

1H-BENZO[D]IMIDAZOLE DERIVATIVES AS TLR9 INHIBITORS FOR
THE TREATMENT OF FIBROSIS

CROSS REFERENCE

- 5 This application claims the benefit of U.S. Provisional Application Serial No. 63/067,587 filed August 19, 2020 which is incorporated herein in its entirety.

DESCRIPTION

10 The present invention generally relates to substituted benzimidazole compounds useful as inhibitors of signaling through Toll-like receptor 9 (TLR9). Provided herein are substituted benzimidazole 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 or prophylaxis of fibrotic diseases and other diseases, disorders, and conditions
15 for which a TLR9 inhibitor is indicated.

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

 TLR9 levels are higher in lung biopsies of rapid idiopathic pulmonary fibrosis (IPF) progressors than in the healthy or stable IPF progressors (Sci. Transl. Med. 2010, 2(57):57ra82). Circulating mtDNA, the ligand for TLR9 has recently been identified as a
30 mechanism-based prognostic biomarker of IPF (Am J. Resp. and Crit. Care Med. 2017, 196(12), 1502). In addition, it has been observed that TLR9 is up-regulated in human and

murine non-alcoholic steatohepatitis (NASH) (Clin. Sci. 2017, 131(16), 2145), while hepatocyte mitochondrial DNA drives NASH via activation of TLR9 (J. Clin. Inv. 2016, 126(3), 859. Accordingly, inhibitors/antagonists of TLR9 are predicted to have efficacy as novel therapeutic agents to treat fibrotic diseases.

5 TLR9 inhibition has been recognized as a potential route to therapies for fibrotic diseases including idiopathic pulmonary fibrosis (Trujillo et al. *Sci. Transl. Med.* 2010, 2(57):57ra82; Yoshizaki et al. *Ann Rheum Dis.* 2016 Oct;75(10):1858-65), non-alcoholic steatohepatitis (Garcia-Martinez et al. *J Clin Invest* 2016 126: 859–864; Gabele et al. *Biochem Biophys Res Commun.* 2008;376:271–276), hepatic injury (Shaker et al. *Biochem Pharmacol.* 2016. 112:90-101; Hoeque et al. *J. Immun.* 2013, 190:4297-304),
10 and scleroderma (systemic sclerosis or SSc) (Yoshizaki et al. *Ann Rheum Dis.* 2016 Oct;75(10):1858-65); as well as heart failure (Oka et al. *Nature* 485, pages 251–255(2012)), and hypertension (McCarthy et al. *Cardiovascular Research*, 2015, Pages 119–130).

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

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

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

SUMMARY OF THE INVENTION

The present invention relates to a new class of substituted benzimidazole
30 compounds found to be effective inhibitors of signaling through TLR9. These compounds are provided to be useful as pharmaceuticals with desirable stability, bioavailability, therapeutic index, and toxicity values that are important to their

drugability.

The present invention provides compounds of Formula (I) that are useful as inhibitors of signaling through TLR9 and are useful for the treatment of fibrotic diseases, or stereoisomers, N-oxides, tautomers, pharmaceutically acceptable salts, solvates or
5 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.

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

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

The present invention also provides a method of treating a disease or disorder associated with TLR9 activity, the method comprising administering to a mammal in
20 need thereof, at least one of the compounds of Formula (I) or salts, solvates, and prodrugs thereof.

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

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

The present invention also provides the use of at least one of the compounds of Formula (I) or salts, solvates, and prodrugs thereof, for the manufacture of a medicament for the treatment of prophylaxis of TLR9 related conditions, such as fibrotic diseases, allergic diseases, autoimmune diseases, and inflammatory diseases.

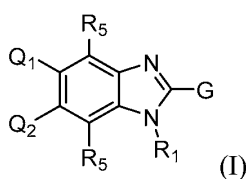
30 The compound of Formula (I) and compositions comprising the compounds of Formula (I) may be used in treating, preventing, or curing various TLR9 related conditions. Pharmaceutical compositions comprising these compounds are useful for

treating, preventing, or slowing the progression of diseases or disorders in a variety of therapeutic areas, such as fibrotic diseases, allergic diseases, autoimmune diseases, and inflammatory diseases.

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 Formula (I):



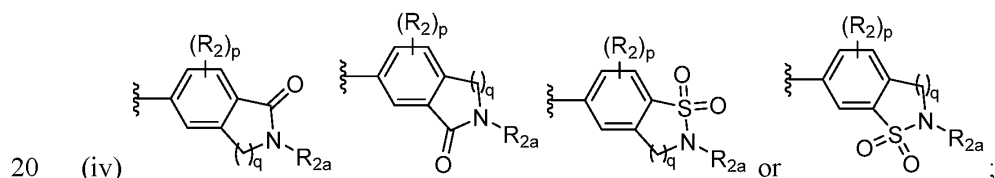
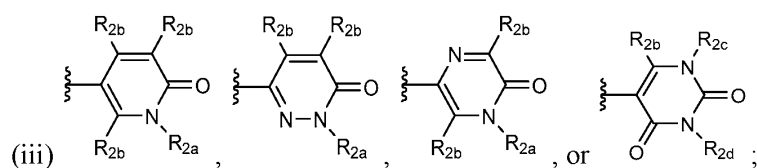
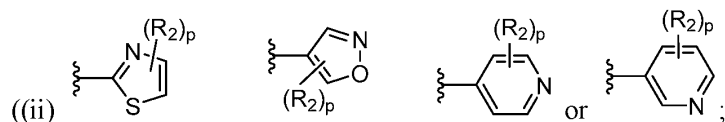
or stereoisomers, tautomer, solvates or salts thereof, wherein:

one of Q₁ and Q₂ is A and the other of Q₁ and Q₂ is R₅;

G is:

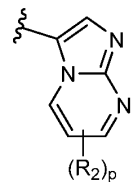
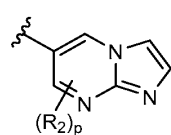
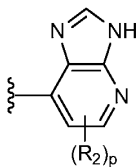
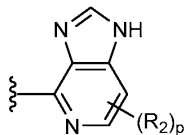
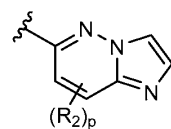
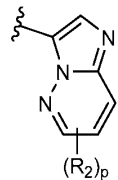
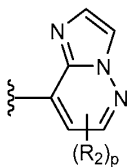
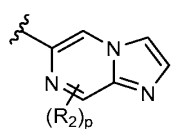
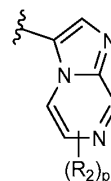
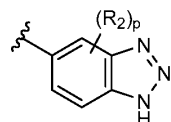
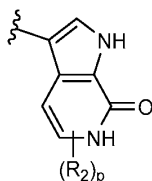
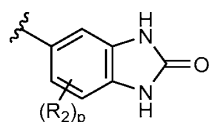
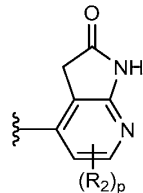
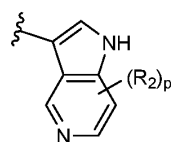
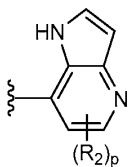
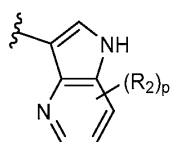
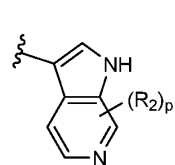
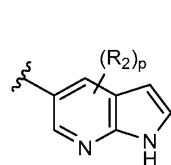
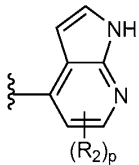
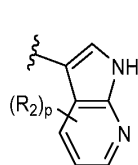
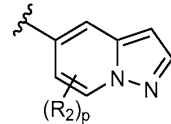
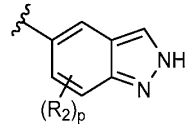
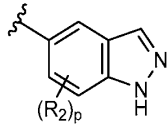
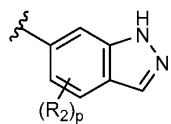
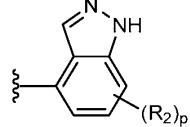
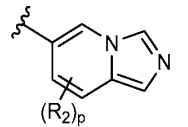
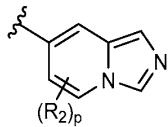
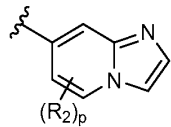
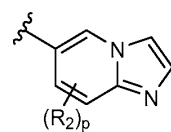
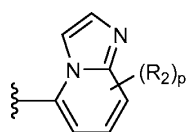
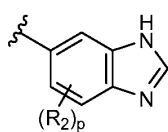
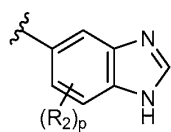
(i) phenyl substituted with 1 to 2 substituents independently selected from F, Cl, Br, -CN,

C₁₋₃ alkyl, C₁₋₂ fluoroalkyl, C₁₋₃ alkoxy, C₁₋₂ fluoroalkoxy, C₃₋₆ cycloalkyl, -NR_xR_x, -C(O)NR_yR_y, -S(O)₂(C₁₋₃ alkyl), -S(O)₂(phenyl), -S(O)₂NR_xR_x, -NR_xS(O)₂(C₁₋₃ alkyl), -S(O)(NH)NR_xR_x, and -P(O)(OCH₂CH₃)₂;

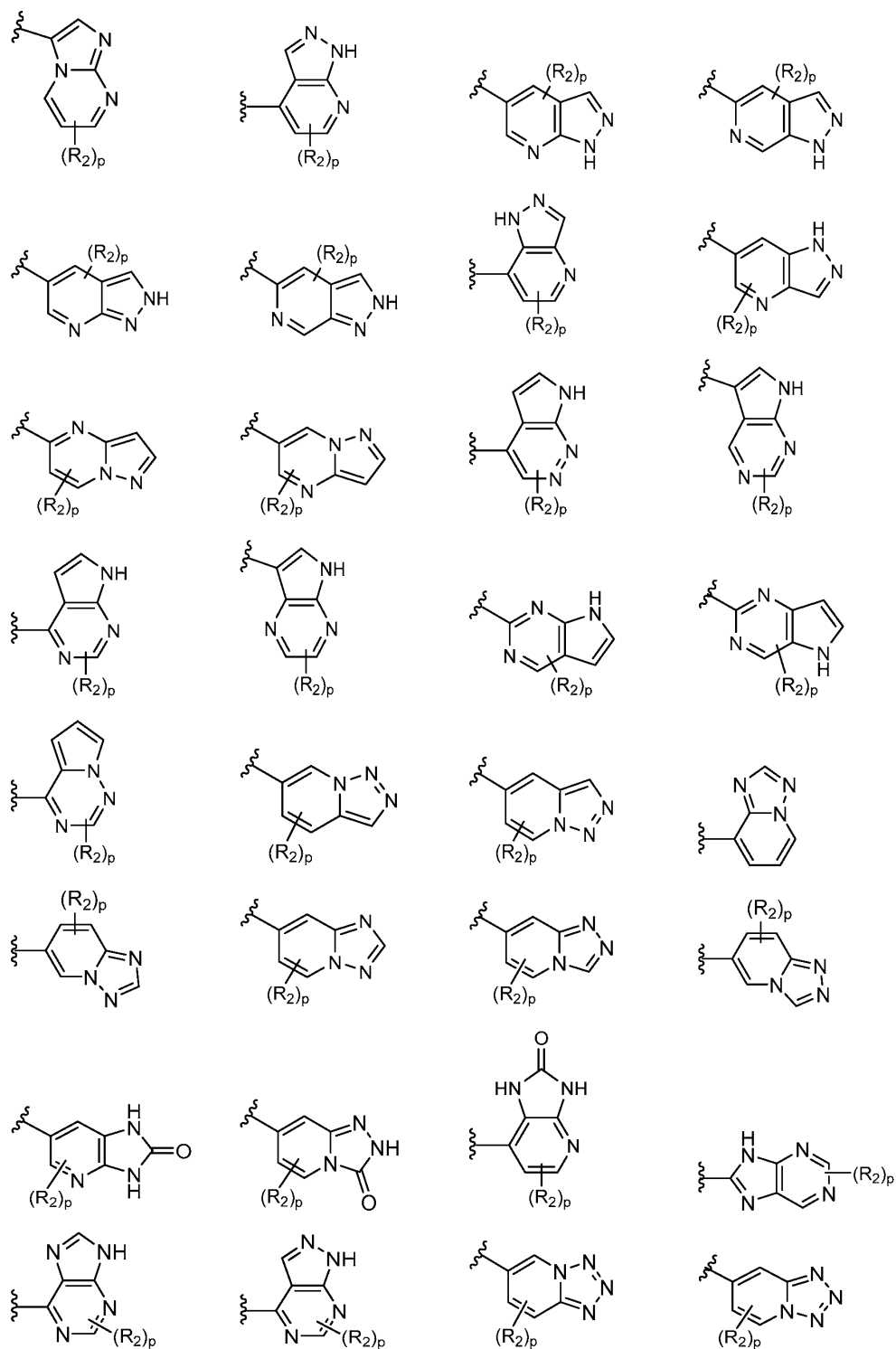


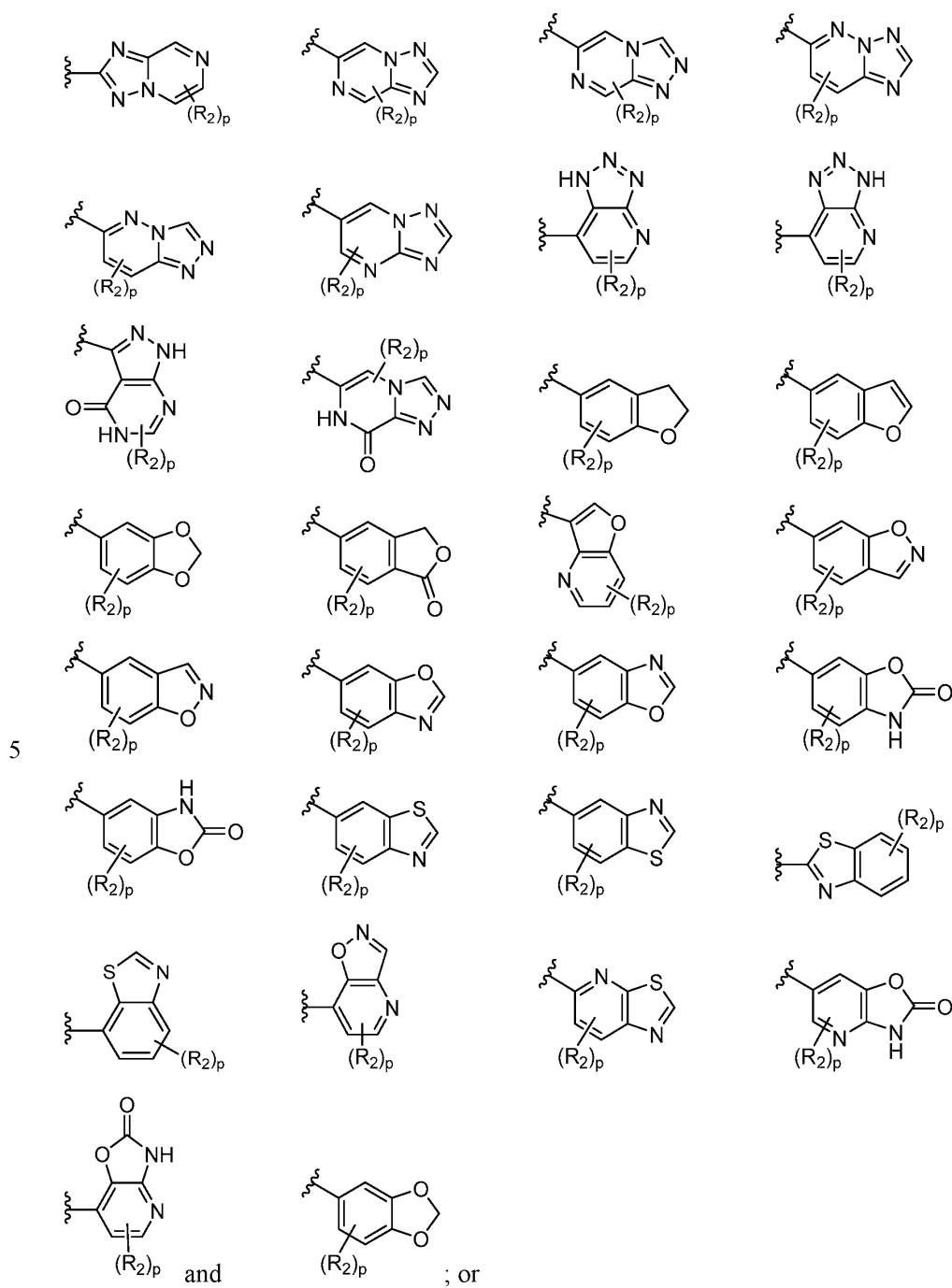
(v) a 9-membered heterocyclic ring selected from:

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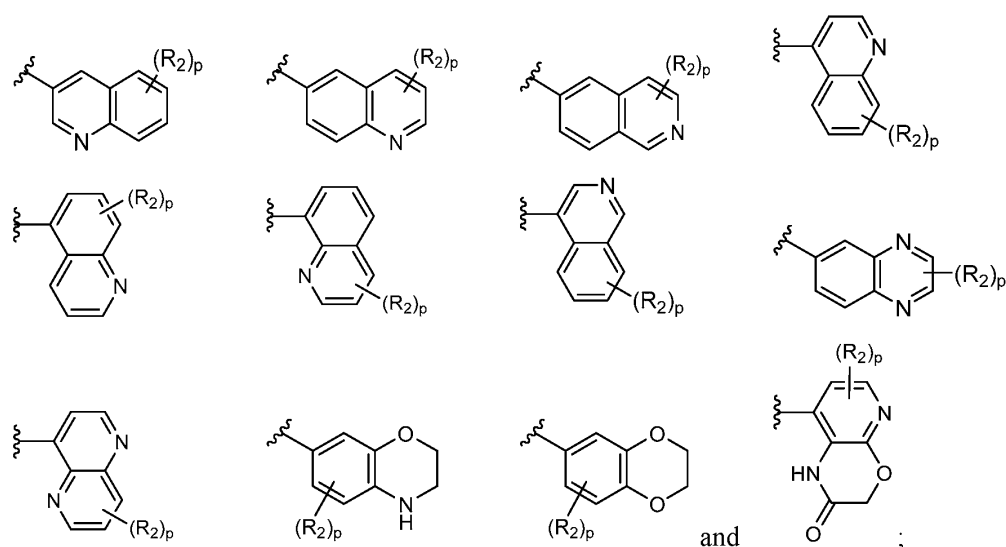


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(vi) 10-membered heterocyclic ring selected from:



A is piperidinyl, phenyl, pyridinyl, pyrimidinyl, 6-azabicyclo[3.2.1]octanyl, or

5 azabicyclo[3.2.1]octanyl, each substituted with $-L-R_4$ and zero to 3 R_{4b} ;

L is a bond, $-(\text{CR}_x\text{R}_x)_{1-2}-$, $-\text{O}-$, or $-\text{C}(\text{O})(\text{CR}_x\text{R}_x)_{0-2}-$;

R₁ is hydrogen, C₁₋₃ alkyl, C₁₋₂ fluoroalkyl, or C₃₋₄ cycloalkyl;

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

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), -NR_xS(O)₂(C₃₋₆ cycloalkyl), -NR_xC(O)(C₁₋₃ alkyl), -NR_xCH₂(C₃₋₆ cycloalkyl), -S(O)₂(C₁₋₃ alkyl), -S(O)₂N(C₁₋₃ alkyl)₂, -S(O)(NH)N(C₁₋₃ alkyl)₂, -(CH₂)₀₋₂(C₃₋₆ cycloalkyl), -(CH₂)₀₋₂(phenyl), morpholinyl, dioxothiomorpholinyl, dimethyl pyrazolyl, methylpiperidinyl, methylpiperazinyl, amino-oxadiazolyl, imidazolyl, triazolyl, or -C(O)(thiazolyl);

20 R_{2a} is C₁₋₆ alkyl, C₁₋₃ fluoroalkyl, C₁₋₆ hydroxyalkyl, C₁₋₃ aminoalkyl, $-(CH_2)_{0-4}O(C_{1-3}$ alkyl), C₃₋₆ cycloalkyl, $-(CH_2)_{1-3}C(O)NR_xR_x$, $-CH_2(C_{3-6}$ cycloalkyl), $-CH_2$ (phenyl), tetrahydrofuranyl, tetrahydropyranyl, or phenyl;

each R_{2b} is independently hydrogen, halo, -CN, -NR_xR_x, C₁₋₆ alkyl, C₁₋₃ fluoroalkyl,

C₁₋₃ hydroxyalkyl, C₁₋₃ fluoroalkoxy, $-(CH_2)_{0-2}O(C_{1-3} \text{ alkyl})$, $-(CH_2)_{0-3}C(O)NR_xR_x$,
 $-(CH_2)_{1-3}(C_{3-6} \text{ cycloalkyl})$, $-C(O)O(C_{1-3} \text{ alkyl})$, $-C(O)NR_x(C_{1-3} \text{ alkyl})$,
 $-CR_x=CR_xR_x$, or $-CR_x=CH(C_{3-6} \text{ cycloalkyl})$;

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

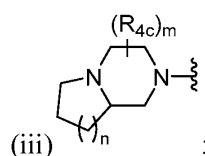
- 5 R_{2d} is R_{2a} or R_{2b}; provided that one of R_{2c} and R_{2d} is R_{2a}, and the other of R_{2c} and R_{2d} is R_{2b};

R₄ is:

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

(ii) pyrrolidinyl, piperidinyl, piperazinyl, or pyridinyl, each substituted with zero to 2

- 10 R_{4a}; or



each R_{4a} is independently C₁₋₆ alkyl, C₁₋₃ fluoroalkyl, $-(CH_2)_{1-2}O(C_{1-2} \text{ alkyl})$, C₃₋₆
cycloalkyl, $-CH_2(C_{3-6} \text{ cycloalkyl})$, $-CH_2(\text{oxetanyl})$, $-C(O)(C_{1-4} \text{ alkyl})$, $-C(O)(C_{3-6}$
cycloalkyl), $-C(O)(\text{phenyl})$, $-C(O)CH_2(C_{3-6} \text{ cycloalkyl})$, $-C(O)CH_2(\text{phenyl})$,
15 $-C(O)O(C_{1-4} \text{ alkyl})$, $-NR_x(C_{1-3} \text{ alkyl})$, $-NR_x(C_{3-6} \text{ cycloalkyl})$, azetidiny, oxetanyl,
tetrahydropyranyl, pyrrolidinyl, phenyl, or piperidinyl substituted with zero to 2
substituents selected from $-OH$ or $-CH_3$;

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

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

each R₅ is independently hydrogen, F, Cl, C₁₋₂ alkyl, C₁₋₂ fluoroalkyl, or cyclopropyl;

each R_x is independently hydrogen or $-CH_3$;

each R_y is independently hydrogen or C₁₋₆ alkyl;

m is zero, 1, or 2;

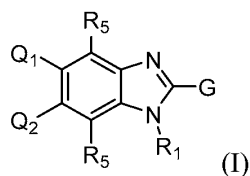
- 25 n is zero, 1, or 2;

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

q is 1 or 2.

The second aspect of the present invention provides at least one compound of

Formula (I):

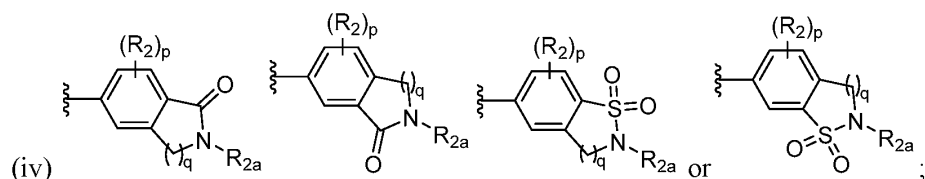
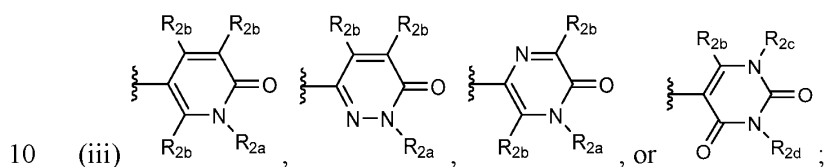
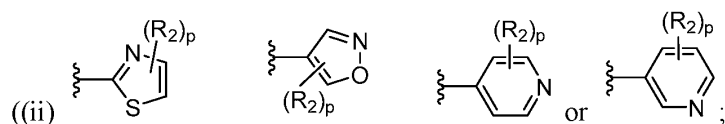


or a salt thereof, wherein:

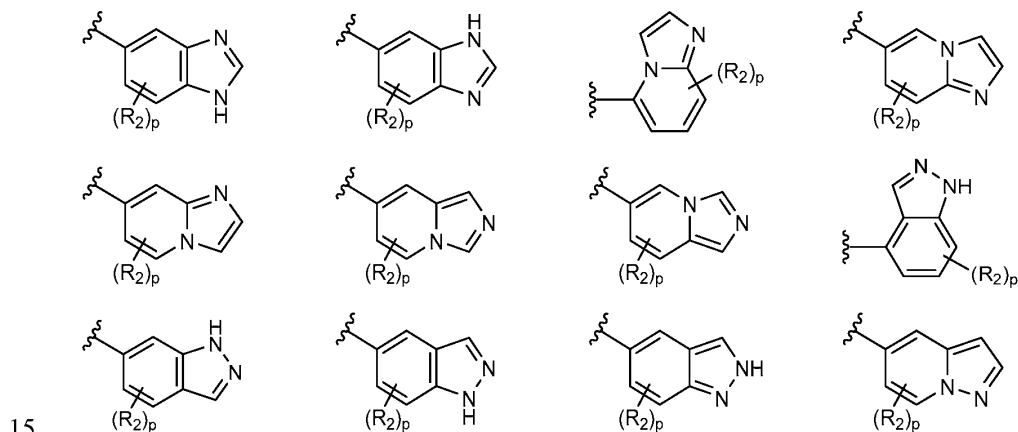
one of Q₁ and Q₂ is A and the other of Q₁ and Q₂ is R₅;

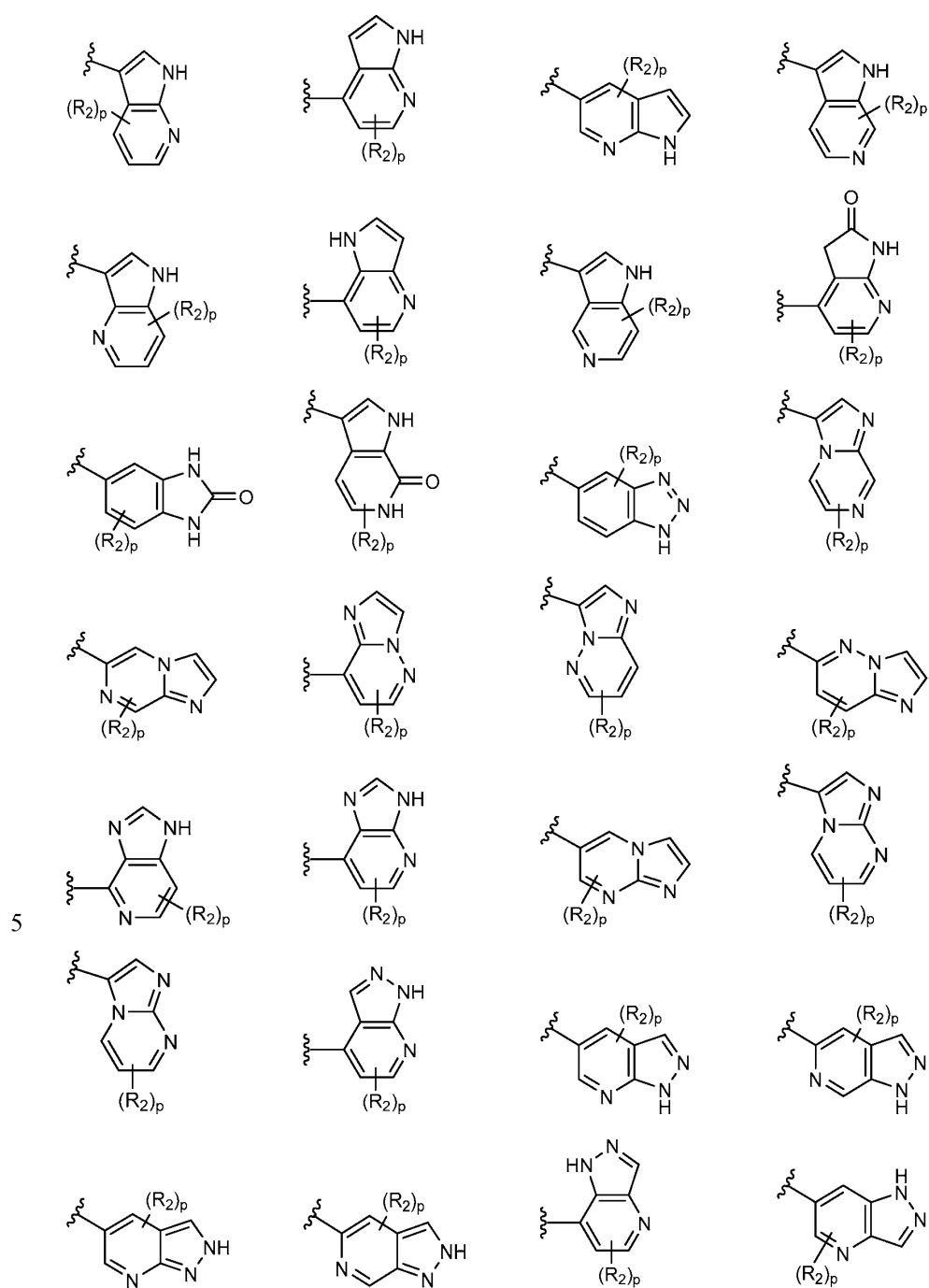
5 G is:

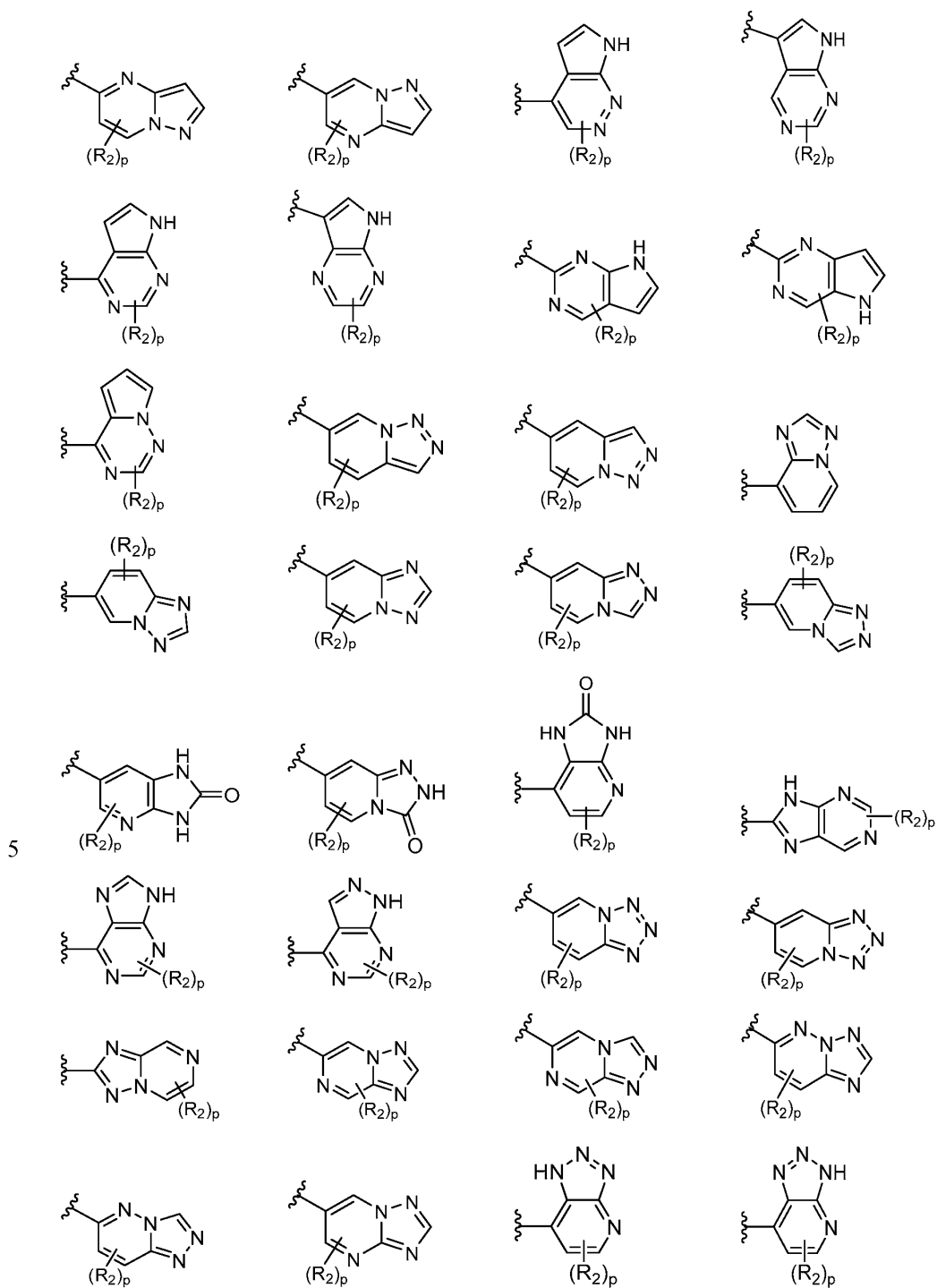
- (i) phenyl substituted with 1 to 2 substituents independently selected from F, Cl, Br, C₁₋₂ alkoxy, C₁₋₂ fluoroalkoxy, C₃₋₄ cycloalkyl -C(O)NR_yR_y, -S(O)₂CH₃, -S(O)₂(phenyl), -S(O)₂NR_xR_x, and -S(O)(NH)NR_xR_x;

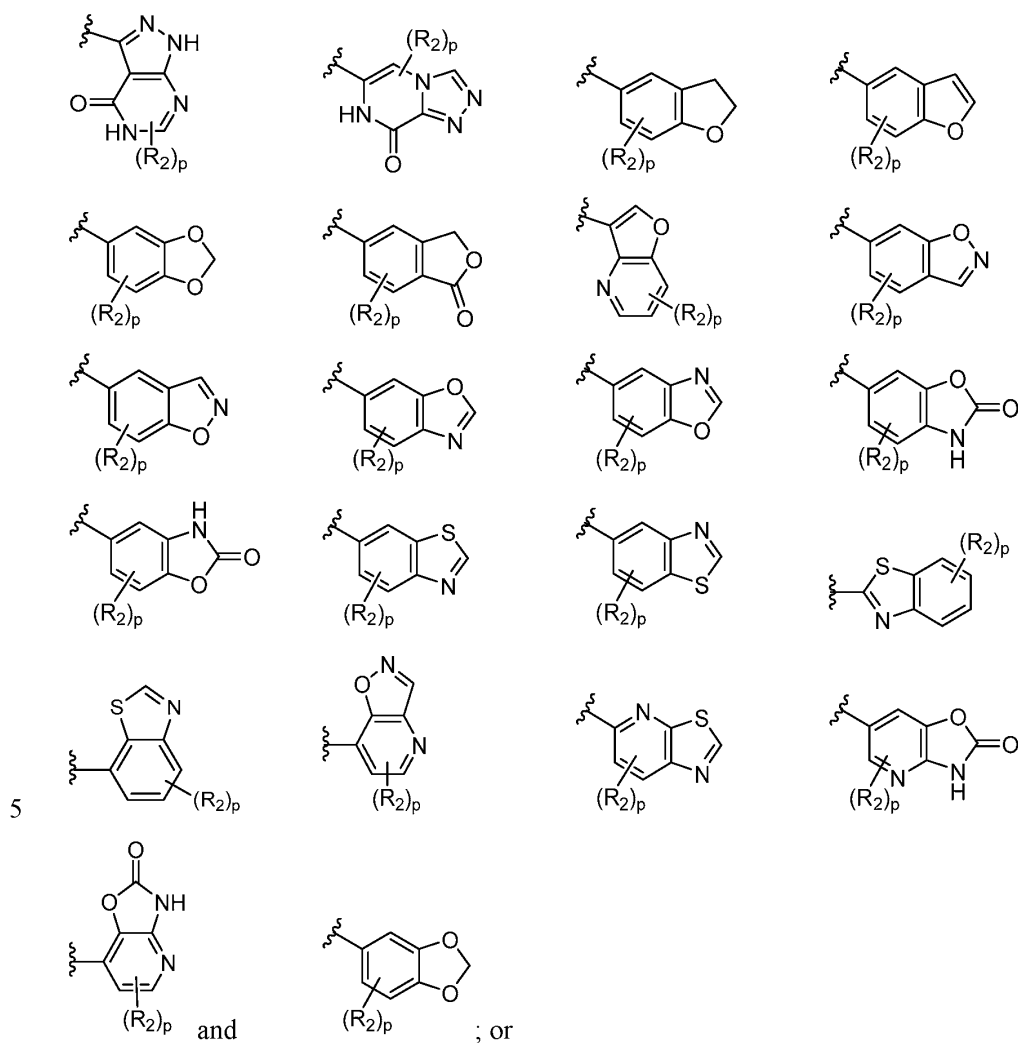


- (v) a 9-membered heterocyclic ring selected from:

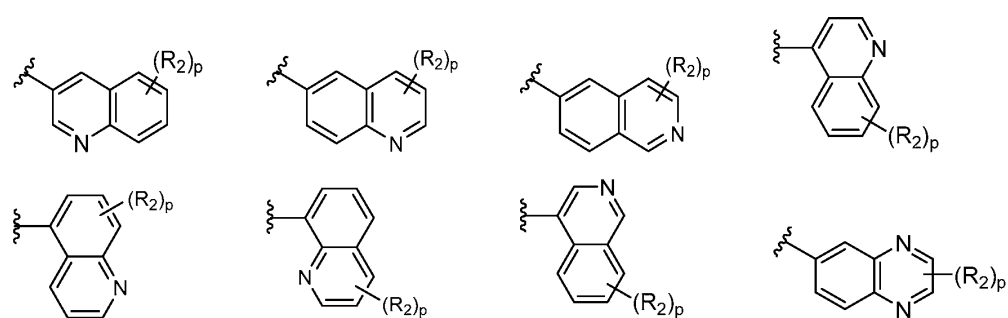


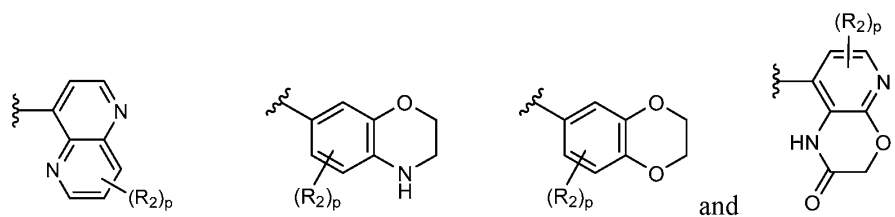






(vi) 10-membered heterocyclic ring selected from:





A is piperidinyl, phenyl, pyridinyl, pyrimidinyl, 6-azabicyclo[3.2.1]octanyl, or azabicyclo[3.2.1]octanyl, each substituted with $-L-R_4$ and zero to 1 R_{4b} ;

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

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

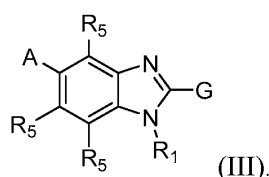
each R_2 is independently halo, $-CN$, $-OH$, $-NO_2$, C_{1-4} alkyl, C_{1-2} fluoroalkyl, C_{1-2} cyanoalkyl, C_{1-3} hydroxyalkyl, C_{1-3} aminoalkyl, $-O(CH_2)_{1-2}OH$, $-(CH_2)_{0-4}O(C_{1-4}$ alkyl), C_{1-3} fluoroalkoxy, $-(CH_2)_{1-4}O(C_{1-3}$ alkyl), $-O(CH_2)_{1-2}OC(O)(C_{1-3}$ alkyl), $-O(CH_2)_{1-2}NR_xR_x$,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

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

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

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

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



In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein G is phenyl substituted with 1 to 2 substituents independently selected from F, Cl, Br, -CN, C₁₋₃ alkyl, C₁₋₂ fluoroalkyl, C₁₋₃ alkoxy, C₁₋₂ fluoroalkoxy, C₃₋₆ cycloalkyl, -NR_xR_x, -C(O)NR_yR_y, -S(O)₂(C₁₋₃ alkyl), -S(O)₂(phenyl), -S(O)₂NR_xR_x, -NR_xS(O)₂(C₁₋₃ alkyl), -S(O)(NH)NR_xR_x, and -P(O)(OCH₂CH₃)₂.

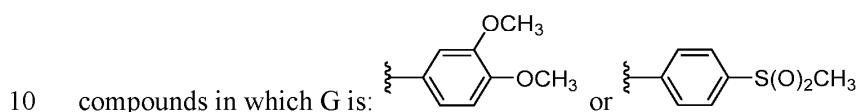
In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein G is phenyl substituted with 1 to 2 substituents independently selected from F, Cl, Br, -CN, -CH₃, -OCH₃, -OCHF₂, -OCF₃, cyclopropyl, -C(O)NR_yR_y, -N(CH₃)₂, -S(O)₂CH₃, -S(O)₂(phenyl), -S(O)₂NR_xR_x, -NHS(O)₂CH₃, -S(O)(NH)NR_xR_x, and -P(O)(OCH₂CH₃)₂.

In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein G is phenyl substituted with 1 to 2 substituents independently selected from F, Cl, Br, -CN, -CH₃, -OCH₃, -OCHF₂, -OCF₃, cyclopropyl, -C(O)NR_yR_y, -N(CH₃)₂, -S(O)₂CH₃, -S(O)₂(phenyl), -S(O)₂NR_xR_x, -NHS(O)₂CH₃, -S(O)(NH)NR_xR_x, and -P(O)(OCH₂CH₃)₂.

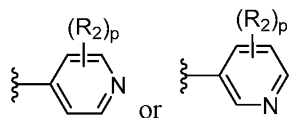
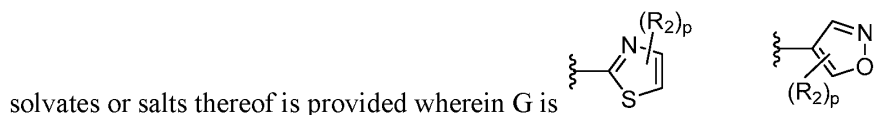
In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein G is phenyl substituted with zero to 2 substituents independently selected from F, Cl, Br, -CN, -CH₃, -OCH₃, -OCHF₂, -OCF₃, cyclopropyl, -N(CH₃)₂, -S(O)₂CH₃, -S(O)₂(phenyl), -NHS(O)₂CH₃, and -P(O)(OCH₂CH₃)₂.

In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein G is phenyl substituted with 1 to 2 substituents independently selected from -OCH₃, -S(O)₂CH₃, or -S(O)₂(phenyl). Included in this embodiment are compounds in which G is phenyl substituted with 1 to 2 substituents selected from -OCH₃. Also included in this embodiment are compounds in which G is phenyl substituted with -S(O)₂CH₃.

In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein G is phenyl substituted with 1 to 2 substituents independently selected from F, Cl, Br, $-\text{OCH}_3$, $-\text{OCHF}_2$, $-\text{OCF}_3$, cyclopropyl, $-\text{C}(\text{O})\text{NR}_y\text{R}_z$, $-\text{S}(\text{O})_2\text{CH}_3$, $-\text{S}(\text{O})_2(\text{phenyl})$, $-\text{S}(\text{O})_2\text{NR}_x\text{R}_y$, and $-\text{S}(\text{O})(\text{NH})\text{NR}_x\text{R}_y$. Included in this embodiment are compounds in which G is phenyl substituted with 1 to 2 substituents independently selected from $-\text{OCH}_3$, $-\text{S}(\text{O})_2\text{CH}_3$, $-\text{S}(\text{O})_2\text{N}(\text{CH}_3)_2$, and $-\text{S}(\text{O})(\text{NH})\text{N}(\text{CH}_3)_2$. Also included in this embodiment are compounds in which G is phenyl substituted with 1 to 2 substituents independently selected from $-\text{OCH}_3$ and $-\text{S}(\text{O})_2\text{CH}_3$. Additionally, included in this embodiment are



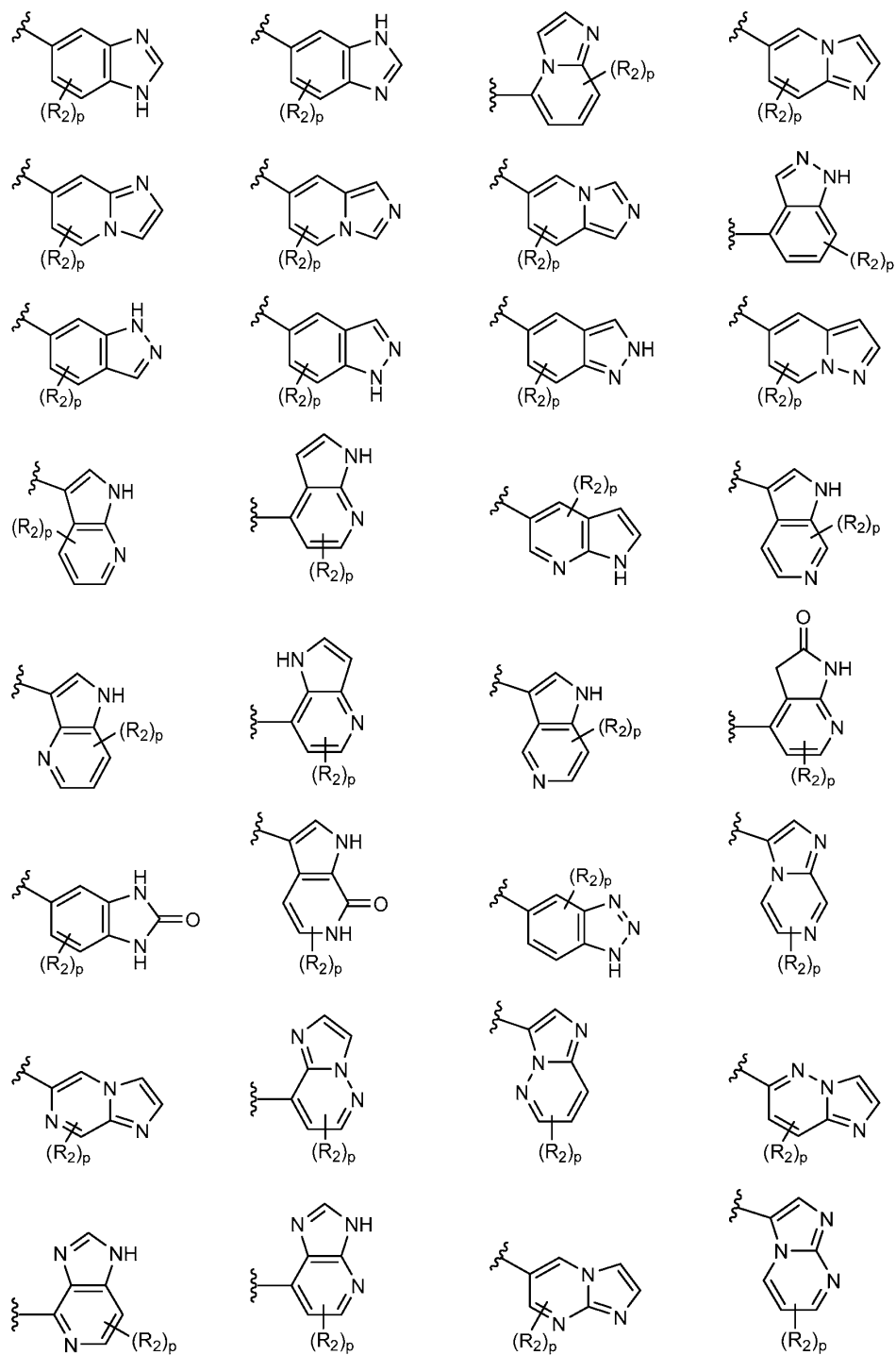
In one embodiment, a compound of Formula (I) or stereoisomers, tautomer,



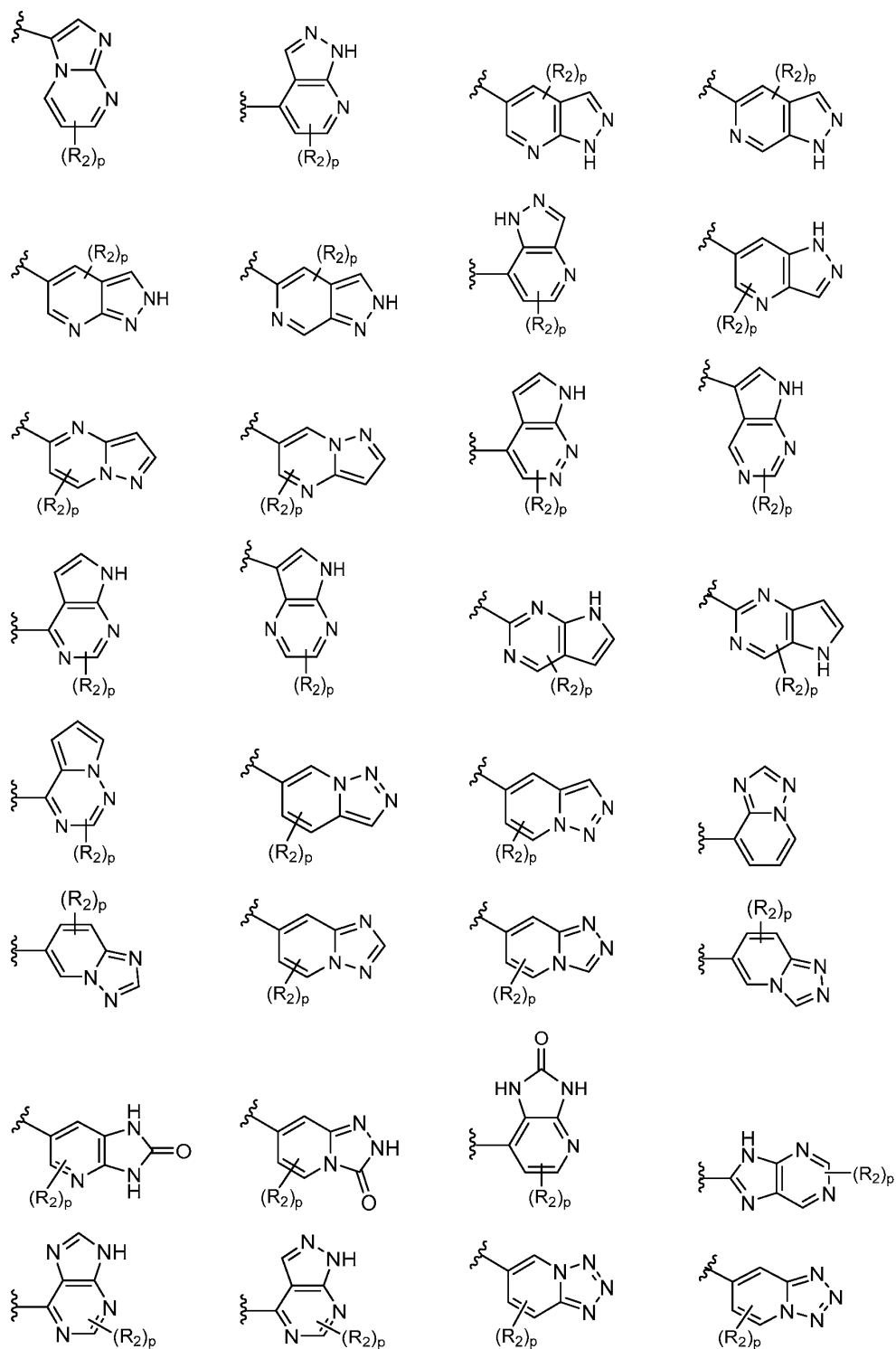
Included in this embodiment are compounds in which each R_2 is independently F, Cl, Br, $-\text{CN}$, $-\text{OH}$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CF}_3$, $-\text{CH}_2\text{OH}$, $-\text{C}(\text{CH}_3)_2\text{OH}$, $-\text{CH}_2\text{NH}_2$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{OCH}(\text{CH}_3)_2$, $-\text{OCH}_2\text{CH}_2\text{OCH}_3$, $-\text{OCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $-\text{OCHF}_2$, $-\text{C}(\text{O})\text{OCH}_3$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NH}(\text{CH}_2\text{CH}_3)$, $-\text{C}(\text{O})(\text{thiazolyl})$, $-\text{NH}_2$, $-\text{NH}(\text{CH}_3)$, $-\text{NH}(\text{CH}_2\text{CH}_3)$, $-\text{N}(\text{CH}_3)_2$, $-\text{NHC}(\text{O})\text{CH}_3$, $-\text{NHC}(\text{O})\text{C}(\text{CH}_3)_3$, $-\text{NH}(\text{CH}_2\text{-cyclopropyl})$, cyclopropyl, methylpiperidinyl, methylpiperazinyl, amino-oxadiazolyl, imidazolyl, or triazolyl. Also included in this embodiment are compounds in which each R_2 is independently F, Cl, $-\text{CN}$, $-\text{CH}_3$, $-\text{OCH}_3$, $-\text{NH}_2$, or cyclopropyl. Additionally, included in this embodiment are compounds in which p is 2; one R_2 is $-\text{CH}_3$; and the other R_2 is F, Cl, $-\text{CN}$, $-\text{CH}_3$, $-\text{OCH}_3$, $-\text{NH}_2$, or cyclopropyl.

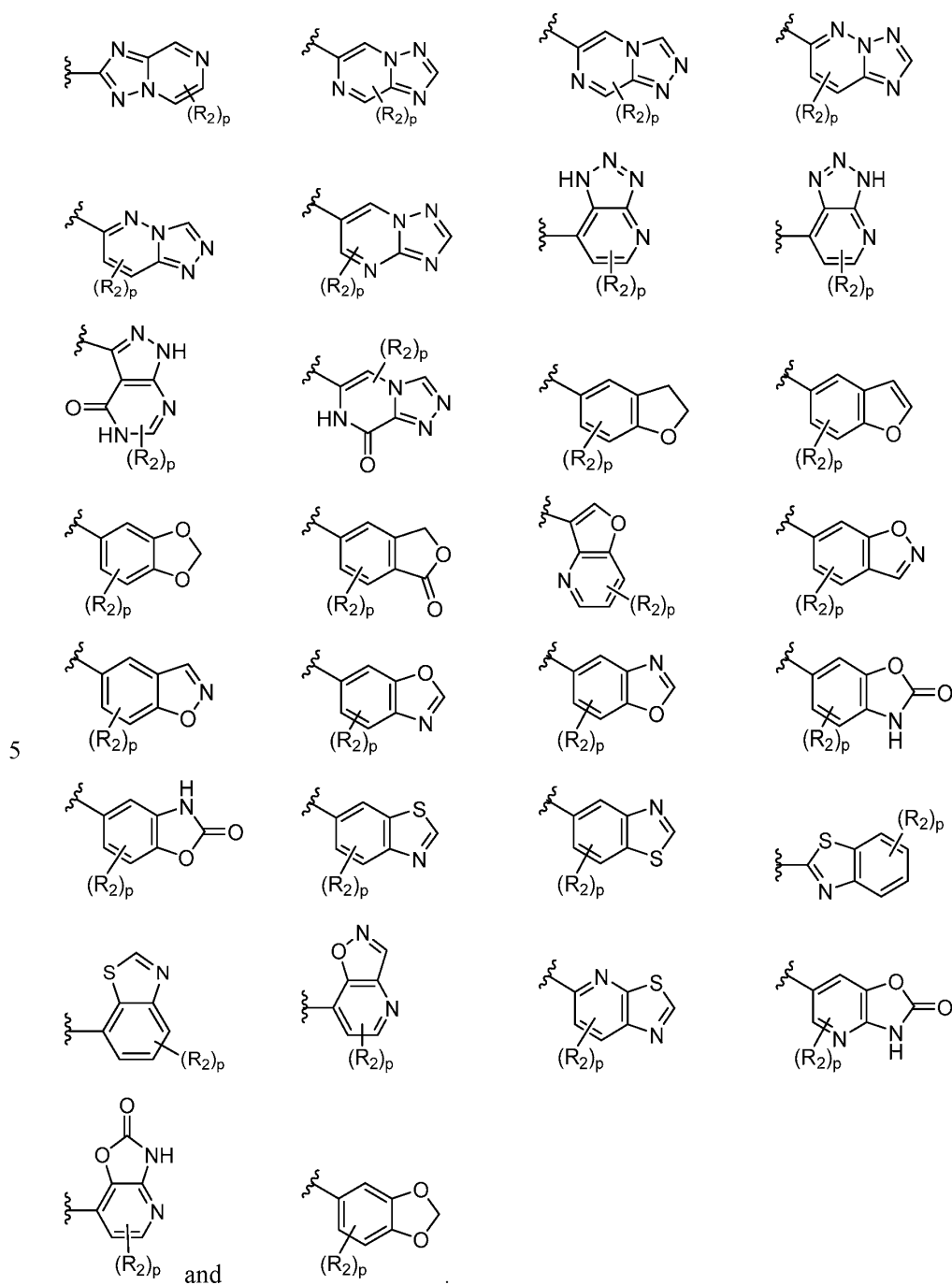
In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein G is a 9-membered heterocyclic ring selected from:

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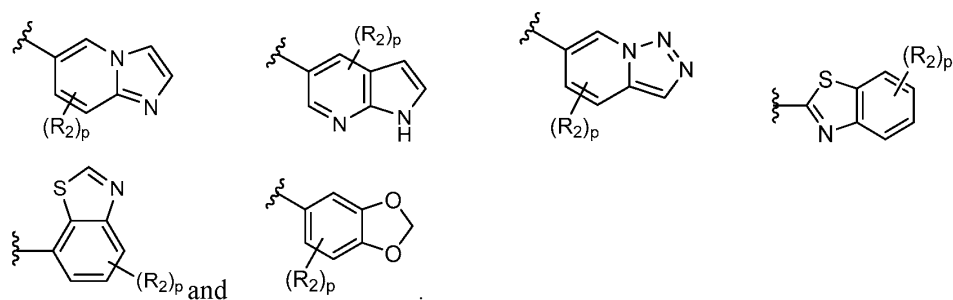


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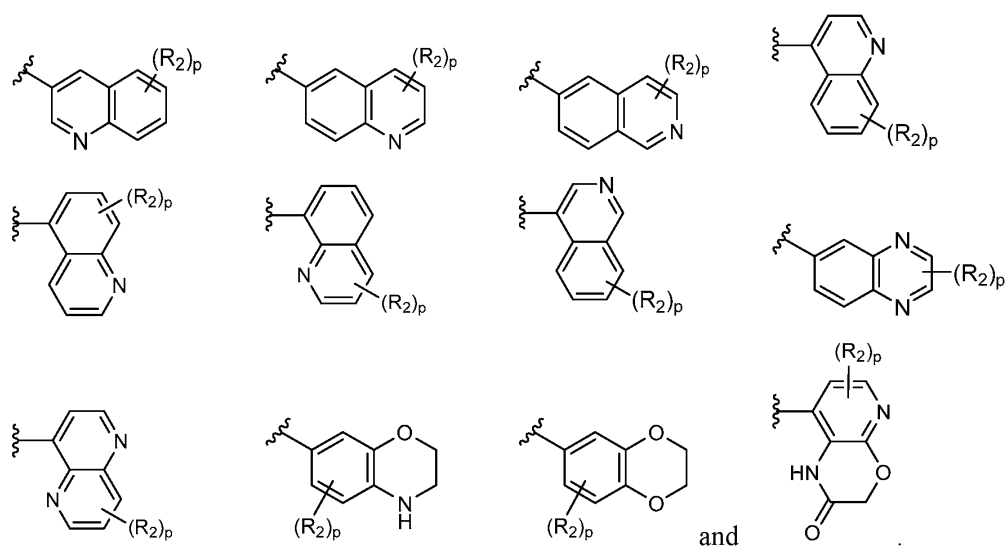




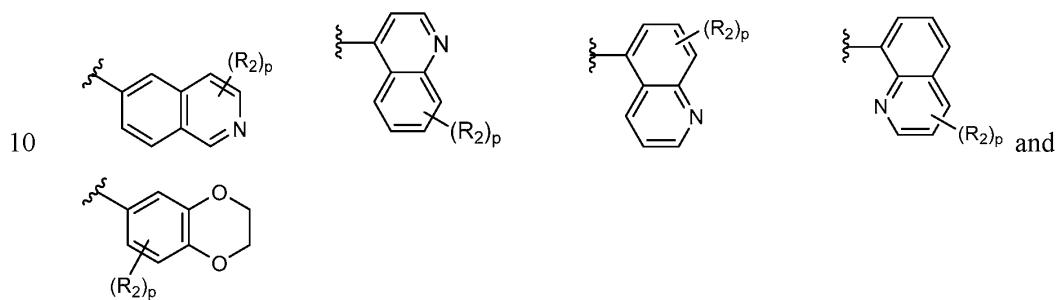
Included in this embodiment are compounds in which G is:



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



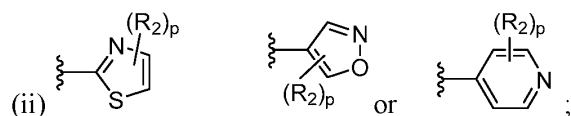
Included in this embodiment are compounds in which G is:



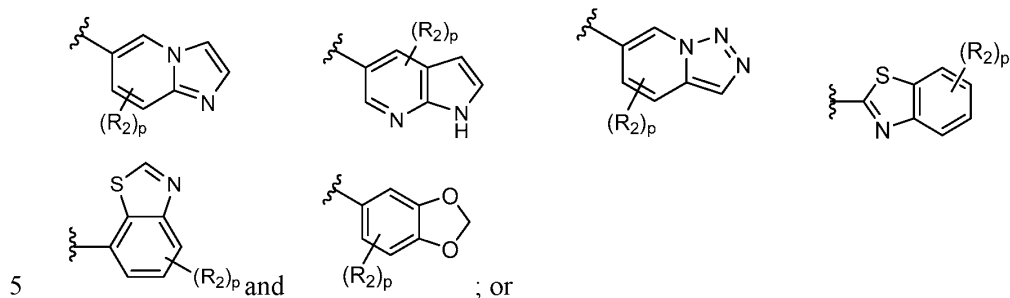
In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein G is:

(i) phenyl substituted with 1 to 2 substituents independently selected from F, Cl, Br,

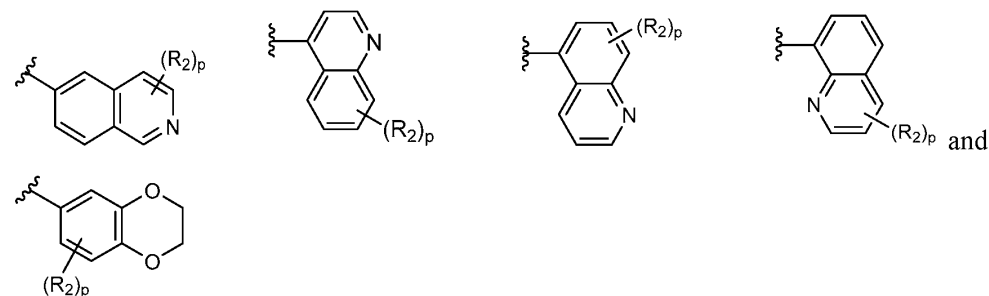
–OCH₃, –OCHF₂, –OCF₃, cyclopropyl, –S(O)₂CH₃, or –S(O)₂(phenyl);



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



(iv) 10-membered heterocyclic ring selected from:



10 Included in this embodiment are compounds in which each R₂ is independently F, Cl, –CH₃, –CH₂CH₃, –CH₂OH, –CH₂CH₂OH, –CH₂CN, –OCH₃, –CH₂OCH₃, or –CH₂CH₂S(O)₂CH₃. Also included in this embodiment are compounds in which each R₂ is independently F, –CH₃, or –OCH₃.

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

In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein A is piperidinyl, phenyl, pyridinyl, pyrimidinyl, 6-azabicyclo[3.2.1]octanyl, or azabicyclo[3.2.1]octanyl, each substituted with –L–R₄ and zero to 1 R_{4b}.

20 In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein A is piperidinyl, phenyl, pyridinyl, 6-

azabicyclo[3.2.1]octanyl, or azabicyclo[3.2.1]octanyl, each substituted with $-L-R_4$ and zero to 3 R_{4b} . Included in this embodiment are compounds in which A is piperidinyl, phenyl, pyridinyl, pyrimidinyl, or azabicyclo[3.2.1]octanyl, each substituted with $-L-R_4$ and zero to 2 R_{4b} .

5 In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein A is piperidinyl, phenyl, or pyridinyl, each substituted with $-L-R_4$ and zero to 1 R_{4b} . Included in this embodiment are compounds in which A is piperidinyl or phenyl, each substituted with $-L-R_4$ and zero to 1 R_{4b} . Also, included in this embodiment are compounds in which A is phenyl or pyridinyl, each
10 substituted with $-L-R_4$ and zero to 1 R_{4b} .

In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein A is piperidinyl, phenyl, pyridinyl, or pyrimidinyl, each substituted with $-L-R_4$ and zero to 1 R_{4b} ; and L is a bond. Included in this embodiment are compounds in which A is piperidinyl, phenyl, or pyridinyl, each
15 substituted with $-L-R_4$ and zero to 1 R_{4b} ; and L is a bond.

In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein L is a bond, $-CH_2-$, $-CH_2CH_2-$, $-O-$, or $-C(O)(CH_2)_{0-2}-$. Included in this embodiment are compounds in which L is a bond, $-CH_2-$, $-CH_2CH_2-$, or $-O-$.

20 In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein L is a bond.

In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein L is a $-(CR_xR_x)_{1-2}-$.

In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein L is $-CR_xR_x-$. Included in this embodiment
25 are compounds in which L is $-CH_2-$.

In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein L is $-CR_xR_x-$. Included in this embodiment are compounds in which L is $-CH_2CH_2-$.

30 In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein L is $-O-$.

In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein L is $-\text{C}(\text{O})(\text{CR}_x\text{R}_x)_{0-2}-$. Included in this embodiment are compounds in which L is $-\text{C}(\text{O})(\text{CH}_2)_{0-2}-$. Also included in this embodiment are compounds in which L is $-\text{C}(\text{O})(\text{CH}_2)_{0-1}-$. Additionally, included in this

5 embodiment are compounds in which L is $-\text{C}(\text{O})-$.

In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein L is $-\text{CR}_x\text{R}_x-$ or $-\text{C}(\text{O})(\text{CR}_x\text{R}_x)_{0-2}-$. Included in this embodiment are compounds in which L is $-\text{CR}_x\text{R}_x-$ or $-\text{C}(\text{O})(\text{CR}_x\text{R}_x)_{0-1}-$. Also included in this embodiment are compounds in which L is $-\text{CR}_x\text{R}_x-$ or $-\text{C}(\text{O})-$.

10 Additionally, included in this embodiment are compounds in which each R_x is hydrogen.

In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein L is a bond, $-\text{CH}_2-$ or $-\text{C}(\text{O})(\text{CH}_2)_{0-2}-$. Included in this embodiment are compounds in which L is a bond or $-\text{C}(\text{O})-$.

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

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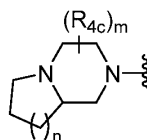
In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein R_4 is pyrrolidinyl, piperidinyl, piperazinyl, azepanyl, diazepanyl, pyridinyl, azaspiro[3.3]heptanyl, azabicyclo[3.2.1]octanyl, diazaspiro[3.3]heptanyl, or hexahydropyrrolo[3,4-c]pyrrolyl, each substituted with zero to

20 2 R_{4a} .

In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein R_4 is pyrrolidinyl, piperidinyl, piperazinyl, pyridinyl, azaspiro[3.3]heptanyl, or azabicyclo[3.2.1]octanyl, each substituted with zero to 2 R_{4a} . Included in this embodiment are compounds in which R_4 is pyrrolidinyl, piperidinyl, piperazinyl, or pyridinyl. Also included in this embodiment are compounds

25 in which R_4 is piperidinyl, piperazinyl, or pyridinyl.

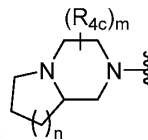
In one embodiment, a compound of Formula (I) or stereoisomers, tautomer,



solvates or salts thereof is provided wherein R_4 is . Included in this

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

In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein R₄ is pyrrolidinyl, piperidinyl, piperazinyl, or



pyridinyl, each substituted with zero to 2 R_{4a}; or

In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein R_{4a} is independently –CH₃, –CH₂CH₃, –CH(CH₃)₂, –CH₂CH(CH₃)₂, –CH₂CH₂OCH₃, –C(O)CH(CH₃)₂, cyclopropyl, cyclobutyl, –CH₂(cyclopropyl), –CH₂(cyclobutyl), –CH₂(oxetanyl), –N(CH₃)₂, –N(CH₃)(CH₂CH₃), –N(CH₃)(cyclopropyl), azetidiny, oxetanyl, tetrahydropyranyl, pyrrolidinyl, phenyl, or piperidinyl substituted with zero to 2 substituents selected from –OH or –CH₃.

In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein R_{4b} is F or Cl. Included in this embodiment are compounds in which R_{4b} is F.

In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein each R_{4a} is independently C₁₋₆ alkyl, C₁₋₃ fluoroalkyl, –(CH₂)₁₋₂OCH₃, C₃₋₆ cycloalkyl, –CH₂(C₃₋₆ cycloalkyl), –CH₂(oxetanyl), –C(O)(C₁₋₄ alkyl), –C(O)(C₃₋₆ cycloalkyl), –C(O)(phenyl), –C(O)CH₂(C₃₋₆ cycloalkyl), –C(O)CH₂(phenyl), –C(O)O(C₁₋₄ alkyl), –NR_x(C₁₋₃ alkyl), –NR_x(cyclopropyl), azetidiny, oxetanyl, tetrahydropyranyl, pyrrolidinyl, phenyl, or piperidinyl substituted with zero to 2 substituents selected from –OH or –CH₃.

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

C₃₋₄ cycloalkyl.

In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein R₁ is hydrogen, C₁₋₂ alkyl, -CH₂F, -CHF₂, -CF₃, or C₃₋₄ cycloalkyl. Included in this embodiment are compounds in which R₁ is hydrogen, -CH₃, -CF₃, or cyclopropyl. Also included in this embodiment are compounds in which R₁ is hydrogen or -CH₃.

In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein R₁ is hydrogen, -CH₃, -CH₂CH₃, -CH(CH₃)₂, -CH₂CHF₂, or cyclopropyl.

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

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

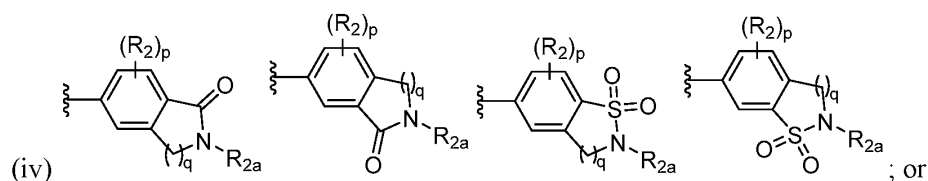
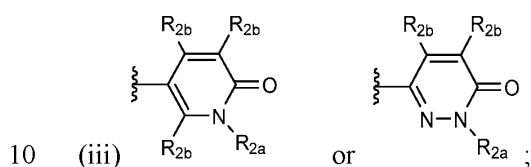
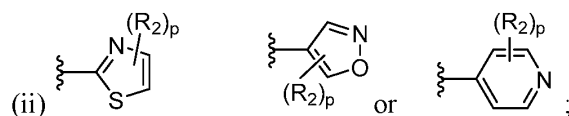
In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein each R₅ is independently hydrogen, F, Cl, -CH₃, -CHF₂, -CF₃, or cyclopropyl. Included in this embodiment are compounds in which each R₅ is independently hydrogen, F, Cl, -CH₃, -CF₃, or cyclopropyl. Also

included are compounds in which each R_5 is hydrogen $-\text{CH}_3$, or $-\text{CF}_3$.

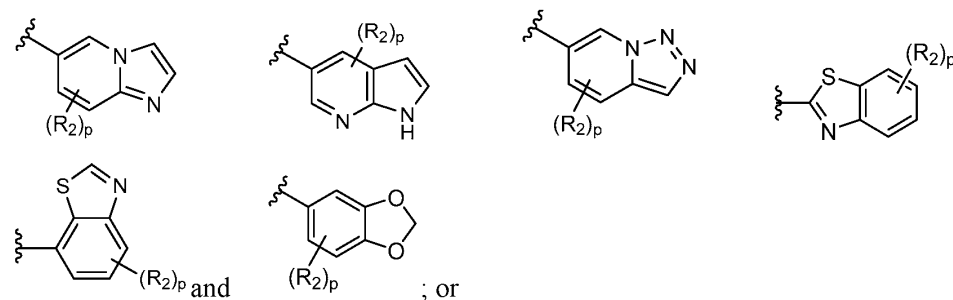
In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof, wherein:

G is:

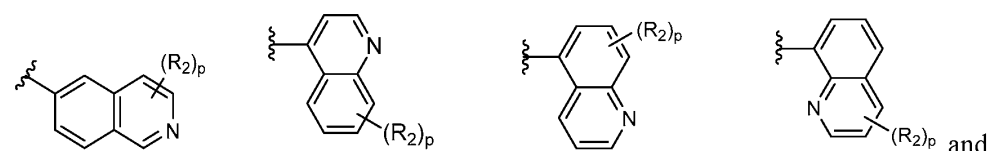
- 5 (i) phenyl substituted with 1 to 2 substituents independently selected from F, Cl, Br, $-\text{CN}$, $-\text{CH}_3$, $-\text{OCH}_3$, $-\text{OCHF}_2$, $-\text{OCF}_3$, cyclopropyl, $-\text{C}(\text{O})\text{NR}_y\text{R}_y$, $-\text{N}(\text{CH}_3)_2$, $-\text{S}(\text{O})_2\text{CH}_3$, $-\text{S}(\text{O})_2(\text{phenyl})$, $-\text{S}(\text{O})_2\text{NR}_x\text{R}_x$, $-\text{NHS}(\text{O})_2\text{CH}_3$, $-\text{S}(\text{O})(\text{NH})\text{NR}_x\text{R}_x$, and $-\text{P}(\text{O})(\text{OCH}_2\text{CH}_3)_2$;

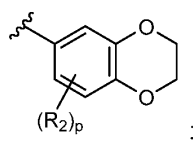


(v) a 9-membered heterocyclic ring selected from:



- 15 (vi) 10-membered heterocyclic ring selected from:





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

L is a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{O}-$, or $-\text{C}(\text{O})(\text{CH}_2)_{0-2}-$;

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

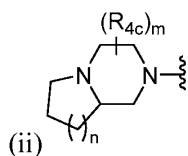
each R_2 is independently F, Cl, $-\text{CN}$, $-\text{OH}$, C_{1-3} alkyl, C_{1-2} fluoroalkyl, C_{1-2} cyanoalkyl, C_{1-3} hydroxyalkyl, C_{1-2} aminoalkyl, $-(\text{CH}_2)_{0-2}\text{O}(\text{C}_{1-3} \text{ alkyl})$, C_{3-6} cycloalkyl, $-\text{NR}_x\text{R}_x$, $-(\text{CH}_2)_{0-2}\text{C}(\text{O})\text{NR}_x\text{R}_x$, $-\text{CH}_2(\text{C}_{3-6} \text{ cycloalkyl})$, $-\text{CH}_2(\text{phenyl})$, 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, $-\text{CH}_2\text{C}(\text{O})\text{NR}_x\text{R}_x$, $-\text{CH}_2(\text{C}_{3-6} \text{ cycloalkyl})$, $-\text{CH}_2(\text{phenyl})$, tetrahydrofuranyl, or phenyl;

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

R_4 is:

(i) pyrrolidinyl, piperidinyl, piperazinyl, pyridinyl, azaspiro[3.3]heptanyl, or azabicyclo[3.2.1]octanyl, each substituted with zero to 2 R_{4a} ; or



20 each R_{4a} is independently C_{1-6} alkyl, C_{1-3} fluoroalkyl, $-(\text{CH}_2)_{1-2}\text{OCH}_3$, C_{3-6} cycloalkyl, $-\text{CH}_2(\text{C}_{3-6} \text{ cycloalkyl})$, $-\text{CH}_2(\text{oxetanyl})$, $-\text{C}(\text{O})(\text{C}_{1-4} \text{ alkyl})$, $-\text{C}(\text{O})(\text{C}_{3-6} \text{ cycloalkyl})$, $-\text{C}(\text{O})(\text{phenyl})$, $-\text{C}(\text{O})\text{CH}_2(\text{C}_{3-6} \text{ cycloalkyl})$, $-\text{C}(\text{O})\text{CH}_2(\text{phenyl})$, $-\text{C}(\text{O})\text{O}(\text{C}_{1-4} \text{ alkyl})$, $-\text{NR}_x(\text{C}_{1-3} \text{ alkyl})$, $-\text{NR}_x(\text{cyclopropyl})$, azetidiny, oxetanyl, tetrahydropyranyl, pyrrolidinyl, phenyl, or piperidinyl substituted with zero to 2 substituents selected from $-\text{OH}$ or $-\text{CH}_3$;

R_{4b} is F or -CH₃;

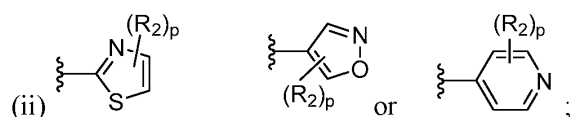
each R_{4c} is independently C₁₋₆ alkyl, C₁₋₃ fluoroalkyl, -CH₂(C₃₋₆ cycloalkyl), -C(O)(C₁₋₄ alkyl), -C(O)(phenyl), -C(O)CH₂(phenyl), -C(O)OCH₂CH₃, or C₃₋₆ cycloalkyl; and

each R₅ is independently hydrogen, F, Cl, C₁₋₂ alkyl, C₁₋₂ fluoroalkyl, or
 5 cyclopropyl.

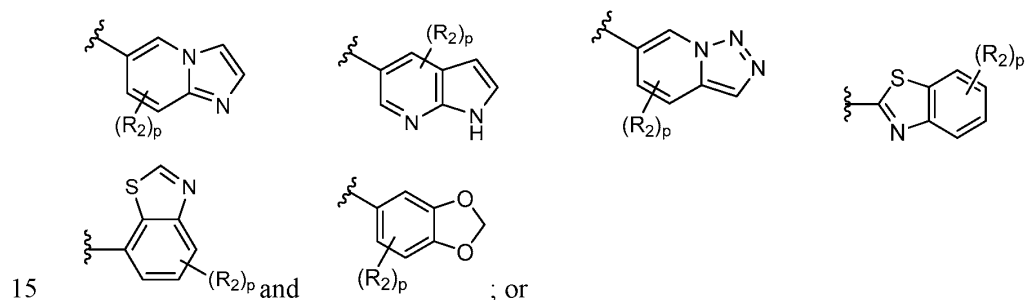
In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein:

G is:

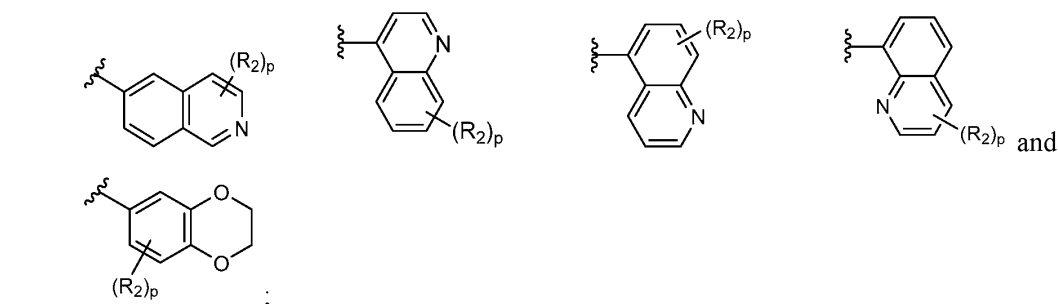
- (i) phenyl substituted with zero to 2 substituents independently selected from F, Cl, Br,
 10 -CN, -CH₃, -OCH₃, -OCHF₂, -OCF₃, cyclopropyl, -N(CH₃)₂, -S(O)₂CH₃,
 -S(O)₂(phenyl), -NHS(O)₂CH₃, and -P(O)(OCH₂CH₃)₂;



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



- (iv) 10-membered heterocyclic ring selected from:



A is piperidinyl, phenyl, pyridinyl, or azabicyclo[3.2.1]octanyl, each substituted with

20 -L-R₄ and zero to 2 R_{4b};

L is a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, or $-\text{O}-$;

R_1 is hydrogen, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CHF}_2$, or cyclopropyl;

each R_2 is independently F, $-\text{CH}_3$, or $-\text{OCH}_3$;

R_4 is pyrrolidinyl, piperidinyl, piperazinyl, azepanyl, diazepanyl, pyridinyl,

- 5 azaspiro[3.3]heptanyl, azabicyclo[3.2.1]octanyl, diazaspiro[3.3]heptanyl, or hexahydropyrrolo[3,4-c]pyrrolyl, each substituted with zero to 2 R_{4a} ;

R_{4a} is independently $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{OCH}_3$,

$-\text{C}(\text{O})\text{CH}(\text{CH}_3)_2$, cyclopropyl, cyclobutyl, $-\text{CH}_2(\text{cyclopropyl})$, $-\text{CH}_2(\text{cyclobutyl})$,

$-\text{CH}_2(\text{oxetanyl})$, $-\text{N}(\text{CH}_3)_2$, $-\text{N}(\text{CH}_3)(\text{CH}_2\text{CH}_3)$, $-\text{N}(\text{CH}_3)(\text{cyclopropyl})$, azetidyl,

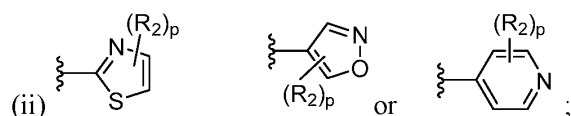
- 10 oxetanyl, tetrahydropyranyl, pyrrolidinyl, phenyl, or piperidinyl substituted with zero to 2 substituents selected from $-\text{OH}$ or $-\text{CH}_3$; and

each R_5 is independently hydrogen, $-\text{CH}_3$, or $-\text{CF}_3$.

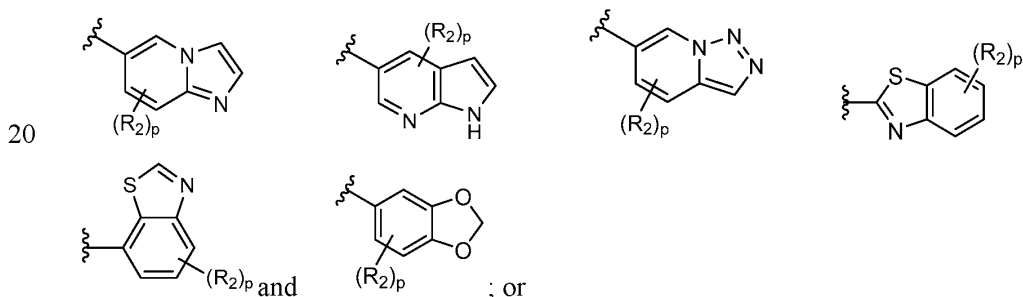
In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein:

- 15 G is:

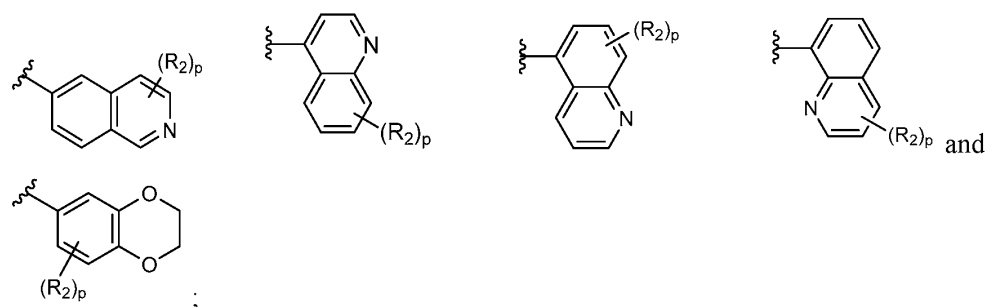
- (i) phenyl substituted with 1 to 2 substituents independently selected from F, Cl, Br, $-\text{OCH}_3$, $-\text{OCHF}_2$, $-\text{OCF}_3$, cyclopropyl, $-\text{S}(\text{O})_2\text{CH}_3$, and $-\text{S}(\text{O})_2(\text{phenyl})$;



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



- (iv) 10-membered heterocyclic ring selected from:



A is piperidinyl or azabicyclo[3.2.1]octanyl, each substituted with $-L-R_4$;

L is a bond;

5 R_1 is hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, or $-CH_2CHF_2$;

each R_2 is independently F, $-CH_3$, or $-OCH_3$;

R_4 is piperidinyl, azaspiro[3.3]heptanyl, or azabicyclo[3.2.1]octanyl, each substituted with zero to 2 R_{4a} ;

R_{4a} is independently $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-C(O)CH(CH_3)_2$, cyclopropyl,

10 cyclobutyl, or $-CH_2$ (cyclopropyl); and

each R_5 is independently hydrogen, $-CH_3$, or $-CF_3$.

In one embodiment, a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof is provided wherein: Q_1 is A; Q_2 is R_5 ; G is dimethoxyphenyl; A is piperidinyl substituted with $-L-R_4$; L is a bond; R_4 is piperidinyl substituted with zero to 2 R_{4a} ; R_{4a} is independently $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, or cyclopropyl; and each R_5 is independently hydrogen, $-CH_3$, or $-CF_3$.

One embodiment provides a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof, wherein said compound is: 2-(3,4-dimethoxyphenyl)-5-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1-methyl-1H-benzo[d]imidazole (5); 2-(3,4-dimethoxyphenyl)-1-isopropyl-5-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (6); 1-(2,2-difluoroethyl)-2-(3,4-dimethoxyphenyl)-5-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (7); 2-(3,4-dimethoxyphenyl)-1-ethyl-5-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (9); 2-(3,4-dimethoxyphenyl)-5-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-6-(trifluoromethyl)-1H-benzo[d]imidazole (10); 2-(3,4-dimethoxyphenyl)-5-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1-methyl-1H-benzo[d]imidazole (34); 5-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3,4-

dimethoxyphenyl)-1-methyl-1H-benzo[d]imidazole (35); 2-(3,4-dimethoxyphenyl)-5-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1-isopropyl-1H-benzo[d]imidazole (36); 5-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3,4-dimethoxyphenyl)-1-isopropyl-1H-benzo[d]imidazole (37); 1-(2,2-difluoroethyl)-2-(3,4-dimethoxyphenyl)-5-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (38); 5-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-1-(2,2-difluoroethyl)-2-(3,4-dimethoxyphenyl)-1H-benzo[d]imidazole (39); 2-(3,4-dimethoxyphenyl)-1-ethyl-5-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (41); 2-(3,4-dimethoxyphenyl)-5-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-6-(trifluoromethyl)-1H-benzo[d]imidazole (42); 4-fluoro-5-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (88); 4-fluoro-5-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (89-90); 7-fluoro-5-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (91); 7-fluoro-5-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (92-93); 6-fluoro-5-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (99); 6-fluoro-5-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (100-101); 4-fluoro-5-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (184); 5-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (185); 4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1'-(oxetan-3-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (186); 4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1'-(tetrahydro-2H-pyran-4-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (187); 4-fluoro-5-(1'-(2-methoxyethyl)-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (188); 4-fluoro-5-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (189-190); 5-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (191-192); 4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1-(8-(oxetan-3-ylmethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1H-benzo[d]imidazole (193-194); 4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1-(8-(oxetan-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-

- yl)-1H-benzo[d]imidazole (195-196); 4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1-(8-(tetrahydro-2H-pyran-4-yl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1H-benzo[d]imidazole (197-198); 4-fluoro-5-(1-(8-(2-methoxyethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (199-200); 7-fluoro-5-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (201); 5-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (202); 5-(1'-(cyclopropylmethyl)-[1,4'-bipiperidin]-4-yl)-7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (203); 7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1'-(oxetan-3-ylmethyl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (204); 5-(1'-cyclobutyl-[1,4'-bipiperidin]-4-yl)-7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (205); 7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1'-(oxetan-3-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (206); 7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1'-(tetrahydro-2H-pyran-4-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (207); 7-fluoro-5-(1'-(2-methoxyethyl)-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (208); 7-fluoro-5-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (209-210); 7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1-(8-(tetrahydro-2H-pyran-4-yl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1H-benzo[d]imidazole (211-212); 7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1-(8-(oxetan-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1H-benzo[d]imidazole (213-214); 5-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (215-216); 5-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (217-218); 6-fluoro-5-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (240); 5-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-6-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (241); 5-(1'-(cyclopropylmethyl)-[1,4'-bipiperidin]-4-yl)-6-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (242); 5-(1'-cyclobutyl-[1,4'-bipiperidin]-4-yl)-6-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (243); 6-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1'-(oxetan-3-yl)-[1,4'-

bipiperidin]-4-yl)-1H-benzo[d]imidazole (244); 6-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1'-(tetrahydro-2H-pyran-4-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (245); 6-fluoro-5-(1'-(2-methoxyethyl)-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (246); 6-fluoro-5-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (247-248); 5-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-6-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (249-250); 5-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-6-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (251-252); 6-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1-(8-(oxetan-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1H-benzo[d]imidazole (253-254); 6-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1-(8-(tetrahydro-2H-pyran-4-yl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1H-benzo[d]imidazole (255-256); or 6-fluoro-5-(1-(8-(2-methoxyethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (257-258).

One embodiment provides a compound of Formula (I) or stereoisomers, tautomer, solvates or salts thereof, wherein said compound is: 2-(3,4-dimethoxyphenyl)-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1-methyl-1H-benzo[d]imidazole (1); 2-(3,4-dimethoxyphenyl)-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (2); 2-(3,4-dimethoxyphenyl)-1-isopropyl-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (3); 1-(2,2-difluoroethyl)-2-(3,4-dimethoxyphenyl)-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (4); 2-(3,4-dimethoxyphenyl)-1-ethyl-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (8); 2-(3,4-dimethoxyphenyl)-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole (11); 2-(3,4-dimethoxyphenyl)-6-(1-(2-isopropyl-2-azaspiro[3.3]heptan-6-yl)piperidin-4-yl)-4-methyl-1H-benzo[d]imidazole (12); 6-([1,4'-bipiperidin]-4-yl)-2-(3,4-dimethoxyphenyl)-4-methyl-1H-benzo[d]imidazole tris(2,2,2-trifluoroacetate) (13); 1-(4-(2-(3,4-dimethoxyphenyl)-4-methyl-1H-benzo[d]imidazol-6-yl)-[1,4'-bipiperidin]-1'-yl)-2-methylpropan-1-one (14); 2-(3,4-dimethoxyphenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-1H-benzo[d]imidazole tris(2,2,2-trifluoroacetate) (15); 2-(3,4-dimethoxyphenyl)-6-(1-(2-isopropyl-2-azaspiro[3.3]heptan-6-yl)piperidin-4-yl)-1,4-dimethyl-1H-benzo[d]imidazole tris(2,2,2-trifluoroacetate) (16);

- 2-(3,4-dimethoxyphenyl)-6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-1H-benzo[d]imidazole (17-18); 2-(3,4-dimethoxyphenyl)-6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-methyl-1H-benzo[d]imidazole (19-20); 2-(3,4-dimethoxyphenyl)-6-(8-(1-isopropylpiperidin-4-yl)-8-azabicyclo[3.2.1]octan-3-yl)-1,4-dimethyl-1H-benzo[d]imidazole (21); 6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (22); 2-(3-fluoro-4-methoxyphenyl)-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-1H-benzo[d]imidazole (23); 2-(3-fluoro-4-methoxyphenyl)-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole (24); 2-(imidazo[1,2-a]pyridin-6-yl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole (25); 2-(3,4-dimethoxyphenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1-methyl-1H-benzo[d]imidazole (26); 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3,4-dimethoxyphenyl)-1-methyl-1H-benzo[d]imidazole (27); 2-(3,4-dimethoxyphenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (28); 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3,4-dimethoxyphenyl)-1H-benzo[d]imidazole (29); 2-(3,4-dimethoxyphenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1-isopropyl-1H-benzo[d]imidazole (30); 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3,4-dimethoxyphenyl)-1-isopropyl-1H-benzo[d]imidazole (31); 1-(2,2-difluoroethyl)-2-(3,4-dimethoxyphenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (32); 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-1-(2,2-difluoroethyl)-2-(3,4-dimethoxyphenyl)-1H-benzo[d]imidazole (33); 2-(3,4-dimethoxyphenyl)-1-ethyl-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (40); 2-(3,4-dimethoxyphenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole tris(2,2,2-trifluoroacetate) (43); 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3,4-dimethoxyphenyl)-4-methyl-1H-benzo[d]imidazole (44); 2-(3,4-dimethoxyphenyl)-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-1H-benzo[d]imidazole (45); 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3,4-dimethoxyphenyl)-1,4-dimethyl-1H-benzo[d]imidazole tris(2,2,2-trifluoroacetate) (46); 2-(3,4-dimethoxyphenyl)-6-(1-(2-isobutyl-2-azaspiro[3.3]heptan-6-yl)piperidin-4-yl)-1,4-dimethyl-1H-benzo[d]imidazole tris(2,2,2-trifluoroacetate) (47); 6-(1-(2-(cyclopropylmethyl)-2-azaspiro[3.3]heptan-6-yl)piperidin-4-yl)-2-(3,4-dimethoxyphenyl)-1,4-dimethyl-1H-benzo[d]imidazole (48); 6-(1-(2-cyclobutyl-2-azaspiro[3.3]heptan-6-yl)piperidin-4-yl)-2-(3,4-dimethoxyphenyl)-1,4-dimethyl-1H-benzo[d]imidazole (49); 2-(3,4-dimethoxyphenyl)-6-(8-(1-

- isobutylpiperidin-4-yl)-8-azabicyclo[3.2.1]octan-3-yl)-1,4-dimethyl-1H-benzo[d]imidazole (50); 6-(8-(1-cyclopropylpiperidin-4-yl)-8-azabicyclo[3.2.1]octan-3-yl)-2-(3,4-dimethoxyphenyl)-1,4-dimethyl-1H-benzo[d]imidazole (51); 6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (52); 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (53); 2-(3-fluoro-4-methoxyphenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-1H-benzo[d]imidazole (54); 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3-fluoro-4-methoxyphenyl)-1,4-dimethyl-1H-benzo[d]imidazole (55); 2-(3-fluoro-4-methoxyphenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole (56); 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3-fluoro-4-methoxyphenyl)-4-methyl-1H-benzo[d]imidazole (57); 6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole tris(2,2,2-trifluoroacetate) (58); 4-(6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazol-2-yl)quinoline (59); 2-(2,6-dimethylpyridin-4-yl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole (60); 6-(6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazol-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine tris(2,2,2-trifluoroacetate) (61); 2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole (62); 6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-2-(4-(trifluoromethoxy)phenyl)-1H-benzo[d]imidazole (63); 2-(3-chloro-4-methoxyphenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole (64); 2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole tris(2,2,2-trifluoroacetate) (65); 2-(3-fluoro-4-(methylsulfonyl)phenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole (66); 2-(3-bromo-4-(methylsulfonyl)phenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole (67); 2-(4-cyclopropylphenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole (68); 2-(4-(difluoromethoxy)-3-fluorophenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole tris(2,2,2-trifluoroacetate) (69); 2-(6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazol-2-yl)benzo[d]thiazole tris(2,2,2-trifluoroacetate) (70); 4-(6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazol-2-yl)-3,5-dimethylisoxazole (71); 5-(6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazol-2-yl)quinoline tris(2,2,2-trifluoroacetate) (72); 2-(3-chloro-4-

- (trifluoromethoxy)phenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole tris(2,2,2-trifluoroacetate) (73); 6-(6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazol-2-yl)isoquinoline (74); 6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-2-(4-(phenylsulfonyl)phenyl)-1H-benzo[d]imidazole tris(2,2,2-trifluoroacetate) (75); 2-(3-(difluoromethoxy)phenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole (76); 7-(6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazol-2-yl)benzo[d]thiazole (77); 2-(4-(difluoromethoxy)phenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole (78); 2-(6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazol-2-yl)thiazole (79); 6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-2-(2-(trifluoromethoxy)phenyl)-1H-benzo[d]imidazole tris(2,2,2-trifluoroacetate) (80); 6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-2-(1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-benzo[d]imidazole (81); 8-(6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazol-2-yl)quinoline (82); 2-(3,4-dimethoxyphenyl)-4-fluoro-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (83); 6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (84-85); 6-(4-(4-isopropylpiperazin-1-yl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (86); 7-fluoro-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (87); 7-fluoro-6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (94-95); 5-fluoro-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (96); 5-fluoro-6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (97-98); 7-fluoro-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (102); 7-fluoro-6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (103-104); 4-fluoro-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (105); 4-fluoro-6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (106-107); 4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(1-(oxetan-3-yl)azepan-4-yl)piperidin-4-yl)-1H-benzo[d]imidazole (108-109); 6-(1-(1-(cyclobutylazepan-4-yl)piperidin-4-yl)-1,4-

- dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (110-111); 4-(6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-1H-benzo[d]imidazol-2-yl) benzenesulfonamide (112); 7-fluoro-6-(1-(1-isopropylazepan-4-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (113-114); 1-cyclopropyl-4-fluoro-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (115); 1-cyclopropyl-4-fluoro-6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (116-117); 6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (118); 6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (119); 6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1,5-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (120); 6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (121); 2-(3-fluoro-4-(methylsulfonyl)phenyl)-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-1H-benzo[d]imidazole (122); 6-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(3-fluoro-4-(methylsulfonyl)phenyl)-1,4-dimethyl-1H-benzo[d]imidazole (123-124); 6-(6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-1H-benzo[d]imidazol-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (125); 6-(6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-1H-benzo[d]imidazol-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (126); 2-(3,4-dimethoxyphenyl)-4-fluoro-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (127); 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3,4-dimethoxyphenyl)-4-fluoro-1H-benzo[d]imidazole (128); 2-(3,4-dimethoxyphenyl)-5-fluoro-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (129); 2-(3,4-dimethoxyphenyl)-5-fluoro-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (130); 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3,4-dimethoxyphenyl)-5-fluoro-1H-benzo[d]imidazole (131); 2-(3,4-dimethoxyphenyl)-7-fluoro-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (132); 2-(3,4-dimethoxyphenyl)-7-fluoro-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (133); 6-(1-(1-isopropylazepan-4-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (134); 6-(1-(1-cyclobutylazepan-4-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (135); 6-(1-(1-isobutylazepan-4-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)

- phenyl)-1H-benzo[d]imidazole (136); 6-(1-(1-(cyclopropylmethyl)azepan-4-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (137); 6-(1-(1-(cyclobutylmethyl)azepan-4-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (138); 6-(1-(2-isopropyl-2-azaspiro[3.3]heptan-6-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (139); 6-(1-(2-cyclobutyl-2-azaspiro[3.3]heptan-6-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (140); 6-(1-(2-isobutyl-2-azaspiro[3.3]heptan-6-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (141); 6-(1-(2-(cyclopropylmethyl)-2-azaspiro[3.3]heptan-6-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (142); 6-(1-(2-(cyclobutylmethyl)-2-azaspiro[3.3]heptan-6-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (143); 2-(3,4-dimethoxyphenyl)-6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-1H-benzo[d]imidazole (144-145); 6-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(3,4-dimethoxyphenyl)-1,4-dimethyl-1H-benzo[d]imidazole (146-147); 6-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(3,4-dimethoxyphenyl)-1,4-dimethyl-1H-benzo[d]imidazole (148-149); 6-(1-(8-(cyclobutylmethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(3,4-dimethoxyphenyl)-1,4-dimethyl-1H-benzo[d]imidazole (150-151); 6-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (152-153); 6-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (154-155); 6-(1-(8-(cyclobutylmethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (156-157); 1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(8-(oxetan-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1H-benzo[d]imidazole (158-159); 1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(8-(tetrahydro-2H-pyran-4-yl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1H-benzo[d]imidazole (160-161); 6-(1-(8-(2-methoxyethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (162-163); 2-(3,4-dimethoxyphenyl)-1,4-dimethyl-6-(1-(8-(oxetan-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1H-benzo[d]imidazole (164-165); 2-(3,4-dimethoxyphenyl)-1,4-dimethyl-6-(1-(8-(tetrahydro-2H-pyran-4-yl)-8-

azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1H-benzo[d]imidazole (166-167); 2-(3,4-dimethoxyphenyl)-6-(1-(8-(2-methoxyethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-1H-benzo[d]imidazole (168-169); 6-(4-(4-isobutylpiperazin-1-yl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (170); 6-(4-(4-(cyclopropylmethyl)piperazin-1-yl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (171); 6-(4-(4-(cyclobutylmethyl)piperazin-1-yl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (172); 6-(4-(4-(2-methoxyethyl)piperazin-1-yl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (173); 6-(4-(4-cyclobutylpiperazin-1-yl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (174); 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3,4-dimethoxyphenyl)-7-fluoro-1H-benzo[d]imidazole (175); 1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(4-(4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl)phenyl)-1H-benzo[d]imidazole (176); 7-fluoro-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (177); 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-7-fluoro-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (178); 6-(1'-(cyclopropylmethyl)-[1,4'-bipiperidin]-4-yl)-7-fluoro-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (179); 6-(1'-cyclobutyl-[1,4'-bipiperidin]-4-yl)-7-fluoro-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (180); 7-fluoro-2-(4-(methylsulfonyl)phenyl)-6-(1'-(oxetan-3-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (181); 7-fluoro-2-(4-(methylsulfonyl)phenyl)-6-(1'-(tetrahydro-2H-pyran-4-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (182); 7-fluoro-2-(4-(methylsulfonyl)phenyl)-6-(1'-(oxetan-3-yl)methyl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (183); 7-fluoro-6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (219-220); 5-fluoro-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (221); 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-5-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (222); 6-(1'-cyclobutyl-[1,4'-bipiperidin]-4-yl)-5-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (223); 6-(1'-(cyclopropylmethyl)-[1,4'-bipiperidin]-4-yl)-5-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (224); 5-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1'-(oxetan-3-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (225); 5-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1'-(tetrahydro-2H-pyran-4-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (226); 5-

fluoro-6-(1'-(2-methoxyethyl)-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (227); 5-fluoro-6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (228-229); 6-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-5-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (230-231); 6-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-5-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (232-233); 5-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(8-(oxetan-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1H-benzo[d]imidazole (234-235); 5-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(8-(tetrahydro-2H-pyran-4-yl)-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-1H-benzo[d]imidazole (236-237); 5-fluoro-6-(1-(8-(2-methoxyethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (238-239); 7-fluoro-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (259); 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (260); 6-(1'-(cyclopropylmethyl)-[1,4'-bipiperidin]-4-yl)-7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (261); 6-(1'-cyclobutyl-[1,4'-bipiperidin]-4-yl)-7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (262); 7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1'-(oxetan-3-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (263); 7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1'-(tetrahydro-2H-pyran-4-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (264); 7-fluoro-6-(1'-(2-methoxyethyl)-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (265); 7-fluoro-6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (266-267); 6-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (268-269); 6-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (270-271); 7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(8-(oxetan-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1H-benzo[d]imidazole (272-273); 7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(8-(tetrahydro-2H-pyran-4-yl)-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-1H-benzo[d]imidazole (274-275); 7-fluoro-6-(1-(8-(2-methoxyethyl)-8-

- azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (276-277); 4-fluoro-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (278); 4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1'-(oxetan-3-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (279); 4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1'-(tetrahydro-2H-pyran-4-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (280); 4-fluoro-6-(1'-(2-methoxyethyl)-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (281); 6-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (282-283); 4-fluoro-6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (284-285); 4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(8-(oxetan-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1H-benzo[d]imidazole (286-287); 4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(8-(tetrahydro-2H-pyran-4-yl)-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-1H-benzo[d]imidazole (288-289); 4-fluoro-6-(1-(8-(2-methoxyethyl)-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (290-291); 6-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (292-293); 4-fluoro-6-(1-(1-isopropylazepan-4-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (294-295); 4-fluoro-6-(1-(1-isobutylazepan-4-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (296-297); 6-(1-(1-(cyclopropylmethyl)azepan-4-yl)piperidin-4-yl)-4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (298-299); 4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(1-(tetrahydro-2H-pyran-4-yl)azepan-4-yl)piperidin-4-yl)-1H-benzo[d]imidazole (300-301); 4-fluoro-6-(1-(1-(2-methoxyethyl)azepan-4-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (302-303); 1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(1-(oxetan-3-yl) azepan-4-yl)piperidin-4-yl)-1H-benzo[d]imidazole (304-305); 1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(1-(tetrahydro-2H-pyran-4-yl)azepan-4-yl)piperidin-4-yl)-1H-benzo[d]imidazole (306-307); 6-(1-(1-(2-methoxyethyl)azepan-4-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (308-309); 7-fluoro-6-(1-(1-isobutylazepan-4-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)

- phenyl)-1H-benzo[d]imidazole (310-311); 6-(1-(1-cyclobutylazepan-4-yl)piperidin-4-yl)-7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (312-313); 7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(1-(oxetan-3-yl)azepan-4-yl)piperidin-4-yl)-1H-benzo[d]imidazole (314-315); 7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(1-(tetrahydro-2H-pyran-4-yl)azepan-4-yl)piperidin-4-yl)-1H-benzo[d]imidazole (316-317); 1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(1'-phenyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (318); 1-cyclopropyl-4-fluoro-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (319); 1-cyclopropyl-6-(1'-(cyclopropylmethyl)-[1,4'-bipiperidin]-4-yl)-4-fluoro-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (320); 1-cyclopropyl-4-fluoro-2-(4-(methylsulfonyl)phenyl)-6-(1'-(tetrahydro-2H-pyran-4-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (321); 1-cyclopropyl-4-fluoro-6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (322-323); 1-cyclopropyl-6-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-fluoro-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (324-325); 6-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-cyclopropyl-4-fluoro-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (326-327); 1-cyclopropyl-4-fluoro-2-(4-(methylsulfonyl)phenyl)-6-(1-(8-(tetrahydro-2H-pyran-4-yl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1H-benzo[d]imidazole (328-329); 6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (330); 6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1,5-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (331); 6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (332-333); 6-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (334); 6-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (335-336); 6-(1'-cyclobutyl-[1,4'-bipiperidin]-4-yl)-2-(3-fluoro-4-(methylsulfonyl)phenyl)-1,4-dimethyl-1H-benzo[d]imidazole (337); 6-(1'-(cyclopropylmethyl)-[1,4'-bipiperidin]-4-yl)-2-(3-fluoro-4-(methylsulfonyl)phenyl)-1,4-dimethyl-1H-benzo[d]imidazole (338); 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3-fluoro-4-(methylsulfonyl)phenyl)-1,4-dimethyl-1H-benzo[d]imidazole (339); 6-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl)

- piperidin-4-yl)-2-(3-fluoro-4-(methylsulfonyl)phenyl)-1,4-dimethyl-1H-benzo[d]imidazole (340-341); 2-(3-fluoro-4-(methylsulfonyl)phenyl)-6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-1H-benzo[d]imidazole (342); 2-(3-fluoro-4-(methylsulfonyl)phenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-1H-benzo[d]imidazole (343); 2-(3-fluoro-4-(methylsulfonyl)phenyl)-6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-1H-benzo[d]imidazole (344); 6-(1-(8-cyclopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(3-fluoro-4-(methylsulfonyl)phenyl)-1,4-dimethyl-1H-benzo[d]imidazole (345); 2-(3-fluoro-4-(methylsulfonyl)phenyl)-6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-methyl-1H-benzo[d]imidazole (346); 6-(1-(8-cyclopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(3-fluoro-4-(methylsulfonyl)phenyl)-4-methyl-1H-benzo[d]imidazole (347); 2-(3-fluoro-4-(methylsulfonyl)phenyl)-6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-methyl-1H-benzo[d]imidazole (348); 6-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(3-fluoro-4-(methylsulfonyl)phenyl)-4-methyl-1H-benzo[d]imidazole (349-350); 6-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(3-fluoro-4-(methylsulfonyl)phenyl)-4-methyl-1H-benzo[d]imidazole (351-352); 6-(6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-1H-benzo[d]imidazol-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (353); 6-(6-(1-(8-cyclopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-1H-benzo[d]imidazol-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (354); 6-(6-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-1H-benzo[d]imidazol-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (355-356); 6-(6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-1H-benzo[d]imidazol-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (357); 6-(6-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-1H-benzo[d]imidazol-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (358); 6-(6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-methyl-1H-benzo[d]imidazol-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (359); 6-(6-(1-(8-cyclopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-methyl-1H-benzo[d]imidazol-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (360); 6-(6-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-methyl-1H-benzo[d]imidazol-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (361); 6-(6-(1-(8-isopropyl-8-

azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-methyl-1H-benzo[d]imidazol-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (362); 1,4-dimethyl-6-(4-(1-methylpiperidin-4-yl)phenyl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (363); 1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(4-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl)phenyl)-1H-benzo[d]imidazole (364); 6-(6-(1-isopropylpiperidin-4-yl)pyridin-3-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (365); 1-(4-(1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)phenethyl)-4-methylpiperidin-4-ol (366); 1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(4-(4-(pyrrolidin-1-yl)piperidin-1-yl)phenyl)-1H-benzo[d]imidazole (367); 1-(4-(1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)phenyl)-N,N-dimethylpiperidin-4-amine (368); 1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(4-((4-(pyrrolidin-1-yl)piperidin-1-yl) methyl)phenyl)-1H-benzo[d]imidazole (369); 1,4-dimethyl-6-(4-((6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (370); 6-(4-((6-isobutyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (371); 1-cyclopropyl-4-methyl-2-(4-(methylsulfonyl)phenyl)-6-(4-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)phenyl)-1H-benzo[d]imidazole (372); N,N-dimethyl-1-(4-(1-methyl-2-phenyl-1H-benzo[d]imidazol-6-yl)benzyl)piperidin-4-amine (374); N,N-dimethyl-1-(4-(1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)benzyl)piperidin-4-amine (375); 1-(4-(2-(4-methoxyphenyl)-1-methyl-1H-benzo[d]imidazol-6-yl)benzyl)-N,N-dimethylpiperidin-4-amine (376); 1-(4-(2-(3-fluorophenyl)-1-methyl-1H-benzo[d]imidazol-6-yl)benzyl)-N,N-dimethylpiperidin-4-amine (377); 1-(4-(2-(4-fluorophenyl)-1-methyl-1H-benzo[d]imidazol-6-yl)benzyl)-N,N-dimethylpiperidin-4-amine (378); N,N-dimethyl-1-(4-(1-methyl-2-(2-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)benzyl)piperidin-4-amine (379); 1-(4-(2-(2-fluoro-4-(methylsulfonyl)phenyl)-1-methyl-1H-benzo[d]imidazol-6-yl)benzyl)-N,N-dimethylpiperidin-4-amine (380); 1-(4-(2-(3,5-difluorophenyl)-1-methyl-1H-benzo[d]imidazol-6-yl)benzyl)-N,N-dimethylpiperidin-4-amine (381); 1-(4-(2-(3,4-difluorophenyl)-1-methyl-1H-benzo[d]imidazol-6-yl)benzyl)-N,N-dimethylpiperidin-4-amine (382); 4-(6-(4-((4-(dimethylamino)piperidin-1-yl)methyl)phenyl)-1-methyl-1H-benzo[d]imidazol-2-yl)benzonitrile (383); N,N-dimethyl-1-(4-(1-methyl-2-(3-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)benzyl)piperidin-4-amine (384); 1-

- (4-(1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)benzyl)-N,N-dimethylpiperidin-4-amine (385); 1-(4-(1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)phenyl)-N-ethyl-N-methylpiperidin-4-amine (386); 6-(3-fluoro-4-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (387); 6-(3-fluoro-4-((cis-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methyl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (388); 6-(4-((4-ethyl-1,4-diazepan-1-yl)methyl)-3-fluorophenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (389); 1-(4-(1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)-2-fluorobenzyl)-N,N-dimethylpiperidin-4-amine (390); 6-(3,5-difluoro-4-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (391); 1-(4-(1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)-2,6-difluorobenzyl)-N,N-dimethylpiperidin-4-amine (392); N-cyclopropyl-1-(4-(1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)benzyl)-N-methylpiperidin-4-amine (393); N-cyclopropyl-1-(4-(1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)-2-fluorobenzyl)-N-methylpiperidin-4-amine (394); 1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(4-(pyrrolidin-1-yl)methyl)phenyl)-1H-benzo[d]imidazole (395); 6-(4-((cis-5-isobutylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methyl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (396); 6-(4-((cis-5-isopropylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methyl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (397); 1,4-dimethyl-6-(4-((cis-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methyl)phenyl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (398); 6-(4-((6-isopropyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (399); 1,4-dimethyl-6-(4-(1'-methyl-[1,4'-bipiperidin]-4-yl)phenyl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (400); 6-(4-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (401); 6-(4-((4-(azetidin-1-yl)piperidin-1-yl)methyl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (402); 6-(4-((4-(azetidin-1-yl)piperidin-1-yl)methyl)-3-fluorophenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (403); 6-(3-fluoro-4-((6-isopropyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (404);

- 6-(3-fluoro-5-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (405); 6-(3-((4-(azetidin-1-yl)piperidin-1-yl)methyl)-5-fluorophenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (405); 1-cyclopropyl-4-methyl-2-(4-(methylsulfonyl)phenyl)-6-(3-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)phenyl)-1H-benzo[d]imidazole (407); 1-cyclopropyl-4-fluoro-2-(4-(methylsulfonyl)phenyl)-6-(4-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)phenyl)-1H-benzo[d]imidazole (408); 4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(4-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)phenyl)-1H-benzo[d]imidazole (409); 1-cyclopropyl-4-fluoro-6-(4-((6-isopropyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (410); 1-cyclopropyl-4-fluoro-6-(4-((6-isobutyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (411); 1-cyclopropyl-4-fluoro-2-(4-(methylsulfonyl)phenyl)-6-(4-((6-(tetrahydro-2H-pyran-4-yl)-2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-1H-benzo[d]imidazole (412); 6-(4-((4-isopropylpiperazin-1-yl)methyl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (413); 6-(4-((4-isobutylpiperazin-1-yl)methyl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (414); 1-cyclopropyl-7-fluoro-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (415); 6-(4-((1-isopropylpiperidin-4-yl)oxy)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (416); 6-(4-((1-isobutylpiperidin-4-yl)oxy)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (417); 6-(1-((2,6-dimethylpyridin-4-yl)methyl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (418); 1,4-dimethyl-6-(1-((6-methylpyridin-3-yl)methyl)piperidin-4-yl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (419); diethyl (4-(6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-1H-benzo[d]imidazol-2-yl)phenyl)phosphonate (420); diethyl (4-(6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-1H-benzo[d]imidazol-2-yl)phenyl)phosphonate (421); diethyl (4-(6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-1H-benzo[d]imidazol-2-yl)phenyl)phosphonate (422); 1-((4-(1-(115-ethyl)-2-(p-tolyl)-1H-benzo[d]imidazol-6-yl)phenyl)methyl)-N,N-dimethylpiperidin-4-amine (423); N-(4-(6-(4-((4-(dimethylamino)piperidin-1-yl)methyl)phenyl)-1-methyl-1H-benzo[d]imidazol-2-yl)phenyl)methanesulfonamide (424); 1-(4-(2-(4-(dimethylamino)phenyl)-1-methyl-1H-benzo[d]imidazol-6-yl)benzyl)-N,N-

dimethylpiperidin-4-amine (425); 1-(4-(2-(4-(1H-imidazol-1-yl)phenyl)-1-methyl-1H-benzo[d]imidazol-6-yl)benzyl)-N,N-dimethylpiperidin-4-amine (426); or N-(3-(6-(4-((4-(dimethylamino)piperidin-1-yl)methyl)phenyl)-1-methyl-1H-benzo[d]imidazol-2-yl)phenyl)methanesulfonamide (427).

