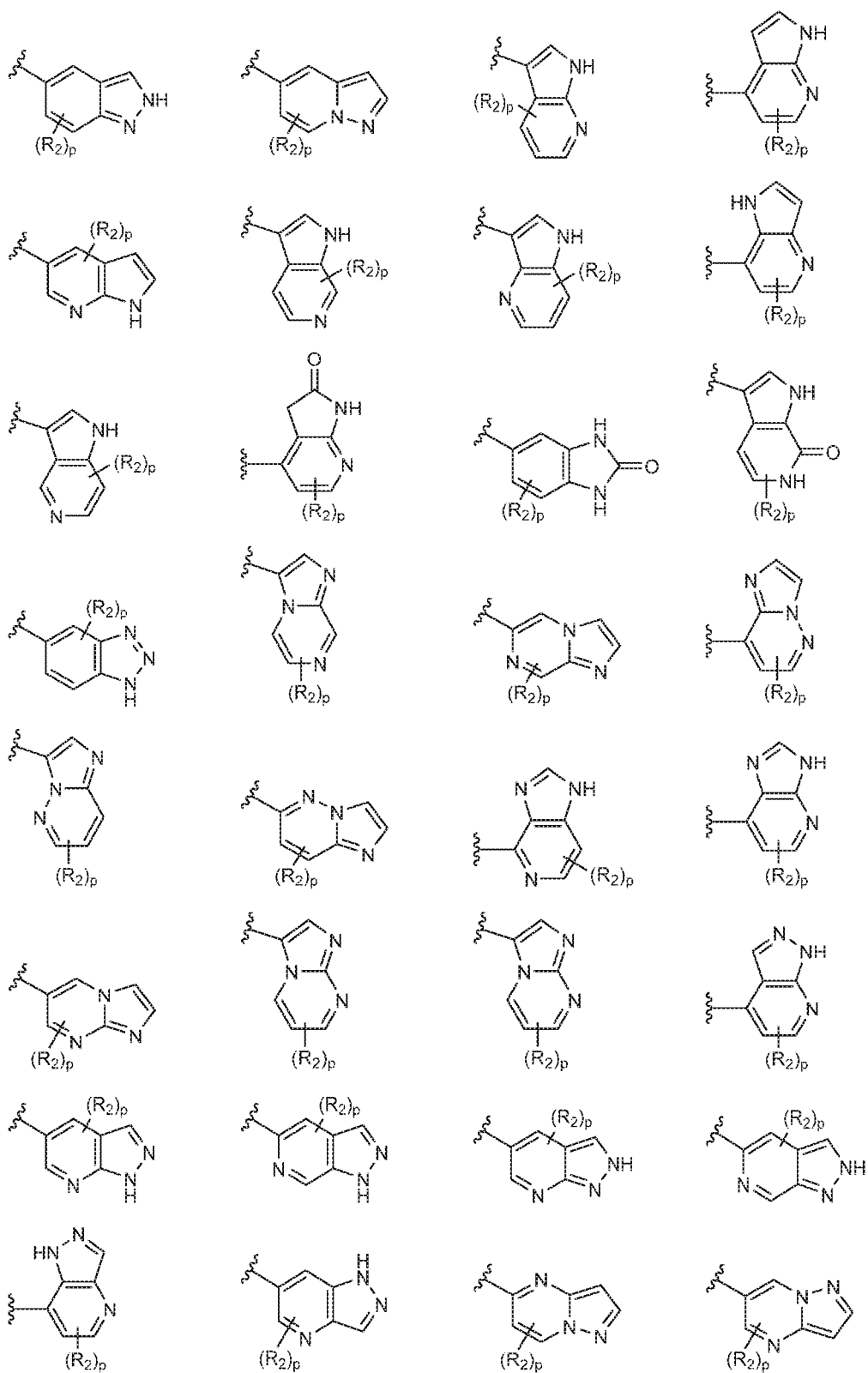
G is:

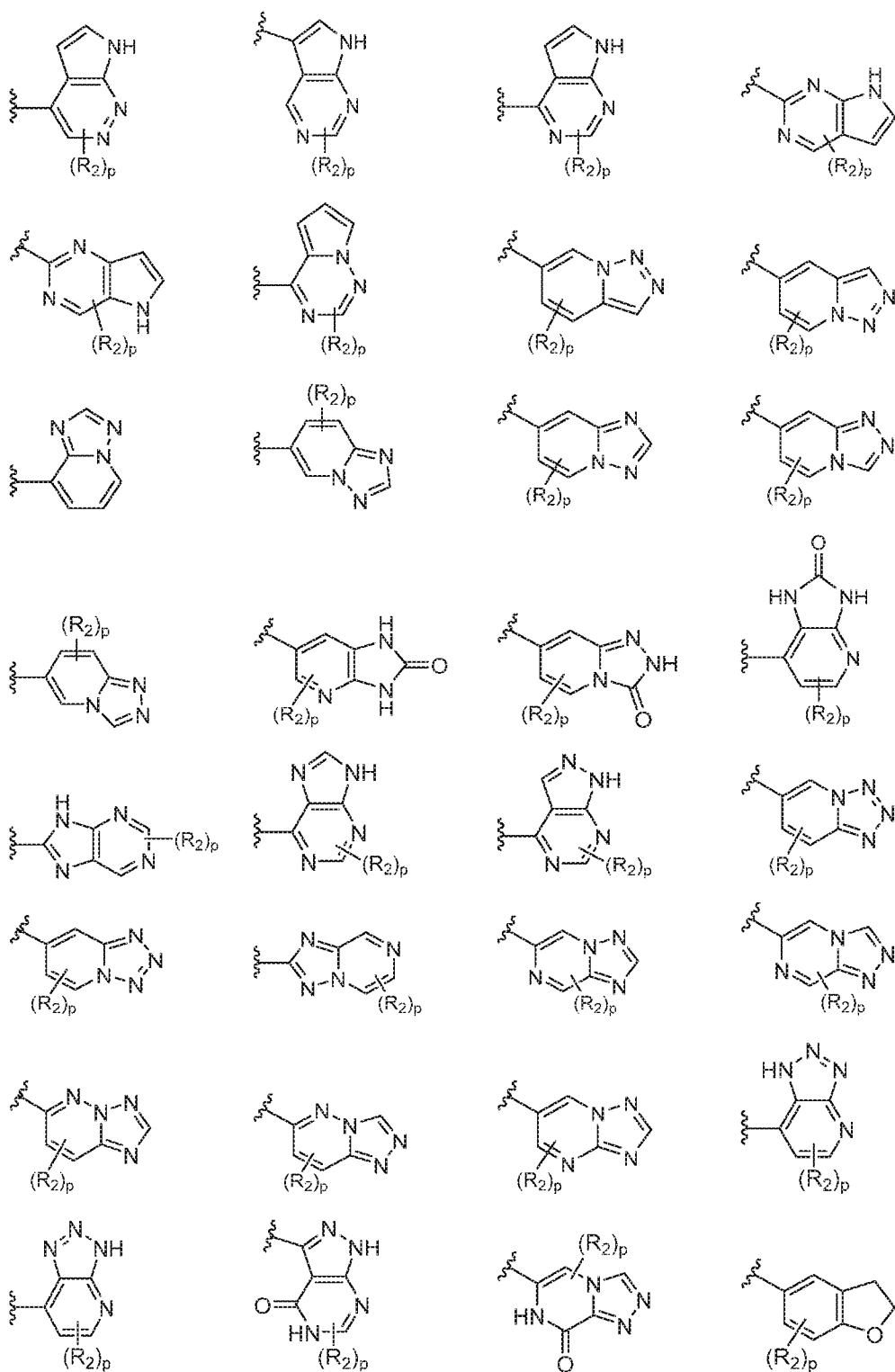


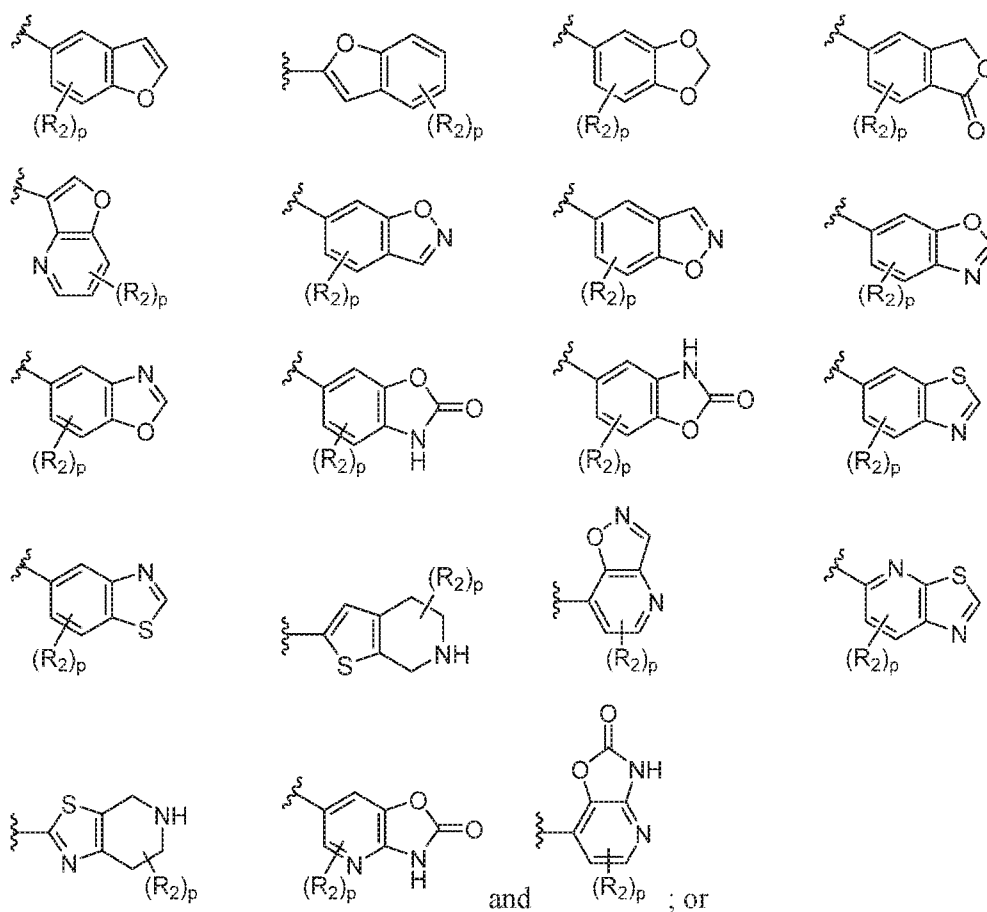
(iv) a 9-membered heterocyclic ring selected from:



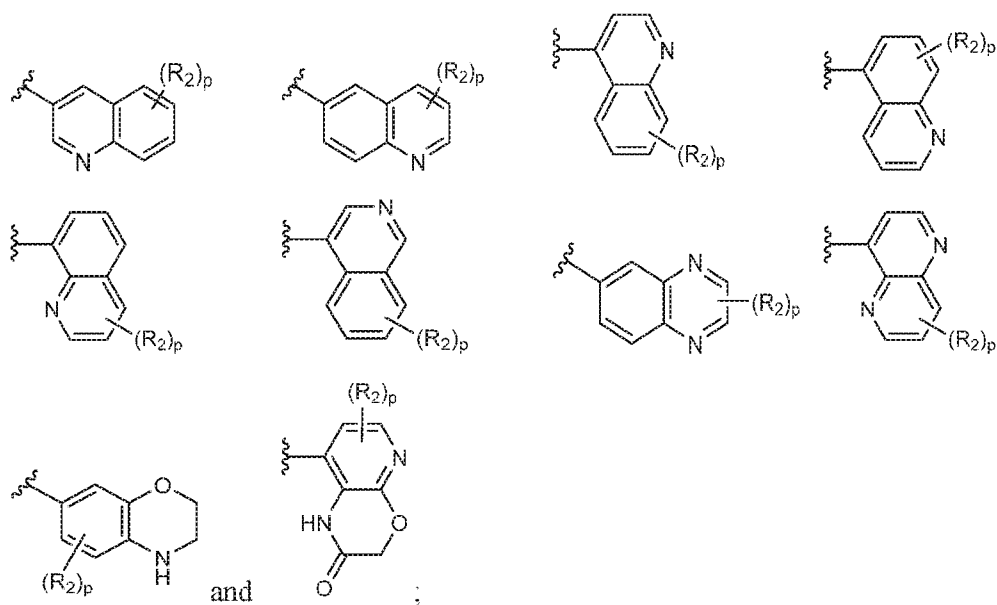
5







(v) a 10-membered heterocyclic ring selected from:



10 L₂ is a bond or $-(CR_xR_x)_{1-3}-$;

R₁ is H, Cl, -CN, C₁₋₄ alkyl, C₁₋₃ fluoroalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ hydroxy-fluoroalkyl, -CR_x=CH₂, C₃₋₆ cycloalkyl, -CH₂(C₃₋₆ cycloalkyl), -C(O)O(C₁₋₃ alkyl), or tetrahydropyranyl;

each R₂ is independently halo, -CN, -OH, -NO₂, C₁₋₄ alkyl, C₁₋₂ fluoroalkyl, C₁₋₂