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

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

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

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

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

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

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

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

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

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

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

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

5

DEFINITIONS

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

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

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

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

The definitions set forth herein take precedence over definitions set forth in any patent, patent application, and/or patent application publication incorporated herein by reference.

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

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

In accordance with a convention used in the art,



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

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

5 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, “C₁₋₆ alkyl” denotes straight and branched chain alkyl groups with one to six carbon atoms.

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

The term “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 “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 "cyanoalkyl" includes both branched and straight-chain saturated alkyl groups substituted with one or more cyano groups. For example, "aminoalkyl" includes $-\text{CH}_2\text{CN}$, $-\text{CH}_2\text{CH}_2\text{CN}$, and C_{1-4} cyanoalkyl.

5 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 ($-\text{OCH}_3$). For example, " C_{1-3} alkoxy" denotes alkoxy groups with one to three carbon atoms.

The terms "fluoroalkoxy" and " $-\text{O}(\text{fluoroalkyl})$ " represent a fluoroalkyl group as defined above attached through an oxygen linkage ($-\text{O}-$). For example, " C_{1-4} fluoroalkoxy" is intended to include C_1 , C_2 , C_3 , and C_4 fluoroalkoxy groups.

10 The term "alkoxyalkyl," as used herein, refers to an alkoxy group attached through its oxygen atom to an alkyl group, which is attached to the parent molecular moiety through a carbon atom, for example, methoxymethyl group ($-\text{CH}_2\text{OCH}_3$). For example, " C_{2-4} alkoxyalkyl" denotes alkoxyalkyl groups with two to four carbon atoms, such as $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{OCH}_2\text{CH}_3$, and $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$.

15 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
20 number of carbon atoms that a particular cycloalkyl group may contain. For example, " C_{3-6} cycloalkyl" denotes cycloalkyl groups with three to six carbon atoms.

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

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

30 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”
5 encompasses both solution-phase and isolable solvates. Exemplary solvates include hydrates, ethanlates, methanlates, 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 Rautio, J. et al., *Nature Review Drug Discovery*, 17, 559-587 (2018).

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

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

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

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

The compounds of the present invention are intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same

atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium (D) and tritium (T). Isotopes of carbon include ^{13}C and ^{14}C . Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by
5 processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed. For example, methyl ($-\text{CH}_3$) also includes deuterated methyl groups such as $-\text{CD}_3$.

UTILITY

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

In another embodiment, the present invention provides a combined preparation of a compound of the present invention and additional therapeutic agent(s) for simultaneous,

separate or sequential use in therapy.

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

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

In one embodiment, additional therapeutic agent(s) used in combined
10 pharmaceutical compositions or combined methods or combined uses, are selected from one or more, preferably one to three, of the following therapeutic agents: TGF β receptor inhibitors (for example, galunisertib), inhibitors of TGF β synthesis (for example, pirfenidone), inhibitors of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) receptor kinases (for example,
15 nintedanib), humanized anti- $\alpha_v\beta_6$ integrin monoclonal antibody (for example, 3G9), human recombinant pentraxin-2, recombinant human Serum Amyloid P, recombinant human antibody against TGF β -1, -2, and -3, endothelin receptor antagonists (for example, macitentan), interferon gamma, c-Jun amino-terminal kinase (JNK) inhibitor (for example, 4-[[9-[(3S)-tetrahydro-3-furanyl]-8-[(2,4,6-trifluorophenyl)amino]-9H-purin-2-yl]amino]-trans-cyclohexanol, 3-pentylbenzeneacetic acid (PBI-4050), tetra-substituted
20 porphyrin derivative containing manganese (III), monoclonal antibody targeting eotaxin-2, interleukin-13 (IL-13) antibody (for example, lebrikizumab, tralokinumab), bispecific antibody targeting interleukin 4 (IL-4) and interleukin 13 (IL-13), NK1 tachykinin receptor agonist (for example, Sar⁹, Met(O₂)¹¹-Substance P), Cintredekin Besudotox,
25 human recombinant DNA-derived, IgG1 kappa monoclonal antibody to connective growth factor, and fully human IgG1 kappa antibody, selective for CC-chemokine ligand 2 (for example, carlumab, CCX140), antioxidants (for example, N-acetylcysteine), phosphodiesterase 5 (PDE5) inhibitors (for example, sildenafil), agents for treatment of obstructive airway diseases such as muscarinic antagonists (for example, tiotropium, ipatropium bromide), adrenergic β_2 agonists (for example, salbutamol, salmeterol),
30 corticosteroids (for example, triamcinolone, dexamethasone, fluticasone),

immunosuppressive agents (for example, tacrolimus, rapamycin, pimecrolimus), and therapeutic agents useful for the treatment of fibrotic conditions, such as liver, biliary, and kidney fibrosis, Non-Alcoholic Fatty Liver Disease (NALFD), Non-Alcoholic Steato-Hepatitis (NASH), cardiac fibrosis, Idiopathic Pulmonary Fibrosis (IPF), and systemic sclerosis. The therapeutic agents useful for the treatment of such fibrotic conditions include, but are not limited to, FXR agonists (for example OCA, GS-9674, and LJN452), LOXL2 inhibitors (for example simtuzumab), LPA1 antagonists (for example, BMS-986020 and SAR 100842), PPAR modulators (for example, elafibrinor, pioglitazone, and saroglitazar, IVA337), SSAO/VAP-1 inhibitors (for example, PXS-4728A and SZE5302), ASK-1 inhibitors (for example GS-4997 or selonsertib), ACC inhibitors (for example, CP-640186 and NDI-010976 or GS-0976), FGF21 mimetics (for example, LY2405319 and BMS-986036), caspase inhibitors (for example, emricasan), NOX4 inhibitors (for example, GKT137831), MGAT2 inhibitor (for example, BMS-963272), α V integrin inhibitors (for example, abituzumab) and bile acid/fatty acid conjugates (for example aramchol). The FXR agonists of various embodiments of the present invention may also be used in combination with one or more therapeutic agents such as CCR2/5 inhibitors (for example, cenicriviroc), Galectin-3 inhibitors (for example, TD-139, GR-MD-02), leukotriene receptor antagonists (for example, tiplelukast, montelukast), SGLT2 inhibitors (for example, dapagliflozin, remogliflozin), GLP-1 receptor agonists (for example, liraglutide and semaglutide), FAK inhibitors (for example, GSK-2256098), CB1 inverse agonists (for example, JD-5037), CB2 agonists (for example, APD-371 and JBT-101), autotaxin inhibitors (for example, GLPG1690), prolyl t-RNA synthetase inhibitors (for example, halofuginone), FPR2 agonists (for example, ZK-994), and THR agonists (for example, MGL:3196). In another embodiment, additional therapeutic agent(s) used in combined pharmaceutical compositions or combined methods or combined uses, are selected from one or more, preferably one to three, of immunoncology agents, such as Alemtuzumab, Atezolizumab, Ipilimumab, Nivolumab, Ofatumumab, Pembrolizumab, and Rituximab.

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

of TLR9.

The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts indicated in the *Physicians' Desk Reference* (PDR) or as otherwise determined by one of
5 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 TLR9-associated conditions.

The inventive compositions may contain other therapeutic agents as described
10 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.

15 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
20 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
25 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 pharmaceutically acceptable carriers, and factors involved in their selection, are found in
30 a variety of readily available sources such as, for example, *Remington: The Science and Practice of Pharmacy*, 22nd Edition (2013).

Compounds in accordance with Formula (I) can be administered by any means

suitable for the condition to be treated, which can depend on the need for site-specific treatment or quantity of Formula (I) compound to be delivered.

The compounds of Formula (I) may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and compositions of the present invention may, for example, be administered orally, mucosally, or parentally including intravascularly, intravenously, intraperitoneally, subcutaneously, intramuscularly, and intrasternally in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles. For example, the pharmaceutical carrier may contain a mixture of mannitol or lactose and microcrystalline cellulose. The mixture may contain additional components such as a lubricating agent, e.g. magnesium stearate and a disintegrating agent such as 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) 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.

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, hydroxypropylmethylcellulose, sodium alginate, alginic acid, polyvinyl-pyrrolidone, gum tragacanth, and gum acacia; dispersing or wetting agents, such as, for example, a naturally-occurring phosphatide, e.g., lecithin; condensation products of alkylene oxide with fatty acids, such

as, for example, polyoxyethylene stearate; condensation products of ethylene oxide with long chain aliphatic alcohols, such as, for example heptadecaethylene-oxycetanol; condensation products of ethylene oxide with partial esters derived from fatty acids and 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 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. 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-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 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 manner. The oil phase can be provided by, but is not limited to, for example, a vegetable oil, such as, for example, olive oil and arachis oil; a mineral oil, such as, for example,

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

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

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

with cyclodextrin (i.e. Captisol), cosolvent solubilization (i.e. propylene glycol) or micellar solubilization (i.e. Tween 80).

The sterile injectable preparation may also be a sterile injectable solution or 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.

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 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 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 stating that the pharmaceutical composition can be used for the treatment of a cardiovascular disorder, diuresis, and/or natriuresis. In another embodiment, the package insert states that the pharmaceutical composition can be used in combination (as defined previously) with a second therapeutic agent to treat cardiovascular disorder, diuresis, and/or natriuresis. The article of manufacture can further comprise: (d) a second 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 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 sacks. The package insert can be physically attached to the outside of the first container via tape, glue, staple, or another method of attachment, or it can rest inside the second

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

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

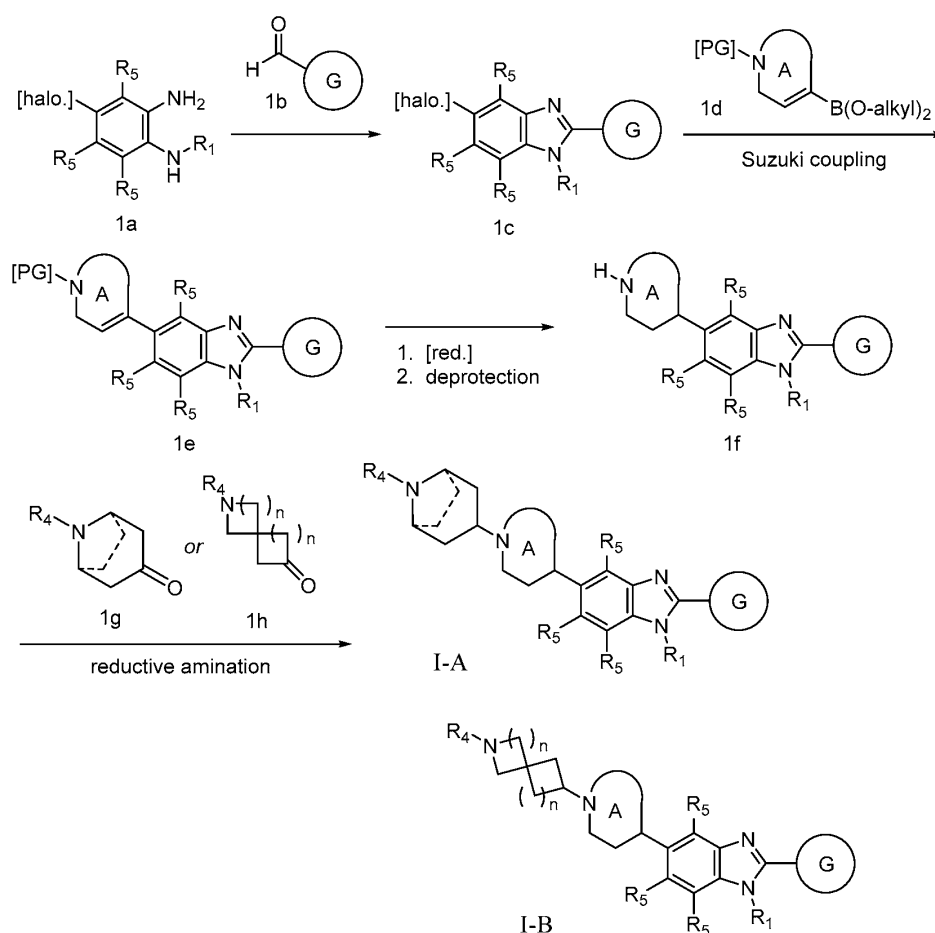
METHODS OF PREPARATION

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.

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

molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents that are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention. It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene et al. (*Protective Groups in Organic Synthesis*, Third Edition, Wiley and Sons (1999)).

SCHEME 1



Scheme 1 describes the synthesis of compounds of Formula I-A and I-B, a subset of Formula I. The term “halo.” in this scheme refers to any halogen that one of ordinary skill in the art would deem suitable to achieve the intended transformation. The term “PG” refers to any suitable amino protective group, such as alkyl carbamate, alkyl amide, or alkyl. Ring A as shown in Formula I-A and I-B is substituted at the 5-position of the 1H-benzo[d]imidazole ring, however, a person of ordinary skill can readily modify this synthetic scheme to install Ring A at the 6-position by using appropriate starting material.

Compound 1a can be reacted with aldehyde 1b, in any typical reaction solvent (e.g. EtOH, DMF, DMSO, NMP) with heating. The reaction can be conducted in the presence of base such as potassium carbonate or sodium bicarbonate, but is not necessary. Addition of additive sodium metabisulfite is not necessary but expedites the reaction. Compound 1c can be coupled with boronate ester 1d under standard Suzuki coupling

- conditions. The resultant alkene can be reduced by catalytic hydrogenation using a catalyst such as Pd or Pt. Protective group PG can be removed by one of ordinary skill in the art using appropriate reagents and conditions. Reductive amination of amine 1f with ketone 1g or 1h, can be achieved with a reducing agent such as sodium triacetoxyborohydride or sodium cyanoborohydride, with or without an acid catalyst (i.e. AcOH), to furnish compounds of Formula I-A and I-B.

EXAMPLES

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

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

- Column chromatography was performed with pre-packed silica gel cartridges using an Isco medium pressure chromatography apparatus (Teledyne Corporation), eluting with the solvent or solvent mixture indicated. Preparative high performance liquid chromatography (HPLC) was performed using a reverse phase column (Waters

Sunfire C₁₈, Waters Xbridge C₁₈, PHENOMENEX® Axia C₁₈, YMC S5 ODS or the like) of a size appropriate to the quantity of material being separated, generally eluting with a gradient of increasing concentration of methanol or acetonitrile in water, also containing 0.05% or 0.1% trifluoroacetic acid or 10 mM ammonium acetate, at a rate of elution

5 suitable to the column size and separation to be achieved. Chemical names were determined using ChemDraw Ultra, version 9.0.5 (CambridgeSoft). The following abbreviations are used:

	ACN	acetonitrile
10	AcOH	acetic acid
	aq.	aqueous
	brine	saturated aqueous sodium chloride
	DCE	dichloroethane
	DCM	dichloromethane
15	DEA	diethylamine
	DMAP	dimethylaminopyridine
	DMF	<i>N,N</i> -dimethylformamide
	DMSO	dimethyl sulfoxide
	EtOAc	ethyl acetate
20	FA	formic acid
	g	gram(s)
	h	hour(s)
	Hex	hexanes
	HPLC	High Performance Liquid Chromatography
25	IPA	isopropyl alcohol
	LCMS	Liquid Chromatography-Mass Spectroscopy
	MeCN	acetonitrile
	MeOH	methanol
	NMP	<i>N</i> -methylpyrrolidinone
30	Oxone	potassium peroxydisulfate
	Pd(dppf)Cl ₂	[1,1'- <i>bis</i> (diphenylphosphino)ferrocene]dichloropalladium(II)
	pet ether	petroleum ether

TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
XPhos-Pd-G3	(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-
5	(2'-amino-1,1'-biphenyl)] palladium(II) methanesulfonate

PREPARATION

All reagents purchased from commercial sources were used without further purification unless otherwise noted. All reactions involving air or moisture sensitive reagents were performed under an inert atmosphere. Proton magnetic resonance spectra were recorded either on a Bruker 400 or a JEOL Eclipse 500 spectrometer.

Analytical LC/MS Methods

Method 1: Column: Waters XBridge C18, 2.1 mm 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 %B to 100 %B over 3 min, then a 0.50 min hold at 100 %B; Flow: 1 mL/min; Detection: MS and UV (220 nm).

Method 2: Column: Waters XBridge C18, 2.1 mm 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: 50 °C; Gradient: 0 %B to 100 %B over 3 min, then a 0.50 min hold at 100 %B; Flow: 1 mL/min; Detection: MS and UV (220 nm).

Method 3: Column: Waters Acquity BEH C18, 2.1 x 50mm, 1.7 µm particles;
Mobile Phase A: 5:95 acetonitrile:water with 0.05 % trifluoroacetic acid; Mobile Phase B: 95:5 acetonitrile:water with 0.05 % trifluoroacetic acid; Temperature: 60 °C; Gradient: 2 %B to 98 %B over 1 min, then a 0.50 min hold at 98 %B; Flow: 0.8 mL/min; Detection: MS and UV (220 nm).

Method 4: Column: Waters Acquity BEH C18, 2.1 x 50 mm, 1.7 µm particles;
Mobile Phase A: 5:95 acetonitrile:water with 0.05 % trifluoroacetic acid; Mobile Phase B: 95:5 acetonitrile:water with 0.05 % trifluoroacetic acid; Temperature: 50 °C; Gradient: 0 %B to 100 %B over 3 min, then a 0.50 min hold at 100 %B; Flow: 1.0 mL/min;

Detection: MS and UV (220, 254 nm).

Method 5: Column: Waters Acquity BEH C18, 2.1 x 50 mm, 1.7 µm particles;
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 %B to 100
5 %B over 3 min, then a 0.50 min hold at 100 %B; Flow: 1.0 mL/min; Detection: MS and
UV (220 nm).

Method 6: Column: HALO C18, 3.0 x 30 mm, 2.7 µm particles; Mobile Phase A:
water with 0.05 % trifluoroacetic acid; Mobile Phase B: acetonitrile with 0.05 %
trifluoroacetic acid; Temperature: 40 °C; Gradient: 5 %B to 50 %B over 2 min, 50 %B to
10 100 %B over 0.4 min, then a 0.40 min hold at 100 %B; Flow: 1.5 mL/min; Detection: MS
and UV (220 nm).

Method 7: Column: HALO C18, 3.0 x 30 mm, 2.0 µm particles; Mobile Phase A:
water with 0.1 % formic acid; Mobile Phase B: acetonitrile with 0.05 % formic acid;
Temperature: 40 °C; Gradient: 5 %B to 100 %B over 1.2 min, then a 0.60 min hold at 100
15 %B; Flow: 1.2 mL/min; Detection: MS and UV (220 nm).

Method 8: Column: HALO C18, 3.0 x 30 mm, 2.7 µm particles; Mobile Phase A:
water with 0.05 % trifluoroacetic acid; Mobile Phase B: acetonitrile with 0.05 %
trifluoroacetic acid; Temperature: 40 °C; Gradient: 5 %B to 100 %B over 1.3 min, then a
0.50 min hold at 100 %B; Flow: 1.5 mL/min; Detection: MS and UV (220 nm).

20 Method 9: Column: Shim-pack Scepter C18, 3.0 mm x 33 mm, 3.0 µm particles;
Mobile Phase A: water with 5 mM ammonium bicarbonate; Mobile Phase B: acetonitrile;
Temperature: 40 °C; Gradient: 50 %B to 95 %B over 2 min, then a 0.70 min hold at 95
%B; Flow: 1.5 mL/min; Detection: MS and UV (220 nm).

25 Chiral Analytical Methods

SFC Method 1: Instrument: Shimadzu Nexera UC SFC; Column: Chiral OD, 4.6 x
100 mm, 5 micron; Mobile Phase: 70% CO₂/ 30% MeOH w/0.1%DEA; Flow Conditions:
2 mL/min; Detector Wavelength: 220 nm.

SFC Method 2: Instrument: Shimadzu Nexera UC SFC; Column: Chiral OD, 4.6 x
30 100 mm, 5 micron; Mobile Phase: 60% CO₂/ 40% MeOH-NH₄OH; Flow Conditions: 2
mL/min; Detector Wavelength: 220 nm.

SFC Method 3: Instrument: Shimadzu Nexera UC SFC; Column: Chiral OD, 4.6 x

100 mm, 5 micron; Mobile Phase: 65% CO₂/ 35% MeOH w/0.1%DEA; Flow Conditions: 2 mL/min; Detector Wavelength: 220 nm.

SFC Method 4: Instrument: Shimadzu Nexera UC SFC; Column: Chiral OD, 4.6 x 100 mm, 5 micron; Mobile Phase: 70% CO₂/ 30% IPA w/0.3%DEA/0.2%FA; Flow
5 Conditions: 2 mL/min; Detector Wavelength: 220 nm.

SFC Method 5: Instrument: Shimadzu Nexera UC SFC; Column: Chiral OD, 4.6 x 100 mm, 5 micron; Mobile Phase: 60% CO₂/ 40% IPA w/0.3%DEA/0.2%FA; Flow
Conditions: 2 mL/min; Detector Wavelength: 220 nm.

SFC Method 6: Instrument: Shimadzu Nexera UC SFC; Column: Chiral OD, 4.6 x
10 100 mm, 5 micron; Mobile Phase: 70% CO₂/ 30% IPA w/0.1%DEA/0.1%FA; Flow
Conditions: 2 mL/min; Detector Wavelength: 220 nm.

SFC Method 7: Instrument: Shimadzu Nexera UC SFC; Column: Chiral OD, 4.6 x 100 mm, 5 micron; Mobile Phase: 60% CO₂/ 40% IPA w/0.5%DEA/0.3%FA; Flow
Conditions: 2 mL/min; Detector Wavelength: 220 nm.

SFC Method 8: Instrument: Shimadzu Nexera UC SFC; Column: Chiral OD, 4.6 x
15 100 mm, 5 micron; Mobile Phase: 60% CO₂/ 40% MeOH w/0.2%DEA/0.2%FA; Flow
Conditions: 2 mL/min; Detector Wavelength: 220 nm.

SFC Method 9: Instrument: Shimadzu Nexera UC SFC; Column: Chiral OD, 4.6 x
100 mm, 5 micron; Mobile Phase: 70% CO₂/ 30% IPA w/0.1%DEA; Flow Conditions: 2
20 mL/min; Detector Wavelength: 220 nm.

Preparative HPLC Methods

Prep Method 1: Column: XBridge C18, 200 mm x 19 mm, 5-μm particles; Mobile
Phase A: 5:95 acetonitrile: water with ammonium acetate; Mobile Phase B: 95:5
25 acetonitrile: water with ammonium acetate; Gradient: (variable; dependent on substrate)
%B over 20 minutes, then a 0-minute hold at 100% B; Flow Rate: 20 mL/min; Column
Temperature: 25 °C. Fraction collection was triggered by MS and UV signals. Fractions
containing the desired product were combined and dried via centrifugal evaporation.

Prep Method 2: Column: XBridge C18, 200 mm x 19 mm, 5-μm particles; Mobile
30 Phase A: 5:95 acetonitrile: water with 0.05% trifluoroacetic acid; Mobile Phase B: 95:5
acetonitrile: water with 0.05% trifluoroacetic acid; Gradient: (variable; dependent on
substrate) % B over 20 minutes, then a 0-minute hold at 100% B; Flow Rate: 20 mL/min;

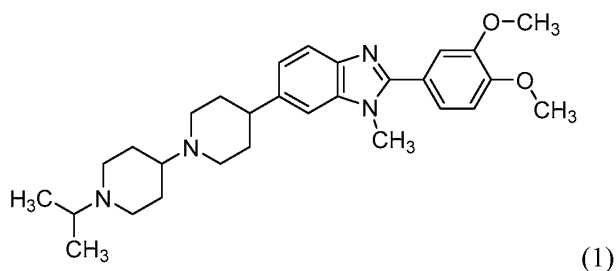
Column Temperature: 25 °C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation.

Prep Method 3: Column: XBridge Prep C18 OBD Column, 19 x150 mm 5 µm;
5 Mobile Phase A: Water (10mmol/L NH₄HCO₃), Mobile Phase B: ACN; Flow rate:20 mL/min; Gradient: (variable; dependent on substrate); 254/210 nm. Fractions containing the desired product were combined and dried via centrifugal evaporation.

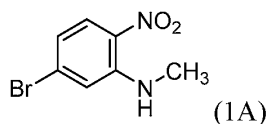
Prep Method 4: Column: Luna 5u C18, 100 mm x 21mm. 5-µm particles; Solvent A: 90% H₂O-10% methanol-0.1%TFA; Solvent B: 10% methanol-90% H₂O 0.1% TFA.
10 Flow rate: 20 mL/min. Gradient Time: 15 minutes. Start B: variable; dependent on substrate); Final B: 100%. Fractions containing the desired product were combined and dried via centrifugal evaporation.

EXAMPLE 1

15 2-(3,4-dimethoxyphenyl)-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1-methyl-1H-benzo[d]imidazole



Step A. Intermediate 1A. Preparation of 5-bromo-N-methyl-2-nitroaniline

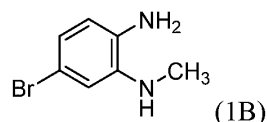


20 To a 1 L round bottomed flask were added 4-bromo-2-fluoro-1-nitrobenzene (16 g, 73 mmol) and DCM (400 mL). To this mixture was added methylamine (2.0 M solution in THF) (88 mL, 180 mmol). Upon addition of amine, the solution rapidly changed from a pale yellow to a bright orange solution. The reaction mixture was stirred at room temperature under a closed system. After 18 h, the reaction mixture was filtered
25 through a plug of SiO₂ (250 g), with 2:1 Hex:EtOAc as eluent. The filtrate was

concentrated and dried in vacuo to afford the title compound (16 g, 69 mmol, 95 % yield) as a yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.05 (d, *J*=9.1 Hz, 1H), 7.18 (d, *J*=1.9 Hz, 1H), 6.85-6.78 (m, 1H), 3.02 (s, 3H). Analytical LC/MS (Method 3): Observed Mass: 232.9; Retention Time: 0.97 min.

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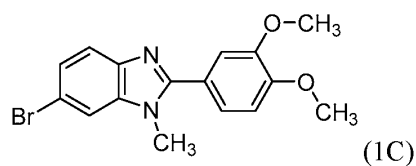
Step B. Intermediate 1B. Preparation of 5-bromo-N¹-methylbenzene-1,2-diamine



To a solution of Intermediate 1A (16 g, 69 mmol) in MeOH (200 mL) was added tin(II) chloride dihydrate (48 g, 210 mmol). The reaction mixture was stirred at reflux. After 3 h, the reaction mixture was cooled and carefully poured into ice cold 20% NaOH solution (500 mL). The aqueous suspension was partitioned into EtOAc (500 mL), upon which a fine white precipitate formed. The suspension was filtered and the layers were separated. The aqueous phase was extracted with EtOAc (250 mL), the organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (330 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100%B; flow rate = 120 mL/min). The fractions corresponding to product were combined, concentrated and dried in vacuo to afford the title compound (12 g, 60 mmol, 87 % yield) as a dark oil. ¹H NMR (500 MHz, METHANOL-d₄) δ 6.66-6.62 (m, 2H), 6.60-6.57 (m, 1H), 2.81 (s, 3H). Analytical LC/MS (Method 3): Observed Mass: 200.9; Retention Time: 0.60 min.

20

Step C. Intermediate 1C. Preparation of 6-bromo-2-(3,4-dimethoxyphenyl)-1-methyl-1H-benzo[d]imidazole



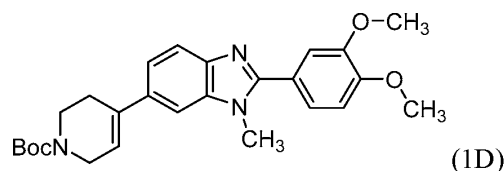
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To a 40 mL vial were added Intermediate 1B (0.75 g, 3.7 mmol), 3,4-dimethoxybenzaldehyde (0.74 g, 4.4 mmol) and MeOH (5 mL). The vial was capped and the mixture was stirred at 60 °C. After 18 h, the reaction mixture was cooled, diluted

with water (100 mL) and extracted with EtOAc (2 x 50 mL). The organic phase was combined, washed with brine, dried over MgSO_4 , filtered and concentrated. The residue was purified by flash column chromatography (80 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100%B; flow rate = 60 mL/min). The fractions corresponding to product were combined, concentrated and dried in vacuo to afford the title compound (0.31 g, 0.89 mmol, 24 % yield) as a yellow solid. ^1H NMR (500 MHz, METHANOL- d_4) δ 7.79-7.77 (m, 1H), 7.61-7.57 (m, 1H), 7.45-7.42 (m, 1H), 7.41-7.39 (m, 1H), 7.38-7.35 (m, 1H), 7.19-7.15 (m, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.90 (s, 3H). Analytical LC/MS (Method 3): Observed Mass: 346.9; Retention Time: 0.68 min.

10

Step D. Intermediate 1D. Preparation of tert-butyl 4-(2-(3,4-dimethoxyphenyl)-1-methyl-1H-benzo[d]imidazol-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate

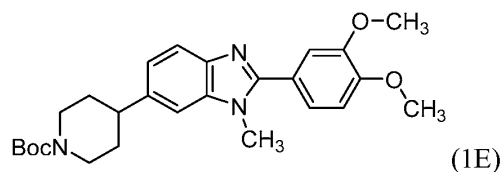


To a 40 mL vial were added Intermediate 1C (0.31 g, 0.89 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (0.33 g, 1.1 mmol), followed by 1,4-dioxane (10 mL) and potassium phosphate tribasic (0.57 g, 2.7 mmol) dissolved in water (1 mL). The vial was purged with N_2 , then 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.036 g, 0.045 mmol) was added. The vial was purged again with N_2 , and the reaction stirred at 75 °C. After 18 h, the reaction mixture was cooled and the mixture was partitioned into water (30 mL) and ethyl acetate (30 mL). The layers were separated, the aqueous phase was extracted with EtOAc (20 mL), the organic phase was combined, washed with brine, dried over MgSO_4 , filtered and concentrated. The residue was purified by flash column chromatography (80 g silica gel cartridge; A = Hex, B = EtOAc; 20 min grad.; 0% B to 100%B; flow rate = 60 mL/min). The fractions corresponding to product were combined, concentrated and dried in vacuo to afford the title compound (0.37 g, 0.82 mmol, 92 % yield) as a pale yellow solid. ^1H NMR (500 MHz, METHANOL- d_4) δ 7.65-7.60 (m, 1H), 7.59-7.55 (m, 1H), 7.47-7.42 (m, 1H), 7.41-7.39 (m, 1H), 7.38-7.35 (m, 1H), 7.20-7.15 (m, 1H), 6.24-6.14 (m, 1H), 4.16-4.10 (m, 2H),

3.95 (s, 6H), 3.94-3.91 (m, 3H), 3.75-3.66 (m, 2H), 2.70-2.65 (m, 2H), 1.53 (s, 9H).

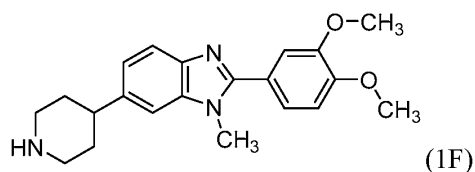
Analytical LC/MS (Method 3): Observed Mass: 450.2; Retention Time: 0.91 min.

Step E. Intermediate 1E. Preparation of tert-butyl 4-(2-(3,4-dimethoxyphenyl)-1-methyl-1H-benzo[d]imidazol-6-yl)piperidine-1-carboxylate



To a 100 mL pear shaped flask were added Intermediate 1D (0.37 g, 0.82 mmol) and MeOH (20 mL). The vessel was evacuated and purged with N₂, then Pd-C (10% wt.) (0.088 g, 0.082 mmol) was added and the reaction mixture was stirred under hydrogen at 1 atm. After 2.5 h, the catalyst was filtered and the filtrate was concentrated. The product was dried in vacuo to afford the title compound (0.34 g, 0.75 mmol, 91 % yield) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.60 (s, 1H), 7.44-7.42 (m, 1H), 7.41-7.38 (m, 1H), 7.38-7.34 (m, 1H), 7.25-7.21 (m, 1H), 7.19-7.15 (m, 1H), 4.32-4.24 (m, 2H), 3.95 (s, 6H), 3.91 (s, 3H), 2.99-2.88 (m, 3H), 1.97-1.90 (m, 2H), 1.79-1.69 (m, 2H), 1.52 (s, 9H). Analytical LC/MS (Method 3): Observed Mass: 452.2; Retention Time: 0.81 min.

Step F. Intermediate 1F. Preparation of 2-(3,4-dimethoxyphenyl)-1-methyl-6-(piperidin-4-yl)-1H-benzo[d]imidazole bis(2,2,2-trifluoroacetate)



To a 100 mL pear shaped flask were added Intermediate 1E (0.34 g, 0.75 mmol), DCM (8 mL), and TFA (2 mL). After stirring 15 min, the solvent was concentrated, the residue was co-evaporated with toluene (2x), and the product was dried in vacuo to afford the title compound (0.41 g, 0.71 mmol, 95 % yield) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.87-7.84 (m, 1H), 7.83-7.80 (m, 1H), 7.65-7.62 (m, 1H), 7.56-7.52 (m, 1H), 7.50-7.46 (m, 1H), 7.34-7.31 (m, 1H), 4.15 (s, 3H), 4.00 (s, 3H), 3.98 (s,

3H), 3.63-3.57 (m, 2H), 3.29-3.19 (m, 3H), 2.28-2.18 (m, 2H), 2.14-2.00 (m, 2H).

Analytical LC/MS (Method 3): Observed Mass: 352.1; Retention Time: 0.51 min.

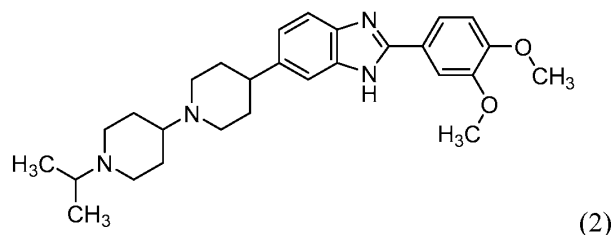
Step G. Example 1

5 To a 40 mL vial were added Intermediate 1F (50 mg, 0.086 mmol), 1-isopropylpiperidin-4-one (61 mg, 0.43 mmol), AcOH (5.7 mg, 0.095 mmol), magnesium sulfate (220 mg, 1.8 mmol), and DMF (2 mL). The reaction mixture was stirred for 20 min, then sodium triacetoxyborohydride (91 mg, 0.43 mmol) was added and the reaction mixture was stirred. After 18 h, the reaction mixture was filtered and the filter cake was washed with 10% IPA/chloroform (20 mL). The filtrate was washed with 10% aqueous NaOH (10 mL), brine, dried over MgSO₄, filtered and concentrated. The crude material was purified via preparative HPLC (Prep Method 1) to afford the title compound (13 mg, 0.027 mmol, 31 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 7.55 (d, *J*=8.2 Hz, 1H), 7.45 (s, 1H), 7.41-7.35 (m, 2H), 7.14 (dd, *J*=8.2, 4.0 Hz, 2H), 3.90-3.83 (m, 9H), 3.04-2.97 (m, 10 2H), 2.89-2.80 (m, 2H), 2.72-2.57 (m, 2H), 2.31-2.24 (m, 2H), 2.24-2.18 (m, 1H), 2.15-2.03 (m, 2H), 1.86-1.80 (m, 2H), 1.80-1.71 (m, 4H), 1.50-1.39 (m, 2H), 0.97 (d, *J*=6.4 Hz, 6H). TLR9 IC₅₀ (nM) = 56. Analytical LC/MS (Method 1): Purity: 96.9 %; Observed Mass: 477.18; Retention Time: 0.61 min. (Method 2): Purity: 100 %; Observed Mass: 476.96; Retention Time: 1.26 min.

20

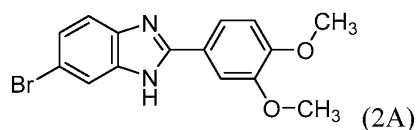
EXAMPLE 2

2-(3,4-dimethoxyphenyl)-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole



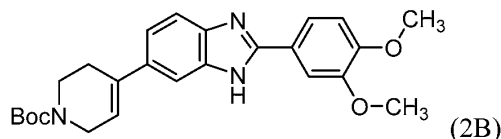
Step A. Intermediate 2A. Preparation of 6-bromo-2-(3,4-dimethoxyphenyl)-1H-benzo[d]imidazole

25



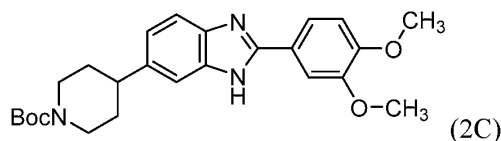
Intermediate 2A was synthesized according to methods described for the preparation of Intermediate 1C, using 4-bromobenzene-1,2-diamine (6 g, 32 mmol) as starting material to afford the title compound (3.7 g, 11 mmol, 34 % yield) as an off white solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.77-7.71 (m, 1H), 7.70-7.65 (m, 1H), 7.59-7.44 (m, 2H), 7.41-7.34 (m, 1H), 7.17-7.10 (m, 1H), 4.00-3.95 (m, 3H), 3.93 (s, 3H). Analytical LC/MS (Method 1): Observed Mass: 335.2; Retention Time: 0.65 min.

Step B. Intermediate 2B. Preparation of tert-butyl 4-(2-(3,4-dimethoxyphenyl)-1H-benzo[d]imidazol-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate



Intermediate 2B was synthesized according to methods described for the preparation of Intermediate 1D, using Intermediate 2A (1.2 g, 3.6 mmol) as starting material to afford the title compound (1.4 g, 3.2 mmol, 89 % yield) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.75 (d, *J*=2.2 Hz, 1H), 7.71-7.66 (m, 1H), 7.65-7.50 (m, 2H), 7.41-7.37 (m, 1H), 7.13 (d, *J*=8.5 Hz, 1H), 6.19-6.09 (m, 1H), 4.16-4.09 (m, 2H), 3.98 (s, 3H), 3.93 (s, 3H), 3.75-3.67 (m, 2H), 2.70-2.58 (m, 2H), 1.53 (s, 9H). Analytical LC/MS (Method 3): Observed Mass: 436.3; Retention Time: 0.81 min.

Step C. Intermediate 2C. Preparation of tert-butyl 4-(2-(3,4-dimethoxyphenyl)-1H-benzo[d]imidazol-6-yl)piperidine-1-carboxylate

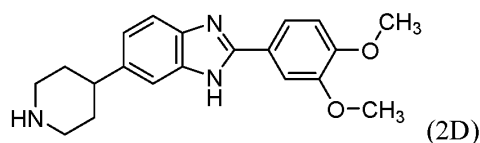


Intermediate 2C was synthesized according to methods described for the preparation of Intermediate 1E, using Intermediate 2B (1.4 g, 3.2 mmol) as starting material to afford the title compound (0.98 g, 2.1 mmol, 69 % yield) as an off white solid.

¹H NMR (500 MHz, METHANOL-d₄) δ 7.76-7.73 (m, 1H), 7.70-7.65 (m, 1H), 7.57-7.49 (m, 1H), 7.48-7.40 (m, 1H), 7.19-7.16 (m, 1H), 7.14-7.10 (m, 1H), 4.30-4.22 (m, 2H), 4.00-3.97 (m, 3H), 3.95-3.92 (m, 3H), 2.99-2.81 (m, 3H), 1.97-1.88 (m, 2H), 1.76-1.63 (m, 2H), 1.53-1.49 (m, 9H). Analytical LC/MS (Method 3): Observed Mass: 438.2;

5 Retention Time: 0.81 min.

Step D. Intermediate 2D. Preparation of 2-(3,4-dimethoxyphenyl)-6-(piperidin-4-yl)-1H-benzo[d]imidazole dihydrochloride



10 To a 100 mL pear shaped flask were added Intermediate 4C (430 mg, 0.98 mmol) and a minimal amount of MeOH. To this mixture was added 4 M HCl in dioxane (20 mL) and the reaction mixture was stirred. After 15 min, the solvent was concentrated, and the residue was co-evaporated with toluene. The product was dried in vacuo to afford the title compound (400 mg, 0.97 mmol, 99 % yield) as an off white solid. ¹H NMR (500
15 MHz, METHANOL-d₄) δ 7.81-7.74 (m, 3H), 7.71-7.67 (m, 1H), 7.56-7.51 (m, 1H), 7.31-7.27 (m, 1H), 4.02 (s, 3H), 4.00 (s, 3H), 3.63-3.55 (m, 2H), 3.28-3.18 (m, 3H), 2.24-2.17 (m, 2H), 2.12-2.01 (m, 2H). Analytical LC/MS (Method 3): Observed Mass: 338.3; Retention Time: 0.58 min.

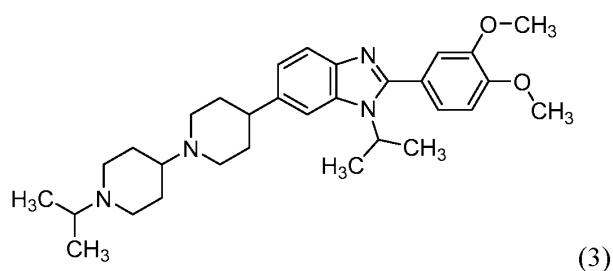
20 Step E. Example 2

To a 40 mL vial were added Intermediate 2D (60 mg, 0.15 mmol), 1-isopropylpiperidin-4-one (110 mg, 0.78 mmol), AcOH (11 mg, 0.18 mmol), magnesium sulfate (220 mg, 1.8 mmol), and DMF (2 mL). The reaction mixture was stirred for 20 min, then sodium triacetoxyborohydride (170 mg, 0.80 mmol) was added and the reaction
25 mixture was stirred. After 18 h, the reaction mixture was filtered and the filter cake was washed with 10% IPA/chloroform (20 mL). The filtrate was washed with 10% aqueous NaOH (10 mL), brine, dried over MgSO₄, filtered and concentrated. The crude material was purified via preparative HPLC (Prep Method 1) to afford the title compound (37 mg, 0.080 mmol, 53 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 7.75 (s, 1H), 7.74-7.70 (m,

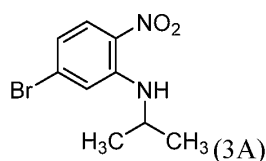
1H), 7.55-7.45 (m, 1H), 7.44-7.31 (m, 1H), 7.14-7.11 (m, 1H), 7.11-7.05 (m, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.53-3.41 (m, 1H), 3.06-2.98 (m, 2H), 2.96-2.87 (m, 2H), 2.83-2.71 (m, 1H), 2.66-2.58 (m, 1H), 2.38-2.28 (m, 3H), 2.26-2.16 (m, 2H), 1.86-1.78 (m, 3H), 1.75-1.66 (m, 2H), 1.56-1.45 (m, 2H), 1.03-0.98 (m, 6H). TLR9 IC₅₀ (nM) = 120. Analytical
 5 LC/MS (Method 1): Purity: 98 %; Observed Mass: 463.03; Retention Time: 0.97 min.
 (Method 2): Purity: 100 %; Observed Mass: 463.16; Retention Time: 1.23 min.

EXAMPLE 3

2-(3,4-dimethoxyphenyl)-1-isopropyl-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1H-
 10 benzo[d]imidazole

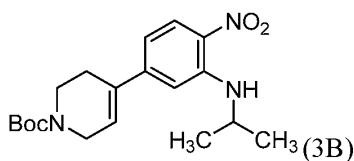


Step A. Intermediate 3A. Preparation of 5-bromo-N-isopropyl-2-nitroaniline



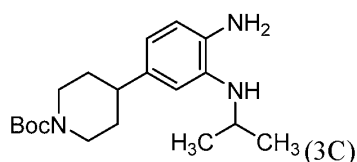
Intermediate 3A was synthesized according to methods described for the
 15 preparation of Intermediate 1A, using 4-bromo-2-fluoro-1-nitrobenzene (1.0 g, 4.5 mmol)
 as starting material, and substituting propan-2-amine (0.67 g, 11 mmol) where appropriate
 to afford the title compound (1.1 g, 4.2 mmol, 93 % yield) as a yellow solid. ¹H NMR
 (500 MHz, METHANOL-d₄) δ 8.06-8.03 (m, 1H), 7.25-7.19 (m, 1H), 6.84-6.78 (m, 1H),
 3.98-3.87 (m, 1H), 1.35-1.33 (m, 6H). Analytical LC/MS (Method 3): Observed Mass:
 20 259.1; Retention Time: 1.07 min.

Step B. Intermediate 3B. Preparation of tert-butyl 4-(3-(isopropylamino)-4-nitrophenyl)-
 3,6-dihydropyridine-1(2H)-carboxylate



To a 40 mL vial were added Intermediate 3A (1.1 g, 4.2 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.7 g, 5.5 mmol), followed by 1,4-dioxane (10 mL) and potassium phosphate tribasic (2.9 g, 14 mmol) dissolved in water (2 mL). The vessel degassed with N₂, 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.19 g, 0.23 mmol) was added, the vial capped and the reaction mixture was stirred at 75 °C. After 18 h, the reaction mixture was cooled, diluted with water (100 mL) and extracted with EtOAc (2x50 mL). The organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (80 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100%B; flow rate = 60 mL/min). The fractions corresponding to product were combined, concentrated and dried in vacuo to afford the title compound (1.4 g, 3.9 mmol, 93 % yield) as a yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.13-8.08 (m, 1H), 6.97-6.93 (m, 1H), 6.81-6.75 (m, 1H), 6.36-6.29 (m, 1H), 4.17-4.08 (m, 2H), 3.70-3.63 (m, 2H), 2.59-2.51 (m, 2H), 1.52 (s, 9H), 1.38-1.34 (m, 6H) (one proton obscured). Analytical LC/MS (Method 3): Observed Mass: 362.2; Retention Time: 1.16 min.

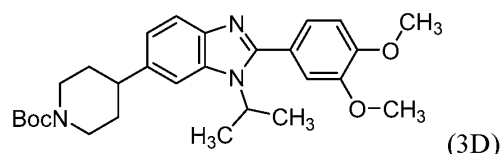
Step C. Intermediate 3C. Preparation of tert-butyl 4-(4-amino-3-(isopropylamino)phenyl)piperidine-1-carboxylate



To a 100 mL round bottomed flask were added Intermediate 3B (1.4 g, 3.9 mmol) and MeOH (50 mL). The vessel was evacuated and purged with N₂ (2x), then Pd-C (10% wt.) (0.42 g, 0.39 mmol) was added. The reaction mixture was stirred under hydrogen at 1 atm. After 18 h, the reaction mixture was filtered, the filtrate concentrated and the product was dried in vacuo to afford the title compound (1.3 g, 3.9 mmol, 100 % yield) as

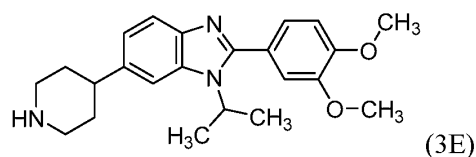
a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 6.70-6.67 (m, 1H), 6.56-6.52 (m, 1H), 6.48-6.44 (m, 1H), 4.24-4.14 (m, 2H), 3.68-3.57 (m, 1H), 2.93-2.77 (m, 2H), 2.63-2.53 (m, 1H), 1.83-1.75 (m, 2H), 1.59-1.51 (m, 2H), 1.50 (s, 9H), 1.23 (d, *J*=6.3 Hz, 6H). Analytical LC/MS (Method 3): Observed Mass: 334.3; Retention Time: 0.76 min.

Step D. Intermediate 3D. Preparation of tert-butyl 4-(2-(3,4-dimethoxyphenyl)-1-isopropyl-1H-benzo[d]imidazol-6-yl)piperidine-1-carboxylate



To a 40 mL vial were added Intermediate 3C (0.57 g, 1.7 mmol) and NMP (7 mL). To this mixture was added sodium metabisulfite (0.49 g, 2.6 mmol), followed by 3,4-dimethoxybenzaldehyde (0.33 g, 2.0 mmol). The reaction mixture was heated to 70 °C and stirred. After 24 h, the reaction mixture was cooled, diluted with water (100 mL) and extracted with EtOAc (50 mL). The organic phase was washed with water (50 mL) and the combined aqueous phase was extracted with EtOAc (20 mL). The organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (80 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100%B; flow rate = 60 mL/min). The fractions corresponding to product were combined, concentrated and dried in vacuo to afford the title compound (0.77 g, 1.6 mmol, 94 % yield) as a light yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.63-7.59 (m, 2H), 7.24 (d, *J*=1.9 Hz, 1H), 7.23-7.20 (m, 2H), 7.17 (s, 1H), 4.31-4.24 (m, 2H), 3.95 (s, 3H), 3.93 (s, 3H), 3.01-2.86 (m, 3H), 1.96-1.90 (m, 2H), 1.78-1.70 (m, 2H), 1.69 (s, 3H), 1.68 (s, 3H), 1.52 (s, 9H) (one proton obscured). Analytical LC/MS (Method 3): Observed Mass: 480.5; Retention Time: 0.85 min.

Step E. Intermediate 3E. Preparation of 2-(3,4-dimethoxyphenyl)-1-isopropyl-6-(piperidin-4-yl)-1H-benzo[d]imidazole dihydrochloride



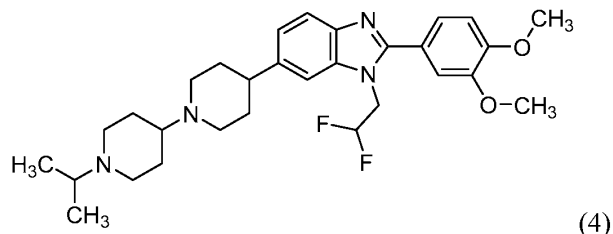
To a 100 mL pear shaped flask were added Intermediate 3D (0.77 g, 1.6 mmol) and a minimal amount of MeOH. To this mixture was added 4 M HCl in dioxane (20 mL) and the reaction mixture was stirred. After 2 h, the solvent was concentrated, and the residue was co-evaporated with toluene. The product was dried in vacuo to afford the title compound (0.68 g, 1.5 mmol, 94 % yield) as an off white solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.04 (s, 1H), 7.86-7.83 (m, 1H), 7.67-7.64 (m, 1H), 7.45-7.42 (m, 1H), 7.41-7.39 (m, 1H), 7.33-7.30 (m, 1H), 4.01-3.99 (m, 3H), 3.98-3.95 (m, 3H), 3.63-3.58 (m, 2H), 3.31-3.20 (m, 4H), 2.25-2.18 (m, 2H), 2.16-2.08 (m, 2H), 1.84 (s, 3H), 1.83 (s, 3H). Analytical LC/MS (Method 3): Observed Mass: 380.4; Retention Time: 0.57 min.

Step F. Example 3

To a 40 mL vial were added Intermediate 3E (65 mg, 0.14 mmol), 1-isopropylpiperidin-4-one (110 mg, 0.78 mmol), AcOH (11 mg, 0.18 mmol), magnesium sulfate (220 mg, 1.8 mmol), and DMF (2 mL). The reaction mixture was stirred for 20 min, then sodium triacetoxyborohydride (170 mg, 0.80 mmol) was added and the reaction mixture was stirred. After 18 h, the reaction mixture was filtered and the filter cake was washed with 10% IPA/chloroform (20 mL). The filtrate was washed with 10% aqueous NaOH (10 mL), brine, dried over MgSO₄, filtered and concentrated. The crude material was purified via preparative HPLC (Prep Method 1) to afford the title compound (61 mg, 0.12 mmol, 86 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 7.60-7.54 (m, 2H), 7.15 (br d, *J*=2.4 Hz, 4H), 4.82-4.71 (m, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.58-3.44 (m, 4H), 3.09-2.93 (m, 3H), 2.74-2.62 (m, 1H), 2.43-2.21 (m, 4H), 1.88-1.80 (m, 3H), 1.80-1.70 (m, 2H), 1.59 (d, *J*=6.9 Hz, 6H), 1.57-1.46 (m, 2H), 1.03 (s, 3H), 1.02 (s, 3H). TLR9 IC₅₀ (nM) = 170. Analytical LC/MS (Method 1): Purity: 90.4 %; Observed Mass: 505.02; Retention Time: 1.00 min. (Method 2) Purity: 90.8 %; Observed Mass: 504.96; Retention Time: 1.37 min.

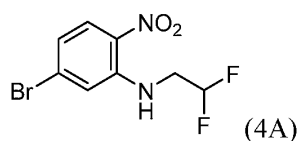
EXAMPLE 4

1-(2,2-difluoroethyl)-2-(3,4-dimethoxyphenyl)-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-
1H-benzo[d]imidazole



(4)

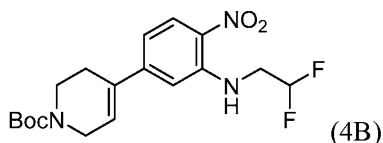
5 Step A. Intermediate 4A. Preparation of 5-bromo-N-(2,2-difluoroethyl)-2-nitroaniline



(4A)

To a 40 mL vial were added 4-bromo-2-fluoro-1-nitrobenzene (1.0 g, 4.6 mmol),
and MeCN (20 mL). To this mixture was added 2,2-difluoroethan-1-amine (0.92 g, 12
mmol), the vial was capped and the reaction mixture was stirred at 80 °C. After 18 h, the
10 reaction mixture was cooled, the solvent concentrated and the residue was purified by
flash column chromatography (120 g silica gel cartridge; A = Hex, B = EtOAc; 35 min
grad.; 0% B to 100%B; flow rate = 80 mL/min). The fractions corresponding to product
were combined, concentrated and dried in vacuo to afford the title compound (1.2 g, 4.3
mmol, 93 % yield) as a yellow solid. ¹H NMR (400 MHz, METHANOL-d₄) δ 8.10-8.05
15 (m, 1H), 7.39-7.34 (m, 1H), 6.95-6.87 (m, 1H), 6.29-5.93 (m, 1H), 3.92-3.79 (m, 2H).
Analytical LC/MS (Method 3): Observed Mass: 281.1; Retention Time: 0.98 min.

Step B. Intermediate 4B. Preparation of tert-butyl 4-(3-((2,2-difluoroethyl)amino)-4-
nitrophenyl)-3,6-dihydropyridine-1(2H)-carboxylate



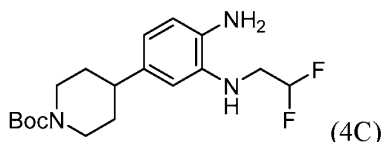
(4B)

Intermediate 4B was synthesized according to methods described for the
preparation of Intermediate 3B, using Intermediate 4A (1.2 g, 4.3 mmol) as starting
material to afford the title compound (1.6 g, 4.2 mmol, 98 % yield) as a yellow solid. ¹H

NMR (400 MHz, METHANOL- d_4) δ 8.18 (d, $J=2.2$ Hz, 1H), 7.70 (s, 1H), 7.15 (d, $J=9.0$ Hz, 1H), 6.25-5.94 (m, 1H), 6.13 (br s, 1H), 4.14-4.05 (m, 2H), 3.93-3.81 (m, 2H), 3.70-3.62 (m, 2H), 2.57-2.48 (m, 2H), 1.51 (s, 9H). Analytical LC/MS (Method 3): Observed Mass: 328.3 (-tBu); Retention Time: 1.07 min.

5

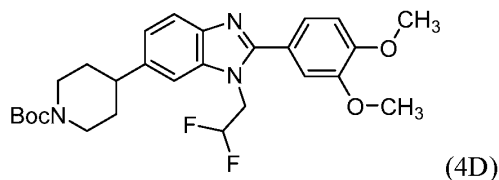
Step C. Intermediate 4C. Preparation of tert-butyl 4-(4-amino-3-((2,2-difluoroethyl)amino)phenyl)piperidine-1-carboxylate



Intermediate 4C was synthesized according to methods described for the preparation of Intermediate 3C, using Intermediate 4B (1.6 g, 4.2 mmol) as starting material to afford the title compound (1.5 g, 4.2 mmol, 100 % yield) as a pale yellow solid. ^1H NMR (500 MHz, METHANOL- d_4) δ 6.83-6.77 (m, 2H), 6.76-6.73 (m, 1H), 6.15-5.89 (m, 1H), 4.24-4.16 (m, 2H), 3.59-3.48 (m, 2H), 3.34-3.32 (m, 2H), 2.93-2.77 (m, 2H), 2.65-2.55 (m, 1H), 1.85-1.75 (m, 2H), 1.51-1.49 (m, 9H). Analytical LC/MS (Method 3): Observed Mass: 300.3 (-tBu); Retention Time: 0.81 min.

15

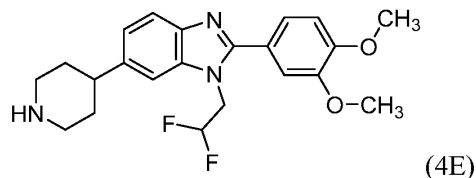
Step D. Intermediate 4D. Preparation of tert-butyl 4-(1-(2,2-difluoroethyl)-2-(3,4-dimethoxyphenyl)-1H-benzo[d]imidazol-6-yl)piperidine-1-carboxylate



Intermediate 4D was synthesized according to methods described for the preparation of Intermediate 3D, using Intermediate 4C (1.5 g, 4.2 mmol) as starting material to afford the title compound (1.5 g, 3.0 mmol, 71 % yield). ^1H NMR (500 MHz, METHANOL- d_4) δ 7.61-7.55 (m, 2H), 7.34-7.28 (m, 3H), 7.20-7.15 (m, 1H), 6.41-6.13 (m, 1H), 4.77-4.67 (m, 2H), 4.30-4.23 (m, 2H), 3.95 (s, 3H), 3.93 (s, 3H), 3.02-2.86 (m, 3H), 1.99-1.89 (m, 2H), 1.76-1.64 (m, 2H), 1.52 (s, 9H). Analytical LC/MS (Method 3): Observed Mass: 502.4; Retention Time: 0.85 min.

25

Step E. Intermediate 4E. Preparation of 1-(2,2-difluoroethyl)-2-(3,4-dimethoxyphenyl)-6-(piperidin-4-yl)-1H-benzo[d]imidazole dihydrochloride



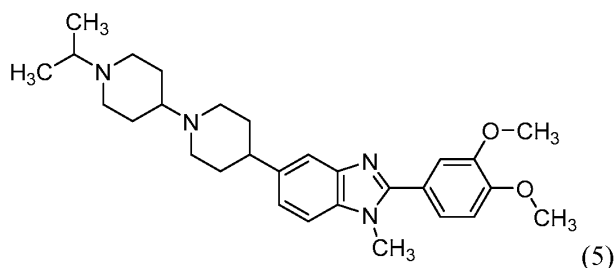
5 Intermediate 4E was synthesized according to methods described for the preparation of Intermediate 3E, using Intermediate 4D (1.4 g, 2.8 mmol) as starting material to afford the title compound (1.4 g, 2.7 mmol, 96 % yield) as a tan solid. ¹H NMR (500 MHz, METHANOL-*d*₄) δ 8.01-7.96 (m, 1H), 7.81-7.78 (m, 1H), 7.70-7.65 (m, 1H), 7.52-7.49 (m, 1H), 7.47-7.45 (m, 1H), 7.34-7.29 (m, 1H), 6.60-6.32 (m, 1H),
10 5.10-5.00 (m, 2H), 4.00 (s, 3H), 3.97 (s, 3H), 3.63-3.54 (m, 2H), 3.24 (br d, *J*=3.0 Hz, 3H), 2.25-2.18 (m, 2H), 2.15-2.02 (m, 2H). Analytical LC/MS (Method 3): Observed Mass: 402.3; Retention Time: 0.56 min.

Step F. Example 4

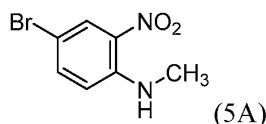
15 To a 40 mL vial were added Intermediate 4E (65 mg, 0.14 mmol), 1-isopropylpiperidin-4-one (110 mg, 0.78 mmol), AcOH (11 mg, 0.18 mmol), magnesium sulfate (220 mg, 1.8 mmol), and DMF (2 mL). The reaction mixture was stirred for 20 min, then sodium triacetoxyborohydride (170 mg, 0.80 mmol) was added and the reaction mixture was stirred. After 18 h, the reaction mixture was filtered and the filter cake was
20 washed with 10% IPA/chloroform (20 mL). The filtrate was washed with 10% aqueous NaOH (10 mL), brine, dried over MgSO₄, filtered and concentrated. The crude material was purified via preparative HPLC (Prep Method 1) to afford the title compound (63 mg, 0.12 mmol, 86 % yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.59 (br d, *J*=8.2 Hz, 1H), 7.53 (s, 1H), 7.29 (s, 2H), 7.24-7.11 (m, 2H), 6.56-6.29 (m, 1H), 4.81-4.71 (m, 2H), 3.86
25 (s, 3H), 3.84 (s, 3H), 3.06-2.99 (m, 2H), 2.97-2.88 (m, 2H), 2.85-2.76 (m, 1H), 2.69-2.60 (m, 1H), 2.40-2.30 (m, 3H), 2.29-2.19 (m, 2H), 1.88-1.78 (m, 4H), 1.78-1.68 (m, 2H), 1.57-1.46 (m, 2H), 1.02 (br d, *J*=6.7 Hz, 6H). TLR9 IC₅₀ (nM) = 250. Analytical LC/MS (Method 1): Purity: 98.7 %; Observed Mass: 527.24; Retention Time: 1.00 min. (Method 2): Purity: 98.8 %; Observed Mass: 527.25; Retention Time: 1.36 min.

EXAMPLE 5

2-(3,4-dimethoxyphenyl)-5-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1-methyl-1H-benzo[d]imidazole

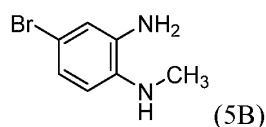


Step A. Intermediate 5A. Preparation of 4-bromo-N-methyl-2-nitroaniline



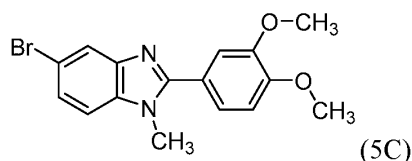
Intermediate 5A was synthesized according to methods described for the preparation of Intermediate 1A, using 4-bromo-1-fluoro-2-nitrobenzene (11 g, 50 mmol) as starting material to afford the title compound (11 g, 48 mmol, 96 % yield) as a yellow solid. ¹H NMR (500 MHz, CHLOROFORM-d) δ 8.35 (d, *J*=2.5 Hz, 1H), 8.12-7.98 (m, 1H), 7.55 (dd, *J*=9.1, 2.2 Hz, 1H), 6.78 (d, *J*=9.1 Hz, 1H), 3.07-3.02 (m, 3H). Analytical LC/MS (Method 3): Observed Mass: 230.8; Retention Time: 0.97 min.

Step B. Intermediate 5B. Preparation of 4-bromo-N¹-methylbenzene-1,2-diamine



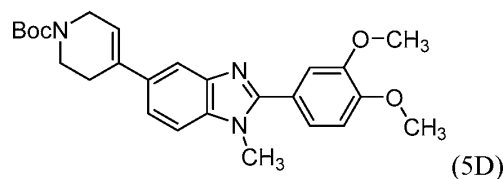
Intermediate 5B was synthesized according to methods described for the preparation of Intermediate 1B, using Intermediate 5A (16 g, 69 mmol) as starting material to afford the title compound (6.5 g, 32 mmol, 46 % yield) as a pale yellow solid. ¹H NMR (500 MHz, CHLOROFORM-d) δ 6.99-6.94 (m, 1H), 6.87-6.84 (m, 1H), 6.56-6.48 (m, 1H), 3.44-3.30 (m, 2H), 2.86 (s, 3H). Analytical LC/MS (Method 3): Observed Mass: 200.8; Retention Time: 0.56 min.

Step C. Intermediate 5C. Preparation of 5-bromo-2-(3,4-dimethoxyphenyl)-1-methyl-1H-benzo[d]imidazole



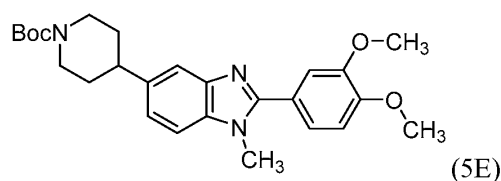
Intermediate 5C was synthesized according to methods described for the
 5 preparation of Intermediate 1C, using Intermediate 5B (0.75 g, 3.7 mmol) as starting material to afford the title compound (0.62 g, 1.8 mmol, 49 % yield) as a yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.25-7.23 (m, 1H), 7.06-7.03 (m, 1H), 6.99-6.95 (m, 1H), 6.74-6.70 (m, 1H), 6.56-6.53 (m, 1H), 6.30-6.25 (m, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 2.54 (s, 3H). Analytical LC/MS (Method 3): Observed Mass: 348.9; Retention
 10 Time: 0.67 min.

Step D. Intermediate 5D. Preparation of tert-butyl 4-(2-(3,4-dimethoxyphenyl)-1-methyl-1H-benzo[d]imidazol-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate



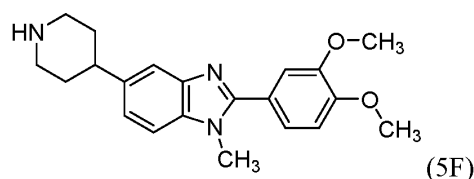
Intermediate 5D was synthesized according to methods described for the
 15 preparation of Intermediate 1D, using Intermediate 5C (0.62 g, 1.8 mmol) as starting material to afford the title compound (0.38 g, 0.85 mmol, 47 % yield) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.70 (d, *J*=0.8 Hz, 1H), 7.54-7.46 (m, 2H), 7.40 (s, 1H), 7.39-7.35 (m, 1H), 7.19-7.16 (m, 1H), 6.17-6.10 (m, 1H), 4.16-4.08 (m,
 20 2H), 3.95 (s, 6H), 3.92 (s, 3H), 3.74-3.67 (m, 2H), 2.68-2.61 (m, 2H), 1.53 (s, 9H). Analytical LC/MS (Method 3): Observed Mass: 450.2; Retention Time: 0.82 min.

Step E. Intermediate 5E. Preparation of tert-butyl 4-(2-(3,4-dimethoxyphenyl)-1-methyl-1H-benzo[d]imidazol-5-yl)piperidine-1-carboxylate



Intermediate 5E was synthesized according to methods described for the preparation of Intermediate 1E, using Intermediate 5D (0.38 g, 0.85 mmol) as starting material to afford the title compound (0.33 g, 0.73 mmol, 86 % yield) as a pale yellow semisolid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.55-7.53 (m, 1H), 7.50-7.47 (m, 1H), 7.40-7.38 (m, 1H), 7.37-7.34 (m, 1H), 7.28-7.25 (m, 1H), 7.18-7.15 (m, 1H), 4.29-4.23 (m, 2H), 3.94 (s, 6H), 3.90 (s, 3H), 3.00-2.84 (m, 3H), 1.95-1.88 (m, 2H), 1.75-1.65 (m, 2H), 1.52 (s, 9H). Analytical LC/MS (Method 3): Observed Mass: 452.2; Retention Time: 0.81 min.

Step F. Intermediate 5F. Preparation of 2-(3,4-dimethoxyphenyl)-1-methyl-5-(piperidin-4-yl)-1H-benzo[d]imidazole bis(2,2,2-trifluoroacetate)



Intermediate 5F was synthesized according to the general methods described for the preparation of Intermediate 1F, using Intermediate 5E (0.33 g, 0.73 mmol) as starting material to afford the title compound (0.42 g, 0.72 mmol, 99 % yield) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.95-7.91 (m, 1H), 7.74-7.71 (m, 1H), 7.67-7.62 (m, 1H), 7.57-7.53 (m, 1H), 7.51-7.46 (m, 1H), 7.34-7.30 (m, 1H), 4.13 (s, 3H), 4.00 (s, 3H), 3.99 (s, 3H), 3.63-3.55 (m, 2H), 3.28-3.18 (m, 3H), 2.25-2.18 (m, 2H), 2.10-1.99 (m, 2H). Analytical LC/MS (Method 3): Observed Mass: 352.1; Retention Time: 0.54 min.

Step G. Example 5

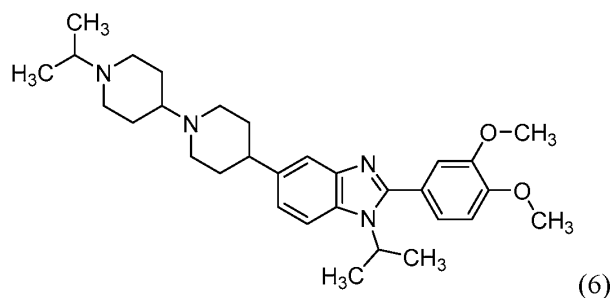
To a 40 mL vial were added Intermediate 5F (50 mg, 0.086 mmol), 1-isopropylpiperidin-4-one (61 mg, 0.43 mmol), AcOH (5.7 mg, 0.095 mmol), magnesium sulfate (220 mg, 1.8 mmol), and DMF (2 mL). The reaction mixture was stirred for 20

min, then sodium triacetoxyborohydride (91 mg, 0.43 mmol) was added and the reaction mixture was stirred. After 18 h, the reaction mixture was filtered and the filter cake was washed with 10% IPA/chloroform (20 mL). The filtrate was washed with 10% aqueous NaOH (10 mL), brine, dried over MgSO₄, filtered and concentrated. The crude material was purified via preparative HPLC (Prep Method 1) to afford the title compound (17 mg, 0.036 mmol, 42 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 7.55-7.47 (m, 2H), 7.41-7.36 (m, 2H), 7.22-7.18 (m, 1H), 7.17-7.13 (m, 1H), 3.86 (br d, *J*=1.5 Hz, 6H), 3.61-3.53 (m, 1H), 3.25-3.14 (m, 3H), 2.81-2.61 (m, 4H), 2.40-2.31 (m, 1H), 2.05-1.97 (m, 2H), 1.95-1.88 (m, 2H), 1.85-1.65 (m, 5H), 1.15 (br d, *J*=6.1 Hz, 6H) (4 protons obscured).

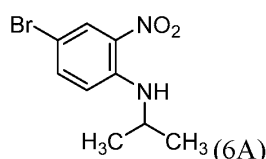
TLR9 IC₅₀ (nM) = 250. Analytical LC/MS (Method 1): Purity: 99 %; Observed Mass: 477.12; Retention Time: 0.92 min. (Method 2): Purity: 100 %; Observed Mass: 477.13; Retention Time: 1.32 min.

EXAMPLE 6

2-(3,4-dimethoxyphenyl)-1-isopropyl-5-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole



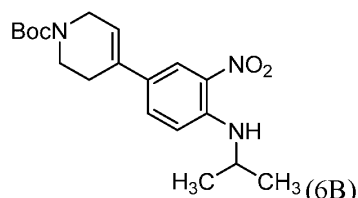
Step A. Intermediate 6A. Preparation of 4-bromo-N-isopropyl-2-nitroaniline



Intermediate 6A was synthesized according to methods described for the preparation of Intermediate 1A, using 4-bromo-1-fluoro-2-nitrobenzene (1.0 g, 4.5 mmol) as starting material, and substituting propan-2-amine (0.67 g, 11 mmol) where appropriate to afford the title compound (1.1 g, 4.2 mmol, 93 % yield) as a yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.26-8.23 (m, 1H), 7.60-7.55 (m, 1H), 7.04-6.98 (m, 1H),

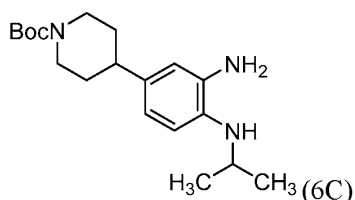
3.35-3.31 (m, 1H), 1.34 (s, 3H), 1.33 (s, 3H). Analytical LC/MS (Method 3): Observed Mass: 259.1; Retention Time: 1.08 min.

- Step B. Intermediate 6B. Preparation of tert-butyl 4-(4-(isopropylamino)-3-nitrophenyl)-3,6-dihydropyridine-1(2H)-carboxylate



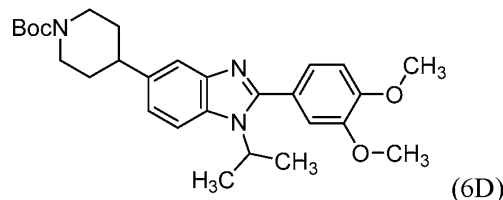
- Intermediate 6B was synthesized according to methods described for the preparation of Intermediate 3B, using Intermediate 6A (1.1 g, 4.2 mmol) as starting material to afford the title compound (1.2 g, 3.3 mmol, 79 % yield) as a yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.17-8.14 (m, 1H), 7.72-7.67 (m, 1H), 7.08-7.03 (m, 1H), 6.14-6.07 (m, 1H), 4.11-4.04 (m, 2H), 4.04-3.91 (m, 1H), 3.69-3.63 (m, 2H), 2.55-2.49 (m, 2H), 1.51 (s, 9H), 1.36-1.35 (m, 3H), 1.35-1.34 (m, 3H). Analytical LC/MS (Method 3): Observed Mass: 362.2; Retention Time: 1.17 min.

- Step C. Intermediate 6C. Preparation of tert-butyl 4-(3-amino-4-(isopropylamino)phenyl)piperidine-1-carboxylate



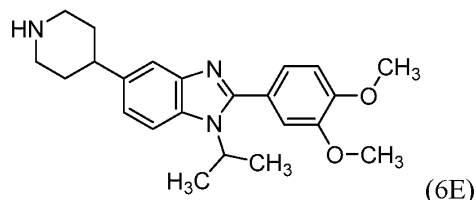
- Intermediate 6C was synthesized according to methods described for the preparation of Intermediate 3C, using Intermediate 6B (1.2 g, 3.3 mmol) as starting material to afford the title compound (1.1 g, 3.3 mmol, 100 % yield) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 6.66-6.64 (m, 1H), 6.64-6.61 (m, 1H), 6.60-6.56 (m, 1H), 4.25-4.14 (m, 2H), 3.62-3.53 (m, 1H), 2.95-2.77 (m, 2H), 2.61-2.50 (m, 1H), 1.81-1.75 (m, 2H), 1.59-1.51 (m, 2H), 1.49 (s, 9H), 1.23-1.22 (m, 3H), 1.22-1.20 (m, 3H). Analytical LC/MS (Method 3): Observed Mass: 334.3; Retention Time: 0.76 min.

Step D. Intermediate 6D. Preparation of tert-butyl 4-(2-(3,4-dimethoxyphenyl)-1-isopropyl-1H-benzo[d]imidazol-5-yl)piperidine-1-carboxylate



5 Intermediate 6D was synthesized according to methods described for the preparation of Intermediate 3D, using Intermediate 6C (0.53 g, 1.6 mmol) as starting material to afford the title compound (0.62 g, 1.3 mmol, 81 % yield) as a light yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.74-7.70 (m, 1H), 7.55-7.52 (m, 1H), 7.25-7.20 (m, 3H), 7.19-7.15 (m, 1H), 4.29-4.23 (m, 2H), 3.95 (s, 3H), 3.93 (s, 3H), 3.02-
10 2.83 (m, 3H), 1.95-1.88 (m, 2H), 1.75-1.69 (m, 1H), 1.68 (s, 3H), 1.67 (s, 3H), 1.51 (s, 9H) (two protons obscured). Analytical LC/MS (Method 3): Observed Mass: 480.4; Retention Time: 0.85 min.

Step E. Intermediate 6E. Preparation of 2-(3,4-dimethoxyphenyl)-1-isopropyl-5-(piperidin-4-yl)-1H-benzo[d]imidazole dihydrochloride



Intermediate 6E was synthesized according to methods described for the preparation of Intermediate 3E, using Intermediate 6D (0.62 g, 1.3 mmol) as starting material to afford the title compound (0.59 g, 1.3 mmol, 100 % yield) as an off white
20 solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.17-8.13 (m, 1H), 7.77-7.73 (m, 1H), 7.64-7.59 (m, 1H), 7.43-7.40 (m, 1H), 7.40-7.37 (m, 1H), 7.33-7.29 (m, 1H), 5.12-5.05 (m, 1H), 4.00 (s, 3H), 3.97 (s, 3H), 3.62-3.56 (m, 2H), 3.27-3.18 (m, 3H), 2.25-2.18 (m, 2H), 2.10-2.00 (m, 2H), 1.81 (s, 3H), 1.80 (s, 3H). Analytical LC/MS (Method 3): Observed Mass: 380.4; Retention Time: 0.59 min.

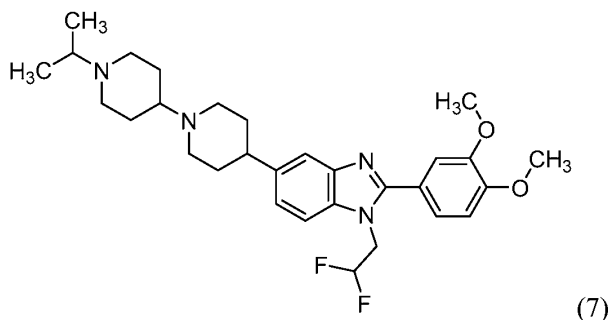
25

Step F. Example 6

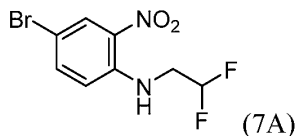
To a 40 mL vial were added Intermediate 6E (65 mg, 0.14 mmol), 1-isopropylpiperidin-4-one (110 mg, 0.78 mmol), AcOH (11 mg, 0.18 mmol), magnesium sulfate (220 mg, 1.8 mmol), and DMF (2 mL). The reaction mixture was stirred for 20 min, then sodium triacetoxyborohydride (170 mg, 0.80 mmol) was added and the reaction mixture was stirred. After 18 h, the reaction mixture was filtered and the filter cake was washed with 10% IPA/chloroform (20 mL). The filtrate was washed with 10% aqueous NaOH (10 mL), brine, dried over MgSO₄, filtered and concentrated. The crude material was purified via preparative HPLC (Prep Method 1) to afford the title compound (61 mg, 0.12 mmol, 86 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 7.69 (d, *J*=8.5 Hz, 1H), 7.49 (s, 1H), 7.19-7.17 (m, 1H), 7.17-7.12 (m, 3H), 4.80-4.72 (m, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.04-2.97 (m, 2H), 2.91-2.84 (m, 2H), 2.75-2.67 (m, 1H), 2.63-2.57 (m, 1H), 2.34-2.22 (m, 3H), 2.19-2.10 (m, 2H), 1.80 (br s, 4H), 1.75-1.66 (m, 2H), 1.58 (s, 3H), 1.57 (s, 3H), 1.51-1.42 (m, 2H), 0.99 (s, 3H), 0.98 (s, 3H). TLR9 IC₅₀ (nM) = 190. Analytical LC/MS (Method 1): Purity: 98.6 %; Observed Mass: 505.33; Retention Time: 1.05 min. (Method 2): Purity: 98.7 %; Observed Mass: 505.02; Retention Time: 1.47 min.

EXAMPLE 7

1-(2,2-difluoroethyl)-2-(3,4-dimethoxyphenyl)-5-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole



Step A. Intermediate 7A. Preparation of 4-bromo-N-(2,2-difluoroethyl)-2-nitroaniline

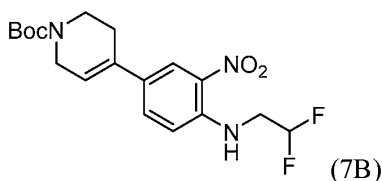


Intermediate 7A was synthesized according to methods described for the

preparation of Intermediate 4A, using 4-bromo-1-fluoro-2-nitrobenzene (1.0 g, 4.6 mmol) as starting material to afford the title compound (1.3 g, 4.6 mmol, 100 % yield) as a yellow solid. ¹H NMR (400 MHz, METHANOL-d₄) δ 8.30-8.25 (m, 1H), 7.66-7.59 (m, 1H), 7.17-7.08 (m, 1H), 6.27-5.93 (m, 1H), 3.91-3.78 (m, 2H). Analytical LC/MS

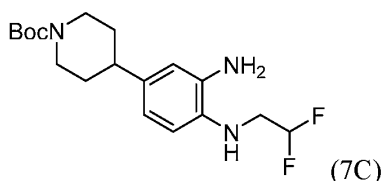
5 (Method 3): Observed Mass: 281.2; Retention Time: 0.98 min.

Step B. Intermediate 7B. Preparation of tert-butyl 4-(4-((2,2-difluoroethyl)amino)-3-nitrophenyl)-3,6-dihydropyridine-1(2H)-carboxylate



10 Intermediate 7B was synthesized according to methods described for the preparation of Intermediate 3B, using Intermediate 7A (1.3 g, 4.6 mmol) as starting material to afford the title compound (1.7 g, 4.4 mmol, 100 % yield) as a yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.20-8.16 (m, 1H), 7.71 (dd, *J*=8.9, 2.3 Hz, 1H), 7.18-7.12 (m, 1H), 6.23-5.97 (m, 1H), 6.13 (br s, 1H), 4.14-4.05 (m, 2H), 3.92-3.83 (m, 15 2H), 3.70-3.64 (m, 2H), 2.57-2.49 (m, 2H), 1.51 (s, 9H). Analytical LC/MS (Method 3): Observed Mass: 328.2 (-tBu); Retention Time: 1.07 min.

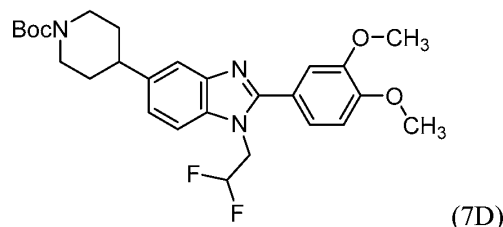
Step C. Intermediate 7C. Preparation of tert-butyl 4-(3-amino-4-((2,2-difluoroethyl)amino)phenyl)piperidine-1-carboxylate



20 Intermediate 7C was synthesized according to methods described for the preparation of Intermediate 3C, using Intermediate 7B (1.7 g, 4.4 mmol) as starting material to afford the title compound (1.5 g, 4.2 mmol, 95 % yield) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 6.80-6.77 (m, 1H), 6.77-6.75 (m, 1H), 6.74-6.72 (m, 1H), 6.14-5.88 (m, 1H), 4.25-4.15 (m, 2H), 3.58-3.47 (m, 2H), 2.96-2.77 (m, 2H), 25 2.64-2.51 (m, 1H), 1.82-1.74 (m, 2H), 1.62-1.51 (m, 2H), 1.49 (s, 9H). Analytical

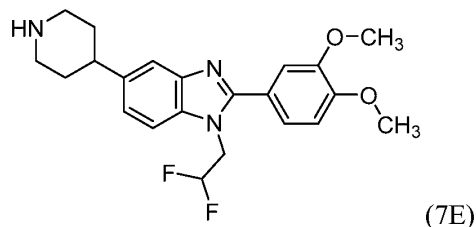
LC/MS (Method 3): Observed Mass: 300.3 (-tBu); Retention Time: 0.81 min.

Step D. Intermediate 7D. Preparation of tert-butyl 4-(1-(2,2-difluoroethyl)-2-(3,4-dimethoxyphenyl)-1H-benzo[d]imidazol-5-yl)piperidine-1-carboxylate



Intermediate 7D was synthesized according to methods described for the preparation of Intermediate 3D, using Intermediate 7C (1.5 g, 4.2 mmol) as starting material to afford the title compound (1.7 g, 3.4 mmol, 81 % yield) as a light yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.60-7.58 (m, 1H), 7.57-7.56 (m, 1H), 7.34-7.29 (m, 3H), 7.19-7.16 (m, 1H), 6.39-6.14 (m, 1H), 4.77-4.67 (m, 2H), 4.31-4.23 (m, 2H), 3.95 (s, 3H), 3.93 (s, 3H), 3.05-2.84 (m, 3H), 1.97-1.89 (m, 2H), 1.76-1.65 (m, 2H), 1.52 (s, 9H). Analytical LC/MS (Method 3): Observed Mass: 502.4; Retention Time: 0.85 min.

Step E. Intermediate 7E. Preparation of 1-(2,2-difluoroethyl)-2-(3,4-dimethoxyphenyl)-5-(piperidin-4-yl)-1H-benzo[d]imidazole dihydrochloride



Intermediate 7E was synthesized according to methods described for the preparation of Intermediate 3E, using Intermediate 7D (1.7 g, 3.4 mmol) as starting material to afford the title compound (1.5 g, 3.2 mmol, 94 % yield) as a tan solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.05-7.98 (m, 1H), 7.82 (s, 1H), 7.73-7.66 (m, 1H), 7.55-7.51 (m, 1H), 7.48 (d, *J*=2.2 Hz, 1H), 7.33 (d, *J*=8.5 Hz, 1H), 6.60-6.33 (m, 1H), 5.13-5.02 (m, 2H), 4.00 (s, 3H), 3.98 (s, 3H), 3.63-3.56 (m, 2H), 3.30-3.21 (m, 3H), 2.27-2.18 (m, 2H), 2.17-2.05 (m, 2H). Analytical LC/MS (Method 3): Observed Mass: 402.3;

Retention Time: 0.56 min.

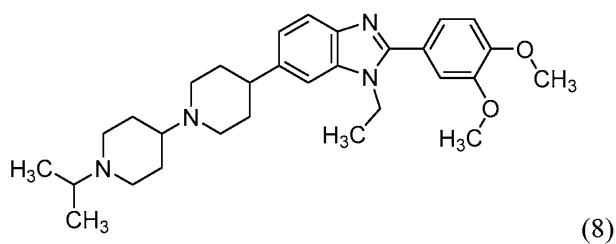
Step G. Example 7

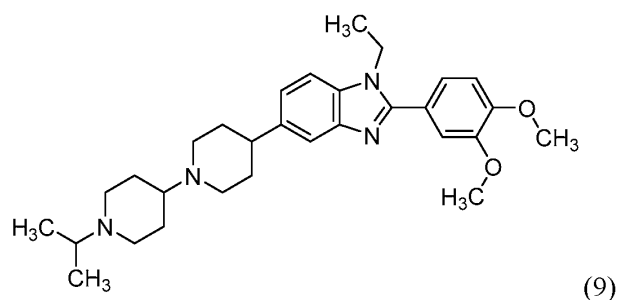
To a 40 mL vial were added Intermediate 7E (65 mg, 0.14 mmol), 1-isopropylpiperidin-4-one (110 mg, 0.78 mmol), AcOH (11 mg, 0.18 mmol), magnesium sulfate (220 mg, 1.8 mmol), and DMF (2 mL). The reaction mixture was stirred for 20 min, then sodium triacetoxyborohydride (170 mg, 0.80 mmol) was added and the reaction mixture was stirred. After 18 h, the reaction mixture was filtered and the filter cake was washed with 10% IPA/chloroform (20 mL). The filtrate was washed with 10% aqueous NaOH (10 mL), brine, dried over MgSO₄, filtered and concentrated. The crude material was purified via preparative HPLC (Prep Method 1) to afford the title compound (58 mg, 0.11 mmol, 79 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 7.57 (br d, *J*=8.1 Hz, 1H), 7.51 (s, 1H), 7.30-7.25 (m, 2H), 7.20 (d, *J*=8.5 Hz, 1H), 7.14 (s, 1H), 6.53-6.25 (m, 1H), 4.79-4.68 (m, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.03-2.93 (m, 2H), 2.87-2.79 (m, 2H), 2.71-2.56 (m, 2H), 2.33-2.16 (m, 3H), 2.14-2.03 (m, 2H), 1.84-1.63 (m, 6H), 1.49-1.37 (m, 2H), 0.96 (s, 3H), 0.95 (s, 3H). TLR9 IC₅₀ (nM) = 280. Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 527.04; Retention Time: 1.02 min. (Method 2): Purity: 100 %; Observed Mass: 527.30; Retention Time: 1.45 min.

20

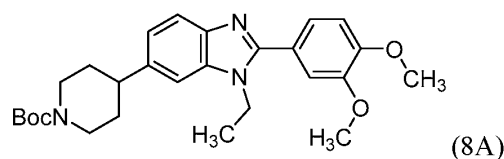
EXAMPLES 8 AND 9

2-(3,4-dimethoxyphenyl)-1-ethyl-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (8) and 2-(3,4-dimethoxyphenyl)-1-ethyl-5-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (9)





Step A. Intermediate 8A. Preparation of tert-butyl 4-(2-(3,4-dimethoxyphenyl)-1-ethyl-1H-benzo[d]imidazol-6-yl)piperidine-1-carboxylate (regioisomeric mixture)



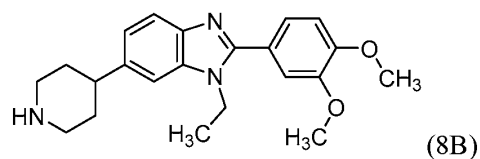
5 To a 250 mL round bottomed flask were added Intermediate 2C (0.53 g, 1.2 mmol) and THF (20 mL). The reaction mixture was cooled to 0 °C, then NaH (60% dispersion in mineral oil) (0.24 g, 6.1 mmol) was added. After stirring 10 min at the above temperature, iodoethane (0.95 g, 6.1 mmol) was added and the reaction mixture was allowed to reach room temperature. After stirring 18 h, the reaction was quenched

10 with water (200 mL) and extracted with EtOAc (2x100 mL). The organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (80 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100%B; flow rate = 60 mL/min). The fractions corresponding to product were combined, concentrated and dried in vacuo to afford the

15 title compound (0.56 g, 1.2 mmol, 100 % yield) as a colorless oil. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.64-7.44 (m, 2H), 7.34-7.28 (m, 2H), 7.28-7.21 (m, 1H), 7.20-7.15 (m, 1H), 4.41-4.32 (m, 2H), 4.31-4.22 (m, 2H), 4.17-4.08 (m, 1H), 3.94 (d, *J*=5.0 Hz, 6H), 3.02-2.83 (m, 2H), 1.99-1.86 (m, 2H), 1.80-1.66 (m, 2H), 1.54-1.49 (m, 9H), 1.47-1.40 (m, 3H). Analytical LC/MS (Method 3): Observed Mass: 466.5; Retention Time:

20 0.82 min.

Step B. Intermediate 8B. Preparation of 2-(3,4-dimethoxyphenyl)-1-ethyl-6-(piperidin-4-yl)-1H-benzo[d]imidazole dihydrochloride (regioisomeric mixture)



To a 250 mL round bottomed flask were added Intermediate 8A (0.56 g, 1.2 mmol) and 4 M HCl in dioxane (20 mL). After stirring 2 h, the solvent was concentrated and the residue was co-evaporated with toluene. The product was dried in vacuo to afford the title compound (0.53 g, 1.2 mmol, 100 % yield) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.02-7.76 (m, 2H), 7.69-7.64 (m, 1H), 7.53-7.49 (m, 1H), 7.47-7.44 (m, 1H), 7.35-7.31 (m, 1H), 4.67-4.58 (m, 2H), 4.01 (s, 3H), 3.98 (s, 3H), 3.63-3.57 (m, 2H), 3.29-3.20 (m, 3H), 2.26-2.16 (m, 2H), 2.15-2.02 (m, 2H), 1.65-1.57 (m, 3H). Analytical LC/MS (Method 3): Observed Mass: 366.4; Retention Time: 0.57 min.

10

Step C. Examples 8 and 9

To a 40 mL vial were added Intermediate 8B (regioisomeric mixture) (120 mg, 0.27 mmol), 1-isopropylpiperidin-4-one (200 mg, 1.4 mmol), AcOH (18 mg, 0.30 mmol), magnesium sulfate (220 mg, 1.8 mmol) and DMF (2 mL). The reaction mixture was stirred for 20 min, then sodium triacetoxyborohydride (300 mg, 1.4 mmol) was added and the reaction mixture was stirred. After 18 h, the reaction mixture was filtered and the filter cake was washed with 10% IPA/chloroform (20 mL). The filtrate was washed with 10% aqueous NaOH (10 mL), brine, dried over MgSO₄, filtered and concentrated. The crude material was purified via preparative HPLC (Prep Method 1) to afford the regioisomeric mixture of products (98 mg, 0.20 mmol, 74 % yield). The mixture of regioisomers was separated by chiral SFC chromatography under the following conditions: Column: Chiral OD, 30 x 250 mm, 5 micron; Flow Rate: 100 mL/min; Oven Temperature: 40 °C; BPR Setting: 120 bar; UV wavelength: 220 nm; Mobile Phase: 75% CO₂ / 25% MeOH w/0.1%DEA (isocratic); Injection: 300 µL of 98 mg/ 3 mL MeOH.

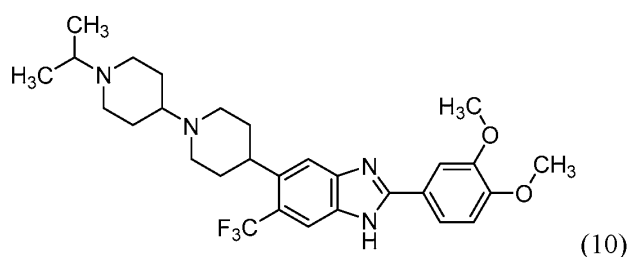
Example 8 (24 mg, 0.049 mmol, 18 % yield) was isolated as the 1st eluting regioisomer. ¹H NMR (500 MHz, DMSO-d₆) δ 7.78-7.74 (m, 1H), 7.73-7.67 (m, 1H), 7.43-7.35 (m, 3H), 7.28-7.22 (m, 1H), 4.47-4.37 (m, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.69-3.47 (m, 2H), 3.26-3.02 (m, 5H), 2.42-2.31 (m, 2H), 2.21-2.13 (m, 2H), 2.13-1.96 (m, 4H), 1.43 (t, *J*=7.2 Hz, 3H), 1.27 (br d, *J*=6.7 Hz, 6H) (4 protons obscured). TLR9 IC₅₀

(nM) = 210. Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 491.15; Retention Time: 0.98 min. (Method 2): Purity: 100 %; Observed Mass: 490.90; Retention Time: 1.26 min.

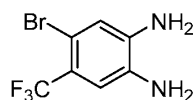
Example 9 (24 mg, 0.049 mmol, 18 % yield) was isolated as the 2nd eluting regioisomer. ¹H NMR (500 MHz, DMSO-d₆) δ 7.55-7.48 (m, 2H), 7.31-7.26 (m, 2H), 7.21-7.16 (m, 1H), 7.16-7.12 (m, 1H), 4.32-4.24 (m, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.06-3.00 (m, 2H), 2.98-2.91 (m, 2H), 2.85-2.75 (m, 1H), 2.68-2.58 (m, 1H), 2.40-2.30 (m, 3H), 2.29-2.20 (m, 2H), 1.87-1.80 (m, 4H), 1.78-1.67 (m, 2H), 1.58-1.46 (m, 2H), 1.34 (s, 3H), 1.03-0.98 (m, 6H). TLR9 IC₅₀ (nM) = 250. Analytical LC/MS (Method 1): Purity: 99.3 %; Observed Mass: 491.00; Retention Time: 1.00 min. (Method 2): Purity: 96.4 %; Observed Mass: 491.35; Retention Time: 1.63 min.

EXAMPLE 10

2-(3,4-dimethoxyphenyl)-5-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-6-(trifluoromethyl)-1H-benzo[d]imidazole



Step A. Intermediate 10A. Preparation of 4-bromo-5-(trifluoromethyl)benzene-1,2-diamine

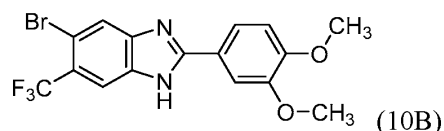


To a 200 mL pear shaped flask were added 4-bromo-2-nitro-5-(trifluoromethyl)aniline (2.0 g, 7.0 mmol), MeOH (100 mL), and tin(II) chloride dihydrate (7.0 g, 31 mmol). The reaction mixture was stirred at reflux. After 18 h, the reaction mixture was cooled, partitioned into 10% KOH (400 mL) and extracted with EtOAc (2x). The organic phase was combined washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (120 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100%B; flow rate = 80 mL/min). The fractions

corresponding to product were combined, concentrated and dried in vacuo to afford the title compound (1.7 g, 6.7 mmol, 96 % yield) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.03-6.99 (m, 1H), 6.95-6.92 (m, 1H). Analytical LC/MS (Method 3): Observed Mass: 257.0; Retention Time: 0.79 min.

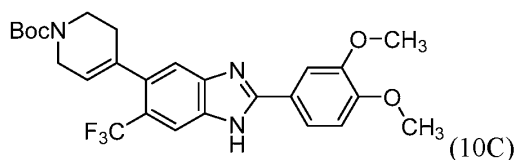
5

Step B. Intermediate 10B. Preparation of 5-bromo-2-(3,4-dimethoxyphenyl)-6-(trifluoromethyl)-1H-benzo[d]imidazole 2,2,2-trifluoroacetate



To a 250 mL round bottomed flask were added Intermediate 10A (1.7 g, 6.7 mmol), MeOH (100 mL), followed by 3,4-dimethoxybenzaldehyde (1.2 g, 7.2 mmol). The reaction mixture was stirred at reflux. After 72 h, the reaction mixture was cooled, the solvent concentrated and the residue was purified by flash column chromatography (120 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100%B; flow rate = 60 mL/min). The fractions corresponding to product were combined, concentrated and dried in vacuo. The product was further purified by flash column chromatography (300 g reverse phase C18 GOLD silica gel cartridge; A = water:MeCN:TFA 90:10:0.05%, B = water:MeCN:TFA 10:90:0.05%; 40 min grad.; 10% B to 100%B; flow rate = 120 mL/min). Fractions containing product were combined, the solvent concentrated, and the product was dried in vacuo to afford the title compound (1.8 g, 3.5 mmol, 52 % yield) as a tan solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.07-8.04 (m, 2H), 7.78-7.74 (m, 2H), 7.24-7.20 (m, 1H), 4.00 (s, 3H), 3.97 (s, 3H). Analytical LC/MS (Method 3): Observed Mass: 403.0; Retention Time: 0.88 min.

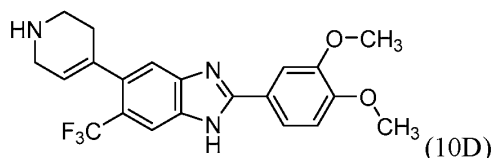
Step C. Intermediate 10C. Preparation of tert-butyl 4-(2-(3,4-dimethoxyphenyl)-6-(trifluoromethyl)-1H-benzo[d]imidazol-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate



To a 40 mL vial were added Intermediate 10B (0.98 g, 1.9 mmol), tert-butyl 4-

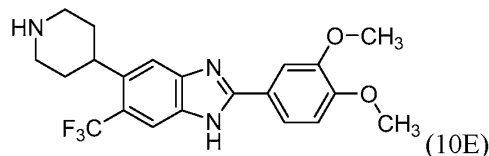
(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (0.69 g, 2.2 mmol), followed by 1,4-dioxane (10 mL) and potassium phosphate tribasic (1.2 g, 5.7 mmol) dissolved in water (2 mL). The vessel degassed with N₂, then 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.076 g, 0.093 mmol) was added. The vial was blanketed with N₂, capped and stirred at 75 °C. After 18 h, the reaction mixture was cooled, the mixture was diluted with water (200 mL) and extracted with EtOAc (2x100 mL). The organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (120 g silica gel cartridge; A = Hex, B = EtOAc; 20 min grad.; 0% B to 100%B; hold for 10 min then; A = DCM, B = MeOH; 30 min grad.; 0%B to 10%B; flow rate = 120 mL/min). The fractions corresponding to product were combined, concentrated and dried in vacuo to afford the title compound (0.69 g, 1.4 mmol, 74 % yield) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.96-7.89 (m, 1H), 7.79-7.76 (m, 1H), 7.75-7.71 (m, 1H), 7.49-7.42 (m, 1H), 7.18-7.13 (m, 1H), 5.75-5.62 (m, 1H), 4.11-4.04 (m, 2H), 3.99 (s, 3H), 3.95 (s, 3H), 3.72-3.64 (m, 2H), 2.48-2.42 (m, 2H), 1.56-1.52 (m, 9H). Analytical LC/MS (Method 3): Observed Mass: 504.2; Retention Time: 0.91 min.

Step D. Intermediate 10D. Preparation of 2-(3,4-dimethoxyphenyl)-5-(1,2,3,6-tetrahydropyridin-4-yl)-6-(trifluoromethyl)-1H-benzo[d]imidazole dihydrochloride



To a 100 mL pear shaped flask were added Intermediate 10C (0.69 g, 1.4 mmol) and 4 M HCl in dioxane (10 mL). After stirring 15 min, the solvent was concentrated and the residue was co-evaporated with toluene (2x). The product was dried in vacuo to afford the title compound (0.62 g, 1.3 mmol, 93 % yield) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.18-8.15 (m, 1H), 7.89-7.85 (m, 1H), 7.84-7.80 (m, 2H), 7.35-7.31 (m, 1H), 5.89-5.83 (m, 1H), 4.05-4.03 (m, 3H), 4.03-4.00 (m, 3H), 3.93-3.90 (m, 2H), 3.56-3.51 (m, 2H), 2.80-2.73 (m, 2H). Analytical LC/MS (Method 3): Observed Mass: 404.4; Retention Time: 0.57 min.

Step E. Intermediate 10E. Preparation of 2-(3,4-dimethoxyphenyl)-5-(piperidin-4-yl)-6-(trifluoromethyl)-1H-benzo[d]imidazole dihydrochloride



To a 250 mL round bottomed flask were added Intermediate 10D (0.62 g, 1.3 mmol), and MeOH (40 mL). The vessel was evacuated and purged with N₂, then platinum(IV) oxide (120 mg, 0.53 mmol) was added and the reaction mixture was stirred under hydrogen at 1 atm. After 18 h, the catalyst was filtered, the filtrate was concentrated and the product was dried in vacuo to afford the title compound (0.56 g, 1.2 mmol, 92 % yield) as a pale yellow solid. ¹H NMR (400 MHz, METHANOL-d₄) δ 8.11-8.09 (m, 1H), 7.99-7.97 (m, 1H), 7.86-7.82 (m, 1H), 7.82-7.79 (m, 1H), 7.32-7.28 (m, 1H), 4.03 (s, 3H), 4.00 (s, 3H), 3.72-3.66 (m, 1H), 3.64-3.57 (m, 2H), 3.30-3.20 (m, 2H), 2.16 (br s, 4H). Analytical LC/MS (Method 3): Observed Mass: 406.2; Retention Time: 0.61 min.

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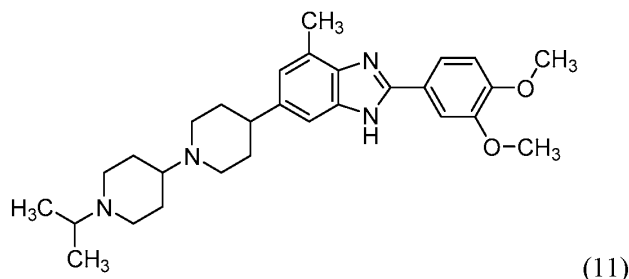
Step F. Example 10

To a 40 mL vial were added Intermediate 10E (62 mg, 0.13 mmol), 1-isopropylpiperidin-4-one (92 mg, 0.65 mmol), AcOH (8.6 mg, 0.14 mmol), magnesium sulfate (220 mg, 1.8 mmol), and DMF (2 mL). The reaction mixture was stirred for 20 min, then sodium triacetoxyborohydride (140 mg, 0.66 mmol) was added and the reaction mixture was stirred. After 18 h, the reaction mixture was filtered and the filter cake was washed with 10% IPA/chloroform (20 mL). The filtrate was washed with 10% aqueous NaOH (10 mL), brine, dried over MgSO₄, filtered and concentrated. The crude material was purified via preparative HPLC (Prep Method 1) to afford the title compound (40 mg, 0.075 mmol, 58 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 7.91-7.84 (m, 1H), 7.80-7.74 (m, 2H), 7.73-7.67 (m, 1H), 7.20-7.14 (m, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.64-3.51 (m, 1H), 3.19-3.03 (m, 6H), 2.97-2.85 (m, 2H), 2.39-2.31 (m, 2H), 1.88-1.75 (m, 5H), 1.71-1.58 (m, 2H), 1.12 (br d, *J*=5.8 Hz, 6H) (one proton obscured). TLR9 IC₅₀ (nM) = 240. Analytical LC/MS (Method 1): Purity: 98.7 %; Observed Mass: 531.31; Retention

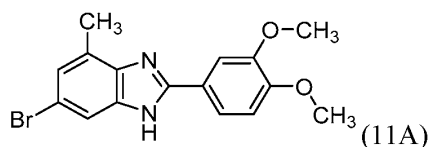
Time: 1.03 min. (Method 2); Purity: 100 %; Observed Mass: 531.04; Retention Time: 1.52 min.

EXAMPLE 11

5 2-(3,4-dimethoxyphenyl)-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole



Step A. Intermediate 11A. Preparation of 6-bromo-2-(3,4-dimethoxyphenyl)-4-methyl-1H-benzo[d]imidazole



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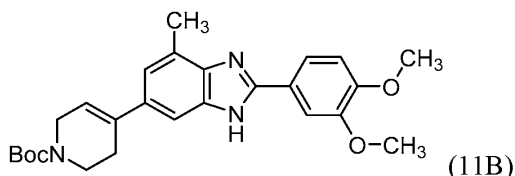
To a 500 mL pear shaped flask were added 5-bromo-3-methylbenzene-1,2-diamine (6.0 g, 30 mmol) and NMP (120 mL). To this mixture was added sodium metabisulfite (8.6 g, 45 mmol), followed by 3,4-dimethoxybenzaldehyde (6.0 g, 36 mmol). The reaction mixture was heated to 70 °C and stirred under N₂. After 18 h, the reaction mixture was cooled, diluted with water (500 mL) and extracted with EtOAc (250 mL). The organic phase was washed with water (100 mL) and the combined aqueous phase was extracted with EtOAc (100 mL). The organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (220 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100%B; flow rate = 120 mL/min). The fractions corresponding to desired product were combined, concentrated and dried in vacuo to afford the title compound (8.0 g, 23 mmol, 77 % yield) as a light yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.81-7.77 (m, 1H), 7.75-7.70 (m, 1H), 7.59-7.54 (m, 1H), 7.21-7.17 (m, 1H), 7.15-7.11 (m, 1H), 4.03-3.97 (m, 3H), 3.96-3.92 (m, 3H), 2.68-2.57 (m, 3H). Analytical LC/MS

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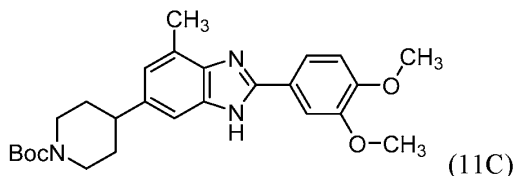
(Method 3): Observed Mass: 349.2; Retention Time: 0.72 min.

Step B. Intermediate 11B. Preparation of tert-butyl 4-(2-(3,4-dimethoxyphenyl)-4-methyl-1H-benzo[d]imidazol-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate



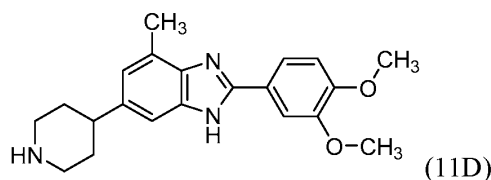
To a 200 mL pear shaped flask were added Intermediate 11A (3.2 g, 9.2 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (3.4 g, 11 mmol), followed by 1,4-dioxane (40 mL) and potassium phosphate tribasic (5.9 g, 28 mmol) dissolved in water (10 mL). The vessel evacuated and purged with N₂, then 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.38 g, 0.46 mmol) was added. The vessel was evacuated and purged again and stirred at 75 °C. After 18 h, the reaction mixture was cooled, diluted with water (200 mL) and extracted with EtOAc (2x100 mL). The organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (220 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100%B; flow rate = 80 mL/min). The fractions corresponding to desired product were combined, concentrated and dried in vacuo to afford the title compound (4.0 g, 8.9 mmol, 97 % yield) as a light yellow solid. ¹H NMR (400 MHz, METHANOL-d₄) δ 7.81-7.78 (m, 1H), 7.75-7.70 (m, 1H), 7.45-7.42 (m, 1H), 7.20-7.17 (m, 1H), 7.15-7.11 (m, 1H), 6.17-6.05 (m, 1H), 4.15-4.08 (m, 2H), 3.99 (s, 3H), 3.94 (s, 3H), 3.72-3.67 (m, 2H), 2.67-2.60 (m, 2H), 2.64 (s, 3H), 1.53 (s, 9H). Analytical LC/MS (Method 3): Observed Mass: 450.4; Retention Time: 0.83 min.

Step C. Intermediate 11C. Preparation of tert-butyl 4-(2-(3,4-dimethoxyphenyl)-4-methyl-1H-benzo[d]imidazol-6-yl)piperidine-1-carboxylate



To a 250 mL round bottomed flask were added Intermediate 11B (4.0 g, 8.8 mmol) and MeOH (50 mL). The vessel was evacuated and purged with N₂, then Pd-C (10% wt.) (0.94 g, 0.88 mmol) was added and reaction mixture was stirred under hydrogen at 1 atm. After 18 h, the catalyst was filtered and the filtrate concentrated. The product was dried in vacuo to afford the title compound (3.8 g, 8.4 mmol, 95 % yield) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.81-7.78 (m, 1H), 7.74-7.68 (m, 1H), 7.30-7.22 (m, 1H), 7.15-7.11 (m, 1H), 6.98-6.94 (m, 1H), 4.29-4.22 (m, 2H), 3.99 (s, 3H), 3.93 (s, 3H), 3.80-3.72 (m, 1H), 2.86-2.77 (m, 1H), 2.65-2.59 (m, 3H), 1.93-1.86 (m, 2H), 1.73-1.61 (m, 3H), 1.52 (s, 9H). Analytical LC/MS (Method 3):
Observed Mass: 452.5; Retention Time: 0.83 min.

Step D. Intermediate 11D. Preparation of 2-(3,4-dimethoxyphenyl)-4-methyl-6-(piperidin-4-yl)-1H-benzo[d]imidazole bis(2,2,2-trifluoroacetate)



To a 500 mL pear shaped flask were added Intermediate 11C (3.8 g, 8.4 mmol), DCM (50 mL), and TFA (50 mL). After stirring 2 h, the solvent was concentrated and the residue was co-evaporated with toluene. The product was dried in vacuo to afford the title compound (4.8 g, 8.3 mmol, 99 % yield) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.85-7.82 (m, 1H), 7.81-7.80 (m, 1H), 7.51-7.48 (m, 1H), 7.35-7.33 (m, 1H), 7.31-7.28 (m, 1H), 4.02 (s, 3H), 4.00 (s, 3H), 3.61-3.54 (m, 2H), 3.24-3.18 (m, 3H), 2.73 (s, 3H), 2.22-2.15 (m, 2H), 2.07-1.98 (m, 2H). Analytical LC/MS (Method 3):
Observed Mass: 352.4; Retention Time: 0.53 min.

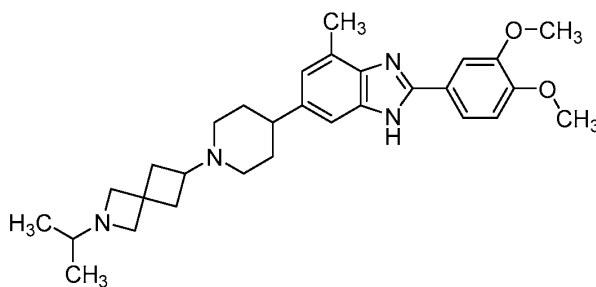
Step E. Example 11

To a 40 mL vial were added Intermediate 11D (81 mg, 0.14 mmol), 1-isopropylpiperidin-4-one (110 mg, 0.78 mmol), AcOH (11 mg, 0.18 mmol), magnesium sulfate (220 mg, 1.8 mmol), and DMF (2 mL). The reaction mixture was stirred for 20 min, then sodium triacetoxyborohydride (170 mg, 0.80 mmol) was added and the reaction mixture was stirred. After 18 h, the reaction mixture was filtered and the filter cake was

washed with 10% IPA/chloroform (20 mL). The filtrate was washed with 10% aqueous NaOH (10 mL), brine, dried over MgSO₄, filtered and concentrated. The crude material was purified via preparative HPLC (Prep Method 1) to afford the title compound (52 mg, 0.11 mmol, 79 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 7.80-7.72 (m, 2H), 7.22-7.16 (m, 1H), 7.14-7.09 (m, 1H), 6.89-6.86 (m, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.04-2.97 (m, 2H), 2.92-2.86 (m, 2H), 2.78-2.70 (m, 1H), 2.54 (s, 3H), 2.34-2.25 (m, 3H), 2.21-2.13 (m, 2H), 1.85-1.75 (m, 5H), 1.74-1.64 (m, 2H), 1.53-1.43 (m, 2H), 0.99 (d, *J*=6.7 Hz, 6H). TLR9 IC₅₀ (nM) = 33. Analytical LC/MS (Method 1): Purity: 98.6 %; Observed Mass: 477.16; Retention Time: 1.00 min. (Method 2): Purity: 100 %; Observed Mass: 477.18; Retention Time: 1.26 min.

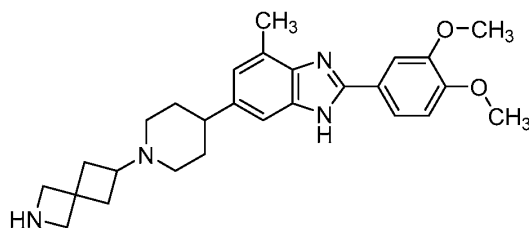
EXAMPLE 12

2-(3,4-dimethoxyphenyl)-6-(1-(2-isopropyl-2-azaspiro[3.3]heptan-6-yl)piperidin-4-yl)-4-methyl-1H-benzo[d]imidazole



(12)

Step A. Intermediate 12A. Preparation of 6-(1-(2-azaspiro[3.3]heptan-6-yl)piperidin-4-yl)-2-(3,4-dimethoxyphenyl)-4-methyl-1H-benzo[d]imidazole trihydrochloride



(12A)

To a 40 mL vial were added Intermediate 11D (140 mg, 0.24 mmol), tert-butyl 6-oxo-2-azaspiro[3.3]heptane-2-carboxylate (150 mg, 0.71 mmol), AcOH (16 mg, 0.26 mmol), magnesium sulfate (220 mg, 1.8 mmol), and DMF (2 mL). The reaction mixture was stirred for 20 min, then sodium triacetoxyborohydride (150 mg, 0.71 mmol) was

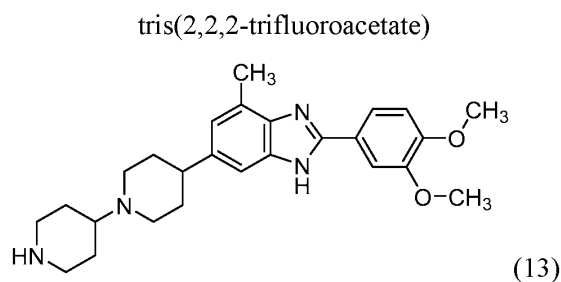
added and the reaction mixture was stirred. After 18 h, the reaction mixture was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (40 g silica gel cartridge; A = DCM, B = MeOH; 30 min grad.; 0% B to 30%B; flow rate = 40 mL/min). The fractions corresponding to product were combined and concentrated. The resultant residue was dissolved in 4 M HCl in dioxane (20 mL) and stirred. After 15 min, the solvent was concentrated and the residue was co-evaporated with toluene. The product was dried in vacuo to afford the title compound (100 mg, 0.180 mmol, 75 % yield) as an off white solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.84-7.80 (m, 2H), 7.53-7.49 (m, 1H), 7.37-7.33 (m, 1H), 7.30-7.27 (m, 1H), 4.03 (s, 3H), 4.00 (s, 3H), 3.78-3.74 (m, 4H), 3.71-3.67 (m, 7H), 3.63-3.59 (m, 4H), 2.84-2.79 (m, 3H), 2.74-2.71 (m, 3H). Analytical LC/MS (Method 3): Observed Mass: 447.5; Retention Time: 0.50 min.

Step B. Example 12

To a 40 mL vial were added Intermediate 12A (100 mg, 0.18 mmol), propan-2-one (52 mg, 0.90 mmol), AcOH (12 mg, 0.20 mmol), magnesium sulfate (220 mg, 1.8 mmol), and DMF (2 mL). The reaction mixture was stirred for 5 min, then sodium triacetoxyborohydride (190 mg, 0.90 mmol) was added and the reaction mixture was stirred. After 18 h, the reaction mixture was filtered and the filter cake was washed with 10% IPA/chloroform (20 mL). The filtrate was washed with 10% aqueous NaOH (10 mL), brine, dried over MgSO₄, filtered and concentrated. The crude material was purified via preparative HPLC (Prep Method 1) to afford the title compound (37 mg, 0.076 mmol, 42 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 7.80-7.71 (m, 2H), 7.24-7.14 (m, 1H), 7.14-7.08 (m, 1H), 6.89-6.84 (m, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.62-3.55 (m, 2H), 3.32-3.26 (m, 1H), 3.19-3.14 (m, 1H), 2.91-2.85 (m, 2H), 2.61-2.57 (m, 1H), 2.53 (s, 3H), 2.44-2.36 (m, 1H), 2.22-2.15 (m, 2H), 1.84-1.74 (m, 4H), 1.70-1.61 (m, 2H), 0.89-0.84 (m, 6H) (three protons obscured). TLR9 IC₅₀ (nM) = 60. Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 489.29; Retention Time: 1.01 min. (Method 2): Purity: 100 %; Observed Mass: 488.96; Retention Time: 1.21 min.

EXAMPLE 13

6-([1,4'-bipiperidin]-4-yl)-2-(3,4-dimethoxyphenyl)-4-methyl-1H-benzo[d]imidazole

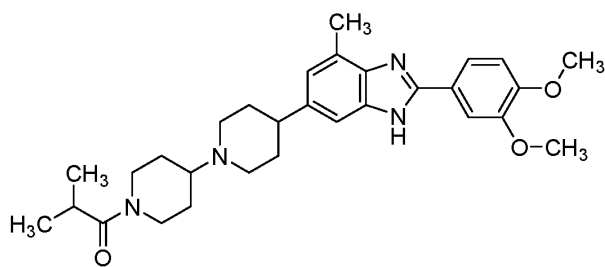


To a 40 mL vial were added Intermediate 11D (1.0 g, 1.7 mmol), tert-butyl 4-oxopiperidine-1-carboxylate (1.0 g, 5.0 mmol), AcOH (110 mg, 1.8 mmol), magnesium sulfate (3.0 g, 25 mmol), and DMF (10 mL). The reaction mixture was stirred for 20 min, then sodium triacetoxyborohydride (1.1 g, 5.2 mmol) was added and the reaction mixture was stirred. After 18 h, the reaction mixture was filtered, the filter cake was washed with DCM/MeOH and the filtrate was concentrated. The remaining DMF solution was loaded onto a Celite cartridge and purified by flash column chromatography (275 g reverse phase C18 GOLD silica gel cartridge; A = water:MeCN:TFA 90:10:0.05%, B = water:MeCN:TFA 10:90:0.05%; 20 min grad.; 0% B to 100%B; flow rate = 120 mL/min). The fractions corresponding to product were combined and the solvent was concentrated. The resultant residue was dissolved in a minimal amount of MeOH, then 4 M HCl in dioxane (30 mL) was added and the reaction mixture was stirred. After 2 h, the solvent was concentrated and the residue was co-evaporated with toluene. The crude product was purified by preparative HPLC (Prep Method 2) to afford the title compound (0.42 g, 0.54 mmol, 32 % yield) as a tan solid. ¹H NMR (500 MHz, DMSO-d₆) δ 7.84-7.72 (m, 2H), 7.29-7.17 (m, 1H), 7.16-7.11 (m, 1H), 6.91-6.87 (m, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.51-3.43 (m, 1H), 3.22-3.14 (m, 2H), 3.04-2.94 (m, 2H), 2.74-2.65 (m, 2H), 2.57-2.55 (m, 3H), 2.50-2.45 (m, 1H), 2.35-2.26 (m, 2H), 1.87-1.79 (m, 4H), 1.75-1.65 (m, 2H), 1.59-1.49 (m, 2H). TLR9 IC₅₀ (nM) = 620. Analytical LC/MS (Method 1): Purity: 99.3 %; Observed Mass: 435.31; Retention Time: 0.92 min. (Method 2): Purity: 100 %; Observed Mass: 435.15; Retention Time: 1.2 min.

25

EXAMPLE 14

1-(4-(2-(3,4-dimethoxyphenyl)-4-methyl-1H-benzo[d]imidazol-6-yl)-[1,4'-bipiperidin]-1'-yl)-2-methylpropan-1-one

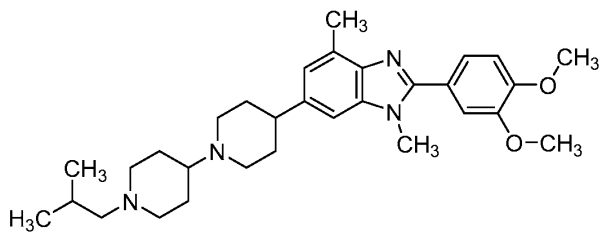


(14)

To a 40 mL vial were added Example 13 (85 mg, 0.11 mmol), isobutyric acid (11 mg, 0.12 mmol), TEA (56 mg, 0.55 mmol), DMAP (13 mg, 0.11 mmol), and DMF (2 mL). To this mixture was added EDC (42 mg, 0.22 mmol), the vial was capped and the reaction mixture was stirred. After 4 d, the reaction mixture was diluted with water (20 mL), saturated with solid NaCl, and extracted with EtOAc (5x10 mL). The organic phase was combined, dried over MgSO₄, filtered and concentrated. The crude product was purified by preparative HPLC (Prep Method 1) to afford the title compound (31 mg, 0.061 mmol, 55 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 7.81-7.76 (m, 1H), 7.75-7.68 (m, 1H), 7.14-7.09 (m, 1H), 7.28-7.08 (m, 1H), 6.89-6.85 (m, 1H), 4.48-4.40 (m, 1H), 4.03-3.95 (m, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.03-2.94 (m, 3H), 2.91-2.83 (m, 1H), 2.53 (s, 3H), 2.34-2.24 (m, 2H), 1.87-1.75 (m, 4H), 1.72-1.61 (m, 2H), 1.41-1.32 (m, 1H), 1.31-1.20 (m, 1H), 1.03-0.94 (m, 6H) (three protons obscured). TLR9 IC₅₀ (nM) = 510. Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 505.17; Retention Time: 1.08 min. (Method 2): Purity: 100 %; Observed Mass: 505.22; Retention Time: 1.29 min.

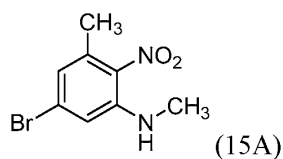
EXAMPLE 15

2-(3,4-dimethoxyphenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-1H-benzo[d]imidazole tris(2,2,2-trifluoroacetate)



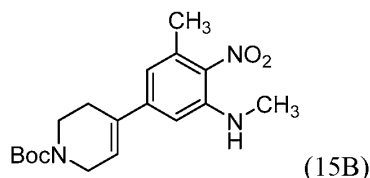
(15)

Step A. Intermediate 15A. Preparation of 5-bromo-N,3-dimethyl-2-nitroaniline



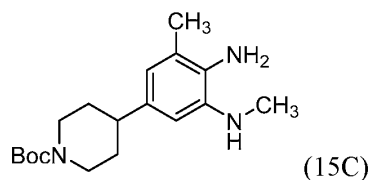
Intermediate 15A was synthesized according to methods described for the preparation of Intermediate 1A, using 5-bromo-1-fluoro-3-methyl-2-nitrobenzene (1.0 g, 4.3 mmol) as starting material to afford the title compound (1.0 g, 4.1 mmol, 95 % yield) as a yellow solid. ¹H NMR (400 MHz, METHANOL-d₄) δ 6.94-6.89 (m, 1H), 6.75-6.73 (m, 1H), 2.89 (s, 3H), 2.38 (s, 3H). Analytical LC/MS (Method 3): Observed Mass: 247.1; Retention Time: 1.03 min.

Step B. Intermediate 15B. Preparation of tert-butyl 4-(3-methyl-5-(methylamino)-4-nitrophenyl)-3,6-dihydropyridine-1(2H)-carboxylate



Intermediate 15B was synthesized according to methods described for the preparation of Intermediate 3B, using Intermediate 15A (1.0 g, 4.1 mmol) as starting material to afford the title compound (1.4 g, 4.0 mmol, 98 % yield) as a yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 6.74-6.70 (m, 1H), 6.68-6.65 (m, 1H), 6.28-6.22 (m, 1H), 4.15-4.06 (m, 2H), 3.70-3.61 (m, 2H), 2.95 (s, 3H), 2.58-2.51 (m, 2H), 2.45 (s, 3H), 1.51 (s, 9H). Analytical LC/MS (Method 3): Observed Mass: 348.3; Retention Time: 1.12 min.

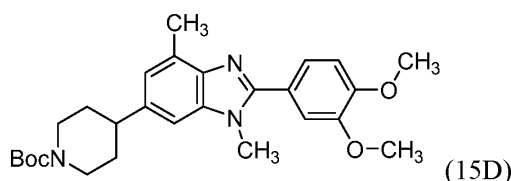
Step C. Intermediate 15C. Preparation of tert-butyl 4-(4-amino-3-methyl-5-(methylamino)phenyl)piperidine-1-carboxylate



Intermediate 15C was synthesized according to methods described for the

preparation of Intermediate 3C, using Intermediate 15B (1.4 g, 4.0 mmol) as starting material to afford the title compound (1.2 g, 3.8 mmol, 95 % yield) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 6.43-6.37 (m, 2H), 4.25-4.15 (m, 2H), 2.92-2.78 (m, 2H), 2.83 (s, 3H) 2.62-2.51 (m, 1H), 2.18 (s, 3H), 1.82-1.75 (m, 2H), 1.59-1.53 (m, 2H), 1.50 (s, 9H). Analytical LC/MS (Method 3): Observed Mass: 320.4; Retention Time: 0.75 min.

Step D. Intermediate 15D. Preparation of tert-butyl 4-(2-(3,4-dimethoxyphenyl)-1,4-dimethyl-1H-benzo[d]imidazol-6-yl)piperidine-1-carboxylate

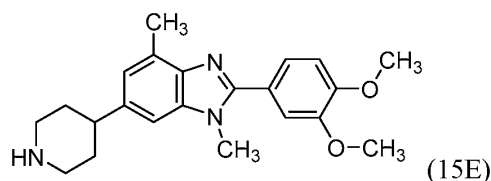


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Intermediate 15D was synthesized according to methods described for the preparation of Intermediate 3D, using Intermediate 15C (1.2 g, 3.8 mmol, 95 % yield) as starting material to afford the title compound (1.7 g, 3.7 mmol, 97 % yield) as a pale yellow semisolid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.40-7.38 (m, 1H), 7.35-7.32 (m, 1H), 7.24-7.22 (m, 1H), 7.19-7.15 (m, 1H), 7.03-7.01 (m, 1H), 4.32-4.21 (m, 2H), 3.97-3.93 (m, 6H), 3.86 (s, 3H), 2.99-2.83 (m, 3H), 2.62 (s, 3H), 1.95-1.89 (m, 2H), 1.77-1.67 (m, 2H), 1.52 (s, 9H). Analytical LC/MS (Method 3): Observed Mass: 466.4; Retention Time: 0.83 min.

15

Step E. Intermediate 15E. Preparation of 2-(3,4-dimethoxyphenyl)-1,4-dimethyl-6-(piperidin-4-yl)-1H-benzo[d]imidazole dihydrochloride



Intermediate 15E was synthesized according to methods described for the preparation of Intermediate 3E, using Intermediate 15D (1.7 g, 3.7 mmol) as starting material to afford the title compound (1.4 g, 3.2 mmol, 86 % yield) as a light tan solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.67 (s, 1H), 7.55-7.52 (m, 1H), 7.50 (s, 1H),

25

7.44-7.41 (m, 1H), 7.34-7.30 (m, 1H), 4.11 (s, 3H), 4.01-4.00 (m, 3H), 3.99-3.98 (m, 3H), 3.62-3.56 (m, 2H), 3.27-3.20 (m, 2H), 3.20-3.14 (m, 1H), 2.71 (s, 3H), 2.23-2.17 (m, 2H), 2.14-2.04 (m, 2H). Analytical LC/MS (Method 3): Observed Mass: 366.3; Retention Time: 0.53 min.

5

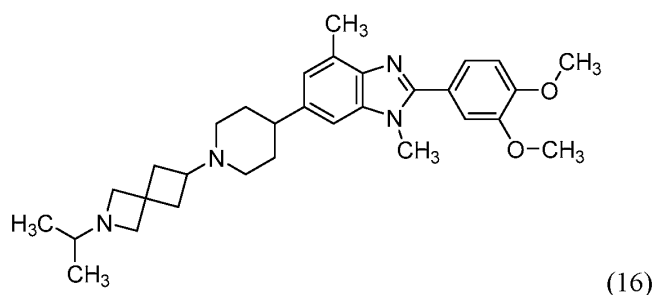
Step F. Example 15

To a 40 mL vial were added Intermediate 15E (70 mg, 0.16 mmol), 1-isobutylpiperidin-4-one (120 mg, 0.77 mmol), AcOH (11 mg, 0.18 mmol), magnesium sulfate (220 mg, 1.8 mmol), and DMF (2 mL). The reaction mixture was stirred for 20 min, then sodium triacetoxyborohydride (170 mg, 0.8 mmol) was added and the reaction mixture was stirred. After 18 h, the reaction mixture was filtered and the filter cake was washed with 10% IPA/chloroform (20 mL). The filtrate was washed with 10% aqueous NaOH (10 mL), brine, dried over MgSO₄, filtered and concentrated. The crude material was purified via preparative HPLC (Prep Method 2) to afford the title compound (85 mg, 0.10 mmol, 63 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 7.56-7.52 (m, 1H), 7.51-7.48 (m, 1H), 7.47 (s, 1H), 7.27 (s, 1H), 7.25-7.21 (m, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 3.73-3.56 (m, 1H), 3.25-3.16 (m, 1H), 3.13-2.90 (m, 4H), 2.61 (s, 3H), 2.38-2.25 (m, 2H), 2.21-1.99 (m, 7H), 0.97 (d, *J*=6.6 Hz, 6H) (6 protons obscured). TLR9 IC₅₀ (nM) = 19. Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 505.09; Retention Time: 0.99 min. (Method 2): Purity: 99.5 %; Observed Mass: 505.90; Retention Time: 1.6 min.

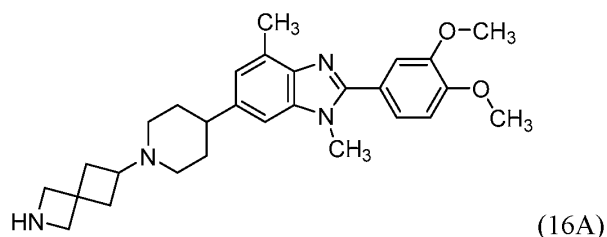
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EXAMPLE 16

2-(3,4-dimethoxyphenyl)-6-(1-(2-isopropyl-2-azaspiro[3.3]heptan-6-yl)piperidin-4-yl)-1,4-dimethyl-1H-benzo[d]imidazole tris(2,2,2-trifluoroacetate)



Step A. Intermediate 16A. Preparation of 6-(1-(2-azaspiro[3.3]heptan-6-yl)piperidin-4-yl)-2-(3,4-dimethoxyphenyl)-1,4-dimethyl-1H-benzo[d]imidazole trihydrochloride



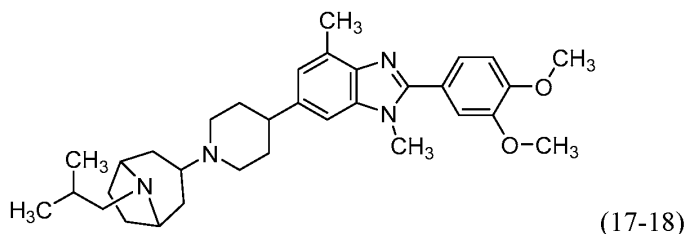
To a 40 mL vial were added Intermediate 15E (0.50 g, 1.1 mmol), tert-butyl 6-oxo-2-azaspiro[3.3]heptane-2-carboxylate (0.70 g, 3.3 mmol), AcOH (0.078 g, 1.3 mmol), magnesium sulfate (1.9 g, 16 mmol), and DMF (10 mL). The reaction mixture was stirred for 20 min, then sodium triacetoxyborohydride (0.73 g, 3.4 mmol) was added and the reaction mixture was stirred. After 18 h, the reaction mixture was filtered, the filter cake was washed with DCM/MeOH and the filtrate was concentrated. The remaining DMF solution was loaded onto a Celite cartridge and purified by flash column chromatography (275 g reverse phase C18 GOLD silica gel cartridge; A = water:MeCN:TFA 90:10:0.05%, B = water:MeCN:TFA 10:90:0.05%; 20 min grad.; 10% B to 100%B; flow rate = 125 mL/min). The fractions corresponding to product were combined and concentrated while maintaining the rotovap bath at 30 °C. The resultant residue was dissolved in a minimal amount of MeOH, then further diluted with THF (20 mL). To this mixture was added 4 M HCl in dioxane (4 mL) and the reaction mixture was stirred. After 6 h, the solvent was concentrated while maintaining the rotovap bath at 30 °C, the residue was co-evaporated with toluene and the product was dried in vacuo to afford the title compound (0.63 g, 1.1 mmol, 100 % yield) as an off white solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.72-7.64 (m, 1H), 7.57-7.52 (m, 1H), 7.51-7.48 (m, 1H), 7.46-7.40 (m, 1H), 7.34-7.29 (m, 1H), 4.25-4.22 (m, 1H), 4.17-4.14 (m, 1H), 4.11 (s, 3H), 3.99 (s, 3H), 3.98 (s, 3H), 3.94-3.88 (m, 1H), 3.77-3.69 (m, 1H), 3.68-3.60 (m, 2H), 3.23-3.14 (m, 1H), 3.11-2.97 (m, 2H), 2.88-2.75 (m, 3H), 2.73-2.62 (m, 1H), 2.69 (s, 3H), 2.61-2.49 (m, 1H), 2.38-2.17 (m, 4H). Analytical LC/MS (Method 3): Observed Mass: 461.5; Retention Time: 0.56 min.

Step B. Example 16

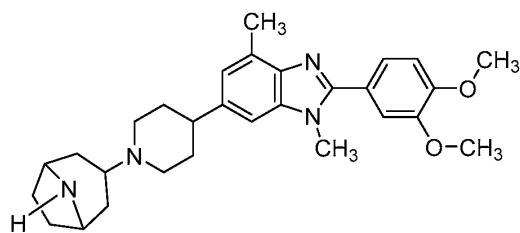
To a 40 mL vial were added Intermediate 16A (50 mg, 0.088 mmol), propan-2-one (26 mg, 0.45 mmol), AcOH (6 mg, 0.10 mmol), magnesium sulfate (220 mg, 1.8 mmol), and DMF (2 mL). The reaction mixture was stirred for 20 min, then sodium triacetoxyborohydride (95 mg, 0.45 mmol) was added and the reaction mixture was stirred. After 18 h, the reaction mixture was filtered and the filter cake was washed with 10% IPA/chloroform (20 mL). The filtrate was washed with 10% aqueous NaOH (10 mL), brine, dried over MgSO₄, filtered and concentrated. The crude material was purified via preparative HPLC (Prep Method 2) to afford the title compound (27 mg, 0.032 mmol, 36 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 7.45-7.38 (m, 3H), 7.23-7.19 (m, 1H), 7.14-7.09 (m, 1H), 4.20-4.11 (m, 2H), 4.10-3.98 (m, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.74-3.62 (m, 2H), 3.53-3.42 (m, 1H), 3.41-3.31 (m, 1H), 3.06-2.96 (m, 1H), 2.95-2.79 (m, 2H), 2.76-2.67 (m, 1H), 2.58-2.56 (m, 3H), 2.49-2.39 (m, 1H), 2.14-2.04 (m, 2H), 1.99-1.88 (m, 2H), 1.10 (d, *J*=6.4 Hz, 6H) (two protons obscured). TLR9 IC₅₀ (nM) = 100. Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 503.16; Retention Time: 1.00 min. (Method 2): Purity: 99.2 %; Observed Mass: 503.19; Retention Time: 1.38 min.

EXAMPLES 17 AND 18

20 2-(3,4-dimethoxyphenyl)-6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-1H-benzo[d]imidazole



Step A. Intermediate 17A. Preparation of 6-(1-(8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(3,4-dimethoxyphenyl)-1,4-dimethyl-1H-benzo[d]imidazole trihydrochloride



To a 40 mL vial were added Intermediate 15E (0.44 g, 1.0 mmol), DCE (1 mL), DME (1 mL), followed by tert-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (1.0 g, 4.4 mmol). To the resultant suspension was added titanium(IV) isopropoxide (1.5 g, 5.3 mmol), the vessel was flushed with N₂, capped, and the reaction mixture was stirred at 35 °C. After 18 h, DMF (20 mL) was added and the reaction mixture was continued. After 3 h, the reaction mixture was cooled to -40 °C, then sodium triacetoxyborohydride (0.89 g, 4.2 mmol) was added in portions. The reaction mixture was stirred at room temperature for 1 h, then partitioned into 10% NaOH (100 mL), and extracted with 10% IPA/CHCl₃ (3x50 mL). The organic phase was combined, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (100 g reverse phase C18 GOLD silica gel cartridge; A = water:MeCN:TFA 90:10:0.05%, B = water:MeCN:TFA 10:90:0.05%; 20 min grad.; 0% B to 100%B; flow rate = 80 mL/min). The fractions containing product were combined and concentrated. The residue was dissolved in MeOH (10 mL) and 4 M HCl in dioxane (10 mL) and stirred. After 1 h, the solvent was concentrated and the product was dried in vacuo to afford the title compound (0.11 g, 0.19 mmol, 19 % yield) as a colorless oil. Analytical LC/MS (Method 3): Observed Mass: 475.3; Retention Time: 0.68 min.

Step B. Examples 17 and 18

To a 40 mL vial were added Intermediate 17A (0.11 g, 0.19 mmol), isobutyraldehyde (65 mg, 0.90 mmol), AcOH (12 mg, 0.20 mmol), magnesium sulfate (220 mg, 1.8 mmol), and DMF (2 mL). The reaction mixture was stirred for 20 min, then sodium triacetoxyborohydride (120 mg, 0.57 mmol) was added and the reaction mixture was stirred. After 18 h, the reaction mixture was filtered and the filter cake was washed with 10% IPA/chloroform (20 mL). The filtrate was washed with 10% aqueous NaOH (10 mL), brine, dried over MgSO₄, filtered and concentrated. The crude isomeric mixture

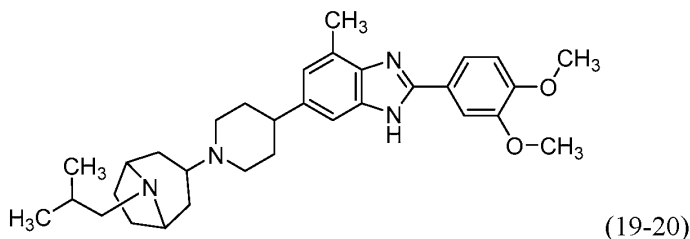
was purified via preparative HPLC with the following conditions: Column: XBridge C18, 200 mm x 19 mm, 5- μ m particles; Mobile Phase A: 5:95 acetonitrile: water with ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with ammonium acetate; Gradient: a 0-minute hold at 15% B, 15-70% B over 25 minutes, then a 0-minute hold at 100% B; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS signals. Fractions corresponding to the respective desired products were combined and dried via centrifugal evaporation.

Example 17 (35 mg, 0.066 mmol, 35 % yield) was isolated as the 1st eluting isomer. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.38-7.32 (m, 2H), 7.25-7.22 (m, 1H), 7.16-7.11 (m, 1H), 6.96-6.92 (m, 1H), 3.86 (s, 6H), 3.82 (s, 3H), 3.27-3.20 (m, 1H), 3.07-3.01 (m, 2H), 2.65-2.57 (m, 2H), 2.56 (s, 3H), 2.26-2.19 (m, 2H), 2.17-2.13 (m, 2H), 1.88-1.79 (m, 4H), 1.77-1.70 (m, 2H), 1.68-1.56 (m, 6H), 1.56-1.50 (m, 2H), 0.92-0.87 (m, 6H). TLR9 IC₅₀ (nM) = 25. Analytical LC/MS (Method 1): Purity: 98 %; Observed Mass: 531.02; Retention Time: 1.01 min. (Method 2): Purity: 100 %; Observed Mass: 531.24; Retention Time: 1.59 min.

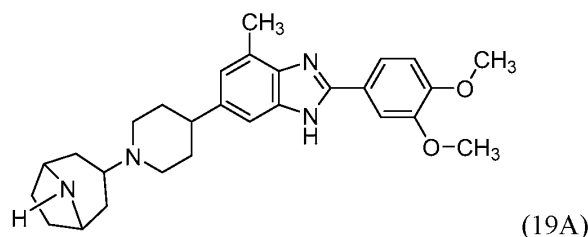
Example 18 (16 mg, 0.030 mmol, 16 % yield) was isolated as the 2nd eluting isomer. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.37 (s, 2H), 7.26-7.22 (m, 1H), 7.16-7.12 (m, 1H), 6.98-6.93 (m, 1H), 3.87 (s, 6H), 3.84 (s, 3H), 2.66-2.58 (m, 1H), 2.55 (s, 3H), 2.49-2.37 (m, 1H), 2.07-1.95 (m, 3H), 1.95-1.83 (m, 8H), 1.82-1.61 (m, 6H), 0.95-0.87 (m, 6H) (4 protons obscured). TLR9 IC₅₀ (nM) = 29. Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 531.23; Retention Time: 1.06 min. (Method 2): Purity: 96.8 %; Observed Mass: 530.90; Retention Time: 1.91 min.

EXAMPLES 19 AND 20

25 2-(3,4-dimethoxyphenyl)-6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-methyl-1H-benzo[d]imidazole



Step A. Intermediate 19A. Preparation of 6-(1-(8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(3,4-dimethoxyphenyl)-4-methyl-1H-benzo[d]imidazole dihydrochloride



Intermediate 19A was synthesized according to the general methods described for the preparation of Intermediate 17A, using Intermediate 11D (640 mg, 1.1 mmol) as starting material to afford the title compound (120 mg, 0.22 mmol, 20 % yield) as a colorless oil. Analytical LC/MS (Method 3): Observed Mass: 461.3; Retention Time: 0.67 min.

Step B. Preparation of Examples 19 and 20

Examples 19 and 20 were synthesized according to the general methods described for the preparation of Examples 17 and 18, using Intermediate 19A (120 mg, 0.22 mmol) as the starting material. The crude isomeric mixture was purified via preparative HPLC with the following conditions: Column: XBridge C18, 200 mm x 19 mm, 5- μ m particles; Mobile Phase A: 5:95 acetonitrile: water with ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with ammonium acetate; Gradient: a 0-minute hold at 11% B, 11-59% B over 20 minutes, then a 0-minute hold at 100% B; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS and UV signals. Fractions corresponding to the respective desired products were combined and dried via centrifugal evaporation.

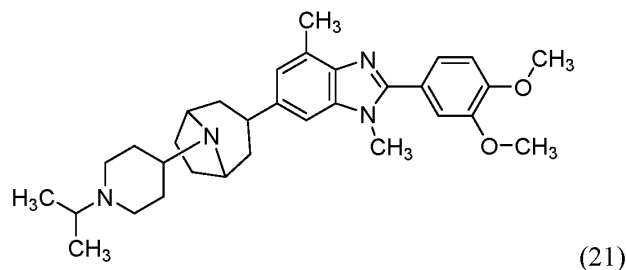
Example 19 (46 mg, 0.089 mmol, 40 % yield) was isolated as the 1st eluting isomer. ¹H NMR (500 MHz, DMSO-d₆) δ 7.85-7.67 (m, 2H), 7.29-7.09 (m, 2H), 6.89-6.84 (m, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.24-2.81 (m, 1H), 2.69-2.57 (m, 2H), 2.48-2.39 (m, 1H), 2.35-2.20 (m, 2H), 1.97-1.84 (m, 7H), 1.80-1.66 (m, 7H), 1.65-1.56 (m, 2H), 0.94-0.87 (m, 6H) (4 protons obscured). TLR9 IC₅₀ (nM) = 28. Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 516.98; Retention Time: 1.05 min. (Method 2): Purity: 98.5 %; Observed Mass: 516.97; Retention Time: 1.45 min.

Example 20 (41 mg, 0.079 mmol, 36 % yield) was isolated as the 2nd eluting isomer. ¹H NMR (500 MHz, DMSO-d₆) δ 7.85-7.68 (m, 2H), 7.32-7.10 (m, 2H), 6.91-6.85 (m, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.77-3.55 (m, 1H), 3.53-3.45 (m, 2H), 3.20-3.15 (m, 1H), 2.55 (s, 5H), 2.49-2.46 (m, 1H), 2.34-2.12 (m, 3H), 2.09-2.00 (m, 3H), 1.96-1.88 (m, 4H), 1.80-1.65 (m, 2H), 0.99-0.91 (m, 6H) (4 protons obscured). TLR9 IC₅₀ (nM) = 69. Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 517.38; Retention Time: 1.04 min. (Method 2): Purity: 99.3 %; Observed Mass: 517.03; Retention Time: 1.63 min.

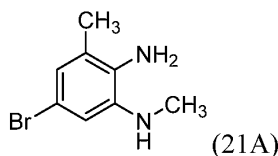
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EXAMPLE 21

2-(3,4-dimethoxyphenyl)-6-(8-(1-isopropylpiperidin-4-yl)-8-azabicyclo[3.2.1]octan-3-yl)-1,4-dimethyl-1H-benzo[d]imidazole (isomeric mixture)



Step A. Intermediate 21A. Preparation of 5-bromo-N¹,3-dimethylbenzene-1,2-diamine

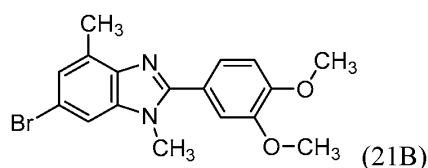


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Intermediate 21A was synthesized according to methods described for the preparation of Intermediate 1B, using Intermediate 15A (2.0 g, 8.2 mmol) as starting material to afford the title compound (1.6 g, 7.4 mmol, 90 % yield) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 6.65-6.60 (m, 1H), 6.57-6.53 (m, 1H), 2.81 (s, 3H), 2.15 (s, 3H). Analytical LC/MS (Method 3): Observed Mass: 215.0; Retention Time: 0.67 min.

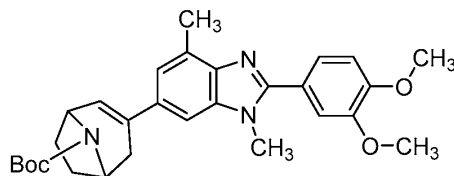
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Step B. Intermediate 21B. Preparation of 6-bromo-2-(3,4-dimethoxyphenyl)-1,4-dimethyl-1H-benzo[d]imidazole



To a 40 mL vial were added Intermediate 21A (0.56 g, 2.6 mmol) and NMP (10 mL). To this mixture was added sodium metabisulfite (0.72 g, 3.8 mmol), followed by 3,4-dimethoxybenzaldehyde (0.52 g, 3.1 mmol). The mixture was stirred at 70 °C. After 18 h, the reaction mixture was cooled, diluted with water (100 mL) and extracted with EtOAc (2x50 mL). The organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (120 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100%B; flow rate = 80 mL/min). The fractions corresponding to product were combined, concentrated and dried in vacuo to afford the title compound (0.83 g, 2.3 mmol, 88 % yield) as a light yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.61-7.58 (m, 1H), 7.41-7.38 (m, 1H), 7.37-7.33 (m, 1H), 7.27-7.24 (m, 1H), 7.21-7.15 (m, 1H), 3.97-3.94 (m, 6H), 3.87-3.84 (m, 3H), 2.64-2.61 (m, 3H). Analytical LC/MS (Method 3): Observed Mass: 363.0; Retention Time: 0.71 min.

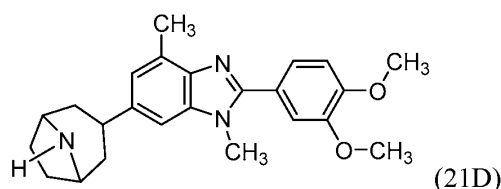
Step C. Intermediate 21C. Preparation of tert-butyl 3-(2-(3,4-dimethoxyphenyl)-1,4-dimethyl-1H-benzo[d]imidazol-6-yl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate



To a 40 mL vial were added Intermediate 21B (270 mg, 0.75 mmol), tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (250 mg, 0.75 mmol), XPhos Pd G3 (63 mg, 0.075 mmol), 1,4-dioxane (15 mL), followed by potassium phosphate tribasic (550 mg, 2.6 mmol) dissolved in water (3 mL). The vessel was flushed with N₂, capped and the reaction mixture was stirred at 85 °C. After 18 h, the reaction mixture was cooled, diluted with water (100 mL) and extracted with EtOAc (2x50 mL). The organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column

chromatography (120 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100%B; flow rate = 80 mL/min). The fractions corresponding to product were combined, concentrated and dried in vacuo to afford the title compound (360 mg, 0.74 mmol, 99 % yield) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.42-7.38 (m, 1H), 7.38-7.32 (m, 2H), 7.23-7.20 (m, 1H), 7.19-7.15 (m, 1H), 6.56-6.51 (m, 1H), 4.56-4.47 (m, 2H), 3.95 (s, 6H), 3.90-3.86 (m, 3H), 3.25-3.11 (m, 1H), 2.63 (s, 3H), 2.51-2.39 (m, 1H), 2.35-2.21 (m, 1H), 2.10-2.04 (m, 2H), 1.88-1.76 (m, 1H), 1.49 (s, 9H). Analytical LC/MS (Method 3): Observed Mass: 490.4; Retention Time: 0.90 min.

- 10 Step D. Intermediate 21D. Preparation of 6-(8-azabicyclo[3.2.1]octan-3-yl)-2-(3,4-dimethoxyphenyl)-1,4-dimethyl-1H-benzo[d]imidazole dihydrochloride



- To a 100 mL pear shaped flask were added Intermediate 21C (360 mg, 0.74 mmol), and MeOH (30 mL). The vessel was evacuated and purged with N₂, then Pd-C (10% wt.) (78 mg, 0.074 mmol) was added and the reaction mixture was stirred under hydrogen at 1 atm. After 18 h, the catalyst was filtered and to the filtrate was added 4 M HCl in dioxane (30 mL). After 30 min, the solvent was concentrated, the residue was co-evaporated with toluene (2x) and the product was dried in vacuo to afford the title compound (300 mg, 0.65 mmol, 88 % yield) as a tan solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.88-7.73 (m, 1H), 7.59-7.47 (m, 3H), 7.34-7.30 (m, 1H), 4.23-4.14 (m, 2H), 4.14-4.09 (m, 3H), 4.00 (d, J=6.9 Hz, 6H), 3.79-3.59 (m, 3H), 3.52-3.37 (m, 1H), 2.73-2.68 (m, 3H), 2.68-2.37 (m, 2H), 2.14-2.05 (m, 2H), 2.00-1.92 (m, 1H). Analytical LC/MS (Method 3): Observed Mass: 392.3; Retention Time: 0.58 min.

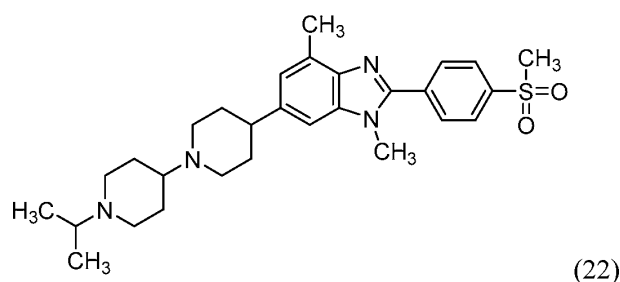
- 25 Step E. Example 21

To a 40 mL vial were added Intermediate 21D (98 mg, 0.21 mmol), 1-isopropylpiperidin-4-one (140 mg, 1.0 mmol), AcOH (14 mg, 0.24 mmol), magnesium sulfate (220 mg, 1.8 mmol), and DMF (2 mL). The reaction mixture was stirred for 20

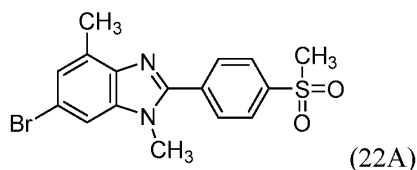
min, then sodium triacetoxyborohydride (210 mg, 1.0 mmol) was added and the reaction mixture was stirred. After 18 h, the reaction mixture was filtered and the filter cake was washed with 10% IPA/chloroform (20 mL). The filtrate was washed with 10% aqueous NaOH (10 mL), brine, dried over MgSO₄, filtered and concentrated. The crude material was purified via preparative HPLC (Prep Method 1) to afford the title compound (72 mg, 0.14 mmol, 67 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 7.37-7.31 (m, 2H), 7.25-7.21 (m, 1H), 7.15-7.11 (m, 1H), 7.02-6.97 (m, 1H), 3.84 (s, 6H), 3.81 (s, 3H), 3.13-3.05 (m, 1H), 2.91-2.86 (m, 2H), 2.78-2.73 (m, 1H), 2.53 (s, 3H), 2.38-2.29 (m, 1H), 2.26-2.20 (m, 3H), 2.00-1.91 (m, 6H), 1.82-1.77 (m, 2H), 1.66-1.58 (m, 2H), 1.45-1.35 (m, 3H), 1.01-0.99 (m, 6H). TLR9 IC₅₀ (nM) = 24. Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 517.08; Retention Time: 1.03 min. (Method 2): Purity: 100 %; Observed Mass: 517.20; Retention Time: 1.43 min.

EXAMPLE 22

6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole



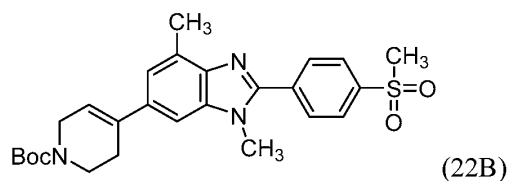
Step A. Intermediate 22A. Preparation of 6-bromo-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole



Intermediate 22A was synthesized according to methods described for the preparation of Intermediate 21B, using Intermediate 21A (200 mg, 0.93 mmol) as starting material and substituting 4-(methylsulfonyl)benzaldehyde (200 mg, 1.1 mmol) where appropriate to afford the title compound (350 mg, 0.92 mmol, 99 % yield) as a light

yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.22-8.18 (m, 2H), 8.11-8.07 (m, 2H), 7.69-7.65 (m, 1H), 7.34-7.29 (m, 1H), 3.90 (s, 3H), 3.24 (s, 3H), 2.67-2.64 (m, 3H). Analytical LC/MS (Method 3): Observed Mass: 381.1; Retention Time: 0.78 min.

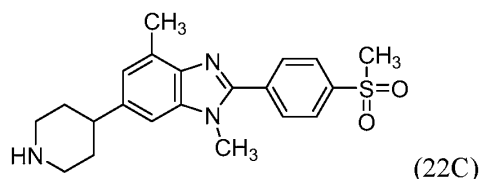
- 5 Step B. Intermediate 22B. Preparation of tert-butyl 4-(1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate



To a 40 mL vial were added Intermediate 22A (350 mg, 0.92 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (340 mg, 1.1 mmol), XPhos Pd G3 (78 mg, 0.092 mmol), 1,4-dioxane (15 mL), followed by potassium phosphate tribasic (680 mg, 3.2 mmol) dissolved in water (3 mL). The vessel was flushed with N₂, capped and the reaction mixture was stirred at 85 °C. After 18 h, the reaction mixture was cooled, diluted with water (100 mL) and extracted with EtOAc (2x50 mL). The organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (80 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100%B; flow rate = 60 mL/min). The fractions corresponding to product were combined, concentrated and dried in vacuo to afford the title compound (400 mg, 0.83 mmol, 90 % yield) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.22-8.16 (m, 2H), 8.08 (br d, *J*=8.3 Hz, 2H), 7.45 (s, 1H), 7.29 (s, 1H), 6.23-6.17 (m, 1H), 4.18-4.08 (m, 2H), 3.92 (s, 3H), 3.76-3.64 (m, 2H), 3.27-3.21 (m, 3H), 2.69-2.64 (m, 2H), 2.66 (s, 3H), 1.53 (s, 9H). Analytical LC/MS (Method 3): Observed Mass: 482.3; Retention Time: 0.79 min.

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Step C. Intermediate 22C. Preparation of 1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(piperidin-4-yl)-1H-benzo[d]imidazole dihydrochloride



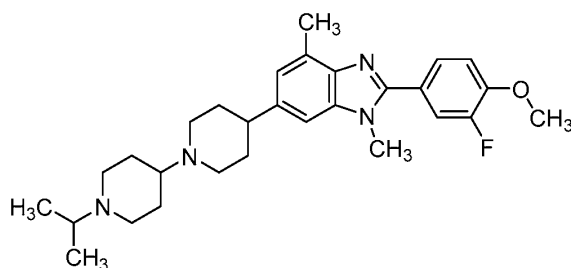
To a 100 mL pear shaped flask were added Intermediate 22B (400 mg, 0.83 mmol), and MeOH (30 mL). The vessel was evacuated and purged with N₂, then Pd-C (10% wt.) (88 mg, 0.083 mmol) was added and the reaction mixture was stirred under hydrogen at 1 atm. After 45 min, the reaction mixture was filtered and to the filtrate was added 4 M HCl in dioxane (30 mL). After stirring 30 min, the solvent was concentrated and the residue was co-evaporated with toluene (2x). The product was dried in vacuo to afford the title compound (370 mg, 0.81 mmol, 98 % yield) as a tan solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.38-8.33 (m, 2H), 8.23-8.19 (m, 2H), 7.74 (s, 1H), 7.70-7.47 (m, 1H), 4.14-4.11 (m, 3H), 3.99-3.93 (m, 1H), 3.79-3.66 (m, 1H), 3.63-3.56 (m, 2H), 3.29 (s, 3H), 3.27-3.17 (m, 2H), 3.04-2.95 (m, 1H), 2.77-2.72 (m, 3H), 2.27-2.06 (m, 2H). Analytical LC/MS (Method 3): Observed Mass: 384.2; Retention Time: 0.52 min.

Step D. Example 22

To a 40 mL vial were added Intermediate 22C (60 mg, 0.13 mmol), 1-isopropylpiperidin-4-one (92 mg, 0.65 mmol), AcOH (9.0 mg, 0.15 mmol), magnesium sulfate (220 mg, 1.8 mmol), and DMF (2 mL). The reaction mixture was stirred for 20 min, then sodium triacetoxyborohydride (140 mg, 0.66 mmol) was added and the reaction mixture was stirred. After 18 h, the reaction mixture was filtered and the filter cake was washed with 10% IPA/chloroform (20 mL). The filtrate was washed with 10% aqueous NaOH (10 mL), brine, dried over MgSO₄, filtered and concentrated. The crude material was purified via preparative HPLC (Prep Method 1) to afford the title compound (14 mg, 0.028 mmol, 22 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 8.16-8.09 (m, 4H), 7.33 (s, 1H), 7.01 (s, 1H), 3.90 (s, 3H), 3.03-2.96 (m, 2H), 2.88-2.82 (m, 2H), 2.72-2.64 (m, 1H), 2.63-2.58 (m, 1H), 2.56 (s, 3H), 2.31-2.19 (m, 3H), 2.14-2.05 (m, 2H), 1.94-1.89 (m, 1H), 1.85-1.71 (m, 6H), 1.49-1.39 (m, 2H), 0.97 (d, J=6.4 Hz, 6H) (two protons obscured). TLR9 IC₅₀ (nM) = 7.6. Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 509.21; Retention Time: 0.86 min. (Method 2): Purity: 100 %; Observed Mass: 509.22; Retention Time: 1.15 min.

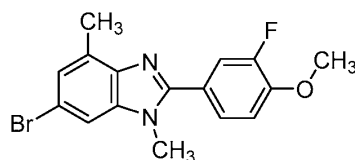
EXAMPLE 23

2-(3-fluoro-4-methoxyphenyl)-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-1H-benzo[d]imidazole



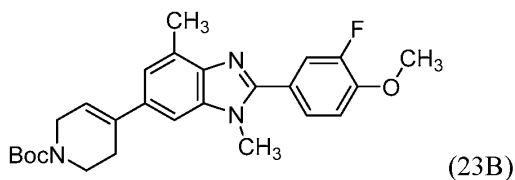
(23)

Step A. Intermediate 23A. Preparation of 6-bromo-2-(3-fluoro-4-methoxyphenyl)-1,4-dimethyl-1H-benzo[d]imidazole



Intermediate 23A was synthesized according to methods described for the preparation of Intermediate 21B, using Intermediate 21A (200 mg, 0.93 mmol) as starting material and substituting 3-fluoro-4-methoxybenzaldehyde (170 mg, 1.1 mmol) where appropriate to afford the title compound (300 mg, 0.86 mmol, 92 % yield) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.63-7.56 (m, 3H), 7.37-7.31 (m, 1H), 7.28-7.24 (m, 1H), 4.00 (s, 3H), 3.85 (s, 3H), 2.62 (s, 3H). Analytical LC/MS (Method 3): Observed Mass: 351.1; Retention Time: 0.79 min.

Step B. Intermediate 23B. Preparation of tert-butyl 4-(2-(3-fluoro-4-methoxyphenyl)-1,4-dimethyl-1H-benzo[d]imidazol-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate

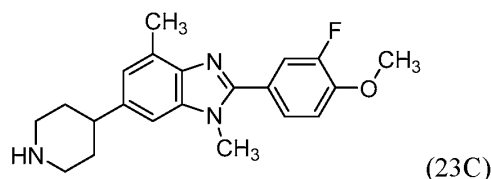


(23B)

Intermediate 23B was synthesized according to methods described for the preparation of Intermediate 22B, using Intermediate 23A (350 mg, 1.0 mmol) as starting

material to afford the title compound (0.45 g, 1.0 mmol, 100 % yield) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.62-7.55 (m, 2H), 7.42-7.38 (m, 1H), 7.37-7.31 (m, 1H), 7.27-7.23 (m, 1H), 6.22-6.14 (m, 1H), 4.18-4.08 (m, 2H), 4.00 (s, 3H), 3.88 (s, 3H), 3.74-3.66 (m, 2H), 2.68-2.63 (m, 2H), 2.64 (s, 3H), 1.22 (s, 9H). Analytical
5 LC/MS (Method 3): Observed Mass: 452.4; Retention Time: 0.90 min.

Step C. Intermediate 23C. Preparation of 2-(3-fluoro-4-methoxyphenyl)-1,4-dimethyl-6-(piperidin-4-yl)-1H-benzo[d]imidazole dihydrochloride



10 Intermediate 23C was synthesized according to methods described for the preparation of Intermediate 22C, using Intermediate 23B (0.45 g, 1.0 mmol) as starting material to afford the title compound (420 mg, 0.99 mmol, 99 % yield) as a tan solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.81-7.75 (m, 2H), 7.71 (s, 1H), 7.54-7.48 (m, 1H), 7.46 (s, 1H), 4.11 (s, 3H), 4.07 (s, 3H), 3.61-3.56 (m, 2H), 3.28-3.16 (m, 3H), 2.71 (s,
15 3H), 2.25-2.16 (m, 2H), 2.16-2.03 (m, 2H). Analytical LC/MS (Method 3): Observed Mass: 354.3; Retention Time: 0.58 min.

Step D. Example 23

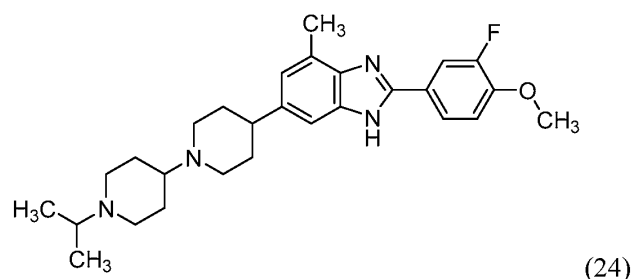
To a 40 mL vial were added Intermediate 23C (60 mg, 0.14 mmol), 1-
20 isopropylpiperidin-4-one (100 mg, 0.71 mmol), AcOH (9.6 mg, 0.16 mmol), magnesium sulfate (220 mg, 1.8 mmol), and DMF (2 mL). The reaction mixture was stirred for 20 min, then sodium triacetoxyborohydride (150 mg, 0.71 mmol) was added and the reaction mixture was stirred. After 18 h, the reaction mixture was filtered and the filter cake was washed with 10% IPA/chloroform (20 mL). The filtrate was washed with 10% aqueous
25 NaOH (10 mL), brine, dried over MgSO₄, filtered and concentrated. The crude material was purified via preparative HPLC (Prep Method 1) to afford the title compound (48 mg, 0.10 mmol, 71 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 7.73-7.67 (m, 1H), 7.66-7.60 (m, 1H), 7.40-7.33 (m, 1H), 7.29-7.23 (m, 1H), 6.99-6.93 (m, 1H), 3.95 (s, 3H), 3.84 (s, 3H), 3.41-3.26 (m, 2H), 3.06-2.99 (m, 2H), 2.96-2.87 (m, 2H), 2.82-2.72 (m, 1H), 2.63-

2.58 (m, 1H), 2.33-2.27 (m, 2H), 2.25-2.16 (m, 2H), 1.85-1.75 (m, 5H), 1.56-1.42 (m, 2H), 1.00 (br d, $J=6.4$ Hz, 6H) (three protons obscured). TLR9 IC₅₀ (nM) = 160.
 Analytical LC/MS (Method 1): Purity: 99.2 %; Observed Mass: 479.19; Retention Time: 0.98 min. (Method 2): Purity: 98.1 %; Observed Mass: 479.19; Retention Time: 1.36 min.

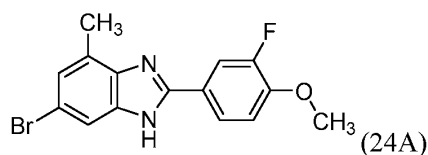
5

EXAMPLE 24

2-(3-fluoro-4-methoxyphenyl)-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole

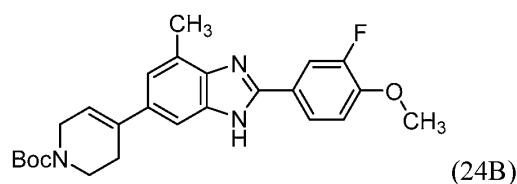


10 Step A. Intermediate 24A. Preparation of 6-bromo-2-(3-fluoro-4-methoxyphenyl)-4-methyl-1H-benzo[d]imidazole



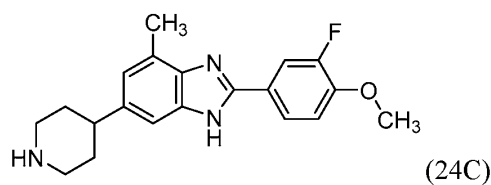
Intermediate 24A was synthesized according to the general procedures described for the preparation of Intermediate 11A, using 5-bromo-3-methylbenzene-1,2-diamine (340 mg, 1.7 mmol) as starting material and substituting 3-fluoro-4-methoxybenzaldehyde (320 mg, 2.1 mmol) where appropriate to afford the title compound (340 mg, 1.0 mmol, 59 % yield) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.96-7.88 (m, 2H), 7.65-7.51 (m, 1H), 7.32-7.27 (m, 1H), 7.23-7.18 (m, 1H), 3.99 (s, 3H), 2.62 (s, 3H). Analytical LC/MS (Method 3): Observed Mass: 337.0; Retention Time: 0.79 min.

Step B. Intermediate 24B. Preparation of tert-butyl 4-(2-(3-fluoro-4-methoxyphenyl)-4-methyl-1H-benzo[d]imidazol-6-yl)-3,6-dihydropyridine-1(2H)-carboxylate



Intermediate 24B was synthesized according to the general procedures described for the preparation of Intermediate 11B, using Intermediate 24A (340 mg, 1.0 mmol) as starting material to provide the title compound (430 mg, 0.98 mmol, 98 % yield) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.97-7.86 (m, 2H), 7.56-7.33 (m, 1H), 7.31-7.25 (m, 1H), 7.21-7.16 (m, 1H), 6.14-6.07 (m, 1H), 4.11 (br s, 2H), 3.98 (s, 3H), 3.72-3.65 (m, 2H), 2.65-2.59 (m, 5H), 1.53 (s, 9H). Analytical LC/MS (Method 3): Observed Mass: 438.4; Retention Time: 0.89 min.

Step C. Intermediate 24C. Preparation of 2-(3-fluoro-4-methoxyphenyl)-4-methyl-6-(piperidin-4-yl)-1H-benzo[d]imidazole dihydrochloride



Intermediate 24C was synthesized according to the general procedures described for the preparation of Intermediate 11D (Steps C-D), using Intermediate 24B (430 mg, 0.98 mmol) as starting material to afford the title compound (260 mg, 0.63 mmol, 64 % yield over two steps) as a tan solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.07-8.00 (m, 2H), 7.56-7.53 (m, 1H), 7.52-7.47 (m, 1H), 7.39-7.37 (m, 1H), 4.06 (s, 3H), 3.63-3.56 (m, 2H), 3.26-3.19 (m, 2H), 3.19-3.11 (m, 1H), 2.73 (s, 3H), 2.22-2.14 (m, 2H), 2.10-1.98 (m, 2H). Analytical LC/MS (Method 3): Observed Mass: 340.2; Retention Time: 0.59 min.

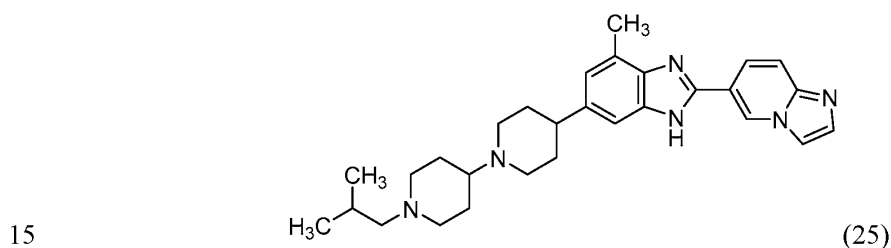
Step D. Example 24

To a 40 mL vial were added Intermediate 24C (62 mg, 0.15 mmol), 1-isopropylpiperidin-4-one (100 mg, 0.71 mmol), AcOH (9.6 mg, 0.16 mmol), magnesium sulfate (220 mg, 1.8 mmol), and DMF (2 mL). The reaction mixture was stirred for 20 min, then sodium triacetoxyborohydride (160 mg, 0.75 mmol) was added and the reaction

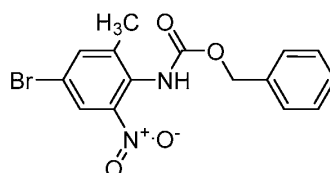
mixture was stirred. After 18 h, the reaction mixture was filtered and the filter cake was washed with 10% IPA/chloroform (20 mL). The filtrate was washed with 10% aqueous NaOH (10 mL), brine, dried over MgSO₄, filtered and concentrated. The crude material was purified via preparative HPLC (Prep Method 1) to afford the title compound (60 mg, 0.13 mmol, 87 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 8.09-7.91 (m, 2H), 7.41-7.32 (m, 1H), 7.30-7.11 (m, 1H), 6.89 (br s, 1H), 3.94 (s, 3H), 3.06-2.99 (m, 2H), 2.98-2.90 (m, 2H), 2.89-2.76 (m, 1H), 2.56 (s, 3H), 2.41-2.19 (m, 5H), 1.87-1.78 (m, 5H), 1.74-1.65 (m, 2H), 1.57-1.46 (m, 2H), 1.02 (br d, *J*=6.4 Hz, 6H). TLR9 IC₅₀ (nM) = 48. Analytical LC/MS (Method 1): Purity: 99.1 %; Observed Mass: 464.93; Retention Time: 1.03 min. (Method 2): Purity: 100 %; Observed Mass: 464.92; Retention Time: 1.34 min.

EXAMPLE 25

2-(imidazo[1,2-a]pyridin-6-yl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole



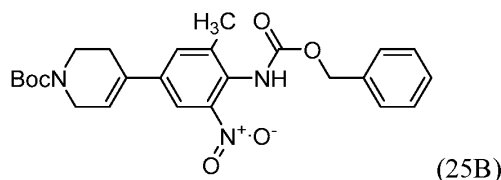
Step A. Intermediate 25A. Preparation of benzyl (4-bromo-2-methyl-6-nitrophenyl)carbamate



To a 500 mL pear shaped flask were added DCM (70 mL) and triphosgene (11 g, 37 mmol). To this mixture was dropwise added 4-bromo-2-methyl-6-nitroaniline (8.1 g, 35 mmol) dissolved in DCM (70 mL). After addition was complete, a solution of TEA (8.1 g, 80 mmol) dissolved in DCM (20 mL) was added dropwise. After stirring 2 h, the solvent was concentrated and the residue was purified by flash column chromatography (220 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100%B; flow rate

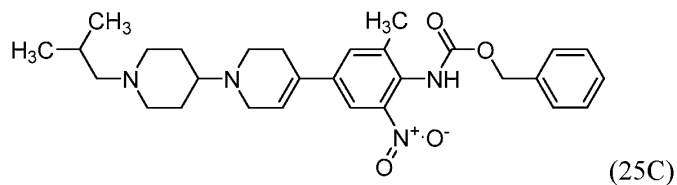
= 120 mL/min). Fractions corresponding to the desired intermediate were combined and concentrated. The resultant residue was dissolved in THF (150 mL), then benzyl alcohol (7.9 g, 73 mmol) was added and the mixture was stirred at reflux. After 18 h, the reaction mixture was cooled, the solvent was concentrated and the residue was purified by flash column chromatography (220 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100%B; flow rate = 120 mL/min). Fractions corresponding to desired product were combined, concentrated and dried in vacuo to afford the title compound (12 g, 33 mmol, 94 % yield) as a pale yellow solid. ¹H NMR (500 MHz, CHLOROFORM-d) δ 8.02-7.98 (m, 1H), 7.67 (d, *J*=1.6 Hz, 1H), 7.66-7.55 (m, 1H), 7.42-7.35 (m, 5H), 5.21 (s, 2H), 2.36 (s, 3H).

Step B. Intermediate 25B. Preparation of tert-butyl 4-(4-(((benzyloxy)carbonyl)amino)-3-methyl-5-nitrophenyl)-3,6-dihydropyridine-1(2H)-carboxylate



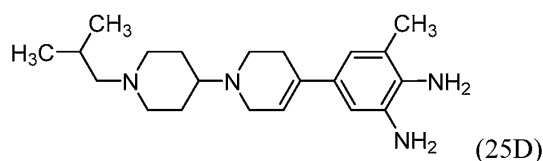
To a 500 mL pear shaped flask were added Intermediate 25A (12 g, 33 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (11 g, 36 mmol), 1,4-dioxane (150 mL), followed by potassium phosphate tribasic (25 g, 120 mmol) dissolved in water (30 mL). The vessel was flushed with N₂, then 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (1.4 g, 1.7 mmol) was added and the reaction mixture was stirred at 85 °C. After 18 h, the reaction mixture was cooled, diluted with water (400 mL) and extracted with EtOAc (2x200 mL). The organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (330 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100%B; flow rate = 120 mL/min). Fractions corresponding to desired product were combined, concentrated and dried in vacuo to afford the title compound (15 g, 32 mmol, 97 % yield) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.79-7.77 (m, 1H), 7.64-7.61 (m, 1H), 7.45-7.32 (m, 5H), 6.27-6.20 (m, 1H), 5.22-5.13 (m, 2H), 4.12-4.06 (m, 2H), 3.67-3.61 (m, 2H), 2.56-2.51 (m, 2H), 2.34 (s, 3H), 1.51 (s, 9H).

Step C. Intermediate 25C. Preparation of benzyl (4-(1-(1-isobutylpiperidin-4-yl)-1,2,3,6-tetrahydropyridin-4-yl)-2-methyl-6-nitrophenyl)carbamate bis(2,2,2-trifluoroacetate)



- 5 To a 500 mL pear shaped flask were added Intermediate 25B (15 g, 32 mmol), MeOH (30 mL) and 4 M HCl in dioxane (100 mL). After stirring 30 min, the solvent was concentrated and the residue was co-evaporated with toluene (2x). The resultant residue was dissolved in DMF (150 mL), and to this mixture was added 1-(2-methylpropyl)-4-piperidone (11 g, 71 mmol), MgSO₄ (60 g, 500 mmol), and AcOH (2.1 g, 35 mmol).
- 10 After stirring for 10 min, sodium triacetoxyborohydride (21 g, 100 mmol) was added and the reaction mixture was stirred under N₂. After 18 h, the reaction mixture was filtered and the filter cake was washed with 10%IPA/CHCl₃. The filtrate was concentrated and the remaining DMF solution was loaded onto Celite cartridges and purified by flash column chromatography (3x275 g reverse phase C18 GOLD silica gel cartridge; A =
- 15 water:MeCN:TFA 90:10:0.05%, B = water:MeCN:TFA 10:90:0.05%; 20 min grad.; 10% B to 100%B; flow rate = 120 mL/min). The fractions corresponding to product were combined, concentrated, the residue was co-evaporated with toluene (2x), and the product was dried in vacuo to afford the title compound (15 g, 20 mmol, 63 % yield) as a tan solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.88-7.86 (m, 1H), 7.72-7.69 (m, 1H),
- 20 7.46-7.31 (m, 5H), 6.34-6.29 (m, 1H), 5.27-5.13 (m, 2H), 4.06-3.96 (m, 2H), 3.87-3.73 (m, 2H), 3.67-3.51 (m, 3H), 3.17-3.05 (m, 2H), 3.05-2.99 (m, 2H), 2.96-2.90 (m, 2H), 2.53-2.42 (m, 2H), 2.38 (s, 3H), 2.29-2.15 (m, 3H), 1.10-1.06 (m, 6H). Analytical LC/MS (Method 3): Observed Mass: 507.3; Retention Time: 0.68 min.

- 25 Step D. Intermediate 25D. Preparation of 5-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-3-methylbenzene-1,2-diamine



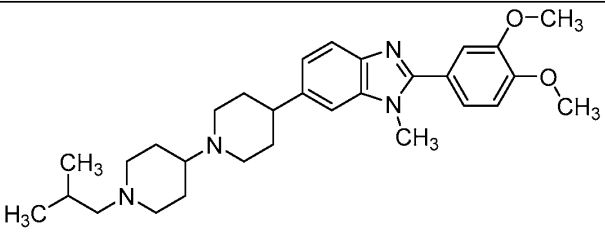
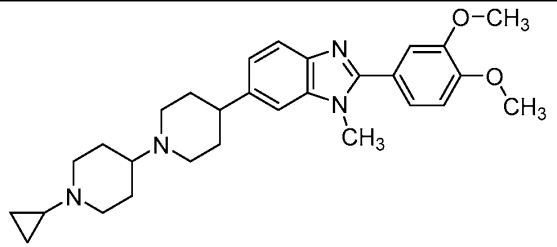
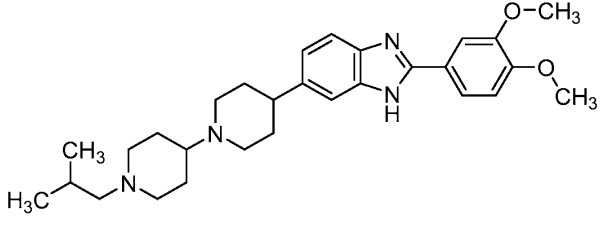
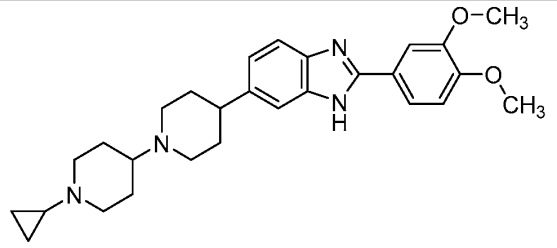
- To a 2 L round bottomed flask were added Intermediate 25C (15 g, 20 mmol), and MeOH (500 mL). The vessel was evacuated and purged with N₂, then Pd-C (5% wt.) (2.7 g, 1.3 mmol) was added and the reaction mixture was stirred under hydrogen at 1 atm.
- 5 After 18 h, the reaction mixture was filtered and to the filtrate was added Dowex 550A (OH) anion exchange resin (50 g) and stirred. After 2 h, the resin was filtered, and the filtrate was concentrated. The residue was dissolved in MeOH (500 mL), the vessel was evacuated and purged with N₂, then Pd-C (5% wt.) (2.7 g, 1.3 mmol) was added and the reaction mixture was stirred under hydrogen at 1 atm. After 18 h, the catalyst was
- 10 filtered, the filtrate was concentrated and the product was dried in vacuo to afford the title compound (6.2 g, 18 mmol, 90 % yield) as a tan solid. ¹H NMR (500 MHz, DMSO-d₆) δ 6.30-6.27 (m, 1H), 6.19-6.16 (m, 1H), 3.05-2.90 (m, 2H), 2.89-2.79 (m, 2H), 2.30-2.12 (m, 4H), 1.82 (br s, 2H), 1.71 (br s, 6H), 1.55-1.38 (m, 5H), 0.84 (d, *J*=6.6 Hz, 6H) (three protons obscured). Analytical LC/MS (Method 3): Observed Mass: 345.3; Retention
- 15 Time: 0.58 min.

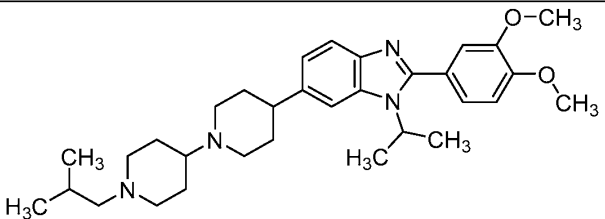
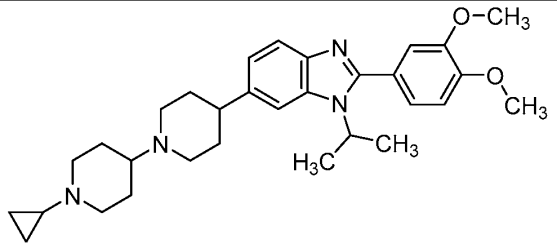
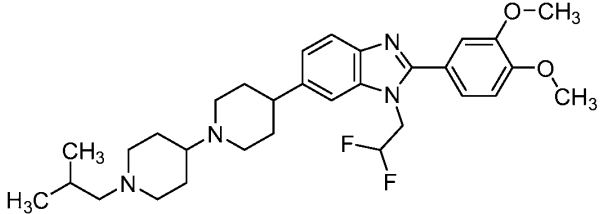
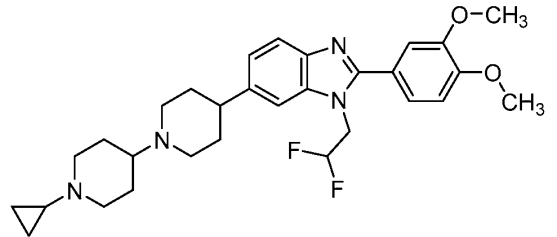
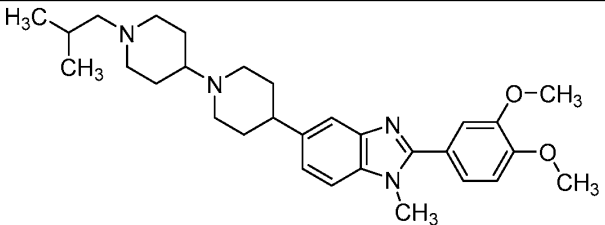
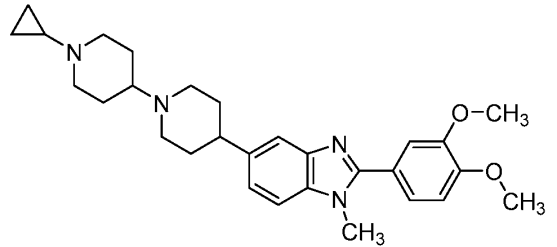
Step E. Example 25

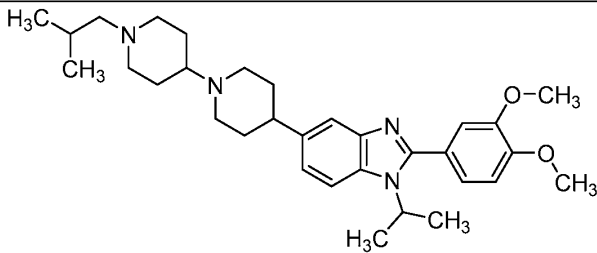
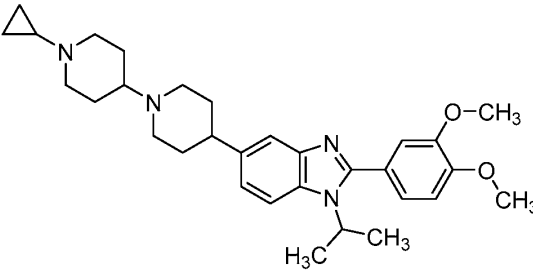
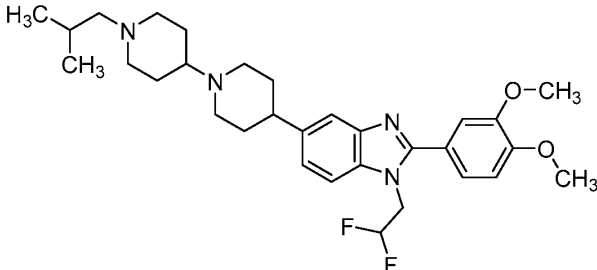
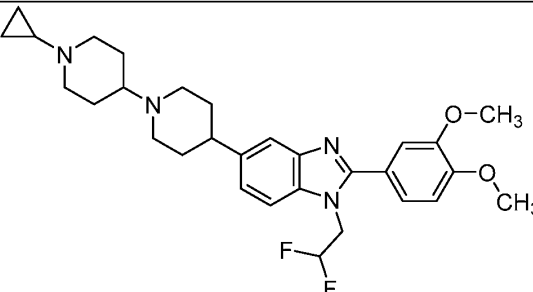
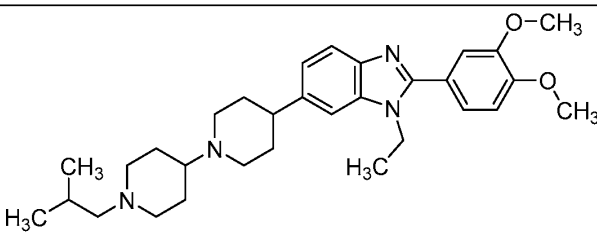
- To a 40 mL vial were added Intermediate 25D (52 mg, 0.15 mmol) and NMP (2 mL). To this mixture was added sodium metabisulfite (42 mg, 0.22 mmol), followed by
- 20 imidazo[1,2-a]pyridine-6-carbaldehyde (22 mg, 0.15 mmol). The vial was capped and the reaction mixture was stirred at 70 °C. After 20 h, the solution was filtered, and the filtrate was diluted with water (20 mL) and extracted with EtOAc (2x10 mL). The organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The crude material was purified via preparative HPLC (Prep Method 1) to
- 25 afford the title compound (42 mg, 0.089 mmol, 59 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 9.44-9.30 (m, 1H), 8.15-8.08 (m, 1H), 8.07-7.92 (m, 1H), 7.77-7.71 (m, 1H), 7.70-7.64 (m, 1H), 7.33-7.15 (m, 1H), 6.96-6.88 (m, 1H), 3.02-2.94 (m, 2H), 2.89-2.80 (m, 2H), 2.56-2.54 (m, 3H), 2.31-2.17 (m, 3H), 2.03-1.96 (m, 2H), 1.86-1.63 (m, 9H), 1.52-1.40 (m, 2H), 0.84 (d, *J*=6.5 Hz, 6H) (one proton obscured). TLR9 IC₅₀ (nM) = 160.

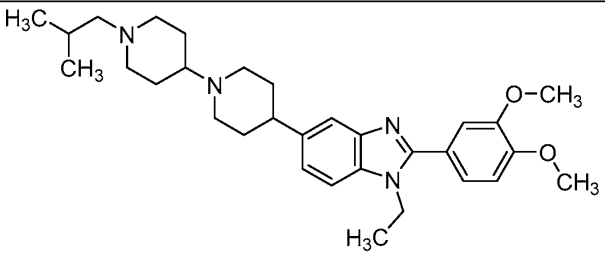
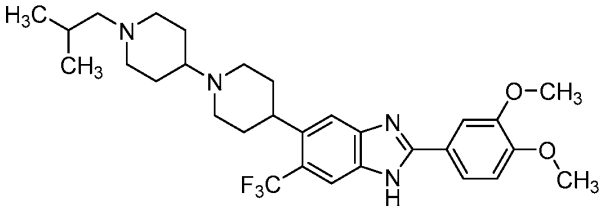
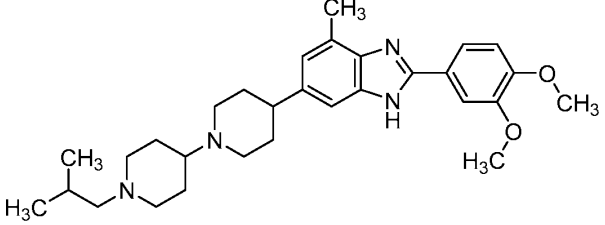
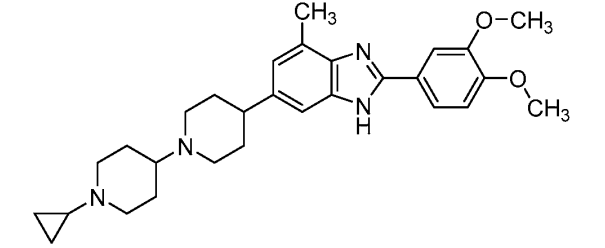
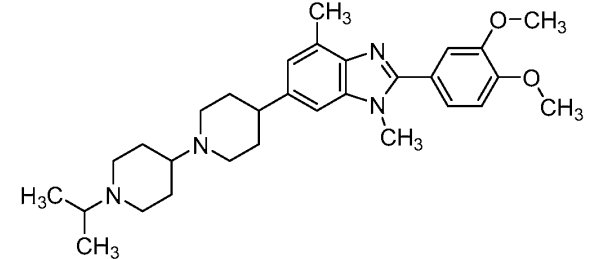
Analytical LC/MS (Method 1): Purity: 95 %; Observed Mass: 470.93; Retention Time: 0.86 min. (Method 2): Purity: 98.4 %; Observed Mass: 469.17; Retention Time: 1.35 min.

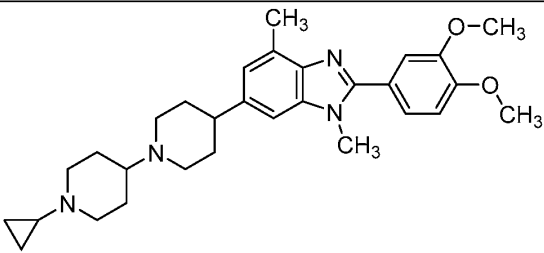
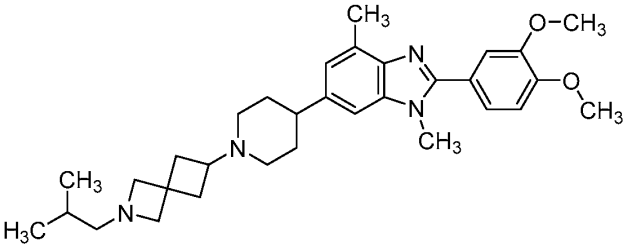
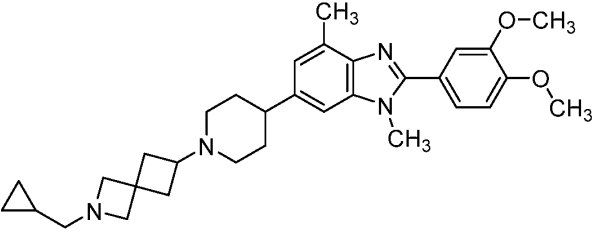
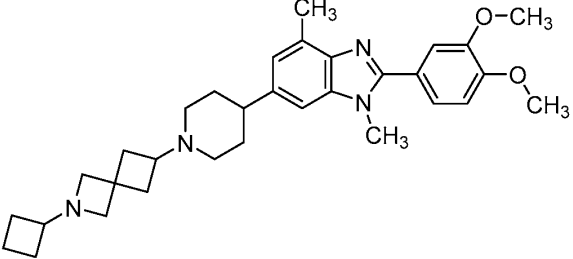
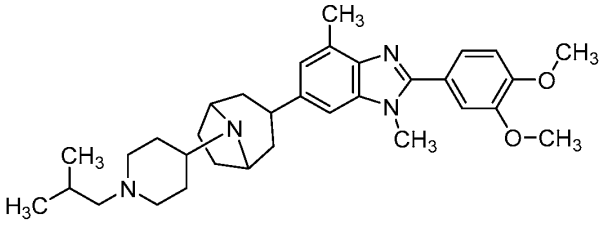
The following Examples were prepared according to the general methods
5 described elsewhere herein using appropriate starting materials, reagents and conditions.

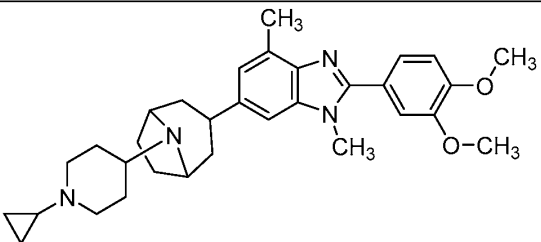
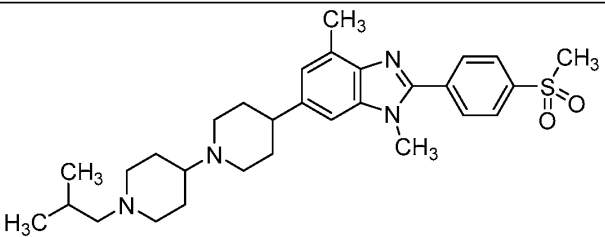
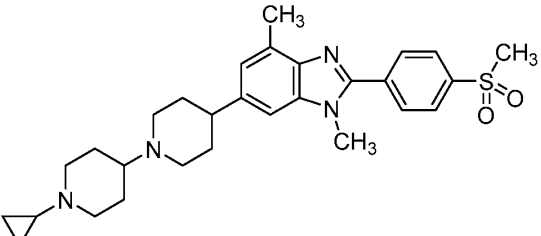
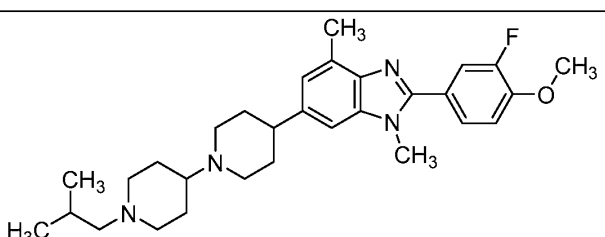
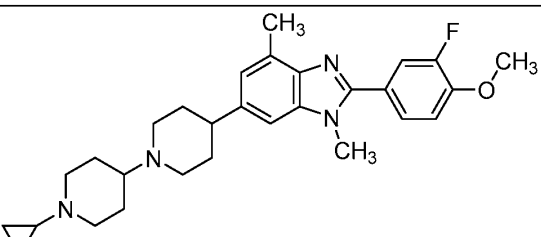
Ex. No.	Structure	Prep Method
26		Ex. 1 Step G
27		Ex. 1 Step G
28		Ex. 2 Step E
29		Ex. 2 Step E

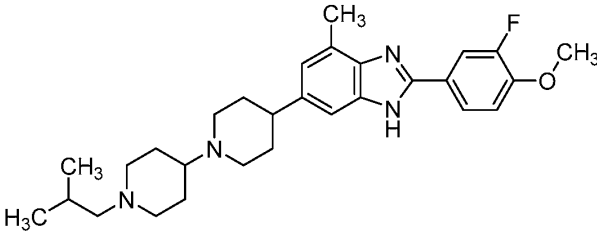
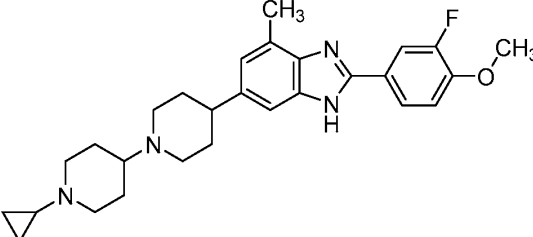
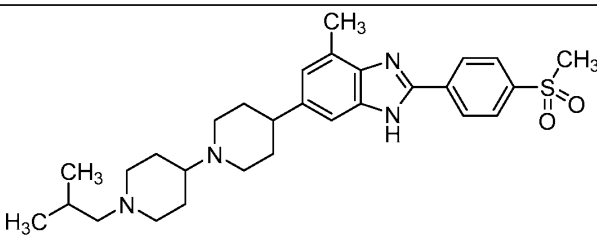
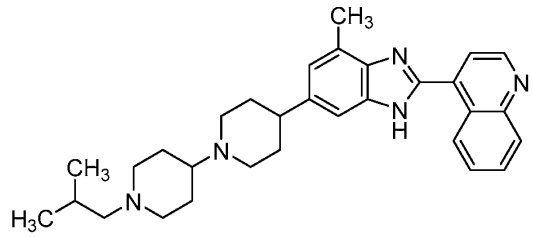
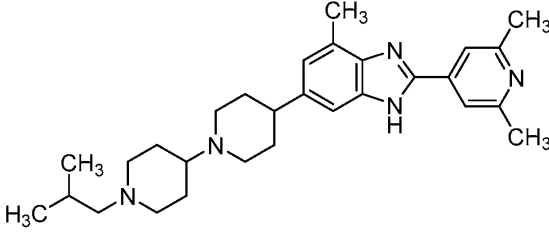
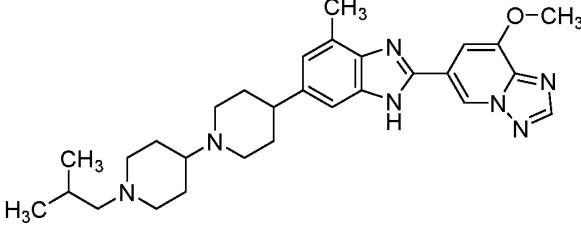
30		Ex. 3 Step F
31		Ex. 3 Step F
32		Ex. 4 Step F
33		Ex. 4 Step F
34		Ex. 5 Step G
35		Ex. 5 Step G

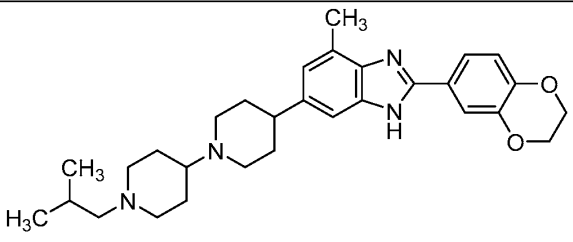
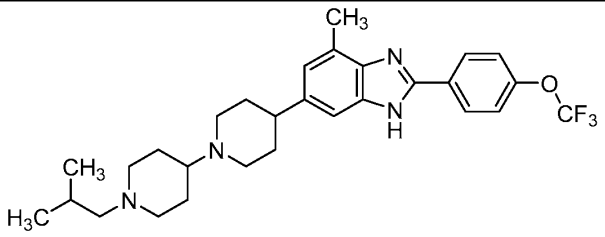
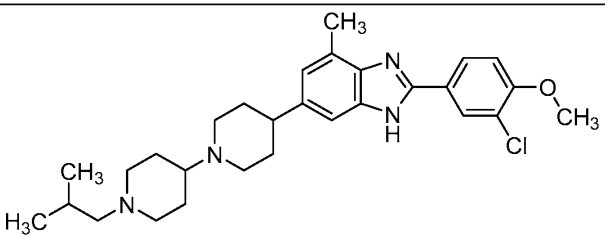
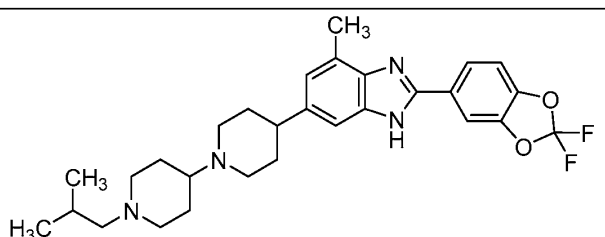
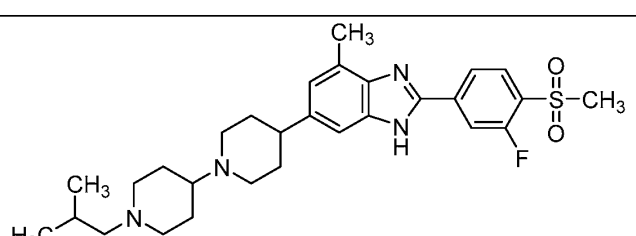
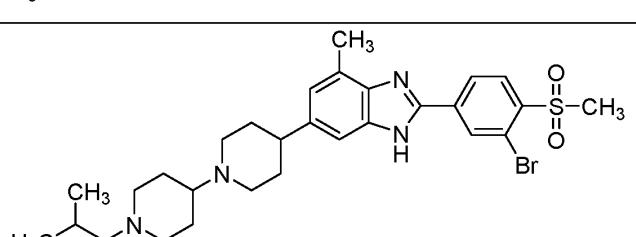
36		Ex. 6 Step F
37		Ex. 6 Step F
38		Ex. 7 Step G
39		Ex. 7 Step G
40		Ex. 8-9 Step C

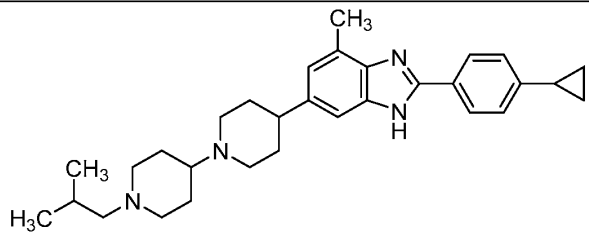
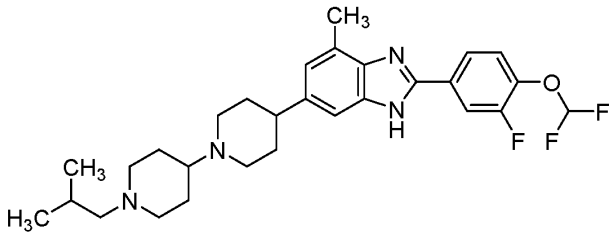
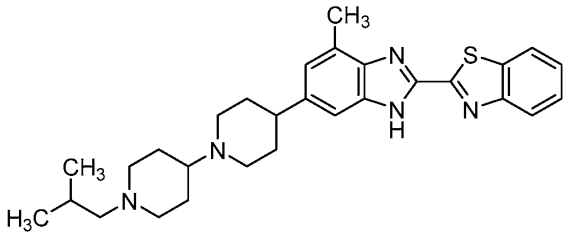
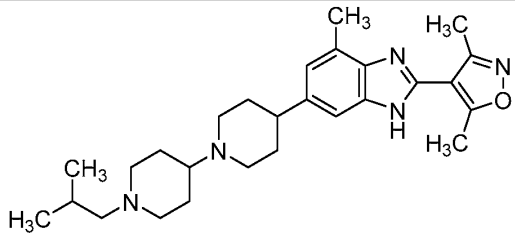
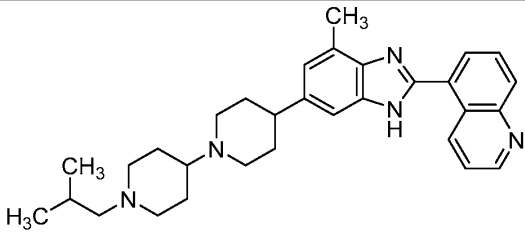
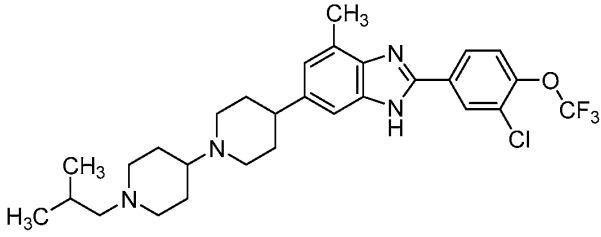
41		Ex. 8-9 Step C
42		Ex. 10 Step F
43		Ex. 11 Step E
44		Ex. 11 Step E
45		Ex. 15 Step F

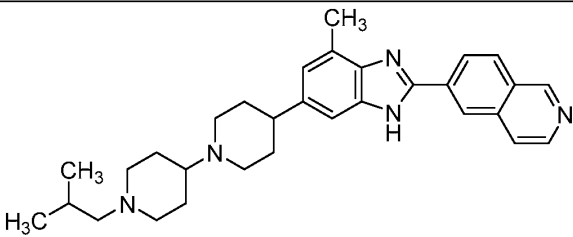
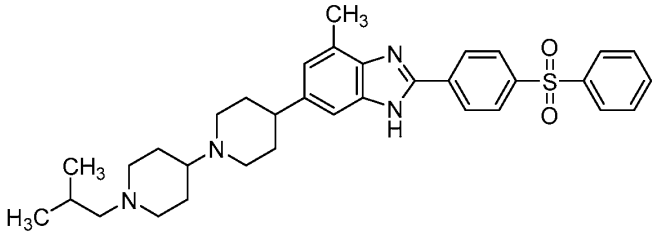
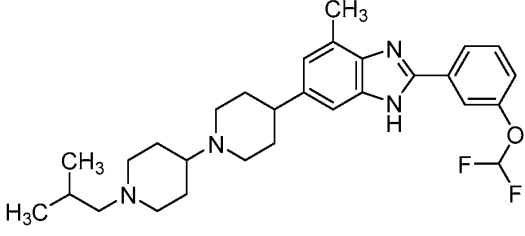
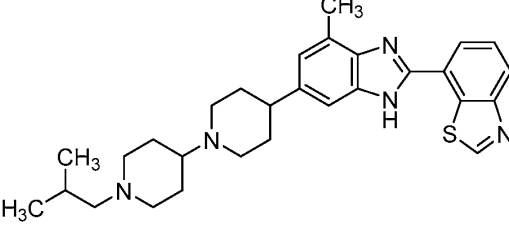
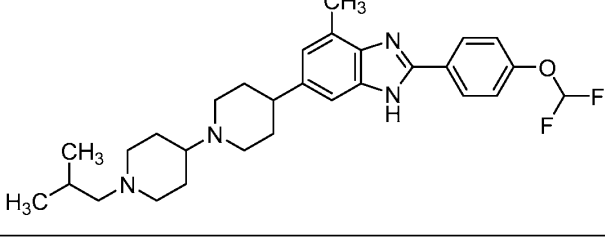
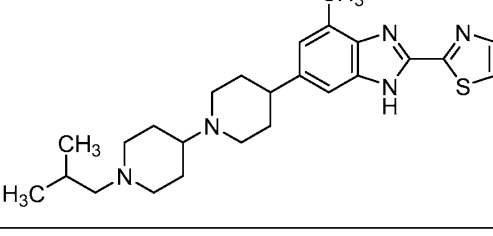
46		Ex. 15 Step F
47		Ex. 16 Step B
48		Ex. 16 Step B
49		Ex. 16 Step B
50		Ex. 21 Step E

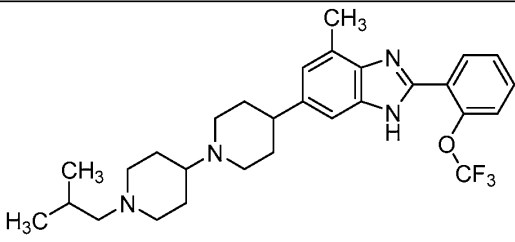
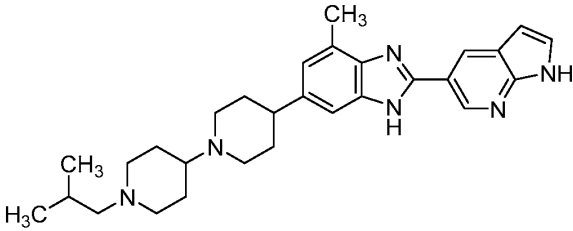
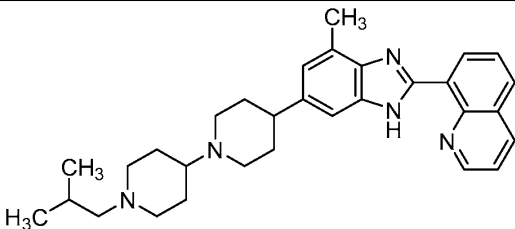
51		Ex. 21 Step E
52		Ex. 22 Step D
53		Ex. 22 Step D
54		Ex. 23 Step D
55		Ex. 23 Step D

56		Ex. 24 Step D
57		Ex. 24 Step D
58		Ex. 25 Step E
59		Ex. 25 Step E
60		Ex. 25 Step E
61		Ex. 25 Step E

62	 <chem>CC(C)CN1CCN(CC1)C2CCN(CC2)C3=CC=C(C=C3C4=CC=CC=C4N5C(=N5)C6=CC=CC=C6O7COC6=O7)C</chem>	Ex. 25 Step E
63	 <chem>CC(C)CN1CCN(CC1)C2CCN(CC2)C3=CC=C(C=C3C4=CC=CC=C4N5C(=N5)C6=CC=C(C=C6)OC(F)(F)F)C</chem>	Ex. 25 Step E
64	 <chem>CC(C)CN1CCN(CC1)C2CCN(CC2)C3=CC=C(C=C3C4=CC=CC=C4N5C(=N5)C6=CC=C(C=C6)OC)C7=CC=CC=C7Cl</chem>	Ex. 25 Step E
65	 <chem>CC(C)CN1CCN(CC1)C2CCN(CC2)C3=CC=C(C=C3C4=CC=CC=C4N5C(=N5)C6=CC=CC=C6O7C(F)(F)O7C6=O)C</chem>	Ex. 25 Step E
66	 <chem>CC(C)CN1CCN(CC1)C2CCN(CC2)C3=CC=C(C=C3C4=CC=CC=C4N5C(=N5)C6=CC=C(C=C6)S(=O)(=O)C)C7=CC=CC=C7F</chem>	Ex. 25 Step E
67	 <chem>CC(C)CN1CCN(CC1)C2CCN(CC2)C3=CC=C(C=C3C4=CC=CC=C4N5C(=N5)C6=CC=C(C=C6)S(=O)(=O)C)C7=CC=CC=C7Br</chem>	Ex. 25 Step E

68		Ex. 25 Step E
69		Ex. 25 Step E
70		Ex. 25 Step E
71		Ex. 25 Step E
72		Ex. 25 Step E
73		Ex. 25 Step E

74	 <chem>CC(C)CN1CCN(CC1)C2CCN(CC2)C3CC(C)C=C4C(=C3)N=C(NC4=CC5=CC=CC=C5N6C=CC=CC=C6N)C7=CC=CC=C7N8C=CC=CC=C8</chem>	Ex. 25 Step E
75	 <chem>CC(C)CN1CCN(CC1)C2CCN(CC2)C3CC(C)C=C4C(=C3)N=C(NC4=CC=C(C=C4)S(=O)(=O)C5=CC=CC=C5)C6=CC=CC=C6N7C=CC=CC=C7N8C=CC=CC=C8</chem>	Ex. 25 Step E
76	 <chem>CC(C)CN1CCN(CC1)C2CCN(CC2)C3CC(C)C=C4C(=C3)N=C(NC4=CC=C(C=C4)OC(F)F)C5=CC=CC=C5N6C=CC=CC=C6N7C=CC=CC=C7N8C=CC=CC=C8</chem>	Ex. 25 Step E
77	 <chem>CC(C)CN1CCN(CC1)C2CCN(CC2)C3CC(C)C=C4C(=C3)N=C(NC4=CC=C(C=C4)C5=CC6=CC=CC=C6N7C=CC=CC=C7S5)C8=CC=CC=C8N9C=CC=CC=C9</chem>	Ex. 25 Step E
78	 <chem>CC(C)CN1CCN(CC1)C2CCN(CC2)C3CC(C)C=C4C(=C3)N=C(NC4=CC=C(C=C4)OC(F)F)C5=CC=CC=C5N6C=CC=CC=C6N7C=CC=CC=C7N8C=CC=CC=C8</chem>	Ex. 25 Step E
79	 <chem>CC(C)CN1CCN(CC1)C2CCN(CC2)C3CC(C)C=C4C(=C3)N=C(NC4=CC=C(C=C4)C5=CC=C(C=C5)S6C=NC=CS6)C7=CC=CC=C7N8C=CC=CC=C8</chem>	Ex. 25 Step E

80		Ex. 25 Step E
81		Ex. 25 Step E
82		Ex. 25 Step E

Ex. No.	Analytical LC/MS, Prep Method, Yield, and ¹ H NMR
26	Analytical LC/MS (Method 1): Purity: 99.4 %; Observed Mass: 491.33; Retention Time: 0.66 min. (Method 2): Purity: 98.7 %; Observed Mass: 491.00; Retention Time: 1.44 min. Prep Method 1: 15 mg, 0.031 mmol, 36 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.56 (d, <i>J</i> =8.2 Hz, 1H), 7.45 (s, 1H), 7.41-7.36 (m, 2H), 7.14 (dd, <i>J</i> =8.2, 3.7 Hz, 2H), 3.89-3.84 (m, 9H), 3.06-2.99 (m, 2H), 2.92-2.85 (m, 2H), 2.70-2.58 (m, 2H), 2.35-2.23 (m, 3H), 2.05-1.98 (m, 2H), 1.89-1.80 (m, 4H), 1.80-1.70 (m, 4H), 1.55-1.44 (m, 2H), 0.86 (d, <i>J</i> =6.7 Hz, 6H). TLR9 IC ₅₀ (nM) = 130

27	Analytical LC/MS (Method 1): Purity: 95.6 %; Observed Mass: 475.29; Retention Time: 0.94 min. (Method 2): Purity: 94.9 %; Observed Mass: 474.95; Retention Time: 1.38 min. Prep Method 1: 31 mg, 0.065 mmol, 76 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.31 (d, <i>J</i>=8.2 Hz, 1H), 7.19 (s, 1H), 7.14 (s, 2H), 6.90 (br s, 2H), 3.66-3.56 (m, 9H), 2.85-2.71 (m, 3H), 2.46-2.37 (m, 1H), 2.20-2.06 (m, 3H), 1.95-1.87 (m, 2H), 1.63-1.47 (m, 6H), 1.39-1.30 (m, 1H), 1.26-1.12 (m, 2H), 0.20-0.13 (m, 2H), 0.07-0.01 (m, 2H) (one proton obscured). TLR9 IC₅₀ (nM) = 110
28	Analytical LC/MS (Method 1): Purity: 98.9 %; Observed Mass: 476.97; Retention Time: 1.00 min. (Method 2): Purity: 99.3 %; Observed Mass: 476.98; Retention Time: 1.39 min. Prep Method 1: 26 mg, 0.055 mmol, 37 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.76-7.73 (m, 1H), 7.72-7.68 (m, 1H), 7.53-7.48 (m, 1H), 7.44-7.39 (m, 1H), 7.15-7.08 (m, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 3.21-3.15 (m, 2H), 3.00-2.93 (m, 2H), 2.76-2.64 (m, 2H), 2.11 (br s, 2H), 2.02-1.95 (m, 2H), 1.89-1.73 (m, 8H), 1.63-1.52 (m, 3H), 0.88-0.85 (m, 6H). TLR9 IC₅₀ (nM) = 19
29	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 460.95; Retention Time: 1.05 min. (Method 2): Purity: 100 %; Observed Mass: 461.15; Retention Time: 1.32 min. Prep Method 1: 55 mg, 0.12 mmol, 80 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.73 (br d, <i>J</i>=0.9 Hz, 1H), 7.72-7.68 (m, 1H), 7.60-7.40 (m, 2H), 7.12 (br d, <i>J</i>=8.2 Hz, 2H), 3.88 (s, 3H), 3.83 (s, 3H), 3.32-3.22 (m, 2H), 3.07-3.00 (m, 2H), 2.81-2.64 (m, 5H), 2.24-2.15 (m, 2H), 1.89-1.78 (m, 4H), 1.64-1.59 (m, 1H), 1.55-1.47 (m, 2H), 0.43 (br d, <i>J</i>=4.6 Hz, 2H), 0.32 (br s, 2H) (one proton obscured). TLR9 IC₅₀ (nM) = 110

30	Analytical LC/MS (Method 1): Purity: 98.9 %; Observed Mass: 519.31; Retention Time: 1.03 min. (Method 2): Purity: 100 %; Observed Mass: 519.00; Retention Time: 1.56 min. Prep Method 1: 51 mg, 0.098 mmol, 70 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.63-7.56 (m, 2H), 7.20-7.12 (m, 4H), 4.83-4.72 (m, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.60-3.52 (m, 1H), 3.38-3.26 (m, 1H), 3.10-2.97 (m, 2H), 2.94-2.60 (m, 4H), 2.29-2.03 (m, 4H), 2.02-1.79 (m, 7H), 1.72-1.63 (m, 2H), 1.61 (s, 3H), 1.59 (s, 3H), 0.89 (s, 3H), 0.88 (s, 3H). TLR9 IC₅₀ (nM) = 250
31	Analytical LC/MS (Method 1): Purity: 99.5 %; Observed Mass: 503.21; Retention Time: 1.01 min. (Method 2): Purity: 98.6 %; Observed Mass: 502.97; Retention Time: 1.50 min. Prep Method 1: 60 mg, 0.12 mmol, 86 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.35-7.29 (m, 2H), 6.94-6.85 (m, 4H), 4.59-4.45 (m, 1H), 3.60 (s, 3H), 3.58 (s, 3H), 2.92-2.82 (m, 1H), 2.78-2.72 (m, 2H), 2.52-2.39 (m, 1H), 2.24-2.11 (m, 2H), 1.96-1.87 (m, 2H), 1.67-1.59 (m, 2H), 1.58-1.48 (m, 4H), 1.35 (s, 3H), 1.33 (s, 3H), 1.25-1.15 (m, 2H), 0.19-0.12 (m, 2H), 0.08-0.01 (m, 2H) (three protons obscured). TLR9 IC₅₀ (nM) = 750
32	Analytical LC/MS (Method 1): Purity: 95.9 %; Observed Mass: 540.98; Retention Time: 1.03 min. (Method 2): Purity: 92.9 %; Observed Mass: 540.96; Retention Time: 1.55 min. Prep Method 1: 59 mg, 0.11 mmol, 79 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.63-7.56 (m, 1H), 7.54-7.49 (m, 1H), 7.32-7.26 (m, 2H), 7.24-7.12 (m, 2H), 6.56-6.29 (m, 1H), 4.81-4.70 (m, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.05-2.95 (m, 2H), 2.91-2.82 (m, 2H), 2.64-2.55 (m, 1H), 2.33-2.19 (m, 3H), 2.03-1.98 (m, 2H), 1.87-1.78 (m, 4H), 1.78-1.65 (m, 5H), 1.54-1.42 (m, 2H), 0.86 (d, J=6.4 Hz, 6H). TLR9 IC₅₀ (nM) = 210

33	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 525.02; Retention Time: 1.02 min. (Method 2): Purity: 100 %; Observed Mass: 525.29; Retention Time: 1.53 min. Prep Method 1: 68 mg, 0.13 mmol, 93 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.61-7.56 (m, 1H), 7.54-7.50 (m, 1H), 7.31-7.26 (m, 2H), 7.24-7.19 (m, 1H), 7.17-7.12 (m, 1H), 6.41 (br s, 1H), 4.75 (br s, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.11-2.93 (m, 4H), 2.70-2.60 (m, 1H), 2.46-2.31 (m, 3H), 2.21-2.10 (m, 2H), 1.89-1.81 (m, 2H), 1.80-1.67 (m, 4H), 1.61-1.55 (m, 1H), 1.49-1.38 (m, 2H), 0.45-0.37 (m, 2H), 0.29 (br s, 2H). TLR9 IC₅₀ (nM) = 680
34	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 490.96; Retention Time: 1.05 min. (Method 2): Purity: 100 %; Observed Mass: 490.97; Retention Time: 1.50 min. Prep Method 1: 4.6 mg, 0.0094 mmol, 11 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.56-7.51 (m, 2H), 7.39 (s, 2H), 7.21-7.18 (m, 1H), 7.17-7.13 (m, 1H), 3.87 (s, 3H), 3.86 (d, <i>J</i>=2.7 Hz, 6H), 3.50-3.36 (m, 1H), 3.14-3.00 (m, 2H), 2.99-2.83 (m, 2H), 2.33-2.09 (m, 3H), 2.02 (br s, 4H), 1.92 (br s, 2H), 1.88-1.78 (m, 2H), 1.76-1.66 (m, 2H), 0.89 (br d, <i>J</i>=6.7 Hz, 6H) (three protons obscured). TLR9 IC₅₀ (nM) = 170
35	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 474.94; Retention Time: 0.97 min. (Method 2): Purity: 100 %; Observed Mass: 475.24; Retention Time: 1.43 min. Prep Method 1: 28 mg, 0.059 mmol, 69 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.50 (br d, <i>J</i>=4.9 Hz, 2H), 7.41-7.36 (m, 2H), 7.20-7.17 (m, 1H), 7.16-7.13 (m, 1H), 3.88-3.84 (m, 9H), 3.50-3.39 (m, 1H), 3.11-3.05 (m, 1H), 3.04-2.94 (m, 2H), 2.72-2.60 (m, 1H), 2.48-2.35 (m, 3H), 2.16 (br s, 2H), 1.84 (br s, 2H), 1.81-1.69 (m, 4H), 1.62-1.55 (m, 1H), 1.50-1.39 (m, 2H), 0.41 (br d, <i>J</i>=4.6 Hz, 2H), 0.29 (br s, 2H). TLR9 IC₅₀ (nM) = 850