- 5 cyanoalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ aminoalkyl, -O(CH₂)₁₋₂OH, -(CH₂)₀₋₄O(C₁₋₄ alkyl), C₁₋₃ fluoroalkoxy, -(CH₂)₁₋₄O(C₁₋₃ alkyl), -O(CH₂)₁₋₂OC(O)(C₁₋₃ alkyl), -O(CH₂)₁₋₂NR_xR_x, -C(O)O(C₁₋₃ alkyl), -(CH₂)₀₋₂C(O)NR_yR_y, -C(O)NR_x(C₁₋₅ hydroxyalkyl), -C(O)NR_x(C₂₋₆ alkoxyalkyl), -C(O)NR_x(C₃₋₆ cycloalkyl), -NR_yR_y, -NR_y(C₁₋₃ fluoroalkyl), -NR_y(C₁₋₄ hydroxyalkyl), -NR_xCH₂(phenyl),
- 10 -NR_xS(O)₂(C₃₋₆ cycloalkyl), -NR_xC(O)(C₁₋₃ alkyl), -NR_xCH₂(C₃₋₆ cycloalkyl), -S(O)₂(C₁₋₃ alkyl), -(CH₂)₀₋₂(C₃₋₆ cycloalkyl), -(CH₂)₀₋₂(phenyl), morpholinyl, dioxothiomorpholinyl, dimethyl pyrazolyl, methylpiperidinyl, methylpiperazinyl, amino-oxadiazolyl, imidazolyl, triazolyl, or -C(O)(thiazolyl);

R_{2a} is C₁₋₆ alkyl, C₁₋₃ fluoroalkyl, C₁₋₆ hydroxyalkyl, C₁₋₃ aminoalkyl, -(CH₂)₀₋₄O(C₁₋₃ alkyl), C₃₋₆ cycloalkyl, -(CH₂)₁₋₃C(O)NR_xR_x, -CH₂(C₃₋₆ cycloalkyl), -CH₂(phenyl),

15 tetrahydrofuranyl, tetrahydropyranyl, or phenyl;

each R_{2b} is independently H, halo, -CN, -NR_xR_x, C₁₋₆ alkyl, C₁₋₃ fluoroalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ fluoroalkoxy, -(CH₂)₀₋₂O(C₁₋₃ alkyl), -(CH₂)₀₋₃C(O)NR_xR_x, -(CH₂)₁₋₃(C₃₋₆ cycloalkyl), -C(O)O(C₁₋₃ alkyl), -C(O)NR_x(C₁₋₃ alkyl),

- 20 -CR_x=CR_xR_x, or -CR_x=CH(C₃₋₆ 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};

each R₅ is independently F, Cl, -CN, C₁₋₃ alkyl, C₁₋₂ fluoroalkyl, or -OCH₃;

- 25 R₉ is C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ hydroxy fluoroalkyl, C₁₋₃ aminoalkyl, -(CH₂)₁₋₂O(C₁₋₃ alkyl), -(CH₂)₁₋₃NR_xR_x, -(CH₂)₁₋₂C(O)NR_xR_x, -(CH₂)₁₋₃S(O)₂OH, -(CR_xR_x)₁₋₃NR_xS(O)₂(C₁₋₂ alkyl), or -(CH₂)₀₋₃R_{9a};

R_{9a} is C₃₋₇ cycloalkyl, furanyl, phenyl, piperazinyl, piperidinyl, pyrazolyl, pyridinyl, pyrrolidinyl, quinuclidinyl, thiazolyl, or octahydrocyclopenta[c]pyrrolyl, each

- 30 substituted with zero to 3 substituents independently selected from F, Cl, -OH, C₁₋₄

alkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ hydroxy fluoroalkyl, C₁₋₃ aminoalkyl, -NR_yR_y,
oxetanyl, phenyl, piperazinyl, piperidinyl, and pyrrolidinyl;

R₁₀ is H, C₁₋₄ alkyl, -(CH₂)₁₋₃O(C₁₋₂ alkyl), or C₃₋₆ cycloalkyl;

or R₉ and R₁₀ together with the nitrogen atom to which they are attached form a

- 5 heterocyclic ring selected from azabicyclo[3.1.1]heptanyl, azaspiro[5.5]undecanyl,
diazabicyclo[2.2.1]heptanyl, diazabicyclo[3.1.1]heptanyl,
diazabicyclo[3.2.0]heptanyl, diazaspiro[3.5]nonanyl, diazaspiro[4.4]nonanyl,
diazaspiro[4.5]decanyl, diazepanyl, indolynyl, morpholynyl, octahydropyrrolo[3,4-
c]pyrrolyl, piperazinonyl, piperazinyl, piperidinyl, and pyrrolidinyl, each substituted
10 with zero to 3 R_{10a};

each R_{10a} is independently selected from C₁₋₄ alkyl, C₁₋₄ hydroxyalkyl, -(CH₂)₁₋₃O(C₁₋₃
alkyl), -(CH₂)₁₋₃NR_xR_x, -(CH₂)₁₋₂C(O)NR_xR_x, -(CH₂)₁₋₂(methyltriazolyl),
-CH₂CH₂(phenyl), -CH₂CH₂(morpholynyl), -C(O)(C₁₋₂ alkyl), -C(O)NR_yR_y,
-C(O)CH₂NR_yR_y, -NR_yR_y, -NHC(O)(C₁₋₃ alkyl), -C(O)(furanyl), -O(piperidinyl),
15 -C(O)CH₂(diethylcarbamoylpiperidinyl), methylpiperazinyl, piperidinyl,
methylpiperidinyl, diethylcarbamoylpiperidinyl, isopropylpiperidinyl, pyridinyl,
trifluoromethylpyridinyl, pyrimidinyl, and dihydrobenzo[d]imidazolonyl;

R_v is H, C₁₋₂ alkyl, or C₁₋₂ fluoroalkyl;

each R_x is independently H or -CH₃;

- 20 each R_y is independently H or C₁₋₆ alkyl;

n is zero, 1, or 2; and

p is zero, 1, 2, 3, or 4.

2. The compound according to claim 1, N-oxide, or a salt thereof, wherein:

- 25 L₂ is a bond or -(CR_xR_x)₁₋₂-;

R₁ is H, Cl, -CN, C₁₋₄ alkyl, C₁₋₂ fluoroalkyl, C₁₋₂ hydroxyalkyl, or -C(O)O(C₁₋₂ alkyl);

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;

- 30 R_{2a} is C₁₋₄ alkyl, C₁₋₂ fluoroalkyl, C₁₋₄ hydroxyalkyl, -(CH₂)₁₋₃OCH₃, C₃₋₆ cycloalkyl,

$-\text{CH}_2\text{C}(\text{O})\text{NR}_x\text{R}_x$, $-\text{CH}_2(\text{C}_{3-6} \text{ cycloalkyl})$, $-\text{CH}_2(\text{phenyl})$, tetrahydrofuranyl, or phenyl;

each R_{2b} is independently H, F, Cl, $-\text{CN}$, $-\text{NR}_x\text{R}_x$, C_{1-6} alkyl, C_{1-2} fluoroalkyl, C_{1-3} hydroxyalkyl, $-(\text{CH}_2)_{0-2}\text{O}(\text{C}_{1-2} \text{ alkyl})$, $-(\text{CH}_2)_{0-2}\text{C}(\text{O})\text{NR}_x\text{R}_x$, $-(\text{CH}_2)_{1-3}(\text{cyclopropyl})$,
 5 $-\text{C}(\text{O})\text{O}(\text{C}_{1-2} \text{ alkyl})$, $-\text{C}(\text{O})\text{NR}_x(\text{C}_{1-3} \text{ alkyl})$, $-\text{CR}_x=\text{CH}_2$, or $-\text{CH}=\text{CH}(\text{C}_{3-6} \text{ cycloalkyl})$;

each R_5 is independently F, Cl, $-\text{CN}$, C_{1-2} alkyl, or $-\text{OCH}_3$;

R_9 is C_{1-3} alkyl, C_{1-5} hydroxyalkyl, C_{2-5} hydroxy fluoroalkyl, C_{1-2} aminoalkyl,
 $-(\text{CH}_2)_{1-2}\text{O}(\text{C}_{1-2} \text{ alkyl})$, $-(\text{CH}_2)_{1-3}\text{N}(\text{CH}_3)_2$, $-(\text{CH}_2)_{1-2}\text{C}(\text{O})\text{NH}_2$, $-(\text{CH}_2)_{1-2}\text{S}(\text{O})_2\text{OH}$,
 10 $-(\text{CH}_2)_{1-2}\text{CR}_x\text{R}_x\text{NHS}(\text{O})_2\text{CH}_3$, or $-(\text{CH}_2)_{0-3}\text{R}_{9a}$;

R_{9a} is C_{5-7} cycloalkyl, furanyl, phenyl, piperazinyl, piperidinyl, pyrazolyl, pyridinyl, pyrrolidinyl, quinuclidinyl, thiazolyl, or octahydrocyclopenta[c]pyrrolyl, each substituted with zero to 2 substituents independently selected from $-\text{OH}$, C_{1-3} alkyl, $-\text{NR}_x\text{R}_x$, oxetanyl, phenyl, piperazinyl, piperidinyl, and pyrrolidinyl;

15 R_{10} is H, C_{1-3} alkyl, $-(\text{CH}_2)_{1-2}\text{O}(\text{C}_{1-2} \text{ alkyl})$, or C_{3-6} cycloalkyl;

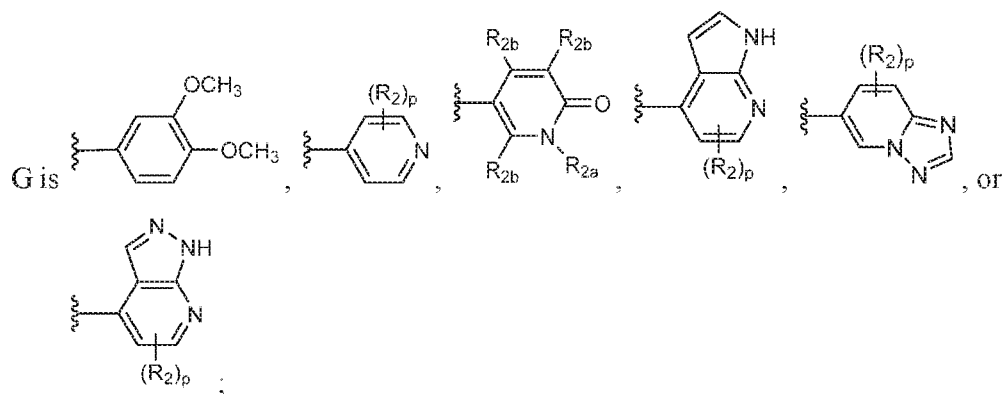
or R_9 and R_{10} together with the nitrogen atom to which they are attached form a heterocyclic ring selected from azabicyclo[3.1.1]heptanyl, azaspiro[5.5]undecanyl, diazabicyclo[2.2.1]heptanyl, diazabicyclo[3.1.1]heptanyl, diazabicyclo[3.2.0]heptanyl, diazaspiro[3.5]nonanyl, diazaspiro[4.4]nonanyl,
 20 diazaspiro[4.5]decanyl, diazepanyl, indolinyl, morpholinyl, octahydropyrrolo[3,4-c]pyrrolyl, piperazinonyl, piperazinyl, piperidinyl, and pyrrolidinyl, each substituted with zero to 3 R_{10a} ;

each R_{10a} is independently selected from C_{1-3} alkyl, C_{1-3} hydroxyalkyl, $-(\text{CH}_2)_{1-2}\text{O}(\text{C}_{1-2} \text{ alkyl})$, $-(\text{CH}_2)_{1-2}\text{NR}_x\text{R}_x$, $-\text{CH}_2\text{C}(\text{O})\text{NR}_x\text{R}_x$, $-\text{CH}_2(\text{methyltriazolyl})$,
 25 $-\text{CH}_2\text{CH}_2(\text{phenyl})$, $-\text{CH}_2\text{CH}_2(\text{morpholinyl})$, $-\text{C}(\text{O})(\text{C}_{1-2} \text{ alkyl})$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{N}(\text{C}_{1-2} \text{ alkyl})_2$, $-\text{C}(\text{O})\text{CH}_2\text{NR}_x\text{R}_x$, $-\text{NR}_x\text{R}_x$, $-\text{NHC}(\text{O})(\text{C}_{1-2} \text{ alkyl})$, $-\text{C}(\text{O})(\text{furanyl})$, $-\text{O}(\text{piperidinyl})$, $-\text{C}(\text{O})\text{CH}_2(\text{diethylcarbamoylpiperidinyl})$, methylpiperazinyl, piperidinyl, methylpiperidinyl, diethylcarbamoylpiperidinyl, isopropylpiperidinyl, pyridinyl, trifluoromethylpyridinyl, pyrimidinyl, and
 30 dihydrobenzo[d]imidazolonyl;

n is zero or 1; and

p is zero, 1, 2, or 3.