36	Analytical LC/MS (Method 1): Purity: 98.3 %; Observed Mass: 518.99; Retention Time: 1.06 min. (Method 2): Purity: 97 %; Observed Mass: 519.08; Retention Time: 1.62 min. Prep Method 1: 62 mg, 0.12 mmol, 93 % yield; ¹H NMR (500 MHz, DMSO-d₆) Shift 7.74-7.68 (m, 1H), 7.52-7.48 (m, 1H), 7.20-7.11 (m, 4H), 4.80-4.71 (m, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.20-3.09 (m, 2H), 3.00-2.90 (m, 2H), 2.73-2.64 (m, 1H), 2.13-2.03 (m, 2H), 1.91 (s, 10H), 1.58 (s, 3H), 1.57 (s, 3H), 0.86 (s, 3H), 0.85 (s, 3H) (4 protons obscured). TLR9 IC₅₀ (nM) = 360
37	Analytical LC/MS (Method 1): Purity: 99.3 %; Observed Mass: 251.92; Retention Time: 1.07 min. (Method 2): Purity: 100 %; Observed Mass: 503.20; Retention Time: 1.63 min. Prep Method 1: 47 mg, 0.093 mmol, 66 % yield; ¹H NMR (500 MHz, DMSO-d₆) Shift 7.47-7.43 (m, 1H), 7.26-7.22 (m, 1H), 6.92 (s, 1H), 6.89 (s, 3H), 4.55-4.46 (m, 1H), 3.60 (s, 3H), 3.57 (s, 3H), 2.94-2.80 (m, 2H), 2.78-2.70 (m, 2H), 2.45-2.35 (m, 1H), 2.24-2.13 (m, 2H), 1.94-1.86 (m, 2H), 1.63-1.57 (m, 2H), 1.56-1.44 (m, 4H), 1.34-1.32 (m, 3H), 1.32-1.31 (m, 3H), 1.25-1.14 (m, 2H), 0.19-0.13 (m, 2H), 0.07-0.01 (m, 2H) (two protons obscured). TLR9 IC₅₀ (nM) = 390
38	Analytical LC/MS (Method 1): Purity: 96.7 %; Observed Mass: 540.99; Retention Time: 1.06 min. (Method 2): Purity: 100 %; Observed Mass: 540.97; Retention Time: 1.61 min. Prep Method 1: 59 mg, 0.11 mmol, 79 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.59-7.54 (m, 1H), 7.51 (s, 1H), 7.26 (s, 2H), 7.22-7.18 (m, 1H), 7.16-7.11 (m, 1H), 6.51-6.25 (m, 1H), 4.81-4.67 (m, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.01-2.95 (m, 2H), 2.88-2.81 (m, 2H), 2.64-2.56 (m, 1H), 2.30-2.18 (m, 3H), 2.04-1.95 (m, 2H), 1.84-1.77 (m, 4H), 1.76-1.66 (m, 5H), 1.53-1.39 (m, 2H), 0.84 (s, 3H), 0.83 (s, 3H). TLR9 IC₅₀ (nM) = 210

39	Analytical LC/MS (Method 1): Purity: 97.8 %; Observed Mass: 525.29; Retention Time: 1.02 min. Purity: 100 %; Observed Mass: 524.94; Retention Time: 1.53 min. Prep Method 1: 68 mg, 0.13 mmol, 93 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.56 (s, 1H), 7.52 (s, 1H), 7.27 (s, 2H), 7.23-7.19 (m, 1H), 7.18-7.12 (m, 1H), 6.39 (br s, 1H), 4.74 (br s, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.67-3.54 (m, 2H), 2.98 (br d, <i>J</i>=7.9 Hz, 3H), 2.64-2.57 (m, 1H), 2.28 (br s, 3H), 2.18-2.09 (m, 2H), 1.84-1.78 (m, 2H), 1.76-1.64 (m, 3H), 1.59-1.53 (m, 1H), 1.47-1.33 (m, 2H), 0.44-0.36 (m, 2H), 0.29 (br d, <i>J</i>=2.4 Hz, 2H). TLR9 IC₅₀ (nM) = 590
40	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 505.01; Retention Time: 1.00 min. (Method 2): Purity: 100 %; Observed Mass: 505.18; Retention Time: 1.71 min. Prep Method 1: 17 mg, 0.034 mmol, 12 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.59-7.55 (m, 1H), 7.47-7.43 (m, 1H), 7.31-7.26 (m, 2H), 7.18-7.13 (m, 2H), 4.31 (br s, 2H), 3.84 (d, <i>J</i>=6.4 Hz, 6H), 3.67-3.54 (m, 2H), 3.10-3.02 (m, 2H), 2.94-2.86 (m, 2H), 2.72-2.61 (m, 1H), 2.41-2.30 (m, 3H), 2.08-2.00 (m, 2H), 1.93-1.82 (m, 3H), 1.81-1.68 (m, 4H), 1.57-1.45 (m, 2H), 1.34 (br t, <i>J</i>=7.2 Hz, 3H), 0.85 (d, <i>J</i>=6.4 Hz, 6H). TLR9 IC₅₀ (nM) = 150
41	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 504.98; Retention Time: 1.02 min. (Method 2): Purity: 99 %; Observed Mass: 505.34; Retention Time: 1.77 min. Prep Method 1: 22 mg, 0.044 mmol, 16 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.55 (br d, <i>J</i>=8.2 Hz, 1H), 7.54-7.50 (m, 1H), 7.31-7.27 (m, 2H), 7.21-7.17 (m, 1H), 7.17-7.13 (m, 1H), 4.34-4.27 (m, 2H), 3.87-3.82 (m, 4H), 3.66-3.54 (m, 3H), 3.32-3.24 (m, 1H), 3.05-2.96 (m, 2H), 2.83-2.62 (m, 4H), 2.21-2.11 (m, 2H), 2.11-2.00 (m, 2H), 1.99-1.88 (m, 4H), 1.87-1.74 (m, 3H), 1.69-1.57 (m, 2H), 1.34 (br t, <i>J</i>=7.0 Hz, 3H), 0.87 (d, <i>J</i>=6.4 Hz, 6H). TLR9 IC₅₀ (nM) = 400

42	Analytical LC/MS (Method 1): Purity: 98.8 %; Observed Mass: 546.10; Retention Time: 0.91 min. (Method 2): Purity: 100 %; Observed Mass: 545.10; Retention Time: 1.95 min. Prep Method 1: 65 mg, 0.12 mmol, 92 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.97-7.91 (m, 1H), 7.76 (br s, 2H), 7.66-7.58 (m, 1H), 7.17-7.14 (m, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.16-3.10 (m, 1H), 3.04-2.89 (m, 3H), 2.47-2.38 (m, 1H), 2.22-2.13 (m, 2H), 2.10-1.99 (m, 2H), 1.90-1.77 (m, 8H), 1.65-1.52 (m, 3H), 0.87 (d, <i>J</i>=6.5 Hz, 6H) (one proton obscured). TLR9 IC₅₀ (nM) = 260
43	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 491.11; Retention Time: 0.98 min. (Method 2): Purity: 98.2 %; Observed Mass: 491.10; Retention Time: 1.48 min. Prep Method 2: 80 mg, 0.096 mmol, 69 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.89 (br d, <i>J</i>=8.4 Hz, 1H), 7.86 (s, 1H), 7.45 (s, 1H), 7.26 (d, <i>J</i>=8.6 Hz, 1H), 7.18 (br s, 1H), 3.90-3.87 (m, 6H), 3.73-3.65 (m, 1H), 3.65-3.55 (m, 2H), 3.24-3.16 (m, 2H), 3.10-2.89 (m, 6H), 2.51 (br s, 3H), 2.37-2.26 (m, 2H), 2.16-2.03 (m, 8H), 0.97 (d, <i>J</i>=6.6 Hz, 6H). TLR9 IC₅₀ (nM) = 9.8
44	Analytical LC/MS (Method 1): Purity: 97.2 %; Observed Mass: 475.29; Retention Time: 0.97 min. (Method 2): Purity: 97.5 %; Observed Mass: 475.27; Retention Time: 1.39 min. Prep Method 1: 24 mg, 0.051 mmol, 36 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.86-7.69 (m, 2H), 7.17-7.07 (m, 2H), 6.89-6.85 (m, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.65-3.47 (m, 2H), 3.02-2.94 (m, 4H), 2.54 (s, 3H), 2.33-2.24 (m, 2H), 2.17-2.08 (m, 2H), 1.82-1.76 (m, 2H), 1.75-1.62 (m, 4H), 1.59-1.53 (m, 1H), 1.45-1.35 (m, 2H), 0.42-0.37 (m, 2H), 0.30-0.26 (m, 2H). TLR9 IC₅₀ (nM) = 52

45	Analytical LC/MS (Method 1): Purity: 98.9 %; Observed Mass: 490.95; Retention Time: 0.95 min. (Method 2): Purity: 100 %; Observed Mass: 490.94; Retention Time: 1.34 min. Prep Method 1: 17 mg, 0.035 mmol, 22 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.34 (s, 2H), 7.24-7.20 (m, 1H), 7.14-7.10 (m, 1H), 6.93 (s, 1H), 3.84 (s, 6H), 3.81 (s, 3H), 3.03-2.96 (m, 2H), 2.90-2.83 (m, 2H), 2.74-2.67 (m, 1H), 2.61-2.55 (m, 1H), 2.52 (s, 3H), 2.33-2.21 (m, 3H), 2.19-2.10 (m, 2H), 1.84-1.68 (m, 6H), 1.51-1.40 (m, 2H), 0.97 (d, <i>J</i>=6.5 Hz, 6H). TLR9 IC₅₀ (nM) = 20
46	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 489.29; Retention Time: 1.03 min. (Method 2): Purity: 100 %; Observed Mass: 488.96; Retention Time: 1.49 min. Prep Method 2: 100 mg, 0.12 mmol, 86 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.55-7.44 (m, 3H), 7.29-7.25 (m, 1H), 7.23-7.17 (m, 1H), 3.98-3.94 (m, 3H), 3.91 (s, 3H), 3.89 (s, 3H), 3.69-3.58 (m, 1H), 3.27-3.16 (m, 1H), 3.14-3.01 (m, 1H), 2.64-2.59 (m, 3H), 2.42-2.28 (m, 2H), 2.22-2.05 (m, 4H), 2.04-1.89 (m, 2H), 1.00-0.89 (m, 2H), 0.87-0.77 (m, 2H) (8 protons obscured). TLR9 IC₅₀ (nM) = 170
47	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 516.90; Retention Time: 1.04 min. (Method 2): Purity: 94.4 %; Observed Mass: 516.90; Retention Time: 1.46 min. Prep Method 2: 30 mg, 0.013 mmol, 27 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.50-7.43 (m, 2H), 7.33-7.20 (m, 2H), 7.19-7.09 (m, 1H), 4.35-4.24 (m, 1H), 4.20-4.06 (m, 3H), 3.94 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H), 3.09-2.98 (m, 4H), 2.98-2.87 (m, 2H), 2.80-2.67 (m, 2H), 2.64-2.59 (m, 5H), 2.16-2.07 (m, 2H), 2.05-1.92 (m, 2H), 1.91-1.74 (m, 2H), 0.91 (d, <i>J</i>=6.7 Hz, 6H) (one proton obscured). TLR9 IC₅₀ (nM) = 13

48	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 514.95; Retention Time: 1.02 min. (Method 2): Purity: 98.2 %; Observed Mass: 515.02; Retention Time: 1.53 min. Prep Method 1: 31 mg, 0.060 mmol, 46 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.18-7.12 (m, 2H), 7.05-6.99 (m, 1H), 6.97-6.91 (m, 1H), 6.76-6.70 (m, 1H), 3.64 (s, 6H), 3.61 (s, 3H), 2.76-2.65 (m, 2H), 2.53-2.42 (m, 3H), 2.35 (s, 3H), 2.19-2.07 (m, 3H), 1.93-1.84 (m, 2H), 1.84-1.77 (m, 2H), 1.72-1.63 (m, 2H), 1.62-1.56 (m, 2H), 1.55-1.45 (m, 3H), 0.66-0.54 (m, 2H), 0.31-0.23 (m, 2H), 0.05--0.02 (m, 2H). TLR9 IC₅₀ (nM) = 19
49	Analytical LC/MS (Method 3): Observed Mass: 515.5; Retention Time: 0.51 min. Prep Method 1: 9.8 mg, 0.019 mmol, 16 % yield; ¹H NMR (500 MHz, METHANOL-d₄) δ 7.39 (d, <i>J</i>=1.9 Hz, 1H), 7.33 (dd, <i>J</i>=8.4, 2.1 Hz, 1H), 7.23 (s, 1H), 7.17 (d, <i>J</i>=8.3 Hz, 1H), 7.03 (s, 1H), 3.95 (s, 6H), 3.75-3.62 (m, 2H), 3.22-3.17 (m, 2H), 3.08-3.01 (m, 1H), 2.82-2.75 (m, 1H), 2.64-2.61 (m, 3H), 2.59-2.52 (m, 2H), 2.35-2.17 (m, 8H), 2.09-1.98 (m, 6H), 1.96-1.80 (m, 6H). TLR9 IC₅₀ (nM) = 65
50	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 531.01; Retention Time: 1.11 min. (Method 2): Purity: 100 %; Observed Mass: 531.05; Retention Time: 1.6 min. Prep Method 1: 81 mg, 0.15 mmol, 71 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.36-7.30 (m, 2H), 7.24-7.20 (m, 1H), 7.14-7.10 (m, 1H), 7.01-6.95 (m, 1H), 3.84 (s, 6H), 3.80 (s, 3H), 3.13-3.03 (m, 1H), 2.86-2.78 (m, 2H), 2.52 (s, 3H), 2.35-2.18 (m, 1H), 2.07-1.97 (m, 2H), 1.86 (br s, 9H), 1.80-1.67 (m, 3H), 1.62-1.55 (m, 1H), 1.49-1.31 (m, 2H), 0.84 (d, <i>J</i>=6.6 Hz, 6H) (two protons obscured). TLR9 IC₅₀ (nM) = 23

51	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 514.95; Retention Time: 1.08 min. (Method 2): Purity: 100 %; Observed Mass: 515.27; Retention Time: 1.48 min. Prep Method 1: 100 mg, 0.20 mmol, 95 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.38-7.32 (m, 2H), 7.27-7.23 (m, 1H), 7.16-7.13 (m, 1H), 7.01-6.98 (m, 1H), 3.86 (s, 6H), 3.83 (s, 3H), 3.64-3.51 (m, 3H), 3.18-3.04 (m, 1H), 3.01-2.92 (m, 2H), 2.55 (s, 3H), 2.40-2.28 (m, 1H), 2.24-2.15 (m, 2H), 1.99-1.87 (m, 4H), 1.87-1.75 (m, 2H), 1.66-1.55 (m, 3H), 1.52-1.45 (m, 1H), 1.40-1.26 (m, 2H), 0.45-0.37 (m, 2H), 0.34-0.27 (m, 2H). TLR9 IC₅₀ (nM) = 130
52	Analytical LC/MS (Method 1): Purity: 98.1 %; Observed Mass: 523.17; Retention Time: 0.94 min. (Method 2): Purity: 97.2 %; Observed Mass: 523.16; Retention Time: 1.53 min. Prep Method 1: 32 mg, 0.061 mmol, 47 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.12 (d, <i>J</i>=3.5 Hz, 4H), 7.31 (s, 1H), 7.00 (s, 1H), 3.90 (s, 3H), 3.00-2.92 (m, 1H), 2.76-2.66 (m, 1H), 2.65-2.58 (m, 1H), 2.56 (s, 3H), 2.49-2.40 (m, 1H), 2.18-2.04 (m, 2H), 1.84 (br d, <i>J</i>=7.1 Hz, 9H), 1.65-1.51 (m, 2H), 0.87 (d, <i>J</i>=6.6 Hz, 6H) (7 protons obscured). TLR9 IC₅₀ (nM) = 130
53	Analytical LC/MS (Method 1): Purity: 95.9 %; Observed Mass: 507.13; Retention Time: 0.90 min. (Method 2): Purity: 100 %; Observed Mass: 507.14; Retention Time: 1.42 min. Prep Method 1: 17 mg, 0.033 mmol, 25 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.91-7.83 (m, 4H), 7.09-7.04 (m, 1H), 6.77-6.72 (m, 1H), 3.64 (s, 3H), 2.81-2.68 (m, 3H), 2.41-2.28 (m, 2H), 2.30 (s, 3H), 2.15-2.00 (m, 3H), 1.95-1.84 (m, 2H), 1.62-1.43 (m, 7H), 1.35-1.27 (m, 1H), 1.22-1.11 (m, 2H), 0.19-0.11 (m, 2H), 0.06-0.00 (m, 2H) (two protons obscured). TLR9 IC₅₀ (nM) = 420

54	Analytical LC/MS (Method 1): Purity: 92.8 %; Observed Mass: 493.25; Retention Time: 1.03 min. (Method 2): Purity: 99.3 %; Observed Mass: 492.9; Retention Time: 1.58 min. Prep Method 1: 47 mg, 0.095 mmol, 68 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.72-7.67 (m, 1H), 7.65-7.61 (m, 1H), 7.38-7.32 (m, 1H), 7.27-7.22 (m, 1H), 6.98-6.93 (m, 1H), 3.94 (s, 3H), 3.84 (s, 3H), 3.08- 2.96 (m, 2H), 2.83-2.68 (m, 2H), 2.54 (s, 5H), 2.23-2.09 (m, 2H), 2.07-1.71 (m, 9H), 1.71-1.57 (m, 2H), 0.88 (br d, <i>J</i>=6.6 Hz, 6H) (two protons obscured). TLR9 IC₅₀ (nM) = 130
55	Analytical LC/MS (Method 1): Purity: 98 %; Observed Mass: 477.17; Retention Time: 0.98 min. (Method 2): Purity: 98.3 %; Observed Mass: 477.17; Retention Time: 1.65 min. Prep Method 1: 36 mg, 0.076 mmol, 54 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.46-7.41 (m, 1H), 7.40-7.35 (m, 1H), 7.13-7.07 (m, 1H), 7.02-6.99 (m, 1H), 6.71-6.68 (m, 1H), 3.69 (s, 3H), 3.58 (s, 3H), 2.85- 2.71 (m, 3H), 2.42-2.33 (m, 1H), 2.28 (s, 3H), 2.19-2.04 (m, 2H), 1.94-1.86 (m, 2H), 1.61-1.47 (m, 6H), 1.35-1.29 (m, 1H), 1.24-1.10 (m, 2H), 0.18-0.13 (m, 2H), 0.05-0.01 (m, 2H) (two protons obscured). TLR9 IC₅₀ (nM) = 140
56	Analytical LC/MS (Method 1): Purity: 96.6 %; Observed Mass: 479.26; Retention Time: 1.06 min. (Method 2): Purity: 98.9 %; Observed Mass: 478.95; Retention Time: 1.50 min. Prep Method 1: 48 mg, 0.10 mmol, 67 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.09-7.91 (m, 2H), 7.40-7.32 (m, 1H), 7.29-7.10 (m, 1H), 6.92-6.86 (m, 1H), 3.94 (s, 3H), 3.02-2.95 (m, 2H), 2.90-2.83 (m, 2H), 2.56 (s, 3H), 2.31-2.19 (m, 3H), 2.04-1.98 (m, 2H), 1.87-1.61 (m, 9H), 1.52- 1.41 (m, 2H), 0.86 (d, <i>J</i>=6.4 Hz, 6H) (one proton obscured). TLR9 IC₅₀ (nM) = 50

57	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 463.15; Retention Time: 1.01 min. (Method 2): Purity: 100 %; Observed Mass: 463.14; Retention Time: 1.41 min. Prep Method 1: 46 mg, 0.10 mmol, 67 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.11-7.90 (m, 2H), 7.39-7.32 (m, 1H), 7.31-7.10 (m, 1H), 6.92-6.86 (m, 1H), 3.94 (s, 3H), 3.03-2.96 (m, 3H), 2.54 (s, 3H), 2.36- 2.27 (m, 3H), 2.18-2.11 (m, 2H), 1.85-1.63 (m, 6H), 1.60-1.55 (m, 1H), 1.48- 1.35 (m, 2H), 0.45-0.38 (m, 2H), 0.33-0.25 (m, 2H) (two protons obscured). TLR9 IC₅₀ (nM) = 170
58	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 509.25; Retention Time: 0.98 min. (Method 2): Purity: 100 %; Observed Mass: 509.27; Retention Time: 1.26 min. Prep Method 2: 19 mg, 0.022 mmol, 15 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.46-8.41 (m, 2H), 8.15-8.10 (m, 2H), 7.36-7.30 (m, 1H), 7.06-6.98 (m, 1H), 3.61-3.41 (m, 1H), 3.29 (s, 3H), 3.23-3.14 (m, 2H), 3.06-2.88 (m, 5H), 2.62-2.58 (m, 3H), 2.50-2.44 (m, 1H), 2.36-2.25 (m, 2H), 2.15-1.95 (m, 8H), 0.97 (br d, <i>J</i>=6.6 Hz, 6H) (two protons obscured). TLR9 IC₅₀ (nM) = 47
59	Analytical LC/MS (Method 1): Purity: 91.5 %; Observed Mass: 482.31; Retention Time: 0.99 min. (Method 2): Purity: 92.8 %; Observed Mass: 482.32; Retention Time: 1.35 min. Prep Method 1: 31 mg, 0.064 mmol, 43 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 9.40-9.19 (m, 1H), 9.13-9.05 (m, 1H), 8.18-8.10 (m, 1H), 8.06-7.94 (m, 1H), 7.91-7.82 (m, 1H), 7.79-7.71 (m, 1H), 7.50-7.22 (m, 1H), 7.08-6.96 (m, 1H), 3.13-3.04 (m, 1H), 2.96-2.84 (m, 2H), 2.70-2.56 (m, 4H), 2.49-2.34 (m, 3H), 2.08-2.01 (m, 2H), 1.91-1.84 (m, 3H), 1.83-1.69 (m, 5H), 1.58-1.47 (m, 2H), 0.90-0.81 (m, 6H) (two protons obscured). TLR9 IC₅₀ (nM) = 100

60	Analytical LC/MS (Method 1): Purity: 95.2 %; Observed Mass: 460.25; Retention Time: 0.89 min. (Method 2): Purity: 100 %; Observed Mass: 460.25; Retention Time: 1.35 min. Prep Method 1: 46 mg, 0.10 mmol, 68 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.86-7.71 (m, 2H), 7.40-7.15 (m, 1H), 7.00-6.91 (m, 1H), 3.06-2.98 (m, 2H), 2.92-2.84 (m, 2H), 2.57-2.55 (m, 6H), 2.54 (s, 3H), 2.34-2.25 (m, 3H), 2.05-2.00 (m, 2H), 1.88-1.66 (m, 10H), 1.53-1.44 (m, 2H), 0.87-0.85 (m, 6H). TLR9 IC₅₀ (nM) = 45
61	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 502.00; Retention Time: 1.06 min. (Method 2): Purity: 98.9 %; Observed Mass: 502.27; Retention Time: 1.32 min. Prep Method 2: 15 mg, 0.018 mmol, 15 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.77 (s, 1H), 8.21-8.16 (m, 1H), 7.52-7.47 (m, 1H), 7.41-7.35 (m, 1H), 7.05-6.99 (m, 1H), 4.12 (s, 3H), 3.75-3.54 (m, 1H), 3.28-3.17 (m, 2H), 3.08-2.92 (m, 4H), 2.63 (s, 3H), 2.52 (br s, 3H), 2.38-2.27 (m, 2H), 2.23-1.98 (m, 7H), 0.99 (br d, <i>J</i>=6.4 Hz, 6H) (two protons obscured). TLR9 IC₅₀ (nM) = 49
62	Analytical LC/MS (Method 1): Purity: 95 %; Observed Mass: 489.18; Retention Time: 1.04 min. (Method 2): Purity: 94.9 %; Observed Mass: 489.33; Retention Time: 1.52 min. Prep Method 1: 12 mg, 0.025 mmol, 43 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.81-7.61 (m, 2H), 7.30-7.09 (m, 1H), 7.04-6.99 (m, 1H), 6.90-6.85 (m, 1H), 4.32 (s, 4H), 3.05-2.97 (m, 2H), 2.92-2.84 (m, 2H), 2.56 (s, 3H), 2.34-2.23 (m, 3H), 2.01 (s, 2H), 1.89-1.63 (m, 10H), 1.53-1.43 (m, 2H), 0.86 (d, <i>J</i>=6.4 Hz, 6H). TLR9 IC₅₀ (nM) = 350
63	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 514.99; Retention Time: 1.21 min. (Method 2): Purity: 92 %; Observed Mass: 515.37; Retention Time: 1.83 min. Prep Method 1: 4.7 mg, 0.0091 mmol, 16 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.41-8.21 (m, 2H), 7.62-7.49 (m, 2H), 7.30-7.19 (m, 1H), 7.00-6.86 (m, 1H), 3.04-2.95 (m, 2H), 2.91-2.83 (m, 2H), 2.56 (s, 3H), 2.30-2.19 (m, 3H), 2.03-1.98 (m, 2H), 1.87-1.77 (m, 5H), 1.77-1.63 (m, 5H), 1.53-1.42 (m, 2H), 0.86 (d, <i>J</i>=6.4 Hz, 6H). TLR9 IC₅₀ (nM) = 200

64	Analytical LC/MS (Method 1): Purity: 91.8 %; Observed Mass: 495.23; Retention Time: 1.12 min. (Method 2): Purity: 91.6 %; Observed Mass: 495.20; Retention Time: 1.65 min. Prep Method 1: 1.6 mg, 0.0032 mmol, 5.5 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.35-8.07 (m, 2H), 7.38-7.31 (m, 1H), 7.30-7.11 (m, 1H), 6.97-6.85 (m, 1H), 4.01-3.90 (m, 3H), 3.16-3.05 (m, 1H), 2.98-2.86 (m, 2H), 2.68-2.53 (m, 6H), 2.49-2.37 (m, 2H), 2.12-2.01 (m, 2H), 1.99-1.67 (m, 9H), 1.62-1.46 (m, 2H), 0.91-0.81 (m, 6H). TLR9 IC₅₀ (nM) = 91
65	Analytical LC/MS (Method 1): Purity: 97.8 %; Observed Mass: 511.12; Retention Time: 1.2 min. (Method 2): Purity: 100 %; Observed Mass: 511.15; Retention Time: 1.79 min. Prep Method 2: 11 mg, 0.013 mmol, 22 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.18-8.12 (m, 1H), 8.10-8.04 (m, 1H), 7.65-7.60 (m, 1H), 7.29-7.24 (m, 1H), 6.99-6.91 (m, 1H), 3.73-3.62 (m, 1H), 3.62-3.48 (m, 2H), 3.24-3.12 (m, 1H), 3.06-2.89 (m, 4H), 2.57 (s, 3H), 2.49-2.40 (m, 1H), 2.36-2.24 (m, 2H), 2.17-1.91 (m, 8H), 0.97 (br d, <i>J</i>=6.6 Hz, 6H) (two protons obscured). TLR9 IC₅₀ (nM) = 300
66	Analytical LC/MS (Method 1): Purity: 94.5 %; Observed Mass: 527.26; Retention Time: 1.05 min. (Method 2): Purity: 95.3 %; Observed Mass: 527.29; Retention Time: 1.28 min. Prep Method 1: 25 mg, 0.047 mmol, 81 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.35-8.19 (m, 2H), 8.11-7.98 (m, 1H), 7.38-7.19 (m, 1H), 7.09-6.93 (m, 1H), 3.05-2.97 (m, 2H), 2.90-2.84 (m, 2H), 2.60-2.57 (m, 4H), 2.32-2.21 (m, 3H), 2.04-2.00 (m, 2H), 1.88-1.78 (m, 5H), 1.78-1.65 (m, 6H), 1.53-1.42 (m, 2H), 0.88-0.85 (m, 6H) (one proton obscured). TLR9 IC₅₀ (nM) = 69
67	Analytical LC/MS (Method 1): Purity: 94 %; Observed Mass: 586.93; Retention Time: 1.06 min. (Method 2): Purity: 98.2 %; Observed Mass: 586.91; Retention Time: 1.52 min. Prep Method 1: 33 mg, 0.056 mmol, 97 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.77-8.60 (m, 1H), 8.51-8.34 (m, 1H), 8.28-8.17 (m, 1H), 7.41-7.17 (m, 1H), 7.06-6.92 (m, 1H), 3.53 (s, 3H), 3.14-3.03 (m, 1H), 2.96-2.85 (m, 2H), 2.68-2.56 (m, 4H), 2.55 (s, 3H), 2.47-2.32 (m, 2H), 2.08-2.03 (m, 1H), 1.96-1.66 (m, 9H), 1.58-1.44 (m, 2H), 0.85 (br d, <i>J</i>=6.1 Hz, 6H). TLR9 IC₅₀ (nM) = 44

68	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 471.02; Retention Time: 1.17 min. (Method 2): Purity: 100 %; Observed Mass: 470.97; Retention Time: 1.83 min. Prep Method 1: 6.1 mg, 0.013 mmol, 22 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.15-7.94 (m, 2H), 7.32-7.06 (m, 3H), 6.88 (s, 1H), 3.03-2.93 (m, 2H), 2.90-2.78 (m, 2H), 2.53 (s, 3H), 2.49-2.46 (m, 1H), 2.30-2.18 (m, 3H), 2.06-1.92 (m, 3H), 1.88-1.75 (m, 4H), 1.75-1.60 (m, 5H), 1.53-1.40 (m, 2H), 1.05-0.99 (m, 2H), 0.85 (d, <i>J</i>=6.5 Hz, 6H), 0.79-0.73 (m, 2H). TLR9 IC₅₀ (nM) = 85
69	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 514.94; Retention Time: 1.14 min. (Method 2): Purity: 100 %; Observed Mass: 515.37; Retention Time: 1.68 min. Prep Method 2: 15 mg, 0.018 mmol, 31 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.23-8.16 (m, 1H), 8.14-8.06 (m, 1H), 7.65-7.58 (m, 1H), 7.34-7.29 (m, 1H), 7.29-7.06 (m, 1H), 7.00 (s, 1H), 3.76-3.56 (m, 1H), 3.25-3.13 (m, 2H), 2.95 (br d, <i>J</i>=6.7 Hz, 5H), 2.56 (s, 3H), 2.36-2.27 (m, 2H), 2.11 (br s, 7H), 0.98 (br d, <i>J</i>=6.4 Hz, 6H) (4 protons obscured). TLR9 IC₅₀ (nM) = 240
70	Analytical LC/MS (Method 1): Purity: 97.5 %; Observed Mass: 488.15; Retention Time: 1.35 min. (Method 2): Purity: 99.2 %; Observed Mass: 488.15; Retention Time: 1.73 min. Prep Method 2: 5.8 mg, 0.0070 mmol, 12 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.26-8.21 (m, 1H), 8.19-8.12 (m, 1H), 7.68-7.61 (m, 1H), 7.61-7.54 (m, 1H), 7.39-7.24 (m, 1H), 7.06-6.97 (m, 1H), 3.78-3.54 (m, 1H), 3.29-3.10 (m, 1H), 3.09-2.86 (m, 2H), 2.62 (s, 3H), 2.42-2.22 (m, 2H), 2.21-1.89 (m, 7H), 0.98 (br d, <i>J</i>=6.4 Hz, 6H) (8 protons obscured). TLR9 IC₅₀ (nM) = 210
71	Analytical LC/MS (Method 1): Purity: 94.8 %; Observed Mass: 450.01; Retention Time: 1.03 min. (Method 2): Purity: 100 %; Observed Mass: 450.20; Retention Time: 1.47 min. Prep Method 1: 2.5 mg, 0.0056 mmol, 9.7 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.34-7.25 (m, 1H), 6.97-6.90 (m, 1H), 3.49-3.45 (m, 1H), 3.08-2.84 (m, 3H), 2.66-2.61 (m, 3H), 2.56-2.53 (m, 9H), 2.48-2.42 (m, 3H), 2.37-2.20 (m, 3H), 2.19-1.87 (m, 8H), 0.97 (br d, <i>J</i>=6.5 Hz, 6H). TLR9 IC₅₀ (nM) = 1800

72	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 481.96; Retention Time: 0.93 min. (Method 2): Purity: 100 %; Observed Mass: 482.16; Retention Time: 1.39 min. Prep Method 2: 13 mg, 0.016 mmol, 28 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 9.46-9.29 (m, 1H), 9.06 (br d, <i>J</i>=2.4 Hz, 1H), 8.27 (d, <i>J</i>=8.2 Hz, 1H), 8.18 (br d, <i>J</i>=7.0 Hz, 1H), 8.01 (t, <i>J</i>=7.9 Hz, 1H), 7.73 (dd, <i>J</i>=8.7, 4.1 Hz, 1H), 7.41 (s, 1H), 7.08 (br s, 1H), 3.79-3.55 (m, 1H), 3.28-3.16 (m, 1H), 3.12-2.87 (m, 4H), 2.64 (s, 3H), 2.38-2.25 (m, 2H), 2.24-1.91 (m, 7H), 0.99 (br d, <i>J</i>=6.7 Hz, 6H) (6 protons obscured). TLR9 IC₅₀ (nM) = 88
73	Analytical LC/MS (Method 1): Purity: 99.2 %; Observed Mass: 549.21; Retention Time: 1.31 min. (Method 2): Purity: 97.9 %; Observed Mass: 549.28; Retention Time: 1.91 min. Prep Method 2: 9.0 mg, 0.010 mmol, 17 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.48 (s, 1H), 8.36-8.23 (m, 1H), 7.84-7.72 (m, 1H), 7.29 (br s, 1H), 6.97 (s, 1H), 3.77-3.55 (m, 1H), 3.28-3.11 (m, 2H), 3.08-2.87 (m, 5H), 2.58 (s, 3H), 2.49-2.44 (m, 1H), 2.36-2.26 (m, 2H), 2.20-1.95 (m, 8H), 0.97 (br s, 6H) (two protons obscured). TLR9 IC₅₀ (nM) = 270
74	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 481.97; Retention Time: 0.96 min. (Method 2): Purity: 95.5 %; Observed Mass: 481.98; Retention Time: 1.43 min. Prep Method 1: 18 mg, 0.038 mmol, 66 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 9.45-9.35 (m, 1H), 8.85-8.71 (m, 1H), 8.63-8.57 (m, 1H), 8.56-8.45 (m, 1H), 8.32-8.26 (m, 1H), 8.00-7.91 (m, 1H), 7.41-7.20 (m, 1H), 7.03-6.94 (m, 1H), 3.26-3.09 (m, 1H), 2.95 (br d, <i>J</i>=8.5 Hz, 2H), 2.79-2.65 (m, 1H), 2.61 (br d, <i>J</i>=8.5 Hz, 3H), 2.14-2.06 (m, 2H), 1.93 (s, 9H), 1.64-1.51 (m, 2H), 0.88 (d, <i>J</i>=6.4 Hz, 6H) (4 protons obscured) TLR9 IC₅₀ (nM) = 37

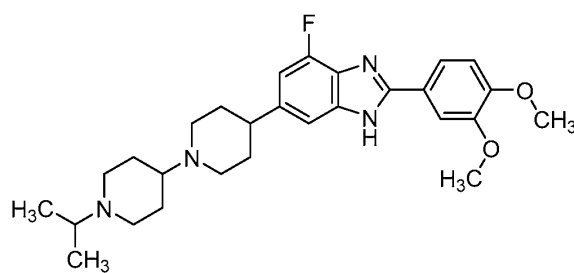
75	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 571.14; Retention Time: 1.24 min. (Method 2): Purity: 98.2 %; Observed Mass: 571.37; Retention Time: 1.67 min. Prep Method 2: 13 mg, 0.014 mmol, 24 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.43-8.38 (m, 2H), 8.19-8.12 (m, 2H), 8.06-7.99 (m, 2H), 7.77-7.71 (m, 1H), 7.71-7.63 (m, 2H), 7.31 (s, 1H), 6.99 (s, 1H), 3.74-3.49 (m, 1H), 3.29-3.12 (m, 2H), 3.08-2.88 (m, 4H), 2.60-2.57 (m, 3H), 2.37-2.22 (m, 2H), 2.18-1.92 (m, 7H), 1.00-0.96 (m, 6H) (5 protons obscured) TLR9 IC₅₀ (nM) = 63
76	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 496.98; Retention Time: 1.08 min. (Method 2): Purity: 100 %; Observed Mass: 497.15; Retention Time: 1.64 min. Prep Method 1: 9.9 mg, 0.020 mmol, 34 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.10-8.04 (m, 1H), 8.02-7.96 (m, 1H), 7.64-7.58 (m, 1H), 7.51-7.32 (m, 1H), 7.32-7.27 (m, 1H), 7.27-7.17 (m, 1H), 6.98-6.90 (m, 1H), 3.06-2.95 (m, 2H), 2.90-2.82 (m, 2H), 2.33-2.22 (m, 3H), 2.05-1.98 (m, 2H), 1.87-1.77 (m, 5H), 1.77-1.65 (m, 5H), 1.54-1.42 (m, 2H), 0.88-0.83 (m, 6H) (three protons obscured). TLR9 IC₅₀ (nM) = 260
77	Analytical LC/MS (Method 1): Purity: 93.2 %; Observed Mass: 487.90; Retention Time: 1.05 min. (Method 2): Purity: 93.8 %; Observed Mass: 488.10; Retention Time: 1.43 min. Prep Method 1: 5.4 mg, 0.011 mmol, 19 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 9.56-9.49 (m, 1H), 8.32-8.16 (m, 2H), 7.87-7.71 (m, 1H), 7.47-7.19 (m, 1H), 6.98 (br s, 1H), 3.04-2.98 (m, 2H), 2.90-2.83 (m, 2H), 2.53 (s, 3H), 2.33-2.23 (m, 3H), 2.05-1.98 (m, 2H), 1.85-1.79 (m, 4H), 1.77-1.66 (m, 6H), 1.52-1.42 (m, 2H), 0.87-0.84 (m, 6H). TLR9 IC₅₀ (nM) = 31

78	Analytical LC/MS (Method 1): Purity: 96.9 %; Observed Mass: 496.98; Retention Time: 1.07 min. (Method 2): Purity: 95.6 %; Observed Mass: 497.28; Retention Time: 1.51 min. Prep Method 1: 27 mg, 0.055 mmol, 95 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.31-8.17 (m, 2H), 7.38-7.34 (m, 2H), 7.22-7.14 (m, 1H), 6.94-6.88 (m, 1H), 3.49-3.39 (m, 1H), 3.15-2.68 (m, 3H), 2.58-2.55 (m, 3H), 2.31-2.06 (m, 2H), 2.06-1.96 (m, 4H), 1.95-1.78 (m, 4H), 1.78-1.62 (m, 2H), 0.88 (br d, <i>J</i>=6.4 Hz, 6H) (6 protons obscured). TLR9 IC₅₀ (nM) = 270
79	Analytical LC/MS (Method 1): Purity: 98.2 %; Observed Mass: 438.20; Retention Time: 0.96 min. (Method 2): Purity: 99.5 %; Observed Mass: 438.19; Retention Time: 1.42 min. Prep Method 1: 17 mg, 0.039 mmol, 67 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.11-8.04 (m, 1H), 7.99-7.92 (m, 1H), 7.36-7.15 (m, 1H), 7.02-6.94 (m, 1H), 3.01 (br s, 2H), 2.88 (br d, <i>J</i>=11.3 Hz, 2H), 2.57-2.56 (m, 4H), 2.27 (br d, <i>J</i>=11.6 Hz, 3H), 2.05-1.99 (m, 2H), 1.90-1.78 (m, 4H), 1.78-1.62 (m, 5H), 1.55-1.43 (m, 2H), 0.90-0.83 (m, 6H). TLR9 IC₅₀ (nM) = 110
80	Analytical LC/MS (Method 1): Purity: 95.9 %; Observed Mass: 515.15; Retention Time: 1.10 min. (Method 2): Purity: 98.5 %; Observed Mass: 515.37; Retention Time: 1.68 min. Prep Method 2: 19 mg, 0.022 mmol, 38 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.09-8.03 (m, 1H), 7.74-7.69 (m, 1H), 7.66-7.59 (m, 2H), 7.35-7.30 (m, 1H), 7.03-6.96 (m, 1H), 3.76-3.56 (m, 1H), 3.27-3.15 (m, 1H), 3.11-2.90 (m, 4H), 2.59-2.53 (m, 6H), 2.36-2.26 (m, 2H), 2.19-1.96 (m, 7H), 1.01-0.96 (m, 6H) (three protons obscured). TLR9 IC₅₀ (nM) = 360
81	Analytical LC/MS (Method 1): Purity: 97 %; Observed Mass: 471.19; Retention Time: 0.91 min. (Method 2): Purity: 98 %; Observed Mass: 471.02; Retention Time: 1.41 min. Prep Method 1: 22 mg, 0.046 mmol, 79 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 11.87 (br s, 1H), 9.12-8.97 (m, 1H), 8.78-8.63 (m, 1H), 7.62-7.52 (m, 1H), 7.34-7.12 (m, 1H), 6.94-6.84 (m, 1H), 6.65-6.55 (m, 1H), 3.14-3.03 (m, 1H), 2.96-2.84 (m, 2H), 2.55 (s, 5H), 2.41 (br s, 3H), 2.05 (br d, <i>J</i>=7.2 Hz, 2H), 1.90-1.66 (m, 9H), 1.60-1.44 (m, 2H), 0.85 (d, <i>J</i>=6.5 Hz, 6H). TLR9 IC₅₀ (nM) = 49

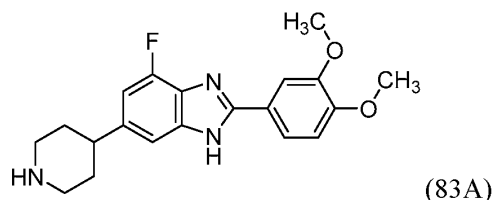
82	Analytical LC/MS (Method 1): Purity: 96.8 %; Observed Mass: 482.16; Retention Time: 0.98 min. (Method 2): Purity: 94.7 %; Observed Mass: 482.01; Retention Time: 1.57 min. Prep Method 1: 20 mg, 0.042 mmol, 72 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 9.21-9.14 (m, 1H), 8.98-8.91 (m, 1H), 8.63-8.54 (m, 1H), 8.20-8.11 (m, 1H), 7.85-7.78 (m, 1H), 7.78-7.70 (m, 1H), 7.45-7.39 (m, 1H), 7.00-6.92 (m, 1H), 3.22-3.07 (m, 2H), 2.98-2.86 (m, 2H), 2.67-2.63 (m, 1H), 2.55 (s, 3H), 2.49-2.44 (m, 2H), 2.12-1.99 (m, 3H), 1.91 (s, 4H), 1.84-1.69 (m, 5H), 1.61-1.48 (m, 2H), 0.86 (br d, <i>J</i>=6.8 Hz, 6H). TLR9 IC₅₀ (nM) = 32
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EXAMPLE 83

2-(3,4-dimethoxyphenyl)-4-fluoro-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole



Step A. Intermediate 83A. Preparation of 2-(3,4-dimethoxyphenyl)-4-fluoro-6-(piperidin-4-yl)-1H-benzo[d]imidazole bis(2,2,2-trifluoroacetate)



Intermediate 83A was synthesized according to the general procedures described for the preparation of Intermediate 11D (Steps A-D), using 5-bromo-3-fluorobenzene-1,2-diamine as starting material. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.78 (s, 2H), 7.42 (s, 1H), 7.22 (d, *J*=8.2 Hz, 1H), 7.20-7.16 (m, 1H), 4.01-3.99 (m, 3H), 3.98-3.96 (m, 3H), 3.60-3.53 (m, 2H), 3.24-3.18 (m, 2H), 3.16-3.10 (m, 1H), 2.23-2.17 (m, 2H), 2.05-1.94 (m, 2H). Analytical LC/MS (Method 4): Observed Mass: 356.1; Retention Time: 0.928

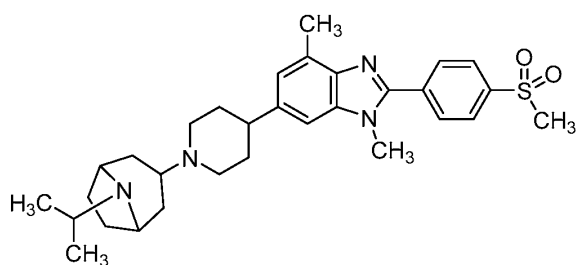
min.

Step B. Example 83

Example 83 was synthesized according to the general procedures described for the preparation of Example 11 (Step E), using Intermediate 83A (80 mg, 0.14 mmol) as starting material. The crude material was purified by preparative HPLC (Prep Method 1) to afford the title compound (49 mg, 0.10 mmol, 71 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 7.80-7.70 (m, 2H), 7.22-7.16 (m, 1H), 7.16-7.09 (m, 1H), 6.94-6.85 (m, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.05-2.93 (m, 2H), 2.90-2.77 (m, 2H), 2.75-2.66 (m, 1H), 2.64-2.57 (m, 1H), 2.34-2.18 (m, 3H), 2.16-2.04 (m, 2H), 1.87-1.72 (m, 4H), 1.72-1.58 (m, 2H), 1.50-1.38 (m, 2H), 0.97 (d, *J*=6.7 Hz, 6H). Analytical LC/MS (Method 1): Purity: 96.9 %; Observed Mass: 481.25; Retention Time: 0.98 min. (Method 2): Purity: 96.4 %; Observed Mass: 481.27; Retention Time: 1.45 min. TLR9 IC₅₀ (nM) = 210.

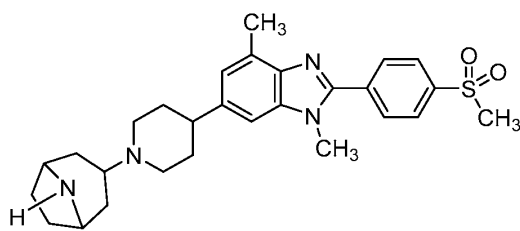
EXAMPLES 84 AND 85

6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole



(84-85)

Step A. Intermediate 84A. Preparation of 6-(1-(8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole dihydrochloride



(84A)

To a 250 mL round bottomed flask were added Intermediate 22C (1.0 g, 2.4 mmol), MeOH (50 mL) and DOWEX 550A anion exchange resin (10 g). The mixture

was stirred for 15 min, the resin was filtered and the filtrate was concentrated. The resultant free amine was dissolved in DCE (15 ml) and DME (15 ml), then tert-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (2.2 g, 9.7 mmol) was added, followed by titanium(IV) isopropoxide (3.6 ml, 12 mmol). The reaction mixture was stirred at 40 °C under N₂. After 18 h, the mixture was cooled to room temperature, then sodium triacetoxyborohydride (2.0 g, 9.7 mmol) was added and the reaction was continued. After stirring 2 h, the reaction mixture was partitioned into 1 M KOH (sat. with solid NaCl) (150 mL) and 10% IPA/chloroform (150 mL). The layers were separated, the aqueous phase was extracted with 10% IPA/chloroform (75 mL), the organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (120 g silica gel cartridge; A = DCM, B = MeOH; 30 min grad.; 0% B to 20%B; flow rate = 80 mL/min.). Fractions corresponding to product were combined, concentrated and dried in vacuo. The resultant residue was dissolved in MeOH (20 mL) and 4 M HCl in dioxane (10 mL) and stirred. After 0.5 h, the solvent was concentrated and the residue was co-evaporated with toluene (2x). The product was dried in vacuo to afford the title compound (0.72 g, 1.3 mmol, 54 % yield) as an off-white solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.37-8.33 (m, 2H), 8.23-8.18 (m, 2H), 7.78-7.72 (m, 1H), 7.51-7.47 (m, 1H), 4.32-4.27 (m, 1H), 4.25-4.19 (m, 1H), 4.13-4.10 (m, 3H), 4.10-4.04 (m, 2H), 4.03-3.95 (m, 1H), 3.89-3.78 (m, 3H), 2.49-2.44 (m, 1H), 2.32-1.96 (m, 17H). Analytical LC/MS (Method 4): Observed Mass: 493.1; Retention Time: 0.827 min.

Step B. Examples 84 and 85

Examples 84 and 85 were synthesized according to the general procedures described for the preparation of Examples 17 and 18 (Step B), using Intermediate 84A (100 mg, 0.18 mmol) as starting material. The crude isomeric mixture was purified via preparative HPLC with the following conditions: Column: XBridge C18, 200 mm x 19 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile: water with ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with ammonium acetate; Gradient: a 0-minute hold at 10% B, 10-55% B over 25 minutes, then a 0-minute hold at 100% B; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS signals. Fractions corresponding to the respective desired products were combined and

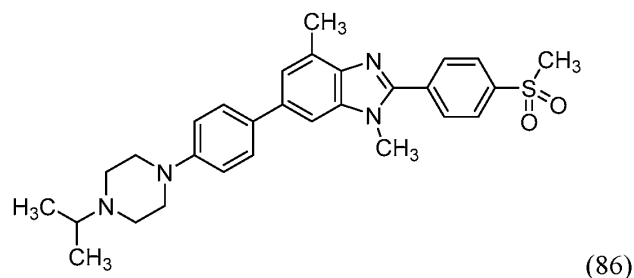
dried via centrifugal evaporation.

Example 84 (39 mg, 0.073 mmol, 41 % yield) was isolated as the 1st eluting isomer. ¹H NMR (500 MHz, DMSO-d₆) δ 8.10 (s, 4H), 7.28 (s, 1H), 6.99 (s, 1H), 3.87 (s, 2H), 3.73-3.51 (m, 2H), 3.36-3.29 (m, 1H), 3.29 (s, 2H), 3.08-2.97 (m, 1H), 2.88-2.76 (m, 1H), 2.55 (s, 5H), 2.24-2.09 (m, 2H), 1.81 (s, 7H), 1.76-1.64 (m, 4H), 1.61-1.49 (m, 3H), 1.05 (br d, *J*=5.8 Hz, 6H). Analytical LC/MS (Method 1): Purity: 99.5 %; Observed Mass: 535.00; Retention Time: 0.90 min. (Method 2): Purity: 100 %; Observed Mass: 534.99; Retention Time: 1.24 min. TLR9 IC₅₀ (nM) = 72.

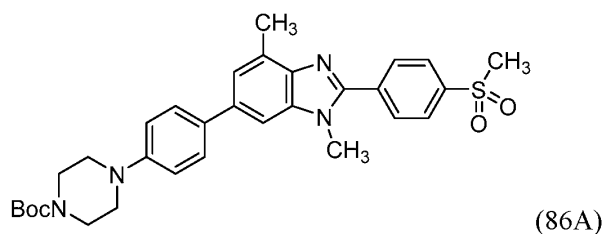
Example 85 (5.5 mg, 0.010 mmol, 6 % yield) was isolated as the 2nd eluting isomer. ¹H NMR (500 MHz, DMSO-d₆) δ 8.10 (s, 4H), 7.29 (s, 1H), 6.99 (s, 1H), 3.88 (s, 2H), 3.53 (s, 3H), 3.42-3.34 (m, 1H), 3.30 (s, 3H), 2.55 (s, 5H), 2.39-2.31 (m, 1H), 1.94-1.66 (m, 15H), 0.99 (d, *J*=6.1 Hz, 6H). Analytical LC/MS (Method 1): Purity: 95.6 %; Observed Mass: 535.24; Retention Time: 1.01 min. (Method 2): Purity: 100 %; Observed Mass: 535.23; Retention Time: 1.48 min. TLR9 IC₅₀ (nM) = 110.

EXAMPLE 86

6-(4-(4-isopropylpiperazin-1-yl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole

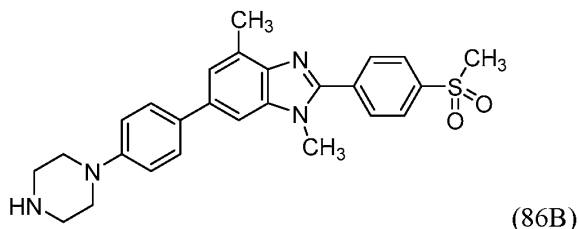


Step A. Intermediate 86A. Preparation of tert-butyl 4-(4-(1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)phenyl)piperazine-1-carboxylate



To a 40 mL vial were added Intermediate 22A (0.53 g, 1.4 mmol), tert-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine-1-carboxylate (0.60 g, 1.5 mmol), XPhos Pd G3 (0.12 g, 0.14 mmol), 1,4-dioxane (10 mL), followed by potassium phosphate tribasic (1.0 g, 4.9 mmol) dissolved in water (3 mL). The vessel was flushed with N₂, capped, and the reaction mixture was stirred at 85 °C. After 18 h, the reaction mixture was cooled, diluted with water (100 mL), and extracted with EtOAc (2x50 mL). The organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (80 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100%B; flow rate = 60 mL/min). The fractions corresponding to product were combined, concentrated and dried in vacuo to afford the title compound (0.78 g, 1.4 mmol, 100 % yield) as a pale yellow solid. ¹H NMR (500 MHz, DMSO-d₆) δ 7.44-7.36 (m, 2H), 7.34-7.23 (m, 2H), 6.88-6.82 (m, 2H), 6.79-6.74 (m, 1H), 6.64-6.58 (m, 1H), 6.35-6.27 (m, 2H), 3.19-3.07 (m, 3H), 2.91-2.74 (m, 5H), 2.43 (s, 6H), 1.93-1.88 (m, 3H), 0.71 (s, 9H). Analytical LC/MS (Method 4): Observed Mass: 561.2; Retention Time: 1.777 min.

Step B. Intermediate 86B. Preparation of 1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(4-(piperazin-1-yl)phenyl)-1H-benzo[d]imidazole dihydrochloride



To a 100 mL pear shaped flask were added Intermediate 86A (0.78 g, 1.4 mmol), MeOH (10 mL), and 4 M HCl in dioxane (5 mL). After stirring 15 min, the solvent was concentrated and the residue was co-evaporated with toluene (2x), and the product was dried in vacuo to afford the title compound (0.74 g, 1.4 mmol, 100 % yield) as a tan solid. ¹H NMR (500 MHz, DMSO-d₆) δ 8.25 (s, 4H), 8.08-7.96 (m, 1H), 7.84-7.73 (m, 2H), 7.72-7.66 (m, 1H), 7.25-7.09 (m, 2H), 4.06 (s, 3H), 3.51-3.45 (m, 4H), 3.38 (s, 3H), 3.29-3.17 (m, 5H), 2.71 (s, 3H). Analytical LC/MS (Method 4): Observed Mass: 461.2; Retention Time: 0.94 min.

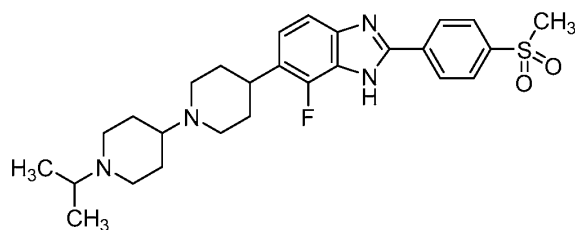
Step C. Example 86

To a 40 mL vial were added Intermediate 86B (70 mg, 0.13 mmol), propan-2-one (38 mg, 0.66 mmol), AcOH (8.3 μ L, 0.14 mmol), magnesium sulfate (240 mg, 1.9 mmol), and DMF (2 mL). The reaction mixture was stirred for 10 min, then sodium triacetoxyborohydride (140 mg, 0.66 mmol) was added and the reaction mixture was stirred. After 18 h, the reaction mixture was diluted with 10% IPA/ CHCl_3 (40 mL) and filtered. The filtrate was partitioned into 10% KOH sat. with solid NaCl (20 mL) and the layers were separated. The aqueous phase was extracted with 10% IPA/ CHCl_3 (10 mL), the organic phase was combined, washed with brine, dried over MgSO_4 , filtered and concentrated. The crude material was purified by preparative HPLC (Prep Method 1) to afford the title compound (27 mg, 0.054 mmol, 42 % yield). ^1H NMR (500 MHz, DMSO-d_6) δ 8.18-8.09 (m, 4H), 7.68-7.62 (m, 3H), 7.41-7.35 (m, 1H), 7.06-6.99 (m, 2H), 3.95 (s, 2H), 3.60-3.46 (m, 3H), 3.30 (s, 2H), 3.19 (br s, 3H), 2.71-2.64 (m, 1H), 2.61-2.57 (m, 2H), 2.51 (br s, 4H), 1.02 (d, $J=6.4$ Hz, 6H) (one proton obscured). Analytical LC/MS (Method 1): Purity: 91.6 %; Observed Mass: 502.96; Retention Time: 1.13 min. (Method 2): Purity: 92.9 %; Observed Mass: 502.96; Retention Time: 1.67 min. TLR9 IC_{50} (nM) = 300.

20

EXAMPLE 87

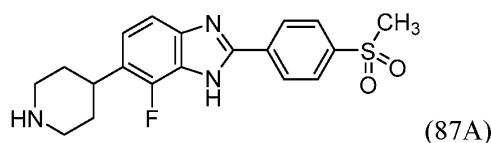
7-fluoro-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole



(87)

Step A. Intermediate 87A. Preparation of 7-fluoro-2-(4-(methylsulfonyl)phenyl)-6-(piperidin-4-yl)-1H-benzo[d]imidazole dihydrochloride

25



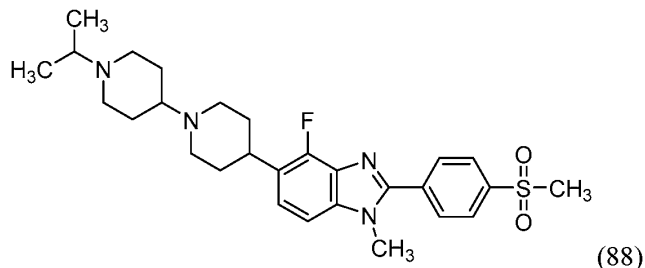
Intermediate 87A was synthesized according to the general procedures described for the preparation of Intermediate 11D (Steps A-D), using 4-bromo-3-fluorobenzene-1,2-diamine (1.4 g, 6.6 mmol) and 4-(methylsulfonyl)benzaldehyde (1.2 g, 6.6 mmol) as starting materials, and using HCl during Boc-deprotection (Step 11D), to afford the title compound (1.5 g, 3.4 mmol, 52 % over 4 steps) as an off-white solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.43-8.38 (m, 2H), 8.32-8.28 (m, 2H), 7.70-7.65 (m, 1H), 7.59-7.54 (m, 1H), 3.63-3.56 (m, 2H), 3.56-3.46 (m, 1H), 3.39-3.36 (m, 2H), 3.29-3.24 (m, 3H), 2.21-2.12 (m, 4H). Analytical LC/MS (Method 4): Observed Mass: 373.9; Retention Time: 0.913 min.

Step B. Example 87

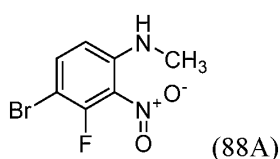
To a 40 mL vial were added Intermediate 87A (70 mg, 0.16 mmol), 1-isopropylpiperidin-4-one (110 mg, 0.78 mmol), AcOH (9.9 μL, 0.17 mmol), magnesium sulfate (280 mg, 2.4 mmol), and DMF (2 mL). The reaction mixture was stirred for 10 min, then sodium triacetoxyborohydride (170 mg, 0.78 mmol) was added and the reaction mixture was stirred. After 18 h, the reaction mixture was diluted with 10% IPA/CHCl₃ (40 mL) and filtered. The filtrate was partitioned into 10% KOH (sat. with solid NaCl) (20 mL) and the layers were separated. The aqueous phase was extracted with 10% IPA/CHCl₃ (10 mL), the organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The crude material was purified by preparative HPLC (Prep Method 1) to afford the title compound (11 mg, 0.022 mmol, 14 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 8.45-8.37 (m, 2H), 8.13-8.07 (m, 2H), 7.44-7.35 (m, 1H), 7.25-7.16 (m, 1H), 3.31-3.24 (m, 2H), 3.03-2.97 (m, 2H), 2.96-2.83 (m, 3H), 2.78-2.66 (m, 2H), 2.35-2.22 (m, 3H), 2.21-2.09 (m, 2H), 1.95-1.86 (m, 2H), 1.82-1.72 (m, 5H), 1.52-1.42 (m, 2H), 0.98 (br d, *J*=6.5 Hz, 6H). Analytical LC/MS (Method 1): Purity: 98.5 %; Observed Mass: 499.01; Retention Time: 0.98 min. (Method 2): Purity: 99.1 %; Observed Mass: 498.94; Retention Time: 1.05 min. TLR9 IC₅₀ (nM) = 950.

EXAMPLE 88

4-fluoro-5-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole

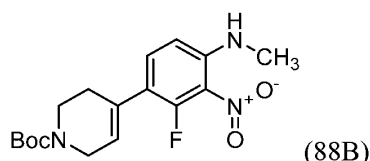


5 Step A. Intermediate 88A. Preparation of 4-bromo-3-fluoro-N-methyl-2-nitroaniline



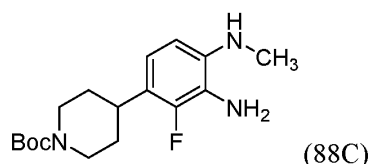
To a 250 mL round bottomed flask were added 4-bromo-3-fluoro-2-nitroaniline (1.0 g, 4.3 mmol), and DMF (30 mL). The reaction mixture was cooled to 0 °C, then NaH (60% dispersion in mineral oil) (0.20 g, 5.1 mmol) was added. After stirring at the above temperature for 30 min, MeI (0.27 mL, 4.3 mmol) was added, the reaction mixture was allowed to slowly reach room temperature, and stirred under N₂. After 18 h, the reaction mixture was diluted with water (150 mL) and extracted with EtOAc (2x75 mL). The organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (120 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 50%B; flow rate = 80 mL/min). The fractions corresponding to product were combined, concentrated and dried in vacuo to afford the title compound (0.93 g, 3.7 mmol, 86 % yield) as a yellow solid. ¹H NMR (500 MHz, CHLOROFORM-d) δ 7.55-7.49 (m, 1H), 7.26-7.15 (m, 1H), 6.59-6.51 (m, 1H), 2.91 (s, 3H). Analytical LC/MS (Method 4): Observed Mass: 250.8; Retention Time: 1.766 min.

Step B. Intermediate 88B. Preparation of tert-butyl 4-(2-fluoro-4-(methylamino)-3-nitrophenyl)-3,6-dihydropyridine-1(2H)-carboxylate



To a 40 mL vial were added Intermediate 88A (0.93 g, 3.7 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.4 g, 4.5 mmol), XPhos Pd G3 (0.16 g, 0.19 mmol), 1,4-dioxane (10 mL), followed by
 5 potassium phosphate tribasic (2.8 g, 13 mmol) dissolved in water (3 mL). The vessel was flushed with N₂, capped, and the reaction mixture was stirred at 85 °C. After 18 h, the reaction mixture was cooled, diluted with water (100 mL), and extracted with EtOAc (2x50 mL). The organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (80
 10 g silica gel cartridge; A = DCM, B = MeOH; 30 min grad.; 0% B to 15%B; flow rate = 60 mL/min). The pure fractions were combined, concentrated and dried in vacuo to afford the title compound (1.3 g, 3.7 mmol, 100 % yield) as a pale yellow solid. ¹H NMR (500 MHz, CHLOROFORM-d) δ 7.32-7.29 (m, 1H), 7.03-6.95 (m, 1H), 6.62-6.54 (m, 1H), 5.90-5.84 (m, 1H), 4.11-4.06 (m, 2H), 3.67-3.59 (m, 2H), 3.04-2.98 (m, 2H), 2.94-2.87
 15 (m, 3H), 1.52-1.52 (m, 9H). Analytical LC/MS (Method 4): Observed Mass: 251.8 (des-Boc); Retention Time: 2.276 min.

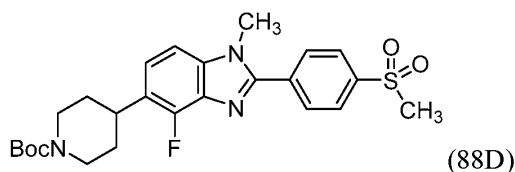
Step C. Intermediate 88C. Preparation of tert-butyl 4-(3-amino-2-fluoro-4-(methylamino)phenyl)piperidine-1-carboxylate



To a 100 mL hydrogenation vessel were added Intermediate 88B (1.3 g, 3.7 mmol), MeOH (30 mL), and 5% Pd-C (% wt. on carbon, wet) (0.79 g, 0.37 mmol). The vessel was purged with N₂ (3x) and stirred under H₂ at 50 psi. After 18 h, the catalyst was filtered and the filtrate was concentrated. The residue was purified by flash column
 25 chromatography (120 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100%B; flow rate = 80 mL/min). The fractions corresponding to product were combined,

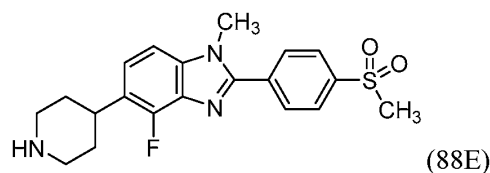
concentrated and dried in vacuo to afford the title compound (0.63 g, 2.0 mmol, 54 % yield) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 6.59-6.53 (m, 1H), 6.38 (d, *J*=8.3 Hz, 1H), 4.25-4.16 (m, 2H), 2.96-2.86 (m, 2H), 2.84-2.80 (m, 3H), 1.84-1.74 (m, 2H), 1.67-1.55 (m, 2H), 1.50 (s, 9H) (one proton obscured). Analytical LC/MS (Method 4): Observed Mass: 267.9 (-tBu); Retention Time: 1.500 min.

Step D. Intermediate 88D. Preparation of tert-butyl 4-(4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-5-yl)piperidine-1-carboxylate



To a 250 mL round bottomed flask were added Intermediate 88C (0.63 g, 2.0 mmol) and NMP (15 mL). To this mixture was added sodium metabisulfite (0.56 g, 2.9 mmol), followed by 4-(methylsulfonyl)benzaldehyde (0.36 g, 2.0 mmol). The reaction mixture was heated to 70 °C and stirred under N₂. After 18 h, the reaction mixture was cooled, the mixture was diluted with water (100 mL) and the organic phase was extracted with EtOAc (2x50 mL), the combined extract was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (120 g silica gel cartridge; A = DCM, B = MeOH; 30 min grad.; 0% B to 15 %B; flow rate = 80 mL/min). The fractions corresponding to product were combined, concentrated and dried in vacuo (0.90 g, 1.8 mmol, 90 % yield) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.22-8.17 (m, 2H), 8.13-8.07 (m, 2H), 7.43-7.39 (m, 1H), 7.35-7.29 (m, 1H), 4.32-4.22 (m, 2H), 3.95 (s, 3H), 3.35-3.32 (m, 5H), 3.26-3.22 (m, 3H), 1.89-1.82 (m, 2H), 1.52 (s, 9H). Analytical LC/MS (Method 4): Observed Mass: 488.1; Retention Time: 1.839 min.

Step E. Intermediate 88E. Preparation of 4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(piperidin-4-yl)-1H-benzo[d]imidazole hydrochloride



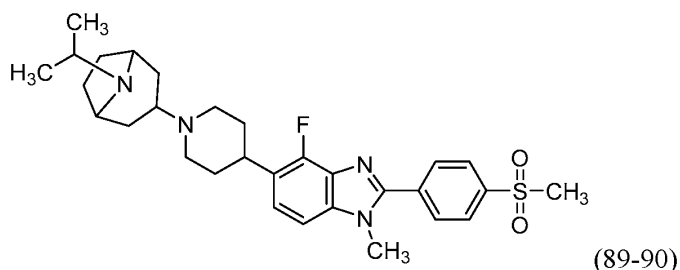
To a 100 mL pear shaped flask were added Intermediate 88D (0.90 g, 1.8 mmol), MeOH (20 mL), and 4 M HCl in dioxane (20 mL). After stirring 30 min, the solvent was concentrated and the residue was co-evaporated with toluene (2x), and the product was dried in vacuo to afford the title compound (0.76 g, 1.8 mmol, 100 % yield) as a tan solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.39-8.32 (m, 2H), 8.24-8.19 (m, 2H), 7.88-7.81 (m, 1H), 7.74-7.67 (m, 1H), 4.17-4.09 (m, 3H), 3.63-3.57 (m, 2H), 3.56-3.44 (m, 2H), 3.29 (s, 3H), 2.90-2.81 (m, 1H), 2.42-2.35 (m, 1H), 2.22-2.13 (m, 3H). Analytical LC/MS (Method 4): Observed Mass: 387.9; Retention Time: 0.934 min.

Step F. Example 88

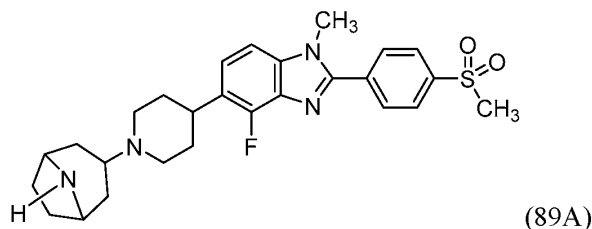
To a 40 mL vial were added Intermediate 88E (64 mg, 0.15 mmol), 1-isopropylpiperidin-4-one (110 mg, 0.76 mmol), AcOH (9.6 μL, 0.17 mmol), magnesium sulfate (280 mg, 2.3 mmol), and DMF (2 mL). The reaction mixture was stirred for 10 min, then sodium triacetoxyborohydride (160 mg, 0.76 mmol) was added and the reaction mixture was stirred. After 18 h, the reaction mixture was diluted with 10% IPA/CHCl₃ (40 mL) and filtered. The filtrate was partitioned into 10% KOH (sat. with solid NaCl) (20 mL) and the layers were separated. The aqueous phase was extracted with 10% IPA/CHCl₃ (10 mL), the organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The crude material was purified by preparative HPLC (Prep Method 1) to afford the title compound (40 mg, 0.078 mmol, 52 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 8.18-8.10 (m, 4H), 7.49-7.42 (m, 1H), 7.33-7.25 (m, 1H), 3.96-3.87 (m, 3H), 3.50-3.48 (m, 6H), 3.05-2.98 (m, 2H), 2.96-2.88 (m, 2H), 2.40-2.27 (m, 3H), 2.27-2.13 (m, 2H), 1.85-1.73 (m, 5H), 1.55-1.42 (m, 2H), 1.00 (br d, *J*=6.2 Hz, 6H). Analytical LC/MS (Method 1): Purity: 98.3 %; Observed Mass: 513.27; Retention Time: 0.96 min. (Method 2): Purity: 97.5 %; Observed Mass: 512.99; Retention Time: 1.19 min. TLR9 IC₅₀ (nM) = 360.

EXAMPLES 89 AND 90

4-fluoro-5-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole



Step A. Intermediate 89A. Preparation of 5-(1-(8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole dihydrochloride



Intermediate 89A was synthesized according to the general procedures described for the preparation of Intermediate 84A, substituting Intermediate 88E (0.41 g, 0.98 mmol) where appropriate to afford the title compound (0.51 g, 0.90 mmol, 92 % yield) as a light tan solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.30-8.24 (m, 2H), 8.19-8.13 (m, 2H), 7.64 (s, 1H), 7.58-7.51 (m, 1H), 4.32-4.20 (m, 3H), 4.12-4.03 (m, 6H), 3.86-3.79 (m, 2H), 3.78-3.74 (m, 1H), 3.72-3.66 (m, 3H), 3.64-3.58 (m, 1H), 3.50-3.43 (m, 2H), 3.30-3.25 (m, 5H), 2.41-2.38 (m, 3H). Analytical LC/MS (Method 4): Observed Mass: 497.2; Retention Time: 0.903 min.

Step B. Examples 89 and 90

Examples 89 and 90 were synthesized according to the general procedures described for the preparation of Examples 17 and 18 (Step B), using Intermediate 89A (75 mg, 0.13 mmol) as starting material. The crude isomeric mixture was purified via preparative HPLC with the following conditions: Column: XBridge C18, 200 mm x 19 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile: water with ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with ammonium acetate; Gradient: a 0-minute

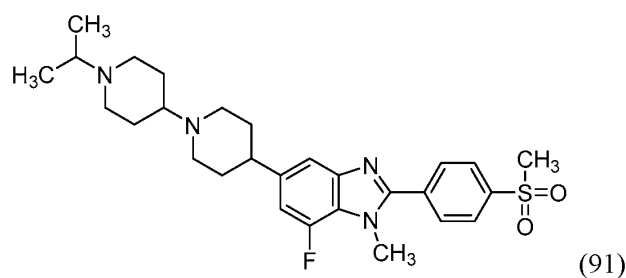
hold at 5% B, 5-55% B over 20 minutes, then a 0-minute hold at 100% B; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS signals. Fractions corresponding to the respective desired products were combined and dried via centrifugal evaporation.

5 Example 89 (14 mg, 0.026 mmol, 20 % yield) was isolated as the 1st eluting isomer. ¹H NMR (500 MHz, DMSO-d₆) δ 8.11 (s, 4H), 7.43 (d, *J*=8.6 Hz, 1H), 7.30-7.24 (m, 1H), 3.88 (s, 3H), 3.28 (s, 3H), 3.05-2.99 (m, 2H), 2.97-2.83 (m, 2H), 2.73-2.60 (m, 1H), 2.27-2.17 (m, 2H), 1.90-1.83 (m, 2H), 1.82-1.65 (m, 8H), 1.64-1.52 (m, 4H), 1.07 (br d, *J*=6.1 Hz, 6H). Analytical LC/MS (Method 1): Purity: 97.4 %; Observed Mass: 539.27; Retention Time: 1.02 min. (Method 2): Purity: 97.4 %; Observed Mass: 539.01; Retention Time: 1.3 min. TLR9 IC₅₀ (nM) = 160.

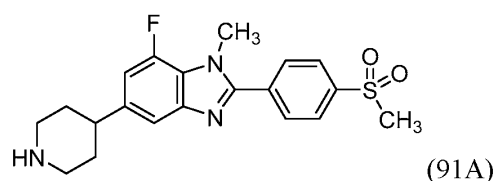
 Example 90 (7.3 mg, 0.014 mmol, 11 % yield) was isolated as the 2nd eluting isomer. ¹H NMR (500 MHz, DMSO-d₆) δ 8.14-8.10 (m, 4H), 7.46-7.42 (m, 1H), 7.31-7.24 (m, 1H), 3.92-3.88 (m, 3H), 3.68-3.54 (m, 5H), 3.28 (s, 4H), 2.00-1.90 (m, 4H), 1.89-1.81 (m, 5H), 1.81-1.70 (m, 6H), 1.14-1.02 (m, 6H). Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 539.01; Retention Time: 1.01 min. (Method 2): Purity: 100 %; Observed Mass: 538.97; Retention Time: 1.50 min. TLR9 IC₅₀ (nM) = 230.

EXAMPLE 91

20 7-fluoro-5-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole



Step A. Intermediate 91A. Preparation of 7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(piperidin-4-yl)-1H-benzo[d]imidazole hydrochloride



Intermediate 91A was synthesized according to the general procedures described for the preparation of Intermediate 88E (Steps A-E), using 4-bromo-2-fluoro-6-nitroaniline (3.0 g, 13 mmol) as starting material to afford the title compound (2.0 g, 4.8 mmol, 37 % yield over 5 steps) as an off-white solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.36 (d, *J*=8.2 Hz, 2H), 8.21 (br d, *J*=8.3 Hz, 2H), 7.66 (s, 1H), 7.55-7.45 (m, 1H), 4.27-4.20 (m, 3H), 3.63-3.55 (m, 2H), 3.29 (s, 3H), 3.28-3.19 (m, 3H), 2.27-2.17 (m, 2H), 2.14-2.01 (m, 2H). Analytical LC/MS (Method 4): Observed Mass: 387.9; Retention Time: 0.969 min.

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Step B. Example 91

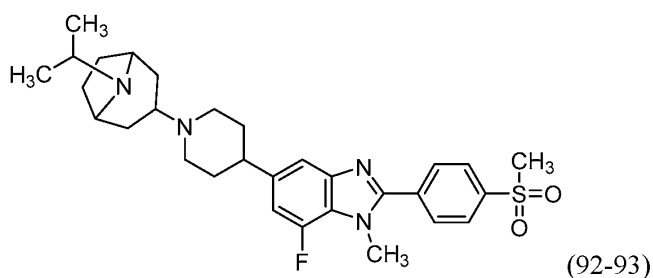
Example 91 was synthesized according to the general procedures described for the preparation of Example 88 (Step F), using Intermediate 91A (60 mg, 0.14 mmol) as starting material. The crude material was purified by preparative HPLC (Prep Method 1) to afford the title compound (58 mg, 0.11 mmol, 85 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 8.17-8.05 (m, 4H), 7.43-7.36 (m, 1H), 7.11-7.01 (m, 1H), 4.00 (s, 3H), 3.55-3.50 (m, 2H), 3.32-3.29 (m, 2H), 3.05-2.99 (m, 2H), 2.98-2.90 (m, 2H), 2.87-2.78 (m, 1H), 2.69-2.58 (m, 1H), 2.39-2.22 (m, 4H), 1.83 (br s, 4H), 1.75-1.64 (m, 2H), 1.56-1.43 (m, 2H), 1.02 (d, *J*=6.6 Hz, 6H). Analytical LC/MS (Method 1): Purity: 97.5 %; Observed Mass: 513.22; Retention Time: 0.95 min. (Method 2): Purity: 97.3 %; Observed Mass: 513.42; Retention Time: 1.17 min. TLR9 IC₅₀ (nM) = 100.

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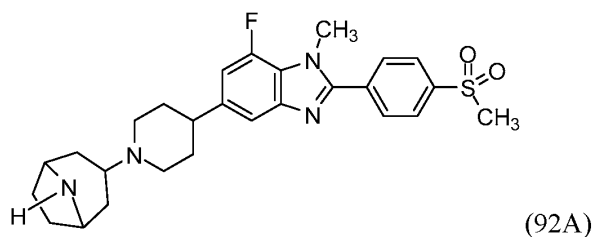
EXAMPLES 92 AND 93

7-fluoro-5-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole

25



Step A. Intermediate 91A. Preparation of 5-(1-(8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole dihydrochloride



5

Intermediate 91A was synthesized according to the general procedures described for the preparation of Intermediate 84A, substituting Intermediate 91A (0.70 g, 1.6 mmol) where appropriate to afford the title compound (0.80 g, 1.4 mmol, 88 % yield) as a tan solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.35-8.30 (m, 2H), 8.20-8.16 (m, 2H), 7.64-7.59 (m, 1H), 7.48-7.40 (m, 1H), 4.30-4.25 (m, 2H), 4.24-4.19 (m, 4H), 4.11-4.02 (m, 4H), 3.83-3.74 (m, 3H), 3.72-3.64 (m, 2H), 3.62-3.58 (m, 1H), 2.40-2.33 (m, 3H), 2.20-2.10 (m, 7H). Analytical LC/MS (Method 4): Observed Mass: 497.2; Retention Time: 0.873 min.

15 Step B. Examples 92 and 93

Examples 92 and 93 were synthesized according to the general procedures described for the preparation of Examples 17 and 18 (Step B), using Intermediate 92A (58 mg, 0.10 mmol) as starting material. The crude isomeric mixture was purified via preparative HPLC with the following conditions: Column: XBridge C18, 200 mm x 19 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile: water with ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with ammonium acetate; Gradient: a 0-minute hold at 4% B, 4-55% B over 20 minutes, then a 0-minute hold at 100% B; Flow Rate: 20

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mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS signals. Fractions corresponding to the respective desired products were combined and dried via centrifugal evaporation.

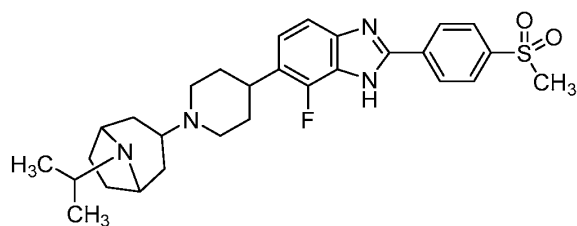
Example 92 (13 mg, 0.026 mmol, 26 % yield) was isolated as the 1st eluting isomer. ¹H NMR (500 MHz, DMSO-d₆) δ 8.16-8.06 (m, 4H), 7.43-7.35 (m, 1H), 7.10-7.02 (m, 1H), 4.01 (s, 3H), 3.32 (s, 2H), 3.01 (br d, *J*=10.4 Hz, 2H), 2.93-2.81 (m, 1H), 2.74-2.57 (m, 2H), 2.55 (s, 3H), 2.29-2.14 (m, 2H), 1.90 (s, 3H), 1.88-1.78 (m, 3H), 1.76-1.60 (m, 4H), 1.59-1.49 (m, 2H), 1.08 (br d, *J*=6.1 Hz, 6H). Analytical LC/MS (Method 1): Purity: 98.3 %; Observed Mass: 539.27; Retention Time: 1.29 min. (Method 2): Purity: 97.6 %; Observed Mass: 538.99; Retention Time: 1.42 min. TLR9 IC₅₀ (nM) = 110.

Example 93 (16 mg, 0.030 mmol, 30 % yield) was isolated as the 2nd eluting isomer. ¹H NMR (500 MHz, DMSO-d₆) δ 8.16-8.05 (m, 4H), 7.39 (s, 1H), 7.07 (br d, *J*=12.8 Hz, 1H), 4.00 (s, 3H), 3.68-3.50 (m, 3H), 3.31-3.25 (m, 4H), 2.85-2.75 (m, 1H), 2.67-2.57 (m, 1H), 2.52 (br s, 4H), 2.40-2.32 (m, 1H), 2.00-1.77 (m, 8H), 1.73-1.62 (m, 2H), 1.09 (br d, *J*=6.1 Hz, 6H). Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 538.93; Retention Time: 0.96 min. (Method 2): Purity: 98.5 %; Observed Mass: 539.02; Retention Time: 1.59 min. TLR9 IC₅₀ (nM) = 650.

20

EXAMPLES 94 AND 95

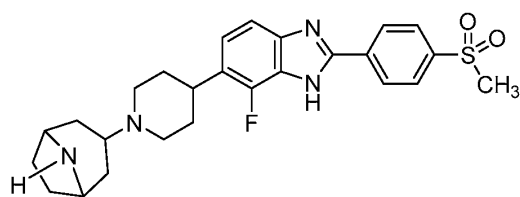
7-fluoro-6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole



(94-95)

Step A. Intermediate 94A. Preparation of 6-(1-(8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-7-fluoro-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole dihydrochloride

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Intermediate 94A was synthesized according to the general procedures described for the preparation of Intermediate 84A, substituting Intermediate 87A (0.48 g, 1.3 mmol) where appropriate to afford the title compound (0.60 g, 1.1 mmol, 85 % yield) as a tan solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.43-8.38 (m, 2H), 8.30-8.27 (m, 2H), 7.68-7.64 (m, 1H), 7.60-7.54 (m, 1H), 4.31-4.27 (m, 2H), 4.26-4.19 (m, 2H), 4.02-3.99 (m, 1H), 3.85-3.80 (m, 2H), 3.79-3.74 (m, 1H), 3.72-3.66 (m, 2H), 3.63-3.59 (m, 1H), 3.57 (s, 2H), 3.38-3.36 (m, 1H), 3.32-3.28 (m, 2H), 3.27-3.23 (m, 5H), 3.20-3.18 (m, 2H), 3.14-3.09 (m, 1H). Analytical LC/MS (Method 4): Observed Mass: 483.1; Retention Time: 0.824 min.

Step B. Examples 94 and 95

Examples 94 and 95 were synthesized according to the general procedures described for the preparation of Examples 17 and 18 (Step B), using Intermediate 94A (100 mg, 0.18 mmol) as starting material. The crude isomeric mixture was purified via preparative HPLC with the following conditions: Column: XBridge C18, 200 mm x 19 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile: water with ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with ammonium acetate; Gradient: a 0-minute hold at 5% B, 5-55% B over 20 minutes, then a 0-minute hold at 100% B; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS signals. Fractions corresponding to the respective desired products were combined and dried via centrifugal evaporation.

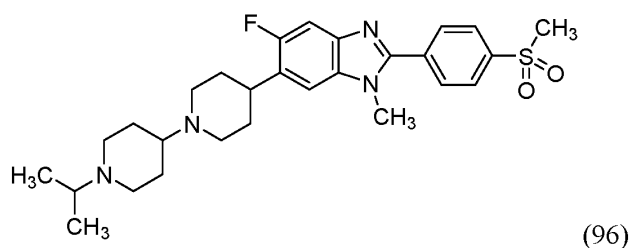
Example 94 (3.8 mg, 0.0072 mmol, 4 % yield) was isolated as the 1st eluting isomer. ¹H NMR (500 MHz, DMSO-d₆) δ 8.56-8.36 (m, 2H), 8.17-8.04 (m, 2H), 7.51-7.37 (m, 1H), 7.28-7.11 (m, 1H), 3.89-3.66 (m, 1H), 3.32-3.28 (m, 1H), 3.21-3.15 (m, 1H), 3.07-3.00 (m, 1H), 2.99-2.86 (m, 2H), 2.83-2.64 (m, 1H), 2.57-2.53 (m, 2H), 2.33-2.21 (m, 2H), 1.98-1.81 (m, 5H), 1.80-1.69 (m, 5H), 1.68-1.49 (m, 4H), 1.17-1.05 (m, 6H). Analytical LC/MS (Method 1): Purity: 97.9 %; Observed Mass: 525.14; Retention

Time: 0.98 min. (Method 2): Purity: 96.9 %; Observed Mass: 525.19; Retention Time: 1.13 min. TLR9 IC₅₀ (nM) = 73.

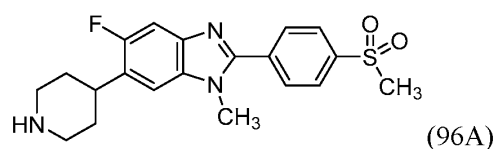
Example 95 (3.0 mg, 0.0057 mmol, 3 % yield) was isolated as the 2nd eluting isomer. ¹H NMR (500 MHz, DMSO-d₆) δ 8.49-8.38 (m, 2H), 8.15-8.07 (m, 2H), 7.45-7.36 (m, 1H), 7.24-7.17 (m, 1H), 3.91 (s, 1H), 3.82-3.66 (m, 1H), 3.55-3.46 (m, 1H), 3.29 (s, 1H), 2.99-2.87 (m, 1H), 2.74-2.62 (m, 1H), 2.57-2.53 (m, 2H), 2.51 (br s, 2H), 2.37 (br s, 1H), 1.97-1.72 (m, 13H), 1.05 (br d, *J*=6.1 Hz, 6H) (one proton obscured). Analytical LC/MS (Method 1): Purity: 96.4 %; Observed Mass: 525.15; Retention Time: 0.98 min. (Method 2): Purity: 97.2 %; Observed Mass: 525.18; Retention Time: 1.34 min. TLR9 IC₅₀ (nM) = 29.

EXAMPLE 96

5-fluoro-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole



Step A. Intermediate 91A. Preparation of 5-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-phenyl)-6-(piperidin-4-yl)-1H-benzo[d]imidazole hydrochloride



Intermediate 96A was synthesized according to the general procedures described for the preparation of Intermediate 88E (Steps B-E), using 5-bromo-4-fluoro-N-methyl-2-nitroaniline (1.1 g, 4.4 mmol) as starting material to afford the title compound (1.4 g, 3.3 mmol, 75 % yield over 4 steps) as a tan solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.39-8.32 (m, 2H), 8.25-8.16 (m, 2H), 8.08-8.00 (m, 1H), 7.74-7.67 (m, 1H), 4.19 (s, 3H), 3.64-3.59 (m, 2H), 3.53-3.45 (m, 1H), 3.35-3.29 (m, 3H), 2.21 (br d, *J*=3.1 Hz, 4H), 2.05 (s, 2H). Analytical LC/MS (Method 4): Observed Mass: 387.9; Retention Time: 0.880

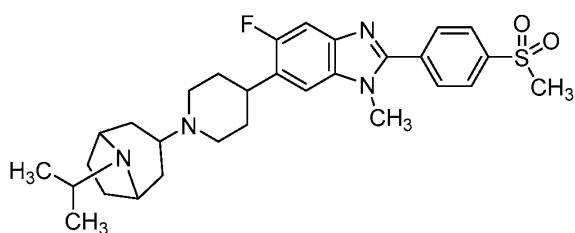
min.

Step B. Example 96

Example 96 was synthesized according to the general procedures described for the preparation of Example 88 (Step F), using Intermediate 96A (75 mg, 0.18 mmol) as starting material. The crude material was purified by preparative HPLC (Prep Method 2) to afford the title compound (24 mg, 0.032 mmol, 18 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 8.15-8.12 (m, 4H), 7.60-7.56 (m, 1H), 7.55-7.51 (m, 1H), 3.98-3.92 (m, 3H), 3.62-3.52 (m, 2H), 3.49-3.38 (m, 1H), 3.36-3.22 (m, 3H), 3.12-3.03 (m, 2H), 2.56-2.54 (m, 3H), 2.53-2.51 (m, 3H), 2.39-2.32 (m, 2H), 2.22-2.09 (m, 4H), 2.09-1.96 (m, 2H), 1.27 (br d, *J*=6.7 Hz, 6H). Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 512.95; Retention Time: 0.89 min. (Method 2): Purity: 100 %; Observed Mass: 513.19; Retention Time: 1.23 min. TLR9 IC₅₀ (nM) = 73.

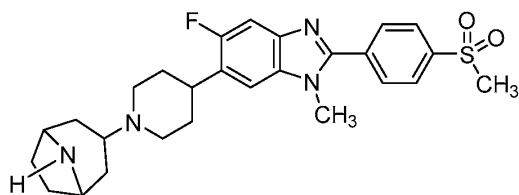
EXAMPLES 97 AND 98

5-fluoro-6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole



(97-98)

Step A. Intermediate 97A. Preparation of 6-(1-(8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-5-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole dihydrochloride



(97A)

Intermediate 97A was synthesized according to the general procedures described for the preparation of Intermediate 84A, substituting Intermediate 96A (0.72 g, 1.7 mmol)

where appropriate to afford the title compound (0.81 g, 1.4 mmol, 82 % yield) as a tan solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.34-8.29 (m, 2H), 8.21-8.15 (m, 2H), 7.96-7.92 (m, 1H), 7.67-7.61 (m, 1H), 4.32-4.27 (m, 2H), 4.25-4.18 (m, 2H), 4.13-4.08 (m, 6H), 3.86-3.82 (m, 2H), 2.42-2.36 (m, 8H), 2.18-2.14 (m, 6H). Analytical LC/MS (Method 4): Observed Mass: 497.2; Retention Time: 0.627 min.

Step B. Examples 97 and 98

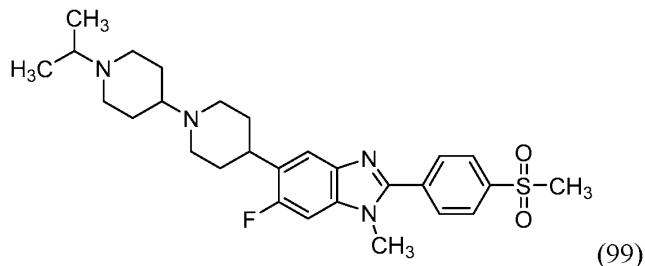
Examples 97 and 98 were synthesized according to the general procedures described for the preparation of Examples 17 and 18 (Step B), using Intermediate 97A (140 mg, 0.24 mmol) as starting material. The crude isomeric mixture was purified via preparative HPLC with the following conditions: Column: XBridge C18, 200 mm x 19 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile: water with ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with ammonium acetate; Gradient: a 0-minute hold at 0% B, 0-48% B over 20 minutes, then a 0-minute hold at 100% B; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS signals. Fractions corresponding to the respective desired products were combined and dried via centrifugal evaporation.

Example 97 (21 mg, 0.039 mmol, 16 % yield) was isolated as the 1st eluting isomer. ¹H NMR (500 MHz, DMSO-d₆) δ 8.11 (s, 4H), 7.58 (br d, *J*=6.7 Hz, 1H), 7.46 (d, *J*=11.0 Hz, 1H), 3.91 (s, 2H), 3.72-3.56 (m, 3H), 3.29 (s, 3H), 3.08-3.00 (m, 2H), 2.94-2.83 (m, 2H), 2.70 (br d, *J*=5.8 Hz, 1H), 2.31-2.18 (m, 2H), 1.90-1.80 (m, 8H), 1.66-1.53 (m, 4H), 1.09 (br d, *J*=6.1 Hz, 6H). Analytical LC/MS (Method 1): Purity: 97.2 %; Observed Mass: 539.11; Retention Time: 0.89 min. (Method 2): Purity: 97.5 %; Observed Mass: 538.95; Retention Time: 1.18 min. TLR9 IC₅₀ (nM) = 79.

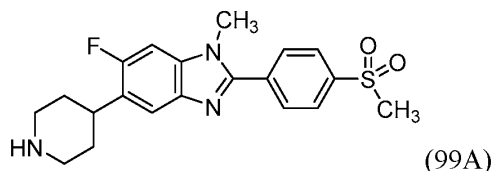
Example 98 (9.4 mg, 0.017 mmol, 7 % yield) was isolated as the 2nd eluting isomer. ¹H NMR (500 MHz, DMSO-d₆) δ 8.17-8.07 (m, 4H), 7.65-7.59 (m, 1H), 7.53-7.44 (m, 1H), 3.95 (s, 3H), 3.69-3.62 (m, 1H), 3.39-3.34 (m, 1H), 3.32 (s, 2H), 3.18 (s, 1H), 2.95-2.80 (m, 2H), 2.37 (br s, 1H), 2.08-1.93 (m, 6H), 1.92-1.77 (m, 10H), 1.12 (br d, *J*=6.1 Hz, 6H). Analytical LC/MS (Method 1): Purity: 97.6 %; Observed Mass: 539.27; Retention Time: 1.37 min. (Method 2): Purity: 100 %; Observed Mass: 539.29; Retention Time: 1.46 min. TLR9 IC₅₀ (nM) = 10.

EXAMPLE 99

6-fluoro-5-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole



- 5 Step A. Intermediate 91A. Preparation of 6-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(piperidin-4-yl)-1H-benzo[d]imidazole hydrochloride



- Intermediate 99A was synthesized according to the general procedures described for the preparation of Intermediate 88E (Steps A-E), using 4-bromo-5-fluoro-2-nitroaniline (3.0 g, 13 mmol) as starting material to afford the title compound (3.4 g, 8.0 mmol, 62 % yield over 5 steps) as an off-white solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.38-8.33 (m, 2H), 8.23-8.19 (m, 2H), 7.94-7.89 (m, 1H), 7.89-7.86 (m, 1H), 4.11 (s, 3H), 3.63-3.57 (m, 2H), 3.53-3.44 (m, 2H), 3.34-3.32 (m, 1H), 3.28 (s, 5H), 2.23-2.19 (m, 2H). Analytical LC/MS (Method 4): Observed Mass: 387.9;
- 15 Retention Time: 0.912 min.

Step B. Example 99

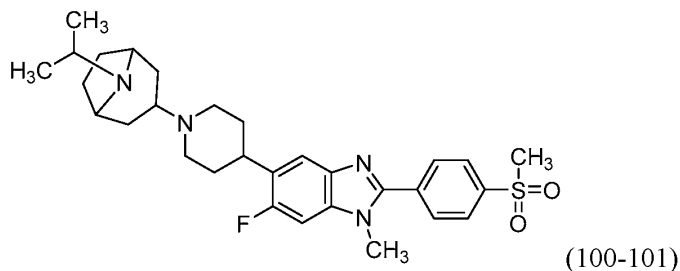
- Example 99 was synthesized according to the general procedures described for the preparation of Example 88 (Step F), using Intermediate 99A (75 mg, 0.18 mmol) as starting material. The crude material was purified by preparative HPLC (Prep Method 1) to afford the title compound (59 mg, 0.12 mmol, 67 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 8.17-8.07 (m, 4H), 7.64-7.59 (m, 1H), 7.56-7.50 (m, 1H), 3.88 (s, 2H), 3.59-3.46 (m, 4H), 3.30 (s, 2H), 3.20-3.15 (m, 1H), 3.05-2.99 (m, 2H), 2.94-2.82 (m, 3H), 2.80-2.71 (m, 1H), 2.31 (br d, *J*=10.1 Hz, 2H), 2.24-2.13 (m, 2H), 1.83-1.72 (m, 4H),
- 20

1.51-1.44 (m, 2H), 1.02-0.92 (m, 6H). Analytical LC/MS (Method 1): Purity: 97 %; Observed Mass: 513.25; Retention Time: 0.94 min. (Method 2): Purity: 96 %; Observed Mass: 513.06; Retention Time: 1.29 min. TLR9 IC₅₀ (nM) = 360.

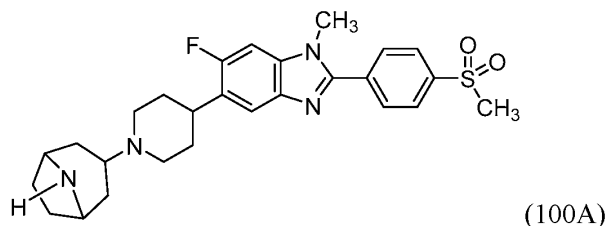
5

EXAMPLES 100 AND 101

6-fluoro-5-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole



Step A. Intermediate 97A. Preparation of 5-(1-(8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-6-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole dihydrochloride



Intermediate 100A was synthesized according to the general procedures described for the preparation of Intermediate 84A, substituting Intermediate 99A (1.6 g, 3.8 mmol) where appropriate to afford the title compound (0.80 g, 1.4 mmol, 37 % yield) as a tan solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.37-8.33 (m, 2H), 8.23-8.17 (m, 2H), 7.93-7.89 (m, 1H), 7.89-7.85 (m, 1H), 4.38-4.33 (m, 2H), 4.32-4.27 (m, 1H), 4.25-4.19 (m, 1H), 4.02-3.98 (m, 1H), 3.88-3.80 (m, 3H), 2.94 (br dd, *J*=17.3, 4.5 Hz, 3H), 2.61-2.58 (m, 1H), 2.57-2.54 (m, 1H), 2.50-2.42 (m, 1H), 2.41-2.31 (m, 4H), 2.31-2.23 (m, 6H), 2.07-2.03 (m, 2H). Analytical LC/MS (Method 4): Observed Mass: 497.0; Retention Time: 0.642 min.

Step B. Examples 100 and 101

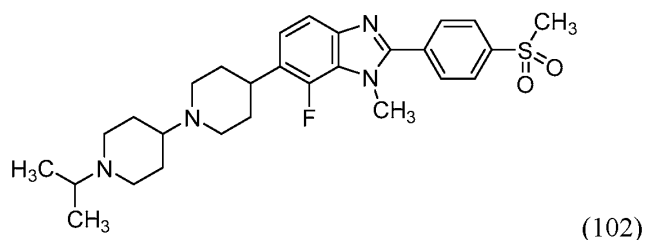
Examples 100 and 101 were synthesized according to the general procedures described for the preparation of Examples 17 and 18 (Step B), using Intermediate 100A (110 mg, 0.20 mmol) as starting material. The crude isomeric mixture was purified via preparative HPLC with the following conditions: Column: XBridge C18, 200 mm x 19 mm, 5- μ m particles; Mobile Phase A: 5:95 acetonitrile: water with ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with ammonium acetate; Gradient: a 0-minute hold at 13% B, 13-55% B over 20 minutes, then a 0-minute hold at 100% B; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS signals. Fractions corresponding to the respective desired products were combined and dried via centrifugal evaporation.

Example 100 (12 mg, 0.022 mmol, 11 % yield) was isolated as the 1st eluting isomer. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.16-8.08 (m, 4H), 7.63-7.59 (m, 1H), 7.57-7.49 (m, 1H), 3.89 (s, 3H), 3.31 (s, 2H), 3.01 (br d, *J*=11.0 Hz, 2H), 2.87-2.72 (m, 2H), 2.68-2.58 (m, 1H), 2.20 (br t, *J*=10.8 Hz, 2H), 1.86 (s, 3H), 1.78 (br s, 4H), 1.75-1.62 (m, 4H), 1.58-1.51 (m, 2H), 1.47-1.40 (m, 2H), 1.01 (d, *J*=6.1 Hz, 6H). Analytical LC/MS (Method 1): Purity: 98.3 %; Observed Mass: 539.23; Retention Time: 0.93 min. (Method 2): Purity: 100 %; Observed Mass: 538.98; Retention Time: 1.39 min. TLR9 IC₅₀ (nM) = 62.

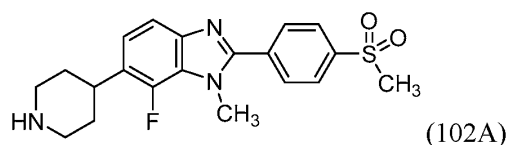
Example 101 (21 mg, 0.039 mmol, 20 % yield) was isolated as the 2nd eluting isomer. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.16-8.07 (m, 4H), 7.64-7.59 (m, 1H), 7.58-7.51 (m, 1H), 3.89 (s, 3H), 3.31 (s, 3H), 2.89-2.79 (m, 1H), 2.72-2.61 (m, 1H), 2.42-2.32 (m, 1H), 1.97-1.69 (m, 17H), 1.04 (d, *J*=5.8 Hz, 6H) (one proton obscured). Analytical LC/MS (Method 1): Purity: 97.7 %; Observed Mass: 539.26; Retention Time: 0.93 min. (Method 2): Purity: 96.4 %; Observed Mass: 538.96; Retention Time: 1.43 min. TLR9 IC₅₀ (nM) = 75.

EXAMPLE 102

7-fluoro-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole



Step A. Intermediate 91A. Preparation of 7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(piperidin-4-yl)-1H-benzo[d]imidazole hydrochloride



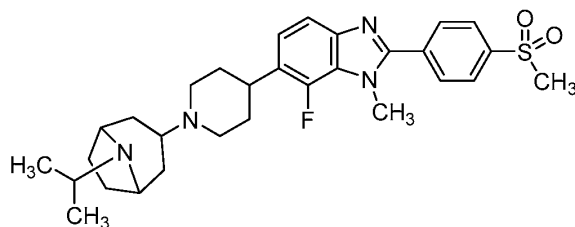
Intermediate 102A was synthesized according to the general procedures described for the preparation of Intermediate 88E (Steps A-E), using 3-bromo-2-fluoro-6-nitroaniline (1.2 g, 5.1 mmol) as starting material to afford the title compound (1.7 g, 4.0 mmol, 78 % yield over 5 steps) as an off-white solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.22-8.17 (m, 2H), 8.11-8.05 (m, 2H), 7.67-7.62 (m, 1H), 7.43-7.40 (m, 1H), 4.29-4.18 (m, 2H), 3.92 (s, 3H), 3.88-3.82 (m, 2H), 3.81-3.75 (m, 1H), 3.23 (s, 3H), 2.10-1.96 (m, 3H), 1.86-1.82 (m, 1H). Analytical LC/MS (Method 4): Observed Mass: 387.9; Retention Time: 0.900 min.

Step B. Example 102

Example 102 was synthesized according to the general procedures described for the preparation of Example 88 (Step F), using Intermediate 102A (71 mg, 0.17 mmol) as starting material. The crude material was purified by preparative HPLC (Prep Method 1) to afford the title compound (30 mg, 0.059 mmol, 35 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 8.16-8.06 (m, 4H), 7.57 (d, *J*=8.5 Hz, 1H), 7.18 (br s, 1H), 4.03 (s, 3H), 3.67-3.46 (m, 4H), 3.42-3.33 (m, 1H), 3.31 (s, 4H), 3.11-3.01 (m, 2H), 2.53 (br d, *J*=18.9 Hz, 3H), 2.39-2.31 (m, 2H), 2.20-1.94 (m, 6H), 1.26 (br d, *J*=6.4 Hz, 6H). Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 512.97; Retention Time: 0.96 min. (Method 2): Purity: 98 %; Observed Mass: 513.19; Retention Time: 1.20 min. TLR9 IC₅₀ (nM) = 30.

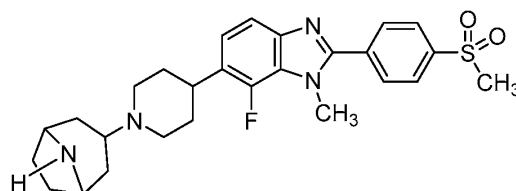
EXAMPLES 103 AND 104

7-fluoro-6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole



(103-104)

- 5 Step A. Intermediate 97A. Preparation of 6-(1-(8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole dihydrochloride



(103A)

- Intermediate 103A was synthesized according to the general procedures described
 10 for the preparation of Intermediate 84A, substituting Intermediate 102A (0.96 g, 2.3 mmol) where appropriate to afford the title compound (1.1 g, 1.9 mmol, 83 % yield) as a tan solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.38-8.34 (m, 2H), 8.23-8.19 (m, 2H), 7.74-7.69 (m, 2H), 4.32-4.28 (m, 2H), 4.27-4.24 (m, 4H), 4.24-4.18 (m, 2H), 4.14-4.07 (m, 2H), 3.86-3.81 (m, 3H), 3.78-3.74 (m, 2H), 3.72-3.66 (m, 3H), 3.62-3.58 (m, 2H),
 15 2.18-2.13 (m, 3H), 2.12-2.08 (m, 3H). Analytical LC/MS (Method 4): Observed Mass: 497.2; Retention Time: 0.892 min.

Step B. Examples 103 and 104

- Examples 103 and 104 were synthesized according to the general procedures
 20 described for the preparation of Examples 17 and 18 (Step B), using Intermediate 103A (150 mg, 0.26 mmol) as starting material. The crude isomeric mixture was purified via preparative HPLC with the following conditions: Column: XBridge C18, 200 mm x 19 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile: water with ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with ammonium acetate; Gradient: a 0-minute

hold at 6% B, 6-56% B over 20 minutes, then a 0-minute hold at 100% B; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS signals. Fractions corresponding to the respective desired products were combined and dried via centrifugal evaporation.

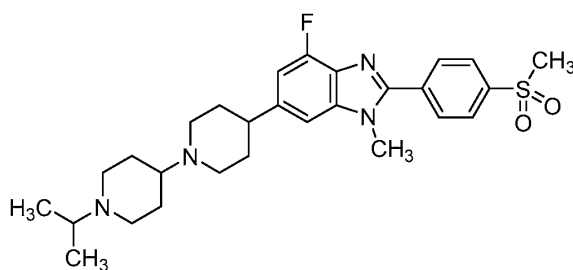
5 Example 103 (25 mg, 0.046 mmol, 18 % yield) was isolated as the 1st eluting isomer. ¹H NMR (500 MHz, DMSO-d₆) δ 8.16-8.06 (m, 4H), 7.53-7.46 (m, 1H), 7.25-7.17 (m, 1H), 4.02 (br d, *J*=0.6 Hz, 3H), 3.77-3.68 (m, 1H), 3.54-3.38 (m, 2H), 3.31 (s, 2H), 3.06-2.88 (m, 2H), 2.83-2.72 (m, 1H), 2.71-2.59 (m, 1H), 2.44-2.34 (m, 1H), 2.27-2.17 (m, 1H), 2.15-2.02 (m, 2H), 1.96-1.72 (m, 8H), 1.71-1.62 (m, 1H), 1.59-1.51 (m, 10 1H), 1.51-1.43 (m, 1H), 1.02 (br d, *J*=6.1 Hz, 6H). Analytical LC/MS (Method 1): Purity: 99.1 %; Observed Mass: 538.96; Retention Time: 1.33 min. (Method 2): Purity: 99.2 %; Observed Mass: 539.01; Retention Time: 1.32 min. TLR9 IC₅₀ (nM) = 54.

 Example 104 (10 mg, 0.019 mmol, 7 % yield) was isolated as the 2nd eluting isomer. ¹H NMR (500 MHz, DMSO-d₆) δ 8.19-8.04 (m, 4H), 7.50 (d, *J*=8.4 Hz, 1H), 15 7.21 (s, 1H), 4.02 (s, 3H), 3.43 (br s, 3H), 3.32 (s, 1H), 3.00-2.88 (m, 1H), 2.68-2.61 (m, 1H), 2.55-2.51 (m, 5H), 2.40-2.34 (m, 1H), 2.05-1.73 (m, 12H), 1.11 (br s, 6H). Analytical LC/MS (Method 1): Purity: 92.2 %; Observed Mass: 539.16; Retention Time: 0.96 min. (Method 2): Purity: 94.9 %; Observed Mass: 539.27; Retention Time: 1.39 min. TLR9 IC₅₀ (nM) = 140.

20

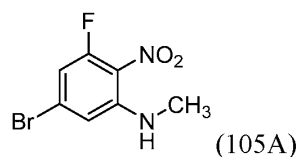
EXAMPLE 105

4-fluoro-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole



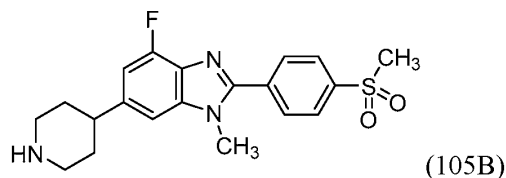
(105)

25 Step A. Intermediate 105A. Preparation of 5-bromo-3-fluoro-N-methyl-2-nitroaniline



To a 250 mL round-bottom flask were added 5-bromo-1,3-difluoro-2-nitrobenzene (7.5 g, 32 mmol), THF (100 mL), followed by the batchwise addition of Cs₂CO₃ (12 g, 38 mmol). The mixture was cooled to 0 °C, and methylamine (2.0 M in THF) (16 mL, 32 mmol) was added dropwise. The mixture was allowed to reach room temperature and stirred under N₂. After 18 h, the reaction mixture was diluted with water (500 mL), extracted with EtOAc (2 x 200 mL), the organic layers were combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (120 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100%B; flow rate = 80 mL/min). The fractions corresponding to product were combined, concentrated and dried in vacuo to afford the title compound (9.5 g, 31 mmol, 97 % yield) as a yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 6.94-6.91 (m, 1H), 6.74-6.69 (m, 1H), 2.96-2.95 (m, 3H). Analytical LC/MS (Method 4): Observed Mass: 250.9; Retention Time: 1.878 min.

Step B. Intermediate 105B. Preparation of 4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(piperidin-4-yl)-1H-benzo[d]imidazole hydrochloride



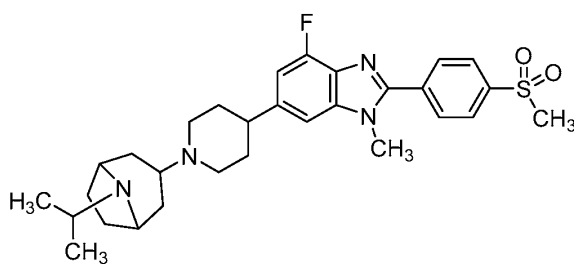
Intermediate 105B was synthesized according to the general procedures described for the preparation of Intermediate 88E (Steps B-E), using Intermediate 105A (3.9 g, 16 mmol) as starting material to afford the title compound (3.6 g, 8.5 mmol, 53 % yield over 4 steps) as a tan solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.34 (d, *J*=8.6 Hz, 2H), 8.21 (d, *J*=8.7 Hz, 2H), 7.80-7.76 (m, 1H), 7.50-7.46 (m, 1H), 4.17-4.12 (m, 3H), 3.63-3.57 (m, 2H), 3.30-3.28 (m, 3H), 3.27-3.20 (m, 3H), 2.28-2.19 (m, 2H), 2.15-2.05 (m, 2H). Analytical LC/MS (Method 4): Observed Mass: 388.0; Retention Time: 0.919 min.

Step C. Example 105

Example 105 was synthesized according to the general procedures described for the preparation of Example 88 (Step F), using Intermediate 105B (40 mg, 0.10 mmol) as starting material. The crude material was purified by preparative HPLC (Prep Method 1) to afford the title compound (36 mg, 0.070 mmol, 70 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 8.19-8.07 (m, 4H), 7.43-7.37 (m, 1H), 7.07-6.99 (m, 1H), 3.92 (s, 3H), 3.46-3.36 (m, 1H), 3.32 (s, 1H), 3.22-3.13 (m, 1H), 3.03-2.96 (m, 2H), 2.90-2.81 (m, 2H), 2.75-2.61 (m, 2H), 2.27 (br s, 3H), 2.16-2.06 (m, 2H), 1.87-1.69 (m, 6H), 1.44 (br d, *J*=9.8 Hz, 2H), 0.97 (d, *J*=6.4 Hz, 6H). Analytical LC/MS (Method 1): Purity: 96.4 %; Observed Mass: 513.37; Retention Time: 1.11 min. (Method 2): Purity: 98.9 %; Observed Mass: 513.37; Retention Time: 1.25 min. TLR9 IC₅₀ (nM) = 95.

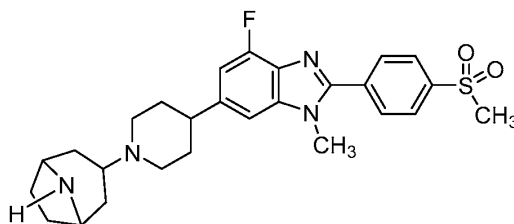
EXAMPLES 106 AND 107

4-fluoro-6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole



(106-107)

Step A. Intermediate 106A. Preparation of 6-(1-(8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole dihydrochloride



(106A)

Intermediate 106A was synthesized according to the general procedures described for the preparation of Intermediate 84A, substituting Intermediate 105B (1.0 g, 2.4 mmol) where appropriate to afford the title compound (0.96 g, 1.7 mmol, 71 % yield) as a tan

solid. ^1H NMR (500 MHz, METHANOL- d_4) δ 8.32-8.28 (m, 2H), 8.19-8.15 (m, 2H), 7.68-7.65 (m, 1H), 7.38-7.33 (m, 1H), 4.31-4.27 (m, 2H), 4.25-4.19 (m, 2H), 4.09 (br d, $J=1.0$ Hz, 9H), 3.85-3.80 (m, 2H), 2.49-2.42 (m, 2H), 2.18-2.11 (m, 9H). Analytical LC/MS (Method 4): Observed Mass: 497.2; Retention Time: 0.868 min.

5

Step B. Examples 106 and 107

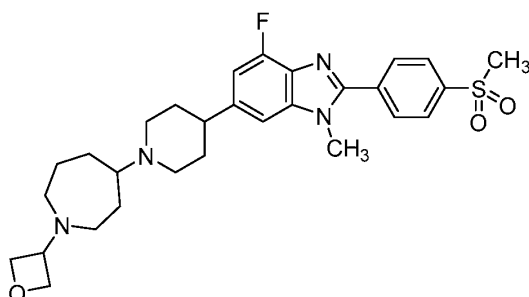
Examples 106 and 107 were synthesized according to the general procedures described for the preparation of Examples 17 and 18 (Step B), using Intermediate 106A (140 mg, 0.25 mmol) as starting material. The crude isomeric mixture was purified via preparative HPLC with the following conditions: Column: XBridge C18, 200 mm x 19 mm, 5- μm particles; Mobile Phase A: 5:95 acetonitrile: water with ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with ammonium acetate; Gradient: a 0-minute hold at 4% B, 4-44% B over 20 minutes, then a 0-minute hold at 100% B; Flow Rate: 20 mL/min; Column Temperature: 25 $^\circ\text{C}$. Fraction collection was triggered by MS signals. Fractions corresponding to the respective desired products were combined and dried via centrifugal evaporation.

Example 106 (11 mg, 0.020 mmol, 8 % yield) was isolated as the 1st eluting isomer. ^1H NMR (500 MHz, DMSO- d_6) δ 8.20-8.08 (m, 4H), 7.43-7.38 (m, 1H), 7.06-6.98 (m, 1H), 3.92 (s, 3H), 3.32 (s, 1H), 3.18 (s, 2H), 3.05-2.99 (m, 2H), 2.85-2.77 (m, 1H), 2.71-2.60 (m, 2H), 2.26-2.15 (m, 2H), 1.91 (s, 3H), 1.87-1.79 (m, 3H), 1.77-1.64 (m, 4H), 1.61-1.53 (m, 2H), 1.52-1.45 (m, 2H), 1.04 (d, $J=6.1$ Hz, 6H). Analytical LC/MS (Method 1): Purity: 95 %; Observed Mass: 539.20; Retention Time: 1.13 min. (Method 2): Purity: 99 %; Observed Mass: 539.20; Retention Time: 1.26 min. TLR9 IC₅₀ (nM) = 390.

Example 107 (10 mg, 0.015 mmol, 6 % yield) was isolated as the 2nd eluting isomer. ^1H NMR (500 MHz, DMSO- d_6) δ 8.17-8.09 (m, 4H), 7.43-7.37 (m, 1H), 7.05-6.98 (m, 1H), 3.93 (s, 3H), 3.32 (s, 3H), 2.70-2.58 (m, 2H), 2.55-2.53 (m, 1H), 2.41-2.32 (m, 1H), 1.96-1.68 (m, 17H), 1.02 (d, $J=5.8$ Hz, 6H). Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 539.20; Retention Time: 1.37 min. (Method 2): Purity: 98 %; Observed Mass: 539.20; Retention Time: 1.46 min. TLR9 IC₅₀ (nM) = 270.

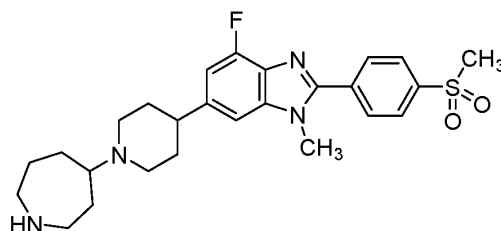
EXAMPLES 108 AND 109

4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(1-(oxetan-3-yl)azepan-4-yl)piperidin-4-yl)-1H-benzo[d]imidazole



(108-109)

Step A. Intermediate 108A. Preparation of 6-(1-(azepan-4-yl)piperidin-4-yl)-4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole dihydrochloride



(108A)

To a 40 mL vial were added Intermediate 105B (1.0 g, 2.4 mmol), tert-butyl 4-oxoazepane-1-carboxylate (2.5 g, 12 mmol), AcOH (0.15 mL, 2.6 mmol), magnesium sulfate (4.3 g, 35 mmol), and DMF (20 mL). The reaction mixture was stirred for 20 min, then sodium triacetoxyborohydride (2.5 g, 12 mmol) was added and the reaction mixture was stirred under N₂. After 18 h, the reaction mixture was diluted with 10% IPA/CHCl₃ (150 mL) and filtered. The filtrate was partitioned into 10% KOH (sat. with solid NaCl) (75 mL) and the layers were separated. The aqueous phase was extracted with 10% IPA/CHCl₃ (75 mL), the organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (40 g silica gel cartridge; A = DCM, B = MeOH; 30 min grad.; 0% B to 20%B; flow rate = 30 mL/min). The fractions corresponding to product were combined, concentrated and dried in vacuo. The resultant residue was dissolved in MeOH (40 mL), and 4 M HCl in dioxane (20 mL) and stirred. After 2 h, the solvent was concentrated and the residue was co-evaporated with toluene (2x), and the product was dried in vacuo to afford the title compound (1.3 g, 2.3 mmol, 96 % yield) as a tan solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.35-8.31 (m, 2H), 8.23-8.19 (m, 2H), 7.82-7.76 (m, 1H), 7.51-

7.45 (m, 1H), 4.14 (s, 3H), 3.75-3.53 (m, 5H), 3.50-3.46 (m, 2H), 3.24-3.20 (m, 4H), 3.18-3.14 (m, 3H), 2.66-2.58 (m, 1H), 2.52-2.26 (m, 7H), 2.24-2.16 (m, 1H). Analytical LC/MS (Method 4): Observed Mass: 485.2; Retention Time: 0.867 min.

5 Step B. Examples 108 and 109

To a 40 mL vial were added Intermediate 108A (150 mg, 0.27 mmol), oxetan-3-one (94 mg, 1.3 mmol), AcOH (0.016 mL, 0.29 mmol), magnesium sulfate (470 mg, 3.9 mmol), and DMF (2 mL). The reaction mixture was stirred for 20 min, then sodium triacetoxyborohydride (280 mg, 1.3 mmol) was added and the reaction mixture was
10 stirred. After 18 h, the reaction mixture was diluted with 10% IPA/CHCl₃ (40 mL) and filtered. The filtrate was partitioned into 10% KOH (sat. with solid NaCl) (20 mL) and the layers were separated. The aqueous phase was extracted with 10% IPA/CHCl₃ (10 mL), the organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The crude material was purified by preparative HPLC (Prep Method 1).
15 The resultant racemic mixture was further purified by SFC-chiral chromatography with the following conditions: Instrument: Waters 100 Prep SFC; Column: Chiral AD, 30 x 250 mm. 5 micron; Mobile Phase: 70% CO₂/30% MeOH w/0.1%DEA; Flow Conditions: 100 mL/min.; Detector Wavelength: 220 nm; Injection Details: 300 μ L, 100 mg dissolved in 3 mL MeOH. Fractions corresponding to the respective desired products were
20 combined and dried via centrifugal evaporation.

Example 108 (13 mg, 0.024 mmol, 9 % yield) was isolated as the 1st eluting enantiomer. ¹H NMR (500 MHz, DMSO-d₆) δ 8.20-8.09 (m, 4H), 7.46-7.37 (m, 1H), 7.01 (d, *J*=12.2 Hz, 1H), 4.52 (s, 2H), 4.36 (s, 2H), 3.93 (s, 3H), 3.67-3.53 (m, 1H), 2.97-2.83 (m, 2H), 2.80-2.70 (m, 1H), 2.68-2.60 (m, 1H), 2.55 (s, 1H), 2.47-2.26 (m, 6H),
25 1.88-1.55 (m, 9H), 1.54-1.46 (m, 1H) (two protons obscured). Analytical LC/MS (Method 1): Purity: 95.3 %; Observed Mass: 541.30; Retention Time: 1.02 min. (Method 2): Purity: 97.7 %; Observed Mass: 541.30; Retention Time: 1.18 min. Chiral analytical (SFC Method 1): Purity: >95 %; Retention Time: 17.28 min. TLR9 IC₅₀ (nM) = 260.

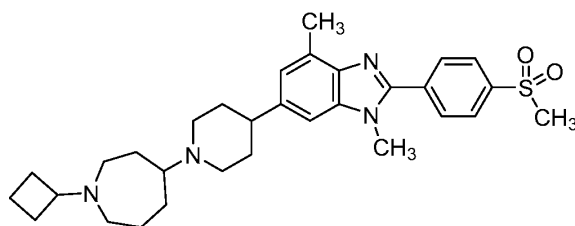
Example 109 (13 mg, 0.024 mmol, 9 % yield) was isolated as the 2nd eluting
30 enantiomer. ¹H NMR (500 MHz, DMSO-d₆) δ 8.22-8.07 (m, 4H), 7.40 (s, 1H), 7.02 (d, *J*=12.2 Hz, 1H), 4.52 (s, 2H), 4.36 (s, 2H), 3.93 (s, 3H), 3.66-3.54 (m, 1H), 3.37-3.27 (m, 1H), 2.98-2.87 (m, 1H), 2.81-2.72 (m, 1H), 2.70-2.60 (m, 1H), 2.55 (s, 1H), 2.49-2.25 (m,

6H), 1.94-1.57 (m, 9H), 1.55-1.45 (m, 1H) (two protons obscured). Analytical LC/MS (Method 1): Purity: 96.9 %; Observed Mass: 541.3; Retention Time: 1.03 min. (Method 2): Purity: 99.3 %; Observed Mass: 541.3; Retention Time: 1.18 min. Chiral analytical (SFC Method 1): Purity: >95 %; Retention Time: 21.24 min. TLR9 IC₅₀ (nM) = 90.

5

EXAMPLES 110 AND 111

6-(1-(1-cyclobutylazepan-4-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole



(110-111)

10 Example 135 (150 mg, 0.27 mmol) was further purified by SFC-chiral chromatography with the following conditions: Instrument: Waters 100 Prep SFC; Column: Chiral AD, 30 x 250 mm. 5 micron; Mobile Phase: 72% CO₂/28% IPA w/0.3%DEA/0.2%FA; Flow Conditions: 100 mL/min.; Detector Wavelength: 220 nm; Injection Details: 500 μ L, 90 mg dissolved in 4 mL IPA. Fractions corresponding to the
15 respective desired products were combined and dried via centrifugal evaporation.

Example 110 (14 mg, 0.026 mmol, 10 % yield) was isolated as the 1st eluting enantiomer. ¹H NMR (500 MHz, DMSO-d₆) δ 8.16-8.06 (m, 4H), 7.36-7.25 (m, 1H), 7.03-6.96 (m, 1H), 3.90 (s, 3H), 2.94-2.87 (m, 3H), 2.82-2.69 (m, 2H), 2.62-2.53 (m, 8H), 2.47-2.34 (m, 5H), 2.05-1.94 (m, 2H), 1.89-1.43 (m, 13H). Analytical LC/MS (Method
20 1): Purity: 97.5 %; Observed Mass: 535.40; Retention Time: 0.89 min. (Method 2): Purity: 100 %; Observed Mass: 535.40; Retention Time: 1.27 min. Chiral analytical (SFC Method 4): Purity: >99 %; Retention Time: 35.0 min. TLR9 IC₅₀ (nM) = 83.

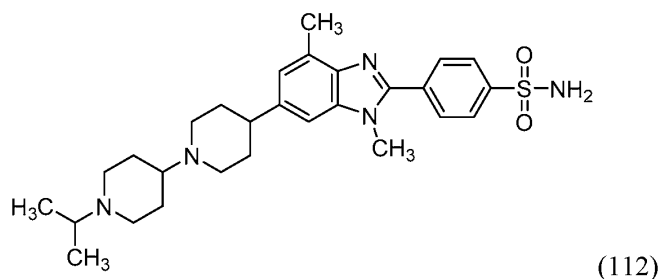
Example 111 (5 mg, 0.0093 mmol, 3 % yield) was isolated as the 2nd eluting enantiomer. ¹H NMR (500 MHz, DMSO-d₆) δ 8.14-8.03 (m, 4H), 7.35-7.25 (m, 1H),
25 7.05-6.96 (m, 1H), 3.88 (br s, 3H), 3.53 (br d, *J*=3.7 Hz, 2H), 3.50-3.34 (m, 3H), 3.30 (br s, 2H), 2.85 (br d, *J*=7.9 Hz, 3H), 2.68 (br s, 1H), 2.48 (dt, *J*=9.1, 4.5 Hz, 1H), 2.42-2.24 (m, 5H), 2.01-1.90 (m, 2H), 1.89-1.39 (m, 14H). Analytical LC/MS (Method 1): Purity:

98.5 %; Observed Mass: 535.20; Retention Time: 0.86 min. (Method 2); Purity: 97.7 %; Observed Mass: 535.30; Retention Time: 1.19 min. Chiral analytical (SFC Method 4): Purity: >99 %; Retention Time: 40.0 min. TLR9 IC₅₀ (nM) = 24.

5

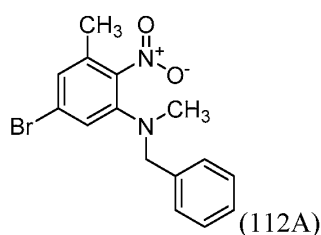
EXAMPLE 112

4-(6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-1H-benzo[d]imidazol-2-yl)benzenesulfonamide



Step A. Intermediate 113A. Preparation of N-benzyl-5-bromo-N,3-dimethyl-2-nitroaniline

10

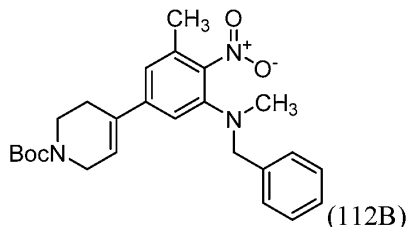


To a 100 mL pear shaped flask were added 5-bromo-1-fluoro-3-methyl-2-nitrobenzene (2.0 g, 8.6 mmol), K₂CO₃ (7.1 g, 51 mmol), DMF (15 mL), followed by N-methyl-1-phenylmethanamine (5.5 mL, 43 mmol). The reaction mixture was stirred at 100 °C for under N₂. After 24 h, the reaction mixture was cooled, diluted with water (150 mL) and extracted with EtOAc (2x75 mL). The organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (120 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100%B; flow rate = 80 mL/min). The pure fractions were combined, concentrated and dried in vacuo to afford the title compound (2.8 g, 8.4 mmol, 98 % yield) as a yellow solid. ¹H NMR (500 MHz, CHLOROFORM-d) δ 7.37-7.31 (m, 2H), 7.30-7.22 (m, 3H), 7.15 (d, *J*=1.8 Hz, 1H), 7.09-7.03 (m, 1H), 4.14 (s, 2H), 2.68-2.62 (m,

20

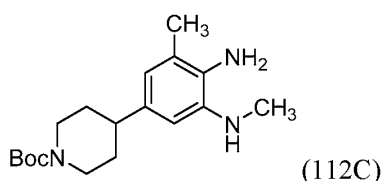
3H), 2.32-2.24 (m, 3H). Analytical LC/MS (Method 4): Observed Mass: 336.9;
Retention Time: 2.519 min.

Step B. Intermediate 112B. Preparation of tert-butyl 4-(3-(benzyl(methyl)amino)-5-methyl-4-nitrophenyl)-3,6-dihydropyridine-1(2H)-carboxylate



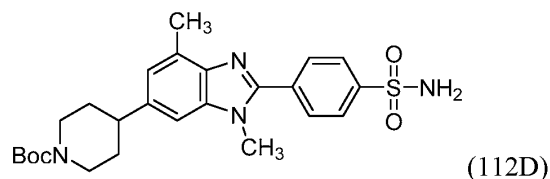
To a 100 mL pear shaped flask were added Intermediate 112A (3.1 g, 9.1 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (3.4 g, 11 mmol), 1,4-dioxane (40 mL), followed by potassium phosphate tribasic (6.8 g, 32 mmol) dissolved in water (8 mL). The vessel was flushed with N₂, Pd(dppf)Cl₂·DCM complex (0.37 g, 0.46 mmol) was added, the vessel flushed again and stirred at 85 °C under N₂. After 18 h, the reaction mixture was cooled, diluted with water (100 mL) and extracted with EtOAc (2x50 mL). The organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (120 g silica gel cartridge; A = Hex, B = EtOAc; 30 min grad.; 0% B to 100%B; flow rate = 80 mL/min). The pure fractions were combined, concentrated and dried in vacuo to afford the title compound (3.8 g, 8.7 mmol, 96 % yield) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.32-7.28 (m, 4H), 7.27-7.22 (m, 1H), 7.21-7.17 (m, 1H), 7.12-7.07 (m, 1H), 6.20-6.07 (m, 1H), 4.16-4.12 (m, 2H), 4.11-4.05 (m, 2H), 3.67-3.60 (m, 2H), 2.65 (s, 3H), 2.55-2.46 (m, 2H), 2.27 (s, 3H), 1.51 (s, 9H). Analytical LC/MS (Method 4): Observed Mass: 438.2; Retention Time: 2.722 min.

Step C. Intermediate 112C. Preparation of tert-butyl 4-(4-amino-3-methyl-5-(methylamino)phenyl)piperidine-1-carboxylate



To a 250 mL pressure vessel was added Intermediate 112B (4.0 g, 9.1 mmol), MeOH (50 mL), and Pd-C (5% wt., wet) (2.0 g, 0.91 mmol). The vessel was evacuated and purged with N₂ (3x) and stirred under H₂ at 50 psi. After 18 h, the reaction mixture was filtered and the filtrate was concentrated. The product was dried in vacuo to afford the title compound (2.9 g, 9.0 mmol, 99 % yield) as a tan semisolid. ¹H NMR (500 MHz, METHANOL-d₄) δ 6.43-6.43 (m, 1H), 6.45-6.40 (m, 1H), 4.26-4.16 (m, 2H), 2.84 (s, 2H), 2.63-2.52 (m, 1H), 2.18 (s, 3H), 1.86-1.75 (m, 2H), 1.63-1.53 (m, 3H), 1.50 (s, 9H), 1.47-1.36 (m, 2H). Analytical LC/MS (Method 4): Observed Mass: 264.0 (-tBu); Retention Time: 1.464 min.

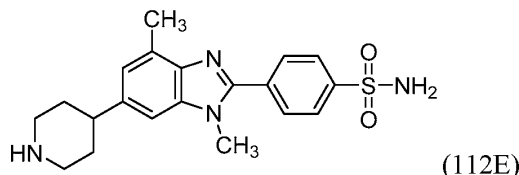
Step D. Intermediate 112D. Preparation of tert-butyl 4-(1,4-dimethyl-2-(4-sulfamoylphenyl)-1H-benzo[d]imidazol-6-yl)piperidine-1-carboxylate



To a 40 mL vial were added Intermediate 112C (0.3 g, 0.94 mmol) and NMP (15 mL). To this mixture was added sodium metabisulfite (0.27 g, 1.4 mmol), followed by 4-formylbenzenesulfonamide (0.19 g, 1.0 mmol). The vessel was capped and the reaction mixture was stirred at 75 °C. After 18 h, the reaction mixture was cooled, diluted with water (250 mL), and extracted with EtOAc (2x100 mL). The organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (120 g silica gel cartridge; A = DCM, B = MeOH; 30 min grad.; 0% B to 15%B; flow rate = 80 mL/min). The fractions corresponding to product were combined, concentrated and dried in vacuo to afford the title compound (0.44 g, 0.91 mmol, 97 % yield) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.14-8.09 (m, 2H), 8.00-7.95 (m, 2H), 7.32-7.26 (m, 1H), 7.10-7.02 (m, 1H), 4.30-4.23 (m, 2H), 3.89 (s, 3H), 3.01-2.86 (m, 3H), 2.64 (s, 3H), 1.96-1.89

(m, 2H), 1.79-1.67 (m, 2H), 1.51 (s, 9H). Analytical LC/MS (Method 4): Observed Mass: 485.2; Retention Time: 1.444 min.

Step E. Intermediate 112E. Preparation of 4-(1,4-dimethyl-6-(piperidin-4-yl)-1H-benzo[d]imidazol-2-yl)benzenesulfonamide hydrochloride



To a 100 mL pear shaped flask were added Intermediate 112D (0.44 g, 0.91 mmol), MeOH (10 mL), and 4 M HCl in dioxane (10 mL). The reaction mixture was stirred for 20 min, the solvent was concentrated and the residue was co-evaporated with toluene (2x). The product was dried in vacuo to afford the title compound (0.38 g, 0. mmol, 99 % yield) as a tan solid. Analytical LC/MS (Method 4): Observed Mass: 385.1; Retention Time: 0.751 min.

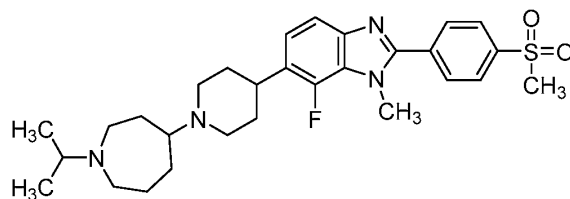
Step F. Example 112

To a 40 mL vial were added Intermediate 112E (100 mg, 0.24 mmol), 1-isopropylpiperidin-4-one (170 mg, 1.2 mmol), AcOH (15 μ L, 0.26 mmol), magnesium sulfate (580 mg, 4.8 mmol), and DMF (2 mL). The reaction mixture was stirred for 10 min, then sodium triacetoxyborohydride (250 mg, 1.2 mmol) was added and the reaction mixture was stirred. After 18 h, the reaction mixture was diluted with 10% IPA/ CHCl_3 (40 mL) and filtered. The filtrate was partitioned into 10% KOH (sat. with solid NaCl) (20 mL) and the layers were separated. The aqueous phase was extracted with 10% IPA/ CHCl_3 (10 mL), the organic phase was combined, washed with brine, dried over MgSO_4 , filtered and concentrated. The crude material was purified by preparative HPLC (Prep Method 1) to afford the title compound to afford the title compound (51 mg, 0.10 mmol, 42 % yield). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.06-7.96 (m, 4H), 7.32-7.27 (m, 1H), 7.02-6.95 (m, 1H), 3.06-2.98 (m, 2H), 2.95-2.87 (m, 2H), 2.83-2.74 (m, 1H), 2.67-2.57 (m, 1H), 2.38-2.26 (m, 3H), 2.25-2.18 (m, 2H), 1.92 (br s, 5H), 1.82 (br s, 6H), 1.56-1.44 (m, 2H), 1.00 (d, $J=6.4$ Hz, 6H) (three protons obscured). Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 510.30; Retention Time: 0.86 min. (Method

2): Purity: 100 %; Observed Mass: 510.20; Retention Time: 1.13 min. TLR9 IC₅₀ (nM) = 130.

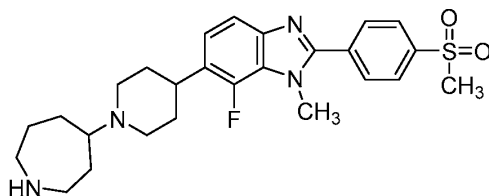
EXAMPLES 113 AND 114

5 7-fluoro-6-(1-(1-isopropylazepan-4-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole



(113-114)

Step A. Intermediate 113A. Preparation of 6-(1-(azepan-4-yl)piperidin-4-yl)-7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole dihydrochloride



(113A)

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Intermediate 114A was synthesized according to the general procedures described for the preparation of Intermediate 109A, substituting Intermediate 102A (1.4 g, 3.3 mmol) where appropriate to afford the title compound (1.6 g, 2.9 mmol, 87 % yield) as a pale yellow solid. Analytical LC/MS (Method 4): Observed Mass: 485.2; Retention

15 Time: 0.887 min.

Step B. Examples 113 and 114

Examples 113 and 114 were synthesized according to the general procedures described for the preparation of Examples 108 and 109 (Step B), using Intermediate 113A (150 mg, 0.27 mmol) as starting material. The crude mixture was purified via preparative HPLC (Prep Method 1). The resultant racemic mixture was further purified by SFC-chiral chromatography with the following conditions: Instrument: Waters 100 Prep SFC; Column: Chiral AD, 30 x 250 mm. 5 micron; Mobile Phase: 62% CO₂/38% IPA w/0.3%DEA/0.2%FA; Flow Conditions: 100 mL/min.; Detector Wavelength: 220 nm;

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Injection Details: 400 μ L, 30 mg dissolved in 2 mL IPA-0.3%DEA/0.2%FA. Fractions corresponding to the respective desired products were combined and dried via centrifugal evaporation.

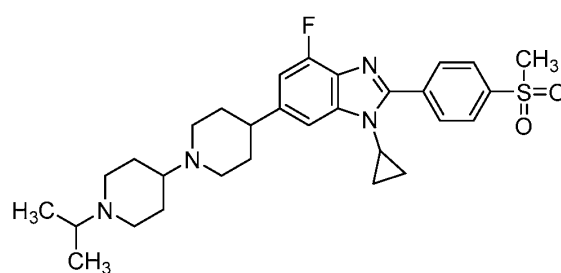
Example 113 (4.2 mg, 0.0080 mmol, 3 % yield) was isolated as the 1st eluting enantiomer. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.15-8.05 (m, 4H), 7.54-7.48 (m, 1H), 7.23-7.17 (m, 1H), 4.02 (s, 3H), 3.32 (s, 1H), 3.00 (br s, 7H), 2.48-2.32 (m, 3H), 2.04-1.94 (m, 1H), 1.81 (br d, *J*=1.4 Hz, 10H), 1.33-1.22 (m, 2H), 1.18-1.09 (m, 6H). Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 527.20; Retention Time: 0.99 min. (Method 2): Purity: 100 %; Observed Mass: 527.10; Retention Time: 1.24 min. Chiral analytical (SFC Method 5): Purity: >99 %; Retention Time: 15.2 min. TLR9 IC₅₀ (nM) = 32.

Example 114 (5.8 mg, 0.011 mmol, 4 % yield) was isolated as the 2nd eluting enantiomer. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.41-8.02 (m, 4H), 7.70-7.44 (m, 1H), 7.35-7.07 (m, 1H), 4.03 (br s, 1H), 3.97-3.86 (m, 1H), 3.41-3.27 (m, 1H), 3.25-3.09 (m, 1H), 3.05-2.72 (m, 3H), 2.57-2.39 (m, 12H), 1.99-1.44 (m, 6H), 1.40-0.77 (m, 8H). Analytical LC/MS (Method 1): Purity: 98.6 %; Observed Mass: 527.20; Retention Time: 0.91 min. (Method 2): Purity: 97.4 %; Observed Mass: 527.30; Retention Time: 1.13 min. Chiral analytical (SFC Method 5): Purity: >95 %; Retention Time: 17.13 min. TLR9 IC₅₀ (nM) = 13.

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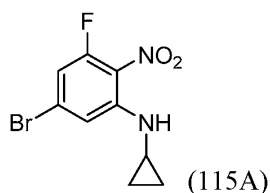
EXAMPLE 115

1-cyclopropyl-4-fluoro-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole



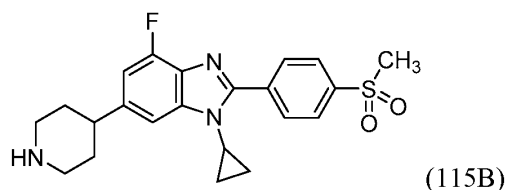
(115)

25 Step A. Intermediate 115A. Preparation of 5-bromo-N-cyclopropyl-3-fluoro-2-nitroaniline



Intermediate 115A was synthesized according to the general procedures described for the preparation of Intermediate 105A, starting with 5-bromo-1,3-difluoro-2-nitrobenzene (8.0 g, 34 mmol), and substituting cyclopropanamine (1.9 g, 34 mmol) where appropriate, to afford the title compound (9.4 g, 34 mmol, 100 % yield) as a yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 7.35-7.27 (m, 1H), 6.81-6.75 (m, 1H), 2.61-2.52 (m, 1H), 0.95-0.89 (m, 2H), 0.63 (dt, *J*=3.4, 1.4 Hz, 2H). Analytical LC/MS (Method): Observed Mass: 276.7; Retention Time: 2.173 min.

- 10 Step B. Intermediate 115B. Preparation of 1-cyclopropyl-4-fluoro-2-(4-(methylsulfonyl)phenyl)-6-(piperidin-4-yl)-1H-benzo[d]imidazole hydrochloride



Intermediate 115B was synthesized according to the general procedures described for the preparation of Intermediate 88E (Steps B-E), using Intermediate 115A (3.6 g, 13 mmol) as starting material to afford the title compound (2.2 g, 4.9 mmol, 38 % yield over 4 steps) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.35-8.29 (m, 4H), 7.80-7.78 (m, 1H), 7.48-7.44 (m, 1H), 4.07-3.97 (m, 1H), 3.64-3.57 (m, 3H), 3.29 (s, 3H), 3.28-3.22 (m, 2H), 2.27-2.21 (m, 2H), 2.15-2.08 (m, 2H), 1.38-1.29 (m, 2H), 0.92-0.82 (m, 2H). Analytical LC/MS (Method 4): Observed Mass: 414.1; Retention Time: 1.009 min.

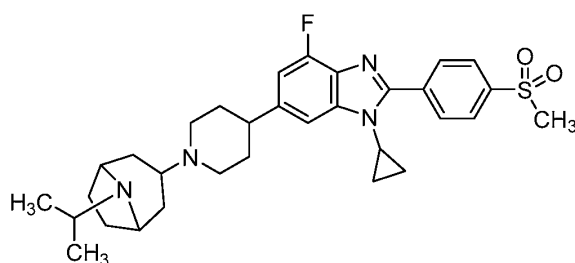
Step C. Example 115

Example 115 was synthesized according to the general procedures described for the preparation of Example 88 (Step F), using Intermediate 115B (75 mg, 0.17 mmol) as starting material. The crude material was purified by preparative HPLC (Prep Method 2)

to afford the title compound (33 mg, 0.043 mmol, 25 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 8.29 (d, *J*=8.5 Hz, 2H), 8.11 (d, *J*=8.2 Hz, 2H), 7.44-7.34 (m, 1H), 7.06-6.95 (m, 1H), 3.93-3.81 (m, 1H), 3.65-3.37 (m, 2H), 3.33 (s, 1H), 3.06 (br s, 3H), 2.59-2.48 (m, 8H), 2.40-2.30 (m, 2H), 2.21-1.92 (m, 6H), 1.27 (br d, *J*=6.7 Hz, 6H), 1.16 (br d, *J*=6.4 Hz, 2H), 0.67 (br s, 2H). Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 539.20; Retention Time: 0.97 min. (Method 2): Purity: 96.8 %; Observed Mass: 539.30; Retention Time: 1.28 min. TLR9 IC₅₀ (nM) = 24.

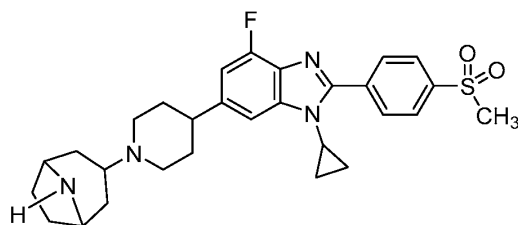
EXAMPLES 116 AND 117

10 1-cyclopropyl-4-fluoro-6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole



(116-117)

Step A. Intermediate 116A. Preparation of 6-(1-(8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-cyclopropyl-4-fluoro-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole dihydrochloride



(116A)

Intermediate 116A was synthesized according to the general procedures described for the preparation of Intermediate 84A, substituting Intermediate 115B (0.68 g, 1.5 mmol) where appropriate to afford the title compound (0.90 g, 1.5 mmol, 100 % yield) as a tan solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.36-8.27 (m, 4H), 7.85-7.81 (m, 1H), 7.19-7.16 (m, 1H), 4.33-4.26 (m, 1H), 4.25-4.17 (m, 1H), 4.08-3.96 (m, 1H), 3.91-3.79 (m, 3H), 3.72-3.65 (m, 1H), 3.29-3.26 (m, 1H), 3.02-2.90 (m, 1H), 2.52-2.42 (m, 1H), 2.40-2.04 (m, 14H), 1.38-1.30 (m, 2H), 0.93-0.85 (m, 2H). Analytical LC/MS

(Method 4): Observed Mass: 523.1; Retention Time: 0.966 min.

Step B. Examples 116 and 117

Examples 116 and 117 were synthesized according to the general procedures described for the preparation of Examples 17 and 18 (Step B), using Intermediate 116A (180 mg, 0.30 mmol) as starting material. The crude isomeric mixture was purified via preparative HPLC with the following conditions: Column: XBridge C18, 200 mm x 19 mm, 5- μ m particles; Mobile Phase A: 5:95 acetonitrile: water with ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with ammonium acetate; Gradient: a 0-minute hold at 3% B, 3-48% B over 20 minutes, then a 0-minute hold at 100% B; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS signals. Fractions corresponding to the respective desired products were combined and dried via centrifugal evaporation.

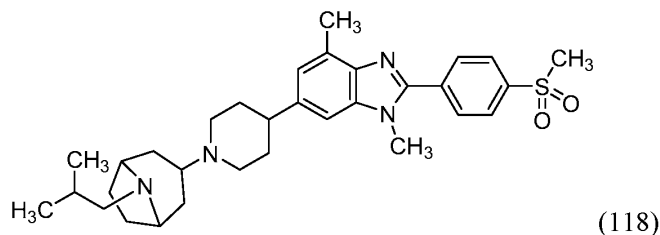
Example 116 (53 mg, 0.094 mmol, 31 % yield) was isolated as the 1st eluting isomer. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.33-8.24 (m, 2H), 8.14-8.06 (m, 2H), 7.38-7.30 (m, 1H), 7.07-6.98 (m, 1H), 3.90-3.80 (m, 1H), 3.33 (s, 1H), 3.05-2.98 (m, 3H), 2.83-2.73 (m, 1H), 2.72-2.57 (m, 2H), 2.18 (br s, 2H), 1.90-1.76 (m, 7H), 1.74-1.60 (m, 4H), 1.54 (br d, *J*=7.6 Hz, 2H), 1.49-1.39 (m, 2H), 1.16 (br d, *J*=6.1 Hz, 2H), 1.02 (d, *J*=5.8 Hz, 6H), 0.65 (br s, 2H). Analytical LC/MS (Method 1): Purity: 97.2 %; Observed Mass: 565.60; Retention Time: 1.01 min. (Method 2): Purity: 95.8 %; Observed Mass: 565.40; Retention Time: 1.31 min. TLR9 IC₅₀ (nM) = 51.

Example 117 (26 mg, 0.046 mmol, 15 % yield) was isolated as the 2nd eluting isomer. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.34-8.22 (m, 2H), 8.16-8.05 (m, 2H), 7.41-7.34 (m, 1H), 7.08-7.00 (m, 1H), 4.26-4.05 (m, 2H), 3.93-3.77 (m, 1H), 3.66-3.39 (m, 2H), 3.32 (s, 3H), 3.20-2.91 (m, 1H), 2.72-2.57 (m, 1H), 2.49-2.34 (m, 1H), 2.33-1.90 (m, 10H), 1.32 (br s, 6H), 1.15 (br d, *J*=6.1 Hz, 3H), 0.66 (br s, 2H) (three protons obscured). Analytical LC/MS (Method 1): Purity: 94.8 %; Observed Mass: 565.30; Retention Time: 1.05 min. (Method 2): Purity: 96.2 %; Observed Mass: 565.30; Retention Time: 1.53 min. TLR9 IC₅₀ (nM) = 71.

EXAMPLE 118

6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-

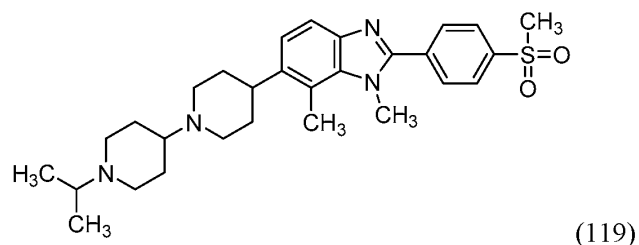
(methylsulfonyl)phenyl)-1H-benzo[d]imidazole



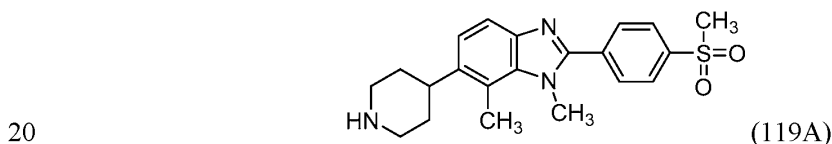
To a solution of NaBH₃CN (50 mg, 0.78 mmol) in methanol (2 mL) was added a solution of ZnCl₂ (0.5 M in THF) (0.13 mL, 0.26 mmol), Intermediate 22C (free amine form) (100 mg, 0.26 mmol) and 8-isobutyl-8-azabicyclo[3.2.1]octan-3-one (140 mg, 0.78 mmol) in sequence. The resulting suspension was stirred at 60 °C for 8 hours. The reaction mixture was purified by preparative HPLC (Prep Method 3) to afford the title compound (27 mg, 0.048 mmol, 18 % yield) as a white solid. ¹H NMR (300 MHz, DMSO-d₆) δ 8.16-8.04 (m, 4H), 7.30 (s, 1H), 6.97 (s, 1H), 3.88 (s, 3H), 3.31-3.29 (m, 2H), 3.22-3.10 (m, 3H), 3.07-2.95 (m, 2H), 2.59-2.51 (m, 5H), 2.24-2.04 (m, 4H), 1.87-1.44 (m, 13H), 0.87 (d, J=5.4 Hz, 6H). Analytical LC/MS (Method 6): Purity: 96.5%; Observed Mass: 549.4; Retention Time: 2.368 min. TLR9 IC₅₀ (nM) = 120.

EXAMPLE 119

6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole



Step A. Intermediate 119A. Preparation of 1,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(piperidin-4-yl)-1H-benzo[d]imidazole



Intermediate 119A was synthesized according to the general procedures described

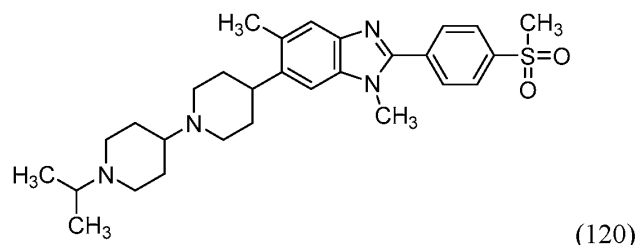
for the preparation of Intermediate 88E (Steps A-E), using 1-bromo-3-fluoro-2-methyl-4-nitro-benzene as starting material. Analytical LC/MS (Method 7): Observed Mass: 384.1; Retention Time: 0.613 min.

5 Step B. Example 119

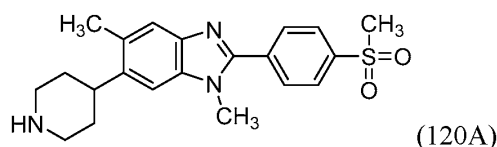
To a solution of ZnCl₂ (2 M solution in THF) (0.1 mL) in methanol (2 mL) was added NaBH₃CN (50 mg, 0.78 mmol). The resulting mixture was stirred at room temperature for 10 min., then Intermediate 119A (60 mg, 0.16 mmol) and 1-isopropylpiperidin-4-one (110.5 mg, 0.78 mmol) were added. After stirring the mixture at 60 °C for 2h, the crude material was purified by preparative HPLC (Prep Method 3) to afford the title compound (22 mg, 27 % yield) as a white solid. ¹H NMR (300 MHz, Chloroform-*d*) δ 8.12 (d, J = 6.9 Hz, 2H), 7.95 (d, J = 6.9 Hz, 2H), 7.65 (d, J = 8.5 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 4.08 (s, 3H), 3.19-3.00 (m, 7H), 2.95-2.86 (m, 2H), 2.78 (s, 3H), 2.47 (s, 3H), 2.35-2.10 (m, 2H), 2.01-1.77 (m, 8H), 1.13 (s, 6H). Analytical LC/MS (Method 6): Purity: 97.9%; Observed Mass: 509.2; Retention Time: 0.562 min. TLR9 IC₅₀ (nM) = 1100.

EXAMPLE 120

6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1,5-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole



Step A. Intermediate 119A. Preparation of 1,5-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(piperidin-4-yl)-1H-benzo[d]imidazole



Intermediate 120A was synthesized according to the general procedures described

for the preparation of Intermediate 88E (Steps A-E), using 1-bromo-5-fluoro-2-methyl-4-nitro-benzene as starting material. Analytical LC/MS (Method 7): Observed Mass: 384.2; Retention Time: 0.584 min.

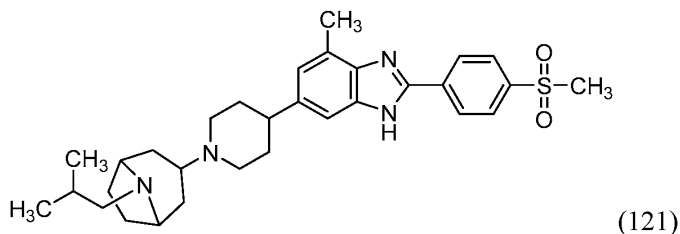
5 Step B. Example 120

Example 120 was synthesized according to the general procedures described for the preparation of Example 119, using Intermediate 120A (100 mg, 0.26 mmol) as starting material. The crude material was purified by preparative HPLC (Prep Method 3) to afford the title compound (51 mg, 37 % yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.15-8.05 (m, 4H), 7.49 (d, J = 15.1 Hz, 2H), 3.91 (s, 3H), 3.31 (s, 3H), 3.00 (dd, J = 10.7, 3.6 Hz, 2H), 2.82 (dd, J = 8.6, 5.9 Hz, 2H), 2.79-2.62 (m, 2H), 2.42 (s, 3H), 2.37-2.15 (m, 3H), 2.08 (t, J = 11.5, 2.2 Hz, 2H), 1.85-1.71 (m, 6H), 1.51-1.35 (m, 2H), 0.95 (d, J = 6.6 Hz, 6H). Analytical LC/MS (Method 6): Purity: 95.6%; Observed Mass: 509.2; Retention Time: 0.57 min. TLR9 IC₅₀ (nM) = 180.

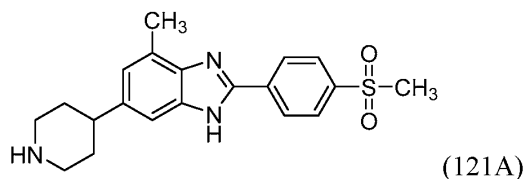
15

EXAMPLE 121

6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole



20 Step A. Intermediate 121A. Preparation of 4-methyl-2-(4-(methylsulfonyl)phenyl)-6-(piperidin-4-yl)-1H-benzo[d]imidazole



Intermediate 121A was synthesized according to the general procedures described for the preparation of Intermediate 11D (Steps A-E), substituting 4-

methylsulfonylbenzaldehyde where appropriate. Analytical LC/MS (Method 8):
Observed Mass: 370.1; Retention Time: 0.873 min.

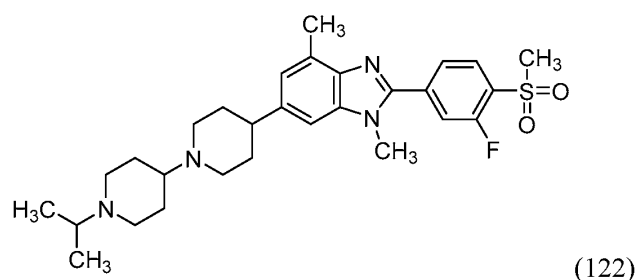
Step B. Example 121

5 Example 121 was synthesized according to the general procedures described for
the preparation of Example 118, using Intermediate 121A (100 mg, 0.27 mmol) as
starting material. The crude material was purified by preparative HPLC (Prep Method 3)
to afford the title compound (65 mg, 0.11 mmol, 43 % yield) as a white solid. ¹H NMR
(400 MHz, Methanol-*d*₄) δ 8.37 (d, *J*=8.4 Hz, 1H), 8.13 (d, *J*=8.4 Hz, 1H), 7.34 (s, 1H),
10 7.04 (s, 1H), 3.34-3.38 (m, 2H), 3.23-3.14 (m, 5H), 2.72-2.60 (m, 5H), 2.33-2.24 (m, 4H),
2.04-1.69 (m, 11H), 1.68-1.61 (m, 2H), 0.98 (d, *J*=5.4 Hz, 6H) (two protons obscured).
Analytical LC/MS (Method 6): Purity: 96.7%; Observed Mass: 535.2; Retention Time:
2.41 min. TLR9 IC₅₀ (nM) = 19.

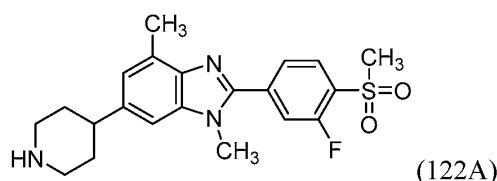
15

EXAMPLE 122

2-(3-fluoro-4-(methylsulfonyl)phenyl)-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1,4-
dimethyl-1H-benzo[d]imidazole



20 Step A. Intermediate 122A. Preparation of 2-(3-fluoro-4-(methylsulfonyl)phenyl)-1,4-
dimethyl-6-(piperidin-4-yl)-1H-benzo[d]imidazole



Intermediate 122A was synthesized according to the general procedures described
for the preparation of Intermediate 112E (Step D-E), substituting 3-fluoro-4-
(methylsulfonyl)benzaldehyde where appropriate. Analytical LC/MS (Method 7):

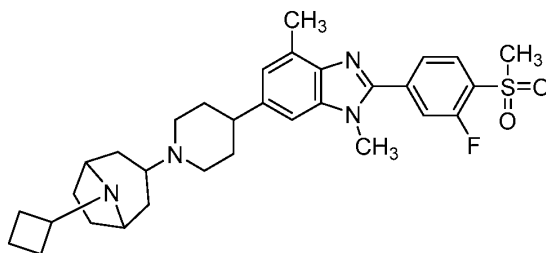
Observed Mass: 402.2; Retention Time: 0.442 min.

Step B. Example 122

Example 121 was synthesized according to the general procedures described for the preparation of Example 119, using Intermediate 122A (100 mg, 0.25 mmol) as starting material. The crude material was purified by preparative HPLC (Prep Method 3) to afford the title compound (19 mg, 0.036, 14 % yield) as a white solid. ¹H NMR (400 MHz, Methanol-d₄) δ 8.19-8.11 (m, 1H), 7.93-7.85 (m, 2H), 7.30 (s, 1H), 7.09 (s, 1H), 3.93 (s, 3H), 3.36 (s, 3H), 3.24-3.12 (m, 4H), 2.95-2.87 (m, 1H), 2.80-2.70 (m, 1H), 2.64 (s, 3H), 2.54-2.38 (m, 5H), 2.06-1.83 (m, 6H), 1.74-1.65 (m, 2H), 1.17 (d, J = 6.6 Hz, 6H). Analytical LC/MS (Method 6): Purity: 97.2%; Observed Mass: 527.1; Retention Time: 1.387 min. TLR9 IC₅₀ (nM) = 140.

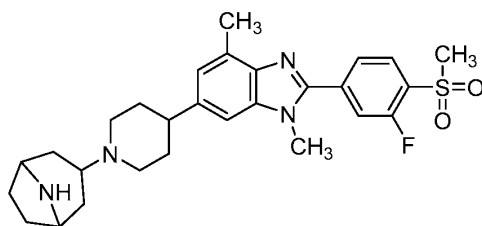
EXAMPLES 123 AND 124

6-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(3-fluoro-4-(methylsulfonyl)phenyl)-1,4-dimethyl-1H-benzo[d]imidazole



(123-124)

Step A. Intermediate 123A. Preparation of 6-(1-(8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(3-fluoro-4-(methylsulfonyl)phenyl)-1,4-dimethyl-1H-benzo[d]imidazole



(123A)

Intermediate 123A was synthesized according to the general procedures described for the preparation of Intermediate 84A, substituting Intermediate 122A to afford the title

compound. Analytical LC/MS (Method 8): Observed Mass: 511.3; Retention Time: 0.590 min.

Step B. Examples 123 and 124

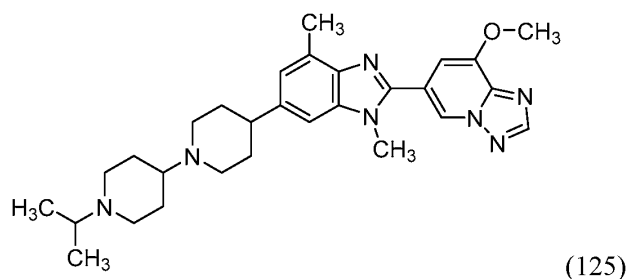
5 To a mixture of Intermediate 123A (100 mg, 0.20 mmol) and cyclobutanone (100 mg, 1.4 mmol) in methanol (5 mL) was added AcOH (0.20 mL, 3.5 mmol). After stirring 0.5 h, NaBH₃CN (150 mg, 2.3 mmol) was added and the reaction mixture was stirred under N₂. After 18 h, the crude reaction mixture was purified by preparative HPLC (Prep Method 3) to afford the title compounds.

10 Example 123 (1.3 mg, 1 % yield) was isolated as a white solid and was the 1st eluting isomer. ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.03 (dd, *J* = 8.3, 7.2 Hz, 1H), 7.77-7.75 (m, 2H), 7.17 (s, 1H), 6.96 (s, 1H), 3.81 (s, 3H), 3.38 (s, 3H), 3.34-3.20 (m, 4H), 3.06-3.03 (m, 1H), 2.60-2.58 (m, 1H), 2.56 (s, 3H), 2.45-2.43 (m, 1H), 2.05-1.53 (m, 20H). Analytical LC/MS (Method 6): Purity: 92.7%; Observed Mass: 565.3; Retention Time: 0.869 min. TLR9 IC₅₀ (nM) = 890.

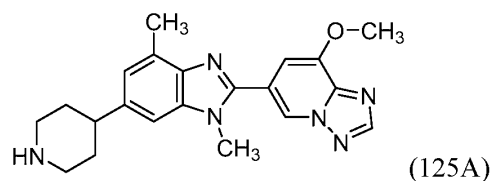
15 Example 124 (9.1 mg, 8 % yield) was isolated as a white solid and was the 2nd eluting isomer. ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.03 (dd, *J* = 8.3, 7.2 Hz, 1H), 7.78-7.74 (m, 2H), 7.17 (s, 1H), 6.96 (s, 1H), 3.81 (s, 3H), 3.23 (s, 3H), 3.21-3.20 (m, 2H), 3.18-3.12 (m, 1H), 3.02 (d, *J* = 11.3 Hz, 2H), 2.65-2.58 (m, 2H), 2.52 (s, 3H), 2.27-2.22 (m, 2H), 2.00-1.96 (m, 2H), 1.90-1.80 (m, 6H), 1.77-1.54 (m, 10H). Analytical LC/MS (Method 6): Purity: 96.2%; Observed Mass: 565.3; Retention Time: 0.882 min. TLR9 IC₅₀ (nM) = 580.

EXAMPLE 125

25 6-(6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-1H-benzo[d]imidazol-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine



Step A. Intermediate 125A. Preparation of 6-(1,4-dimethyl-6-(piperidin-4-yl)-1H-benzo[d]imidazol-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine



Intermediate 124A was synthesized according to the general procedures described for the preparation of Intermediate 112E (Step D-E), substituting 8-methoxy-[1,2,4]triazolo[1,5-a]pyridine-6-carbaldehyde where appropriate. Analytical LC/MS (Method 8): Observed Mass: 377.2; Retention Time: 0.485 min.

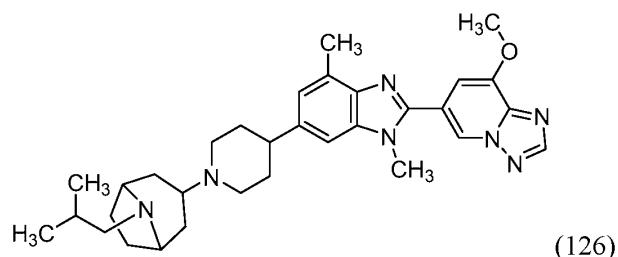
Step B. Example 125

Example 125 was synthesized according to the general procedures described for the preparation of Example 119, using Intermediate 125A (60 mg, 0.16 mmol) as starting material. The crude material was purified by preparative HPLC (Prep Method 3) to afford the title compound (35 mg, 0.069 mmol, 43 % yield) as a white solid. ¹H NMR (300 MHz, Methanol-*d*₄) δ 8.87 (s, 1H), 8.49 (s, 1H), 7.54 (s, 1H), 7.31 (s, 1H), 7.09 (s, 1H), 4.15 (s, 3H), 3.95 (s, 3H), 3.22-3.12 (m, 2H), 3.10-3.01 (m, 2H), 2.80-2.71 (m, 2H), 2.63 (s, 3H), 2.47-2.37 (m, 3H), 2.30-2.24 (m, 2H), 2.03-1.86 (m, 6H), 1.72-1.62 (m, 2H), 1.11 (d, *J* = 8.4 Hz, 6H). Analytical LC/MS (Method 6): Purity: 98.2 %; Observed Mass: 502.1; Retention Time: 0.909 min. TLR9 IC₅₀ (nM) = 28.

20

EXAMPLE 126

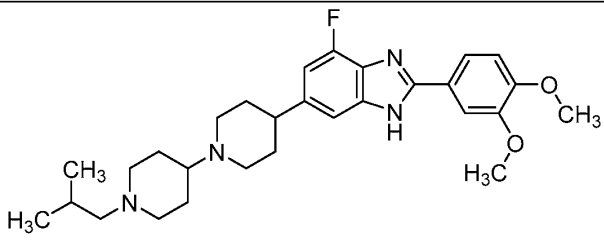
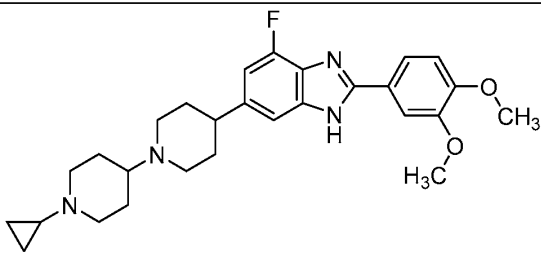
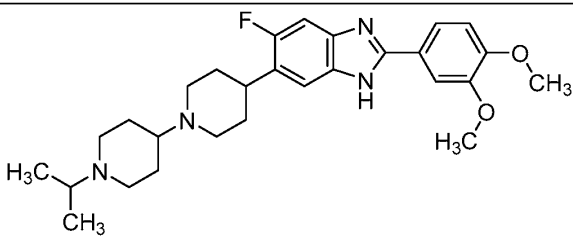
6-(6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-1H-benzo[d]imidazol-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine

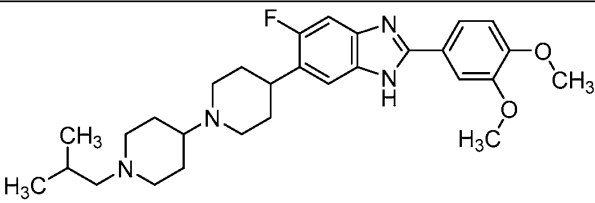
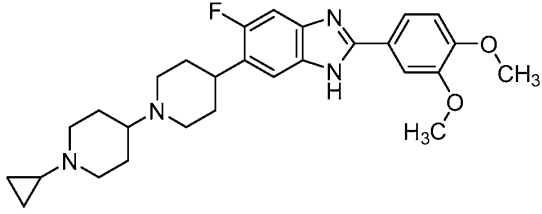
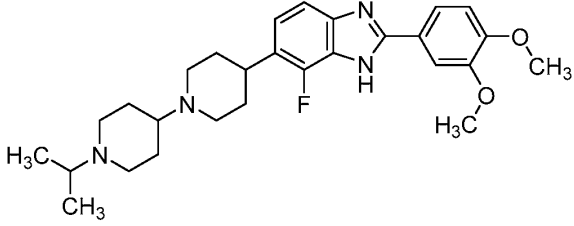
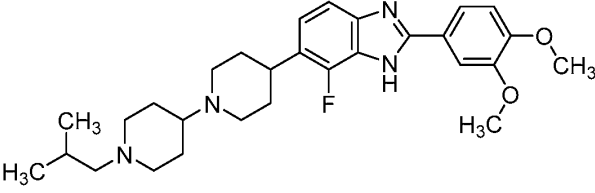
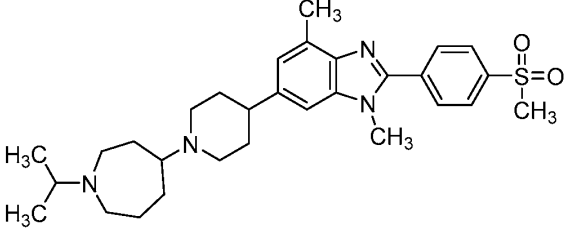
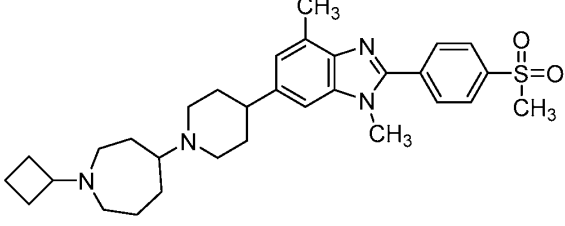


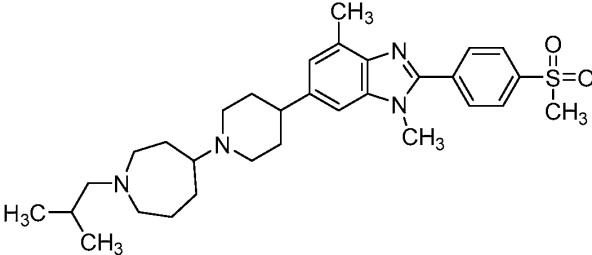
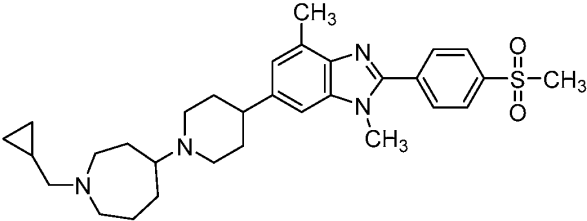
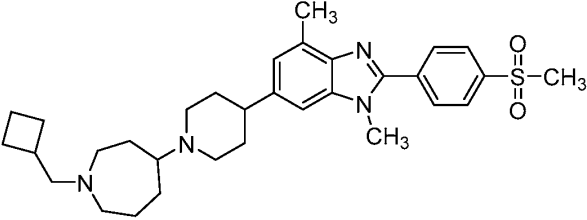
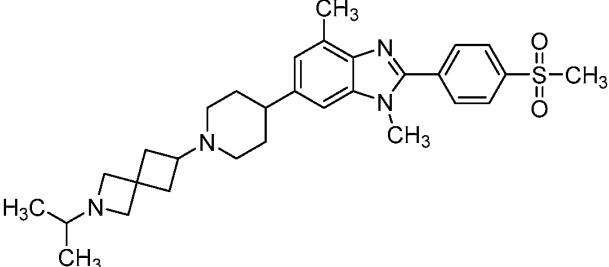
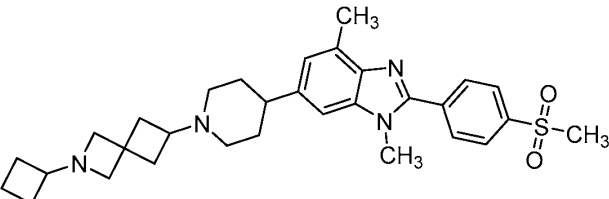
Example 126 was synthesized according to the general procedures described for

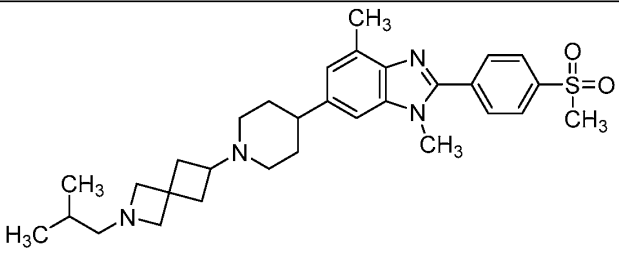
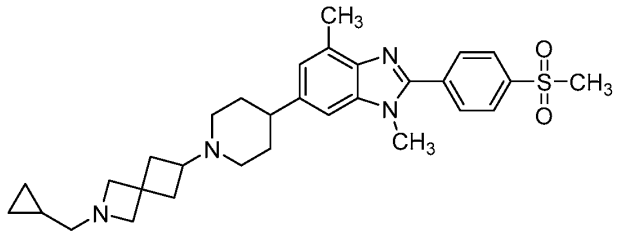
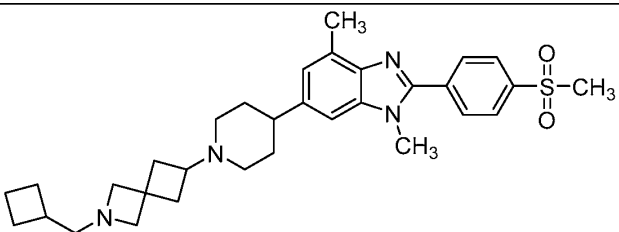
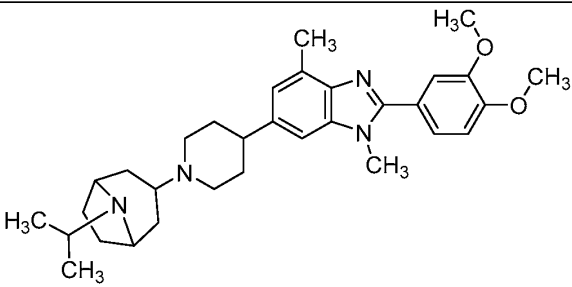
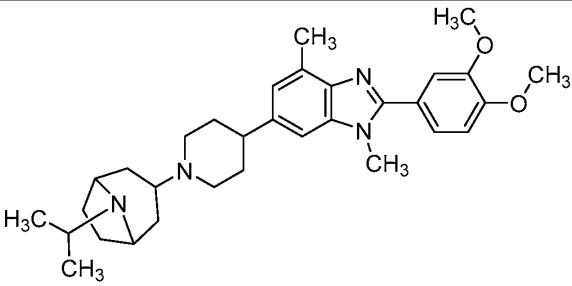
the preparation of Example 118, using Intermediate 125A (80 mg, 0.21 mmol) as starting material. The crude material was purified by preparative HPLC (Prep Method 3) to afford the title compound (21 mg, 0.037 mmol, 17 % yield) as a white solid. ¹H NMR (300 MHz, Methanol-*d*₄) δ 8.88 (s, 1H), 8.48 (s, 1H), 7.48 (s, 1H), 7.29 (s, 1H), 7.07 (s, 1H), 4.17 (s, 3H), 3.96 (s, 3H), 3.34-3.32 (m, 2H), 3.23-3.14 (m, 2H), 2.78-2.60 (m, 5H), 2.35-2.23 (m, 4H), 2.07-1.56 (m, 13H), 0.96 (d, *J* = 6.9 Hz, 6H). Analytical LC/MS (Method 6): Purity: 97.8 %; Observed Mass: 542.3; Retention Time: 0.596 min. TLR9 IC₅₀ (nM) = 590.

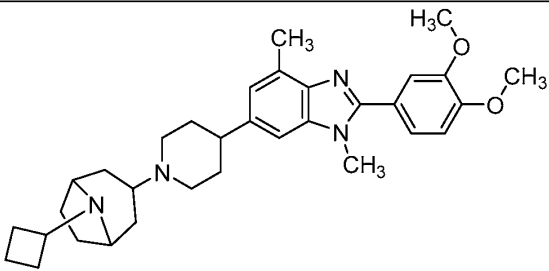
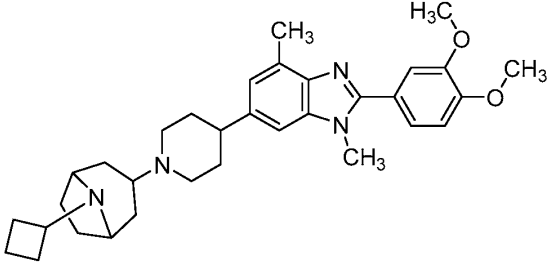
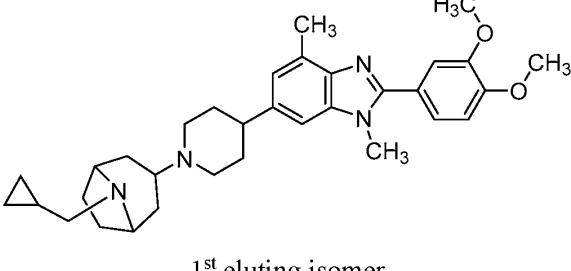
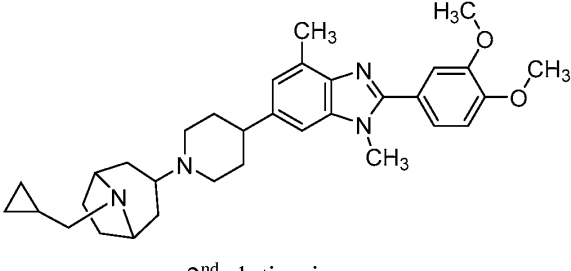
10 The following Examples were prepared according to the general methods described elsewhere herein using appropriate starting materials, reagents and conditions.

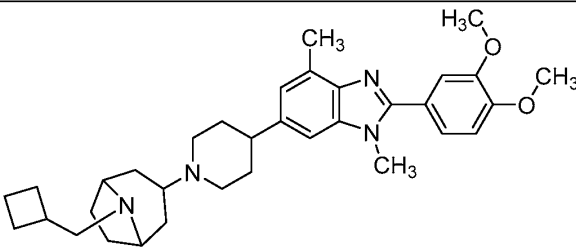
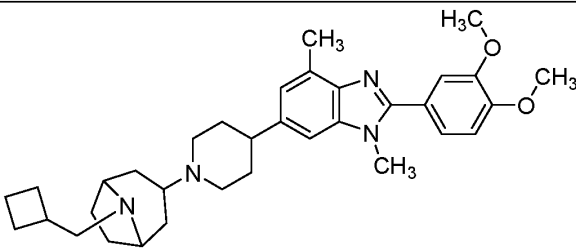
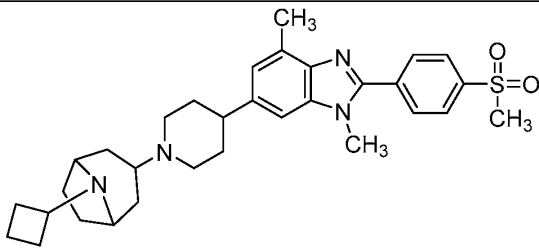
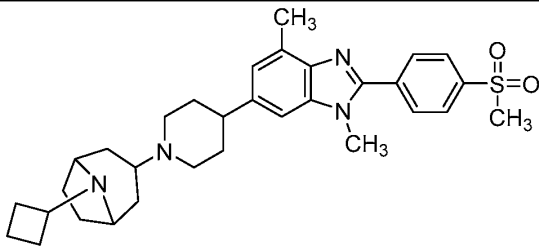
Ex. No.	Structure	Method
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128		Ex. 83
129		Ex. 83

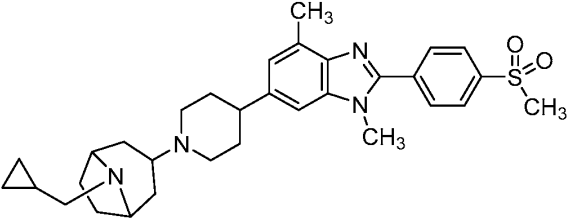
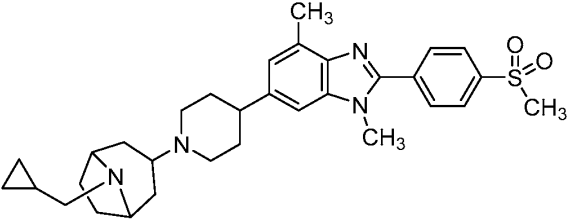
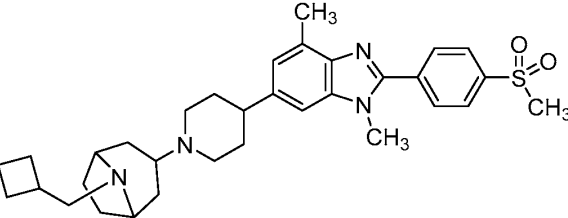
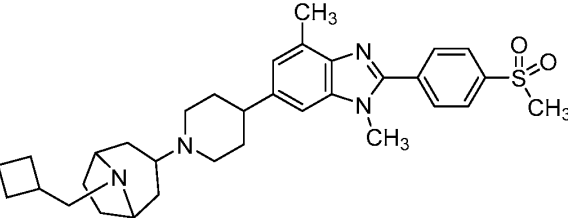
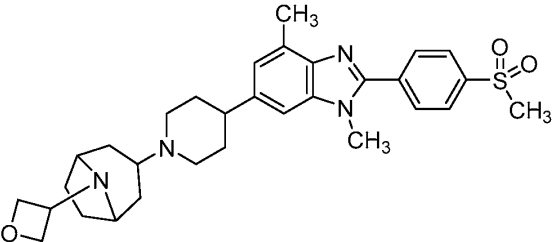
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132		Ex. 83
133		Ex. 83
134		Ex. 22
135		Ex. 22

136		Ex. 22
137		Ex. 22
138		Ex. 22
139		Ex. 22
140		Ex. 22

141		Ex. 22
142		Ex. 22
143		Ex. 22
144	 1st eluting isomer	Ex. 17
145	 2nd eluting isomer	Ex. 17

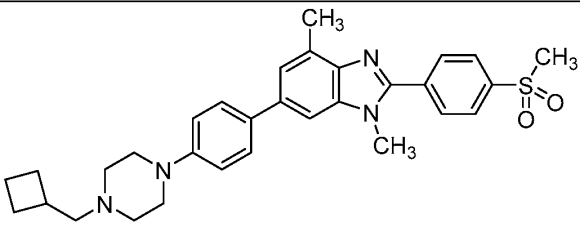
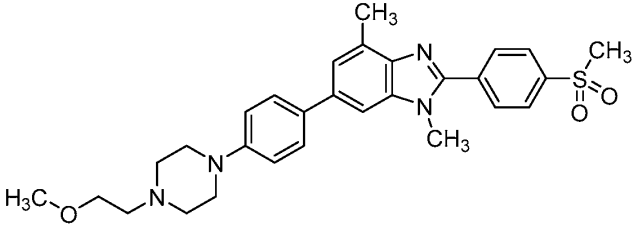
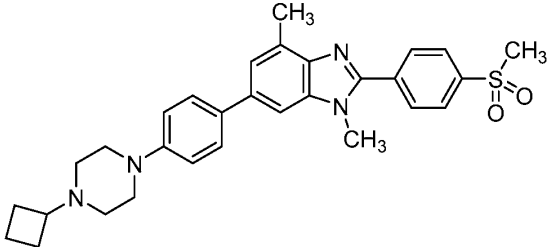
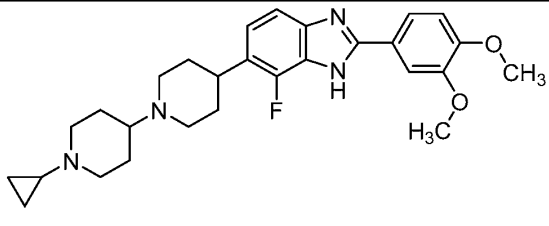
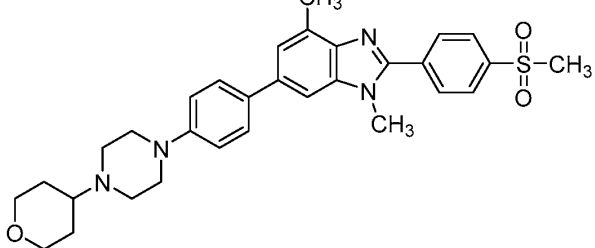
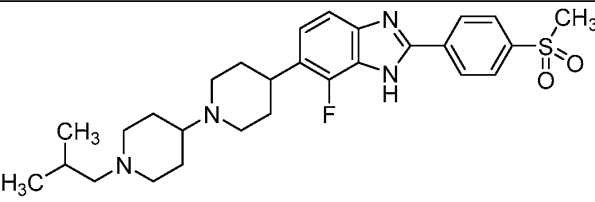
146	 1st eluting isomer	Ex. 17
147	 2nd eluting isomer	Ex. 17
148	 1st eluting isomer	Ex. 17
149	 2nd eluting isomer	Ex. 17

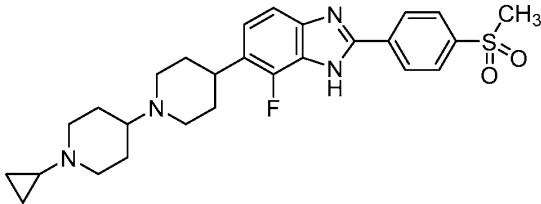
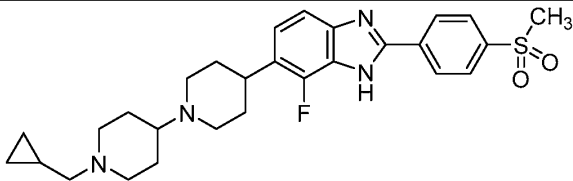
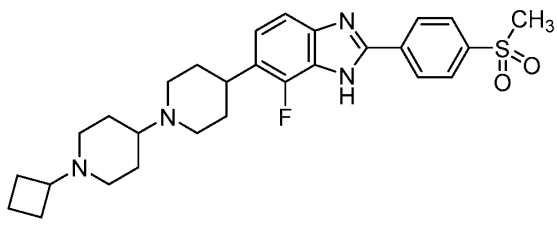
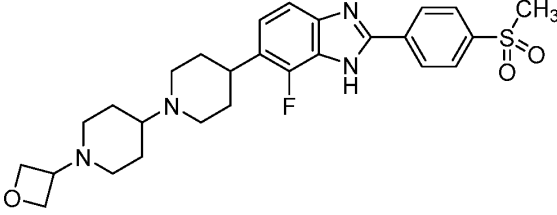
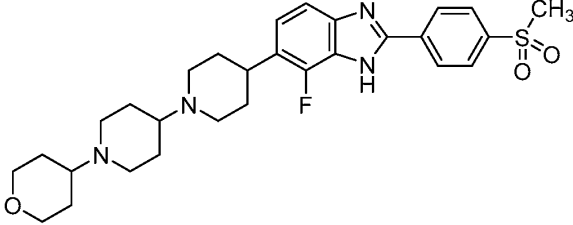
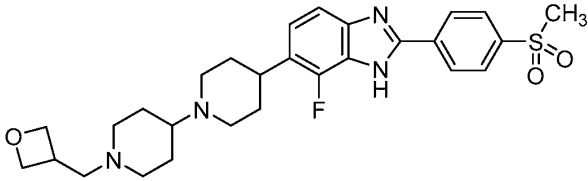
150	 1st eluting isomer	Ex. 17
151	 2nd eluting isomer	Ex. 17
152	 1st eluting isomer	Ex. 84
153	 2nd eluting isomer	Ex. 84

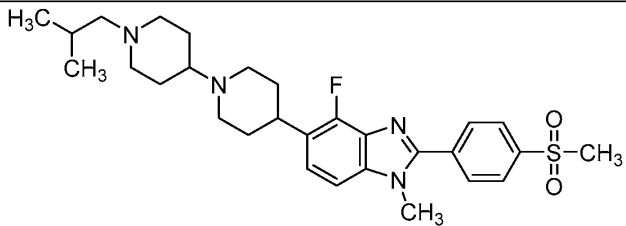
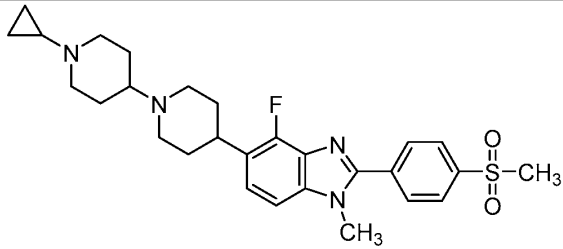
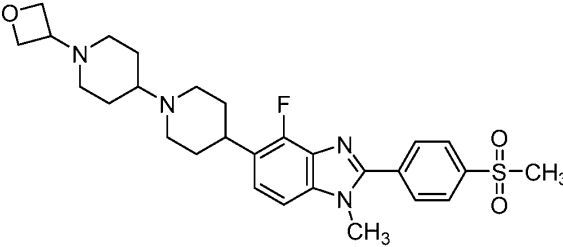
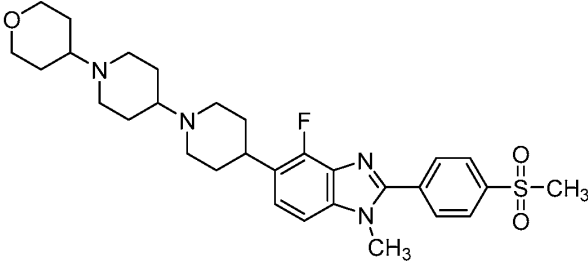
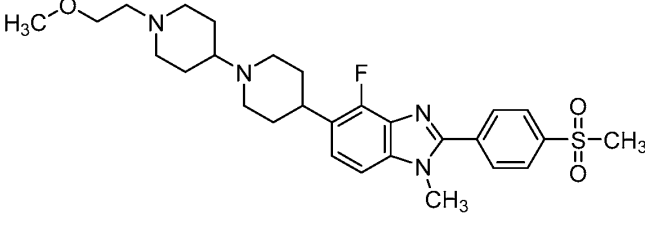
154	 1st eluting isomer	Ex. 84
155	 2nd eluting isomer	Ex. 84
156	 1st eluting isomer	Ex. 84
157	 2nd eluting isomer	Ex. 84
158	 1st eluting isomer	Ex. 84

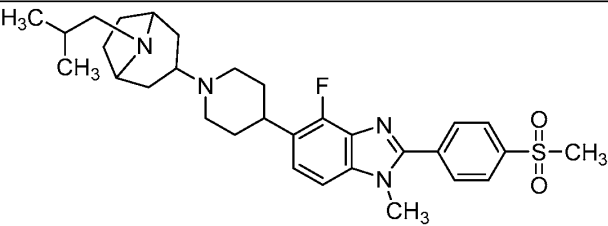
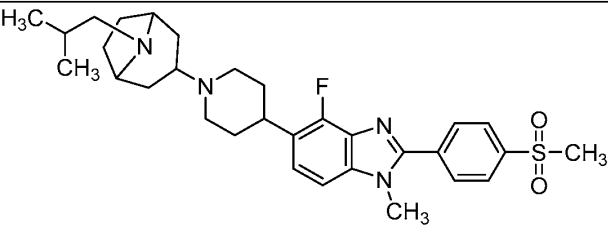
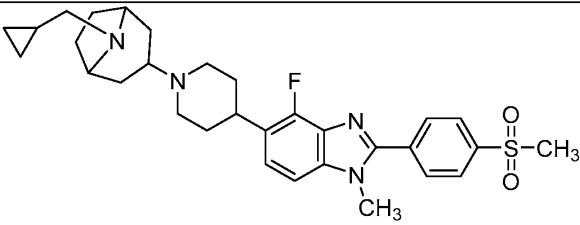
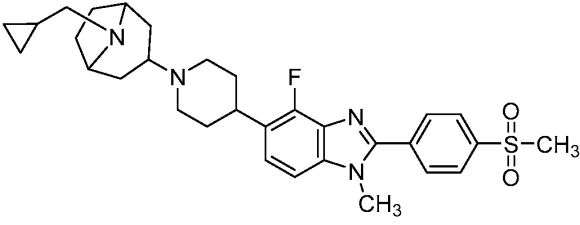
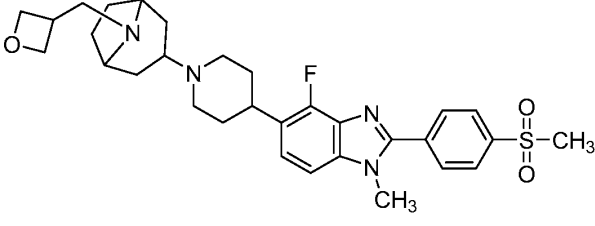
159	2nd eluting isomer	Ex. 84
160	1st eluting isomer	Ex. 84
161	2nd eluting isomer	Ex. 84
162	1st eluting isomer	Ex. 84

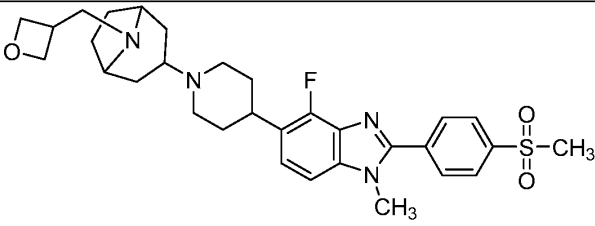
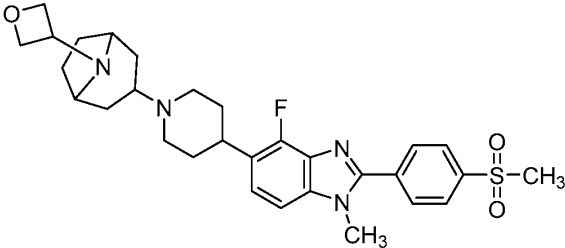
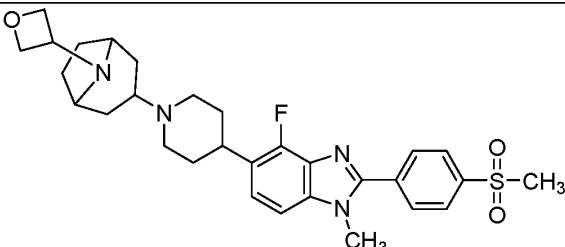
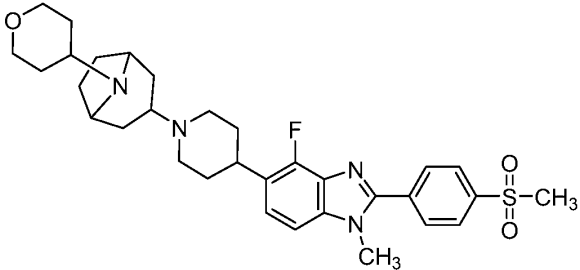
167	2nd eluting isomer	Ex. 17
168	1st eluting isomer	Ex. 17
169	2nd eluting isomer	Ex. 17
170		Ex. 86
171		Ex. 86

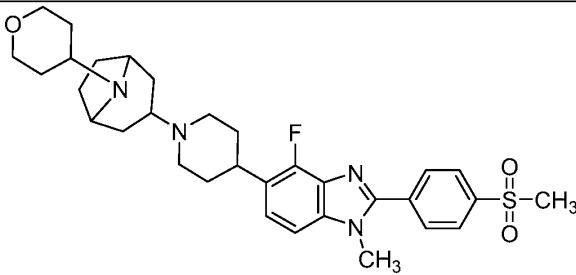
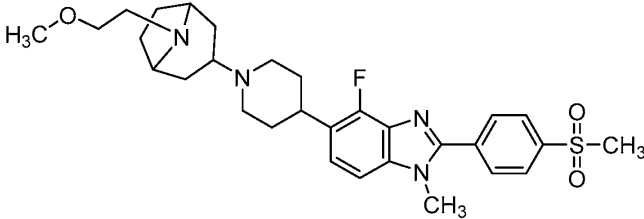
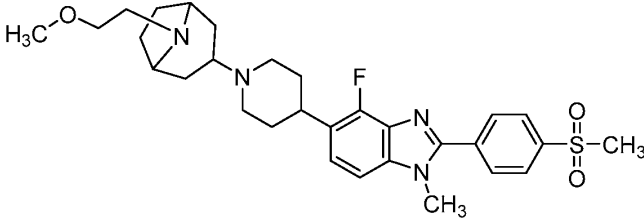
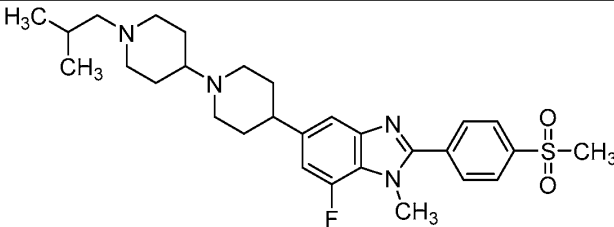
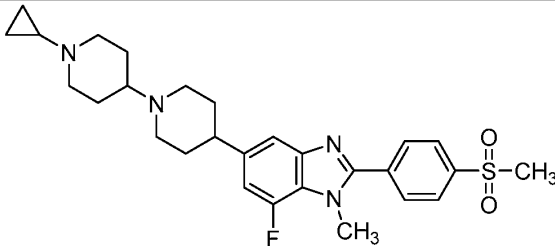
172		Ex. 86
173		Ex. 86
174		Ex. 86
175		Ex. 83
176		Ex. 86
177		Ex. 87

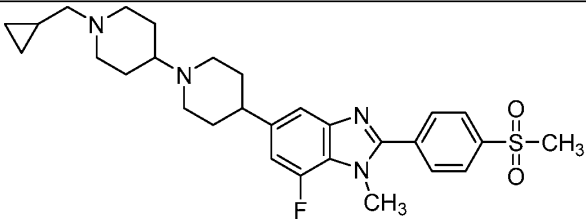
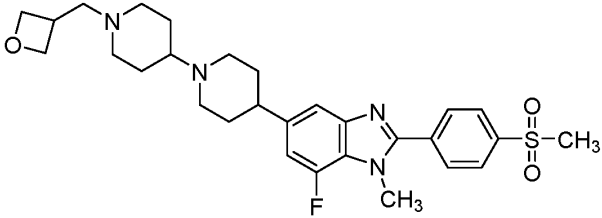
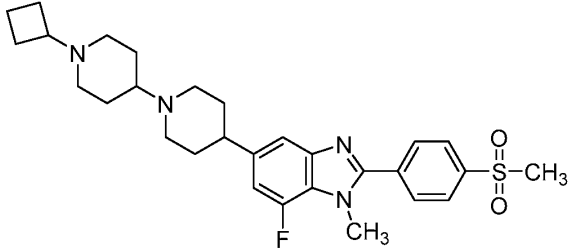
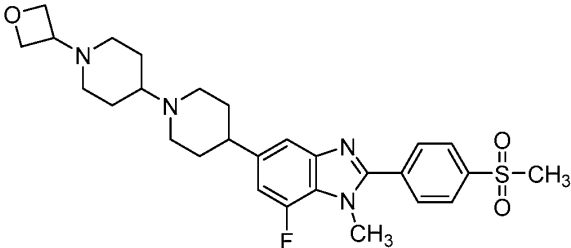
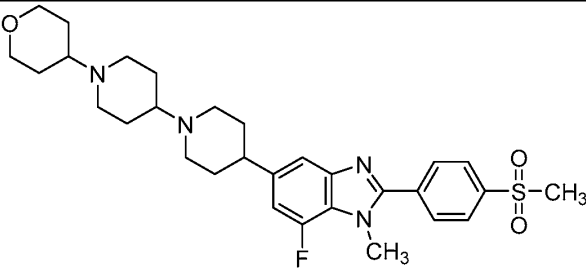
178		Ex. 87
179		Ex. 87
180		Ex. 87
181		Ex. 87
182		Ex. 87
183		Ex. 87

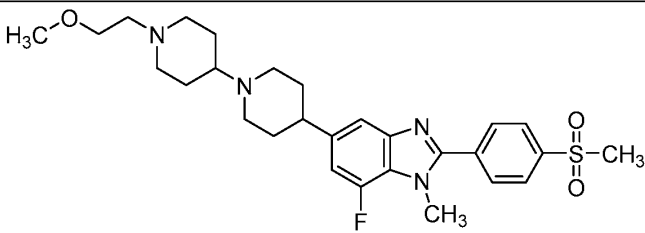
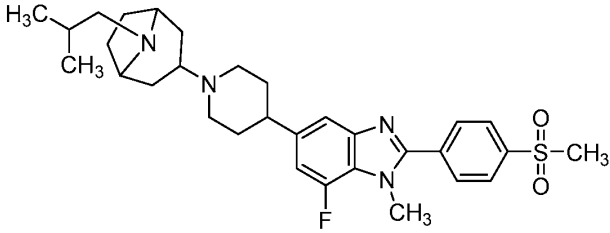
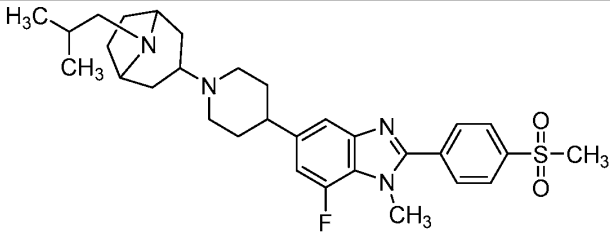
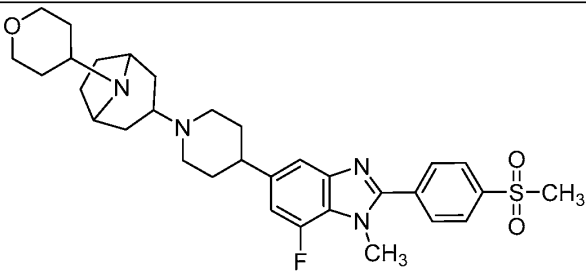
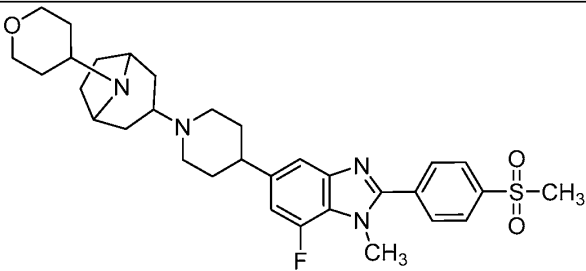
184		Ex. 88
185		Ex. 88
186		Ex. 88
187		Ex. 88
188		Ex. 88

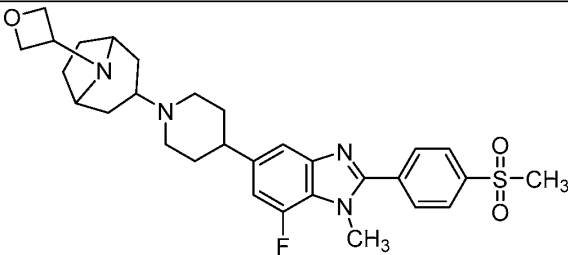
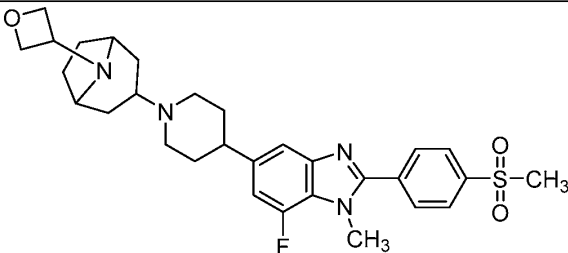
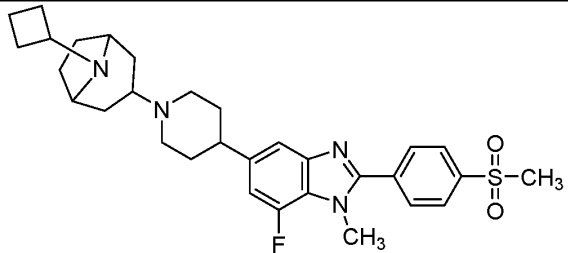
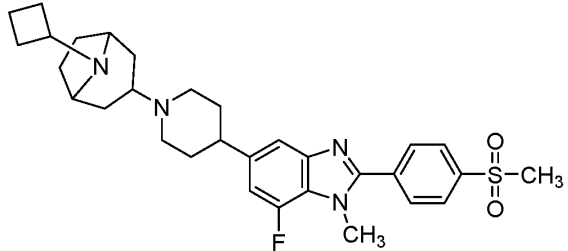
189	 1st eluting isomer	Ex. 89
190	 2nd eluting isomer	Ex. 89
191	 1st eluting isomer	Ex. 89
192	 2nd eluting isomer	Ex. 89
193	 1st eluting isomer	Ex. 89

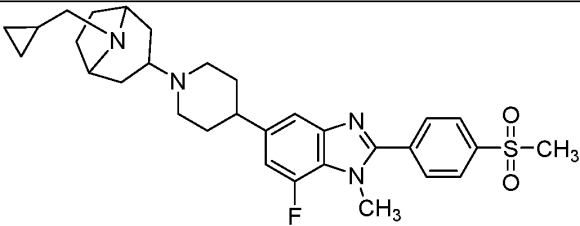
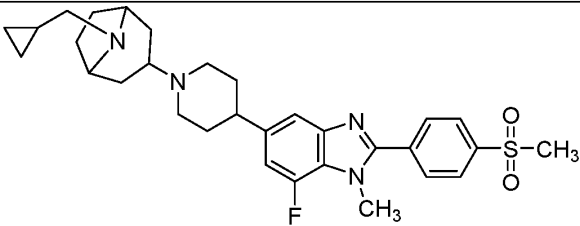
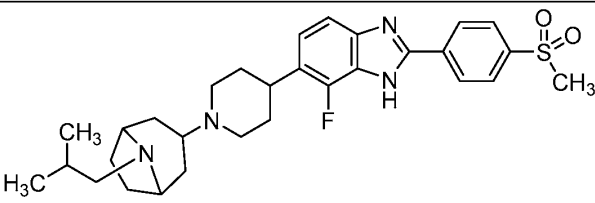
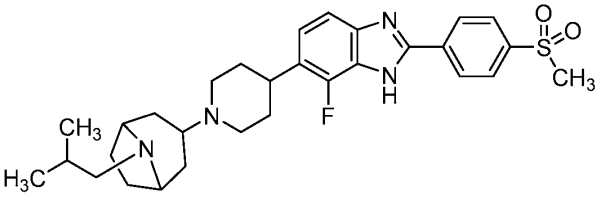
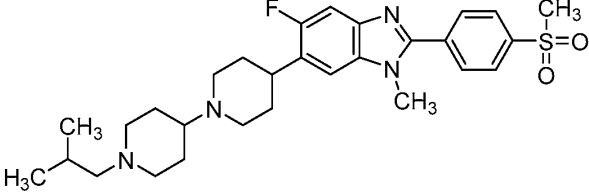
194	 2nd eluting isomer	Ex. 89
195	 1st eluting isomer	Ex. 89
196	 2nd eluting isomer	Ex. 89
197	 1st eluting isomer	Ex. 89

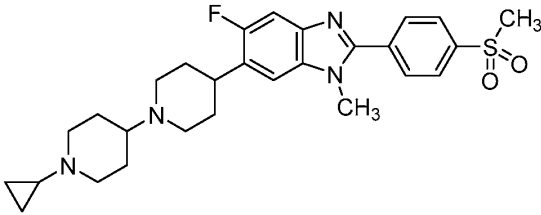
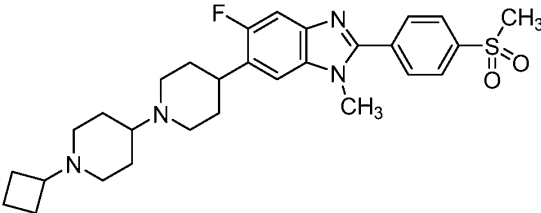
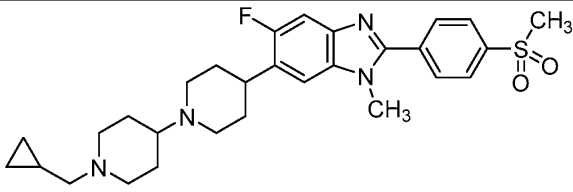
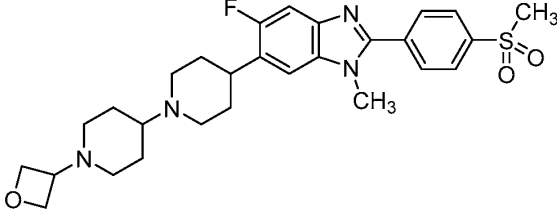
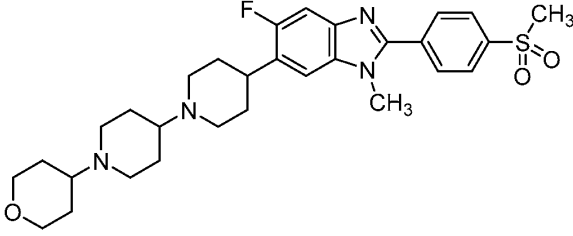
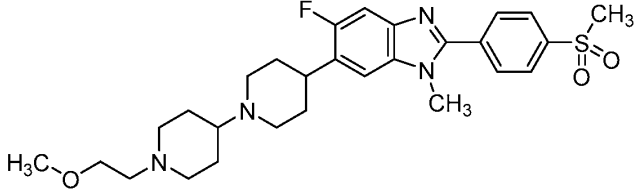
198	 2nd eluting isomer	Ex. 89
199	 1st eluting isomer	Ex. 89
200	 2nd eluting isomer	Ex. 89
201		Ex. 91
202		Ex. 91

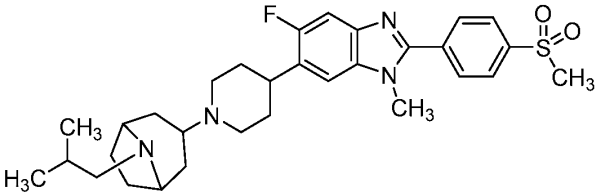
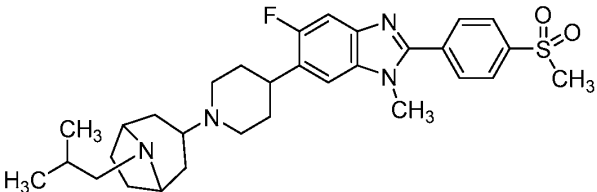
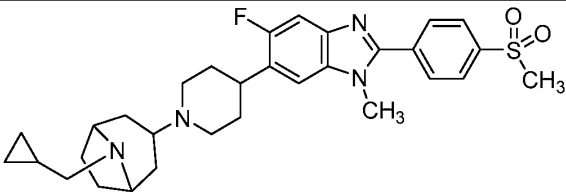
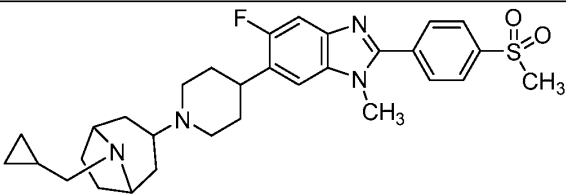
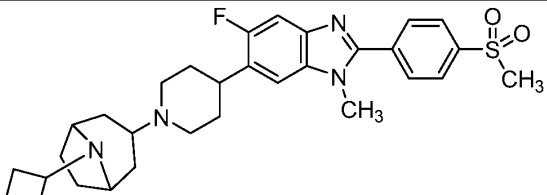
203		Ex. 91
204		Ex. 91
205		Ex. 91
206		Ex. 91
207		Ex. 91

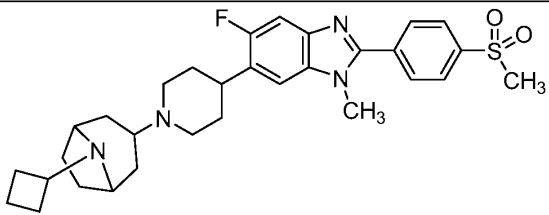
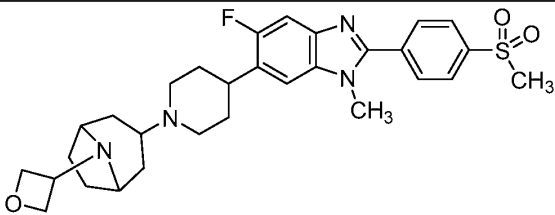
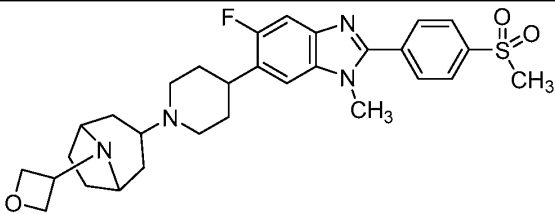
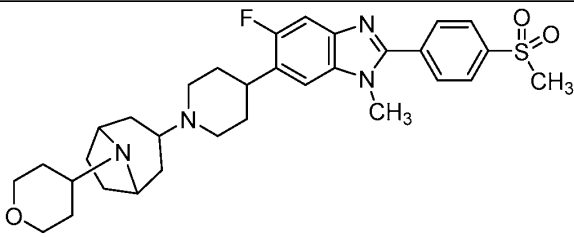
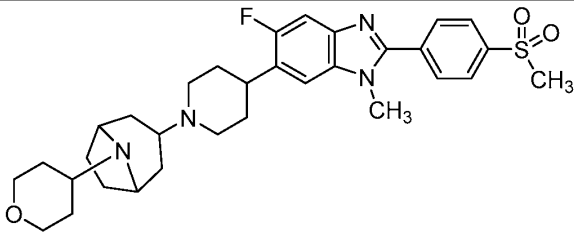
208		Ex. 91
209	 1 st eluting isomer	Ex. 92
210	 2 nd eluting isomer	Ex. 92
211	 1 st eluting isomer	Ex. 92
212	 2 nd eluting isomer	Ex. 92

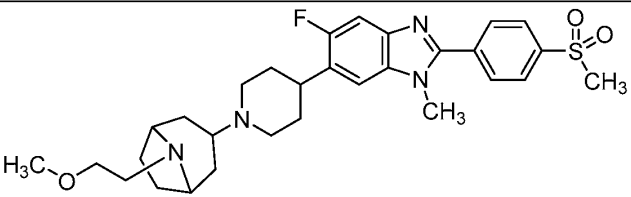
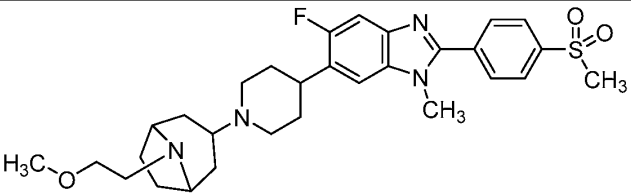
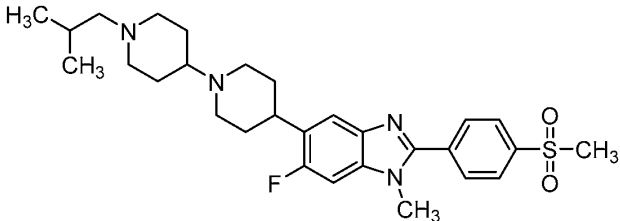
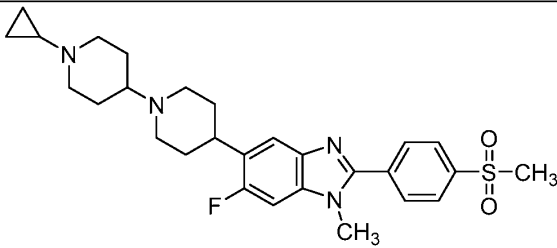
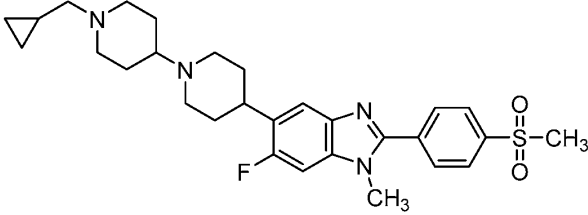
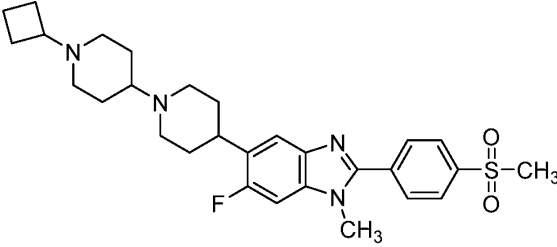
213	 1st eluting isomer	Ex. 92
214	 2nd eluting isomer	Ex. 92
215	 1st eluting isomer	Ex. 92
216	 2nd eluting isomer	Ex. 92

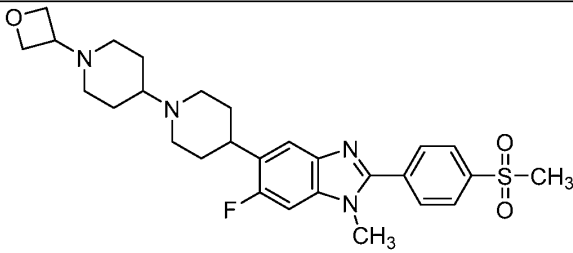
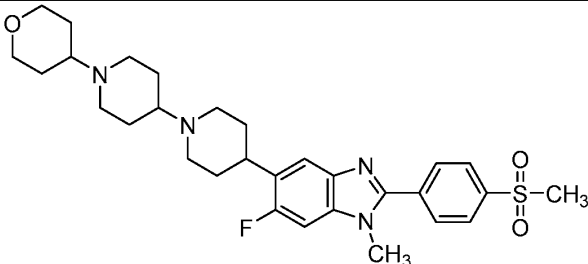
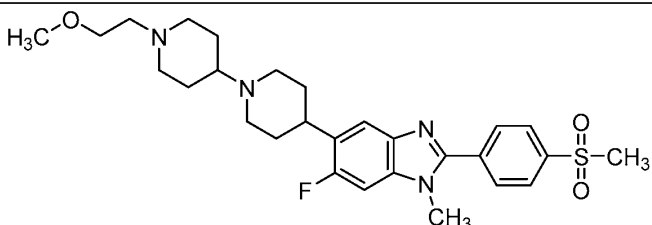
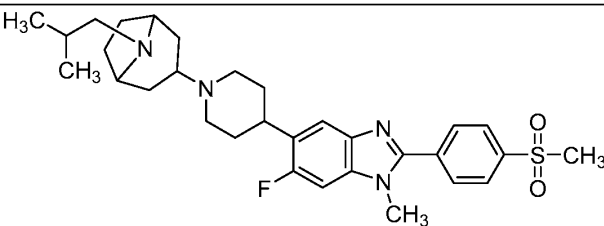
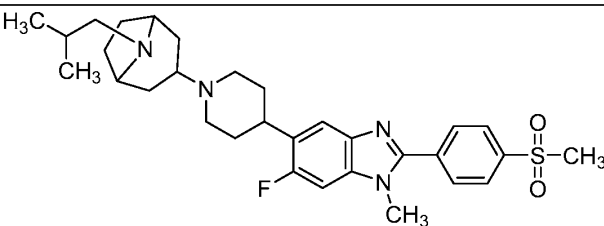
217	 1st eluting isomer	Ex. 92
218	 2nd eluting isomer	Ex. 92
219	 1st eluting isomer	Ex. 94
220	 2nd eluting isomer	Ex. 94
221		Ex. 96

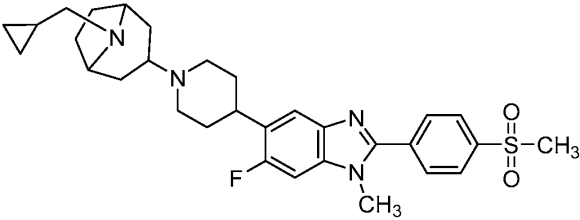
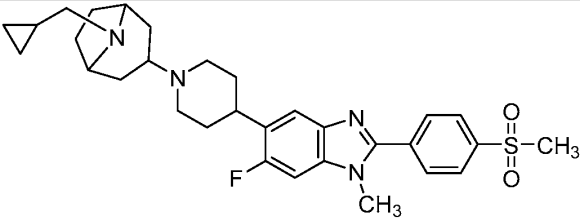
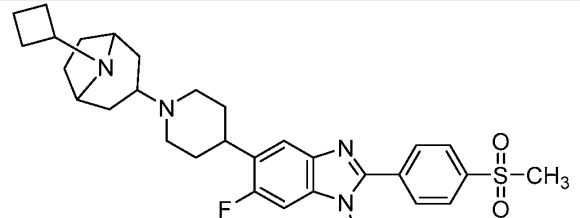
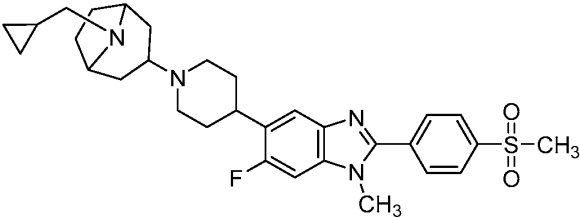
222		Ex. 96
223		Ex. 96
224		Ex. 96
225		Ex. 96
226		Ex. 96
227		Ex. 96

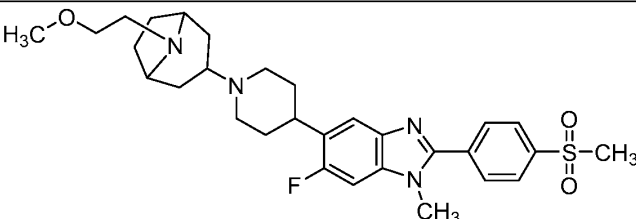
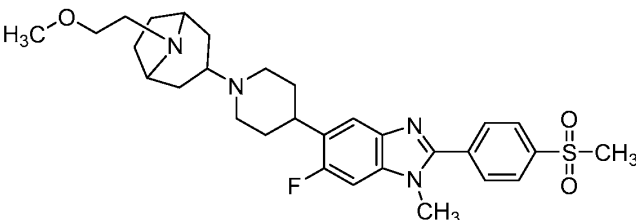
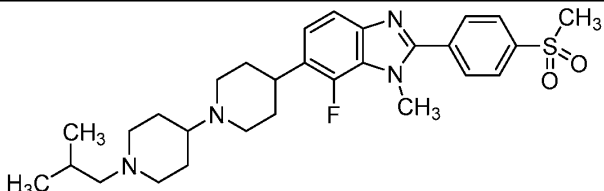
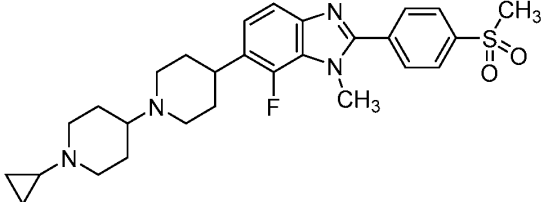
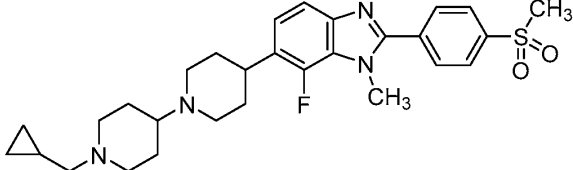
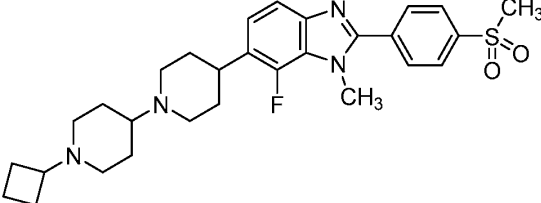
228	 1st eluting isomer	Ex. 97
229	 2nd eluting isomer	Ex. 97
230	 1st eluting isomer	Ex. 97
231	 2nd eluting isomer	Ex. 97
232	 1st eluting isomer	Ex. 97