3. The compound according to claim 1, N-oxide, or a salt thereof, wherein:



L₂ is a bond, $-\text{CH}(\text{CH}_3)-$, $-\text{C}(\text{CH}_3)_2-$, or $-\text{CH}_2\text{CH}_2-$;

R₁ is $-\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CHF}_2$, or $-\text{CH}_2\text{CF}_3$;

each R₂ is independently $-\text{CH}_3$, $-\text{OCH}_3$, or $-\text{NH}_2$;

R_{2a} is $-\text{CH}_3$;

10 each R_{2b} is independently H, Cl, or $-\text{CH}_3$;

R₉ is $-\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{OH}$, $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2\text{OH}$,
 $-\text{CH}_2\text{CHFC}(\text{CH}_3)_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_2\text{OH}$, $-\text{CH}(\text{CH}_2\text{OH})_2$, $-\text{CH}_2\text{CH}_2\text{OCH}_3$,
 $-\text{CH}_2\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$,
 $-\text{CH}_2\text{S}(\text{O})_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_2\text{NHS}(\text{O})_2\text{CH}_3$, or $-(\text{CH}_2)_{0-3}\text{R}_{9a}$;

15 R_{9a} is cyclohexyl, cycloheptyl, furanyl, phenyl, piperazinyl, piperidinyl, pyrazolyl,
 pyridinyl, pyrrolidinyl, quinuclidinyl, thiazolyl, or octahydrocyclopenta[c]pyrrolyl,
 each substituted with zero to 2 substituents independently selected from $-\text{OH}$, C₁₋₃
 alkyl, $-\text{NH}_2$, $-\text{N}(\text{CH}_3)_2$, oxetanyl, phenyl, piperazinyl, piperidinyl, and pyrrolidinyl;

R₁₀ is H, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{OCH}_3$, or cyclopropyl;

20 or R₉ and R₁₀ together with the nitrogen atom to which they are attached form a
 heterocyclic ring selected from azabicyclo[3.1.1]heptanyl, azaspiro[5.5]undecanyl,
 diazabicyclo[2.2.1]heptanyl, diazabicyclo[3.1.1]heptanyl,
 diazabicyclo[3.2.0]heptanyl, diazasp[3.5]nonanyl, diazasp[4.4]nonanyl,
 diazasp[4.5]decanyl, diazepanyl, indolinyl, morpholinyl, octahydropyrrolo[3,4-
 25 c]pyrrolyl, piperazinonyl, piperazinyl, piperidinyl, and pyrrolidinyl, each substituted

with zero to 2 R_{10a};

each R_{10a} is independently selected from -CH₃, -CH₂CH₃, -CH(CH₃)₂, -CH₂OH,
 -CH₂CH₂OH, -CH₂OCH₃, -CH₂CH₂OCH₃, -CH₂NH₂, -CH₂CH₂NH₂,
 -CH₂CH₂NH(CH₃), -CH₂C(O)NH(CH₃), -CH₂C(O)N(CH₃)₂, -CH₂(methyltriazolyl),
 5 -CH₂CH₂(phenyl), -CH₂CH₂(morpholinyl), -C(O)CH₃, -C(O)NH₂,
 -C(O)N(CH₂CH₃)₂, -C(O)CH₂NH(CH₃), -C(O)CH₂N(CH₃)₂, -NH₂, -N(CH₃)₂,
 -NHC(O)CH₃, -C(O)(furanyl), -O(piperidinyl),
 -C(O)CH₂(diethylcarbamoylpiperidinyl), methylpiperazinyl, piperidinyl,
 methylpiperidinyl, diethylcarbamoylpiperidinyl, isopropylpiperidinyl, pyridinyl,
 10 trifluoromethylpyridinyl, pyrimidinyl, and dihydrobenzo[d]imidazolonyl;

n is zero; and

p is zero, 1, or 2.

4. The compound according to claim 1, N-oxide, or a salt thereof, wherein:

- 15 R₉ is C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ hydroxy fluoroalkyl, C₁₋₃ aminoalkyl,
 -(CH₂)₁₋₂O(C₁₋₃ alkyl), -(CH₂)₁₋₃NR_xR_x, -(CH₂)₁₋₂C(O)NR_xR_x, -(CH₂)₁₋₃S(O)₂OH,
 -(CR_xR_x)₁₋₃NR_xS(O)₂(C₁₋₂ alkyl), or -(CH₂)₀₋₃R_{9a}; and
 R₁₀ is H, C₁₋₄ alkyl, -(CH₂)₁₋₃O(C₁₋₂ alkyl), or C₃₋₆ cycloalkyl.

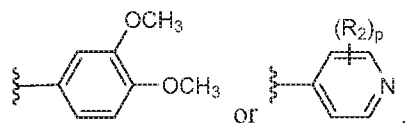
- 20 5. The compound according to claim 1, N-oxide, or a salt thereof, wherein R₉ and R₁₀
 together with the nitrogen atom to which they are attached form a heterocyclic ring
 selected from azabicyclo[3.1.1]heptanyl, azaspiro[5.5]undecanyl,
 diazabicyclo[2.2.1]heptanyl, diazabicyclo[3.1.1]heptanyl, diazabicyclo[3.2.0]heptanyl,
 diazaspiro[3.5]nonanyl, diazaspiro[4.4]nonanyl, diazaspiro[4.5]decanyl, diazepanyl,
 25 indolinyl, morpholinyl, octahydropyrrolo[3,4-c]pyrrolyl, piperazinonyl, piperazinyl,
 piperidinyl, and pyrrolidinyl, each substituted with zero to 3 R_{10a}.

6. The compound according to claim 1, N-oxide, or a salt thereof, wherein L₂ is a bond.

- 30 7. The compound according to claim 1, N-oxide, or a salt thereof, wherein L₂ is
 -(CR_xR_x)₁₋₂-.

8. The compound according to claim 1, N-oxide, or a salt thereof, wherein L₂ is -CH(CH₃)-, -C(CH₃)₂-, or -CH₂CH₂-.

5 9. The compound according to claim 1, N-oxide, or a salt thereof, wherein G is:



10. The compound according to claim 1, N-oxide, or a salt thereof, wherein said compound is selected from: 2-(3,4-dimethoxyphenyl)-5-{octahydropyrrolo[3,4-c]pyrrole-2-carbonyl}-3-(propan-2-yl)-1H-indole (1); (2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl)(4-methyl-1,4-diazepan-1-yl)methanone (2); 2-(3,4-dimethoxyphenyl)-3-isopropyl-N,N-dimethyl-1H-indole-5-carboxamide (3); 2-(3,4-dimethoxyphenyl)-3-isopropyl-N-methyl-1H-indole-5-carboxamide (4); ((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl)methanone (5); 2-{5-[2-(3,4-dimethoxyphenyl)-3-(propan-2-yl)-1H-indole-5-carbonyl]-octahydropyrrolo[3,4-c]pyrrol-2-yl}-N,N-dimethylacetamide (6); 2-(5-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-methylacetamide (7); 1-(2-{5-[2-(3,4-dimethoxyphenyl)-3-(propan-2-yl)-1H-indole-5-carbonyl]-octahydropyrrolo[3,4-c]pyrrol-2-yl}-2-oxoethyl)-N,N-diethylpiperidine-3-carboxamide (8); 1-(5-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-(dimethylamino)ethan-1-one (9); 1-(2-{5-[2-(3,4-dimethoxyphenyl)-3-(propan-2-yl)-1H-indole-5-carbonyl]-octahydropyrrolo[3,4-c]pyrrol-2-yl}-2-oxoethyl)-N,N-diethylpiperidine-3-carboxamide (10-11); 3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl)(5-(2-(methylamino)ethyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (12); (2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl)(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (13); (2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl)(5-isopropylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (14); (2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl)(5-(1-methylpiperidin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (15); 1-(5-(2-(3,4-dimethoxyphenyl)-