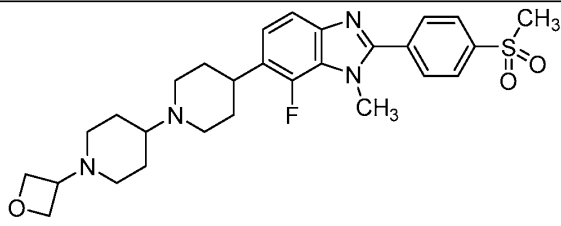
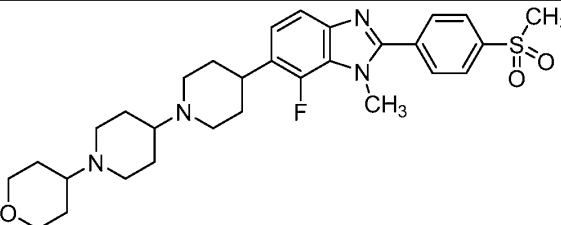
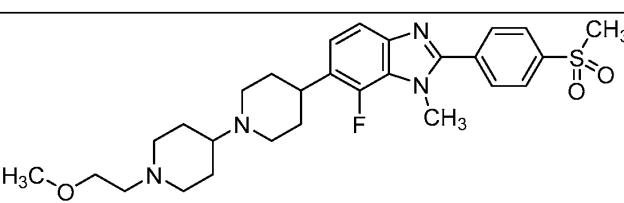
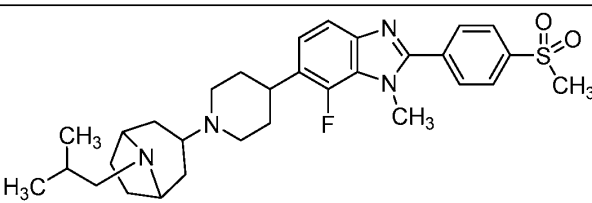
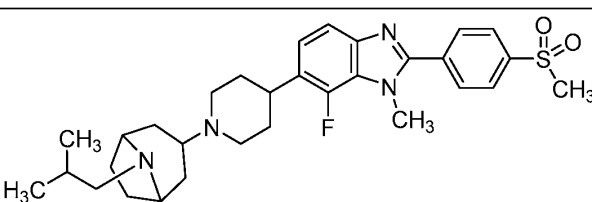
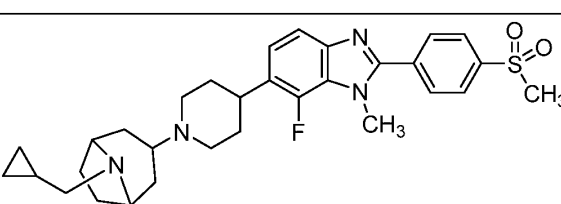
233	 2nd eluting isomer	Ex. 97
234	 1st eluting isomer	Ex. 97
235	 2nd eluting isomer	Ex. 97
236	 1st eluting isomer	Ex. 97
237	 2nd eluting isomer	Ex. 97

238	 1st eluting isomer	Ex. 97
239	 2nd eluting isomer	Ex. 97
240		Ex. 99
241		Ex. 99
242		Ex. 99
243		Ex. 99

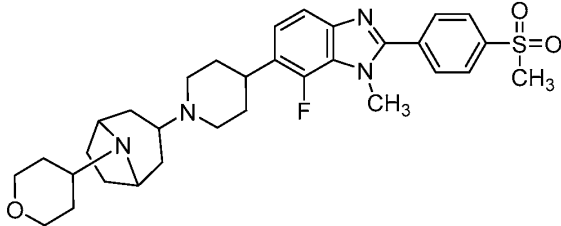
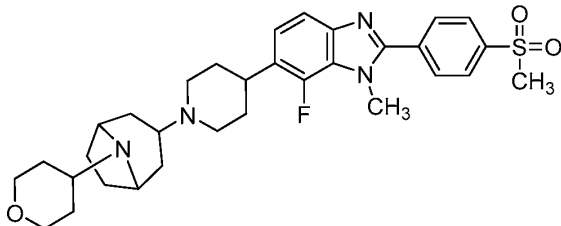
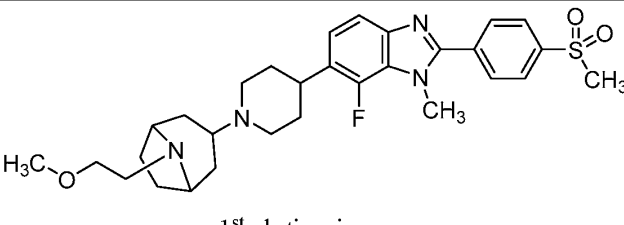
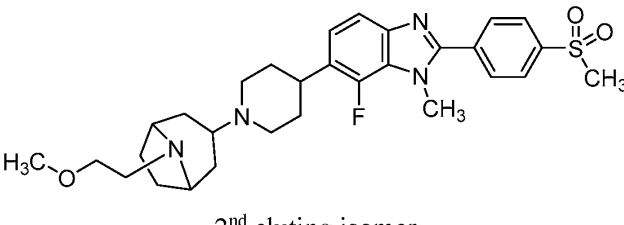
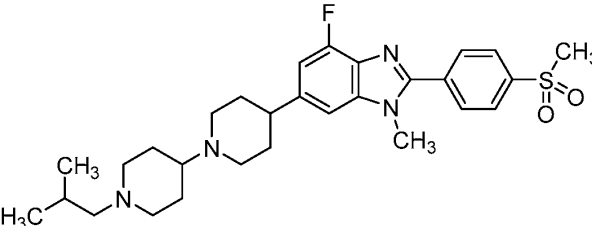
244		Ex. 99
245		Ex. 99
246		Ex. 99
247	 1st eluting isomer	Ex. 100
248	 2nd eluting isomer	Ex. 100

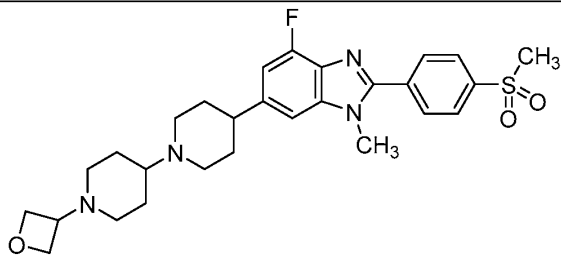
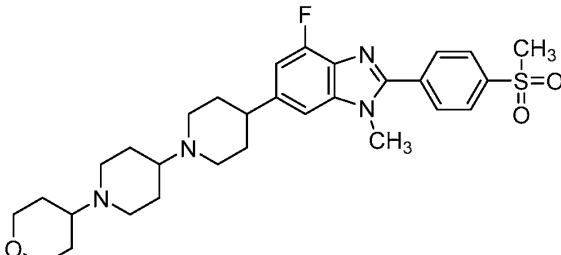
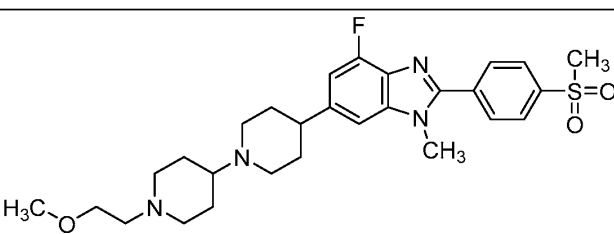
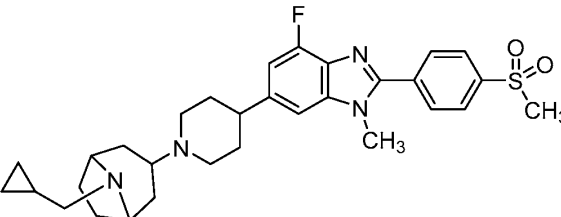
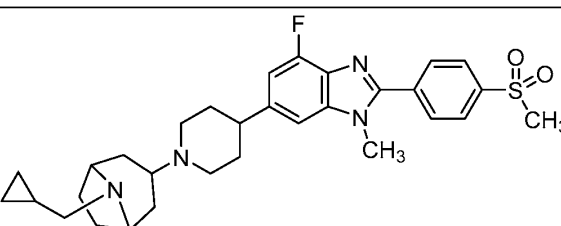
249	 1st eluting isomer	Ex. 100
250	 2nd eluting isomer	Ex. 100
251	 1st eluting isomer	Ex. 100
252	 2nd eluting isomer	Ex. 100

257	 1st eluting isomer	Ex. 100
258	 2nd eluting isomer	Ex. 100
259		Ex. 102
260		Ex. 102
261		Ex. 102
262		Ex. 102

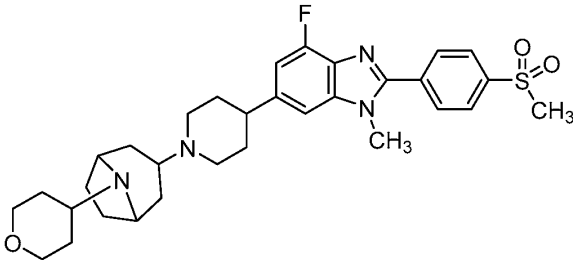
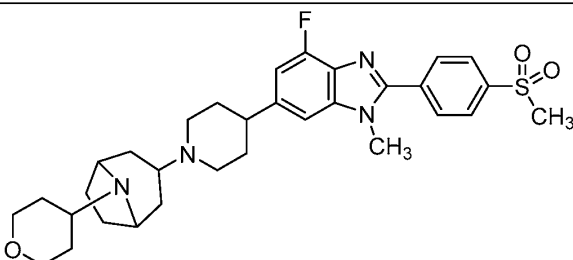
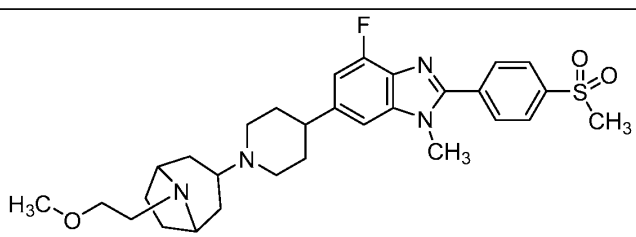
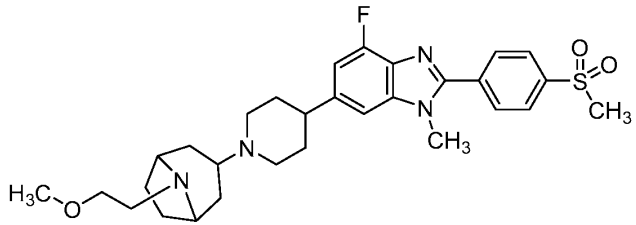
263		Ex. 102
264		Ex. 102
265		Ex. 102
266	 1 st eluting isomer	Ex. 103
267	 2 nd eluting isomer	Ex. 103
268	 1 st eluting isomer	Ex. 103

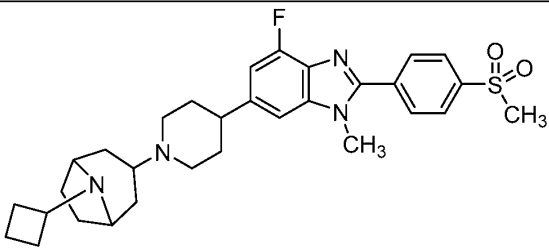
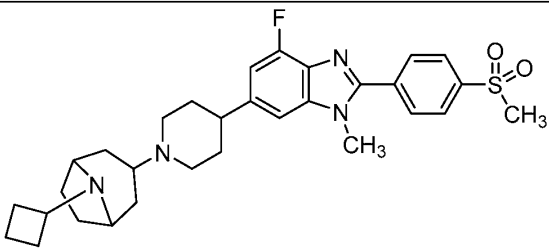
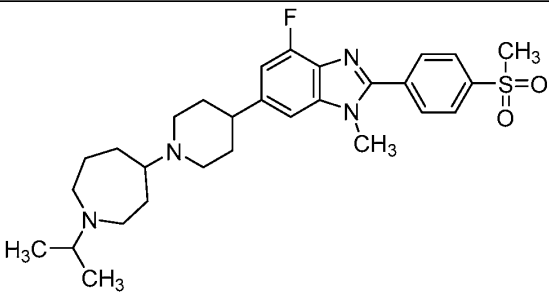
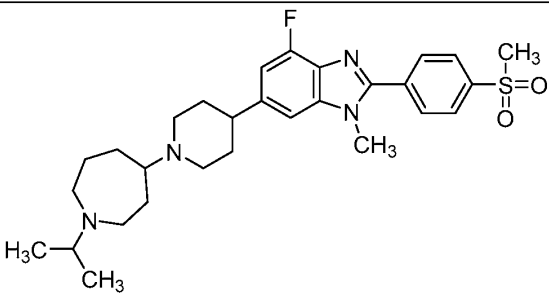
269	2nd eluting isomer	Ex. 103
270	1st eluting isomer	Ex. 103
271	2nd eluting isomer	Ex. 103
272	1st eluting isomer	Ex. 103
273	2nd eluting isomer	Ex. 103

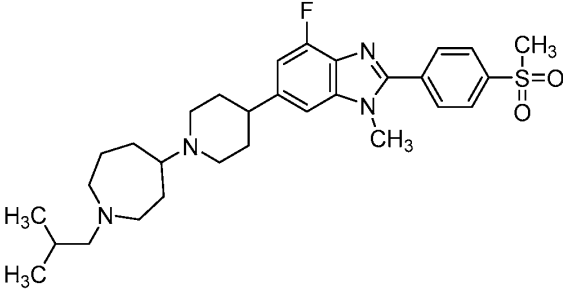
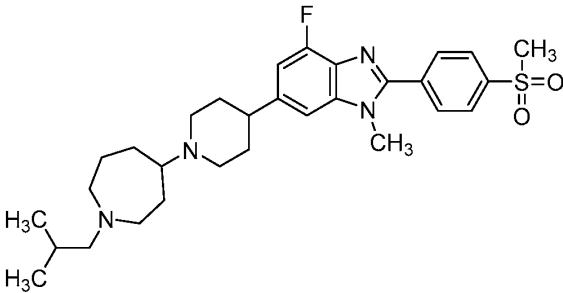
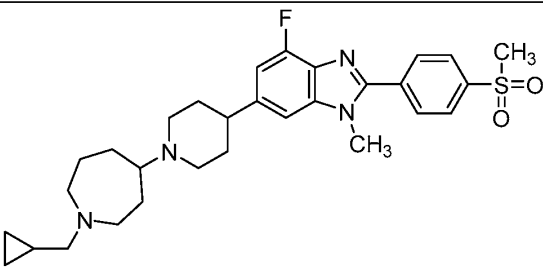
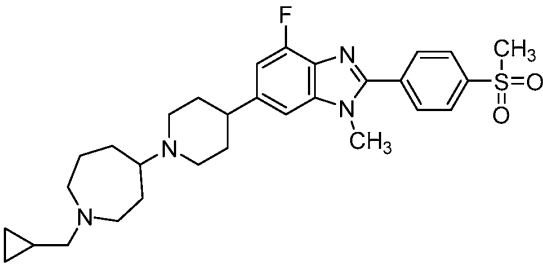
274	 1st eluting isomer	Ex. 103
275	 2nd eluting isomer	Ex. 103
276	 1st eluting isomer	Ex. 103
277	 2nd eluting isomer	Ex. 103
278		Ex. 105

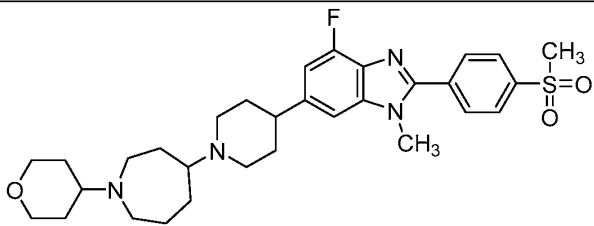
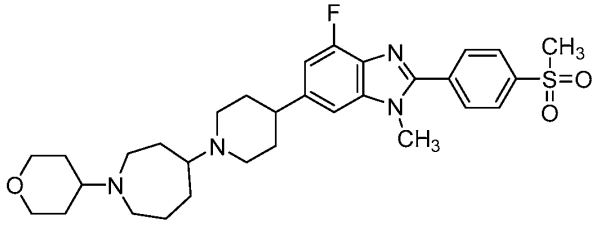
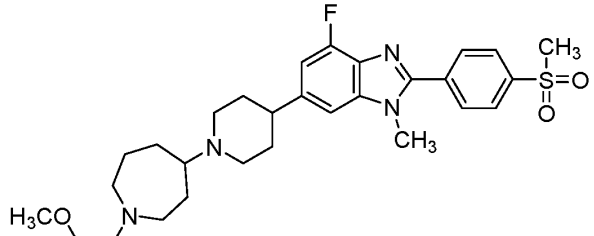
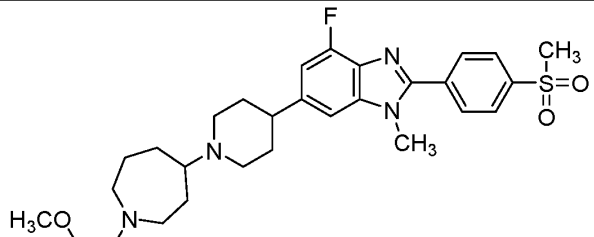
279		Ex. 105
280		Ex. 105
281		Ex. 105
282	 1st eluting isomer	Ex. 106
283	 2nd eluting isomer	Ex. 106

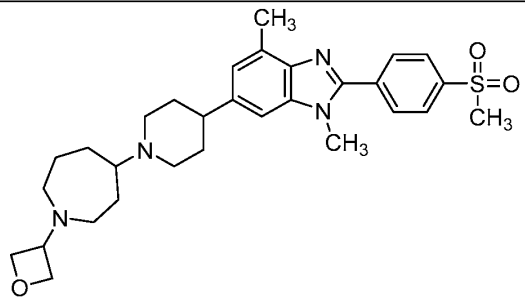
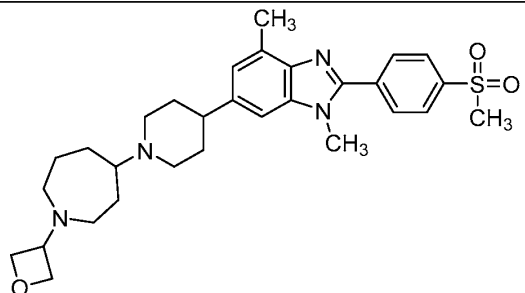
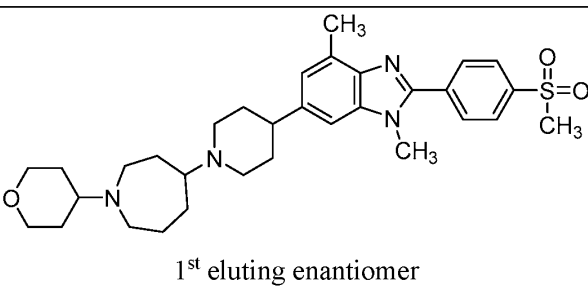
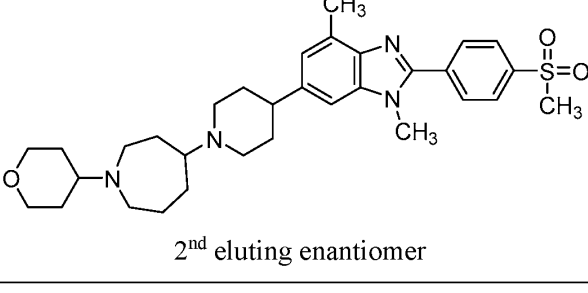
284	1st eluting isomer	Ex. 106
285	2nd eluting isomer	Ex. 106
286	1st eluting isomer	Ex. 106
287	2nd eluting isomer	Ex. 106

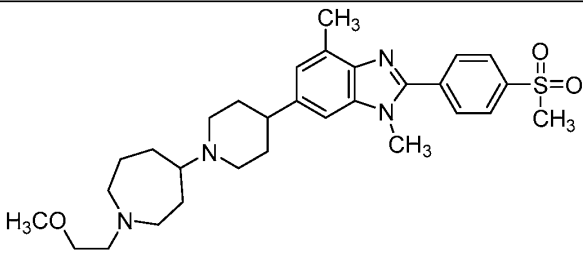
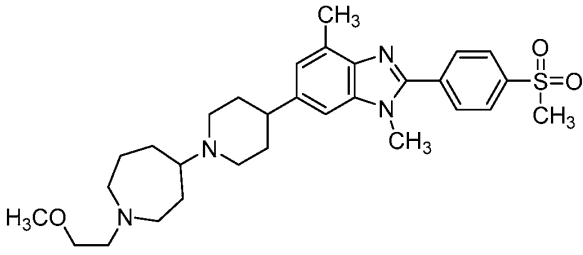
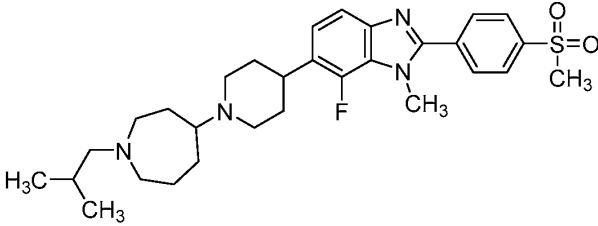
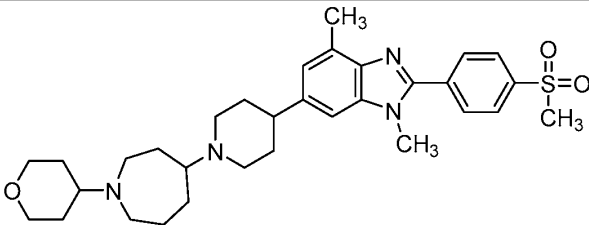
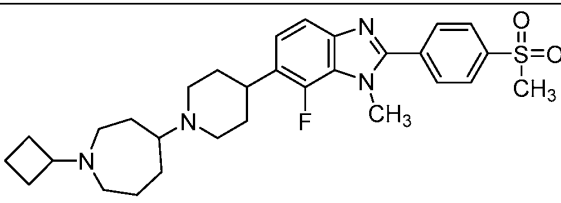
288	 1st eluting isomer	Ex. 106
289	 2nd eluting isomer	Ex. 106
290	 1st eluting isomer	Ex. 106
291	 2nd eluting isomer	Ex. 106

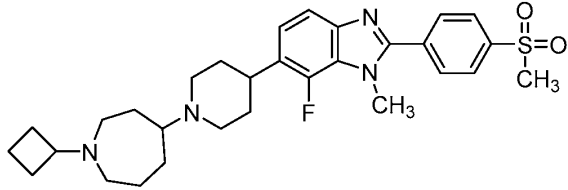
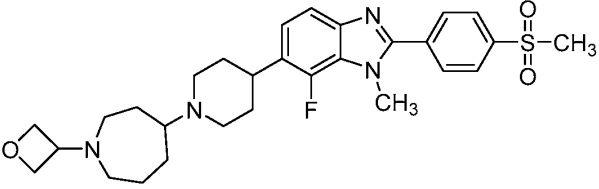
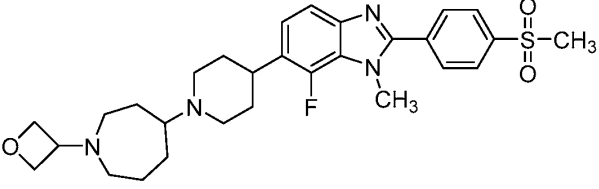
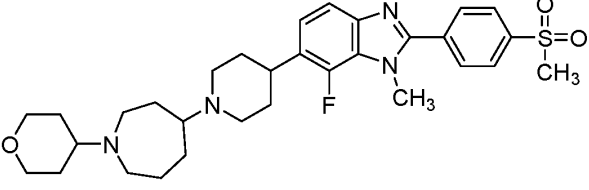
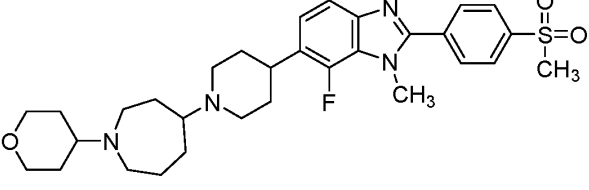
292	 1st eluting isomer	Ex. 106
293	 2nd eluting isomer	Ex. 106
294	 1st eluting enantiomer	Ex. 108
295	 2nd eluting enantiomer	Ex. 108

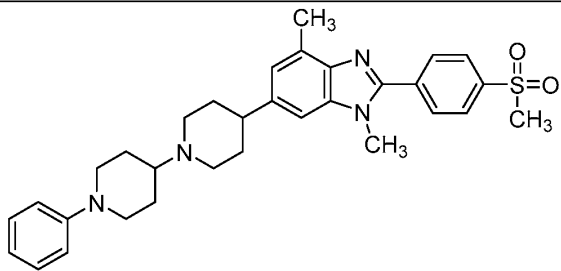
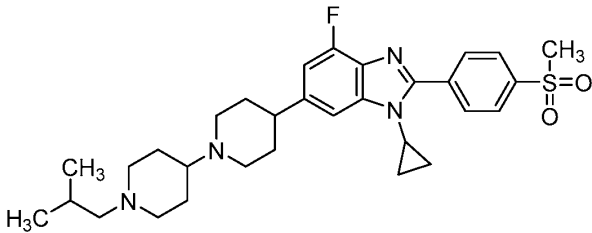
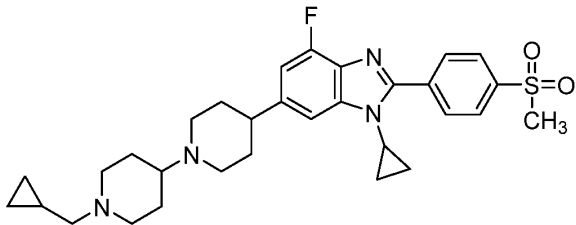
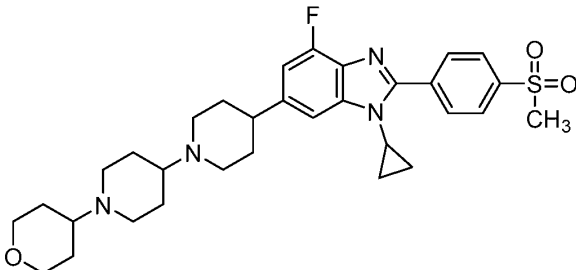
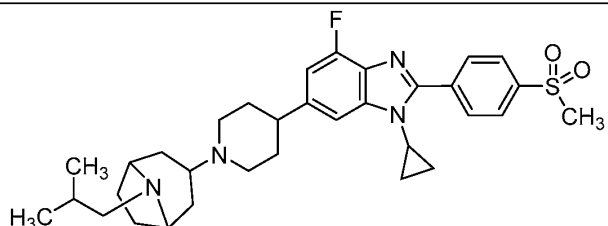
296	 1st eluting enantiomer	Ex. 108
297	 2nd eluting enantiomer	Ex. 108
298	 1st eluting enantiomer	Ex. 108
299	 2nd eluting enantiomer	Ex. 108

300	 1st eluting enantiomer.	Ex. 108
301	 2nd eluting enantiomer	Ex. 108
302	 1st eluting enantiomer	Ex. 108
303	 2nd eluting enantiomer	Ex. 108

304	 1st eluting enantiomer	Ex. 110
305	 2nd eluting enantiomer	Ex. 110
306	 1st eluting enantiomer	Ex. 110
307	 2nd eluting enantiomer	Ex. 110

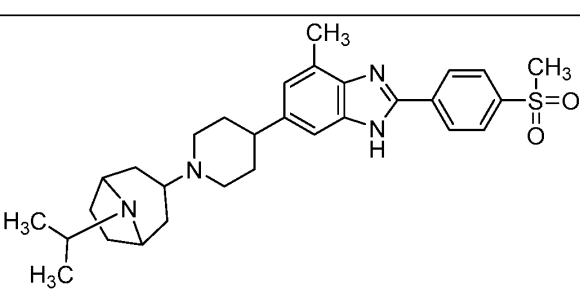
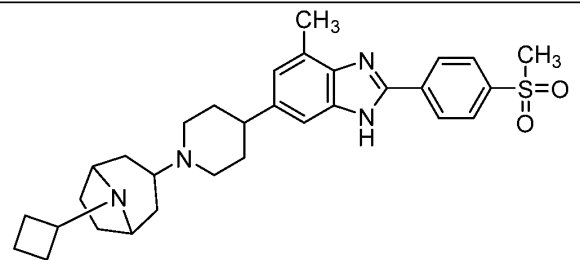
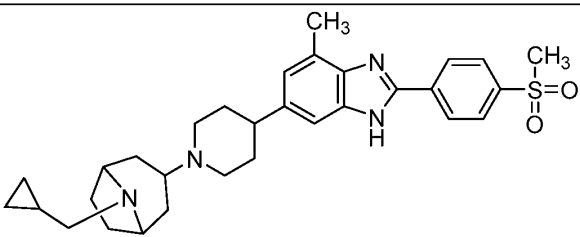
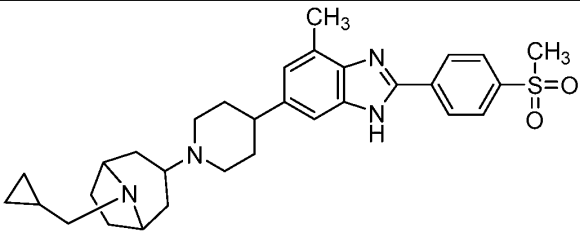
308	 1st eluting enantiomer	Ex. 110
309	 2nd eluting enantiomer	Ex. 110
310	 1st eluting enantiomer.	Ex. 113
311	 2nd eluting enantiomer	Ex. 113
312	 1st eluting enantiomer	Ex. 113

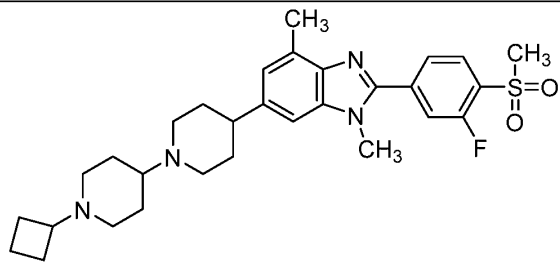
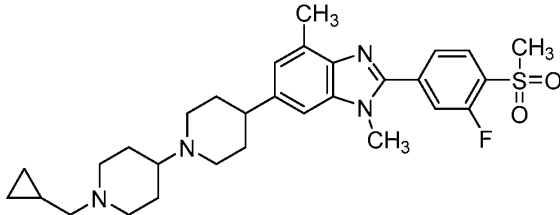
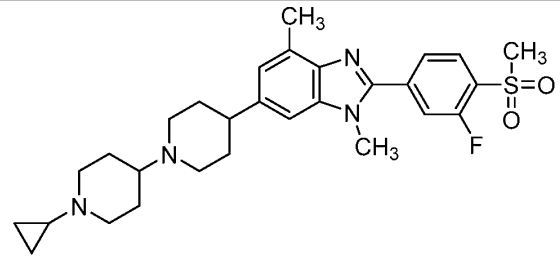
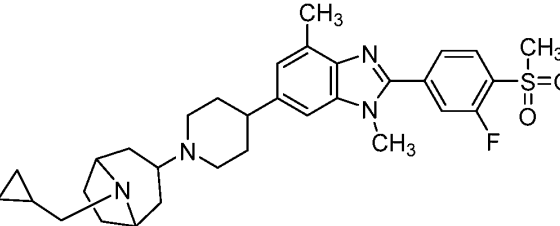
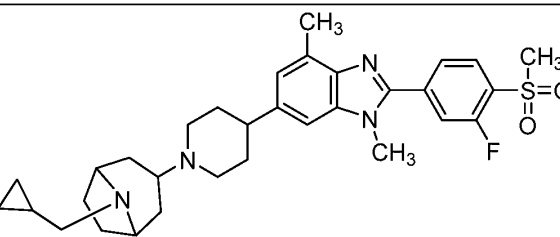
313	 2nd eluting enantiomer	Ex. 113
314	 1st eluting enantiomer	Ex. 113
315	 2nd eluting enantiomer	Ex. 113
316	 1st eluting enantiomer	Ex. 113
317	 2nd eluting enantiomer	Ex. 113

318		Ex. 22
319		Ex. 115
320		Ex. 115
321		Ex. 115
322	 1 st eluting isomer	Ex. 116

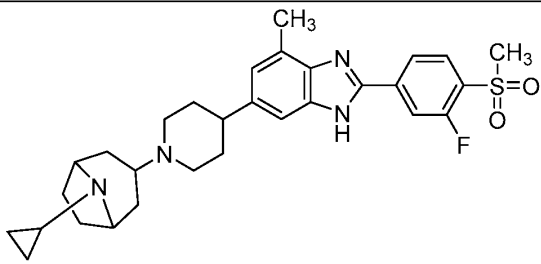
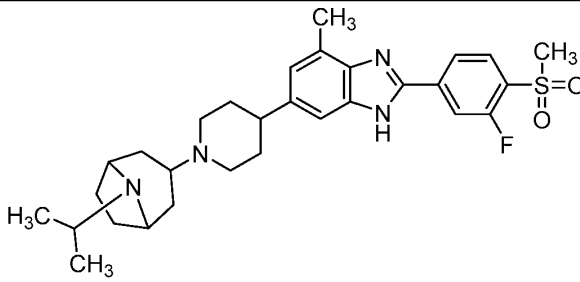
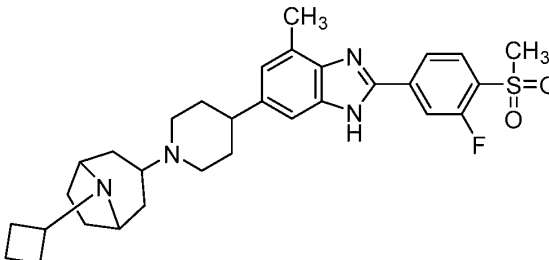
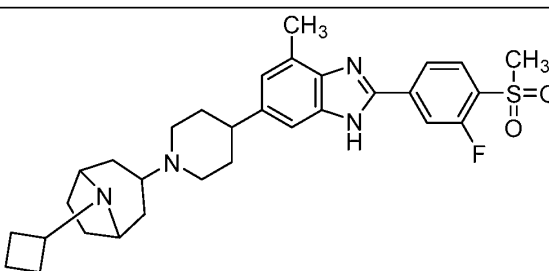
323	2nd eluting isomer	Ex. 116
324	1st eluting isomer	Ex. 116
325	2nd eluting isomer	Ex. 116
326	1st eluting isomer	Ex. 116
327	2nd eluting isomer	Ex. 116

328	1st eluting isomer	Ex. 116
329	2nd eluting isomer	Ex. 116
330	1st eluting isomer	Ex. 119
331	2nd eluting isomer	Ex. 120
332	1st eluting isomer	Ex. 121

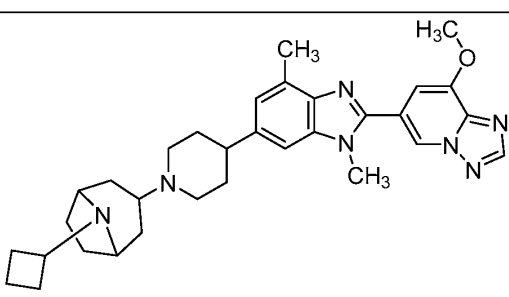
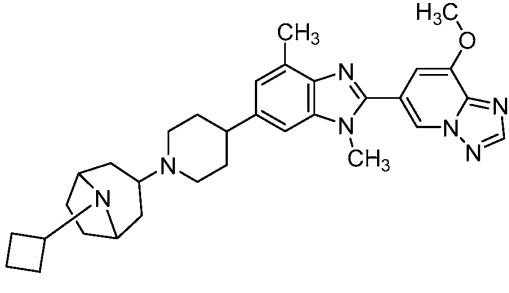
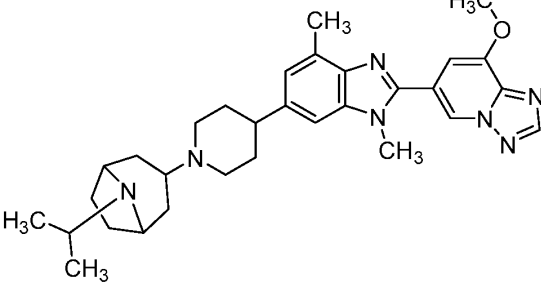
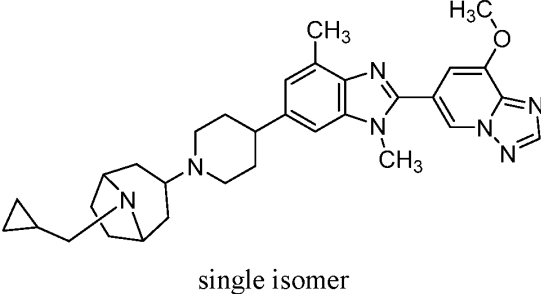
333	 2nd eluting isomer	Ex. 121
334	 single isomer	Ex. 121
335	 1st eluting isomer	Ex. 121
336	 2nd eluting isomer	Ex. 121

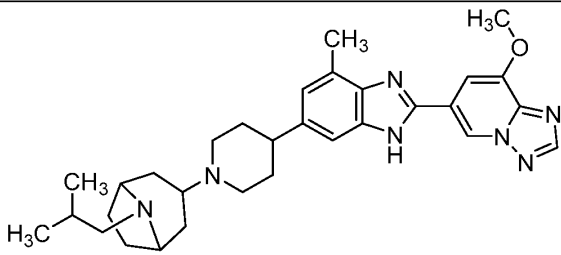
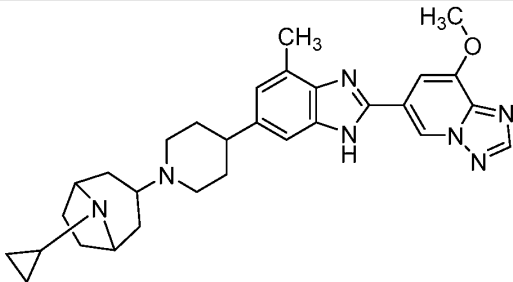
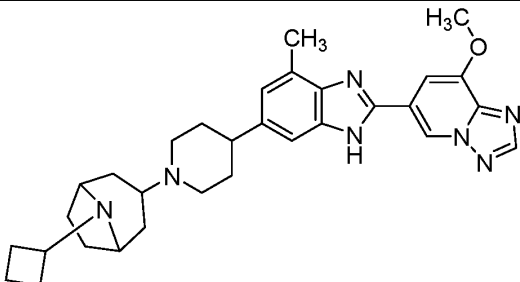
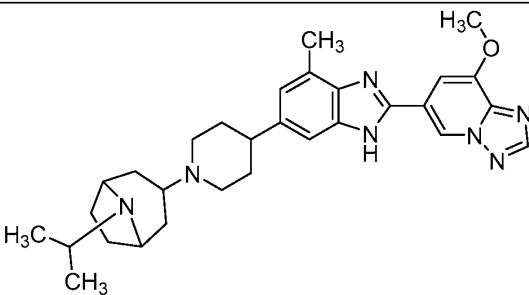
337		Ex. 122
338		Ex. 122
339		Ex. 122
340	 1st eluting isomer	Ex. 123
341	 2nd eluting isomer	Ex. 123

342	single isomer	Ex. 123
343	single isomer	Ex. 122
344	single isomer	Ex. 123
345	single isomer	Ex. 123
346	single isomer	Ex. 123

347	 single isomer	Ex. 123
348	 single isomer	Ex. 123
349	 1st eluting isomer	Ex. 123
350	 2nd eluting isomer	Ex. 123

351	1st eluting isomer	Ex. 123
352	2nd eluting isomer	Ex. 123
353	single isomer	Ex. 124
354	single isomer	Ex. 125

355	 1st eluting isomer	Ex. 125
356	 2nd eluting isomer	Ex. 125
357	 single isomer	Ex. 125
358	 single isomer	Ex. 125

359	 single isomer	Ex. 125
360	 single isomer	Ex. 125
361	 single isomer	Ex. 125
362	 single isomer	Ex. 125

Ex. No.	Analytical LC/MS, Preparative HPLC method, yield, and ¹ H NMR
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127	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 494.95; Retention Time: 0.99 min. (Method 2): Purity: 100 %; Observed Mass: 495.00; Retention Time: 1.46 min. Prep Method 2: 17 mg, 17 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.79 (s, 2H), 7.25 (s, 1H), 7.16 (br d, <i>J</i>=8.9 Hz, 1H), 6.99-6.89 (m, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.74-3.53 (m, 1H), 3.25-3.12 (m, 2H), 3.07-2.91 (m, 4H), 2.51 (br s, 3H), 2.36-2.24 (m, 2H), 2.21-1.94 (m, 8H), 0.98 (br d, <i>J</i>=6.7 Hz, 6H) (two protons obscured). TLR9 IC₅₀ (nM) = 31
128	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 479.23; Retention Time: 1.0 min. (Method 1): Purity: 94 %; Observed Mass: 479.22; Retention Time: 1.39 min. Prep Method 2: 7.8 mg, 11 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.74 (br s, 2H), 7.22-7.16 (m, 1H), 7.13 (d, <i>J</i>=8.2 Hz, 1H), 6.94-6.84 (m, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.02-2.91 (m, 4H), 2.65-2.56 (m, 1H), 2.32-2.19 (m, 3H), 2.17-2.04 (m, 2H), 1.85-1.77 (m, 2H), 1.75-1.59 (m, 4H), 1.58-1.50 (m, 1H), 1.46-1.31 (m, 2H), 0.45-0.34 (m, 2H), 0.32-0.23 (m, 2H). TLR9 IC₅₀ (nM) = 270
129	Analytical LC/MS (Method 1): Purity: 95.5 %; Observed Mass: 481.25; Retention Time: 0.97 min. (Method 2): Purity: 96.1 %; Observed Mass: 481.16; Retention Time: 1.34 min. Prep Method 1: 61 mg, 88 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 7.74-7.66 (m, 2H), 7.47-7.37 (m, 1H), 7.35-7.27 (m, 1H), 7.15-7.08 (m, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.03-2.95 (m, 2H), 2.90-2.77 (m, 3H), 2.75-2.63 (m, 1H), 2.33-2.18 (m, 3H), 2.15-2.07 (m, 2H), 1.83-1.66 (m, 6H), 1.52-1.39 (m, 2H), 0.97 (d, <i>J</i>=6.4 Hz, 6H) (one proton obscured). TLR9 IC₅₀ (nM) = 190

130	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 495.28; Retention Time: 1.0 min. (Method 1): Purity: 100 %; Observed Mass: 495.22; Retention Time: 1.68 min. Prep Method 2: 16 mg, 34 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.75-7.63 (m, 2H), 7.49-7.38 (m, 1H), 7.35-7.26 (m, 1H), 7.16-7.07 (m, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.66-3.49 (m, 3H), 3.05-2.97 (m, 2H), 2.92-2.78 (m, 4H), 2.36-2.20 (m, 3H), 2.04-1.98 (m, 2H), 1.87-1.66 (m, 6H), 1.55-1.42 (m, 2H), 0.84 (br d, <i>J</i> =6.7 Hz, 6H). TLR9 IC ₅₀ (nM) = 22
131	Analytical LC/MS (Method 1): Purity: 97.2 %; Observed Mass: 479.22; Retention Time: 0.98 min. (Method 2): Purity: 100 %; Observed Mass: 479.22; Retention Time: 1.4 min. Prep Method 1: 19 mg, 29 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.73 (s, 2H), 7.54-7.23 (m, 2H), 7.14-7.09 (m, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.03-2.93 (m, 4H), 2.86-2.76 (m, 1H), 2.35-2.25 (m, 3H), 2.17-2.05 (m, 2H), 1.84-1.65 (m, 6H), 1.60-1.50 (m, 1H), 1.45-1.34 (m, 2H), 0.43-0.36 (m, 2H), 0.32-0.21 (m, 2H) (one proton obscured). TLR9 IC ₅₀ (nM) = 59
132	Analytical LC/MS (Method 1): Purity: 93.4 %; Observed Mass: 480.98; Retention Time: 1.01 min. (Method 2): Purity: 92.7 %; Observed Mass: 480.91; Retention Time: 1.24 min. Prep Method 1: 43 mg, 59 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.76 (br s, 2H), 7.35-7.27 (m, 1H), 7.19-7.05 (m, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 3.02-2.94 (m, 2H), 2.93-2.79 (m, 3H), 2.73-2.62 (m, 1H), 2.34-2.17 (m, 3H), 2.15-2.05 (m, 2H), 1.79-1.71 (m, 6H), 1.49-1.38 (m, 2H), 0.96 (d, <i>J</i> =6.4 Hz, 6H) (one proton obscured). TLR9 IC ₅₀ (nM) = 200

133	Analytical LC/MS (Method 1): Purity: 95 %; Observed Mass: 494.94; Retention Time: 1.01 min. (Method 2): Purity: 97.9 %; Observed Mass: 495.26; Retention Time: 1.45 min. Prep Method 1: 24 mg, 32 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.87-7.72 (m, 2H), 7.36-7.26 (m, 1H), 7.25-7.10 (m, 2H), 3.88 (s, 3H), 3.86-3.80 (m, 3H), 3.06-2.96 (m, 2H), 2.95-2.80 (m, 3H), 2.33-2.16 (m, 3H), 2.03-1.97 (m, 2H), 1.89-1.69 (m, 8H), 1.57-1.40 (m, 3H), 0.84 (br d, J=6.4 Hz, 6H) (one proton obscured). TLR9 IC ₅₀ (nM) = 2200
134	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 522.98; Retention Time: 0.91 min. (Method 2): Purity: 99.2 %; Observed Mass: 523.25; Retention Time: 1.18 min. Prep Method 1: 45 mg, 80 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.17-8.01 (m, 4H), 7.35-7.19 (m, 1H), 7.06-6.91 (m, 1H), 3.88 (s, 2H), 3.30 (s, 2H), 2.92-2.78 (m, 3H), 2.74-2.59 (m, 3H), 2.55 (s, 8H), 2.44-2.27 (m, 2H), 1.88-1.67 (m, 7H), 1.66-1.40 (m, 3H), 0.96 (br d, J=2.7 Hz, 6H). TLR9 IC ₅₀ (nM) = 21
135	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 535.19; Retention Time: 1.08 min. (Method 2): Purity: 100 %; Observed Mass: 535.23; Retention Time: 1.23 min. Prep Method 1: 51 mg, 88 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.11 (s, 4H), 7.30 (s, 1H), 6.99 (s, 1H), 3.49-3.41 (m, 1H), 2.91-2.81 (m, 3H), 2.75-2.66 (m, 1H), 2.53 (br d, J=18.9 Hz, 8H), 2.43-2.26 (m, 5H), 2.02-1.92 (m, 2H), 1.85-1.66 (m, 9H), 1.65-1.39 (m, 5H) (two protons obscured). TLR9 IC ₅₀ (nM) = 23
136	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 536.95; Retention Time: 0.94 min. (Method 2): Purity: 100 %; Observed Mass: 537.27; Retention Time: 1.35 min. Prep Method 2: 57 mg, 70 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.13 (s, 4H), 7.35-7.28 (m, 1H), 7.12-7.03 (m, 1H), 3.66-3.39 (m, 1H), 3.29-3.15 (m, 1H), 3.12-2.92 (m, 3H), 2.60-2.49 (m, 14H), 2.39-1.96 (m, 9H), 1.96-1.70 (m, 2H), 0.98 (dd, J=6.4, 2.7 Hz, 6H) (two protons obscured). TLR9 IC ₅₀ (nM) = 140

137	Analytical LC/MS (Method 1): Purity: 97.5 %; Observed Mass: 535.19; Retention Time: 1.09 min. (Method 2): Purity: 100 %; Observed Mass: 534.97; Retention Time: 1.22 min. Prep Method 1: 47 mg, 79 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.03 (s, 4H), 7.22 (s, 1H), 6.91 (s, 1H), 3.80 (s, 3H), 3.46-3.29 (m, 2H), 3.22 (s, 2H), 2.85-2.68 (m, 3H), 2.67-2.55 (m, 3H), 2.45 (br d, <i>J</i> =19.5 Hz, 3H), 2.33-2.23 (m, 4H), 1.80-1.58 (m, 8H), 1.56-1.38 (m, 3H), 0.80-0.70 (m, 1H), 0.41-0.33 (m, 2H), 0.06--0.07 (m, 2H). TLR9 IC ₅₀ (nM) = 19
138	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 548.97; Retention Time: 0.97 min. (Method 2): Purity: 100 %; Observed Mass: 549.00; Retention Time: 1.34 min. Prep Method 2: 58 mg, 70 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.15 (s, 4H), 7.36 (s, 1H), 7.10-7.01 (m, 1H), 3.97-3.88 (m, 3H), 3.66-3.40 (m, 1H), 3.34-3.29 (m, 3H), 3.30-3.14 (m, 3H), 3.14-2.96 (m, 2H), 2.80-2.66 (m, 1H), 2.61-2.57 (m, 3H), 2.53-2.49 (m, 3H), 2.40-2.28 (m, 2H), 2.27-2.00 (m, 8H), 1.98-1.77 (m, 6H), 1.75-1.61 (m, 1H) (two protons obscured). TLR9 IC ₅₀ (nM) = 62
139	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 521.23; Retention Time: 0.92 min. (Method 2): Purity: 100 %; Observed Mass: 521.22; Retention Time: 1.18 min. Prep Method 1: 40 mg, 62 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.12 (s, 4H), 7.31 (s, 1H), 6.99 (s, 1H), 3.89 (s, 3H), 3.50-3.37 (m, 1H), 3.31 (s, 2H), 3.17-3.09 (m, 1H), 3.05-2.98 (m, 2H), 2.93-2.85 (m, 2H), 2.55 (s, 5H), 2.27-2.13 (m, 3H), 1.94-1.67 (m, 8H), 0.83 (d, <i>J</i> =6.1 Hz, 6H) (one proton obscured). TLR9 IC ₅₀ (nM) = 210
140	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 532.96; Retention Time: 0.93 min. (Method 2): Purity: 97.9 %; Observed Mass: 533.18; Retention Time: 1.3 min. Prep Method 1: 33 mg, 49 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.16-8.08 (m, 4H), 7.35-7.28 (m, 1H), 7.02-6.94 (m, 1H), 3.89 (s, 3H), 3.49-3.39 (m, 3H), 3.35-3.28 (m, 2H), 3.23-3.13 (m, 1H), 2.97-2.85 (m, 2H), 2.73-2.56 (m, 4H), 2.29-2.18 (m, 2H), 2.16-2.00 (m, 3H), 1.98-1.52 (m, 14H). TLR9 IC ₅₀ (nM) = 290

141	Analytical LC/MS (Method 1): Purity: 99.3 %; Observed Mass: 535.02; Retention Time: 0.98 min. (Method 2): Purity: 100 %; Observed Mass: 535.02; Retention Time: 0.98 min. Prep Method 1: 35 mg, 54 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.16-8.05 (m, 4H), 7.35-7.25 (m, 1H), 7.03-6.96 (m, 1H), 3.96-3.75 (m, 4H), 3.63-3.40 (m, 6H), 3.34-3.25 (m, 3H), 2.96-2.86 (m, 2H), 2.82-2.71 (m, 1H), 2.55 (s, 5H), 2.41-2.30 (m, 2H), 2.29-2.17 (m, 2H), 2.16-2.03 (m, 3H), 2.00-1.90 (m, 2H), 1.88-1.54 (m, 6H). TLR9 IC ₅₀ (nM) = 250
142	Analytical LC/MS (Method 1): Purity: 97.5 %; Observed Mass: 532.97; Retention Time: 0.94 min. (Method 2): Purity: 96.2 %; Observed Mass: 533.2; Retention Time: 1.21 min. Prep Method 1: 39 mg, 57 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.11-8.03 (m, 4H), 7.30-7.24 (m, 1H), 6.98-6.92 (m, 1H), 3.84 (s, 3H), 3.43-3.32 (m, 1H), 3.29-3.22 (m, 2H), 3.17-3.09 (m, 1H), 3.06-3.00 (m, 1H), 2.89-2.80 (m, 2H), 2.50 (s, 5H), 2.20-2.10 (m, 4H), 2.09-1.99 (m, 1H), 1.87-1.80 (m, 3H), 1.79-1.62 (m, 6H), 0.68-0.60 (m, 1H), 0.35-0.28 (m, 2H), 0.01 (br d, <i>J</i> =4.3 Hz, 2H). TLR9 IC ₅₀ (nM) = 68
143	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 547.35; Retention Time: 1.01 min. (Method 2): Purity: 100 %; Observed Mass: 546.97; Retention Time: 1.26 min. Prep Method 1: 37 mg, 55 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.11 (s, 4H), 7.34-7.28 (m, 1H), 7.02-6.96 (m, 1H), 3.89 (s, 3H), 3.49-3.37 (m, 1H), 3.33-3.23 (m, 2H), 3.21-3.10 (m, 1H), 2.94-2.83 (m, 2H), 2.53 (br d, <i>J</i> =19.2 Hz, 8H), 2.31-2.17 (m, 3H), 2.16-2.03 (m, 1H), 2.00-1.85 (m, 5H), 1.85-1.68 (m, 8H), 1.67-1.56 (m, 2H). TLR9 IC ₅₀ (nM) = 85

144	Analytical LC/MS (Method 1): Purity: 95.1 %; Observed Mass: 517.3; Retention Time: 0.99 min. (Method 2): Purity: 95.8 %; Observed Mass: 517.02; Retention Time: 1.37 min. Prep Method 1: 41 mg, 45 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.38-7.31 (m, 2H), 7.25-7.21 (m, 1H), 7.16-7.11 (m, 1H), 6.95-6.91 (m, 1H), 3.88-3.83 (m, 6H), 3.05-2.98 (m, 2H), 2.83-2.73 (m, 1H), 2.70-2.59 (m, 1H), 2.56-2.49 (m, 7H), 2.23-2.15 (m, 2H), 1.95-1.87 (m, 2H), 1.86-1.76 (m, 4H), 1.76-1.62 (m, 4H), 1.60-1.51 (m, 2H), 1.50-1.42 (m, 2H), 1.03 (d, <i>J</i> =6.1 Hz, 6H). TLR9 IC ₅₀ (nM) = 62
145	Analytical LC/MS (Method 1): Purity: 94.3 %; Observed Mass: 516.9; Retention Time: 0.99 min. (Method 2): Purity: 98.1 %; Observed Mass: 517.00; Retention Time: 1.58 min. Prep Method 1: 51 mg, 57 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.35 (s, 2H), 7.22 (s, 1H), 7.13 (d, <i>J</i> =8.2 Hz, 1H), 6.94 (s, 1H), 3.85 (s, 6H), 3.35-3.26 (m, 1H), 2.71-2.57 (m, 2H), 2.53 (br d, <i>J</i> =19.5 Hz, 7H), 2.41-2.32 (m, 1H), 1.96-1.67 (m, 16H), 1.07-0.99 (m, 6H). TLR9 IC ₅₀ (nM) = 24
146	Analytical LC/MS (Method 1): Purity: 95.8 %; Observed Mass: 528.99; Retention Time: 0.98 min. (Method 2): Purity: 95.6 %; Observed Mass: 529.29; Retention Time: 1.46 min. Prep Method 1: 47 mg, 52 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.38-7.30 (m, 2H), 7.23-7.18 (m, 1H), 7.15-7.10 (m, 1H), 6.96-6.92 (m, 1H), 3.84 (s, 3H), 3.64 (br s, 5H), 3.33-3.27 (m, 2H), 3.16-3.07 (m, 1H), 3.04-2.97 (m, 2H), 2.69-2.56 (m, 2H), 2.55 (s, 3H), 2.24-2.14 (m, 2H), 2.06-1.95 (m, 2H), 1.92-1.77 (m, 7H), 1.76-1.52 (m, 10H). TLR9 IC ₅₀ (nM) = 70
147	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 528.97; Retention Time: 0.99 min. (Method 2): Purity: 98.9 %; Observed Mass: 529.11; Retention Time: 1.64 min. Prep Method 1: 32 mg, 37 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.39-7.30 (m, 2H), 7.25-7.20 (m, 1H), 7.17-7.09 (m, 1H), 6.97-6.90 (m, 1H), 3.85 (s, 6H), 3.29-3.22 (m, 1H), 3.19-3.11 (m, 1H), 3.04-2.94 (m, 1H), 2.59-2.48 (m, 8H), 2.42-2.30 (m, 1H), 2.02-1.53 (m, 21H). TLR9 IC ₅₀ (nM) = 200

148	Analytical LC/MS (Method 1): Purity: 97.8 %; Observed Mass: 528.98; Retention Time: 1.06 min. (Method 2): Purity: 96 %; Observed Mass: 528.96; Retention Time: 1.39 min. Prep Method 1: 27 mg, 30 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.25-7.17 (m, 2H), 7.10-7.05 (m, 1H), 7.02-6.97 (m, 1H), 6.83-6.77 (m, 1H), 3.71 (s, 5H), 3.49-3.33 (m, 2H), 2.92-2.83 (m, 2H), 2.55-2.47 (m, 1H), 2.45-2.42 (m, 2H), 2.22 (br d, <i>J</i> =6.1 Hz, 2H), 2.13-2.02 (m, 2H), 1.74 (br s, 4H), 1.70-1.63 (m, 2H), 1.62-1.41 (m, 8H), 0.79-0.69 (m, 1H), 0.34 (br d, <i>J</i> =6.7 Hz, 2H), 0.01 (br d, <i>J</i> =4.0 Hz, 2H) (four protons obscured). TLR9 IC ₅₀ (nM) = 34
149	Analytical LC/MS (Method 1): Purity: 99.5 %; Observed Mass: 528.99; Retention Time: 1.02 min. (Method 2): Purity: 99.3 %; Observed Mass: 529.03; Retention Time: 1.65 min. Prep Method 1: 15 mg, 17 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.25-7.15 (m, 2H), 7.06 (s, 1H), 6.98 (br d, <i>J</i> =8.5 Hz, 1H), 6.79 (s, 1H), 3.69 (s, 4H), 3.55-3.37 (m, 3H), 3.36-3.26 (m, 1H), 3.20-3.08 (m, 2H), 2.47-2.41 (m, 2H), 2.20 (br d, <i>J</i> =4.9 Hz, 3H), 1.90-1.62 (m, 13H), 1.62-1.50 (m, 2H), 0.78-0.70 (m, 1H), 0.33 (br d, <i>J</i> =8.2 Hz, 2H), 0.01 (br d, <i>J</i> =4.6 Hz, 2H) (four protons obscured). TLR9 IC ₅₀ (nM) = 47
150	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 542.98; Retention Time: 1.04 min. (Method 2): Purity: 100 %; Observed Mass: 542.99; Retention Time: 1.52 min. Prep Method 1: 38 mg, 43 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.38-7.29 (m, 2H), 7.25-7.19 (m, 1H), 7.17-7.10 (m, 1H), 6.96-6.89 (m, 1H), 3.85 (s, 5H), 3.25-3.15 (m, 2H), 3.04-2.93 (m, 2H), 2.58-2.55 (m, 3H), 2.43-2.37 (m, 3H), 2.35-2.27 (m, 1H), 2.23-2.12 (m, 2H), 2.08-1.95 (m, 3H), 1.95-1.56 (m, 16H), 1.55-1.47 (m, 4H). TLR9 IC ₅₀ (nM) = 32

151	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 542.99; Retention Time: 1.01 min. (Method 2): Purity: 96.8 %; Observed Mass: 543.01; Retention Time: 1.77 min. Prep Method 1: 31 mg, 34 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.38-7.30 (m, 2H), 7.22-7.18 (m, 1H), 7.15-7.10 (m, 1H), 6.97-6.89 (m, 1H), 3.84 (s, 4H), 3.82-3.79 (m, 2H), 3.67-3.56 (m, 1H), 3.27-3.15 (m, 4H), 2.53 (s, 3H), 2.46-2.37 (m, 3H), 2.36-2.30 (m, 1H), 2.04-1.90 (m, 4H), 1.84 (br s, 11H), 1.78-1.61 (m, 8H). TLR9 IC ₅₀ (nM) = 170
152	Analytical LC/MS (Method 1): Purity: 97.4 %; Observed Mass: 547.25; Retention Time: 0.94 min. (Method 2): Purity: 97.4 %; Observed Mass: 546.94; Retention Time: 1.26 min. Prep Method 1: 33 mg, 33 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.10 (s, 4H), 7.29 (s, 1H), 6.98 (s, 1H), 3.92-3.83 (m, 3H), 3.59-3.54 (m, 3H), 3.32-3.22 (m, 4H), 3.15-3.05 (m, 1H), 3.03-2.95 (m, 2H), 2.67-2.56 (m, 2H), 2.27-2.16 (m, 2H), 2.04-1.94 (m, 2H), 1.92-1.76 (m, 8H), 1.75-1.49 (m, 9H). TLR9 IC ₅₀ (nM) = 84
153	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 546.95; Retention Time: 0.94 min. (Method 2): Purity: 100 %; Observed Mass: 547.26; Retention Time: 1.46 min. Prep Method 1: 14 mg, 14 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.10 (s, 4H), 7.28 (s, 1H), 6.99 (s, 1H), 3.87 (s, 2H), 3.69-3.54 (m, 3H), 3.25-3.18 (m, 2H), 3.13-2.99 (m, 1H), 2.55 (d, <i>J</i> =2.7 Hz, 4H), 2.52 (br s, 5H), 2.41-2.32 (m, 1H), 2.03-1.89 (m, 4H), 1.89-1.78 (m, 9H), 1.77-1.55 (m, 5H). TLR9 IC ₅₀ (nM) = 120
154	Analytical LC/MS (Method 1): Purity: 99.1 %; Observed Mass: 546.98; Retention Time: 0.89 min. (Method 2): Purity: 99.3 %; Observed Mass: 546.99; Retention Time: 1.33 min. Prep Method 1: 32 mg, 33 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.98 (s, 4H), 7.16 (s, 1H), 6.91-6.84 (m, 1H), 3.75 (s, 3H), 3.49-3.30 (m, 2H), 3.17 (s, 2H), 2.94-2.81 (m, 2H), 2.56-2.43 (m, 3H), 2.28-2.18 (m, 2H), 2.13-2.03 (m, 2H), 1.76 (br s, 7H), 1.63-1.41 (m, 8H), 0.79-0.69 (m, 1H), 0.38-0.29 (m, 2H), 0.05--0.04 (m, 2H). TLR9 IC ₅₀ (nM) = 30

155	Analytical LC/MS (Method 1): Purity: 99.2 %; Observed Mass: 546.99; Retention Time: 0.89 min. (Method 2): Purity: 98 %; Observed Mass: 546.99; Retention Time: 1.52 min. Prep Method 1: 32 mg, 33 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.00 (s, 4H), 7.19 (s, 1H), 6.88 (s, 1H), 3.78 (s, 3H), 3.27-3.22 (m, 1H), 3.19 (s, 3H), 2.52-2.45 (m, 2H), 2.40 (br s, 4H), 2.30-2.21 (m, 1H), 2.19-2.09 (m, 2H), 1.90-1.81 (m, 2H), 1.74 (br d, <i>J</i> =7.9 Hz, 13H), 0.77-0.69 (m, 1H), 0.39-0.27 (m, 2H), 0.04--0.03 (m, 2H). TLR9 IC ₅₀ (nM) = 160
156	Analytical LC/MS (Method 1): Purity: 99.2 %; Observed Mass: 560.99; Retention Time: 0.98 min. (Method 2): Purity: 100 %; Observed Mass: 560.97; Retention Time: 1.42 min. Prep Method 1: 34 mg, 34 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.11 (s, 4H), 7.29 (s, 1H), 7.01-6.96 (m, 1H), 3.88 (s, 2H), 3.30 (s, 2H), 3.24-3.16 (m, 2H), 3.04-2.94 (m, 2H), 2.60-2.57 (m, 1H), 2.51 (br s, 5H), 2.44-2.38 (m, 3H), 2.22-2.13 (m, 2H), 2.06-1.95 (m, 3H), 1.91-1.58 (m, 12H), 1.52 (br s, 4H). TLR9 IC ₅₀ (nM) = 31
157	Analytical LC/MS (Method 1): Purity: 96.9 %; Observed Mass: 561.03; Retention Time: 0.92 min. (Method 2): Purity: 96.8 %; Observed Mass: 561.32; Retention Time: 1.64 min. Prep Method 1: 21 mg, 21 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.10 (s, 4H), 7.29 (s, 1H), 6.99 (s, 1H), 3.88 (s, 2H), 3.63-3.52 (m, 4H), 3.29 (s, 4H), 3.23-3.14 (m, 2H), 2.61-2.57 (m, 1H), 2.45-2.39 (m, 3H), 2.38-2.30 (m, 1H), 2.04-1.90 (m, 5H), 1.86 (br s, 8H), 1.80-1.62 (m, 8H). TLR9 IC ₅₀ (nM) = 340
158	Analytical LC/MS (Method 1): Purity: 97 %; Observed Mass: 548.96; Retention Time: 0.89 min. (Method 2): Purity: 100 %; Observed Mass: 549.25; Retention Time: 1.21 min. Prep Method 1: 13 mg, 16 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.14-8.07 (m, 4H), 7.30 (s, 1H), 7.00 (s, 1H), 4.59-4.53 (m, 2H), 4.38-4.28 (m, 2H), 3.88 (s, 2H), 3.59-3.47 (m, 2H), 3.30 (s, 3H), 3.17-3.08 (m, 3H), 2.80-2.61 (m, 3H), 2.55 (s, 3H), 2.43-2.30 (m, 2H), 1.90-1.72 (m, 6H), 1.65 (br s, 4H), 1.56-1.50 (m, 2H). TLR9 IC ₅₀ (nM) = 160

159	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 548.94; Retention Time: 0.90 min. (Method 2): Purity: 95.9 %; Observed Mass: 549.26; Retention Time: 1.26 min. Prep Method 1: 9.1 mg, 11 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.14-8.06 (m, 4H), 7.32-7.25 (m, 1H), 7.03-6.96 (m, 1H), 4.53 (s, 2H), 4.31 (s, 2H), 3.87 (s, 2H), 3.71-3.52 (m, 3H), 3.28 (s, 3H), 3.24-3.18 (m, 1H), 3.02 (br s, 2H), 2.63-2.53 (m, 2H), 2.49-2.43 (m, 1H), 2.27-2.17 (m, 1H), 2.04-1.79 (m, 8H), 1.78-1.62 (m, 7H). TLR9 IC ₅₀ (nM) = 930
160	Analytical LC/MS (Method 1): Purity: 98.1 %; Observed Mass: 576.95; Retention Time: 0.91 min. (Method 2): Purity: 100 %; Observed Mass: 576.98; Retention Time: 1.24 min. Prep Method 1: 30 mg, 34 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.11 (s, 4H), 7.30 (s, 1H), 7.03-6.92 (m, 1H), 3.88 (s, 4H), 3.60-3.49 (m, 1H), 3.30 (s, 4H), 3.13-3.00 (m, 2H), 2.72-2.57 (m, 3H), 2.55 (s, 4H), 2.53-2.50 (m, 3H), 2.27-2.16 (m, 2H), 1.86-1.70 (m, 7H), 1.69-1.62 (m, 2H), 1.60-1.47 (m, 4H), 1.39-1.22 (m, 2H). TLR9 IC ₅₀ (nM) = 52
161	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 576.93; Retention Time: 0.92 min. (Method 2): Purity: 97.4 %; Observed Mass: 576.96; Retention Time: 1.40 min. Prep Method 1: 15 mg, 17 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.12 (s, 4H), 7.31 (s, 1H), 7.00 (s, 1H), 3.89 (s, 4H), 3.51-3.34 (m, 3H), 3.31 (s, 3H), 2.61-2.54 (m, 5H), 2.51 (br s, 6H), 2.47-2.33 (m, 2H), 1.93-1.80 (m, 7H), 1.78-1.65 (m, 6H), 1.33-1.19 (m, 2H). TLR9 IC ₅₀ (nM) = 210
162	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 551.24; Retention Time: 0.90 min. (Method 2): Purity: 99.2 %; Observed Mass: 551.29; Retention Time: 1.26 min. Prep Method 1: 13 mg, 15 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.11 (s, 4H), 7.30 (s, 1H), 6.99 (s, 1H), 3.88 (s, 2H), 3.54-3.38 (m, 2H), 3.30 (s, 2H), 3.25 (s, 3H), 3.03-2.94 (m, 2H), 2.55 (s, 6H), 2.52 (br s, 5H), 2.23-2.11 (m, 2H), 1.86 (s, 5H), 1.76-1.65 (m, 2H), 1.60 (br s, 2H), 1.56-1.46 (m, 3H). TLR9 IC ₅₀ (nM) = 61

163	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 550.98; Retention Time: 0.88 min. (Method 2): Purity: 100 %; Observed Mass: 551.32; Retention Time: 1.39 min. Prep Method 1: 6.7 mg, 8 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.17-8.05 (m, 4H), 7.30 (s, 1H), 6.99 (s, 1H), 3.89 (s, 3H), 3.48-3.36 (m, 1H), 3.31 (s, 2H), 3.24 (s, 3H), 3.20-3.11 (m, 2H), 2.56 (s, 4H), 2.52 (br s, 2H), 2.39 (s, 2H), 2.36-2.30 (m, 1H), 1.95-1.63 (m, 13H) (three protons obscured). TLR9 IC ₅₀ (nM) = 600
164	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 531.03; Retention Time: 0.93 min. (Method 2): Purity: 98.9 %; Observed Mass: 531.04; Retention Time: 1.23 min. Prep Method 1: 8.3 mg, 14 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.39-7.33 (m, 2H), 7.26-7.22 (m, 1H), 7.17-7.11 (m, 1H), 6.97-6.89 (m, 1H), 4.56 (s, 2H), 4.36-4.26 (m, 2H), 3.88-3.81 (m, 7H), 3.72-3.62 (m, 1H), 3.44-3.26 (m, 2H), 3.16-3.07 (m, 2H), 3.05-2.99 (m, 1H), 2.54 (br d, <i>J</i> =8.2 Hz, 6H), 2.33-2.21 (m, 2H), 1.81 (br s, 6H), 1.66-1.48 (m, 6H). TLR9 IC ₅₀ (nM) = 110
165	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 530.96; Retention Time: 0.96 min. (Method 2): Purity: 100 %; Observed Mass: 531.00; Retention Time: 1.37 min. Prep Method 1: 19 mg, 33 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.38-7.31 (m, 2H), 7.24-7.20 (m, 1H), 7.16-7.10 (m, 1H), 6.96-6.90 (m, 1H), 4.53 (s, 2H), 4.31 (s, 2H), 3.88-3.80 (m, 7H), 3.59-3.43 (m, 1H), 3.29-3.19 (m, 2H), 3.01 (br s, 2H), 2.58-2.55 (m, 3H), 2.47-2.37 (m, 1H), 2.00-1.65 (m, 17H). TLR9 IC ₅₀ (nM) = 1300
166	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 559.04; Retention Time: 0.94 min. (Method 2): Purity: 100 %; Observed Mass: 559.06; Retention Time: 1.24 min. Prep Method 2: 34 mg, 39 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.64-7.56 (m, 1H), 7.54-7.46 (m, 2H), 7.33-7.25 (m, 2H), 4.45-4.37 (m, 1H), 4.34-4.21 (m, 1H), 3.98 (s, 4H), 3.90 (d, <i>J</i> =13.4 Hz, 6H), 3.85-3.71 (m, 1H), 3.40-3.27 (m, 1H), 3.18 (s, 2H), 2.62 (s, 3H), 2.55 (s, 5H), 2.53-2.51 (m, 2H), 2.32-1.96 (m, 13H), 1.75-1.58 (m, 2H). TLR9 IC ₅₀ (nM) = 40

167	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 559.0; Retention Time: 0.96 min. (Method 2): Purity: 100 %; Observed Mass: 559.02; Retention Time: 1.52 min. Prep Method 1: 25 mg, 41 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.37-7.32 (m, 2H), 7.26-7.21 (m, 1H), 7.17-7.11 (m, 1H), 6.96-6.92 (m, 1H), 3.91-3.82 (m, 8H), 3.49-3.25 (m, 5H), 2.57-2.53 (m, 6H), 2.46-2.33 (m, 2H), 2.11-1.66 (m, 16H), 1.46-1.26 (m, 4H). TLR9 IC ₅₀ (nM) = 790
168	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 533.04; Retention Time: 0.97 min. (Method 2): Purity: 100 %; Observed Mass: 533.02; Retention Time: 1.36 min. Prep Method 1: 13 mg, 22 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.38-7.31 (m, 2H), 7.23-7.20 (m, 1H), 7.16-7.11 (m, 1H), 6.97-6.89 (m, 1H), 3.85 (s, 5H), 3.81 (s, 2H), 3.58-3.45 (m, 1H), 3.44-3.38 (m, 1H), 3.33-3.28 (m, 1H), 3.25 (s, 2H), 3.05-2.98 (m, 2H), 2.69-2.53 (m, 8H), 2.28-2.18 (m, 2H), 1.93-1.77 (m, 6H), 1.64 (br s, 5H), 1.59-1.48 (m, 4H). TLR9 IC ₅₀ (nM) = 51
169	Analytical LC/MS (Method 1): Purity: 99.4 %; Observed Mass: 532.96; Retention Time: 0.97 min. (Method 2): Purity: 100 %; Observed Mass: 533.01; Retention Time: 1.54 min. Prep Method 1: 16 mg, 28 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.39-7.30 (m, 2H), 7.24-7.18 (m, 1H), 7.17-7.10 (m, 1H), 6.96-6.90 (m, 1H), 3.84 (s, 4H), 3.81 (s, 2H), 3.69-3.54 (m, 3H), 3.42 (s, 1H), 3.24 (s, 6H), 2.55 (s, 5H), 2.47 (s, 2H), 2.36 (br s, 1H), 2.02-1.92 (m, 2H), 1.92-1.78 (m, 9H), 1.71 (br d, J=12.5 Hz, 4H). TLR9 IC ₅₀ (nM) = 200
170	Analytical LC/MS (Method 1): Purity: 99.2 %; Observed Mass: 517.26; Retention Time: 1.18 min. (Method 2): Purity: 100 %; Observed Mass: 517.20; Retention Time: 2.32 min. Prep Method 1: 18 mg, 26 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.22-8.06 (m, 4H), 7.70-7.35 (m, 4H), 7.09-7.00 (m, 2H), 3.96 (s, 3H), 3.49 (br d, J=4.9 Hz, 4H), 3.31 (s, 2H), 3.26-3.12 (m, 1H), 2.63 (s, 3H), 2.55 (s, 2H), 2.28-2.06 (m, 2H), 1.96-1.72 (m, 2H), 1.32-1.19 (m, 1H), 0.90 (br d, J=6.4 Hz, 6H). TLR9 IC ₅₀ (nM) = 4400

171	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 515.00; Retention Time: 1.17 min. (Method 2): Purity: 100 %; Observed Mass: 515.25; Retention Time: 1.84 min. Prep Method 1: 28 mg, 41 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.06-7.97 (m, 4H), 7.56-7.49 (m, 3H), 7.28-7.23 (m, 1H), 6.97-6.88 (m, 2H), 3.84 (s, 3H), 3.42-3.26 (m, 3H), 3.19 (s, 2H), 3.16-3.07 (m, 2H), 2.55-2.52 (m, 2H), 2.39 (br s, 5H), 2.21-2.08 (m, 2H), 0.82-0.71 (m, 1H), 0.44-0.36 (m, 2H), 0.05--0.04 (m, 2H). TLR9 IC ₅₀ (nM) = 650
172	Analytical LC/MS (Method 4): Purity: 97.9 %; Observed Mass: 529.1; Retention Time: 1.182 min. (Method 2): Purity: 91.3 %; Observed Mass: 529.1; Retention Time: 1.728 min. Prep Method 1: 26 mg, 37 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.22-8.08 (m, 4H), 7.69-7.63 (m, 3H), 7.40-7.35 (m, 1H), 7.06-7.00 (m, 2H), 3.97 (s, 3H), 3.23-3.15 (m, 3H), 2.65-2.60 (m, 3H), 2.42-2.36 (m, 4H), 2.10-2.01 (m, 8H), 1.93-1.77 (m, 3H), 1.72-1.64 (m, 2H). TLR9 IC ₅₀ (nM) = 1800
173	Analytical LC/MS (Method 1): Purity: 95.3 %; Observed Mass: 519.19; Retention Time: 1.07 min. (Method 2): Purity: 97.8 %; Observed Mass: 519.16; Retention Time: 1.70 min. Prep Method 1: 37 mg, 51 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.20-8.08 (m, 4H), 7.70-7.62 (m, 3H), 7.41-7.35 (m, 1H), 7.08-7.00 (m, 2H), 3.96 (br s, 3H), 3.53-3.42 (m, 2H), 3.31 (br s, 2H), 3.29-3.26 (m, 1H), 3.24-3.17 (m, 2H), 2.63 (br s, 7H), 2.57-2.55 (m, 1H), 2.52 (br s, 5H) (one proton obscured). TLR9 IC ₅₀ (nM) = 1100
174	Analytical LC/MS (Method 4): Purity: 98.7 %; Observed Mass: 515.1; Retention Time: 1.080 min. (Method 5): Purity: 92 %; Observed Mass: 515.3; Retention Time: 1.775 min. Prep Method 1: 44 mg, 64 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.20-8.10 (m, 4H), 7.69-7.61 (m, 3H), 7.41-7.36 (m, 1H), 7.07-7.00 (m, 2H), 3.99-3.95 (m, 3H), 3.22-3.17 (m, 6H), 2.81-2.72 (m, 1H), 2.63 (s, 3H), 2.44-2.40 (m, 5H), 2.05-1.97 (m, 2H), 1.89-1.79 (m, 2H), 1.71-1.63 (m, 2H). TLR9 IC ₅₀ (nM) = 480

175	Analytical LC/MS (Method 1): Purity: 95.5 %; Observed Mass: 479.2; Retention Time: 1.01 min. (Method 2): Purity: 98.5 %; Observed Mass: 478.94; Retention Time: 1.35 min. Prep Method 1: 9.2 mg, 13 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.86-7.69 (m, 2H), 7.45-7.23 (m, 1H), 7.17-7.06 (m, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 2.97 (br d, J=10.7 Hz, 3H), 2.93-2.83 (m, 1H), 2.52 (br s, 3H), 2.33-2.23 (m, 2H), 2.18-2.07 (m, 2H), 1.97-1.85 (m, 1H), 1.74 (br s, 5H), 1.60-1.49 (m, 1H), 1.46-1.31 (m, 2H), 0.45-0.36 (m, 2H), 0.33-0.24 (m, 2H). TLR9 IC ₅₀ (nM) = 530
176	Analytical LC/MS (Method 4): Purity: 98.4 %; Observed Mass: 545.1; Retention Time: 1.019 min. (Method 5): Purity: 95 %; Observed Mass: 545.1; Retention Time: 1.574 min. Prep Method 1: 27 mg, 37 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.20-8.07 (m, 4H), 7.70-7.62 (m, 3H), 7.40-7.35 (m, 1H), 7.07-7.01 (m, 2H), 4.13-4.06 (m, 1H), 3.97 (s, 3H), 3.94-3.89 (m, 2H), 3.22-3.16 (m, 8H), 2.68-2.62 (m, 7H), 2.47-2.36 (m, 4H) (one proton obscured). TLR9 IC ₅₀ (nM) = 680
177	Analytical LC/MS (Method 1): Purity: 95.8 %; Observed Mass: 512.91; Retention Time: 1.03 min. (Method 2): Purity: 100 %; Observed Mass: 513.23; Retention Time: 1.40 min. Prep Method 1: 8.2 mg, 10 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.45-8.37 (m, 2H), 8.10 (br d, J=8.5 Hz, 2H), 7.45-7.36 (m, 1H), 7.26-7.16 (m, 1H), 3.30-3.26 (m, 2H), 3.07-3.00 (m, 2H), 3.00-2.80 (m, 4H), 2.42-2.23 (m, 4H), 2.12-1.96 (m, 5H), 1.76 (br d, J=7.2 Hz, 5H), 1.56-1.44 (m, 3H), 0.91-0.80 (m, 6H). TLR9 IC ₅₀ (nM) = 120
178	Analytical LC/MS (Method 1): Purity: 97.5 %; Observed Mass: 496.93; Retention Time: 0.94 min. (Method 2): Purity: 95.3 %; Observed Mass: 497.00; Retention Time: 1.28 min. Prep Method 1: 35 mg, 43 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.49-8.37 (m, 2H), 8.15-8.08 (m, 2H), 7.46-7.31 (m, 1H), 7.26-7.14 (m, 1H), 3.54-3.50 (m, 3H), 3.29 (s, 2H), 3.14-3.05 (m, 1H), 3.04-2.95 (m, 2H), 2.55 (s, 3H), 2.49-2.39 (m, 2H), 2.21-2.10 (m, 2H), 1.80 (br s, 5H), 1.63-1.55 (m, 1H), 1.50-1.39 (m, 2H), 0.43-0.37 (m, 2H), 0.29 (br d, J=2.4 Hz, 2H). TLR9 IC ₅₀ (nM) = 240

179	Analytical LC/MS (Method 1): Purity: 98.7 %; Observed Mass: 511.23; Retention Time: 0.96 min. (Method 2): Purity: 98.3 %; Observed Mass: 511.24; Retention Time: 1.23 min. Prep Method 1: 22 mg, 33 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.40-8.30 (m, 2H), 8.07-7.99 (m, 2H), 7.37-7.29 (m, 1H), 7.20-7.11 (m, 1H), 3.54 (br s, 3H), 3.21 (s, 2H), 3.02-2.91 (m, 4H), 2.89-2.79 (m, 1H), 2.45 (s, 4H), 2.28-2.16 (m, 3H), 2.12 (br d, <i>J</i> =6.5 Hz, 2H), 1.93-1.80 (m, 3H), 1.45 (br d, <i>J</i> =2.0 Hz, 2H), 0.82-0.72 (m, 1H), 0.39 (br d, <i>J</i> =7.6 Hz, 2H), 0.01 (br d, <i>J</i> =4.6 Hz, 2H). TLR9 IC ₅₀ (nM) = 180
180	Analytical LC/MS (Method 1): Purity: 98.1 %; Observed Mass: 510.89; Retention Time: 1.01 min. (Method 2): Purity: 100 %; Observed Mass: 510.92; Retention Time: 1.31 min. Prep Method 1: 14 mg, 21 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.49-8.35 (m, 2H), 8.10 (br d, <i>J</i> =8.3 Hz, 2H), 7.45-7.35 (m, 1H), 7.21 (s, 1H), 3.53 (br s, 3H), 3.28 (s, 2H), 3.05-2.97 (m, 2H), 2.97-2.89 (m, 1H), 2.88-2.81 (m, 2H), 2.75-2.61 (m, 1H), 2.39-2.23 (m, 3H), 2.02-1.90 (m, 2H), 1.76 (br s, 9H), 1.65-1.55 (m, 2H), 1.50-1.39 (m, 2H). TLR9 IC ₅₀ (nM) = 25
181	Analytical LC/MS (Method 1): Purity: 96.6 %; Observed Mass: 513.40; Retention Time: 0.90 min. (Method 2): Purity: 100 %; Observed Mass: 513.40; Retention Time: 1.01 min. Prep Method 1: 27 mg, 39 % yield. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.20-8.05 (m, 4H), 7.62-7.55 (m, 1H), 7.20-7.13 (m, 1H), 4.78-4.67 (m, 4H), 4.32-4.16 (m, 1H), 4.04 (s, 3H), 3.67-3.57 (m, 1H), 3.33 (s, 2H), 3.29-3.21 (m, 1H), 2.86-2.67 (m, 1H), 2.55 (s, 5H), 2.41-2.29 (m, 2H), 2.07 (br s, 6H) (one proton obscured). TLR9 IC ₅₀ (nM) = 640

182	Analytical LC/MS (Method 1): Purity: 95.1 %; Observed Mass: 541.01; Retention Time: 0.98 min. (Method 2): Purity: 97.8 %; Observed Mass: 541.14; Retention Time: 1.06 min. Prep Method 1: 8.4 mg, 11 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.48-8.37 (m, 2H), 8.15-8.07 (m, 2H), 7.44-7.35 (m, 1H), 7.26-7.18 (m, 1H), 3.92-3.83 (m, 2H), 3.56-3.54 (m, 3H), 3.05-2.89 (m, 4H), 2.51 (br s, 5H), 2.44-2.35 (m, 1H), 2.34-2.18 (m, 3H), 2.13-2.03 (m, 2H), 1.75 (br s, 5H), 1.70-1.62 (m, 2H), 1.49-1.34 (m, 4H). TLR9 IC₅₀ (nM) = 320
183	Analytical LC/MS (Method 1): Purity: 94.9 %; Observed Mass: 527.23; Retention Time: 0.93 min. (Method 2): Purity: 98.4 %; Observed Mass: 527.15; Retention Time: 1.12 min. Prep Method 1: 8.3 mg, 11 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.42 (br d, <i>J</i>=7.9 Hz, 2H), 8.11 (br d, <i>J</i>=8.2 Hz, 2H), 7.40 (br d, <i>J</i>=4.6 Hz, 1H), 7.21 (br t, <i>J</i>=7.3 Hz, 1H), 4.64 (s, 2H), 4.25 (s, 2H), 3.57-3.35 (m, 3H), 3.22-3.09 (m, 2H), 3.08-2.89 (m, 3H), 2.80 (br d, <i>J</i>=11.0 Hz, 2H), 2.63-2.58 (m, 2H), 2.41-2.24 (m, 3H), 1.95-1.91 (m, 2H), 1.76 (br d, <i>J</i>=5.5 Hz, 6H), 1.52-1.38 (m, 2H). TLR9 IC₅₀ (nM) = 110
184	Analytical LC/MS (Method 1): Purity: 97.5 %; Observed Mass: 526.94; Retention Time: 1.04 min. (Method 2): Purity: 98.4 %; Observed Mass: 526.94; Retention Time: 1.43 min. Prep Method 1: 17 mg, 21 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.20-8.08 (m, 4H), 7.46 (d, <i>J</i>=8.5 Hz, 1H), 7.33-7.23 (m, 1H), 3.91 (s, 3H), 3.48 (br s, 7H), 3.12-3.04 (m, 1H), 3.03-2.87 (m, 2H), 2.47-2.31 (m, 2H), 2.15-2.01 (m, 2H), 1.98-1.86 (m, 2H), 1.85-1.71 (m, 6H), 1.59-1.46 (m, 2H), 0.85 (d, <i>J</i>=6.6 Hz, 6H). TLR9 IC₅₀ (nM) = 850

185	Analytical LC/MS (Method 1): Purity: 98.2 %; Observed Mass: 511.15; Retention Time: 1.01 min. (Method 2): Purity: 100 %; Observed Mass: 511.22; Retention Time: 1.35 min. Prep Method 1: 36 mg, 45 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.19-8.08 (m, 4H), 7.44 (d, <i>J</i> =8.5 Hz, 1H), 7.33-7.23 (m, 1H), 3.91 (s, 3H), 3.52-3.47 (m, 2H), 3.07-2.91 (m, 4H), 2.55-2.48 (m, 2H), 2.42-2.31 (m, 3H), 2.19-2.08 (m, 2H), 1.76 (br s, 6H), 1.61-1.53 (m, 1H), 1.47-1.34 (m, 2H), 0.46-0.36 (m, 2H), 0.28 (br d, <i>J</i> =2.1 Hz, 2H). TLR9 IC ₅₀ (nM) = 700
186	Analytical LC/MS (Method 1): Purity: 98.2 %; Observed Mass: 526.96; Retention Time: 1.16 min. (Method 2): Purity: 100 %; Observed Mass: 526.94; Retention Time: 1.16 min. Prep Method 1: 20 mg, 37 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.13 (d, <i>J</i> =2.5 Hz, 4H), 7.45 (br d, <i>J</i> =8.5 Hz, 1H), 7.31-7.25 (m, 1H), 4.56-4.48 (m, 2H), 4.45-4.37 (m, 2H), 3.90 (s, 2H), 3.53 (br s, 6H), 3.47-3.34 (m, 1H), 3.16-2.97 (m, 2H), 2.80-2.72 (m, 2H), 2.56-2.53 (m, 3H), 1.88-1.71 (m, 7H), 1.60-1.46 (m, 2H). TLR9 IC ₅₀ (nM) = 7300
187	Analytical LC/MS (Method 1): Purity: 98.5 %; Observed Mass: 555.25; Retention Time: 0.93 min. (Method 2): Purity: 98.9 %; Observed Mass: 555.26; Retention Time: 1.08 min. Prep Method 1: 12 mg, 22 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.24-8.06 (m, 4H), 7.52-7.44 (m, 1H), 7.34-7.24 (m, 1H), 3.92 (s, 4H), 3.52-3.35 (m, 3H), 3.32 (s, 1H), 3.30-3.23 (m, 1H), 3.19-2.97 (m, 4H), 2.55-2.51 (m, 6H), 2.49-2.42 (m, 1H), 2.30-2.12 (m, 2H), 1.91-1.76 (m, 5H), 1.76-1.67 (m, 2H), 1.58-1.38 (m, 4H). TLR9 IC ₅₀ (nM) = 520

188	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 529.27; Retention Time: 0.93 min. (Method 2): Purity: 98.9 %; Observed Mass: 529.44; Retention Time: 1.09 min. Prep Method 1: 28 mg, 52 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.12 (s, 4H), 7.47-7.40 (m, 1H), 7.32-7.24 (m, 1H), 3.77-3.72 (m, 6H), 3.45-3.39 (m, 1H), 3.29 (s, 3H), 3.21 (s, 2H), 3.02-2.96 (m, 2H), 2.95-2.87 (m, 2H), 2.46-2.41 (m, 2H), 2.32-2.18 (m, 3H), 1.99-1.89 (m, 2H), 1.84-1.68 (m, 6H), 1.52-1.41 (m, 2H). TLR9 IC ₅₀ (nM) = 440
189	Analytical LC/MS (Method 1): Purity: 97.6 %; Observed Mass: 553.31; Retention Time: 1.07 min. (Method 2): Purity: 100 %; Observed Mass: 553.22; Retention Time: 1.42 min. Prep Method 1: 16 mg, 21 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.11 (s, 4H), 7.46-7.42 (m, 1H), 7.29-7.25 (m, 1H), 3.28 (s, 3H), 3.09-3.00 (m, 2H), 2.99-2.90 (m, 1H), 2.31-2.16 (m, 5H), 1.91-1.83 (m, 4H), 1.81-1.72 (m, 5H), 1.72-1.61 (m, 6H), 1.59-1.51 (m, 3H), 0.89-0.85 (m, 6H). TLR9 IC ₅₀ (nM) = 150
190	Analytical LC/MS (Method 1): Purity: 95.3 %; Observed Mass: 553.30; Retention Time: 0.99 min. (Method 2): Purity: 95.6 %; Observed Mass: 553.28; Retention Time: 1.51 min. Prep Method 1: 6.7 mg, 9 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.17-8.08 (m, 4H), 7.46-7.42 (m, 1H), 7.30-7.25 (m, 1H), 4.07-4.02 (m, 4H), 3.60-3.48 (m, 3H), 3.31-3.14 (m, 5H), 3.02-2.90 (m, 2H), 2.61-2.56 (m, 2H), 2.09-1.98 (m, 3H), 1.84 (br s, 3H), 1.81-1.62 (m, 7H), 0.91-0.82 (m, 6H). TLR9 IC ₅₀ (nM) = 2600
191	Analytical LC/MS (Method 1): Purity: 96.8 %; Observed Mass: 550.95; Retention Time: 0.97 min. (Method 2): Purity: 99 %; Observed Mass: 551.26; Retention Time: 1.19 min. Prep Method 1: 19 mg, 25 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.06-7.94 (m, 4H), 7.32 (br d, <i>J</i> =8.5 Hz, 1H), 7.15 (br s, 1H), 3.79 (s, 2H), 3.44-3.25 (m, 2H), 3.19 (s, 2H), 2.90-2.84 (m, 2H), 2.84-2.76 (m, 1H), 2.56-2.46 (m, 1H), 2.21 (br d, <i>J</i> =6.1 Hz, 2H), 2.16-2.05 (m, 2H), 1.77 (s, 4H), 1.62 (br s, 6H), 1.50-1.36 (m, 4H), 0.81-0.67 (m, 1H), 0.37-0.31 (m, 2H), 0.03--0.05 (m, 2H). TLR9 IC ₅₀ (nM) = 96

192	Analytical LC/MS (Method 1): Purity: 98.4 %; Observed Mass: 551.26; Retention Time: 1.43 min. (Method 2): Purity: 97.4 %; Observed Mass: 551.26; Retention Time: 1.43 min. Prep Method 1: 11 mg, 14 %; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.05-7.96 (m, 4H), 7.36-7.28 (m, 1H), 7.19-7.11 (m, 1H), 3.78 (s, 3H), 3.44-3.24 (m, 2H), 3.18 (s, 3H), 2.89-2.75 (m, 1H), 2.29-2.22 (m, 1H), 2.16 (br d, <i>J</i> =6.1 Hz, 2H), 1.93-1.80 (m, 2H), 1.74 (br s, 7H), 1.69-1.54 (m, 5H), 0.81-0.67 (m, 1H), 0.34 (br d, <i>J</i> =6.7 Hz, 2H), 0.01 (br d, <i>J</i> =3.7 Hz, 2H) (two protons obscured). TLR9 IC ₅₀ (nM) = 190
193	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 567.01; Retention Time: 1.0 min. (Method 2): Purity: 98.7 %; Observed Mass: 567.02; Retention Time: 1.25 min. Prep Method 1: 13 mg, 17 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.18-8.08 (m, 4H), 7.44 (d, <i>J</i> =8.5 Hz, 1H), 7.27 (s, 1H), 4.62 (br d, <i>J</i> =7.5 Hz, 2H), 4.27 (t, <i>J</i> =6.1 Hz, 2H), 3.91 (s, 3H), 3.45 (br s, 5H), 3.19-3.12 (m, 1H), 3.10-2.86 (m, 3H), 2.66 (br d, <i>J</i> =7.1 Hz, 3H), 2.29-2.16 (m, 2H), 1.89-1.80 (m, 2H), 1.74 (br s, 4H), 1.63-1.47 (m, 6H). TLR9 IC ₅₀ (nM) = 82
194	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 567.00; Retention Time: 0.99 min. (Method 2): Purity: 100 %; Observed Mass: 566.99; Retention Time: 1.38 min. Prep Method 1: 12 mg, 16 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.18-8.09 (m, 4H), 7.45 (d, <i>J</i> =8.5 Hz, 1H), 7.27 (s, 1H), 4.62 (dd, <i>J</i> =7.6, 5.8 Hz, 2H), 4.26 (t, <i>J</i> =6.0 Hz, 2H), 3.92 (s, 3H), 3.47-3.42 (m, 6H), 3.28-3.19 (m, 1H), 3.04 (br d, <i>J</i> =7.0 Hz, 2H), 2.97-2.85 (m, 1H), 2.57-2.52 (m, 2H), 2.34 (br s, 1H), 1.93-1.63 (m, 13H). TLR9 IC ₅₀ (nM) = 630

195	Analytical LC/MS (Method 1): Purity: 95.5 %; Observed Mass: 553.23; Retention Time: 0.92 min. (Method 2): Purity: 86.9 %; Observed Mass: 553.24; Retention Time: 1.11 min. Prep Method 1: 6.1 mg, 7 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.13 (br d, <i>J</i> =4.8 Hz, 4H), 7.44 (br d, <i>J</i> =8.6 Hz, 1H), 7.31-7.24 (m, 1H), 4.57-4.49 (m, 2H), 4.35-4.26 (m, 2H), 3.91 (s, 3H), 3.70-3.59 (m, 2H), 3.31 (s, 2H), 3.11-3.07 (m, 1H), 3.02-2.86 (m, 3H), 2.66-2.57 (m, 1H), 2.55 (s, 2H), 2.32-2.18 (m, 2H), 1.92-1.87 (m, 1H), 1.83-1.70 (m, 6H), 1.61-1.55 (m, 2H), 1.54-1.48 (m, 2H). TLR9 IC ₅₀ (nM) = 490
196	Analytical LC/MS (Method 1): Purity: 91.8 %; Observed Mass: 552.94; Retention Time: 0.93 min. (Method 2): Purity: 95.1 %; Observed Mass: 553.22; Retention Time: 1.17 min. Prep Method 1: 6.7 mg, 7 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.13 (br d, <i>J</i> =4.8 Hz, 4H), 7.49-7.42 (m, 1H), 7.31-7.25 (m, 1H), 4.61-4.50 (m, 2H), 4.37-4.24 (m, 2H), 3.91 (s, 3H), 3.70-3.58 (m, 2H), 3.31 (s, 2H), 3.13-3.05 (m, 1H), 3.02-2.86 (m, 3H), 2.68-2.56 (m, 1H), 2.56-2.52 (m, 2H), 2.34-2.18 (m, 2H), 1.93-1.89 (m, 1H), 1.84-1.69 (m, 6H), 1.62-1.47 (m, 4H). TLR9 IC ₅₀ (nM) = 580
197	Analytical LC/MS (Method 1): Purity: 93.7 %; Observed Mass: 580.99; Retention Time: 1.01 min. (Method 2): Purity: 88.7 %; Observed Mass: 581.31; Retention Time: 1.28 min. Prep Method 1: 11 mg, 13 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.13 (br d, <i>J</i> =5.1 Hz, 4H), 7.50-7.41 (m, 1H), 7.31-7.23 (m, 1H), 3.96-3.89 (m, 3H), 3.88-3.81 (m, 2H), 3.47-3.41 (m, 2H), 3.36-3.28 (m, 2H), 3.08-3.02 (m, 1H), 2.99-2.86 (m, 1H), 2.72-2.58 (m, 2H), 2.51 (br s, 5H), 2.28-2.15 (m, 2H), 1.84-1.71 (m, 7H), 1.69-1.59 (m, 2H), 1.59-1.52 (m, 2H), 1.52-1.43 (m, 2H), 1.35-1.19 (m, 2H). TLR9 IC ₅₀ (nM) = 160

198	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 581.04; Retention Time: 1.02 min. (Method 2): Purity: 100 %; Observed Mass: 581.05; Retention Time: 1.44 min. Prep Method 1: 5.7 mg, 8 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.19-8.05 (m, 4H), 7.51-7.42 (m, 1H), 7.34-7.23 (m, 1H), 3.92 (s, 3H), 3.88-3.81 (m, 2H), 3.46-3.39 (m, 4H), 3.32 (s, 2H), 3.01-2.88 (m, 1H), 2.55 (s, 2H), 2.53-2.48 (m, 5H), 2.43-2.34 (m, 1H), 1.96-1.69 (m, 13H), 1.38-1.21 (m, 2H). TLR9 IC ₅₀ (nM) = 57
199	Analytical LC/MS (Method 1): Purity: 98.8 %; Observed Mass: 555.00; Retention Time: 0.95 min. (Method 2): Purity: 98.3 %; Observed Mass: 555.27; Retention Time: 1.15 min. Prep Method 1: 16 mg, 21 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.15-8.10 (m, 4H), 7.46-7.40 (m, 1H), 7.29-7.22 (m, 1H), 3.88 (s, 3H), 3.44-3.38 (m, 2H), 3.23 (s, 3H), 3.03-2.96 (m, 2H), 2.95-2.87 (m, 1H), 2.61-2.48 (m, 6H), 2.23-2.13 (m, 2H), 1.89-1.67 (m, 8H), 1.66-1.46 (m, 6H). TLR9 IC ₅₀ (nM) = 75
200	Analytical LC/MS (Method 1): Purity: 95.3 %; Observed Mass: 555.0; Retention Time: 1.02 min. (Method 2): Purity: 99.3 %; Observed Mass: 555.0; Retention Time: 1.47 min. Prep Method 1: 10 mg, 13 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.14-8.09 (m, 4H), 7.43 (d, <i>J</i> =8.5 Hz, 1H), 7.30-7.23 (m, 1H), 3.40-3.35 (m, 2H), 3.28 (s, 3H), 3.22 (s, 6H), 2.98-2.85 (m, 1H), 2.51 (s, 5H), 2.39 (br s, 3H), 1.74 (br dd, <i>J</i> =11.7, 5.4 Hz, 11H), 1.63 (br dd, <i>J</i> =14.1, 1.9 Hz, 2H). TLR9 IC ₅₀ (nM) = 380
201	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 527.02; Retention Time: 1.05 min. (Method 2): Purity: 100 %; Observed Mass: 527.09; Retention Time: 1.53 min. Prep Method 1: 63 mg, 84 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.17-8.04 (m, 4H), 7.41 (s, 1H), 7.11-7.02 (m, 1H), 4.00 (s, 3H), 3.82-3.67 (m, 2H), 3.60-3.59 (m, 2H), 3.30 (s, 2H), 3.28-3.18 (m, 1H), 3.04-2.98 (m, 1H), 2.83-2.56 (m, 3H), 2.26-1.99 (m, 4H), 1.98-1.84 (m, 4H), 1.84-1.71 (m, 3H), 1.69-1.54 (m, 2H), 0.88-0.83 (m, 6H). TLR9 IC ₅₀ (nM) = 97

202	Analytical LC/MS (Method 1): Purity: 99.5 %; Observed Mass: 511.23; Retention Time: 0.95 min. (Method 2): Purity: 98.9 %; Observed Mass: 510.92; Retention Time: 1.26 min. Prep Method 1: 62 mg, 85 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.20-8.03 (m, 4H), 7.46-7.36 (m, 1H), 7.10-7.00 (m, 1H), 4.00 (s, 3H), 3.74 (br s, 1H), 3.30 (s, 2H), 3.25-3.14 (m, 1H), 3.05-2.96 (m, 2H), 2.81-2.57 (m, 3H), 2.56-2.52 (m, 2H), 2.25-2.10 (m, 2H), 1.96-1.70 (m, 6H), 1.67-1.56 (m, 1H), 1.54-1.37 (m, 2H), 0.50-0.36 (m, 2H), 0.30 (br s, 2H). TLR9 IC ₅₀ (nM) = 500
203	Analytical LC/MS (Method 1): Purity: 99.4 %; Observed Mass: 525.11; Retention Time: 1.15 min. (Method 2): Purity: 98.3 %; Observed Mass: 525.21; Retention Time: 1.31 min. Prep Method 1: 29 mg, 48 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.10-7.97 (m, 4H), 7.35-7.30 (m, 1H), 7.04-6.96 (m, 1H), 3.94 (s, 3H), 3.25 (s, 1H), 3.04-2.87 (m, 3H), 2.61-2.51 (m, 1H), 2.44 (br s, 2H), 2.28-2.16 (m, 3H), 2.12 (br d, <i>J</i> =6.1 Hz, 2H), 1.88 (br t, <i>J</i> =11.0 Hz, 2H), 1.79-1.55 (m, 6H), 1.49-1.38 (m, 2H), 0.83-0.70 (m, 1H), 0.39 (br d, <i>J</i> =7.6 Hz, 2H), 0.01 (br d, <i>J</i> =4.3 Hz, 2H) (one proton obscured). TLR9 IC ₅₀ (nM) = 110
204	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 540.93; Retention Time: 1.0 min. (Method 2): Purity: 99.2 %; Observed Mass: 540.93; Retention Time: 1.24 min. Prep Method 1: 47 mg, 75 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.22-7.98 (m, 4H), 7.46-7.36 (m, 1H), 7.13-7.00 (m, 1H), 4.64 (s, 2H), 4.25 (s, 2H), 4.01 (s, 3H), 3.50-3.38 (m, 2H), 3.32 (s, 2H), 3.22-3.13 (m, 1H), 3.12-3.01 (m, 1H), 2.83 (br d, <i>J</i> =11.0 Hz, 2H), 2.63 (br d, <i>J</i> =6.7 Hz, 3H), 2.55 (s, 1H), 2.47-2.35 (m, 2H), 1.99-1.82 (m, 4H), 1.81-1.63 (m, 4H), 1.56-1.41 (m, 2H). TLR9 IC ₅₀ (nM) = 780

205	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 525.24; Retention Time: 0.96 min. (Method 2): Purity: 99.2 %; Observed Mass: 525.26; Retention Time: 1.33 min. Prep Method 2: 19 mg, 22 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.18-8.04 (m, 4H), 7.50-7.36 (m, 1H), 7.18-7.00 (m, 1H), 4.03 (s, 3H), 3.67-3.53 (m, 1H), 3.44-3.37 (m, 1H), 3.33 (s, 1H), 3.25-3.10 (m, 1H), 3.09-2.97 (m, 1H), 2.90-2.73 (m, 1H), 2.58-2.54 (m, 1H), 2.51 (br s, 2H), 2.43-2.27 (m, 2H), 2.26-2.09 (m, 6H), 2.08-1.87 (m, 4H), 1.83-1.65 (m, 2H) (five protons obscured). TLR9 IC ₅₀ (nM) = 110
206	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 526.93; Retention Time: 0.98 min. (Method 2): Purity: 100 %; Observed Mass: 526.94; Retention Time: 1.17 min. Prep Method 2: 31 mg, 36 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.16-8.09 (m, 4H), 7.46-7.41 (m, 1H), 7.11-7.04 (m, 1H), 4.78-4.66 (m, 4H), 4.29-4.15 (m, 1H), 4.03 (s, 3H), 3.69-3.57 (m, 1H), 3.33 (s, 2H), 3.22-3.13 (m, 1H), 3.08-2.98 (m, 1H), 2.79-2.65 (m, 1H), 2.55 (s, 5H), 2.52-2.47 (m, 2H), 2.41-2.26 (m, 2H), 2.21-2.10 (m, 2H), 2.07-1.87 (m, 4H). TLR9 IC ₅₀ (nM) = 840
207	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 555.28; Retention Time: 0.97 min. (Method 2): Purity: 98.2 %; Observed Mass: 554.97; Retention Time: 1.22 min. Prep Method 2: 22 mg, 25 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.16-8.09 (m, 4H), 7.45-7.40 (m, 1H), 7.08-7.04 (m, 1H), 4.03 (s, 5H), 3.75-3.57 (m, 2H), 3.33 (s, 1H), 3.25-3.13 (m, 1H), 3.11-2.97 (m, 2H), 2.55 (s, 6H), 2.52-2.49 (m, 2H), 2.44-2.31 (m, 2H), 2.19-2.10 (m, 2H), 2.09-1.91 (m, 6H), 1.77-1.61 (m, 2H) (two protons obscured). TLR9 IC ₅₀ (nM) = 110

208	Analytical LC/MS (Method 1): Purity: 93.1 %; Observed Mass: 528.93; Retention Time: 0.99 min. (Method 2): Purity: 93.4 %; Observed Mass: 528.93; Retention Time: 1.26 min. Prep Method 1: 54 mg, 83 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.19-8.03 (m, 4H), 7.44-7.26 (m, 1H), 7.10-7.03 (m, 1H), 4.00 (s, 3H), 3.55-3.45 (m, 3H), 3.44-3.39 (m, 1H), 3.23 (s, 2H), 3.20-3.16 (m, 1H), 3.01-2.89 (m, 3H), 2.68-2.58 (m, 2H), 2.48-2.39 (m, 2H), 2.31-2.19 (m, 3H), 1.99-1.88 (m, 3H), 1.88-1.78 (m, 2H), 1.77-1.62 (m, 4H), 1.54-1.39 (m, 2H). TLR9 IC ₅₀ (nM) = 940
209	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 553.27; Retention Time: 1.40 min. (Method 2): Purity: 98.8 %; Observed Mass: 552.99; Retention Time: 1.52 min. Prep Method 1: 7.5 mg, 13 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.15-8.06 (m, 4H), 7.39 (s, 1H), 7.11-7.01 (m, 1H), 4.01 (s, 3H), 3.32 (s, 1H), 3.11-3.00 (m, 1H), 2.74-2.59 (m, 2H), 2.58-2.54 (m, 1H), 2.51 (br s, 3H), 2.33-2.09 (m, 4H), 1.85 (br d, <i>J</i> =12.8 Hz, 4H), 1.76-1.48 (m, 9H), 0.89 (br d, <i>J</i> =6.4 Hz, 6H) (one proton obscured). TLR9 IC ₅₀ (nM) = 81
210	Analytical LC/MS (Method 1): Purity: 96 %; Observed Mass: 552.96; Retention Time: 1.0 min. (Method 2): Purity: 96.1 %; Observed Mass: 553.22; Retention Time: 1.74 min. Prep Method 1: 7.3 mg, 12 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.16-8.05 (m, 4H), 7.42-7.35 (m, 1H), 7.11-7.01 (m, 1H), 4.00 (s, 3H), 3.59-3.38 (m, 1H), 3.31 (s, 2H), 3.28-3.21 (m, 1H), 2.63 (br s, 1H), 2.55 (s, 1H), 2.51 (br s, 4H), 2.46-2.37 (m, 1H), 2.23-2.09 (m, 2H), 2.08-1.99 (m, 2H), 1.98-1.59 (m, 11H), 0.97-0.84 (m, 6H). TLR9 IC ₅₀ (nM) = 120

211	Analytical LC/MS (Method 1): Purity: 98.7 %; Observed Mass: 580.96; Retention Time: 0.96 min. (Method 2): Purity: 100 %; Observed Mass: 581.18; Retention Time: 1.39 min. Prep Method 1: 3.9 mg, 7 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.15-8.07 (m, 4H), 7.42-7.39 (m, 1H), 7.10-7.05 (m, 1H), 4.04-3.98 (m, 3H), 3.92-3.80 (m, 3H), 3.73-3.60 (m, 3H), 3.58-3.39 (m, 3H), 3.11-2.99 (m, 3H), 2.74-2.61 (m, 4H), 2.27-2.18 (m, 3H), 1.86-1.61 (m, 6H), 1.60-1.48 (m, 4H), 1.35-1.22 (m, 3H). TLR9 IC ₅₀ (nM) = 270
212	Analytical LC/MS (Method 1): Purity: 96 %; Observed Mass: 581.29; Retention Time: 0.96 min. (Method 2): Purity: 98 %; Observed Mass: 580.95; Retention Time: 1.42 min. Prep Method 1: 12 mg, 20 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.12 (q, <i>J</i> =8.3 Hz, 4H), 7.40 (s, 1H), 7.07 (br d, <i>J</i> =12.8 Hz, 1H), 4.01 (s, 3H), 3.89-3.80 (m, 2H), 3.32 (s, 3H), 2.68-2.57 (m, 1H), 2.57-2.54 (m, 3H), 2.47-2.34 (m, 2H), 1.94-1.79 (m, 10H), 1.74 (br s, 4H), 1.69 (br s, 4H), 1.31-1.19 (m, 2H) (one proton obscured). TLR9 IC ₅₀ (nM) = 460
213	Analytical LC/MS (Method 1): Purity: 96.5 %; Observed Mass: 552.92; Retention Time: 0.95 min. (Method 2): Purity: 97.4 %; Observed Mass: 553.21; Retention Time: 1.23 min. Prep Method 1: 8.9 mg, 15 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.18-8.04 (m, 4H), 7.39 (s, 1H), 7.06 (br d, <i>J</i> =13.1 Hz, 1H), 4.58-4.51 (m, 2H), 4.35-4.29 (m, 2H), 3.64-3.48 (m, 2H), 3.30 (s, 2H), 3.14-3.07 (m, 2H), 3.03-2.97 (m, 2H), 2.66-2.57 (m, 2H), 2.55 (s, 3H), 2.28-2.16 (m, 2H), 1.89 (br s, 3H), 1.85-1.75 (m, 3H), 1.75-1.56 (m, 3H), 1.56-1.36 (m, 3H). TLR9 IC ₅₀ (nM) = 340

214	Analytical LC/MS (Method 1): Purity: 97.9 %; Observed Mass: 553.23; Retention Time: 0.95 min. (Method 2): Purity: 98.1 %; Observed Mass: 552.94; Retention Time: 1.28 min. Prep Method 1: 12 mg, 20 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.15-8.04 (m, 4H), 7.43-7.36 (m, 1H), 7.11-7.01 (m, 1H), 4.53 (s, 2H), 4.30 (s, 2H), 4.00 (s, 2H), 3.64-3.50 (m, 2H), 3.31-3.29 (m, 2H), 3.23-3.15 (m, 2H), 3.01 (br s, 2H), 2.65-2.57 (m, 1H), 2.48-2.41 (m, 1H), 2.02-1.81 (m, 8H), 1.75-1.71 (m, 3H), 1.70-1.59 (m, 4H). TLR9 IC ₅₀ (nM) = 4700
215	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 550.97; Retention Time: 0.99 min. (Method 2): Purity: 96.4 %; Observed Mass: 551.26; Retention Time: 1.35 min. Prep Method 1: 9.9 mg, 17 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.11 (q, <i>J</i> =8.4 Hz, 4H), 7.39 (s, 1H), 7.06 (br d, <i>J</i> =12.8 Hz, 1H), 4.01 (s, 3H), 3.32 (s, 1H), 3.28-3.21 (m, 1H), 3.13-3.04 (m, 1H), 3.02-2.93 (m, 2H), 2.67-2.57 (m, 2H), 2.21 (br s, 2H), 2.05-1.96 (m, 2H), 1.91 (s, 3H), 1.87-1.72 (m, 6H), 1.71-1.49 (m, 9H) (one proton obscured). TLR9 IC ₅₀ (nM) = 70
216	Analytical LC/MS (Method 1): Purity: 95.4 %; Observed Mass: 551.24; Retention Time: 0.99 min. (Method 2): Purity: 98.1 %; Observed Mass: 550.95; Retention Time: 1.54 min. Prep Method 1: 10 mg, 17 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.16-8.05 (m, 4H), 7.41-7.36 (m, 1H), 7.09-7.03 (m, 1H), 4.00 (s, 3H), 3.57-3.46 (m, 1H), 3.31 (s, 2H), 3.27-3.15 (m, 3H), 3.09-2.97 (m, 1H), 2.69-2.56 (m, 2H), 2.47-2.32 (m, 1H), 2.03-1.72 (m, 16H), 1.71-1.55 (m, 4H). TLR9 IC ₅₀ (nM) = 270

217	Analytical LC/MS (Method 1): Purity: 97.8 %; Observed Mass: 551.16; Retention Time: 1.04 min. (Method 2): Purity: 95.5 %; Observed Mass: 551.16; Retention Time: 1.36 min. Prep Method 1: 13 mg, 22 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.07-7.88 (m, 4H), 7.33-7.23 (m, 1H), 7.01-6.89 (m, 1H), 3.87 (s, 2H), 3.53-3.33 (m, 2H), 3.17 (s, 2H), 2.91-2.80 (m, 2H), 2.56-2.44 (m, 2H), 2.26-2.17 (m, 2H), 2.12-2.01 (m, 2H), 1.74 (s, 4H), 1.70-1.64 (m, 2H), 1.58-1.40 (m, 7H), 0.79-0.70 (m, 1H), 0.40-0.27 (m, 2H), 0.01 (br d, <i>J</i> =4.0 Hz, 2H) (one proton obscured). TLR9 IC ₅₀ (nM) = 130
218	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 550.97; Retention Time: 1.05 min. (Method 2): Purity: 100 %; Observed Mass: 550.98; Retention Time: 1.60 min. Prep Method 1: 9.4 mg, 17 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.13-7.81 (m, 4H), 7.42-7.09 (m, 1H), 7.01-6.83 (m, 1H), 3.87 (s, 3H), 3.50-3.35 (m, 1H), 3.32-3.25 (m, 1H), 3.21-3.09 (m, 4H), 2.52-2.44 (m, 1H), 2.27-2.21 (m, 1H), 2.20-2.13 (m, 2H), 1.91-1.82 (m, 2H), 1.73 (br d, <i>J</i> =12.5 Hz, 11H), 1.61-1.48 (m, 2H), 0.79-0.69 (m, 1H), 0.38-0.25 (m, 2H), 0.07--0.07 (m, 2H). TLR9 IC ₅₀ (nM) = 140
219	Analytical LC/MS (Method 1): Purity: 96.9 %; Observed Mass: 538.95; Retention Time: 1.01 min. (Method 2): Purity: 95.6 %; Observed Mass: 538.99; Retention Time: 1.33 min. Prep Method 1: 4.5 mg, 4 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.43 (br d, <i>J</i> =8.5 Hz, 2H), 8.10 (br d, <i>J</i> =8.2 Hz, 2H), 7.40 (br d, <i>J</i> =8.5 Hz, 1H), 7.22-7.15 (m, 1H), 3.28 (s, 3H), 3.22-3.17 (m, 2H), 3.05-2.99 (m, 2H), 2.96-2.87 (m, 1H), 2.64-2.57 (m, 1H), 2.29-2.18 (m, 2H), 2.14 (br d, <i>J</i> =7.0 Hz, 2H), 1.86-1.81 (m, 2H), 1.75 (br s, 5H), 1.66-1.47 (m, 7H), 0.88 (d, <i>J</i> =6.7 Hz, 6H). TLR9 IC ₅₀ (nM) = 65

220	Analytical LC/MS (Method 1): Purity: 95.5 %; Observed Mass: 539.37; Retention Time: 1.14 min. (Method 2): Purity: 97.9 %; Observed Mass: 538.93; Retention Time: 1.56 min. Prep Method 2: 5.5 mg, 6 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.45 (br d, <i>J</i> =8.5 Hz, 2H), 8.13 (d, <i>J</i> =8.5 Hz, 2H), 7.47 (br d, <i>J</i> =7.9 Hz, 1H), 7.17 (br d, <i>J</i> =3.4 Hz, 1H), 4.06-3.95 (m, 1H), 3.30 (s, 2H), 2.99-2.86 (m, 1H), 2.85-2.72 (m, 2H), 2.57-2.55 (m, 2H), 2.51 (br s, 6H), 2.34-1.91 (m, 12H), 0.99 (br d, <i>J</i> =6.1 Hz, 6H) (one proton obscured). TLR9 IC ₅₀ (nM) = 680
221	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 526.95; Retention Time: 0.93 min. (Method 2): Purity: 100 %; Observed Mass: 526.96; Retention Time: 1.43 min. Prep Method 1: 56 mg, 60 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.17-8.09 (m, 4H), 7.64-7.59 (m, 1H), 7.54-7.47 (m, 1H), 3.94 (s, 3H), 3.35-3.28 (m, 1H), 3.02-2.92 (m, 1H), 2.55-2.50 (m, 9H), 2.21-1.95 (m, 3H), 1.94-1.69 (m, 8H), 1.64-1.51 (m, 2H), 0.90-0.85 (m, 6H). TLR9 IC ₅₀ (nM) = 350
222	Analytical LC/MS (Method 1): Purity: 96.5 %; Observed Mass: 511.24; Retention Time: 0.87 min. (Method 2): Purity: 93.6 %; Observed Mass: 510.88; Retention Time: 1.3 min. Prep Method 2: 78 mg, 60 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.16-8.10 (m, 4H), 7.58-7.54 (m, 1H), 7.54-7.49 (m, 1H), 3.94 (s, 3H), 3.60 (br d, <i>J</i> =11.3 Hz, 1H), 3.32 (s, 2H), 3.28-3.20 (m, 1H), 3.13 (s, 1H), 2.55 (s, 4H), 2.51 (br s, 3H), 2.40-2.23 (m, 2H), 2.21-2.01 (m, 4H), 2.00-1.77 (m, 2H), 0.96-0.70 (m, 5H) (one proton obscured). TLR9 IC ₅₀ (nM) = 130
223	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 524.94; Retention Time: 0.94 min. (Method 2): Purity: 100 %; Observed Mass: 524.96; Retention Time: 1.36 min. Prep Method 1: 23 mg, 33 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.19-8.08 (m, 4H), 7.64-7.56 (m, 1H), 7.51-7.44 (m, 1H), 3.92 (s, 2H), 3.59-3.44 (m, 4H), 3.30 (s, 2H), 3.21-3.14 (m, 1H), 3.11-3.01 (m, 2H), 2.97-2.87 (m, 2H), 2.84-2.69 (m, 1H), 2.46-2.32 (m, 3H), 2.04-1.94 (m, 2H), 1.83 (br s, 8H), 1.68-1.57 (m, 2H), 1.55-1.44 (m, 2H). TLR9 IC ₅₀ (nM) = 290

224	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 525.21; Retention Time: 0.96 min. (Method 2): Purity: 100 %; Observed Mass: 525.22; Retention Time: 1.32 min. Prep Method 1: 22 mg, 33 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.03 (s, 4H), 7.53 (br d, <i>J</i> =6.7 Hz, 1H), 7.38 (br d, <i>J</i> =11.6 Hz, 1H), 3.84 (s, 2H), 3.43-3.29 (m, 1H), 3.22 (s, 2H), 3.05-2.90 (m, 3H), 2.89-2.76 (m, 1H), 2.31-2.10 (m, 5H), 2.02-1.88 (m, 2H), 1.73 (br s, 6H), 1.51-1.35 (m, 2H), 0.81-0.68 (m, 1H), 0.44-0.32 (m, 2H), 0.01 (br d, <i>J</i> =2.1 Hz, 2H) (two protons obscured). TLR9 IC ₅₀ (nM) = 190
225	Analytical LC/MS (Method 1): Purity: 97.1 %; Observed Mass: 527.22; Retention Time: 0.85 min. (Method 2): Purity: 99.2 %; Observed Mass: 526.92; Retention Time: 1.17 min. Prep Method 1: 12 mg, 17 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.12 (s, 4H), 7.62-7.58 (m, 1H), 7.52-7.46 (m, 1H), 4.58-4.51 (m, 2H), 4.45-4.40 (m, 2H), 3.93 (s, 3H), 3.56-3.45 (m, 5H), 3.31 (s, 2H), 2.81-2.74 (m, 2H), 2.55 (s, 2H), 1.94-1.71 (m, 7H), 1.59-1.46 (m, 4H). TLR9 IC ₅₀ (nM) = 5400
226	Analytical LC/MS (Method 1): Purity: 97.6 %; Observed Mass: 554.99; Retention Time: 0.92 min. (Method 2): Purity: 97.1 %; Observed Mass: 555.05; Retention Time: 1.24 min. Prep Method 1: 9.8 mg, 13 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.17-8.00 (m, 4H), 7.69-7.61 (m, 1H), 7.53-7.45 (m, 1H), 3.94 (s, 2H), 3.92-3.82 (m, 2H), 3.34-3.23 (m, 2H), 3.07-2.85 (m, 4H), 2.55 (s, 1H), 2.46-2.36 (m, 2H), 2.35-2.15 (m, 4H), 2.14-1.99 (m, 3H), 1.92 (s, 1H), 1.86-1.72 (m, 6H), 1.68 (br d, <i>J</i> =10.7 Hz, 2H), 1.49-1.37 (m, 4H). TLR9 IC ₅₀ (nM) = 900
227	Analytical LC/MS (Method 1): Purity: 96.7 %; Observed Mass: 529.22; Retention Time: 0.87 min. (Method 2): Purity: 98.6 %; Observed Mass: 529.22; Retention Time: 1.21 min. Prep Method 1: 8.8 mg, 13 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.16-8.08 (m, 4H), 7.65-7.59 (m, 1H), 7.50-7.45 (m, 1H), 3.93 (s, 3H), 3.51-3.39 (m, 1H), 3.31 (s, 2H), 3.24 (s, 2H), 3.09-3.01 (m, 2H), 2.99-2.87 (m, 3H), 2.56-2.52 (m, 1H), 2.48 (br s, 2H), 2.40-2.26 (m, 3H), 2.06-1.94 (m, 2H), 1.82 (br s, 6H), 1.58-1.41 (m, 2H) (two protons obscured). TLR9 IC ₅₀ (nM) = 410

228	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 553.28; Retention Time: 0.92 min. (Method 2): Purity: 98.2 %; Observed Mass: 553.28; Retention Time: 1.29 min. Prep Method 1: 15 mg, 11 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.18-8.06 (m, 4H), 7.63-7.57 (m, 1H), 7.52-7.43 (m, 1H), 3.93 (s, 3H), 3.31 (s, 2H), 3.16-3.08 (m, 1H), 2.97-2.87 (m, 1H), 2.85-2.71 (m, 1H), 2.45-2.21 (m, 4H), 1.99-1.55 (m, 14H), 0.96-0.84 (m, 8H) (one proton obscured). TLR9 IC ₅₀ (nM) = 69
229	Analytical LC/MS (Method 1): Purity: 95.5 %; Observed Mass: 552.97; Retention Time: 1.62 min. (Method 2): Purity: 95.6 %; Observed Mass: 553.32; Retention Time: 1.61 min. Prep Method 1: 5.5 mg, 4 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.08 (s, 4H), 7.64-7.57 (m, 1H), 7.47 (d, <i>J</i> =11.0 Hz, 1H), 3.94 (s, 3H), 3.55-3.39 (m, 1H), 3.31 (s, 2H), 3.28-3.22 (m, 1H), 3.16-3.10 (m, 2H), 2.90-2.82 (m, 1H), 2.47-2.36 (m, 1H), 2.05 (br d, <i>J</i> =7.3 Hz, 2H), 2.01-1.74 (m, 13H), 1.73-1.57 (m, 3H), 0.88 (d, <i>J</i> =6.7 Hz, 6H). TLR9 IC ₅₀ (nM) = 95
230	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 550.98; Retention Time: 1.37 min. (Method 2): Purity: 100 %; Observed Mass: 550.99; Retention Time: 1.36 min. Prep Method 1: 17 mg, 13 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.00 (s, 4H), 7.50 (br d, <i>J</i> =6.4 Hz, 1H), 7.35 (d, <i>J</i> =11.0 Hz, 1H), 3.81 (s, 3H), 3.20 (s, 2H), 2.95-2.86 (m, 2H), 2.82-2.72 (m, 1H), 2.58-2.47 (m, 1H), 2.20 (br d, <i>J</i> =6.1 Hz, 2H), 2.15-2.03 (m, 2H), 1.81-1.72 (m, 4H), 1.67 (br s, 4H), 1.53 (br d, <i>J</i> =11.0 Hz, 2H), 1.48-1.38 (m, 4H), 0.74 (br s, 1H), 0.38-0.30 (m, 2H), 0.01 (br d, <i>J</i> =4.3 Hz, 2H) (one proton obscured). TLR9 IC ₅₀ (nM) = 36

231	Analytical LC/MS (Method 1): Purity: 99.3 %; Observed Mass: 550.98; Retention Time: 1.52 min. (Method 2): Purity: 99.3 %; Observed Mass: 550.99; Retention Time: 1.51 min. Prep Method 1: 20 mg, 15 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.87 (s, 4H), 7.38-7.31 (m, 1H), 7.22 (s, 1H), 3.68 (s, 2H), 3.49-3.31 (m, 4H), 3.16-3.10 (m, 2H), 3.05 (s, 3H), 2.70-2.61 (m, 1H), 2.19-2.09 (m, 1H), 1.86 (br d, <i>J</i> =7.0 Hz, 4H), 1.80 (br s, 2H), 1.74-1.68 (m, 2H), 1.66-1.51 (m, 7H), 0.78-0.66 (m, 1H), 0.31 (br d, <i>J</i> =7.0 Hz, 2H), 0.01 (br d, <i>J</i> =4.0 Hz, 2H). TLR9 IC ₅₀ (nM) = 58
232	Analytical LC/MS (Method 1): Purity: 96 %; Observed Mass: 550.97; Retention Time: 0.96 min. (Method 2): Purity: 98.7 %; Observed Mass: 550.96; Retention Time: 1.35 min. Prep Method 1: 14 mg, 11 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.14-8.09 (m, 4H), 7.61-7.56 (m, 1H), 7.49-7.43 (m, 1H), 3.92 (s, 3H), 3.67-3.51 (m, 2H), 3.16-3.07 (m, 1H), 3.02 (br d, <i>J</i> =10.7 Hz, 2H), 2.88 (br s, 1H), 2.74-2.60 (m, 1H), 2.32-2.19 (m, 2H), 2.06-1.95 (m, 3H), 1.91-1.74 (m, 11H), 1.70-1.53 (m, 7H). TLR9 IC ₅₀ (nM) = 45
233	Analytical LC/MS (Method 1): Purity: 98.6 %; Observed Mass: 550.97; Retention Time: 0.95 min. (Method 2): Purity: 97.6 %; Observed Mass: 551.29; Retention Time: 1.50 min. Prep Method 1: 8.9 mg, 7 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.17-8.03 (m, 4H), 7.62-7.55 (m, 1H), 7.51-7.43 (m, 1H), 3.98-3.90 (m, 3H), 3.59-3.46 (m, 1H), 3.32-3.27 (m, 4H), 3.26-3.20 (m, 1H), 3.19-3.16 (m, 1H), 3.11-3.00 (m, 1H), 2.93-2.82 (m, 1H), 2.42-2.34 (m, 1H), 2.04-1.73 (m, 18H), 1.72-1.55 (m, 2H). TLR9 IC ₅₀ (nM) = 58

234	Analytical LC/MS (Method 1): Purity: 98.3 %; Observed Mass: 553.37; Retention Time: 0.91 min. (Method 2): Purity: 94.9 %; Observed Mass: 553.24; Retention Time: 1.14 min. Prep Method 1: 10 mg, 7 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.19-8.07 (m, 4H), 7.66-7.60 (m, 1H), 7.51-7.43 (m, 1H), 4.59-4.50 (m, 2H), 4.37-4.26 (m, 2H), 3.94 (s, 3H), 3.72-3.61 (m, 1H), 3.32 (s, 1H), 3.14-3.07 (m, 2H), 3.05-2.98 (m, 2H), 2.92-2.86 (m, 1H), 2.69-2.59 (m, 1H), 2.31-2.19 (m, 2H), 1.91 (s, 3H), 1.80 (br s, 6H), 1.58 (br d, <i>J</i> =1.2 Hz, 5H). TLR9 IC ₅₀ (nM) = 150
235	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 553.27; Retention Time: 1.31 min. (Method 2): Purity: 100 %; Observed Mass: 553.04; Retention Time: 1.31 min. Prep Method 1: 7.0 mg, 5 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.18-8.09 (m, 4H), 7.64-7.59 (m, 1H), 7.51-7.46 (m, 1H), 4.54 (t, <i>J</i> =6.1 Hz, 2H), 4.32 (s, 2H), 3.95 (s, 3H), 3.63-3.52 (m, 1H), 3.32 (s, 1H), 3.07-3.00 (m, 1H), 2.95-2.86 (m, 1H), 2.55 (s, 4H), 2.36-2.24 (m, 1H), 1.99 (br d, <i>J</i> =2.7 Hz, 3H), 1.94-1.68 (m, 11H) (one proton obscured). TLR9 IC ₅₀ (nM) = 1700
236	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 580.98; Retention Time: 1.29 min. (Method 2): Purity: 100 %; Observed Mass: 580.99; Retention Time: 1.29 min. Prep Method 1: 21 mg, 15 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.16-8.08 (m, 4H), 7.61-7.57 (m, 1H), 7.49-7.45 (m, 1H), 3.92 (s, 2H), 3.90-3.84 (m, 2H), 3.63-3.52 (m, 7H), 3.30 (s, 3H), 3.11-3.06 (m, 2H), 2.95-2.88 (m, 2H), 2.73-2.67 (m, 2H), 2.30-2.23 (m, 2H), 1.85-1.79 (m, 6H), 1.71-1.63 (m, 3H), 1.61-1.51 (m, 4H). TLR9 IC ₅₀ (nM) = 99
237	Analytical LC/MS (Method 1): Purity: 97.7 %; Observed Mass: 581.04; Retention Time: 1.42 min. (Method 2): Purity: 98.9 %; Observed Mass: 580.99; Retention Time: 1.41 min. Prep Method 1: 14 mg, 10 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.17-8.08 (m, 4H), 7.64-7.59 (m, 1H), 7.50-7.45 (m, 1H), 3.94 (s, 3H), 3.89-3.82 (m, 2H), 3.31 (s, 4H), 2.92-2.84 (m, 1H), 2.43-2.35 (m, 1H), 1.89 (s, 22H), 1.33-1.23 (m, 2H). TLR9 IC ₅₀ (nM) = 87

238	Analytical LC/MS (Method 1): Purity: 96.1 %; Observed Mass: 554.96; Retention Time: 1.32 min. (Method 2): Purity: 96 %; Observed Mass: 555.01; Retention Time: 1.31 min. Prep Method 1: 15 mg, 11 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.14-8.06 (m, 4H), 7.64-7.56 (m, 1H), 7.46 (d, <i>J</i>=11.0 Hz, 1H), 3.92 (s, 3H), 3.58-3.48 (m, 1H), 3.44-3.39 (m, 1H), 3.30 (s, 3H), 3.24 (s, 2H), 3.04-2.98 (m, 2H), 2.92-2.83 (m, 1H), 2.60 (br s, 1H), 2.55-2.52 (m, 2H), 2.27-2.18 (m, 2H), 1.92-1.83 (m, 4H), 1.82-1.74 (m, 4H), 1.68-1.58 (m, 2H), 1.58-1.48 (m, 4H) (one proton obscured). TLR9 IC₅₀ (nM) = 58
239	Analytical LC/MS (Method 1): Purity: 97 %; Observed Mass: 554.99; Retention Time: 1.43 min. (Method 2): Purity: 97 %; Observed Mass: 555.00; Retention Time: 1.44 min. Prep Method 1: 12 mg, 9 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.11 (s, 4H), 7.59 (d, <i>J</i>=6.4 Hz, 1H), 7.47 (d, <i>J</i>=11.0 Hz, 1H), 3.93 (s, 3H), 3.58-3.46 (m, 1H), 3.45-3.39 (m, 1H), 3.34-3.21 (m, 7H), 2.92-2.83 (m, 1H), 2.46 (s, 2H), 2.41-2.32 (m, 1H), 1.98-1.70 (m, 17H). TLR9 IC₅₀ (nM) = 290
240	Analytical LC/MS (Method 1): Purity: 98.1 %; Observed Mass: 527.00; Retention Time: 0.99 min. (Method 2): Purity: 96.3 %; Observed Mass: 527.38; Retention Time: 1.38 min. Prep Method 1: 51 mg, 54 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.11 (s, 4H), 7.65-7.59 (m, 1H), 7.55-7.49 (m, 1H), 3.89-3.86 (m, 2H), 3.29 (s, 3H), 3.19-3.15 (m, 1H), 3.08-3.02 (m, 2H), 2.92-2.83 (m, 3H), 2.41-2.28 (m, 3H), 2.06-2.00 (m, 3H), 1.90-1.71 (m, 8H), 1.54-1.45 (m, 2H), 0.84 (br d, <i>J</i>=6.4 Hz, 6H). TLR9 IC₅₀ (nM) = 120

241	Analytical LC/MS (Method 1): Purity: 97.5 %; Observed Mass: 511.37; Retention Time: 0.95 min. (Method 2): Purity: 100 %; Observed Mass: 511.21; Retention Time: 1.29 min. Prep Method 1: 31 mg, 34 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.16-8.09 (m, 4H), 7.64-7.59 (m, 1H), 7.59-7.53 (m, 1H), 3.89 (s, 3H), 3.46-3.39 (m, 1H), 3.31 (s, 1H), 3.11-3.04 (m, 1H), 2.99 (br d, <i>J</i> =10.4 Hz, 2H), 2.94-2.85 (m, 1H), 2.50-2.34 (m, 2H), 2.15 (br t, <i>J</i> =11.2 Hz, 2H), 1.88-1.72 (m, 6H), 1.62-1.54 (m, 1H), 1.49-1.38 (m, 2H), 0.44-0.37 (m, 2H), 0.31-0.25 (m, 2H) (three protons obscured). TLR9 IC ₅₀ (nM) = 1700
242	Analytical LC/MS (Method 1): Purity: 97.8 %; Observed Mass: 525.15; Retention Time: 0.97 min. (Method 2): Purity: 97.6 %; Observed Mass: 524.96; Retention Time: 1.44 min. Prep Method 1: 30 mg, 43 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.11-7.98 (m, 4H), 7.58-7.50 (m, 1H), 7.49-7.41 (m, 1H), 3.81 (s, 3H), 3.42-3.32 (m, 1H), 3.23 (s, 2H), 3.01-2.92 (m, 3H), 2.82-2.71 (m, 1H), 2.42 (br s, 2H), 2.23 (br d, <i>J</i> =11.6 Hz, 3H), 2.13 (br d, <i>J</i> =6.4 Hz, 2H), 1.90 (br s, 2H), 1.79-1.61 (m, 5H), 1.49-1.39 (m, 2H), 0.82-0.71 (m, 1H), 0.39 (br d, <i>J</i> =7.9 Hz, 2H), 0.01 (br d, <i>J</i> =4.3 Hz, 2H). TLR9 IC ₅₀ (nM) = 160
243	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 524.95; Retention Time: 0.95 min. (Method 2): Purity: 98.4 %; Observed Mass: 525.24; Retention Time: 1.37 min. Prep Method 1: 11 mg, 16 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.15-8.09 (m, 4H), 7.64-7.60 (m, 1H), 7.56-7.51 (m, 1H), 3.88 (s, 2H), 3.49 (br s, 3H), 3.30 (s, 1H), 3.21-3.15 (m, 2H), 3.04-2.97 (m, 2H), 2.87-2.78 (m, 3H), 2.70-2.60 (m, 3H), 2.40-2.13 (m, 5H), 1.90 (br s, 4H), 1.83-1.54 (m, 6H). TLR9 IC ₅₀ (nM) = 940

244	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 527.20; Retention Time: 0.97 min. (Method 2): Purity: 100 %; Observed Mass: 527.19; Retention Time: 1.25 min. Prep Method 1: 30 mg, 44 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.12 (s, 4H), 7.66-7.60 (m, 1H), 7.59-7.51 (m, 1H), 4.53 (s, 2H), 4.42 (s, 2H), 3.89 (s, 3H), 3.46-3.34 (m, 1H), 3.32 (s, 1H), 3.17-3.04 (m, 1H), 2.98-2.83 (m, 1H), 2.80-2.73 (m, 2H), 2.55 (s, 5H), 2.47-2.33 (m, 2H), 1.87-1.72 (m, 7H), 1.57-1.46 (m, 2H). TLR9 IC ₅₀ (nM) = 3600
245	Analytical LC/MS (Method 1): Purity: 99.3 %; Observed Mass: 554.96; Retention Time: 0.98 min. (Method 2): Purity: 100 %; Observed Mass: 555.25; Retention Time: 1.30 min. Prep Method 1: 16 mg, 23 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.17-8.07 (m, 4H), 7.65-7.60 (m, 1H), 7.58-7.52 (m, 1H), 3.89 (s, 4H), 3.51-3.41 (m, 2H), 3.31 (s, 3H), 3.12-2.84 (m, 5H), 2.44-2.34 (m, 3H), 2.22-2.10 (m, 2H), 1.82 (br d, <i>J</i> =2.4 Hz, 8H), 1.54-1.35 (m, 5H) (one proton obscured). TLR9 IC ₅₀ (nM) = 1100
246	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 529.35; Retention Time: 0.96 min. (Method 2): Purity: 99.3 %; Observed Mass: 529.01; Retention Time: 1.36 min. Prep Method 1: 7.2 mg, 11 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.16-8.05 (m, 4H), 7.64-7.58 (m, 1H), 7.58-7.48 (m, 1H), 3.88 (s, 3H), 3.51-3.38 (m, 1H), 3.31 (s, 2H), 3.23 (s, 2H), 3.00 (br d, <i>J</i> =11.0 Hz, 2H), 2.92 (br d, <i>J</i> =11.0 Hz, 2H), 2.84 (br s, 1H), 2.51 (br s, 3H), 2.44 (s, 2H), 2.32-2.20 (m, 3H), 1.94 (br s, 2H), 1.84-1.68 (m, 6H), 1.46 (br d, <i>J</i> =9.2 Hz, 2H). TLR9 IC ₅₀ (nM) = 400
247	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 552.99; Retention Time: 1.50 min. (Method 2): Purity: 100 %; Observed Mass: 553.33; Retention Time: 1.49 min. Prep Method 1: 29 mg, 26 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.16-8.07 (m, 4H), 7.63-7.58 (m, 1H), 7.54-7.49 (m, 1H), 3.87 (s, 2H), 3.68-3.56 (m, 6H), 3.29 (s, 3H), 3.26-3.22 (m, 1H), 3.22-3.07 (m, 2H), 3.07-3.02 (m, 2H), 2.91-2.80 (m, 1H), 2.68-2.57 (m, 2H), 2.25 (br s, 2H), 2.17 (br d, <i>J</i> =7.6 Hz, 2H), 1.92-1.50 (m, 6H), 0.88 (d, <i>J</i> =6.7 Hz, 6H). TLR9 IC ₅₀ (nM) = 30

248	Analytical LC/MS (Method 1): Purity: 98.2 %; Observed Mass: 552.99; Retention Time: 1.67 min. (Method 2): Purity: 98.2 %; Observed Mass: 553.01; Retention Time: 1.66 min. Prep Method 1: 30 mg, 26 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.12 (s, 4H), 7.60 (d, <i>J</i> =6.4 Hz, 1H), 7.55 (d, <i>J</i> =10.7 Hz, 1H), 3.89 (s, 3H), 3.32 (s, 1H), 3.27-3.20 (m, 1H), 2.89-2.79 (m, 1H), 2.51 (br s, 3H), 2.46-2.37 (m, 1H), 2.11-1.57 (m, 16H), 0.89 (br d, <i>J</i> =6.4 Hz, 6H) (three protons obscured). TLR9 IC ₅₀ (nM) = 78
249	Analytical LC/MS (Method 1): Purity: 97.6 %; Observed Mass: 550.99; Retention Time: 0.98 min. (Method 2): Purity: 97.6 %; Observed Mass: 551.38; Retention Time: 1.43 min. Prep Method 1: 21 mg, 19 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.02 (s, 4H), 7.50 (d, <i>J</i> =6.7 Hz, 1H), 7.44 (d, <i>J</i> =10.7 Hz, 1H), 3.79 (s, 3H), 3.21 (s, 2H), 2.93-2.85 (m, 2H), 2.77-2.68 (m, 1H), 2.55-2.47 (m, 1H), 2.45 (s, 2H), 2.22-2.16 (m, 2H), 2.15-2.08 (m, 2H), 1.79 (s, 5H), 1.44 (br s, 8H), 0.84-0.66 (m, 1H), 0.40-0.27 (m, 2H), 0.07--0.11 (m, 2H). TLR9 IC ₅₀ (nM) = 32
250	Analytical LC/MS (Method 1): Purity: 98.4 %; Observed Mass: 550.98; Retention Time: 1.0 min. (Method 2): Purity: 100 %; Observed Mass: 551.02; Retention Time: 1.59 min. Prep Method 1: 20 mg, 18 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.01-7.95 (m, 4H), 7.49-7.45 (m, 1H), 7.43-7.37 (m, 1H), 3.75 (s, 3H), 3.48-3.33 (m, 1H), 3.32-3.26 (m, 1H), 3.17 (s, 4H), 2.77-2.64 (m, 1H), 2.30-2.22 (m, 1H), 2.17 (br d, <i>J</i> =6.4 Hz, 2H), 1.85 (br s, 2H), 1.79-1.66 (m, 11H), 1.61 (br s, 2H), 0.81-0.69 (m, 1H), 0.33 (br d, <i>J</i> =6.7 Hz, 2H), 0.01 (br d, <i>J</i> =4.6 Hz, 2H). TLR9 IC ₅₀ (nM) = 110
251	Analytical LC/MS (Method 1): Purity: 99.1 %; Observed Mass: 550.96; Retention Time: 1.44 min. (Method 2): Purity: 99.1 %; Observed Mass: 551.00; Retention Time: 1.44 min. Prep Method 1: 23 mg, 20 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.15-8.06 (m, 4H), 7.63-7.58 (m, 1H), 7.56-7.49 (m, 1H), 3.87 (s, 2H), 3.58-3.49 (m, 1H), 3.30 (s, 2H), 3.25 (br s, 2H), 3.13-3.04 (m, 1H), 3.00 (br d, <i>J</i> =10.1 Hz, 2H), 2.87-2.78 (m, 1H), 2.67-2.57 (m, 1H), 2.23 (br t, <i>J</i> =11.0 Hz, 2H), 1.99 (br d, <i>J</i> =5.5 Hz, 2H), 1.88 (s, 1H), 1.86-1.50 (m, 16H). TLR9 IC ₅₀ (nM) = 71

252	Analytical LC/MS (Method 1): Purity: 92.9 %; Observed Mass: 551.15; Retention Time: 0.98 min. (Method 2): Purity: 93.5 %; Observed Mass: 551.26; Retention Time: 1.49 min. Prep Method 1: 32 mg, 27 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.19-8.07 (m, 4H), 7.64-7.58 (m, 1H), 7.58-7.50 (m, 1H), 3.89 (s, 3H), 3.49-3.41 (m, 1H), 3.31 (s, 1H), 3.28-3.16 (m, 1H), 3.00 (s, 1H), 2.91-2.75 (m, 1H), 2.65-2.50 (m, 5H), 2.43-2.34 (m, 1H), 2.03-1.55 (m, 19H). TLR9 IC ₅₀ (nM) = 59
253	Analytical LC/MS (Method 1): Purity: 98.1 %; Observed Mass: 552.96; Retention Time: 0.94 min. (Method 2): Purity: 94.9 %; Observed Mass: 553.37; Retention Time: 1.33 min. Prep Method 1: 18 mg, 15 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.17-8.07 (m, 4H), 7.64-7.59 (m, 1H), 7.57-7.50 (m, 1H), 4.64-4.49 (m, 2H), 4.32 (s, 2H), 3.89 (s, 3H), 3.73-3.60 (m, 1H), 3.54-3.34 (m, 1H), 3.31 (s, 2H), 3.11 (br d, J=1.2 Hz, 2H), 3.07-2.99 (m, 1H), 2.91-2.79 (m, 1H), 2.74-2.61 (m, 1H), 2.34-2.24 (m, 2H), 1.85-1.67 (m, 6H), 1.65-1.49 (m, 6H) (one proton obscured). TLR9 IC ₅₀ (nM) = 280
254	Analytical LC/MS (Method 1): Purity: 98.3 %; Observed Mass: 552.96; Retention Time: 0.95 min. (Method 2): Purity: 98.4 %; Observed Mass: 553.37; Retention Time: 1.33 min. Prep Method 1: 14 mg, 12 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.18-8.07 (m, 4H), 7.63-7.59 (m, 1H), 7.58-7.52 (m, 1H), 4.54 (t, J=6.1 Hz, 2H), 4.35-4.27 (m, 2H), 3.89 (s, 3H), 3.62-3.52 (m, 1H), 3.28-3.21 (m, 1H), 3.01 (br s, 2H), 2.90-2.79 (m, 1H), 2.55 (s, 2H), 2.48-2.39 (m, 1H), 1.98-1.67 (m, 15H) (one proton obscured). TLR9 IC ₅₀ (nM) = 5300

255	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 580.99; Retention Time: 0.99 min. (Method 2): Purity: 100 %; Observed Mass: 581.27; Retention Time: 1.37 min. Prep Method 1: 11 mg, 10 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.16-8.08 (m, 4H), 7.61 (br d, <i>J</i> =6.7 Hz, 1H), 7.57-7.51 (m, 1H), 3.89 (s, 3H), 3.87-3.83 (m, 1H), 3.35-3.29 (m, 1H), 3.07-3.02 (m, 1H), 2.88-2.79 (m, 1H), 2.72-2.57 (m, 2H), 2.51 (br s, 3H), 2.26-2.15 (m, 2H), 1.79 (br s, 8H), 1.67-1.41 (m, 6H), 1.27 (br d, <i>J</i> =10.7 Hz, 2H) (five protons obscured). TLR9 IC ₅₀ (nM) = 72
256	Analytical LC/MS (Method 1): Purity: 97.3 %; Observed Mass: 581.01; Retention Time: 1.47 min. (Method 2): Purity: 97.2 %; Observed Mass: 581.01; Retention Time: 1.47 min. Prep Method 1: 31 mg, 26 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.17-8.06 (m, 4H), 7.63-7.58 (m, 1H), 7.55-7.48 (m, 1H), 3.87 (s, 3H), 3.73-3.55 (m, 7H), 3.54-3.47 (m, 1H), 3.29 (s, 5H), 2.90-2.80 (m, 1H), 2.62-2.56 (m, 1H), 2.43-2.35 (m, 1H), 1.96-1.70 (m, 14H), 1.38-1.27 (m, 2H). TLR9 IC ₅₀ (nM) = 320
257	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 554.97; Retention Time: 1.0 min. (Method 2): Purity: 100 %; Observed Mass: 554.96; Retention Time: 1.37 min. Prep Method 1: 22 mg, 20 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.15-8.09 (m, 4H), 7.66-7.60 (m, 2H), 4.23-4.12 (m, 2H), 3.90 (s, 2H), 3.84-3.74 (m, 1H), 3.72-3.66 (m, 1H), 3.62-3.51 (m, 1H), 3.33 (d, <i>J</i> =16.8 Hz, 5H), 3.28-3.15 (m, 2H), 2.58-2.48 (m, 7H), 2.32-1.94 (m, 12H). TLR9 IC ₅₀ (nM) = 49
258	Analytical LC/MS (Method 1): Purity: 95.1 %; Observed Mass: 554.99; Retention Time: 1.49 min. (Method 2): Purity: 95.8 %; Observed Mass: 555.31; Retention Time: 1.49 min. Prep Method 1: 35 mg, 30 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.14-8.05 (m, 4H), 7.59 (d, <i>J</i> =6.7 Hz, 1H), 7.51 (d, <i>J</i> =10.7 Hz, 1H), 3.86 (s, 2H), 3.72-3.55 (m, 2H), 3.39 (t, <i>J</i> =6.1 Hz, 2H), 3.29 (s, 3H), 3.25-3.15 (m, 6H), 2.81 (br s, 1H), 2.42 (br t, <i>J</i> =6.1 Hz, 2H), 2.36 (br d, <i>J</i> =5.8 Hz, 1H), 1.99-1.61 (m, 14H). TLR9 IC ₅₀ (nM) = 100

259	Analytical LC/MS (Method 1): Purity: 99.3 %; Observed Mass: 526.95; Retention Time: 0.97 min. (Method 2): Purity: 100 %; Observed Mass: 527.27; Retention Time: 1.47 min. Prep Method 1: 15 mg, 16 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.18-8.02 (m, 4H), 7.58-7.48 (m, 1H), 7.27-7.15 (m, 1H), 4.03 (s, 3H), 3.11-2.88 (m, 1H), 2.76-2.62 (m, 1H), 2.51 (br s, 8H), 2.28-2.04 (m, 2H), 2.03-1.93 (m, 1H), 1.92-1.68 (m, 7H), 1.59 (br d, <i>J</i> =2.4 Hz, 3H), 1.31-1.19 (m, 1H), 0.88 (br d, <i>J</i> =6.1 Hz, 6H). TLR9 IC ₅₀ (nM) = 500
260	Analytical LC/MS (Method 1): Purity: 98.6 %; Observed Mass: 511.20; Retention Time: 0.93 min. (Method 2): Purity: 100 %; Observed Mass: 510.91; Retention Time: 1.42 min. Prep Method 2: 13 mg, 10 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.17-8.06 (m, 4H), 7.60-7.54 (m, 1H), 7.20-7.11 (m, 1H), 4.04 (s, 3H), 3.71-3.52 (m, 2H), 3.32 (s, 2H), 3.29-3.14 (m, 1H), 2.87-2.68 (m, 1H), 2.55 (s, 2H), 2.51 (br s, 4H), 2.37-2.28 (m, 2H), 2.19-1.88 (m, 6H), 0.94 (br s, 2H), 0.83 (br d, <i>J</i> =7.0 Hz, 2H) (two protons obscured). TLR9 IC ₅₀ (nM) = 660
261	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 524.95; Retention Time: 0.95 min. (Method 2): Purity: 100 %; Observed Mass: 525.24; Retention Time: 1.20 min. Prep Method 2: 56 mg, 43 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.16-8.05 (m, 4H), 7.60-7.54 (m, 1H), 7.19-7.14 (m, 1H), 4.04 (s, 3H), 3.78-3.70 (m, 1H), 3.66-3.58 (m, 1H), 3.54-3.41 (m, 1H), 3.32 (s, 3H), 3.01 (br d, <i>J</i> =6.7 Hz, 3H), 2.55 (s, 3H), 2.51 (br s, 2H), 2.41-2.32 (m, 2H), 2.19-1.96 (m, 6H), 1.14-1.04 (m, 1H), 0.67 (br d, <i>J</i> =6.7 Hz, 2H), 0.39 (br d, <i>J</i> =4.0 Hz, 2H) (one proton obscured). TLR9 IC ₅₀ (nM) = 150

262	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 524.96; Retention Time: 0.95 min. (Method 2): Purity: 100 %; Observed Mass: 524.97; Retention Time: 1.37 min. Prep Method 2: 44 mg, 34 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.18-8.06 (m, 4H), 7.63-7.52 (m, 1H), 7.20-7.09 (m, 1H), 4.04 (s, 3H), 3.67-3.52 (m, 1H), 3.33 (s, 1H), 2.91-2.79 (m, 1H), 2.55 (s, 3H), 2.53-2.48 (m, 4H), 2.39-2.30 (m, 2H), 2.27-2.01 (m, 8H), 1.95 (br d, <i>J</i>=10.4 Hz, 2H), 1.85-1.67 (m, 2H) (four protons obscured). TLR9 IC₅₀ (nM) = 170
263	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 526.95; Retention Time: 0.95 min. (Method 2): Purity: 97.4 %; Observed Mass: 527.19; Retention Time: 1.21 min. Prep Method 2: 63 mg, 49 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.20-8.05 (m, 4H), 7.62-7.55 (m, 1H), 7.20-7.13 (m, 1H), 4.78-4.67 (m, 4H), 4.32-4.16 (m, 1H), 4.04 (s, 3H), 3.67-3.57 (m, 1H), 3.33 (s, 2H), 3.29-3.21 (m, 1H), 2.86-2.67 (m, 1H), 2.55 (s, 7H), 2.41-2.29 (m, 2H), 2.07 (br s, 6H) (one proton obscured). TLR9 IC₅₀ (nM) = 1800
264	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 555.35; Retention Time: 0.94 min. (Method 2): Purity: 95.2 %; Observed Mass: 554.96; Retention Time: 1.33 min. Prep Method 2: 94 mg, 71 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.19-8.05 (m, 4H), 7.60-7.53 (m, 1H), 7.18-7.14 (m, 1H), 4.06-4.03 (m, 3H), 4.02-3.97 (m, 2H), 3.74-3.68 (m, 1H), 3.65-3.54 (m, 1H), 3.33 (s, 2H), 3.16-2.98 (m, 2H), 2.51 (br s, 6H), 2.45-2.33 (m, 2H), 2.26-2.11 (m, 2H), 2.10-1.94 (m, 5H), 1.80-1.61 (m, 2H) (five protons obscured). TLR9 IC₅₀ (nM) = 280

265	Analytical LC/MS (Method 1): Purity: 97 %; Observed Mass: 529.22; Retention Time: 0.93 min. (Method 2): Purity: 97 %; Observed Mass: 528.94; Retention Time: 1.24 min. Prep Method 1: 35 mg, 39 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.16-8.04 (m, 4H), 7.53-7.46 (m, 1H), 7.26-7.18 (m, 1H), 4.02 (s, 3H), 3.78-3.62 (m, 1H), 3.46-3.30 (m, 1H), 3.23 (s, 1H), 3.17 (d, <i>J</i> =5.0 Hz, 3H), 3.07-2.96 (m, 2H), 2.92 (br d, <i>J</i> =11.5 Hz, 2H), 2.51 (br s, 4H), 2.48-2.42 (m, 2H), 2.36-2.19 (m, 3H), 1.99-1.88 (m, 2H), 1.76 (br d, <i>J</i> =1.2 Hz, 5H), 1.52-1.40 (m, 2H). TLR9 IC ₅₀ (nM) = 1000
266	Analytical LC/MS (Method 1): Purity: 99.2 %; Observed Mass: 553.15; Retention Time: 0.99 min. (Method 2): Purity: 99.2 %; Observed Mass: 552.98; Retention Time: 1.32 min. Prep Method 1: 16 mg, 11 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.19-8.02 (m, 4H), 7.53-7.47 (m, 1H), 7.27-7.14 (m, 1H), 4.02 (s, 3H), 3.52-3.40 (m, 4H), 3.31 (s, 2H), 3.19-3.16 (m, 1H), 3.14-2.92 (m, 3H), 2.42-2.13 (m, 5H), 1.91 (br s, 3H), 1.78 (br d, <i>J</i> =4.0 Hz, 8H), 0.90 (br d, <i>J</i> =6.4 Hz, 6H). TLR9 IC ₅₀ (nM) = 97
267	Analytical LC/MS (Method 1): Purity: 98.1 %; Observed Mass: 553.18; Retention Time: 0.99 min. (Method 2): Purity: 98.9 %; Observed Mass: 553.07; Retention Time: 1.53 min. Prep Method 1: 16 mg, 11 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.19-8.03 (m, 4H), 7.55-7.48 (m, 1H), 7.25-7.18 (m, 1H), 4.02 (s, 3H), 3.52 (br d, <i>J</i> =4.9 Hz, 4H), 3.31 (s, 3H), 2.67 (s, 3H), 1.91 (s, 3H), 1.87-1.58 (m, 8H), 1.15 (s, 3H), 0.95-0.85 (m, 6H) (two protons obscured). TLR9 IC ₅₀ (nM) = 350
268	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 550.97; Retention Time: 1.39 min. (Method 2): Purity: 100 %; Observed Mass: 550.99; Retention Time: 1.39 min. Prep Method 1: 18 mg, 12 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.03-7.89 (m, 4H), 7.43-7.30 (m, 1H), 7.12-6.97 (m, 1H), 3.88 (s, 3H), 3.18 (s, 1H), 2.87 (br d, <i>J</i> =10.4 Hz, 2H), 2.83-2.73 (m, 1H), 2.59-2.45 (m, 1H), 2.37 (br s, 4H), 2.28-2.17 (m, 2H), 2.16-2.02 (m, 2H), 1.79-1.71 (m, 2H), 1.67-1.59 (m, 4H), 1.57-1.40 (m, 6H), 0.77-0.66 (m, 1H), 0.33 (br d, <i>J</i> =6.7 Hz, 2H), 0.01 (br d, <i>J</i> =3.4 Hz, 2H). TLR9 IC ₅₀ (nM) = 60

269	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 551.26; Retention Time: 1.02 min. (Method 2): Purity: 99.3 %; Observed Mass: 550.94; Retention Time: 1.56 min. Prep Method 1: 12 mg, 8 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.97-7.87 (m, 4H), 7.34-7.28 (m, 1H), 7.05-6.99 (m, 1H), 3.82 (s, 3H), 3.46-3.31 (m, 4H), 3.11 (s, 4H), 2.79-2.71 (m, 1H), 2.26 (br d, <i>J</i> =7.0 Hz, 2H), 2.21-2.16 (m, 1H), 1.81 (br d, <i>J</i> =6.4 Hz, 6H), 1.74-1.70 (m, 2H), 1.65-1.54 (m, 5H), 0.78-0.70 (m, 1H), 0.34-0.30 (m, 2H), 0.04--0.03 (m, 2H). TLR9 IC ₅₀ (nM) = 180
270	Analytical LC/MS (Method 1): Purity: 97.9 %; Observed Mass: 551.30; Retention Time: 1.4 min. (Method 2): Purity: 97.9 %; Observed Mass: 550.99; Retention Time: 1.4 min. Prep Method 1: 22 mg, 15 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.18-8.04 (m, 4H), 7.54-7.45 (m, 1H), 7.27-7.16 (m, 1H), 4.02 (s, 3H), 3.52-3.41 (m, 3H), 3.31 (s, 2H), 3.28-3.23 (m, 1H), 3.20-3.16 (m, 1H), 3.14-3.05 (m, 1H), 3.04-2.88 (m, 4H), 2.67-2.59 (m, 2H), 2.22 (br d, <i>J</i> =9.5 Hz, 2H), 2.04-1.96 (m, 3H), 1.90 (s, 1H), 1.88-1.51 (m, 10H). TLR9 IC ₅₀ (nM) = 65
271	Analytical LC/MS (Method 1): Purity: 95.1 %; Observed Mass: 551.08; Retention Time: 0.94 min. (Method 2): Purity: 95 %; Observed Mass: 551.27; Retention Time: 1.45 min. Prep Method 1: 17 mg, 11 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.18-8.03 (m, 4H), 7.50 (d, <i>J</i> =8.2 Hz, 1H), 7.20 (br t, <i>J</i> =7.5 Hz, 1H), 4.02 (s, 3H), 3.32 (s, 2H), 3.18-3.04 (m, 1H), 2.99-2.87 (m, 1H), 2.68-2.61 (m, 1H), 2.55 (s, 1H), 2.43-2.34 (m, 1H), 2.07-1.73 (m, 17H), 1.72-1.48 (m, 4H) (two protons obscured). TLR9 IC ₅₀ (nM) = 410

272	Analytical LC/MS (Method 1): Purity: 95.5 %; Observed Mass: 552.95; Retention Time: 0.97 min. (Method 2): Purity: 96.3 %; Observed Mass: 553.22; Retention Time: 1.21 min. Prep Method 1: 8.2 mg, 5 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.16-8.05 (m, 4H), 7.52-7.44 (m, 1H), 7.24-7.16 (m, 1H), 4.53 (t, <i>J</i> =6.1 Hz, 2H), 4.30 (t, <i>J</i> =5.7 Hz, 2H), 4.02 (s, 3H), 3.61-3.50 (m, 1H), 3.32 (s, 1H), 3.28-3.22 (m, 1H), 3.00 (br s, 2H), 2.97-2.88 (m, 1H), 2.55 (s, 1H), 2.43 (br s, 1H), 1.97-1.84 (m, 4H), 1.82-1.68 (m, 9H) (three protons obscured).
273	Analytical LC/MS (Method 1): Purity: 99.2 %; Observed Mass: 553.13; Retention Time: 0.95 min. (Method 2): Purity: 100 %; Observed Mass: 553.16; Retention Time: 1.26 min. Prep Method 1: 8.6 mg, 6 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.18-8.04 (m, 4H), 7.53-7.45 (m, 1H), 7.25-7.13 (m, 1H), 4.59-4.52 (m, 2H), 4.31 (s, 2H), 4.02 (s, 3H), 3.71-3.62 (m, 1H), 3.52-3.42 (m, 1H), 3.37-3.29 (m, 1H), 3.13-3.06 (m, 2H), 3.03-2.86 (m, 3H), 2.67-2.57 (m, 1H), 2.27-2.18 (m, 2H), 1.82-1.71 (m, 6H), 1.64-1.48 (m, 6H) (one proton obscured). TLR9 IC ₅₀ (nM) = 300
274	Analytical LC/MS (Method 1): Purity: 98.5 %; Observed Mass: 580.98; Retention Time: 1.31 min. (Method 2): Purity: 98.4 %; Observed Mass: 581.01; Retention Time: 1.31 min. Prep Method 1: 25 mg, 16 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.17-8.06 (m, 4H), 7.50 (d, <i>J</i> =8.5 Hz, 1H), 7.21 (br t, <i>J</i> =7.5 Hz, 1H), 4.03 (s, 3H), 3.90-3.84 (m, 2H), 3.36-3.29 (m, 2H), 3.13-3.03 (m, 2H), 3.02-2.89 (m, 1H), 2.79-2.62 (m, 2H), 2.55 (s, 2H), 2.29-2.18 (m, 2H), 1.92 (s, 2H), 1.86-1.74 (m, 8H), 1.71-1.63 (m, 2H), 1.62-1.48 (m, 4H), 1.36-1.23 (m, 3H). TLR9 IC ₅₀ (nM) = 51
275	Analytical LC/MS (Method 1): Purity: 96.7 %; Observed Mass: 581.01; Retention Time: 1.43 min. (Method 2): Purity: 96.7 %; Observed Mass: 580.97; Retention Time: 1.43 min. Prep Method 1: 18 mg, 12 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.17-8.06 (m, 4H), 7.52-7.46 (m, 1H), 7.26-7.17 (m, 1H), 4.03 (s, 3H), 3.93-3.83 (m, 2H), 3.32 (s, 4H), 3.04-2.89 (m, 2H), 2.44-2.32 (m, 2H), 2.02-1.73 (m, 14H), 1.47-1.25 (m, 4H) (four protons obscured). TLR9 IC ₅₀ (nM) = 89

276	Analytical LC/MS (Method 1): Purity: 96.2 %; Observed Mass: 554.98; Retention Time: 0.95 min. (Method 2): Purity: 96.7 %; Observed Mass: 555.38; Retention Time: 1.29 min. Prep Method 1: 25 mg, 16 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.16-8.06 (m, 4H), 7.53-7.46 (m, 1H), 7.21 (br d, <i>J</i> =7.9 Hz, 1H), 4.02 (s, 3H), 3.54-3.38 (m, 5H), 3.31 (s, 2H), 3.25 (s, 3H), 3.19-3.14 (m, 1H), 3.06-2.89 (m, 4H), 2.65 (s, 2H), 2.28-2.20 (m, 2H), 1.91 (s, 4H), 1.79-1.48 (m, 7H). TLR9 IC ₅₀ (nM) = 170
277	Analytical LC/MS (Method 1): Purity: 91.9 %; Observed Mass: 554.96; Retention Time: 0.95 min. (Method 2): Purity: 97.5 %; Observed Mass: 555.26; Retention Time: 1.39 min. Prep Method 1: 18 mg, 11 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.21-7.97 (m, 4H), 7.49 (d, <i>J</i> =8.5 Hz, 1H), 7.20 (br t, <i>J</i> =7.3 Hz, 1H), 4.03 (s, 2H), 3.25 (s, 2H), 3.21-3.13 (m, 2H), 2.98-2.86 (m, 2H), 2.58-2.54 (m, 2H), 2.51 (br s, 3H), 2.41 (br t, <i>J</i> =6.0 Hz, 5H), 1.95-1.64 (m, 12H) (three protons obscured). TLR9 IC ₅₀ (nM) = 270
278	Analytical LC/MS (Method 1): Purity: 96.7 %; Observed Mass: 527.03; Retention Time: 0.94 min. (Method 2): Purity: 95.6 %; Observed Mass: 527.20; Retention Time: 1.33 min. Prep Method 1: 20 mg, 35 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.17-8.10 (m, 4H), 7.43-7.37 (m, 1H), 7.07-6.99 (m, 1H), 3.92 (s, 3H), 3.33-3.30 (m, 2H), 3.12-3.06 (m, 1H), 3.02-2.98 (m, 1H), 2.96-2.89 (m, 2H), 2.71-2.67 (m, 3H), 2.64-2.59 (m, 3H), 2.48-2.33 (m, 2H), 2.12-2.03 (m, 2H), 1.96-1.84 (m, 2H), 1.81-1.72 (m, 4H), 1.58-1.48 (m, 2H), 0.88-0.83 (m, 6H). TLR9 IC ₅₀ (nM) = 58
279	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 527.60; Retention Time: 0.88 min. (Method 2): Purity: 100 %; Observed Mass: 527.50; Retention Time: 1.06 min. Prep Method 2: 32 mg, 40 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.18-8.11 (m, 4H), 7.43-7.36 (m, 1H), 7.06-7.00 (m, 1H), 4.73 (br d, <i>J</i> =6.1 Hz, 4H), 4.33-4.23 (m, 1H), 3.94 (s, 3H), 3.70-3.59 (m, 1H), 3.33 (s, 2H), 3.23-3.14 (m, 1H), 3.12-3.04 (m, 1H), 2.85-2.72 (m, 1H), 2.53-2.48 (m, 3H), 2.41-2.30 (m, 2H), 2.22-2.13 (m, 2H), 2.07 (br s, 4H) (four protons obscured). TLR9 IC ₅₀ (nM) = 1200

280	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 555.60; Retention Time: 0.89 min. (Method 2): Purity: 98.5 %; Observed Mass: 555.60; Retention Time: 1.11 min. Prep Method 2: 21 mg, 26 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.22-8.07 (m, 4H), 7.44-7.35 (m, 1H), 7.10-6.98 (m, 1H), 4.03-3.97 (m, 2H), 3.94 (s, 3H), 3.73-3.53 (m, 2H), 3.37-3.29 (m, 1H), 3.26-2.94 (m, 2H), 2.55 (s, 5H), 2.51 (s, 4H), 2.42-2.31 (m, 2H), 2.20-1.90 (m, 8H), 1.75-1.62 (m, 2H) (two protons obscured). TLR9 IC ₅₀ (nM) = 73
281	Analytical LC/MS (Method 1): Purity: 96.9 %; Observed Mass: 529.50; Retention Time: 0.91 min. (Method 2): Purity: 100 %; Observed Mass: 529.20; Retention Time: 1.1 min. Prep Method 1: 12 mg, 21 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.21-8.04 (m, 4H), 7.43-7.37 (m, 1H), 7.08-6.99 (m, 1H), 3.92 (s, 3H), 3.32 (s, 1H), 3.24 (s, 2H), 3.09-3.00 (m, 2H), 2.99-2.88 (m, 2H), 2.71-2.62 (m, 1H), 2.55 (s, 2H), 2.50-2.45 (m, 2H), 2.38-2.22 (m, 3H), 1.99 (br d, <i>J</i> =1.5 Hz, 2H), 1.92 (s, 1H), 1.85 (br d, <i>J</i> =10.4 Hz, 2H), 1.75 (br d, <i>J</i> =11.9 Hz, 4H), 1.54-1.42 (m, 2H) (two protons obscured). TLR9 IC ₅₀ (nM) = 120
282	Analytical LC/MS (Method 1): Purity: 99.3 %; Observed Mass: 551.20; Retention Time: 1.04 min. (Method 2): Purity: 99.3 %; Observed Mass: 551.20; Retention Time: 1.33 min. Prep Method 1: 10 mg, 8 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.10-7.93 (m, 4H), 7.33-7.27 (m, 1H), 6.97-6.86 (m, 1H), 3.82 (s, 3H), 3.22 (s, 1H), 2.95-2.85 (m, 2H), 2.58-2.46 (m, 2H), 2.45 (s, 2H), 2.18 (br d, <i>J</i> =6.1 Hz, 2H), 2.14-2.04 (m, 2H), 1.84-1.68 (m, 5H), 1.66-1.38 (m, 8H), 0.77-0.70 (m, 1H), 0.34 (br d, <i>J</i> =6.7 Hz, 2H), 0.01 (br d, <i>J</i> =4.3 Hz, 2H) (one proton obscured). TLR9 IC ₅₀ (nM) = 110

283	Analytical LC/MS (Method 1): Purity: 99.2 %; Observed Mass: 551.20; Retention Time: 1.0 min. (Method 2): Purity: 98.5 %; Observed Mass: 551.20; Retention Time: 1.52 min. Prep Method 1: 14 mg, 10 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.15-7.97 (m, 4H), 7.34-7.28 (m, 1H), 6.97-6.88 (m, 1H), 3.83 (s, 3H), 3.22 (s, 3H), 2.63-2.51 (m, 1H), 2.45 (s, 1H), 2.32-2.23 (m, 1H), 2.13 (br d, <i>J</i> =6.1 Hz, 2H), 1.91-1.82 (m, 2H), 1.82-1.59 (m, 14H), 0.80-0.69 (m, 1H), 0.34 (br d, <i>J</i> =7.9 Hz, 2H), 0.01 (br d, <i>J</i> =4.9 Hz, 2H) (one proton obscured). TLR9 IC ₅₀ (nM) = 16
284	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 553.20; Retention Time: 1.05 min. (Method 2): Purity: 99.4 %; Observed Mass: 553.20; Retention Time: 1.41 min. Prep Method 1: 12 mg, 9 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.20-8.06 (m, 4H), 7.43-7.36 (m, 1H), 7.08-6.97 (m, 1H), 3.92 (s, 3H), 3.32 (s, 1H), 3.18 (s, 1H), 3.10-2.98 (m, 1H), 2.73-2.60 (m, 2H), 2.55 (s, 1H), 2.19 (br s, 4H), 1.94-1.81 (m, 4H), 1.81-1.50 (m, 9H), 0.90 (d, <i>J</i> =6.4 Hz, 6H) (three protons obscured). TLR9 IC ₅₀ (nM) = 120
285	Analytical LC/MS (Method 1): Purity: 96.7 %; Observed Mass: 553.20; Retention Time: 1.05 min. (Method 2): Purity: 93.8 %; Observed Mass: 553.20; Retention Time: 1.62 min. Prep Method 1: 14 mg, 9 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.13 (d, <i>J</i> =5.8 Hz, 4H), 7.44-7.34 (m, 1H), 7.08-6.98 (m, 1H), 3.93 (s, 3H), 3.76-3.58 (m, 1H), 3.32 (s, 1H), 3.28-3.16 (m, 1H), 3.08-2.92 (m, 1H), 2.70-2.60 (m, 1H), 2.57-2.52 (m, 1H), 2.40 (br s, 1H), 2.14-1.51 (m, 17H), 0.92-0.85 (m, 6H) (two protons obscured). TLR9 IC ₅₀ (nM) = 250

286	Analytical LC/MS (Method 1): Purity: 90 %; Observed Mass: 553.20; Retention Time: 0.88 min. (Method 2): Purity: 86.1 %; Observed Mass: 553.20; Retention Time: 1.17 min. Prep Method 1: 15 mg, 10 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.23-8.01 (m, 4H), 7.44-7.36 (m, 1H), 7.10-6.96 (m, 1H), 4.60-4.50 (m, 1H), 4.34-4.27 (m, 1H), 3.93 (s, 3H), 3.64-3.52 (m, 1H), 3.32 (s, 1H), 3.28-3.21 (m, 1H), 3.04-2.96 (m, 1H), 2.70-2.59 (m, 1H), 2.57-2.48 (m, 3H), 2.47-2.37 (m, 1H), 1.99-1.62 (m, 16H), 1.61-1.49 (m, 1H). TLR9 IC ₅₀ (nM) = 41
287	Analytical LC/MS (Method 1): Purity: 96.6 %; Observed Mass: 553.20; Retention Time: 1.0 min. (Method 2): Purity: 94.9 %; Observed Mass: 553.10; Retention Time: 1.21 min. Prep Method 1: 9 mg, 6 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.20-8.08 (m, 4H), 7.43-7.36 (m, 1H), 7.08-6.99 (m, 1H), 4.61-4.50 (m, 2H), 4.38-4.25 (m, 2H), 3.92 (s, 3H), 3.70-3.56 (m, 1H), 3.32 (s, 1H), 3.13-3.08 (m, 1H), 3.03-2.96 (m, 2H), 2.68-2.58 (m, 2H), 2.26-2.17 (m, 2H), 1.90 (s, 3H), 1.81 (br d, <i>J</i> =1.5 Hz, 7H), 1.63-1.48 (m, 5H). TLR9 IC ₅₀ (nM) = 100
288	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 581.20; Retention Time: 0.97 min. (Method 2): Purity: 97.4 %; Observed Mass: 581.20; Retention Time: 1.24 min. Prep Method 1: 20 mg, 14 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.22-8.03 (m, 4H), 7.45-7.37 (m, 1H), 7.07-6.98 (m, 1H), 3.93 (s, 3H), 3.89-3.82 (m, 2H), 3.53-3.47 (m, 1H), 3.10-3.01 (m, 1H), 2.69-2.62 (m, 2H), 2.55 (s, 2H), 2.22-2.14 (m, 2H), 1.91 (s, 3H), 1.78 (br s, 10H), 1.59-1.44 (m, 4H), 1.35-1.20 (m, 2H) (three protons obscured). TLR9 IC ₅₀ (nM) = 110

289	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 581.20; Retention Time: 1.06 min. (Method 2): Purity: 100 %; Observed Mass: 581.20; Retention Time: 1.54 min. Prep Method 1: 15 mg, 10 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.20-8.09 (m, 4H), 7.41-7.34 (m, 1H), 7.05-6.99 (m, 1H), 4.29-4.08 (m, 2H), 3.94 (s, 5H), 3.52-3.38 (m, 1H), 3.32 (s, 2H), 3.18 (s, 2H), 2.98-2.87 (m, 1H), 2.78-2.61 (m, 1H), 2.56-2.49 (m, 5H), 2.32-1.93 (m, 12H), 1.74-1.54 (m, 3H), 1.19-1.13 (m, 1H). TLR9 IC ₅₀ (nM) = 29
290	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 555.20; Retention Time: 1.02 min. (Method 2): Purity: 99.3 %; Observed Mass: 555.20; Retention Time: 1.26 min. Prep Method 1: 11 mg, 8 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.18-8.08 (m, 4H), 7.41-7.37 (m, 1H), 7.06-6.96 (m, 1H), 3.92 (s, 3H), 3.32 (s, 1H), 3.31-3.27 (m, 1H), 3.25 (s, 2H), 3.04-2.95 (m, 2H), 2.69-2.57 (m, 2H), 2.54-2.51 (m, 5H), 2.27-2.16 (m, 2H), 1.91 (s, 3H), 1.89-1.79 (m, 4H), 1.78-1.66 (m, 2H), 1.66-1.58 (m, 2H), 1.53 (br d, <i>J</i> =7.9 Hz, 4H). TLR9 IC ₅₀ (nM) = 150
291	Analytical LC/MS (Method 1): Purity: 95.5 %; Observed Mass: 555.20; Retention Time: 1.02 min. (Method 2): Purity: 95.9 %; Observed Mass: 555.20; Retention Time: 1.42 min. Prep Method 1: 5 mg, 4 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.19-8.08 (m, 4H), 7.44-7.36 (m, 1H), 7.08-6.93 (m, 1H), 3.93 (s, 3H), 3.32 (s, 1H), 3.25 (s, 4H), 2.69-2.59 (m, 1H), 2.53-2.49 (m, 4H), 2.46 (s, 2H), 2.40-2.29 (m, 1H), 1.91 (s, 11H), 1.77-1.64 (m, 4H) (two protons obscured). TLR9 IC ₅₀ (nM) = 57
292	Analytical LC/MS (Method 1): Purity: 94.4 %; Observed Mass: 551.20; Retention Time: 1.09 min. (Method 2): Purity: 92.9 %; Observed Mass: 551.20; Retention Time: 1.48 min. Prep Method 1: 18 mg, 12 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.19-8.06 (m, 4H), 7.44-7.37 (m, 1H), 7.01 (br d, <i>J</i> =11.9 Hz, 1H), 3.92 (s, 3H), 3.34-3.28 (m, 1H), 3.24-3.16 (m, 1H), 3.08-2.95 (m, 3H), 2.66-2.56 (m, 2H), 2.55 (s, 2H), 2.24-2.16 (m, 2H), 2.02-1.95 (m, 2H), 1.92-1.89 (m, 1H), 1.86-1.47 (m, 16H). TLR9 IC ₅₀ (nM) = 150

293	Analytical LC/MS (Method 1): Purity: 94 %; Observed Mass: 551.20; Retention Time: 1.08 min. (Method 2): Purity: 95.2 %; Observed Mass: 551.10; Retention Time: 1.65 min. Prep Method 1: 11 mg, 8 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.17-8.10 (m, 4H), 7.41-7.37 (m, 1H), 7.05-6.94 (m, 1H), 3.92 (s, 3H), 3.33-3.30 (m, 1H), 3.27-3.20 (m, 1H), 3.16-3.10 (m, 1H), 3.00-2.91 (m, 1H), 2.67-2.60 (m, 1H), 2.57-2.54 (m, 1H), 2.41-2.33 (m, 1H), 2.00-1.82 (m, 9H), 1.82-1.53 (m, 14H). TLR9 IC ₅₀ (nM) = 11
294	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 527.30; Retention Time: 1.0 min. (Method 2): Purity: 100 %; Observed Mass: 527.30; Retention Time: 1.15 min. Prep Method 1: 30 mg, 21 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.20-8.05 (m, 4H), 7.44-7.37 (m, 1H), 7.06-6.97 (m, 1H), 3.93 (s, 3H), 3.32 (s, 1H), 2.89 (br d, <i>J</i> =9.5 Hz, 3H), 2.77-2.56 (m, 6H), 2.38 (br d, <i>J</i> =11.0 Hz, 2H), 1.89-1.44 (m, 11H), 1.00 (dd, <i>J</i> =6.4, 4.0 Hz, 6H) (one proton obscured). TLR9 IC ₅₀ (nM) = 55. Chiral analytical (SFC Method 6): Purity: 99 %
295	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 527.30; Retention Time: 0.99 min. (Method 2): Purity: 100 %; Observed Mass: 527.40; Retention Time: 1.18 min. Prep Method 1: 9.9 mg, 7 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.12-8.03 (m, 4H), 7.36-7.33 (m, 1H), 6.99-6.91 (m, 1H), 3.87 (s, 3H), 3.26 (s, 1H), 2.86-2.76 (m, 2H), 2.73-2.61 (m, 2H), 2.56 (br t, <i>J</i> =5.2 Hz, 3H), 2.25 (br d, <i>J</i> =6.1 Hz, 4H), 1.84 (s, 1H), 1.75 (br s, 11H), 0.81-0.73 (m, 1H), 0.43-0.33 (m, 2H), 0.01 (br d, <i>J</i> =4.3 Hz, 2H) (one proton obscured). TLR9 IC ₅₀ (nM) = 24. Chiral analytical (SFC Method 6): Purity: 95 %

296	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 541.40; Retention Time: 0.94 min. (Method 2): Purity: 96.9 %; Observed Mass: 541.30; Retention Time: 1.36 min. Prep Method 1: 10 mg, 7 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.21-8.09 (m, 4H), 7.39-7.34 (m, 1H), 7.06-6.99 (m, 1H), 3.93 (s, 3H), 3.67-3.38 (m, 1H), 3.32 (s, 1H), 3.29-3.17 (m, 1H), 3.09-2.89 (m, 4H), 2.54-2.51 (m, 2H), 2.39-2.28 (m, 2H), 2.27-1.68 (m, 11H), 1.17 (s, 2H), 0.97 (dd, <i>J</i> =6.4, 3.1 Hz, 6H) (two protons obscured). TLR9 IC ₅₀ (nM) = 22. Chiral analytical (SFC Method 6): Purity: >99 %; RT: 39 min.
297	Analytical LC/MS (Method 1): Purity: 99.1 %; Observed Mass: 541.30; Retention Time: 0.94 min. (Method 2): Purity: 98.3 %; Observed Mass: 541.20; Retention Time: 1.37 min. Prep Method 1: 10 mg, 7 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.21-8.09 (m, 4H), 7.41-7.34 (m, 1H), 7.05-7.00 (m, 1H), 3.94 (s, 3H), 3.71-3.36 (m, 1H), 3.28-2.90 (m, 5H), 2.55-2.52 (m, 2H), 2.41-1.72 (m, 12H), 1.17 (t, <i>J</i> =7.3 Hz, 2H), 0.98 (dd, <i>J</i> =6.4, 3.1 Hz, 6H) (four protons obscured). TLR9 IC ₅₀ (nM) = 23. Chiral analytical (SFC Method 6): Purity: >96 %; RT: 45 min.
298	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 539.20; Retention Time: 1.0 min. (Method 2): Purity: 100 %; Observed Mass: 539.20; Retention Time: 1.25 min. Prep Method 1: 60 mg, 43 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.02-7.93 (m, 4H), 7.27-7.22 (m, 1H), 6.90-6.82 (m, 1H), 3.77 (s, 3H), 3.17 (s, 1H), 2.84-2.72 (m, 3H), 2.66 (br s, 6H), 2.24 (br d, <i>J</i> =8.9 Hz, 2H), 1.77-1.37 (m, 11H), 1.12-1.04 (m, 1H), 0.74 (br s, 2H), 0.35 (br d, <i>J</i> =6.7 Hz, 2H), 0.01 (br d, <i>J</i> =4.3 Hz, 2H). TLR9 IC ₅₀ (nM) = 58. Chiral analytical (SFC Method 7): Purity: >99 %; RT: 15.6 min.

299	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 539.30; Retention Time: 1.01 min. (Method 2): Purity: 100 %; Observed Mass: 539.30; Retention Time: 1.26 min. Prep Method 1: 16 mg, 11 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.16-8.01 (m, 4H), 7.38-7.30 (m, 1H), 7.00-6.91 (m, 1H), 3.87 (s, 3H), 3.26 (s, 1H), 2.86-2.77 (m, 2H), 2.56 (br t, <i>J</i> =5.2 Hz, 5H), 2.33-2.21 (m, 4H), 1.84 (s, 1H), 1.80-1.41 (m, 10H), 0.76 (br s, 1H), 0.42-0.34 (m, 2H), 0.03--0.03 (m, 2H) (two protons obscured). TLR9 IC ₅₀ (nM) = 3.3. Chiral analytical (SFC Method 7): Purity: 94 %; RT: 18.8 min.
300	Analytical LC/MS (Method 1): Purity: 96.9 %; Observed Mass: 569.30; Retention Time: 1.04 min. (Method 2): Purity: 97.7 %; Observed Mass: 569.30; Retention Time: 1.2 min. Prep Method 1: 12 mg, 8 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.22-8.08 (m, 4H), 7.45-7.36 (m, 1H), 7.01 (d, <i>J</i> =11.6 Hz, 1H), 3.95-3.85 (m, 5H), 3.35-3.30 (m, 1H), 3.30-3.22 (m, 1H), 2.93-2.82 (m, 2H), 2.61 (br s, 6H), 2.46-2.31 (m, 2H), 1.88-1.67 (m, 7H), 1.60 (br d, <i>J</i> =12.8 Hz, 4H), 1.50-1.37 (m, 3H) (four protons obscured). TLR9 IC ₅₀ (nM) = 20. Chiral analytical (SFC Method 1): Purity: >95 %; RT: 19.86 min.
301	Analytical LC/MS (Method 1): Purity: 96.7 %; Observed Mass: 569.30; Retention Time: 1.03 min. (Method 2): Purity: 96.6 %; Observed Mass: 569.30; Retention Time: 1.2 min. Prep Method 1: 12 mg, 8 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.20-8.06 (m, 4H), 7.43-7.36 (m, 1H), 7.06-6.96 (m, 1H), 3.93 (s, 3H), 3.90-3.84 (m, 2H), 3.35-3.22 (m, 1H), 2.91-2.83 (m, 2H), 2.74-2.56 (m, 6H), 2.43-2.30 (m, 2H), 1.81 (br s, 7H), 1.65-1.51 (m, 4H), 1.49-1.36 (m, 3H) (five protons obscured). TLR9 IC ₅₀ (nM) = 48. Chiral analytical (SFC Method 1): Purity: >95 %; RT: 25.90 min.

302	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 543.20; Retention Time: 0.93 min. (Method 2): Purity: 100 %; Observed Mass: 543.20; Retention Time: 1.14 min. Prep Method 1: 16 mg, 11 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.16-8.07 (m, 4H), 7.44-7.34 (m, 1H), 7.07-6.94 (m, 1H), 3.92 (s, 3H), 3.56-3.40 (m, 1H), 3.32 (s, 2H), 3.25 (s, 2H), 2.95 (br d, <i>J</i>=4.0 Hz, 2H), 2.86-2.75 (m, 2H), 2.74-2.58 (m, 6H), 2.49-2.40 (m, 2H), 1.89-1.46 (m, 10H), 1.21-1.11 (m, 1H) (two protons obscured). TLR9 IC₅₀ (nM) = 48. Chiral analytical (SFC Method 8): Purity: >99 %; RT: 24.1 min.
303	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 543.20; Retention Time: 0.93 min. (Method 2): Purity: 100 %; Observed Mass: 543.20; Retention Time: 1.14 min. Prep Method 1: 16 mg, 11 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.18-8.05 (m, 4H), 7.43-7.34 (m, 1H), 7.07-6.97 (m, 1H), 3.92 (s, 2H), 3.55-3.40 (m, 1H), 3.32 (s, 2H), 3.25 (s, 2H), 2.95 (br s, 2H), 2.81 (br s, 2H), 2.74-2.60 (m, 5H), 2.55-2.40 (m, 6H), 1.91-1.46 (m, 9H), 1.31-1.12 (m, 2H). TLR9 IC₅₀ (nM) = 14. Chiral analytical (SFC Method 8): Purity: >93 %; RT: 27.5 min.
304	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 537.30; Retention Time: 0.89 min. (Method 2): Purity: 100 %; Observed Mass: 537.30; Retention Time: 1.2 min. Prep Method 1: 9.7 mg, 7 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.16-8.06 (m, 4H), 7.35-7.26 (m, 1H), 7.03-6.96 (m, 1H), 4.52 (t, <i>J</i>=6.1 Hz, 2H), 4.36 (t, <i>J</i>=6.0 Hz, 2H), 3.89 (s, 3H), 3.64-3.53 (m, 1H), 3.31 (s, 1H), 2.93-2.85 (m, 2H), 2.79-2.71 (m, 1H), 2.64-2.56 (m, 1H), 2.47-2.27 (m, 6H), 1.89-1.56 (m, 9H), 1.55-1.44 (m, 1H) (five protons obscured). TLR9 IC₅₀ (nM) = 180. Chiral analytical (SFC Method 9): Purity: >95 %; RT: 22.51 min.

305	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 537.30; Retention Time: 0.88 min. (Method 2): Purity: 100 %; Observed Mass: 537.30; Retention Time: 1.2 min. Prep Method 1: 9.2 mg, 6 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.15-8.05 (m, 4H), 7.35-7.28 (m, 1H), 7.05-6.94 (m, 1H), 4.52 (s, 2H), 4.36 (s, 2H), 3.89 (s, 3H), 3.65-3.54 (m, 1H), 3.31 (s, 1H), 2.93-2.83 (m, 2H), 2.78-2.67 (m, 1H), 2.62-2.55 (m, 2H), 2.47-2.26 (m, 6H), 1.89-1.44 (m, 10H) (four protons obscured). TLR9 IC ₅₀ (nM) = 90. Chiral analytical (SFC Method 9): Purity: >95 %; RT: 27.11 min.
306	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 565.30; Retention Time: 0.88 min. (Method 2): Purity: 100 %; Observed Mass: 565.30; Retention Time: 1.23 min. Prep Method 1: 15 mg, 10 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.18-8.06 (m, 4H), 7.35-7.26 (m, 1H), 7.05-6.95 (m, 1H), 3.93-3.81 (m, 4H), 3.31 (s, 2H), 2.94-2.84 (m, 2H), 2.72 (br s, 3H), 2.67-2.55 (m, 5H), 2.46-2.34 (m, 2H), 1.88-1.68 (m, 7H), 1.67-1.52 (m, 4H), 1.51-1.35 (m, 3H) (six protons obscured). TLR9 IC ₅₀ (nM) = 17. Chiral analytical (SFC Method 3): Purity: >95 %; RT: 12.40 min.
307	Analytical LC/MS (Method 1): Purity: 98.6 %; Observed Mass: 565.30; Retention Time: 0.88 min. (Method 2): Purity: 99.4 %; Observed Mass: 565.40; Retention Time: 1.23 min. Prep Method 1: 15 mg, 10 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.14-8.06 (m, 4H), 7.34-7.28 (m, 1H), 6.99 (s, 1H), 3.89 (s, 5H), 3.36-3.21 (m, 2H), 2.95-2.82 (m, 2H), 2.79-2.66 (m, 3H), 2.65-2.54 (m, 7H), 2.46-2.30 (m, 2H), 1.79 (br s, 7H), 1.66-1.52 (m, 4H), 1.51-1.33 (m, 4H) (two protons obscured). TLR9 IC ₅₀ (nM) = 3.5. Chiral analytical (SFC Method 3): Purity: >95 %; RT: 15.06 min.

308	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 539.30; Retention Time: 0.88 min. (Method 2): Purity: 90 %; Observed Mass: 539.30; Retention Time: 1.16 min. Prep Method 1: 13 mg, 8 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.18-8.04 (m, 4H), 7.31 (s, 1H), 6.99 (s, 1H), 3.90 (s, 3H), 3.31 (s, 2H), 3.25 (s, 2H), 2.98-2.86 (m, 4H), 2.83-2.72 (m, 2H), 2.66 (br s, 6H), 2.48-2.40 (m, 2H), 1.82 (br s, 10H), 1.32-1.22 (m, 1H), 1.16 (t, <i>J</i> =7.2 Hz, 4H). TLR9 IC ₅₀ (nM) = 6.7. Chiral analytical (SFC Method 4): Purity: >95 %; RT: 32.2 min.
309	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 539.30; Retention Time: 0.88 min. (Method 2): Purity: 89.2 %; Observed Mass: 539.30; Retention Time: 1.16 min. Prep Method 1: 11 mg, 7 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.17-8.05 (m, 4H), 7.35-7.28 (m, 1H), 7.03-6.95 (m, 1H), 3.90 (s, 2H), 3.43 (s, 1H), 3.31 (s, 2H), 3.25 (s, 2H), 2.90 (br d, <i>J</i> =7.3 Hz, 4H), 2.85-2.75 (m, 2H), 2.73-2.59 (m, 6H), 2.47 (br s, 2H), 1.94-1.47 (m, 10H), 1.24 (br s, 1H), 1.17 (br t, <i>J</i> =7.0 Hz, 3H) (one proton obscured). TLR9 IC ₅₀ (nM) = 34. Chiral analytical (SFC Method 4): Purity: >95 %; RT: 37.5 min.
310	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 541.20; Retention Time: 0.99 min. (Method 2): Purity: 100 %; Observed Mass: 541.10; Retention Time: 1.43 min. Prep Method 1: 11 mg, 8 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.23-7.99 (m, 4H), 7.58-7.44 (m, 1H), 7.31-7.15 (m, 1H), 4.02 (br s, 3H), 3.54-3.19 (m, 5H), 3.01-2.86 (m, 2H), 2.80-2.62 (m, 2H), 2.51-2.38 (m, 5H), 2.25-2.12 (m, 2H), 1.79 (br d, <i>J</i> =15.3 Hz, 10H), 0.95-0.68 (m, 6H). TLR9 IC ₅₀ (nM) = 47. Chiral analytical (SFC Method 2): Purity: >99 %; RT: 12.49 min.

311	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 541.20; Retention Time: 0.99 min. (Method 2): Purity: 100 %; Observed Mass: 541.10; Retention Time: 1.43 min. Prep Method 1: 10 mg, 7 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.23-8.03 (m, 4H), 7.57-7.45 (m, 1H), 7.27-7.15 (m, 1H), 4.02 (br s, 3H), 3.55-3.42 (m, 2H), 3.32 (br s, 3H), 2.97 (br d, <i>J</i> =1.5 Hz, 2H), 2.59 (br s, 4H), 2.23 (br s, 2H), 1.97-1.43 (m, 11H), 0.87 (br s, 6H) (two protons obscured). TLR9 IC ₅₀ (nM) = 72. Chiral analytical (SFC Method 2): Purity: >98 %; RT: 16.62 min.
312	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 539.30; Retention Time: 0.92 min. (Method 2): Purity: 100 %; Observed Mass: 539.30; Retention Time: 1.19 min. Prep Method 1: 5.6 mg, 4 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.19-8.03 (m, 4H), 7.55-7.47 (m, 1H), 7.22-7.16 (m, 1H), 4.02 (br s, 3H), 3.96-3.89 (m, 2H), 3.22-3.16 (m, 2H), 2.96 (br d, <i>J</i> =4.9 Hz, 9H), 2.72-2.63 (m, 3H), 2.34-2.26 (m, 1H), 2.10-1.98 (m, 3H), 1.67-1.47 (m, 6H), 1.21-1.15 (m, 1H), 0.90-0.82 (m, 3H). TLR9 IC ₅₀ (nM) = 64. Chiral analytical (SFC Method 5): Purity: >99 %; RT: 16.70 min.
313	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 539.3; Retention Time: 0.92 min. (Method 2): Purity: 100 %; Observed Mass: 539.30; Retention Time: 1.18 min. Prep Method 1: 8.2 mg, 7 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.15-8.04 (m, 4H), 7.52-7.46 (m, 1H), 7.23-7.17 (m, 1H), 4.01 (s, 3H), 3.19-3.15 (m, 1H), 3.11-2.88 (m, 5H), 2.86-2.60 (m, 4H), 2.48-2.42 (m, 2H), 2.07-1.98 (m, 2H), 1.96-1.68 (m, 7H), 1.67-1.46 (m, 5H), 1.30-1.18 (m, 4H). TLR9 IC ₅₀ (nM) = 69. Chiral analytical (SFC Method 5): Purity: >90 %; RT: 18.45 min.

314	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 541.20; Retention Time: 0.89 min. (Method 2): Purity: 100 %; Observed Mass: 541.30; Retention Time: 1.2 min. Prep Method 1: 9 mg, 6 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.18-8.03 (m, 4H), 7.57-7.46 (m, 1H), 7.27-7.14 (m, 1H), 4.52 (s, 2H), 4.36 (s, 2H), 4.02 (s, 3H), 3.63-3.53 (m, 1H), 3.53-3.38 (m, 1H), 3.31 (s, 2H), 3.02-2.86 (m, 3H), 2.85-2.73 (m, 1H), 2.44 (br s, 3H), 2.39-2.19 (m, 3H), 1.77 (br s, 10H). TLR9 IC ₅₀ (nM) = 190. Chiral analytical (SFC Method 9): Purity: >95 %; RT: 8.53 min.
315	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 541.20; Retention Time: 0.89 min. (Method 2): Purity: 100 %; Observed Mass: 541.30; Retention Time: 1.2 min. Prep Method 1: 9 mg, 6 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.17-8.04 (m, 4H), 7.57-7.45 (m, 1H), 7.24-7.10 (m, 1H), 4.59-4.47 (m, 2H), 4.36 (s, 2H), 4.02 (s, 3H), 3.90 (s, 1H), 3.66-3.55 (m, 1H), 3.51-3.40 (m, 2H), 3.31 (s, 2H), 3.18 (s, 2H), 2.96 (br s, 3H), 2.88-2.78 (m, 1H), 2.49-2.41 (m, 2H), 2.38-2.26 (m, 3H), 1.91-1.44 (m, 7H). TLR9 IC ₅₀ (nM) = 150. Chiral analytical (SFC Method 9): Purity: >95 %; RT: 10.98 min.
316	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 569.20; Retention Time: 0.91 min. (Method 2): Purity: 100 %; Observed Mass: 569.30; Retention Time: 1.14 min. Prep Method 1: 6.2 mg, 4 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.21-8.05 (m, 4H), 7.55-7.48 (m, 1H), 7.26-7.17 (m, 1H), 4.12-4.02 (m, 3H), 3.98-3.85 (m, 4H), 3.43-3.29 (m, 6H), 3.03-2.89 (m, 4H), 2.85-2.71 (m, 4H), 1.84-1.72 (m, 4H), 1.70-1.44 (m, 7H), 1.27-1.19 (m, 3H). TLR9 IC ₅₀ (nM) = 14. Chiral analytical (SFC Method 5): Purity: >99 %; RT: 12.27 min.

317	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 569.30; Retention Time: 0.91 min. (Method 2): Purity: 100 %; Observed Mass: 569.30; Retention Time: 1.14 min. Prep Method 1: 10 mg, 7 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.19-8.00 (m, 4H), 7.53-7.46 (m, 1H), 7.24-7.16 (m, 1H), 4.02 (br s, 3H), 3.94-3.84 (m, 2H), 3.55-3.46 (m, 3H), 3.02-2.86 (m, 3H), 2.80-2.61 (m, 3H), 1.77 (br d, <i>J</i> =2.1 Hz, 4H), 1.68-1.56 (m, 4H), 1.53-1.42 (m, 4H), 1.24 (br s, 6H), 0.92-0.81 (m, 3H). TLR9 IC ₅₀ (nM) = 18. Chiral analytical (SFC Method 5): Purity: >90 %; RT: 14.29 min.
318	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 543.3; Retention Time: 1.08 min. (Method 2): Purity: 98.6 %; Observed Mass: 543.3; Retention Time: 1.604 min. Prep Method 1: 55 mg, 66 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.20-8.02 (m, 4H), 7.38-7.30 (m, 1H), 7.25-7.17 (m, 2H), 7.03-6.99 (m, 1H), 6.98-6.91 (m, 2H), 6.79-6.71 (m, 1H), 3.90 (s, 3H), 3.81-3.73 (m, 2H), 3.16-3.01 (m, 2H), 2.74-2.63 (m, 3H), 2.58-2.54 (m, 7H), 2.45-2.28 (m, 2H), 1.93-1.76 (m, 5H), 1.70-1.54 (m, 2H) (one proton obscured). TLR9 IC ₅₀ (nM) = 270
319	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 553.20; Retention Time: 1.14 min. (Method 2): Purity: 95.8 %; Observed Mass: 553.60; Retention Time: 1.55 min. Prep Method 1: 35 mg, 36 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.29 (d, <i>J</i> =8.2 Hz, 2H), 8.10 (d, <i>J</i> =8.2 Hz, 2H), 7.37 (s, 1H), 7.03 (br d, <i>J</i> =11.9 Hz, 1H), 3.91-3.82 (m, 1H), 3.10-2.99 (m, 1H), 2.93-2.86 (m, 1H), 2.86-2.86 (m, 1H), 2.69 (br s, 1H), 2.54-2.51 (m, 3H), 2.37-2.25 (m, 3H), 2.03 (br d, <i>J</i> =6.7 Hz, 2H), 1.90-1.82 (m, 4H), 1.75 (br d, <i>J</i> =13.1 Hz, 5H), 1.56-1.44 (m, 2H), 1.17 (br d, <i>J</i> =6.1 Hz, 2H), 0.86 (d, <i>J</i> =6.4 Hz, 6H), 0.66 (br s, 2H) (one proton obscured). TLR9 IC ₅₀ (nM) = 94

320	Analytical LC/MS (Method 1): Purity: 87.8 %; Observed Mass: 551.30; Retention Time: 1.0 min. (Method 2): Purity: 85.9 %; Observed Mass: 551.20; Retention Time: 1.24 min. Prep Method 1: 1.2 mg, 1 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.29-8.16 (m, 2H), 8.12-7.96 (m, 2H), 7.38-7.27 (m, 1H), 7.04-6.93 (m, 1H), 3.88-3.70 (m, 1H), 3.28 (s, 1H), 2.96 (br s, 3H), 2.69-2.56 (m, 1H), 2.31-2.14 (m, 3H), 2.09 (br d, <i>J</i>=6.4 Hz, 1H), 1.91-1.76 (m, 3H), 1.75-1.65 (m, 3H), 1.63 (s, 4H), 1.49-1.30 (m, 2H), 1.11 (br s, 2H), 0.84-0.72 (m, 1H), 0.60 (br s, 2H), 0.45-0.32 (m, 2H), 0.01 (br d, <i>J</i>=4.6 Hz, 2H) (two protons obscured). TLR9 IC₅₀ (nM) = 77
321	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 581.20; Retention Time: 1.03 min. (Method 2): Purity: 100 %; Observed Mass: 581.20; Retention Time: 1.35 min. Prep Method 1: 12 mg, 11 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.37-8.24 (m, 2H), 8.19-8.04 (m, 2H), 7.41-7.32 (m, 1H), 7.09-6.95 (m, 1H), 3.94-3.81 (m, 3H), 3.33 (s, 1H), 3.29-3.22 (m, 1H), 3.06-2.89 (m, 3H), 2.67 (br s, 1H), 2.55 (s, 1H), 2.40 (br s, 1H), 2.33-2.17 (m, 3H), 2.08 (br t, <i>J</i>=11.1 Hz, 2H), 1.93-1.54 (m, 9H), 1.52-1.29 (m, 4H), 1.17 (br d, <i>J</i>=6.1 Hz, 2H), 0.66 (br s, 2H) (two protons obscured). TLR9 IC₅₀ (nM) = 36
322	Analytical LC/MS (Method 1): Purity: 98.7 %; Observed Mass: 579.20; Retention Time: 1.14 min. (Method 2): Purity: 92.5 %; Observed Mass: 579.40; Retention Time: 1.51 min. Prep Method 1: 35 mg, 19 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.32-8.24 (m, 2H), 8.15-8.04 (m, 2H), 7.42-7.30 (m, 1H), 7.07-6.93 (m, 1H), 3.96-3.79 (m, 1H), 3.26-3.16 (m, 1H), 3.00 (br s, 2H), 2.65 (br s, 1H), 2.59-2.55 (m, 1H), 2.50-2.47 (m, 1H), 2.24-2.08 (m, 4H), 1.93-1.79 (m, 4H), 1.73-1.47 (m, 9H), 1.16 (br d, <i>J</i>=6.0 Hz, 2H), 0.88 (d, <i>J</i>=6.5 Hz, 6H), 0.65 (br s, 2H) (three protons obscured). TLR9 IC₅₀ (nM) = 12

323	Analytical LC/MS (Method 1): Purity: 98.8 %; Observed Mass: 579.40; Retention Time: 1.03 min. (Method 2): Purity: 97.8 %; Observed Mass: 579.40; Retention Time: 1.71 min. Prep Method 1: 28 mg, 16 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.35-8.21 (m, 2H), 8.15-8.03 (m, 2H), 7.43-7.28 (m, 1H), 7.11-6.94 (m, 1H), 3.89-3.76 (m, 1H), 3.32 (s, 2H), 3.26-3.19 (m, 1H), 3.15-3.06 (m, 2H), 2.71-2.61 (m, 1H), 2.46-2.37 (m, 1H), 2.05-1.79 (m, 13H), 1.77-1.59 (m, 6H), 1.16 (br d, <i>J</i> =6.1 Hz, 2H), 0.88 (d, <i>J</i> =6.7 Hz, 6H), 0.65 (br s, 2H). TLR9 IC ₅₀ (nM) = 60
324	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 577.20; Retention Time: 1.18 min. (Method 2): Purity: 95.9 %; Observed Mass: 577.20; Retention Time: 1.48 min. Prep Method 2: 35 mg, 14 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.31-8.25 (m, 2H), 8.14-8.04 (m, 2H), 7.45-7.36 (m, 1H), 7.07-6.97 (m, 1H), 4.33-4.13 (m, 2H), 3.96-3.74 (m, 2H), 3.66-3.47 (m, 1H), 3.32 (s, 2H), 3.23-3.02 (m, 2H), 2.91 (br s, 1H), 2.38-1.87 (m, 12H), 1.20-1.03 (m, 3H), 0.70-0.60 (m, 4H), 0.45-0.33 (m, 2H) (four protons obscured). TLR9 IC ₅₀ (nM) = 42
325	Analytical LC/MS (Method 1): Purity: 99.1 %; Observed Mass: 557.30; Retention Time: 1.02 min. (Method 2): Purity: 99.5 %; Observed Mass: 557.50; Retention Time: 1.46 min. Prep Method 1: 35 mg, 20 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.25-8.10 (m, 2H), 8.06-7.94 (m, 2H), 7.31-7.21 (m, 1H), 6.95-6.82 (m, 1H), 3.79-3.67 (m, 1H), 3.58-3.42 (m, 2H), 3.32-3.24 (m, 1H), 3.20 (s, 4H), 2.63-2.50 (m, 1H), 2.31-2.22 (m, 1H), 2.14 (br d, <i>J</i> =6.1 Hz, 2H), 1.93-1.84 (m, 2H), 1.83-1.52 (m, 12H), 1.05 (br d, <i>J</i> =6.1 Hz, 2H), 0.80-0.67 (m, 1H), 0.53 (br d, <i>J</i> =1.8 Hz, 2H), 0.34 (br d, <i>J</i> =7.9 Hz, 2H), 0.01 (br d, <i>J</i> =4.6 Hz, 2H). TLR9 IC ₅₀ (nM) = 15

326	Analytical LC/MS (Method 1): Purity: 93.9 %; Observed Mass: 577.40; Retention Time: 1.11 min. (Method 2): Purity: 95 %; Observed Mass: 577.40; Retention Time: 1.42 min. Prep Method 1: 42 mg, 23 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.35-8.22 (m, 2H), 8.16-8.05 (m, 2H), 7.39-7.30 (m, 1H), 7.06-6.95 (m, 1H), 3.91-3.78 (m, 1H), 3.33 (s, 1H), 3.20 (br s, 1H), 2.98 (br d, <i>J</i> =11.0 Hz, 3H), 2.70-2.57 (m, 2H), 2.20 (br t, <i>J</i> =11.0 Hz, 2H), 1.98 (br d, <i>J</i> =7.6 Hz, 2H), 1.90 (s, 1H), 1.86-1.47 (m, 16H), 1.17 (br d, <i>J</i> =6.1 Hz, 2H), 0.65 (br s, 2H) (two protons obscured). TLR9 IC ₅₀ (nM) = 23
327	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 577.20; Retention Time: 1.14 min. (Method 2): Purity: 100 %; Observed Mass: 577.20; Retention Time: 1.68 min. Prep Method 2: 27 mg, 11 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.35-8.22 (m, 2H), 8.14-8.06 (m, 2H), 7.44-7.33 (m, 1H), 7.07-6.98 (m, 1H), 3.94-3.82 (m, 2H), 3.67-3.47 (m, 1H), 3.33 (s, 2H), 3.16-2.90 (m, 1H), 2.81-2.47 (m, 7H), 2.34-1.86 (m, 13H), 1.85-1.62 (m, 2H), 1.16 (br d, <i>J</i> =6.7 Hz, 3H), 0.67 (br s, 2H) (two protons obscured). TLR9 IC ₅₀ (nM) = 110
328	Analytical LC/MS (Method 1): Purity: 95.1 %; Observed Mass: 607.20; Retention Time: 1.08 min. (Method 2): Purity: 90.4 %; Observed Mass: 607.40; Retention Time: 1.34 min. Prep Method 1: 32 mg, 16 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.35-8.22 (m, 2H), 8.15-8.04 (m, 2H), 7.41-7.31 (m, 1H), 7.06-6.94 (m, 1H), 3.85 (br dd, <i>J</i> =7.5, 3.1 Hz, 3H), 3.54-3.42 (m, 1H), 3.32 (s, 2H), 3.10-2.95 (m, 2H), 2.70-2.55 (m, 4H), 2.16 (br s, 2H), 1.90 (s, 2H), 1.87-1.42 (m, 14H), 1.34-1.10 (m, 4H), 0.65 (br s, 2H) (one proton obscured). TLR9 IC ₅₀ (nM) = 12

329	Analytical LC/MS (Method 1): Purity: 97.9 %; Observed Mass: 607.30; Retention Time: 1.04 min. (Method 2): Purity: 100 %; Observed Mass: 607.20; Retention Time: 1.52 min. Prep Method 1: 26 mg, 14 % yield; ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.34-8.23 (m, 2H), 8.14-8.06 (m, 2H), 7.38-7.32 (m, 1H), 7.05-6.97 (m, 1H), 3.91-3.81 (m, 2H), 3.51-3.40 (m, 1H), 3.37-3.22 (m, 6H), 2.74-2.62 (m, 1H), 2.44-2.33 (m, 1H), 1.99-1.65 (m, 20H), 1.39-1.26 (m, 2H), 1.17 (br d, <i>J</i> =6.1 Hz, 2H), 0.66 (br s, 2H). TLR9 IC ₅₀ (nM) = 28
330	Analytical LC/MS (Method 6): Purity: 98.2 %; Observed Mass: 523.3; Retention Time: 0.585 min. Prep Method 3: 15 mg, 18 % yield; ¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 8.10 (d, <i>J</i> = 6.4 Hz, 2H), 7.93 (d, <i>J</i> = 6.4 Hz, 2H), 7.64 (d, <i>J</i> = 8.5 Hz, 1H), 7.32 (d, <i>J</i> = 8.6 Hz, 1H), 4.06 (s, 3H), 3.28-3.11 (m, 1H), 3.11 (s, 3H), 3.09-2.91 (m, 3H), 2.78 (s, 3H), 2.70-2.30 (m, 3H), 2.22-1.45 (m, 14H), 0.91 (d, <i>J</i> = 6.5 Hz, 6H). TLR9 IC ₅₀ (nM) = 1400
331	Analytical LC/MS (Method 6): Purity: 95.0 %; Observed Mass: 523.2; Retention Time: 0.597 min. Prep Method 3: 52 mg, 36 % yield; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.15-8.05 (m, 4H), 7.49 (d, <i>J</i> = 14.2 Hz, 2H), 3.91 (s, 3H), 3.31 (s, 3H), 3.02 (d, <i>J</i> = 11.2 Hz, 2H), 2.86 (d, <i>J</i> = 11.8 Hz, 2H), 2.81-2.70 (m, 1H), 2.42 (s, 3H), 2.35-2.18 (m, 3H), 2.00 (d, <i>J</i> = 7.4 Hz, 2H), 1.87-1.72 (m, 9H), 1.54-1.40 (m, 2H), 0.85 (d, <i>J</i> = 6.5 Hz, 6H). TLR9 IC ₅₀ (nM) = 140
332	Analytical LC/MS (Method 6): Purity: 96.3 %; Observed Mass: 521.3; Retention Time: 0.904 min. Prep Method 3: 2.2 mg, 2 % yield; ¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.37 (d, <i>J</i> = 6.8 Hz, 2H), 8.13 (d, <i>J</i> = 6.8 Hz, 2H), 7.34 (s, 1H), 7.03 (s, 1H), 3.61 (s, 2H), 3.33-3.32 (m, 2H), 3.21 (s, 3H), 2.82-2.79 (m, 1H), 2.67-2.66 (m, 1H), 2.64 (s, 3H), 2.59-2.54 (m, 1H), 2.16-2.09 (m, 2H), 2.01-1.77 (m, 12H), 1.17 (d, <i>J</i> = 6.3 Hz, 6H). TLR9 IC ₅₀ (nM) = 170

333	Analytical LC/MS (Method 6): Purity: 99 %; Observed Mass: 521.3; Retention Time: 0.954 min. Prep Method 3: 6.3 mg, 4 % yield; ¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.24 (d, <i>J</i> = 7.2 Hz, 2H), 8.01 (d, <i>J</i> = 6.8 Hz, 2H), 7.21 (s, 1H), 6.90 (s, 1H), 3.49 (s, 2H), 3.08 (s, 3H), 3.06-3.03 (m, 2H), 2.93-2.87 (m, 1H), 2.62-2.55 (m, 1H), 2.52 (s, 3H), 2.49-2.48 (m, 1H), 2.17-2.11 (m, 2H), 1.88-1.50 (m, 12H), 1.04 (d, <i>J</i> = 6.3 Hz, 6H). TLR9 IC ₅₀ (nM) = 330
334	Analytical LC/MS (Method 6): Purity: 96.5 %; Observed Mass: 533.3; Retention Time: 0.613 min. Prep Method 3: 6.3 mg, 5 % yield; ¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.38 (d, <i>J</i> = 8.4 Hz, 2H), 8.15 (d, <i>J</i> = 7.2 Hz, 2H), 7.37 (s, 1H), 7.05 (s, 1H), 3.95 (s, 2H), 3.80-3.60 (m, 2H), 3.45-3.35 (m, 2H), 3.30-3.25 (m, 1H), 3.20 (s, 3H), 2.90-2.80 (m, 1H), 2.80-2.70 (m, 1H), 2.65 (s, 3H), 2.45-2.15 (m, 9H), 2.15-1.90 (m, 9H). TLR9 IC ₅₀ (nM) = 300
335	Analytical LC/MS (Method 6): Purity: 99.1 %; Observed Mass: 533.2; Retention Time: 0.63 min. Prep Method 3: 22 mg, 15 % yield; ¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.37-8.36 (m, 2H), 8.14-8.12 (m, 2H), 7.33 (s, 1H), 7.03 (s, 1H), 3.60 (d, <i>J</i> = 4.7 Hz, 2H), 3.21 (s, 3H), 3.15-3.12 (m, 2H), 2.76-2.70 (m, 1H), 2.70-2.65 (m, 1H), 2.64 (s, 3H), 2.45 (d, <i>J</i> = 6.6 Hz, 2H), 2.35-2.30 (m, 2H), 2.03-1.69 (m, 12H), 1.03-0.97 (m, 1H), 0.61-0.56 (m, 2H), 0.24-0.20 (m, 2H). TLR9 IC ₅₀ (nM) = 130
336	Analytical LC/MS (Method 6): Purity: 93.8 %; Observed Mass: 533.3; Retention Time: 1.077 min. Prep Method 3: 6.7 mg, 4 % yield; ¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.17-8.15 (m, 2H), 7.94-7.91 (m, 2H), 7.13 (s, 1H), 6.82 (s, 1H), 3.31 (s, 2H), 3.12-3.11 (m, 2H), 3.00 (s, 3H), 2.45-2.43 (m, 1H), 2.41 (s, 3H), 2.33-2.31 (m, 1H), 2.15 (d, <i>J</i> = 6.6 Hz, 2H), 2.00-1.93 (m, 2H), 1.84-1.59 (m, 12H), 0.79-0.71 (m, 1H), 0.39-0.34 (m, 2H), 0.03-0.01 (m, 2H). TLR9 IC ₅₀ (nM) = 77

337	Analytical LC/MS (Method 6): Purity: 94.4 %; Observed Mass: 539.2; Retention Time: 0.605 min. Prep Method 3: 46mg, 57 % yield; ¹ H NMR (300 MHz, Chloroform- <i>d</i>) δ 8.10 (t, <i>J</i> = 7.2, 7.5 Hz, 1H), 7.78-7.67 (m, 2H), 7.13 (s, 1H), 7.06 (s, 1H), 3.88 (s, 3H), 3.27 (s, 3H), 3.13-2.94 (m, 4H), 2.80-2.58 (m, 5H), 2.52-2.35 (m, 3H), 2.14-2.05 (m, 1H), 2.01-1.82 (m, 8H), 1.73-1.55 (m, 7H). TLR9 IC ₅₀ (nM) = 53
338	Analytical LC/MS (Method 9): Purity: 97.9 %; Observed Mass: 539.4; Retention Time: 0.787 min. Prep Method 3: 22 mg, 27 % yield; ¹ H NMR (300 MHz, Chloroform- <i>d</i>) δ 8.10 (t, <i>J</i> = 7.8, 7.5 Hz, 1H), 7.78-7.67 (m, 2H), 7.13 (s, 1H), 7.06 (s, 1H), 3.86 (s, 3H), 3.39-3.02 (m, 8H), 2.76-8-2.62 (m, 4H), 2.50-2.31 (m, 3H), 2.26 (d, <i>J</i> = 6.5 Hz, 2H), 2.09-1.85 (m, 9H), 1.01-0.81 (m, 1H), 0.72-0.48 (m, 2H), 0.17-0.04 (m, 2H). TLR9 IC ₅₀ (nM) = 260
339	Analytical LC/MS (Method 6): Purity: 97.7 %; Observed Mass: 525.2; Retention Time: 0.589 min. Prep Method 3: 17 mg, 21 % yield; ¹ H NMR (300 MHz, Chloroform- <i>d</i>) δ 8.10 (t, <i>J</i> = 7.7 Hz, 1H), 7.72 (t, <i>J</i> = 7.8 Hz, 2H), 7.11 (s, 1H), 7.05 (s, 1H), 3.89 (s, 3H), 3.27 (s, 3H), 3.25-3.01 (m, 4H), 2.79-2.61 (m, 4H), 2.58-2.35 (m, 3H), 2.22 (t, <i>J</i> = 11.7, 10.8 Hz, 2H), 2.01-1.82 (m, 7H), 1.63-1.49 (m, 2H), 0.60-0.36 (m, 4H). TLR9 IC ₅₀ (nM) = 340
340	Analytical LC/MS (Method 6): Purity: 91.9 %; Observed Mass: 565.2; Retention Time: 0.88 min. Prep Method 3: 3.1 mg, 4 % yield; ¹ H NMR (300 MHz, Chloroform- <i>d</i>) δ 8.13 (dd, <i>J</i> = 8.3, 7.1 Hz, 1H), 7.77-7.73 (m, 2H), 7.12-7.07 (m, 2H), 3.89 (s, 3H), 3.46-3.42 (m, 2H), 3.34-3.29 (m, 2H), 3.22 (s, 3H), 2.70 (s, 3H), 2.64-2.61 (m, 2H), 2.33-2.14 (m, 4H), 2.04-1.61 (m, 12H), 0.95-0.92 (m, 1H), 0.56-0.50 (m, 2H), 0.14-0.09 (m, 2H). TLR9 IC ₅₀ (nM) = 84

341	Analytical LC/MS (Method 6): Purity: 95.9 %; Observed Mass: 565.3; Retention Time: 0.89 min. Prep Method 3: 9.7 mg, 13 % yield; ¹ H NMR (300 MHz, Chloroform- <i>d</i>) δ 8.12 (dd, <i>J</i> = 8.3, 7.1 Hz, 1H), 7.76-7.73 (m, 2H), 7.13-7.07 (m, 2H), 3.87 (s, 3H), 3.55-3.52 (m, 2H), 3.29 (s, 3H), 3.13 (d, <i>J</i> = 11.0 Hz, 2H), 2.66 (s, 3H), 2.64-2.59 (m, 2H), 2.38 (d, <i>J</i> = 6.3 Hz, 2H), 2.28-2.25 (m, 2H), 1.95-1.53 (m, 12H), 0.93-0.91 (m, 1H), 0.55-0.49 (m, 2H), 0.16-0.12 (m, 2H). TLR9 IC ₅₀ (nM) = 37
342	Analytical LC/MS(Method 6): Purity: 99.1 %; Observed Mass: 567.2; Retention Time: 0.996 min. Prep Method 3: 20 mg, 14 % yield; ¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 8.20-8.09 (m, 1H), 7.92-7.83 (m, 2H), 7.29 (s, 1H), 7.08 (s, 1H), 3.92 (s, 3H), 3.59-3.42 (m, 2H), 3.35 (s, 3H), 3.19-3.12 (m, 2H), 2.88-2.64 (m, 2H), 2.63 (s, 3H), 2.46 (d, <i>J</i> = 10.5 Hz, 4H), 2.19-1.70 (m, 13H), 1.15 (d, <i>J</i> = 6.5 Hz, 6H). TLR9 IC ₅₀ (nM) = 120
343	Analytical LC/MS (Method 6): Purity: 95.9 %; Observed Mass: 541.1; Retention Time: 0.919 min. Prep Method 3: 16 mg, 23 % yield; ¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 8.10-7.92 (m, 3H), 7.33 (s, 1H), 7.01 (s, 1H), 3.92 (s, 3H), 3.59-3.50 (m, 1H), 3.09 (d, <i>J</i> = 10.9 Hz, 3H), 2.92 (d, <i>J</i> = 11.0 Hz, 2H), 2.70-2.50 (m, 5H), 2.39 (t, <i>J</i> = 11.5 Hz, 3H), 2.06 (d, <i>J</i> = 7.3 Hz, 2H), 1.90-1.68 (m, 9H), 1.60-1.40 (m, 2H), 0.86 (d, <i>J</i> = 6.5 Hz, 6H). TLR9 IC ₅₀ (nM) = 160
344	Analytical LC/MS (Method 6): Purity: 91.2 %; Observed Mass: 553.3; Retention Time: 0.611 min. Prep Method 3: 9.7 mg, 13 % yield; ¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.03 (dd, <i>J</i> = 8.3, 7.3 Hz, 1H), 7.78-7.74 (m, 2H), 7.17 (s, 1H), 6.96 (d, <i>J</i> = 1.4 Hz, 1H), 3.81 (s, 3H), 3.58-3.53 (m, 2H), 3.22 (s, 3H), 3.09-3.06 (m, 2H), 2.94-2.91 (m, 1H), 2.64-2.60 (m, 2H), 2.52 (s, 3H), 2.22-2.16 (m, 2H), 1.90-1.54 (m, 12H), 1.06 (d, <i>J</i> = 6.2 Hz, 6H). TLR9 IC ₅₀ (nM) = 120

345	Analytical LC/MS (Method 6): Purity: 96.9 %; Observed Mass: 551.2; Retention Time: 0.613 min. ¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.02 (dd, <i>J</i> = 8.3, 7.2 Hz, 1H), 7.77-7.73 (m, 2H), 7.16 (d, <i>J</i> = 1.5 Hz, 1H), 6.95 (d, <i>J</i> = 1.3 Hz, 1H), 3.80 (s, 3H), 3.32-3.29 (m, 2H), 3.23 (s, 3H), 3.04 (d, <i>J</i> = 11.3 Hz, 2H), 2.66-2.54 (m, 2H), 2.51 (s, 3H), 2.24-2.19 (m, 2H), 1.97-1.94 (m, 3H), 1.83-1.56 (m, 10H), 0.40-0.36 (m, 4H). TLR9 IC ₅₀ (nM) = 130
346	Analytical LC/MS (Method 6): Purity: 97.2 %; Observed Mass: 553.2; Retention Time: 0.640 min. Prep Method 3: 8.7 mg, 6.0 % yield; ¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.20-8.09 (m, 3H), 7.35 (s, 1H), 7.06 (s, 1H), 3.42-3.30 (m, 5H), 3.19 (d, <i>J</i> = 11.4 Hz, 2H), 2.73-2.62 (m, 5H), 2.34-2.26 (m, 4H), 2.04-1.95 (m, 2H), 1.95-1.70 (m, 9H), 1.66 (d, <i>J</i> = 8.0 Hz, 2H), 0.98 (d, <i>J</i> = 6.6 Hz, 6H). TLR9 IC ₅₀ (nM) = 56
347	Analytical LC/MS (Method 6): Purity: 95.1 %; Observed Mass: 537.2; Retention Time: 1.109 min. ¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.20-8.03 (m, 3H), 7.33 (s, 1H), 7.04 (s, 1H), 3.47-3.38 (m, 2H), 3.31 (s, 3H), 3.22-3.06 (m, 2H), 2.80-2.68 (m, 1H), 2.67-2.58 (m, 4H), 2.32 (t, <i>J</i> = 11.5 Hz, 2H), 2.15-2.00 (m, 3H), 1.98-1.85 (m, 2H), 1.85-1.77 (m, 4H), 1.77-1.64 (m, 4H), 0.57-0.39 (m, 4H). TLR9 IC ₅₀ (nM) = 44
348	Analytical LC/MS (Method 6): Purity: 95.1 %; Observed Mass: 539.2; Retention Time: 1.11 min. ¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 8.21-8.06 (m, 3H), 7.34 (s, 1H), 7.04 (s, 1H), 3.70-3.61 (m, 2H), 3.33 (s, 3H), 3.18 (d, <i>J</i> = 11.0 Hz, 2H), 3.09-3.01 (m, 1H), 2.77-2.69 (m, 2H), 2.64 (s, 3H), 2.31-2.24 (m, 2H), 2.01-1.60 (m, 12H), 1.17 (d, <i>J</i> = 6.0 Hz, 6H). TLR9 IC ₅₀ (nM) = 180
349	Analytical LC/MS (Method 6): Purity: 96.8 %; Observed Mass: 551.3; Retention Time: 0.649 min. ¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.22-8.00 (m, 3H), 7.34 (s, 1H), 7.05 (s, 1H), 3.39 (s, 2H), 3.29-3.24 (m, 4H), 3.13 (d, <i>J</i> = 10.4 Hz, 2H), 2.82-2.71 (m, 1H), 2.71-2.58 (m, 4H), 2.42-2.30 (m, 2H), 2.18-2.07 (m, 2H), 2.06-1.88 (m, 7H), 1.88-1.71 (m, 7H), 1.68 (d, <i>J</i> = 8.1 Hz, 2H). TLR9 IC ₅₀ (nM) = 24

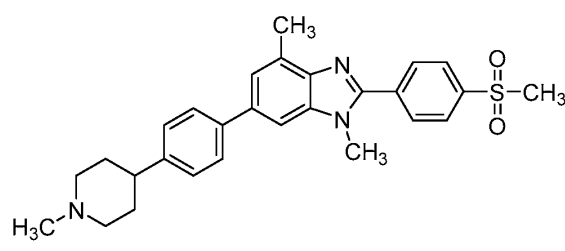
350	Analytical LC/MS (Method 6): Purity: 93.0 %; Observed Mass: 551.3; Retention Time: 1.013 min. ¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.08-7.91 (m, 3H), 7.21 (s, 1H), 6.92 (s, 1H), 3.21-3.20 (m, 4H), 3.20-3.07 (m, 4H), 3.06-2.93 (m, 1H), 2.59-2.35 (m, 5H), 2.05-1.93 (m, 4H), 1.92-1.74 (m, 10H), 1.71-1.59 (m, 5H). TLR9 IC ₅₀ (nM) = 55
351	Analytical LC/MS (Method 6): Purity: 98.7 %; Observed Mass: 551.2; Retention Time: 0.643 min. ¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 8.09-7.97 (m, 3H), 7.28 (s, 1H), 7.04 (s, 1H), 3.46 (s, 2H), 3.36-3.18 (m, 5H), 2.68-2.45 (m, 5H), 2.33-2.16 (m, 4H), 2.00-1.71 (m, 12H), 0.99-0.87 (m, 1H), 0.56-0.45 (m, 2H), 0.20-0.06 (m, 2H). TLR9 IC ₅₀ (nM) = 48
352	Analytical LC/MS (Method 6): Purity: 95.1 %; Observed Mass: 551.3; Retention Time: 2.283 min. ¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.19-8.03 (m, 3H), 7.34 (s, 1H), 7.04 (s, 1H), 3.65 (s, 2H), 3.28 (s, 3H), 3.20-3.05 (m, 2H), 2.84-2.70 (m, 1H), 2.64-2.55 (m, 4H), 2.53-2.42 (m, 2H), 2.34 (t, J = 11.6 Hz, 2H), 2.10-1.99 (m, 2H), 1.97-1.61 (m, 10H), 1.04-0.89 (m, 1H), 0.68-0.49 (m, 2H), 0.22-0.15 (m, 2H). TLR9 IC ₅₀ (nM) = 26
353	Analytical LC/MS (Method 6): Purity: 98.8 %; Observed Mass: 516.2; Retention Time: 0.943 min. Prep Method 3: 60 mg, 71 % yield; ¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 8.89 (s, 1H), 8.49 (s, 1H), 7.47 (s, 1H), 7.29 (s, 1H), 7.07 (s, 1H), 4.15 (s, 3H), 3.95 (s, 3H), 3.21-3.13 (m, 2H), 3.05-2.95 (m, 2H), 2.75-2.65 (m, 1H), 2.63 (s, 3H), 2.45-2.32 (m, 3H), 2.16-2.08 (m, 2H), 2.04-1.78 (m, 9H), 1.75-1.60 (m, 2H), 0.92 (d, J = 6.9 Hz, 6H). TLR9 IC ₅₀ (nM) = 16
354	Analytical LC/MS (Method 6): Purity: 98.7 %; Observed Mass: 526.2; Retention Time: 0.568 min. ¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.76 (d, J = 1.3 Hz, 1H), 8.36 (s, 1H), 7.36 (d, J = 1.3 Hz, 1H), 7.17 (d, J = 1.5 Hz, 1H), 6.95 (s, 1H), 4.05 (s, 3H), 3.85 (s, 3H), 3.32-3.29 (m, 2H), 3.05-3.02 (m, 2H), 2.64-2.59 (m, 2H), 2.52 (s, 3H), 2.25-2.20 (m, 2H), 1.96-1.93 (m, 3H), 1.84-1.56 (m, 10H), 0.40-0.36 (m, 4H). TLR9 IC ₅₀ (nM) = 85

355	Analytical LC/MS (Method 6): Purity: 98.4%; Observed Mass: 540.3. ¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.89 (s, 1H), 8.47 (s, 1H), 7.48 (s, 1H), 7.28 (s, 1H), 7.06 (s, 1H), 4.16 (s, 3H), 3.95 (s, 3H), 3.35 (s, 3H), 3.28-3.18 (m, 1H), 3.16-3.09 (m, 1H), 2.91-2.67 (m, 2H), 2.63 (s, 3H), 2.41-2.30 (m, 2H), 2.17-1.58 (m, 18H). TLR9 IC ₅₀ (nM) = 11
356	Analytical LC/MS (Method 6): Purity: 93.4%; Observed Mass: 540.3. ¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.89 (s, 1H), 8.47 (s, 1H), 7.47 (s, 1H), 7.28 (s, 1H), 7.06 (s, 1H), 4.16 (s, 3H), 3.95 (s, 3H), 3.30 (s, 4H), 3.13-3.07 (m, 1H), 2.74-2.62 (m, 1H), 2.63 (s, 3H), 2.61-2.48 (m, 1H), 2.22-1.60 (m, 20H). TLR9 IC ₅₀ (nM) = 41
357	Analytical LC/MS (Method 6): Purity: 97.4 %; Observed Mass: 528.3; Retention Time: 0.564 min. ¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.89 (s, 1H), 8.49 (s, 1H), 7.47 (s, 1H), 7.28 (s, 1H), 7.07 (s, 1H), 4.16 (s, 3H), 3.95 (s, 3H), 3.63-3.58 (m, 2H), 3.22-3.15 (m, 2H), 3.06-2.95 (m, 1H), 2.80-2.65 (m, 2H), 2.63 (s, 3H), 2.34-2.23 (m, 2H), 2.02-1.89 (m, 4H), 1.90-1.77 (m, 4H), 1.75-1.57 (m, 4H), 1.14 (d, J = 6.0 Hz, 6H). TLR9 IC ₅₀ (nM) = 32
358	Analytical LC/MS (Method 6): Purity: 98.0%; Observed Mass: 540.3; Retention Time: 0.579 min. ¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.89 (s, 1H), 8.47 (s, 1H), 7.47 (s, 1H), 7.28 (s, 1H), 7.06 (s, 1H), 4.16 (s, 3H), 3.94 (s, 3H), 3.58-3.52 (m, 2H), 3.17-3.09 (m, 2H), 2.79-2.65 (m, 2H), 2.63 (s, 3H), 2.42-2.28 (m, 4H), 2.05-1.61 (m, 12H), 1.00-0.88 (m, 1H), 0.60-0.49 (m, 2H), 0.22-0.14 (m, 2H). TLR9 IC ₅₀ (nM) = 8.1
359	Analytical LC/MS (Method 6): Purity: 98.9 %; Observed Mass: 528.2; Retention Time: 0.618 min. ¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 9.16 (s, 1H), 8.44 (s, 1H), 7.85 (s, 1H), 7.32 (s, 1H), 7.02 (s, 1H), 4.21 (s, 3H), 3.39-3.32 (m, 2H), 3.21-3.12 (m, 2H), 2.70-2.59 (m, 5H), 2.33-2.21 (m, 4H), 2.03-1.57 (m, 13H), 0.96 (d, J = 6.6 Hz, 6H). TLR9 IC ₅₀ (nM) = 76

360	Analytical LC/MS (Method 6): Purity: 95.1 %; Observed Mass: 512.2; Retention Time: 2.432 min. ¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 9.03 (d, J = 1.4 Hz, 1H), 8.33 (s, 1H), 7.73 (d, J = 1.4 Hz, 1H), 7.19 (s, 1H), 6.89 (s, 1H), 4.09 (s, 3H), 3.31 (d, J = 4.6 Hz, 2H), 3.03 (d, J = 11.5 Hz, 2H), 2.65-2.62 (m, 1H), 2.55-2.51 (m, 1H), 2.49 (s, 3H), 2.24-2.18 (m, 2H), 1.98-1.93 (m, 3H), 1.82-1.54 (m, 10H), 0.42-0.36 (m, 4H). TLR9 IC ₅₀ (nM) = 9.7
361	Analytical LC/MS (Method 6): Purity: 91.9 %; Observed Mass: 526.2; Retention Time: 0.561 min. ¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 9.02 (d, J = 1.5 Hz, 1H), 8.32 (s, 1H), 7.72 (d, J = 1.6 Hz, 1H), 7.19 (s, 1H), 6.89 (s, 1H), 4.11 (s, 3H), 3.21-3.20 (m, 2H), 3.17-3.11 (m, 1H), 3.00 (d, J = 11.3 Hz, 2H), 2.66-2.61 (m, 1H), 2.58 (s, 3H), 2.51-2.48 (m, 1H), 2.21 (dd, J = 12.9, 10.1 Hz, 2H), 2.01-1.95 (m, 2H), 1.88-1.52 (m, 16H). TLR9 IC ₅₀ (nM) = 21
362	Analytical LC/MS (Method 6): Purity: 95.9 %; Observed Mass: 514.2; Retention Time: 0.593 min. ¹ H NMR (300 MHz, Methanol- <i>d</i> ₄) δ 9.15 (s, 1H), 8.45 (s, 1H), 7.87 (s, 1H), 7.33 (s, 1H), 7.02 (s, 1H), 4.21 (s, 3H), 3.66-3.60 (m, 2H), 3.23-3.14 (m, 2H), 3.11-2.94 (m, 1H), 2.82-2.67 (m, 1H), 2.64 (s, 4H), 2.35-2.21 (m, 2H), 2.08-1.78 (m, 8H), 1.76-1.56 (m, 4H), 1.16 (d, J = 6.3 Hz, 6H). TLR9 IC ₅₀ (nM) = 150

EXAMPLE 363

1,4-dimethyl-6-(4-(1-methylpiperidin-4-yl)phenyl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole



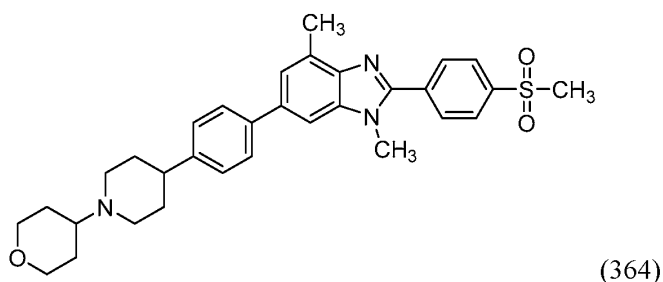
5

A mixture of Intermediate 22A (40 mg, 0.11 mmol), 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine (40 mg, 0.13 mmol), XPhos Pd G3 (8.9 mg, 11 μmol), and potassium phosphate tribasic (0.19 mL, 0.37 mmol) in 1,4-

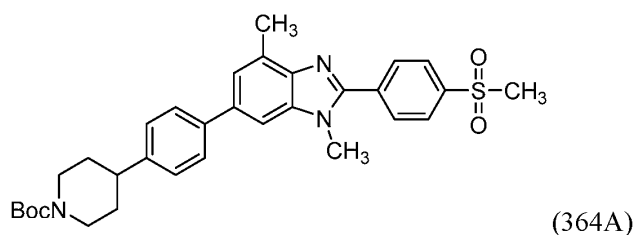
dioxane (2 mL) was degassed and heated in a closed vial at 95 °C for 10 h. Upon cooling to room temperature, the mixture was diluted with MeOH, filtered, and the filtrate was purified by preparative HPLC (Prep Method 4). The obtained product was basified with 1.5 M K₃PO₄ solution, and extracted with dichloromethane (4 x 35 mL). The combined
 5 extract was dried over anhydrous Na₂SO₄. Removal of the solvent under vacuum provided the title product (26 mg, 0.053 mmol, 50 % yield) as a white solid. LCMS (M+H)⁺ = 474.2. ¹H NMR (500 MHz, chloroform-d) δ 8.14 (d, *J*=8.6 Hz, 2H), 8.04 (d, *J*=8.6 Hz, 2H), 7.65 (d, *J*=8.3 Hz, 2H), 7.44 (d, *J*=0.8 Hz, 1H), 7.41 (dd, *J*=1.5, 0.8 Hz, 1H), 7.37 (d, *J*=8.2 Hz, 2H), 3.94 (s, 3H), 3.20-3.10 (m, 2H), 3.13 (s, 3H), 2.78 (s, 3H),
 10 2.68-2.55 (m, 1H), 2.46 (s, 3H), 2.24 (br s, 2H), 2.06-1.93 (m, 4H). TLR9 IC₅₀ = 140 nM.