3-isopropyl-1H-indole-5-carbonyl)hexahydro pyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-(methylamino) ethanone (16); 2-(3,4-dimethoxyphenyl)-N-[2-(dimethylamino)ethyl]-3-ethyl-1H-indole-5-carboxamide (17); (R)-2-(3,4-dimethoxyphenyl)-3-ethyl-N-(2-fluoro-3-hydroxy-3-methylbutyl)-1H-indole-5-carboxamide (18); 2-(3,4-dimethoxyphenyl)-N-(4-(dimethylamino)cyclohexyl)-3-ethyl-1H-indole-5-carboxamide (19); N-cycloheptyl-2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carboxamide (20); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)-1H-indole-5-carboxamide (21); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-methyl-N-(pyridin-3-ylmethyl)-1H-indole-5-carboxamide (22); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-methyl-N-((2-(piperidin-4-yl)thiazol-4-yl)methyl)-1H-indole-5-carboxamide (23); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-methyl-N-(2-(pyridin-2-yl)ethyl)-1H-indole-5-carboxamide (24); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl) (4-(4-methylpiperazin-1-yl)piperidin-1-yl)methanone (25); (R)-1-(1-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carbonyl)pyrrolidin-3-yl)propan-2-one (26); (S)-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(2-(methoxymethyl)pyrrolidin-1-yl)methanone (27); (S)-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone (28); (R)-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(3-(dimethylamino) pyrrolidin-1-yl)methanone (29); (S)-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(3-(dimethylamino)pyrrolidin-1-yl)methanone (30); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(dimethylamino)piperidin-1-yl)methanone (31); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(3,3-dimethylpiperidin-1-yl)methanone (32); 1-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carbonyl)-N,N-diethylpiperidine-3-carboxamide (33); 1-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carbonyl)piperidine-4-carboxamide (34); 1-(4-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carbonyl)-1,4-diazepan-1-yl)ethan-1-one (35); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(1-methylpiperidin-4-yl) piperazin-1-yl)methanone (36); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-phenethylpiperazin-1-yl)methanone (37); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl) (4-isopropylpiperazin-1-yl)methanone (38); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-ethylpiperazin-1-yl)methanone (39); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl) (4-(2-hydroxyethyl)piperazin-1-yl)methanone (40); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(2-methoxyethyl)piperazin-1-yl)methanone (41); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(2-morpholinoethyl)piperazin-

1-yl)methanone (42); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(furan-2-ylmethyl)-1H-indole-5-carboxamide (43); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(pyridin-2-ylmethyl)-1H-indole-5-carboxamide (44); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-((2-phenylthiazol-4-yl)methyl)-1H-indole-5-carboxamide (45); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(4-(piperazin-1-yl)benzyl)-1H-indole-5-carboxamide (46); N-((1r,4r)-4-aminocyclohexyl)-2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carboxamide (47); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(2-(pyrrolidin-1-yl)ethyl)-1H-indole-5-carboxamide (48); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(2-(piperidin-1-yl)ethyl)-1H-indole-5-carboxamide (49); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(2-(pyridin-4-yl)ethyl)-1H-indole-5-carboxamide (50); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(2-(pyridin-3-yl)ethyl)-1H-indole-5-carboxamide (51); N-(4-aminobenzyl)-2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carboxamide (52); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(3-(piperidin-1-yl)propyl)-1H-indole-5-carboxamide (53); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(2-(1-methylpyrrolidin-2-yl)ethyl)-1H-indole-5-carboxamide (54); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(3-(4-methylpiperazin-1-yl)propyl)-1H-indole-5-carboxamide (55); [1,4'-bipiperidin]-1'-yl(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)methanone (56); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone (57); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(pyrazin-2-yl)piperazin-1-yl)methanone (58); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(pyridin-2-yl)piperazin-1-yl)methanone (59); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(furan-2-carbonyl)piperazin-1-yl)methanone (60); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)methanone (61); 4-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carbonyl)piperazin-2-one (62); 1-(1-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carbonyl)piperidin-4-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one (63); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(pyrimidin-2-yl)-1,4-diazepan-1-yl)methanone (64); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(pyridin-2-yl)-1,4-diazepan-1-yl)methanone (65); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(indolin-1-yl)methanone (66); N-(1,3-dihydroxypropan-2-yl)-2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carboxamide (67); N-(3-amino-3-oxopropyl)-2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carboxamide (68); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(2-hydroxyethyl)-1H-indole-5-carboxamide (69); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carboxamido)methanesulfonic acid

(70); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(3-methyl-3-(methylsulfonamido)butyl)-1H-indole-5-carboxamide (71); 2-(3,4-dimethoxyphenyl)-3-ethyl-N-(3-hydroxy-2,2-dimethylpropyl)-1H-indole-5-carboxamide (72); 2-(3,4-dimethoxyphenyl)-N-(2-(dimethylamino)ethyl)-N,3-diethyl-1H-indole-5-carboxamide (73); 2-(3,4-dimethoxyphenyl)-N-(3-(dimethylamino)propyl)-3-ethyl-N-methyl-1H-indole-5-carboxamide (74); 2-(3,4-dimethoxyphenyl)-N-(3-(dimethylamino)propyl)-3-ethyl-1H-indole-5-carboxamide (75); 2-(3,4-dimethoxyphenyl)-N-(2-(dimethylamino)ethyl)-3-ethyl-N-methyl-1H-indole-5-carboxamide (76); 2-(3,4-dimethoxyphenyl)-3-ethyl-N,N-bis(2-methoxyethyl)-1H-indole-5-carboxamide (77); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(piperazin-1-yl)methanone hydrochloride (78); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (79); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(4-(1-isopropylpiperidin-4-yl) piperazin-1-yl)methanone (80); (2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indol-5-yl)(5-isopropylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (81); 2-(5-(2-(3,4-dimethoxyphenyl)-3-ethyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-methylacetamide (82); N-(2-(dimethylamino)ethyl)-N,3-diethyl-2-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-indole-5-carboxamide (83); N-(2-(dimethylamino)ethyl)-N,3-diethyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carboxamide (84); (3-ethyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (85); (3-ethyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)(5-isopropylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (86); 2-(2-aminopyridin-4-yl)-N-(4-(dimethylamino)cyclohexyl)-3-isopropyl-1H-indole-5-carboxamide (87); (2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indol-5-yl)(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone hydrochloride (88); 1-(5-(2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-(dimethylamino)ethan-1-one (89); 2-(5-(2-(3,4-dimethoxyphenyl)-3-(2,2,2-trifluoroethyl)-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N,N-dimethylacetamide (90); 2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-N-(1-isopropylpiperidin-4-yl)-1H-indole-5-carboxamide (91); (2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indol-5-yl)(4-methyl-1,4-diazepan-1-yl)methanone (92); N-(2-(dimethylamino)ethyl)-2-(2,6-dimethylpyridin-4-yl)-N-ethyl-3-isopropyl-1H-indole-5-carboxamide (93); 2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-N,N-dimethyl-1H-indole-5-carboxamide (94); N-(3-(dimethylamino)propyl)-2-

(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indole-5-carboxamide (95); N-(2-(dimethylamino)ethyl)-2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indole-5-carboxamide (96); 2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-N-methyl-1H-indole-5-carboxamide (97); (2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indol-5-yl)(4-((1-methyl-1H-1,2,4-triazol-3-yl)methyl)piperazin-1-yl)methanone (98); N-benzyl-2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-N-methyl-1H-indole-5-carboxamide (99); 2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-N-methyl-N-(pyridin-3-ylmethyl)-1H-indole-5-carboxamide (100); 2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-N-methyl-N-(1-methylpiperidin-4-yl)-1H-indole-5-carboxamide (101); 2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-N-methyl-N-phenethyl-1H-indole-5-carboxamide (102); N-(3-aminobenzyl)-2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-N-methyl-1H-indole-5-carboxamide (103); (4-(dimethylamino)piperidin-1-yl)(2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indol-5-yl)methanone (104); 2-(2,6-dimethylpyridin-4-yl)-N-(2-hydroxyethyl)-3-isopropyl-N-methyl-1H-indole-5-carboxamide (105); 2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-N-(2-methoxyethyl)-N-methyl-1H-indole-5-carboxamide (106); (2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indol-5-yl)(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone, HCl (107); (2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indol-5-yl)(piperazin-1-yl)methanone (108); (2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indol-5-yl)(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (109); (2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indol-5-yl)(5-isopropylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (110); 2-(dimethylamino)-1-(5-(2-(2,6-dimethylpyridin-4-yl)-3-isopropyl-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethanone (111); (hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)methanone, HCl (112); 3-isopropyl-N-(1-isopropylpiperidin-4-yl)-2-(2-methylpyridin-4-yl)-1H-indole-5-carboxamide (113); (3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)(4-methyl-1,4-diazepan-1-yl)methanone (114); (3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (115); (3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)(5-isopropylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (116); 2-(5-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N,N-dimethylacetamide (117); 2-(5-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-N-methylacetamide (118); 1-(5-(3-

isopropyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carbonyl) hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-(methylamino)ethanone (119); 2-(dimethylamino)-1-(5-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indole-5-carbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)ethan-1-one (120); (hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(3-isopropyl-2-(1H-pyrazolo[3,4-b]pyridin-4-yl)-1H-indol-5-yl)methanone, HCl (121); (3-(2,2-difluoroethyl)-2-(2,6-dimethylpyridin-4-yl)-1H-indol-5-yl)(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone (122); 3-(2,2-difluoroethyl)-2-(2,6-dimethylpyridin-4-yl)-N-(1-isopropylpiperidin-4-yl)-1H-indole-5-carboxamide (123); (3-(2,2-difluoroethyl)-2-(2,6-dimethylpyridin-4-yl)-1H-indol-5-yl)(4-methyl-1,4-diazepan-1-yl)methanone (124); 3-(2,2-difluoroethyl)-N-(2-(dimethylamino)ethyl)-2-(2,6-dimethylpyridin-4-yl)-N-ethyl-1H-indole-5-carboxamide (125); (hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(3-isopropyl-2-(8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-1H-indol-5-yl)methanone (126); 3-isopropyl-N-(1-isopropylpiperidin-4-yl)-2-(8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-1H-indole-5-carboxamide (127); (3-isopropyl-2-(8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-1H-indol-5-yl)(4-methyl-1,4-diazepan-1-yl)methanone (128); N-(2-(dimethylamino)ethyl)-3-isopropyl-2-(8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-N-methyl-1H-indole-5-carboxamide (129); N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propanamide (130); N-(2-hydroxy-2-methylpropyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propanamide (131); N-(3-hydroxy-3-methylbutyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propanamide (132); (R)-N-(2-fluoro-3-hydroxy-3-methylbutyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropanamide (133); N-(2-aminoethyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropanamide (134); N-(3-hydroxy-3-methylbutyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropanamide (135); 3-(3-isopropyl-2-(1H-pyrazolo[3,4-b]pyridin-4-yl)-1H-indol-5-yl)-1-morpholinopropan-1-one (136); 3-(2-(3,4-dimethoxyphenyl)-3-isopropyl-1H-indol-5-yl)-1-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)propan-1-one (137); (S)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(pyrrolidin-3-yl)propanamide (138); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-(1-isopropylpiperidin-4-yl)-2-methylpropanamide (139); (R)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(piperidin-3-yl)propanamide (140); (R)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(pyrrolidin-3-

- yl)propanamide (141); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(quinuclidin-3-yl)propanamide (142); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(piperidin-4-yl)propanamide (143); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(octahydrocyclopenta[c]pyrrol-4-yl)propanamide (144); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(1-(pyrrolidin-3-yl)piperidin-4-yl)propanamide (145); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(octahydrocyclopenta[c]pyrrol-4-yl)propanamide (146); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(octahydrocyclopenta[c]pyrrol-4-yl)propanamide (147); 1-(6-amino-3-azabicyclo[3.1.1]heptan-3-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropan-1-one (148); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-1-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)propan-1-one (149); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-1-(2-methyl-2,8-diazaspiro[4.5]decan-8-yl)propan-1-one (150); 1-(3-(aminomethyl)pyrrolidin-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropan-1-one (151); 1-(7-amino-2-azaspiro[5.5]undecan-2-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropan-1-one (152); 1-(4-aminopiperidin-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropan-1-one (153); 1-(3-(2-aminoethyl)piperidin-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropan-1-one (154); (S)-1-(3-aminopiperidin-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropan-1-one (155); 1-(3-(aminomethyl)piperidin-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropan-1-one (156); 1-(2-(aminomethyl)piperidin-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropan-1-one (157); 1-(4-(aminomethyl)piperidin-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropan-1-one (158); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(piperidin-2-ylmethyl)propanamide (159); (S)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(pyrrolidin-3-ylmethyl)propanamide (160); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N,2-dimethyl-N-(piperidin-3-yl)propanamide (161); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N,2-dimethyl-N-(quinuclidin-3-yl)propanamide (162); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(piperidin-3-ylmethyl)propanamide

(163); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(piperidin-4-ylmethyl)propanamide (164); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N,2-dimethyl-N-(piperidin-4-yl)propanamide (165); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-((1R,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)propanamide (166); N-(4-aminocyclohexyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropanamide (167); N-(3-aminocyclohexyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropanamide (168); N-((1R,2R)-2-aminocyclohexyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropanamide (169); N-((1S,2R)-2-aminocyclohexyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropanamide (170); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-N-(2-(piperidin-3-yl)ethyl)propanamide (171); N-(((1r,4r)-4-aminocyclohexyl)methyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropanamide (172); N-((4-hydroxy-1-methylpiperidin-4-yl)methyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropanamide (173); N-((3-hydroxyquinuclidin-3-yl)methyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropanamide (174); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-1-(piperazin-1-yl)propan-1-one (175); 1-(2,5-diazabicyclo[2.2.1]heptan-2-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropan-1-one (176); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-1-(4-(piperidin-4-yloxy)piperidin-1-yl)propan-1-one (177); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-1-(2,7-diazaspiro[4.4]nonan-2-yl)propan-1-one (178); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-1-(2,7-diazaspiro[3.5]nonan-2-yl)propan-1-one (179); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-1-(2,6-diazaspiro[3.5]nonan-6-yl)propan-1-one (180); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-1-(2,8-diazaspiro[4.5]decan-8-yl)propan-1-one (181); 1-([2,4'-bipiperidin]-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropan-1-one (182); 1-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropan-1-one (183); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methyl-1-(2,7-diazaspiro[4.5]decan-7-yl)propan-1-one (184); 1-(3,6-diazabicyclo[3.2.0]heptan-3-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-2-methylpropan-1-one (185); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-(octahydrocyclopenta[c]pyrrol-4-

yl)propanamide (186); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-(octahydrocyclopenta[c]pyrrol-4-yl)propanamide (187); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-((R)-pyrrolidin-3-yl)propanamide (188); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-((S)-pyrrolidin-3-yl)propanamide (189); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-((S)-pyrrolidin-3-yl)propanamide (190); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-(quinuclidin-3-yl)propanamide (191); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-(quinuclidin-3-yl)propanamide (192); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-(piperidin-4-yl)propanamide (193); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-(1-isopropylpiperidin-4-yl)propanamide (194); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-((R)-piperidin-3-yl)propanamide (195); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-((R)-piperidin-3-yl)propanamide (196); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-1-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)propan-1-one (197); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-1-(2-methyl-2,8-diazaspiro[4.5]decan-8-yl)propan-1-one (198); 1-(3-(aminomethyl)pyrrolidin-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propan-1-one (199); 1-(7-amino-2-azaspiro[5.5]undecan-2-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propan-1-one (200); 1-(7-amino-2-azaspiro[5.5]undecan-2-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propan-1-one (201); 1-(4-(aminomethyl)piperidin-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propan-1-one (202); 1-(4-aminopiperidin-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propan-1-one (203); 1-((S)-3-aminopiperidin-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propan-1-one (204); 1-(3-(aminomethyl)piperidin-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propan-1-one (205); 1-(3-(2-aminoethyl)piperidin-1-yl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propan-1-one (206); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-methyl-N-(piperidin-4-yl)propanamide (207); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-(((R)-pyrrolidin-3-yl)methyl)propanamide (208); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-methyl-N-(piperidin-3-yl)propanamide (209); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-methyl-N-(piperidin-3-yl)propanamide (210); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-methyl-N-(quinuclidin-3-yl)propanamide (211); 2-

(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-(((S)-pyrrolidin-3-yl)methyl)propanamide (212); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-(piperidin-3-ylmethyl)propanamide (213); 2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)-N-((1R,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)propanamide (214); N-
 5 ((1R,2R)-2-aminocyclohexyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propanamide (215); N-((1R,2R)-2-aminocyclohexyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propanamide (216); N-(4-aminocyclohexyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propanamide (217); N-(3-aminocyclohexyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propanamide
 10 (218); N-(3-aminocyclohexyl)-2-(3-isopropyl-2-(2-methylpyridin-4-yl)-1H-indol-5-yl)propanamide (219); 3-chloro-5-(3-isopropyl-5-(4-methylpiperazine-1-carbonyl)-1H-indol-2-yl)-1,4-dimethylpyridin-2(1H)-one (220); 2-(5-chloro-1,4-dimethyl-6-oxo-1,6-dihydropyridin-3-yl)-N-cyclopropyl-3-isopropyl-N-(1-propylpiperidin-4-yl)-1H-indole-5-carboxamide (221); and 2-(5-chloro-1,4-dimethyl-6-oxo-1,6-dihydropyridin-3-yl)-N-(2-
 15 (dimethylamino)ethyl)-3-isopropyl-N-methyl-1H-indole-5-carboxamide (222).

11. A pharmaceutical composition comprising a compound according to any one of claims 1-10 or a pharmaceutically-acceptable salt thereof; and a pharmaceutically acceptable carrier.

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12. A compound according to any one of claims 1-10 or a pharmaceutically-acceptable salt thereof, or a pharmaceutically-acceptable salt thereof, for use in treating autoimmune disease or chronic inflammatory disease.

25 13. The compound according to claim 12 or a pharmaceutically-acceptable salt thereof, wherein said autoimmune disease or chronic inflammatory disease is selected from systemic lupus erythematosus (SLE), rheumatoid arthritis, multiple sclerosis (MS), and Sjögren's syndrome.

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER				
INV.	C07D401/14	C07D405/14	C07D401/04	C07D401/12
	C07D403/14	C07D405/12	C07D417/12	C07D417/14
	C07D471/04	C07D471/10	C07D487/04	C07D487/08
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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) 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, CHEM ABS Data				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages			Relevant to claim No.
A	US 6 306 874 B1 (FRALEY MARK E [US] ET AL) 23 October 2001 (2001-10-23) columns 3,4; claim 1			1-13
A	WO 03/057696 A1 (EISAI CO LTD [JP]; DAUN JANE [US]; DAVIS HEATHER A [US]; GUSOVSKY FABI) 17 July 2003 (2003-07-17) page 1; claims 1,9,13,98			1-13
A	US 2011/183967 A1 (ZHENG WANJUN [US] ET AL) 28 July 2011 (2011-07-28) paragraphs [0001] - [0003]; claim 1			1-13
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☐ 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 5 February 2019			Date of mailing of the international search report 18/02/2019	
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 Grassi, Damian	

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