EXAMPLE 364

1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(4-(1-(tetrahydro-2H-pyran-4-yl)piperidin-
 15 4-yl)phenyl)-1H-benzo[d]imidazole



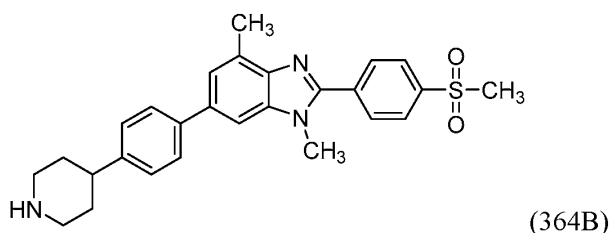
Step A. Intermediate 364A. Preparation of tert-butyl 4-(4-(1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)phenyl)piperidine-1-carboxylate



20 A mixture of Intermediate 22A (400 mg, 1.1 mmol), tert-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine-1-carboxylate (530 mg, 1.4 mmol), XPhos Pd G3 (89 mg, 0.11 mmol), and potassium phosphate tribasic (1.9 mL, 3.7

mmol) in 1,4-dioxane (20 mL) was degassed and heated in a closed vial at 95 °C for 10 h. Upon cooling to room temperature, the mixture was diluted with ethyl acetate (30 mL) and filtered through Celite. The filtrate was further diluted with ethyl acetate (120 mL), washed with brine (25 mL), and dried over anhydrous MgSO_4 and concentrated. The crude product was purified by flash column chromatography (80 g silica gel, solid loading, 45-95% ethyl acetate/hexane). Fractions corresponding to product were combined, concentrated and dried in vacuo to afford the title compound (520 mg, 0.93 mmol, 88 % yield) as a yellow solid. LCMS $(\text{M}+\text{H})^+ = 560.1$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.20-8.15 (m, 2H), 8.15-8.10 (m, 2H), 7.75 (d, $J=1.0$ Hz, 1H), 7.71 (d, $J=8.2$ Hz, 2H), 7.41 (s, 1H), 7.36 (d, $J=8.4$ Hz, 2H), 4.18-4.06 (m, 2H), 3.98 (s, 3H), 3.33 (s, 3H), 2.92-2.69 (m, 3H), 2.65 (s, 3H), 1.81 (br d, $J=12.7$ Hz, 2H), 1.55 (qd, $J=12.6$, 4.0 Hz, 2H), 1.44 (s, 9H).

Step B. Intermediate 364B. Preparation of 1,4-Dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(4-(piperidin-4-yl)phenyl)-1H-benzo[d]imidazole



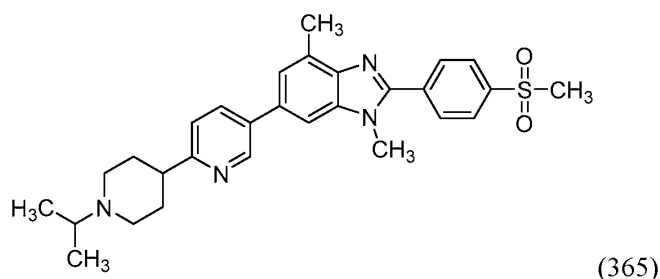
To a solution of Intermediate 364A (520 mg, 0.92 mmol) in dichloromethane (15 mL) at 0 °C was added TFA (15 mL, 200 mmol) over 1 min. The mixture was stirred at 0 °C for 1 h and then concentrated under vacuum to dryness. To the residue was added 1.5 M K_3PO_4 solution (10 mL) and the mixture was extracted with 5% MeOH/DCM (4 x 40 mL). The combined extract was dried over anhydrous Na_2SO_4 . Removal of the solvent under vacuum provided the title compound (420 mg, 0.92 mmol, 100 % yield) as a beige solid. LCMS $(\text{M}+\text{H})^+ = 460.1$. ^1H NMR (500 MHz, DMSO- d_6) δ 8.20-8.17 (m, 2H), 8.15-8.12 (m, 2H), 7.80-7.74 (m, 3H), 7.42 (s, 1H), 7.35 (d, $J=8.2$ Hz, 2H), 3.99 (s, 3H), 3.42 (br d, $J=11.8$ Hz, 2H), 3.33 (s, 3H), 3.05 (q, $J=11.8$ Hz, 2H), 2.92 (tt, $J=12.1$, 3.4 Hz, 1H), 2.65 (s, 3H), 2.05-1.97 (m, 2H), 1.90-1.79 (m, 2H).

Step C. Example 364

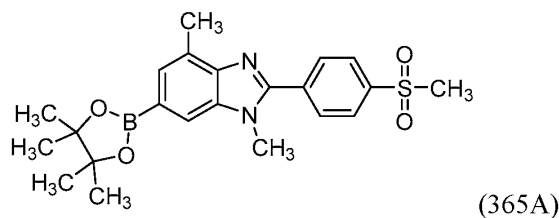
To a solution of Intermediate 364B (45 mg, 0.098 mmol), tetrahydro-4H-pyran-4-one (39 mg, 0.39 mmol), magnesium sulfate (240 mg, 2.0 mmol), and acetic acid (0.056 mL, 0.98 mmol) in acetonitrile (2 mL) at room temperature was added sodium triacetoxyborohydride (93 mg, 0.44 mmol) in one portion. The mixture was stirred at room temperature for 48 h. The heterogeneous mixture was diluted with ethyl acetate (5 mL) and filtered through Celite. The filtrate was concentrated under vacuum to dryness. The crude product was purified by preparative HPLC (Prep Method 4). The obtained product was basified with 1.5 M K_3PO_4 solution, and extracted with dichloromethane (4 x 35 mL). The combined extract was dried over anhydrous Na_2SO_4 . Removal of the solvent under vacuum provided the title compound (15 mg, 0.026 mmol, 27 % yield) as a white solid. LCMS $(M+H)^+ = 544.1$. ^1H NMR (500 MHz, $DMSO-d_6$) δ 8.20-8.16 (m, 2H), 8.15-8.11 (m, 2H), 7.77-7.69 (m, 3H), 7.42 (s, 1H), 7.36 (d, $J=8.2$ Hz, 2H), 3.98 (s, 3H), 3.97-3.88 (m, 2H), 3.33 (s, 3H), 3.14-2.94 (m, 2H), 2.65 (s, 3H), 2.34-2.15 (m, 1H), 1.97-1.44 (m, 8H). TLR9 $IC_{50} = 310$ nM.

EXAMPLE 365

6-(6-(1-isopropylpiperidin-4-yl)pyridin-3-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole



Step A. Intermediate 356A. Preparation of 1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazole



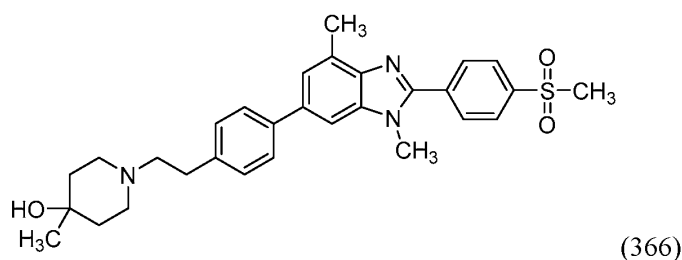
A mixture of Intermediate 22A (200 mg, 0.53 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (210 mg, 0.84 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (43 mg, 0.053 mmol), and potassium acetate (160 mg, 1.6 mmol) in 1,4-dioxane (8 mL) was heated in a pressure reaction vessel at 100 °C for 15 h. The mixture was then cooled, diluted with ethyl acetate (50 mL) and filtered through Celite. The filtrate was concentrated under vacuum, and the residue was purified by flash column chromatography (40 g silica gel, solid loading, 50-90% ethyl acetate/hexane) to provide the title intermediate (170 mg, 0.39 mmol, 75 % yield), as a white solid. LCMS (M+H)⁺ = 426.8. ¹H NMR (400 MHz, chloroform-d) δ 8.17-8.11 (m, 2H), 8.07-8.00 (m, 2H), 7.79 (s, 1H), 7.65-7.61 (m, 1H), 3.93 (s, 3H), 3.13 (s, 3H), 2.73 (s, 3H), 1.42 (s, 12H).

Step B. Example 365

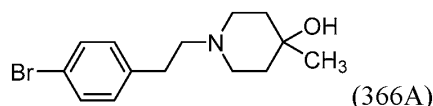
A mixture of Intermediate 365A (57 mg, 0.13 mmol), 5-bromo-2-(1-isopropylpiperidin-4-yl)pyridine (30 mg, 0.11 mmol), XPhos Pd G3 (9.0 mg, 11 μmol), and potassium phosphate tribasic (0.19 mL, 0.37 mmol) in 1,4-dioxane (3 mL) was degassed and heated in a closed vial at 95 °C for 7 h. Upon cooling to room temperature, the residue was dissolved in MeOH and purified by preparative HPLC (Prep Method 4). The obtained residue was basified with 1.5 M K₃PO₄ solution, and extracted with dichloromethane (4 x 35 mL). The combined extract was dried over anhydrous Na₂SO₄. Removal of the solvent under vacuum provided the title compound (25 mg, 0.047 mmol, 44 % yield), as a white solid. LCMS (M+H)⁺ = 503.1. ¹H NMR (500 MHz, chloroform-d) δ 8.85 (d, *J*=1.8 Hz, 1H), 8.15 (d, *J*=8.6 Hz, 2H), 8.04 (d, *J*=8.6 Hz, 2H), 7.93 (dd, *J*=8.2, 2.4 Hz, 1H), 7.43 (d, *J*=0.8 Hz, 1H), 7.38 (s, 1H), 7.34 (d, *J*=8.0 Hz, 1H), 3.95 (s, 3H), 3.24-3.09 (m, 2H), 3.14 (s, 3H), 2.99-2.77 (m, 2H), 2.79 (s, 3H), 2.43 (br s, 2H), 2.19-1.95 (m, 4H), 1.18 (br d, *J*=5.7 Hz, 6H). TLR9 IC₅₀ = 300 nM.

EXAMPLE 366

1-(4-(1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)phenethyl)-4-methylpiperidin-4-ol

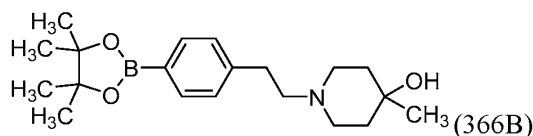


Step A. Intermediate 366A. Preparation of 1-(4-bromophenethyl)-4-methylpiperidin-4-ol



To a solution of 2-(4-bromophenyl)acetaldehyde (380 mg, 1.9 mmol), 4-methylpiperidin-4-ol (650 mg, 5.7 mmol), magnesium sulfate (4500 mg, 38 mmol), and acetic acid (1.1 mL, 19 mmol) in DMF (8 mL) at room temperature was added sodium triacetoxyborohydride (1600 mg, 7.5 mmol) in one portion. The mixture was stirred at room temperature for 20 h. The heterogeneous mixture was diluted with ethyl acetate (10 mL) and filtered through Celite. The filtrate was concentrated under vacuum to dryness. The residue was dissolved in ethyl acetate (120 mL), washed with saturated NaHCO₃ solution (2 x 20 mL), and dried over anhydrous MgSO₄. The crude residue was purified by flash column chromatography (40 g silica gel, 0-8% methanol/dichloromethane). Fractions corresponding to product were combined, concentrated and the product was dried in vacuo to afford the title intermediate (200 mg, 0.68 mmol, 36 % yield) as a white solid. LCMS (M+H)⁺ = 297.9. ¹H NMR (400 MHz, CHLOROFORM-d) δ 7.47-7.29 (m, 2H), 7.16-6.96 (m, 2H), 2.81-2.72 (m, 2H), 2.71-2.54 (m, 4H), 2.44 (td, J=11.0, 2.7 Hz, 2H), 1.78-1.58 (m, 4H), 1.26 (s, 3H).

Step B. Intermediate 366B. Preparation of 4-methyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-
20 dioxaborolan-2-yl)phenethyl)piperidin-4-ol



A mixture of Intermediate 366A (0.20 g, 0.67 mmol), 4,4',4',5',5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.27 g, 1.1 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct

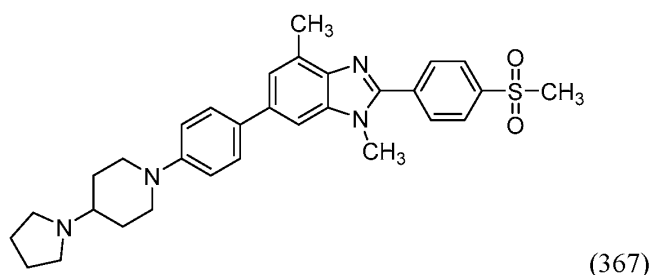
(0.055 g, 0.067 mmol), and potassium acetate (0.20 g, 2.0 mmol) in 1,4-dioxane (6 mL) was heated in a pressure reaction vessel at 100 °C for 16 h. Upon cooling to room temperature, the mixture was diluted with ethyl acetate (10 mL) and filtered through Celite. The filtrate was further diluted with ethyl acetate (60 mL), washed with brine (15 mL), and dried over anhydrous MgSO₄. The crude residue was purified by flash column chromatography (40 g silica gel, 0-10% methanol/dichloromethane). The fractions corresponding to product were combined, concentrated and dried in vacuo to afford the title intermediate (52 mg, 0.15 mmol, 23 % yield) as a beige solid. LCMS (M+H)⁺ = 346.1. ¹H NMR (500 MHz, chloroform-d) δ 7.76 (d, *J*=7.9 Hz, 2H), 7.24 (d, *J*=7.9 Hz, 2H), 2.98-2.87 (m, 2H), 2.85-2.69 (m, 4H), 2.57 (br s, 2H), 1.83 (br s, 2H), 1.66 (br d, *J*=13.2 Hz, 2H), 1.36 (s, 12H), 1.30 (s, 3H).

Step C. Example 366

A mixture of Intermediate 22A (45 mg, 0.12 mmol), Intermediate 366B (51 mg, 0.15 mmol), XPhos Pd G3 (10 mg, 0.012 mmol), and potassium phosphate tribasic (0.21 mL, 0.42 mmol) in 1,4-dioxane (2 mL) was degassed and heated in a closed vial at 95 °C for 10 h. Upon cooling to room temperature, the mixture was diluted with MeOH, filtered, and the filtrate was purified by preparative HPLC (Prep Method 4). The obtained residue was basified with 1.5 M K₃PO₄ solution, and extracted with dichloromethane (4 x 35 mL). The combined extract was dried over anhydrous Na₂SO₄. Removal of the solvent under vacuum provided the title compound (25 mg, 0.048 mmol, 41 % yield) as a white solid. LCMS (M+H)⁺ = 518.1. ¹H NMR (500 MHz, DMSO-d₆) δ 8.20-8.16 (m, 2H), 8.15-8.11 (m, 2H), 7.78-7.70 (m, 3H), 7.43 (s, 1H), 7.37 (br d, *J*=7.1 Hz, 2H), 3.99 (s, 3H), 3.33 (s, 2H), 3.45-2.68 (m, 8H), 2.65 (s, 3H), 1.86-1.41 (m, 4H), 1.17 (br s, 3H). TLR9 IC₅₀ = 450 nM.

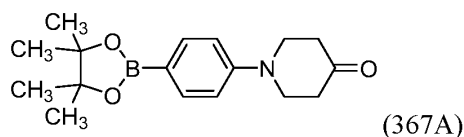
EXAMPLE 367

1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(4-(4-(pyrrolidin-1-yl)piperidin-1-yl)phenyl)-1H-benzo[d]imidazole



(367)

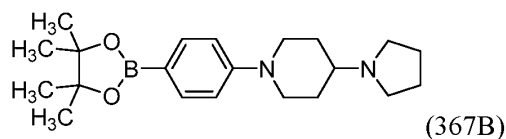
Step A. Intermediate 367A. Preparation of 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-one



(367A)

5 A mixture of 1-(4-bromophenyl)piperidin-4-one (1.0 g, 3.9 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.6 g, 6.3 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (0.32 g, 0.39 mmol), and potassium acetate (1.2 g, 12 mmol) in 1,4-dioxane (25 mL) in a pressure reaction vial was heated at 100 °C for 8 h. The mixture then cooled, diluted with ethyl acetate (50 mL) and filtered through Celite. The filtrate
10 was concentrated under vacuum, and the residue was purified by flash column chromatography (120 g silica gel, solid loading, 10-50% ethyl acetate/hexane). Fractions corresponding to product were combined, concentrated and dried in vacuo to provide the title intermediate (0.54 g, 1.8 mmol, 45 % yield) as a white solid. LCMS (M+H)⁺ = 302.0. ¹H NMR (400 MHz, chloroform-d) δ 7.77 (d, *J*=8.8 Hz, 2H), 6.96 (d, *J*=8.8 Hz,
15 2H), 3.72 (t, *J*=6.1 Hz, 4H), 2.56 (t, *J*=6.1 Hz, 4H), 1.36 (s, 12H).

Step B. Intermediate 367B. Preparation of 4-(pyrrolidin-1-yl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine



(367B)

20 To a solution of Intermediate 367A (200 mg, 0.664 mmol), pyrrolidine (0.17 mL, 2.0 mmol), magnesium sulfate (1600 mg, 13 mmol), and acetic acid (0.38 mL, 6.6 mmol) in DMF (1 mL) was added sodium triacetoxyborohydride (560 mg, 2.7 mmol) in one

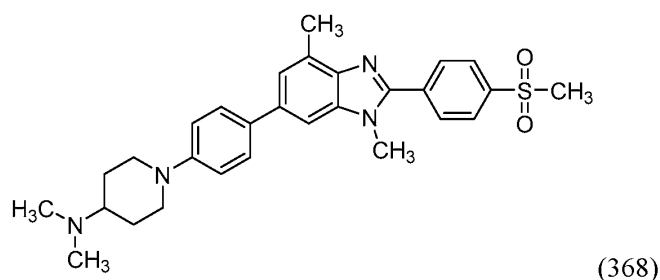
portion. The mixture was stirred at room temperature for 24 h. The heterogeneous mixture was diluted with ethyl acetate (15 mL) and filtered through Celite. The filtrate was concentrated under vacuum to dryness. To the residue was added 1.5 M K₃PO₄ solution (10 mL) and the mixture was extracted with dichloromethane (4 x 40 mL). The combined extract was dried over anhydrous Na₂SO₄ and concentrated. The crude residue was purified by flash column chromatography (40 g silica gel, 5-18% MeOH/CH₂Cl₂). The fractions corresponding to product were combined, concentrated and dried in vacuo to provide the title intermediate (40 mg, 0.11 mmol, 17 % yield) as a white solid. LCMS (M+H)⁺ = 357.1. ¹H NMR (500 MHz, chloroform-d) δ 7.70 (d, *J*=8.6 Hz, 2H), 6.91 (d, *J*=8.7 Hz, 2H), 3.82 (br d, *J*=12.9 Hz, 2H), 2.82 (td, *J*=12.3, 2.4 Hz, 2H), 2.65 (br s, 4H), 2.22 (br s, 1H), 2.06-1.96 (m, 2H), 1.83 (br s, 4H), 1.73-1.66 (m, 2H), 1.35 (s, 12H).

Step C. Example 367

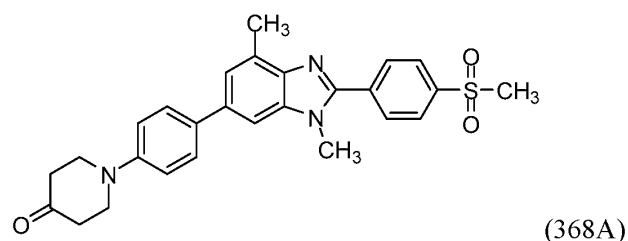
A mixture of Intermediate 22A (34 mg, 0.090 mmol), Intermediate 367B (38 mg, 0.11 mmol), XPhos Pd G3) (7.6 mg, 9.0 μmol), and potassium phosphate tribasic (0.16 mL, 0.31 mmol) in 1,4-dioxane (2 mL) was degassed and heated in a closed vial at 95 °C for 7 h. Upon cooling to room temperature, the mixture was diluted with MeOH, filtered, and the filtrate was purified by preparative HPLC (Prep Method 4). The obtained residue was basified with 1.5 M K₃PO₄ solution, and extracted with dichloromethane (4 x 35 mL). The combined extract was dried over anhydrous Na₂SO₄. Removal of the solvent under vacuum provided the title compound (5.0 mg, 9.2 μmol, 10 % yield) as a pale yellow solid. LCMS (M+H)⁺ = 529.3. ¹H NMR (500 MHz, chloroform-d) δ 8.14 (d, *J*=8.6 Hz, 2H), 8.07-8.00 (m, 2H), 7.60 (d, *J*=8.7 Hz, 2H), 7.42-7.37 (m, 2H), 7.05 (d, *J*=8.9 Hz, 2H), 3.93 (s, 3H), 3.82 (br d, *J*=12.6 Hz, 2H), 3.13 (s, 3H), 2.90-2.72 (m, 8H), 2.10 (br d, *J*=11.7 Hz, 2H), 1.95-1.59 (m, 8H). TLR9 IC₅₀ = 510 nM.

EXAMPLE 368

1-(4-(1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)phenyl)-N,N-dimethylpiperidin-4-amine



Step A. Intermediate 368A. Preparation of 1-(4-(1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)phenyl)piperidin-4-one



5 A mixture of Intermediate 22A (140 mg, 0.36 mmol), 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-one (130 mg, 0.43 mmol), XPhos Pd G3 (30 mg, 0.036 mmol), and potassium phosphate tribasic (0.62 mL, 1.3 mmol) in 1,4-dioxane (5 mL) was degassed and heated in a closed vial at 85 °C for 16 h. Upon cooling to room temperature, the mixture was diluted with ethyl acetate (60 mL), washed with brine (15

10 mL), dried over anhydrous MgSO_4 and concentrated. The crude residue was purified by flash column chromatography (40 g silica gel, solid loading, 0-5% ethyl acetate). The fractions corresponding to product were combined, concentrated and dried in vacuo to afford the title intermediate (98 mg, 0.21 mmol, 58 % yield) as a pale yellow solid.

LCMS ($\text{M}+\text{H}^+$) = 474.2. ^1H NMR (500 MHz, chloroform- d) δ 8.17-8.11 (m, 2H), 8.06-8.01 (m, 2H), 7.68-7.62 (m, 2H), 7.41 (s, 1H), 7.40 (s, 1H), 7.11 (d, $J=8.7$ Hz, 2H), 3.94

15 (s, 3H), 3.73-3.70 (m, 4H), 3.13 (s, 3H), 2.78 (s, 3H), 2.63 (t, $J=6.0$ Hz, 4H).

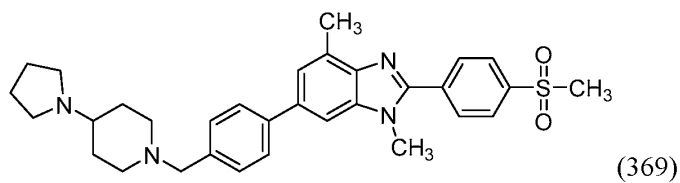
Step B. Example 368

20 To a solution of Intermediate 368A (45 mg, 0.095 mmol), dimethylamine in THF (0.17 mL, 0.33 mmol), magnesium sulfate (230 mg, 1.9 mmol), and acetic acid (0.054 mL, 0.95 mmol) in DMF (1 mL) was added sodium triacetoxyborohydride (81 mg, 0.38 mmol) in one portion. The mixture was stirred at room temperature for 24 h. The

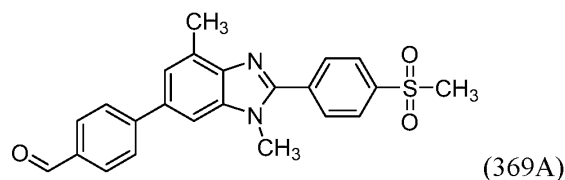
heterogeneous mixture was diluted with ethyl acetate (5 mL) and filtered through Celite. The filtrate was concentrated under vacuum to dryness. The residue was purified by preparative HPLC (Method 4). The obtained residue was basified with 1 N NaOH solution, and extracted with dichloromethane (4 x 35 mL). The combined extract was dried over anhydrous Na₂SO₄. Removal of the solvent under vacuum provided the title compound (16 mg, 0.031 mmol, 33 % yield) as a pale yellow solid. LCMS (M+H)⁺ = 503.3. ¹H NMR (400 MHz, CHLOROFORM-d) δ 8.17-8.11 (m, 2H), 8.07-8.01 (m, 2H), 7.64-7.58 (m, 2H), 7.42-7.38 (m, 2H), 7.06 (d, *J*=8.8 Hz, 2H), 3.93 (s, 3H), 3.85 (br d, *J*=12.5 Hz, 2H), 3.13 (s, 3H), 2.88-2.76 (m, 2H), 2.77 (s, 3H), 2.50 -2.41 (m, 1H), 2.42 (s, 6H), 2.03 (br d, *J*=12.1 Hz, 2H), 1.80-1.69 (m, 2H). TLR9 IC₅₀ = 410 nM.

EXAMPLE 369

1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-((4-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)phenyl)-1H-benzo[d]imidazole



Step A. Intermediate 369A. Preparation of 4-(1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)benzaldehyde



A mixture of Intermediate 22A (400 mg, 1.1 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (310 mg, 1.3 mmol), XPhos Pd G3 (89 mg, 0.11 mmol), and potassium phosphate tribasic (1.9 mL, 3.7 mmol) in 1,4-dioxane (15 mL) was degassed and heated in a closed vial at 95 °C for 7 h. Upon cooling to room temperature, the mixture was diluted with ethyl acetate (30 mL) and filtered through Celite. The filtrate was further diluted with ethyl acetate (120 mL), washed with brine (25 mL), and dried over anhydrous MgSO₄ and concentrated. The crude residue was purified by flash column chromatography (80 g silica gel, solid loading, 45-95% ethyl acetate/hexane).

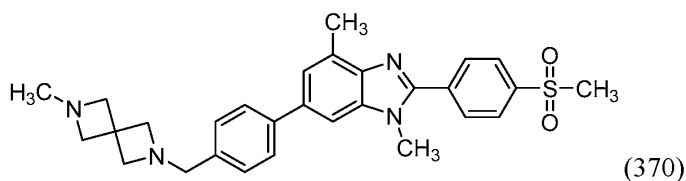
Fractions corresponding to product were combined, concentrated and dried in vacuo to afford the title intermediate (360 mg, 0.89 mmol, 84 % yield) as a yellow solid. LCMS (M+H)⁺ = 405.0. ¹H NMR (500 MHz, chloroform-d) δ 10.11 (s, 1H), 8.18-8.13 (m, 2H), 8.07-8.03 (m, 2H), 8.03-7.99 (m, 2H), 7.87 (d, *J*=8.3 Hz, 2H), 7.52 (d, *J*=1.0 Hz, 1H), 7.47 (s, 1H), 3.98 (s, 3H), 3.14 (s, 3H), 2.81 (s, 3H).

Step B. Example 369

To a solution of Intermediate 369A (40 mg, 0.099 mmol), 4-(pyrrolidin-1-yl) piperidine (46 mg, 0.30 mmol), magnesium sulfate (240 mg, 2.0 mmol), and acetic acid (0.057 mL, 0.99 mmol) in DMF (1 mL) was added sodium triacetoxyborohydride (84 mg, 0.396 mmol) in one portion. The mixture was stirred at room temperature for 18 h. The heterogeneous mixture was diluted with ethyl acetate (5 mL) and filtered through Celite. The filtrate was concentrated under vacuum to dryness. The residue purified by preparative HPLC (Prep Method 4). The obtained residue was basified with 1 N NaOH solution, and extracted with dichloromethane (4 x 35 mL). The combined extract was dried over anhydrous Na₂SO₄. Removal of the solvent under vacuum provided the title compound (13 mg, 0.023 mmol, 24 % yield) as a white solid. LCMS (M+H)⁺ = 543.3. ¹H NMR (500 MHz, chloroform-d) δ 8.15 (d, *J*=8.5 Hz, 2H), 8.07-8.02 (m, 2H), 7.65 (d, *J*=8.0 Hz, 2H), 7.47-7.41 (m, 4H), 3.95 (s, 3H), 3.60 (br s, 2H), 3.14 (s, 3H), 3.05 (br d, *J*=11.2 Hz, 2H), 2.79 (s, 3H), 2.18-1.54 (m, 15H). TLR9 IC₅₀ = 120 nM.

EXAMPLE 370

1,4-dimethyl-6-(4-((6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole

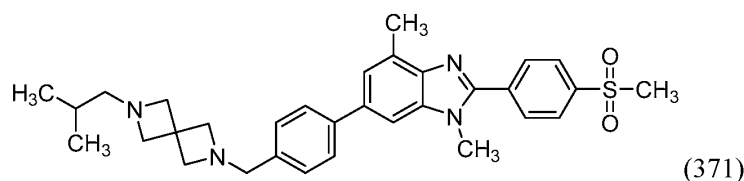


To a solution of Intermediate 369A (35 mg, 0.087 mmol), 2-methyl-2,6-diazaspiro[3.3]heptane dihydrochloride (56 mg, 0.30 mmol), triethylamine (84 μL, 0.61 mmol), magnesium sulfate (210 mg, 1.7 mmol), and acetic acid (59 μL, 1.0 mmol) in DMF (1 mL) was added sodium triacetoxyborohydride (83 mg, 0.389 mmol) in one

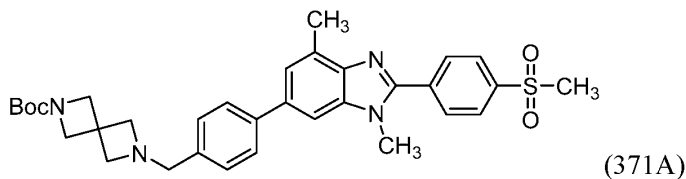
portion. The mixture was stirred at room temperature for 24 h. The heterogeneous mixture was diluted with ethyl acetate (5 mL) and filtered through Celite. The filtrate was concentrated under vacuum to dryness. The crude residue was purified by preparative HPLC (Prep Method 4). The obtained residue was basified with 1.5 M K_3PO_4 solution, and extracted with dichloromethane (4 x 35 mL). The combined extract was dried over anhydrous Na_2SO_4 . Removal of the solvent under vacuum provided the title compound (34 mg, 0.065 mmol, 75 % yield) as a white solid. LCMS $(M+H)^+ = 501.1$. ^1H NMR (400 MHz, chloroform- d) δ 8.17-8.12 (m, 2H), 8.04 (d, $J=8.6$ Hz, 2H), 7.64 (d, $J=8.2$ Hz, 2H), 7.44 (s, 1H), 7.41 (d, $J=1.4$ Hz, 1H), 7.37 (d, $J=8.2$ Hz, 2H), 3.94 (s, 3H), 3.66 (s, 2H), 3.54 (br s, 4H), 3.43 (s, 4H), 3.13 (s, 3H), 2.78 (s, 3H), 2.43 (s, 3H). TLR9 $IC_{50} = 56$ nM.

EXAMPLE 371

6-(4-((6-isobutyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole



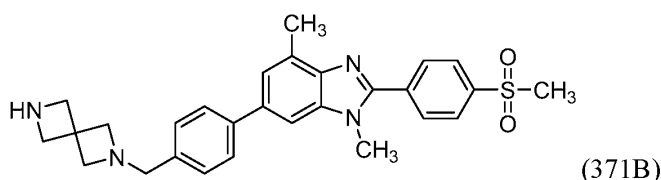
Step A. Intermediate 371A. Preparation of tert-butyl 6-(4-(1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)benzyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate



To a solution of Intermediate 369A (150 mg, 0.37 mmol), tert-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate, oxalic acid salt (370 mg, 1.3 mmol), triethylamine (0.26 mL, 1.9 mmol), magnesium sulfate (890 mg, 7.4 mmol), and acetic acid (59 μ L, 1.0 mmol) in DMF (1 mL) was added sodium triacetoxyborohydride (310 mg, 1.5 mmol) in one portion. The mixture was stirred at room temperature for 22 h. The heterogeneous mixture was diluted with ethyl acetate (15 mL) and filtered through Celite. The filtrate

was diluted with ethyl acetate (120 mL), washed with 1.5 M K₃PO₄ solution (2 x 15 mL), and dried over anhydrous Na₂SO₄. After the solvent was removed under vacuum, the residue was purified by flash column chromatography (40 g silica gel, 0-6% methanol/CH₂Cl₂) to provide the title intermediate (170 mg, 0.290 mmol, 78 % yield) as a white solid. LCMS (M+H)⁺ = 587.3. ¹H NMR (400 MHz, chloroform-d) δ 8.17-8.13 (m, 2H), 8.07-8.02 (m, 2H), 7.65 (d, J=8.2 Hz, 2H), 7.44 (s, 1H), 7.42 (s, 1H), 7.37 (d, J=8.2 Hz, 2H), 4.03 (s, 4H), 3.94 (s, 3H), 3.65 (s, 2H), 3.40 (s, 4H), 3.13 (s, 3H), 2.78 (s, 3H), 1.45 (s, 9H).

Step B. Intermediate 371B. Preparation of 6-(4-((2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole



To a solution of Intermediate 371A (170 mg, 0.28 mmol) in dichloromethane (3 mL) at 0 °C was added TFA (3 mL, 38.9 mmol) over 1 min. The mixture was stirred at 0 °C for 1 h and then concentrated under vacuum to dryness. To the residue was added 1.5 M K₃PO₄ solution (10 mL) and the mixture was extracted with 5% MeOH/DCM (4 x 40 mL). The combined extract was dried over anhydrous Na₂SO₄. Removal of the solvent under vacuum provided the title intermediate (56 mg, 0.12 mmol, 41 % yield) as a beige solid, which was used in the next step without further purification. LCMS (M+H)⁺ = 487.2.

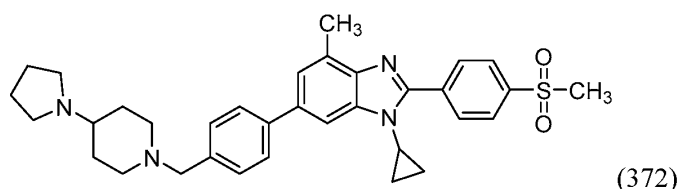
Step C. Example 371

To a solution of Intermediate 371B (26 mg, 0.053 mmol), isobutyraldehyde (15 mg, 0.21 mmol), magnesium sulfate (130 mg, 1.1 mmol), and acetic acid (0.031 mL, 0.53 mmol) in acetonitrile (2 mL) was added sodium triacetoxyborohydride (51 mg, 0.24 mmol) in one portion. The mixture was stirred at room temperature for 36 h. The heterogeneous mixture was diluted with ethyl acetate (5 mL) and filtered through Celite. The filtrate was concentrated under vacuum to dryness. The residue was purified by preparative HPLC (Prep Method 1). The obtained residue was basified with 1 N NaOH

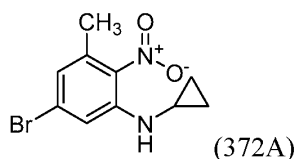
solution, and extracted with dichloromethane (4 x 35 mL). The combined extract was dried over anhydrous Na₂SO₄. Removal of the solvent under vacuum provided the title compound (15 mg, 0.028 mmol, 52 % yield) as a white solid. LCMS (M+H)⁺ = 543.2. ¹H NMR (500 MHz, chloroform-d) δ 8.15 (d, *J*=8.5 Hz, 2H), 8.04 (d, *J*=8.3 Hz, 2H), 7.64 (d, *J*=8.0 Hz, 2H), 7.44 (s, 1H), 7.41 (s, 1H), 7.38 (d, *J*=8.0 Hz, 2H), 3.95 (s, 3H), 3.66 (s, 2H), 3.52-3.30 (m, 8H), 3.14 (s, 3H), 2.78 (s, 3H), 2.29 (br s, 2H), 1.76-1.58 (m, 1H), 0.91 (d, *J*=6.7 Hz, 6H). TLR9 IC₅₀ = 55 nM.

EXAMPLE 372

10 1-cyclopropyl-4-methyl-2-(4-(methylsulfonyl)phenyl)-6-(4-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)phenyl)-1H-benzo[d]imidazole



Step A. Intermediate 371A. Preparation of 5-bromo-N-cyclopropyl-3-methyl-2-nitro-aniline

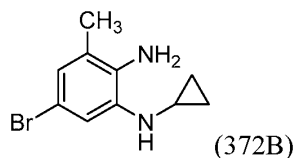


15 To a mixture of 5-bromo-1-fluoro-3-methyl-2-nitro-benzene (5.0 g, 21 mmol) and cyclopropanamine (1.2 g, 21 mmol) in DMSO (40 mL) was added N,N-diisopropylethylamine (5.7 mL, 65 mmol). The resulting mixture was stirred at 90 °C overnight. Upon cooling to room temperature, the mixture was diluted with ethyl acetate (300 mL), washed with water (3 x 100 mL), and dried over anhydrous Na₂SO₄. After the solvent was removed under vacuum, the residue was purified by flash column chromatography (1:3 ethyl acetate/petroleum ether as eluent). Fractions corresponding to product were combined concentrated and dried in vacuo to afford the title intermediate (5.5 g, 95 % yield) as a yellow solid. LCMS (M+H)⁺ = 271.1.

25

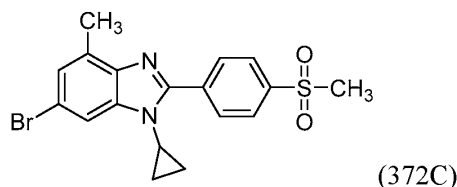
Step B. Intermediate 371B. Preparation of 5-bromo-N1-cyclopropyl-3-methyl-benzene-

1,2-diamine



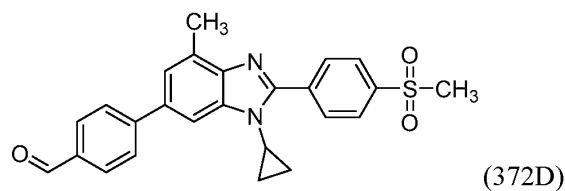
A solution of Intermediate 372A (5.0 g, 18 mmol) in ethanol (30 mL) and water (8 mL) was degassed three times with nitrogen before iron powder (11 g, 190 mmol) was added. The reaction vessel was evacuated and back-filled with nitrogen three times. The mixture was stirred at 70 °C overnight. Upon cooling to room temperature, the insoluble material was removed by filtration. The filtrate was concentrated under vacuum to afford the title intermediate (4.2 g crude) as a light yellow solid. LCMS (M+H)⁺ = 242.1.

Step C. Intermediate 371C. Preparation of 6-bromo-1-cyclopropyl-4-methyl-2-(4-methylsulfonylphenyl)benzimidazole



To a mixture of Intermediate 372B (4.2 g, 17 mmol) and 4-methylsulfonylbenzaldehyde (3.3 g, 17.91 mmol) in DMF (30 mL) and water (1 mL) was added Oxone (11 g, 18 mmol). The mixture was stirred at 90 °C overnight. Upon cooling to room temperature, the reaction mixture was diluted with ethyl acetate (300 mL), washed with water (3 x 100 mL), and dried over anhydrous Na₂SO₄. After the solvent was removed under vacuum, the residue was purified with flash column chromatography to afford the title intermediate (2.6 g, 36% yield) as a gray solid. LCMS (M+H)⁺ = 405.1. ¹H NMR (400 MHz, chloroform-*d*) δ 10.90 (s, 1H), 8.16-8.10 (m, 4H), 7.69 (d, *J* = 1.8 Hz, 1H), 7.36 (s, 1H), 3.63-3.58 (m, 1H), 3.13 (s, 3H), 2.65 (s, 3H), 1.24-1.19 (m, 2H), 0.79-0.75 (m, 2H).

Step D. Intermediate 371D. Preparation of 4-(1-cyclopropyl-4-methyl-2-(4-methylsulfonylphenyl)-1H-benzo[d]imidazol-6-yl)benzaldehyde



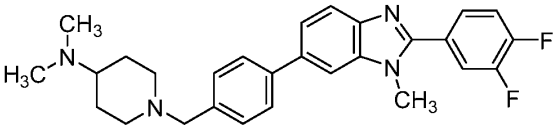
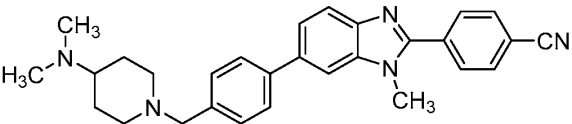
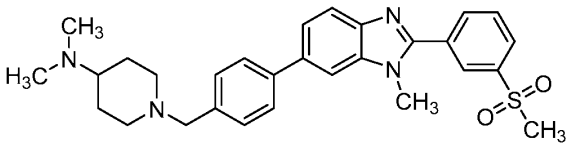
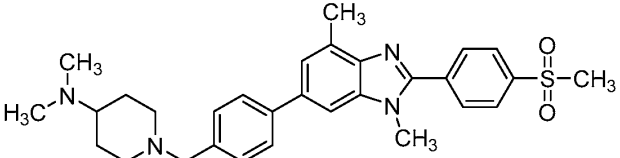
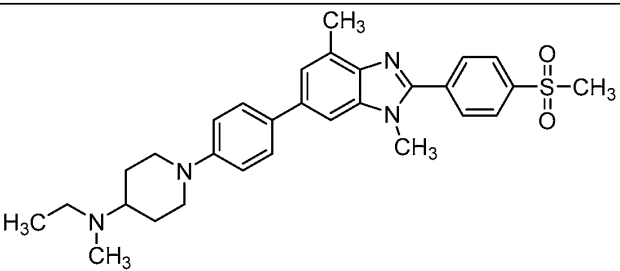
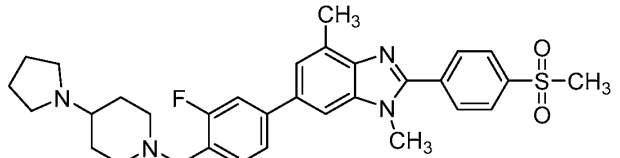
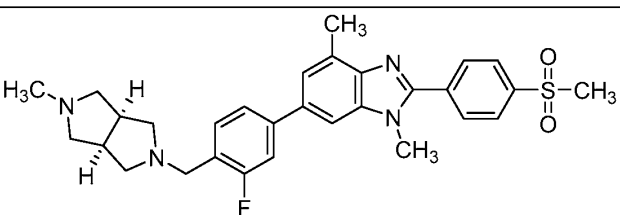
A mixture of Intermediate 372C (300 mg, 0.74 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (220 mg, 0.95 mmol), XPhos Pd G3 (63 mg, 0.074 mmol), and potassium phosphate tribasic (1.3 mL, 2.6 mmol) in 1,4-dioxane (14 mL) was degassed and heated in a closed vial at 95 °C for 8 h. Upon cooling to room temperature, the mixture was diluted with ethyl acetate (120 mL), washed with brine (20 mL), and dried over anhydrous MgSO_4 and concentrated. The crude product was purified by flash column chromatography (80 g silica gel, solid loading, 35-90% ethyl acetate/hexane). Fractions corresponding to product were combined, concentrated and dried in vacuo to afford the title intermediate (110 mg, 0.26 mmol, 35 % yield) as a yellow solid. LCMS $(\text{M}+\text{H})^+ = 431.0$.

Step E. Example 372

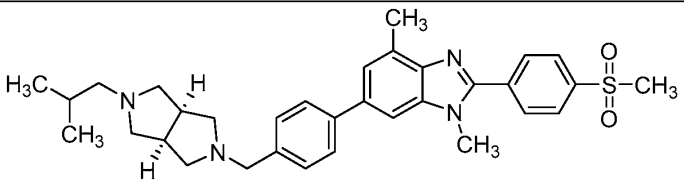
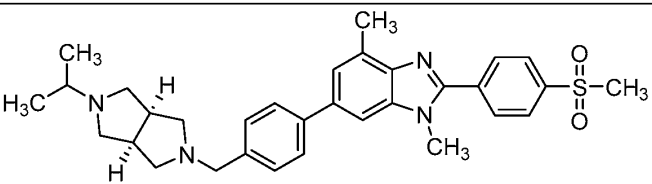
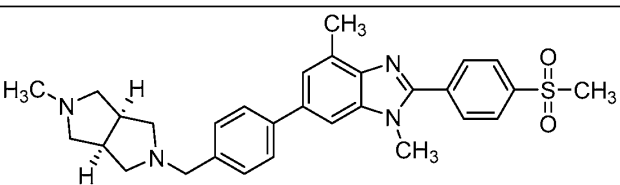
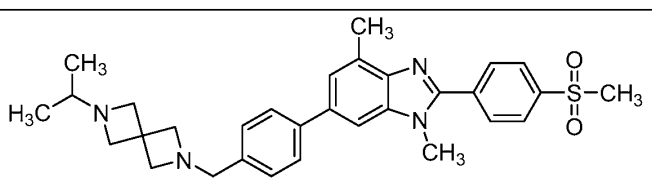
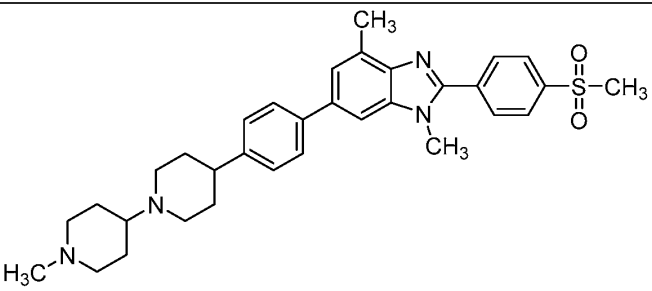
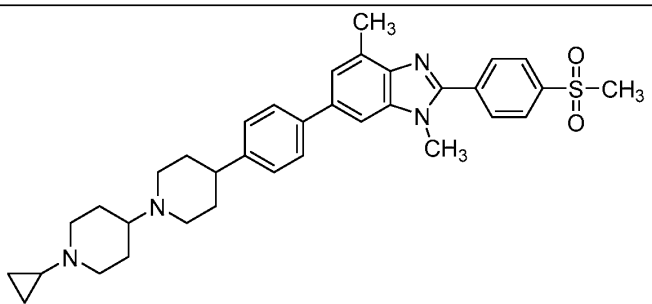
To a solution of Intermediate 372D (30 mg, 0.070 mmol), 4-(pyrrolidin-1-yl)piperidine (38 mg, 0.24 mmol), magnesium sulfate (170 mg, 1.4 mmol), and acetic acid (59 μL , 1.0 mmol) in DMF (1 mL) was added sodium triacetoxyborohydride (67 mg, 0.31 mmol) in one portion. The mixture was stirred at room temperature for 24 h. The heterogeneous mixture was diluted with ethyl acetate (5 mL) and filtered through Celite. The filtrate was concentrated under vacuum to dryness. The residue was purified by preparative HPLC (Prep Method 4). The obtained residue was basified with 1.5 M K_3PO_4 solution, and extracted with dichloromethane (4 x 35 mL). The combined extract was dried over anhydrous Na_2SO_4 . Removal of the solvent under vacuum provided the title compound (12 mg, 0.019 mmol, 27 % yield) as a white solid. LCMS $(\text{M}+\text{H})^+ = 569.1$. ^1H NMR (400 MHz, chloroform- d) δ 8.26-8.19 (m, 2H), 8.14-8.09 (m, 2H), 7.68-7.63 (m, 3H), 7.44 (br d, $J=7.8$ Hz, 2H), 7.40 (s, 1H), 3.67-3.57 (m, 3H), 3.14 (s, 3H), 3.09-2.93 (m, 4H), 2.77 (s, 3H), 2.18-1.77 (m, 13H), 1.22-1.16 (m, 2H), 0.89-0.74 (m, 2H). TLR9 $\text{IC}_{50} = 54$ nM.

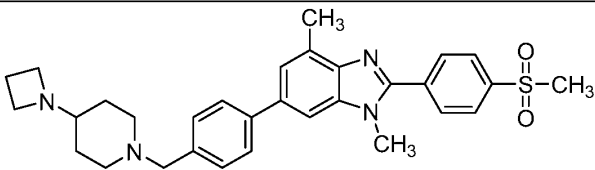
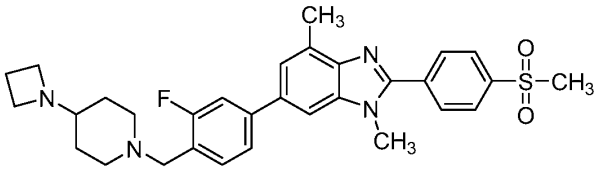
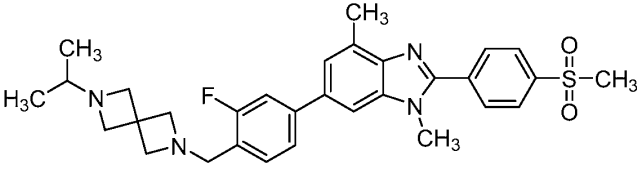
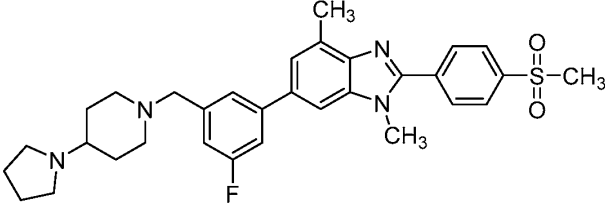
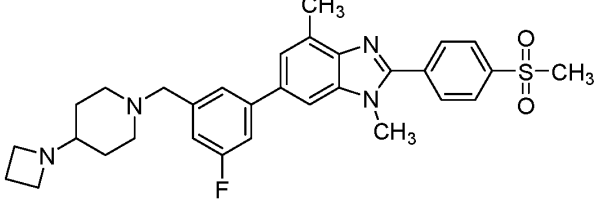
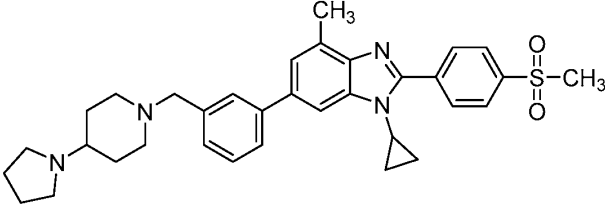
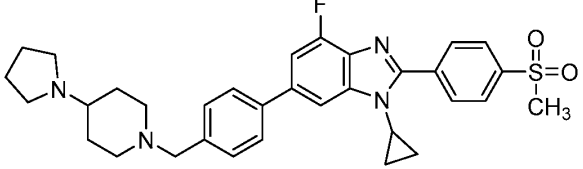
The following Examples were prepared according to the general methods described elsewhere herein using appropriate starting materials, reagents and conditions.

Ex. No.	Structure	Method
374		Ex. 373
375		Ex. 373
376		Ex. 373
377		Ex. 373
378		Ex. 373
379		Ex. 373
380		Ex. 373
381		Ex. 373

382		Ex. 373
383		Ex. 373
384		Ex. 373
385		Ex. 369
386		Ex. 368
387		Ex. 369
388		Ex. 369

389	 <chem>CN1C=NC(C2=CC=C(C=C2)S(=O)(=O)C)C3=CC=C(C=C3C4=CC=C(C=C4)F)CN5CCN(C)CC5</chem>	Ex. 369
390	 <chem>CN1C=NC(C2=CC=C(C=C2)S(=O)(=O)C)C3=CC=C(C=C3C4=CC=C(C=C4)F)CN5CCN(C)CC5</chem>	Ex. 369
391	 <chem>CN1C=NC(C2=CC=C(C=C2)S(=O)(=O)C)C3=CC=C(C=C3C4=CC=C(C=C4)F)CN5CCN(C)CC5</chem>	Ex. 369
392	 <chem>CN1C=NC(C2=CC=C(C=C2)S(=O)(=O)C)C3=CC=C(C=C3C4=CC=C(C=C4)F)CN5CCN(C)CC5</chem>	Ex. 369
393	 <chem>CN1C=NC(C2=CC=C(C=C2)S(=O)(=O)C)C3=CC=C(C=C3C4=CC=C(C=C4)F)CN5CCN(C)CC5</chem>	Ex. 369
394	 <chem>CN1C=NC(C2=CC=C(C=C2)S(=O)(=O)C)C3=CC=C(C=C3C4=CC=C(C=C4)F)CN5CCN(C)CC5</chem>	Ex. 369
395	 <chem>CN1C=NC(C2=CC=C(C=C2)S(=O)(=O)C)C3=CC=C(C=C3C4=CC=C(C=C4)F)CN5CCN(C)CC5</chem>	Ex. 369

396		Ex. 369
397		Ex. 369
398		Ex. 369
399		Ex. 369
400		Ex. 363
401		Ex. 363

402		Ex. 369
403		Ex. 369
404		Ex. 369
405		Ex. 369
406		Ex. 369
407		Ex. 372
408		Ex. 372

409		Ex. 369
410		Ex. 372
411		Ex. 372
412		Ex. 372
413		Ex. 369
414		Ex. 369
415		Ex. 115

Ex. No.	Analytical LC/MS, Preparative HPLC method, yield, and ¹ H NMR
374	Analytical LC/MS (Method 1): Purity: 98.6 %; Observed Mass: 425.20; Retention Time: 1.5 min. (Method 2): Purity: 100 %; Observed Mass: 425.20; Retention Time: 0.99 min. Prep Method 1: 23.9 mg, 27 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.13 (s, 1H), 7.95-7.90 (m, 4H), 7.85 (d, <i>J</i> = 8.5 Hz, 1H), 7.76 (br d, <i>J</i> = 7.9 Hz, 1H), 7.68-7.62 (m, 5H), 4.39 (br s, 2H), 4.01 (s, 3H), 3.08-2.98 (m, 2H), 2.77 (br s, 6H), 2.54-2.53 (m, 3H), 2.30-2.19 (m, 2H), 1.94-1.83 (m, 2H). TLR9 IC ₅₀ (nM) = 280
375	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 503.50; Retention Time: 1.06 min. (Method 2): Purity: 100 %; Observed Mass: 503.50; Retention Time: 0.74 min. Prep Method 1: 29.5 mg, 39 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.20-8.15 (m, 2H), 8.14-8.08 (m, 2H), 7.94 (s, 1H), 7.78 (d, <i>J</i> = 8.2 Hz, 1H), 7.73 (br d, <i>J</i> = 7.9 Hz, 2H), 7.60 (br d, <i>J</i> = 8.5 Hz, 1H), 7.39 (br d, <i>J</i> = 7.6 Hz, 2H), 3.98 (s, 3H), 3.30 (s, 2H), 2.85 (br d, <i>J</i> = 11.0 Hz, 2H), 2.16 (s, 6H), 2.10-2.01 (m, 1H), 1.93 (br t, <i>J</i> = 11.7 Hz, 2H), 1.87 (s, 3H), 1.71 (br d, <i>J</i> = 11.6 Hz, 2H), 1.38 (q, <i>J</i> = 10.9 Hz, 2H). TLR9 IC ₅₀ (nM) = 200
376	Analytical LC/MS (Method 1): Purity: 98 %; Observed Mass: 455.20; Retention Time: 1.52 min. (Method 2): Purity: 98 %; Observed Mass: 455.30; Retention Time: 0.97 min. Prep Method 1: 55.1 mg, 70 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.84 (s, 1H), 7.80 (d, <i>J</i> = 8.5 Hz, 2H), 7.70 (dd, <i>J</i> = 7.9, 4.3 Hz, 3H), 7.57-7.51 (m, 1H), 7.38 (br d, <i>J</i> = 7.9 Hz, 2H), 7.13 (d, <i>J</i> = 8.5 Hz, 2H), 3.90 (s, 3H), 3.84 (s, 3H), 3.68-3.56 (m, 2H), 2.86 (br d, <i>J</i> = 10.4 Hz, 2H), 2.20 (s, 6H), 2.16-2.10 (m, 1H), 1.93 (br t, <i>J</i> = 11.3 Hz, 2H), 1.73 (br d, <i>J</i> = 11.6 Hz, 2H), 1.46-1.32 (m, 2H). TLR9 IC ₅₀ (nM) = 210

377	Analytical LC/MS (Method 1): Purity: 95.3 %; Observed Mass: 443.40; Retention Time: 1.30 min. (Method 2): Purity: 95.5 %; Observed Mass: 443.50; Retention Time: 0.82 min. Prep Method 1: 34.4 mg, 43 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.90 (s, 1H), 7.76-7.69 (m, 4H), 7.68-7.61 (m, 1H), 7.58 (d, <i>J</i> = 9.2 Hz, 1H), 7.44-7.36 (m, 3H), 3.94 (s, 3H), 3.50-3.46 (m, 3H), 2.86 (br d, <i>J</i> = 11.6 Hz, 2H), 2.20 (s, 6H), 2.17-2.09 (m, 1H), 1.93 (br t, <i>J</i> = 11.4 Hz, 2H), 1.73 (br d, <i>J</i> = 12.5 Hz, 2H), 1.44-1.35 (m, 2H). TLR9 IC ₅₀ (nM) = 350
378	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 443.20; Retention Time: 1.54 min. (Method 2): Purity: 100 %; Observed Mass: 443.30; Retention Time: 0.96 min. Prep Method 1: 40.1 mg, 54 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.93 (dd, <i>J</i> = 8.5, 5.5 Hz, 2H), 7.89 (s, 1H), 7.76-7.68 (m, 3H), 7.56 (br d, <i>J</i> = 7.9 Hz, 1H), 7.46-7.36 (m, 4H), 3.93 (s, 3H), 3.47 (br s, 2H), 2.85 (br d, <i>J</i> = 10.4 Hz, 2H), 2.15 (s, 6H), 2.07-2.00 (m, 1H), 1.93 (br t, <i>J</i> = 11.1 Hz, 2H), 1.71 (br d, <i>J</i> = 12.2 Hz, 2H), 1.43-1.31 (m, 2H). TLR9 IC ₅₀ (nM) = 350
379	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 503.20; Retention Time: 1.01 min. (Method 2): Purity: 99.2 %; Observed Mass: 503.20; Retention Time: 1.32 min. Prep Method 2: 34.3 mg, 33 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.18 (d, <i>J</i> = 6.7 Hz, 1H), 8.00 (s, 1H), 7.96-7.87 (m, 3H), 7.78 (d, <i>J</i> = 8.2 Hz, 2H), 7.66-7.57 (m, 3H), 4.37 (br s, 2H), 3.62 (s, 3H), 3.57-3.49 (m, 4H), 3.41 (br s, 3H), 3.11-2.96 (m, 2H), 2.77 (br s, 6H), 2.24 (br d, <i>J</i> = 9.2 Hz, 2H), 1.98-1.81 (m, 2H). TLR9 IC ₅₀ (nM) = 98

380	Analytical LC/MS (Method 1): Purity: 97.5 %; Observed Mass: 521.20; Retention Time: 1.11 min. (Method 2): Purity: 98.3 %; Observed Mass: 521.30; Retention Time: 1.34 min. Prep Method 2: 20.2 mg, 26 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.08-7.97 (m, 6H), 7.90 (br d, <i>J</i> = 7.9 Hz, 2H), 7.83 (d, <i>J</i> = 8.5 Hz, 1H), 7.67 (br d, <i>J</i> = 8.5 Hz, 1H), 7.61 (br d, <i>J</i> = 7.9 Hz, 2H), 4.33 (br s, 2H), 3.82 (s, 3H), 3.61-3.51 (m, 1H), 3.37 (s, 3H), 3.05-2.93 (m, 1H), 2.76 (s, 7H), 2.22 (br d, <i>J</i> = 12.2 Hz, 2H), 1.98-1.81 (m, 2H). TLR9 IC ₅₀ (nM) = 174
381	Analytical LC/MS (Method 1): Purity: 96 %; Observed Mass: 461.20; Retention Time: 1.06 min. (Method 2): Purity: 97.5 %; Observed Mass: 461.30; Retention Time: 1.69 min. Prep Method 1: 12.6 mg, 11 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.94 (s, 1H), 7.76 (d, <i>J</i> = 8.5 Hz, 1H), 7.73 (br d, <i>J</i> = 7.9 Hz, 2H), 7.64-7.56 (m, 3H), 7.48 (br t, <i>J</i> = 9.2 Hz, 1H), 7.39 (br d, <i>J</i> = 8.2 Hz, 2H), 3.98 (s, 3H), 3.65-3.01 (m, 2H), 2.85 (br d, <i>J</i> = 11.3 Hz, 2H), 2.15 (s, 6H), 2.07-2.01 (m, 1H), 1.93 (br t, <i>J</i> = 11.4 Hz, 2H), 1.76-1.62 (m, 2H), 1.45-1.32 (m, 2H). TLR9 IC ₅₀ (nM) = 140
382	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 461.20; Retention Time: 1.06 min. (Method 2): Purity: 100 %; Observed Mass: 461.20; Retention Time: 1.54 min. Prep Method 2: 10.4 mg, 10 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.01-7.93 (m, 2H), 7.90 (br d, <i>J</i> = 7.9 Hz, 2H), 7.80-7.73 (m, 2H), 7.70-7.63 (m, 2H), 7.61 (br d, <i>J</i> = 7.9 Hz, 2H), 4.35 (br s, 2H), 3.96 (s, 3H), 3.83-2.83 (m, 5H), 2.77 (s, 6H), 2.23 (br d, <i>J</i> = 12.2 Hz, 2H), 1.94-1.81 (m, 2H). TLR9 IC ₅₀ (nM) = 3.2
383	Analytical LC/MS (Method 1): Purity: 95.3 %; Observed Mass: 450.20; Retention Time: 0.98 min. (Method 2): Purity: 98.7 %; Observed Mass: 450.30; Retention Time: 1.48 min. Prep Method 1: 6.4 mg, 6 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.12-8.06 (m, 4H), 8.04 (s, 1H), 7.92 (br d, <i>J</i> = 8.2 Hz, 2H), 7.83 (d, <i>J</i> = 8.2 Hz, 1H), 7.68 (br d, <i>J</i> = 8.9 Hz, 1H), 7.62 (br d, <i>J</i> = 7.9 Hz, 2H), 4.38 (br s, 2H), 4.00 (s, 3H), 3.33-2.97 (m, 5H), 2.77 (br s, 6H), 2.23 (br d, <i>J</i> = 9.5 Hz, 2H), 1.96-1.82 (m, 2H). TLR9 IC ₅₀ (nM) = 68

384	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 503.20; Retention Time: 0.87 min. (Method 2): Purity: 100 %; Observed Mass: 503.30; Retention Time: 1.31 min. Prep Method 1: 15.4 mg, 12 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.42 (s, 1H), 8.27 (br d, <i>J</i> = 7.6 Hz, 1H), 8.13 (br d, <i>J</i> = 7.9 Hz, 1H), 8.03 (s, 1H), 7.92-7.87 (m, 3H), 7.81 (d, <i>J</i> = 8.5 Hz, 1H), 7.66 (br d, <i>J</i> = 8.5 Hz, 1H), 7.60 (br d, <i>J</i> = 5.2 Hz, 2H), 4.49-4.20 (m, 2H), 4.02 (s, 3H), 3.58-3.44 (m, 2H), 3.34-3.32 (m, 4H), 3.08-2.85 (m, 2H), 2.76 (br s, 6H), 2.27-2.13 (m, 2H), 1.95-1.77 (m, 2H). TLR9 IC ₅₀ (nM) = 41
385	LCMS (M+H) ⁺ = 517.3. ¹ H NMR (500 MHz, chloroform-d) δ 8.17-8.12 (m, 2H), 8.06-8.03 (m, 2H), 7.66 (d, <i>J</i> = 8.2 Hz, 2H), 7.47-7.40 (m, 4H), 3.95 (s, 3H), 3.61 (br s, 2H), 3.14 (s, 3H), 3.07 (br d, <i>J</i> = 11.5 Hz, 2H), 2.79 (s, 3H), 2.66-2.43 (m, 7H), 2.09 (br s, 2H), 1.95 (br d, <i>J</i> = 11.1 Hz, 2H), 1.75-1.70 (m, 2H). TLR9 IC ₅₀ (nM) = 180
386	LCMS (M+H) ⁺ = 517.3. ¹ H NMR (400 MHz, chloroform-d) δ 8.17-8.10 (m, 2H), 8.07-8.00 (m, 2H), 7.62 (d, <i>J</i> = 8.8 Hz, 2H), 7.40 (s, 1H), 7.39 (d, <i>J</i> = 0.8 Hz, 1H), 7.05 (d, <i>J</i> = 8.8 Hz, 2H), 3.93 (s, 3H), 3.92-3.86 (m, 2H), 3.13 (s, 3H), 3.08-2.95 (m, 2H), 2.86 (td, <i>J</i> = 12.3, 1.9 Hz, 2H), 2.77 (s, 3H), 2.70-2.58 (m, 1H), 2.64 (s, 3H), 2.14 (br d, <i>J</i> = 9.4 Hz, 2H), 1.91 (qd, <i>J</i> = 11.9, 3.0 Hz, 2H), 1.36 (br t, <i>J</i> = 6.7 Hz, 3H). TLR9 IC ₅₀ (nM) = 270
387	LCMS (M+H) ⁺ = 561.3. ¹ H NMR (500 MHz, chloroform-d) δ 8.18-8.13 (m, 2H), 8.07-8.02 (m, 2H), 7.53-7.48 (m, 1H), 7.47-7.44 (m, 2H), 7.42-7.39 (m, 1H), 7.37 (dd, <i>J</i> = 11.1, 1.7 Hz, 1H), 3.95 (s, 3H), 3.66 (s, 2H), 3.14 (s, 3H), 3.01 (br d, <i>J</i> = 11.8 Hz, 2H), 2.91-2.66 (m, 4H), 2.79 (s, 3H), 2.41-2.20 (m, 1H), 2.14 (br t, <i>J</i> = 11.4 Hz, 2H), 2.02-1.86 (m, 6H), 1.76 (br d, <i>J</i> = 9.6 Hz, 2H). TLR9 IC ₅₀ (nM) = 56
388	LCMS (M+H) ⁺ = 533.3. ¹ H NMR (500 MHz, chloroform-d) δ 8.18-8.12 (m, 2H), 8.07-8.02 (m, 2H), 7.51-7.43 (m, 3H), 7.40 (s, 1H), 7.37 (dd, <i>J</i> = 11.1, 1.4 Hz, 1H), 3.95 (s, 3H), 3.77 (s, 2H), 3.14 (s, 3H), 2.89 (br s, 4H), 2.79 (s, 3H), 2.72 (br s, 2H), 2.53 (br d, <i>J</i> = 7.6 Hz, 4H), 2.50 (br s, 3H). TLR9 IC ₅₀ (nM) = 230

389	LCMS (M+H) ⁺ = 535.3. ¹ H NMR (500 MHz, chloroform-d) δ 8.18-8.12 (m, 2H), 8.08-8.01 (m, 2H), 7.57-7.50 (m, 1H), 7.47-7.43 (m, 2H), 7.41 (d, J=1.4 Hz, 1H), 7.37 (dd, J=11.2, 1.7 Hz, 1H), 3.95 (s, 3H), 3.80 (s, 2H), 3.14 (s, 3H), 2.89-2.79 (m, 8H), 2.79 (s, 3H), 2.67 (br d, J=6.5 Hz, 2H), 1.96-1.85 (m, 2H), 1.13 (br t, J=7.1 Hz, 3H). TLR9 IC ₅₀ (nM) = 330
390	LCMS (M+H) ⁺ = 535.3. ¹ H NMR (500 MHz, chloroform-d) δ 8.17-8.13 (m, 2H), 8.06-8.03 (m, 2H), 7.51-7.43 (m, 3H), 7.41-7.36 (m, 2H), 3.95 (s, 3H), 3.67 (s, 2H), 3.14 (s, 3H), 3.07 (br d, J=11.8 Hz, 2H), 2.79 (s, 3H), 2.47 (s, 4H), 2.47 (s, 3H), 2.15 (br t, J=11.4 Hz, 2H), 1.96 (br d, J=11.7 Hz, 2H), 1.75-1.67 (m, 2H). TLR9 IC ₅₀ (nM) = 91
391	LCMS (M+H) ⁺ = 579.3. ¹ H NMR (500 MHz, chloroform-d) δ 8.19-8.13 (m, 2H), 8.08-8.01 (m, 2H), 7.44 (d, J=1.0 Hz, 1H), 7.38 (s, 1H), 7.23 (d, J=8.3 Hz, 2H), 3.96 (s, 3H), 3.78 (s, 2H), 3.14 (s, 3H), 3.04 (br d, J=11.7 Hz, 2H), 2.94-2.63 (m, 4H), 2.79 (s, 3H), 2.42-2.23 (m, 1H), 2.18 (br t, J=11.5 Hz, 2H), 2.02-1.85 (m, 6H), 1.78-1.66 (m, 2H). TLR9 IC ₅₀ (nM) = 180
392	LCMS (M+H) ⁺ = 553.2. ¹ H NMR (500 MHz, chloroform-d) δ 8.16 (d, J=8.5 Hz, 2H), 8.05 (d, J=8.5 Hz, 2H), 7.43 (d, J=1.0 Hz, 1H), 7.40-7.36 (m, 1H), 7.23 (d, J=8.3 Hz, 2H), 3.96 (s, 3H), 3.78 (s, 2H), 3.14 (s, 3H), 3.07 (br d, J=11.7 Hz, 2H), 2.79 (s, 3H), 2.36 (s, 6H), 2.32-2.24 (m, 1H), 2.16 (br t, J=11.4 Hz, 2H), 1.87 (br d, J=12.1 Hz, 2H), 1.68-1.59 (m, 2H). TLR9 IC ₅₀ (nM) = 470
393	LCMS (M+H) ⁺ = 543.3. ¹ H NMR (500 MHz, chloroform-d) δ 8.18-8.12 (m, 2H), 8.07-8.01 (m, 2H), 7.66 (br d, J=8.0 Hz, 2H), 7.51-7.40 (m, 4H), 3.95 (s, 3H), 3.64 (br s, 2H), 3.14 (s, 3H), 3.11-3.01 (m, 2H), 2.79 (s, 3H), 2.66-2.51 (m, 1H), 2.42 (br s, 2H), 2.19-1.69 (m, 8H), 0.65-0.35 (m, 4H). TLR9 IC ₅₀ (nM) = 330

394	LCMS (M+H) ⁺ = 561.3. ¹ H NMR (500 MHz, chloroform-d) δ 8.18-8.12 (m, 2H), 8.07-8.02 (m, 2H), 7.55-7.43 (m, 3H), 7.42-7.35 (m, 2H), 3.95 (s, 3H), 3.71 (br s, 2H), 3.14 (s, 3H), 3.12-3.04 (m, 2H), 2.79 (s, 3H), 2.66-2.49 (m, 1H), 2.42 (br s, 2H), 2.25-2.05 (m, 2H), 2.01-1.67 (m, 6H), 0.69-0.38 (m, 4H). TLR9 IC ₅₀ (nM) = 560
395	LCMS (M+H) ⁺ = 460.2. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.20-8.16 (m, 2H), 8.15-8.11 (m, 2H), 7.76 (s, 1H), 7.73 (d, <i>J</i> =8.0 Hz, 2H), 7.45-7.39 (m, 3H), 3.98 (s, 3H), 3.64 (s, 2H), 3.18 (s, 3H), 2.65 (s, 3H), 2.48 (br s, 4H), 1.72 (br s, 4H). TLR9 IC ₅₀ (nM) = 1400
396	LCMS (M+H) ⁺ = 557.3. ¹ H NMR (500 MHz, chloroform-d) δ 8.15 (d, <i>J</i> =8.6 Hz, 2H), 8.07-8.02 (m, 2H), 7.66 (d, <i>J</i> =8.2 Hz, 2H), 7.50-7.44 (m, 3H), 7.42 (d, <i>J</i> =0.8 Hz, 1H), 3.95 (s, 3H), 3.72 (br s, 2H), 3.14 (s, 3H), 2.92-2.69 (m, 4H), 2.79 (s, 3H), 2.57-2.29 (m, 6H), 1.92-1.69 (m, 3H), 0.99 (br d, <i>J</i> =6.2 Hz, 6H). TLR9 IC ₅₀ (nM) = 200
397	LCMS (M+H) ⁺ = 543.3. ¹ H NMR (500 MHz, chloroform-d) δ 8.17-8.12 (m, 2H), 8.07-8.01 (m, 2H), 7.65 (d, <i>J</i> =8.2 Hz, 2H), 7.48-7.40 (m, 4H), 3.95 (s, 3H), 3.71 (s, 2H), 3.50-3.22 (m, 2H), 3.14 (s, 3H), 2.95 (br s, 2H), 2.82-2.74 (m, 1H), 2.79 (s, 3H), 2.65 (br d, <i>J</i> =8.7 Hz, 2H), 2.47 (br s, 4H), 1.30 (br s, 6H). TLR9 IC ₅₀ (nM) = 86
398	LCMS (M+H) ⁺ = 515.2. ¹ H NMR (500 MHz, chloroform-d) δ 8.17-8.12 (m, 2H), 8.07-8.01 (m, 2H), 7.65 (d, <i>J</i> =8.2 Hz, 2H), 7.47-7.42 (m, 4H), 3.95 (s, 3H), 3.72 (s, 2H), 3.14 (s, 3H), 2.93-2.80 (m, 4H), 2.79 (s, 3H), 2.71 (br s, 2H), 2.59-2.45 (m, 4H), 2.49 (s, 3H). TLR9 IC ₅₀ (nM) = 130
399	LCMS (M+H) ⁺ = 529.1. ¹ H NMR (500 MHz, chloroform-d) δ 8.15 (d, <i>J</i> =8.3 Hz, 2H), 8.06-8.02 (m, 2H), 7.64 (d, <i>J</i> =8.2 Hz, 2H), 7.44 (s, 1H), 7.42 (s, 1H), 7.37 (d, <i>J</i> =8.0 Hz, 2H), 3.95 (s, 3H), 3.66 (s, 2H), 3.49-3.31 (m, 8H), 3.13 (s, 3H), 2.78 (s, 3H), 2.43-2.26 (m, 1H), 0.99 (br d, <i>J</i> =4.9 Hz, 6H). TLR9 IC ₅₀ (nM) = 97

400	LCMS (M+H) ⁺ = 557.2. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.15 (br d, J=1.8 Hz, 4H), 7.77 (s, 3H), 7.51-7.44 (m, 1H), 7.41-7.34 (m, 2H), 3.97 (s, 2H), 3.89 (s, 2H), 3.71-3.55 (m, 3H), 3.31 (s, 2H), 3.17 (s, 5H), 2.80 (br s, 2H), 2.65 (s, 3H), 2.55 (s, 2H), 2.41-2.26 (m, 2H), 2.17-1.86 (m, 6H) (one proton obscured). TLR9 IC ₅₀ (nM) = 76
401	LCMS (M+H) ⁺ = 583.3. ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.25-8.10 (m, 4H), 7.77 (s, 3H), 7.48 (s, 1H), 7.40-7.32 (m, 2H), 3.99 (s, 3H), 3.77-3.55 (m, 2H), 3.33 (s, 2H), 3.26-3.13 (m, 2H), 3.06-2.86 (m, 2H), 2.85-2.76 (m, 1H), 2.66 (s, 3H), 2.57-2.53 (m, 1H), 2.42-2.24 (m, 2H), 2.15-1.87 (m, 6H), 1.26-1.12 (m, 1H), 1.02-0.91 (m, 2H), 0.91-0.76 (m, 2H) (three protons obscured). TLR9 IC ₅₀ (nM) = 100
402	LCMS (M+H) ⁺ = 529.3. ¹ H NMR (500 MHz, chloroform-d) δ 8.17-8.12 (m, 2H), 8.07-8.01 (m, 2H), 7.65 (d, J=8.2 Hz, 2H), 7.48-7.40 (m, 4H), 3.95 (s, 3H), 3.64-3.55 (m, 2H), 3.37 (br d, J=3.6 Hz, 2H), 3.14 (s, 3H), 2.97-2.88 (m, 2H), 2.85-2.76 (m, 1H), 2.79 (s, 3H), 2.30-2.02 (m, 4H), 1.84-1.61 (m, 6H). TLR9 IC ₅₀ (nM) = 3.9
403	LCMS (M+H) ⁺ = 547.3. ¹ H NMR (500 MHz, CHLOROFORM-d) δ 8.17-8.12 (m, 2H), 8.07-8.02 (m, 2H), 7.54-7.43 (m, 3H), 7.40 (s, 1H), 7.36 (dd, J=11.2, 1.6 Hz, 1H), 3.95 (s, 3H), 3.67 (br s, 2H), 3.34 (br s, 2H), 3.14 (s, 3H), 2.94 (br d, J=11.4 Hz, 2H), 2.81-2.75 (m, 1H), 2.79 (s, 3H), 2.15 (br s, 4H), 1.85-1.43 (m, 6H). TLR9 IC ₅₀ (nM) = 81
404	LCMS (M+H) ⁺ = 547.2. ¹ H NMR (500 MHz, CHLOROFORM-d) δ 8.17-8.12 (m, 2H), 8.07-8.02 (m, 2H), 7.46-7.39 (m, 4H), 7.37 (dd, J=11.2, 1.5 Hz, 1H), 3.95 (s, 3H), 3.70 (s, 2H), 3.63-3.32 (m, 7H), 3.14 (s, 3H), 2.78 (s, 3H), 2.61-2.37 (m, 1H), 1.11-0.98 (m, 6H). TLR9 IC ₅₀ (nM) = 69
405	LCMS (M+H) ⁺ = 561.1. ¹ H NMR (500 MHz, chloroform-d) δ 8.15 (d, J=8.6 Hz, 2H), 8.08-8.02 (m, 2H), 7.47-7.38 (m, 3H), 7.27 (br d, J=9.4 Hz, 1H), 7.06 (br d, J=9.4 Hz, 1H), 3.96 (s, 3H), 3.60 (s, 2H), 3.14 (s, 3H), 2.99 (br d, J=10.8 Hz, 2H), 2.87-2.54 (m, 4H), 2.79 (s, 3H), 2.37-2.16 (m, 1H), 2.09 (br t, J=11.3 Hz, 2H), 2.01-1.75 (m, 8H). TLR9 IC ₅₀ (nM) = 21

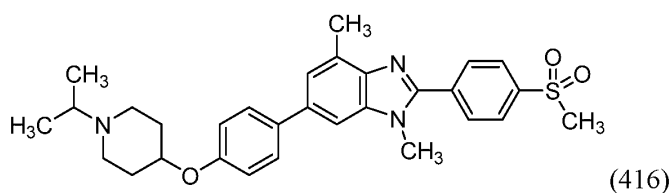
406	LCMS (M+H) ⁺ = 547.3. ¹ H NMR (500 MHz, CHLOROFORM-d) δ 8.18-8.12 (m, 2H), 8.08-8.02 (m, 2H), 7.47-7.38 (m, 3H), 7.28-7.26 (m, 1H), 7.06 (br d, <i>J</i> =9.3 Hz, 1H), 3.96 (s, 3H), 3.60 (s, 2H), 3.35 (br s, 2H), 3.14 (s, 3H), 2.92 (br d, <i>J</i> =10.7 Hz, 2H), 2.84-2.72 (m, 1H), 2.79 (s, 3H), 2.24-2.04 (m, 4H), 1.84-1.53 (m, 6H). TLR9 IC ₅₀ (nM) = 130
407	LCMS (M+H) ⁺ = 569.1. ¹ H NMR (500 MHz, CHLOROFORM-d) δ 8.23 (d, <i>J</i> =8.5 Hz, 2H), 8.12 (d, <i>J</i> =8.3 Hz, 2H), 7.69-7.57 (m, 3H), 7.45 (t, <i>J</i> =7.6 Hz, 1H), 7.40 (s, 1H), 7.34 (br d, <i>J</i> =7.4 Hz, 1H), 3.69-3.61 (m, 3H), 3.14 (s, 3H), 3.05 (br d, <i>J</i> =10.8 Hz, 2H), 2.77 (s, 3H), 3.01-2.49 (m, 3H), 2.17-1.71 (m, 12H), 1.21 (q, <i>J</i> =6.5 Hz, 2H), 0.84-0.78 (m, 2H). TLR9 IC ₅₀ (nM) = 46
408	Analytical LC/MS (Method 1): Purity: 94.1 %; Observed Mass: 573.60; Retention Time: 1.07 min. (Method 2): Purity: 93.7 %; Observed Mass: 573.60; Retention Time: 1.28 min. Prep Method 1: 50 mg, 47 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.34 (d, <i>J</i> =8.5 Hz, 2H), 8.13 (br d, <i>J</i> =8.2 Hz, 2H), 7.79-7.69 (m, 3H), 7.43 (br d, <i>J</i> =8.2 Hz, 3H), 3.98-3.86 (m, 1H), 3.57-3.43 (m, 1H), 3.34 (s, 2H), 2.87-2.75 (m, 2H), 2.57-2.56 (m, 1H), 2.49-2.43 (m, 4H), 2.09-1.90 (m, 3H), 1.88-1.76 (m, 3H), 1.66 (br s, 4H), 1.49-1.33 (m, 2H), 1.29-1.11 (m, 2H), 0.72 (br s, 2H). TLR9 IC ₅₀ (nM) = 140
409	Analytical LC/MS (Method 1): Purity: 99 %; Observed Mass: 547.20; Retention Time: 1.16 min. (Method 2): Purity: 99.4 %; Observed Mass: 547.20; Retention Time: 1.40. Prep Method 1: 83 mg, 88 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.25-8.09 (m, 4H), 7.82 (s, 1H), 7.76 (s, 2H), 7.42 (br d, <i>J</i> =7.9 Hz, 3H), 3.99 (s, 2H), 3.79-3.59 (m, 3H), 3.50 (s, 1H), 3.31 (s, 3H), 3.19-3.15 (m, 1H), 2.85-2.78 (m, 2H), 2.61 (br s, 2H), 2.19-2.09 (m, 1H), 1.97 (br s, 2H), 1.87 (s, 3H), 1.70 (br s, 3H), 1.54-1.35 (m, 2H). TLR9 IC ₅₀ (nM) = 5.3

410	Analytical LC/MS (Method 1): Purity: 95.4 %; Observed Mass: 559.20; Retention Time: 1.23 min. (Method 2): Purity: 100 %; Observed Mass: 559.30; Retention Time: 1.49. Prep Method 1: 76 mg, 94 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.33 (d, <i>J</i> =8.2 Hz, 2H), 8.13 (d, <i>J</i> =8.2 Hz, 2H), 7.78-7.70 (m, 3H), 7.49-7.41 (m, 1H), 7.38 (br d, <i>J</i> =7.9 Hz, 2H), 4.03-3.82 (m, 1H), 3.63-3.44 (m, 1H), 3.34 (s, 2H), 3.21 (br d, <i>J</i> =15.0 Hz, 5H), 2.53-2.49 (m, 4H), 2.32-2.21 (m, 1H), 1.91 (s, 1H), 1.24-1.18 (m, 2H), 0.83 (d, <i>J</i> =6.1 Hz, 6H), 0.72 (br s, 2H). TLR9 IC ₅₀ (nM) = 44
411	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 573.20; Retention Time: 1.13 min. (Method 2): Purity: 97.1 %; Observed Mass: 573.20; Retention Time: 1.49. Prep Method 1: 40 mg, 48 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.41-8.27 (m, 2H), 8.12 (d, <i>J</i> =8.2 Hz, 2H), 7.81-7.66 (m, 3H), 7.49-7.41 (m, 1H), 7.38 (br d, <i>J</i> =7.9 Hz, 2H), 3.97-3.86 (m, 1H), 3.63-3.56 (m, 1H), 3.34 (s, 2H), 3.31-3.23 (m, 3H), 2.55 (s, 3H), 2.25-2.15 (m, 2H), 1.92 (s, 4H), 1.57-1.45 (m, 1H), 1.23-1.17 (m, 2H), 0.82 (d, <i>J</i> =6.7 Hz, 6H), 0.76-0.69 (m, 2H). TLR9 IC ₅₀ (nM) = 0.85
412	Analytical LC/MS (Method 1): Purity: 98.7 %; Observed Mass: 601.30; Retention Time: 1.15 min. (Method 2): Purity: 97.1 %; Observed Mass: 601.30; Retention Time: 1.45. Prep Method 1: 85 mg, 98 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.36-8.36 (m, 1H), 8.34 (br d, <i>J</i> =7.9 Hz, 1H), 8.13 (br d, <i>J</i> =8.2 Hz, 2H), 7.80-7.65 (m, 3H), 7.45 (br d, <i>J</i> =11.6 Hz, 1H), 7.39 (br d, <i>J</i> =7.9 Hz, 2H), 3.98-3.91 (m, 1H), 3.83-3.74 (m, 2H), 3.63-3.52 (m, 1H), 3.35 (s, 2H), 3.30-3.17 (m, 7H), 2.26-2.08 (m, 1H), 1.92 (s, 4H), 1.62-1.49 (m, 2H), 1.21 (br d, <i>J</i> =6.7 Hz, 4H), 0.73 (br s, 2H) (one proton obscured). TLR9 IC ₅₀ (nM) = 77

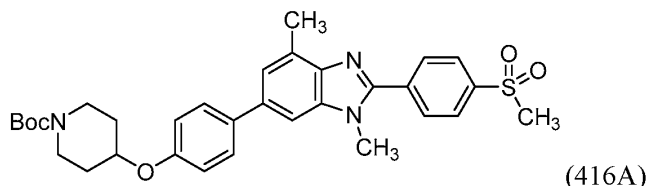
413	Analytical LC/MS (Method 1): Purity: 96.3 %; Observed Mass: 517.19; Retention Time: 1.03 min. (Method 2): Purity: 94.9 %; Observed Mass: 517.19; Retention Time: 1.51. Prep Method 1: 53 mg, 88 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.22-8.10 (m, 4H), 7.81-7.67 (m, 3H), 7.47-7.36 (m, 3H), 4.01-3.96 (m, 3H), 3.60-3.48 (m, 1H), 2.70-2.63 (m, 3H), 2.56-2.50 (m, 8H), 2.49-2.35 (m, 3H), 1.09-0.91 (m, 6H) (two protons obscured). TLR9 IC ₅₀ (nM) = 1900
414	Analytical LC/MS (Method 1): Purity: 96.4 %; Observed Mass: 531.37; Retention Time: 1.06 min. (Method 2): Purity: 96.4 %; Observed Mass: 531.37; Retention Time: 2.01. Prep Method 1: 23 mg, 38 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.24-8.06 (m, 4H), 7.79-7.65 (m, 3H), 7.49-7.32 (m, 3H), 3.98 (s, 3H), 3.54-3.47 (m, 1H), 3.46-3.38 (m, 1H), 3.32 (s, 1H), 2.65 (s, 3H), 2.55 (s, 2H), 2.48-2.13 (m, 5H), 2.02 (br d, <i>J</i> =7.4 Hz, 2H), 1.83-1.55 (m, 1H), 0.84 (d, <i>J</i> =6.5 Hz, 6H) (three protons obscured). TLR9 IC ₅₀ (nM) = 1800
415	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 553.30; Retention Time: 0.98 min. (Method 2): Purity: 100 %; Observed Mass: 553.30; Retention Time: 1.50 min. Prep Method 2: 52 mg, 35 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.28-8.23 (m, 2H), 8.11 (d, <i>J</i> =8.2 Hz, 2H), 7.55 (d, <i>J</i> =8.2 Hz, 1H), 7.17-7.13 (m, 1H), 4.08-3.97 (m, 1H), 3.76-3.54 (m, 1H), 3.34 (s, 1H), 3.33-3.19 (m, 1H), 3.08-2.90 (m, 3H), 2.61-2.49 (m, 4H), 2.38-2.26 (m, 2H), 2.24-1.98 (m, 7H), 1.08 (br d, <i>J</i> =7.0 Hz, 2H), 0.98 (br d, <i>J</i> =6.4 Hz, 6H), 0.70 (br s, 2H) (five protons obscured). TLR9 IC ₅₀ (nM) = 65

EXAMPLE 416

6-(4-((1-isopropylpiperidin-4-yl)oxy)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole

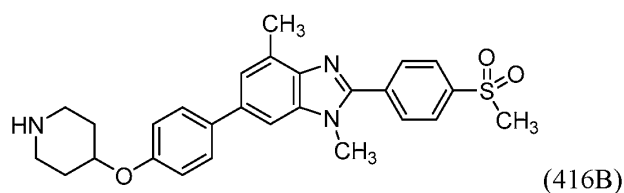


Step A. Intermediate 416A. Preparation of tert-butyl 4-(4-(1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)phenoxy)piperidine-1-carboxylate



- 5 To a 40 mL vial were added Intermediate 22A (230 mg, 0.61 mmol), tert-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine-1-carboxylate (250 mg, 0.61 mmol), XPhos Pd G3 (26 mg, 0.030 mmol), 1,4-dioxane (10 mL), followed by potassium phosphate tribasic (450 mg, 2.1 mmol) dissolved in water (2 mL). The vessel was flushed with N₂ and the reaction mixture was stirred at 85 °C. After 18 h, the
- 10 reaction mixture was cooled, diluted with water (100 mL) and extracted with EtOAc (2x50 mL). The organic phase was combined, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash column chromatography (80 g silica gel cartridge; A = DCM, B = MeOH; 30 min grad.; 0% B to 15%B; flow rate = 60 mL/min). The fractions corresponding to product were combined, concentrated and dried
- 15 in vacuo to afford the title compound (340 mg, 0.59 mmol, 97 % yield) as a pale yellow solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.26-8.18 (m, 2H), 8.15-8.06 (m, 2H), 7.70-7.64 (m, 2H), 7.61-7.57 (m, 1H), 7.44-7.39 (m, 1H), 7.14-7.05 (m, 2H), 4.69-4.62 (m, 1H), 4.00-3.94 (m, 3H), 3.82-3.73 (m, 2H), 3.37 (s, 3H), 2.72 (s, 3H), 2.05-1.97 (m, 2H), 1.79-1.71 (m, 3H), 1.22 (s, 9H) (one proton obscured). Analytical LC/MS (Method
- 20 4): Observed Mass: 576.3; Retention Time: 1.821 min.

Step B. Intermediate 416B. Preparation of 1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(4-(piperidin-4-yloxy)phenyl)-1H-benzo[d]imidazole hydrochloride

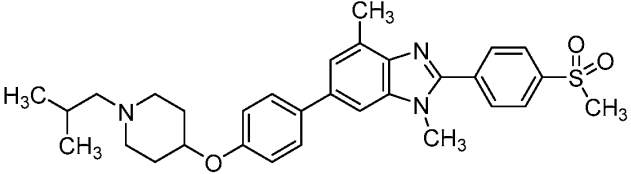
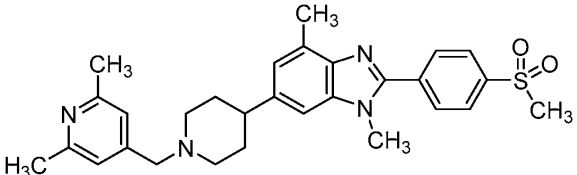
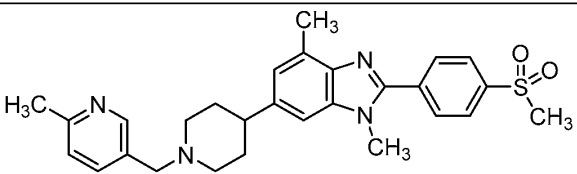
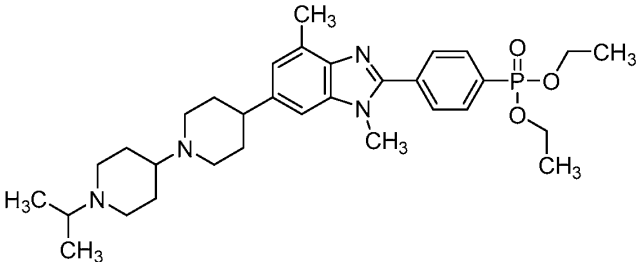
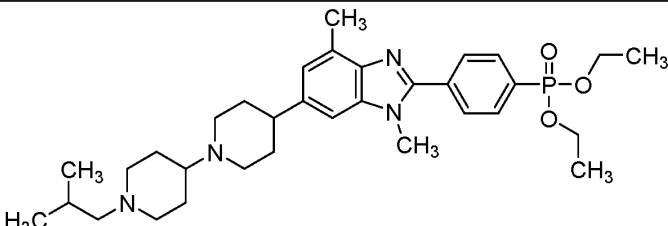


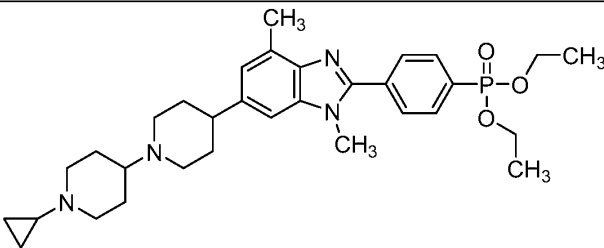
To a 100 mL pear shaped flask were added Intermediate 416A (340 mg, 0.59 mmol), MeOH (20 mL), and 4 M HCl in dioxane (10 mL). After 30 min, the solvent was concentrated and the residue was co-evaporated with toluene (2x), and the product was dried in vacuo to afford the title compound (300 mg, 0.59 mmol, 100 % yield) as a tan solid. ¹H NMR (500 MHz, METHANOL-d₄) δ 8.37-8.31 (m, 2H), 8.23-8.19 (m, 2H), 7.94-7.91 (m, 1H), 7.80-7.74 (m, 2H), 7.73-7.70 (m, 1H), 7.20-7.16 (m, 2H), 4.13 (s, 3H), 3.63-3.60 (m, 1H), 3.50-3.43 (m, 3H), 3.36-3.34 (m, 1H), 3.32-3.29 (m, 3H), 3.28-3.18 (m, 3H), 2.77 (s, 3H) (one proton obscured). Analytical LC/MS (Method 4): Observed Mass: 476.2; Retention Time: 1.025 min.

Step C. Example 416

To a 40 mL vial were added Intermediate 416B (60 mg, 0.12 mmol), propan-2-one (34 mg, 0.59 mmol), AcOH (7.4 μ L, 0.13 mmol), magnesium sulfate (210 mg, 1.8 mmol), and DMF (2 mL). The reaction mixture was stirred for 20 min, then sodium triacetoxyborohydride (120 mg, 0.59 mmol) was added and the reaction mixture was stirred. After 18 h, the reaction mixture was diluted with 10% IPA/ CHCl_3 (40 mL) and filtered. The filtrate was partitioned into 10% KOH (sat. with solid NaCl) (20 mL) and the layers were separated. The aqueous phase was extracted with 10% IPA/ CHCl_3 (10 mL), the organic phase was combined, washed with brine, dried over MgSO_4 , filtered and concentrated. The crude material was purified by preparative HPLC (Prep Method 1) to afford the title compound (49 mg, 0.095 mmol, 79 % yield). ^1H NMR (500 MHz, DMSO-d_6) δ 8.19-8.11 (m, 4H), 7.73-7.65 (m, 3H), 7.41-7.36 (m, 1H), 7.11-7.04 (m, 2H), 4.55-4.46 (m, 1H), 3.96 (s, 3H), 3.31 (s, 2H), 3.02-2.87 (m, 2H), 2.64 (s, 5H), 2.09-2.01 (m, 2H), 1.91 (s, 2H), 1.81-1.67 (m, 2H), 1.08 (br d, $J=6.4$ Hz, 6H). Analytical LC/MS (Method 1): Purity: 97.3 %; Observed Mass: 518.22; Retention Time: 1.14 min. (Method 2): Purity: 97.1 %; Observed Mass: 518.12; Retention Time: 1.50 min. TLR9 IC_{50} (nM) = 1200.

The following Examples were prepared according to the general methods described hereinabove using appropriate starting materials, reagents and conditions.

417		Ex. 416
418		Ex. 22
419		Ex. 22
420		Ex. 22
421		Ex. 22

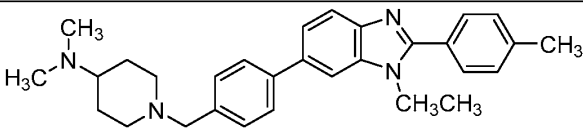
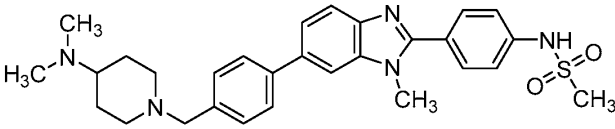
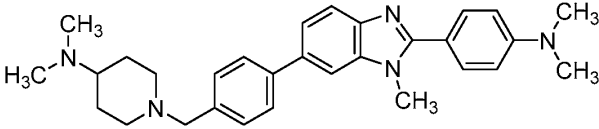
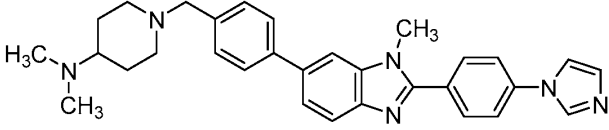
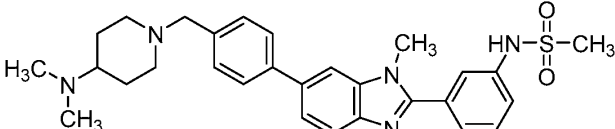
422		Ex. 22
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Ex. No.	LC/MS, Preparative HPLC method, yield, and ¹ H NMR
417	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 531.92; Retention Time: 1.27 min. (Method 2): Purity: 100 %; Observed Mass: 531.95; Retention Time: 1.66 min. Prep Method 1: 21 mg, 33 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.20-8.08 (m, 4H), 7.73-7.65 (m, 3H), 7.41-7.35 (m, 1H), 7.11-6.99 (m, 2H), 4.50-4.38 (m, 1H), 3.97 (s, 3H), 3.32 (s, 1H), 2.63 (s, 4H), 2.57-2.53 (m, 1H), 2.19 (br s, 2H), 2.06 (d, <i>J</i>=7.4 Hz, 2H), 2.00-1.93 (m, 2H), 1.82-1.71 (m, 1H), 1.70-1.58 (m, 2H), 0.87 (d, <i>J</i>=6.6 Hz, 6H) (two protons obscured). TLR9 IC₅₀ (nM) = 800
418	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 503.20; Retention Time: 0.88 min. (Method 2): Purity: 98.4 %; Observed Mass: 503.30; Retention Time: 1.68 min. Prep Method 1: 67 mg, 87 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.18-8.05 (m, 4H), 7.38-7.30 (m, 1H), 7.02 (s, 3H), 3.90 (s, 3H), 3.35-3.27 (m, 1H), 2.97-2.88 (m, 2H), 2.67-2.59 (m, 1H), 2.54-2.50 (m, 5H), 2.42 (s, 5H), 2.17-2.06 (m, 2H), 1.94-1.88 (m, 2H), 1.85-1.76 (m, 4H) (one proton obscured). TLR9 IC₅₀ (nM) = 2500
419	Analytical LC/MS (Method 1): Purity: 98.5 %; Observed Mass: 489.20; Retention Time: 0.93 min. (Method 2): Purity: 92.2 %; Observed Mass: 489.00; Retention Time: 1.48 min. Prep Method 1: 45 mg, 56 % yield; ¹H NMR (500 MHz, DMSO-d₆) δ 8.42-8.35 (m, 1H), 8.17-8.06 (m, 4H), 7.66-7.59 (m, 1H), 7.38-7.30 (m, 1H), 7.26-7.19 (m, 1H), 7.04-6.97 (m, 1H), 3.89 (s, 3H), 3.55-3.49 (m, 1H), 3.31 (s, 1H), 2.97-2.89 (m, 2H), 2.65-2.58 (m, 1H), 2.55-2.50 (m, 3H), 2.46 (s, 3H), 2.09 (br d, <i>J</i>=3.1 Hz, 2H), 1.79 (br d, <i>J</i>=5.8 Hz, 4H) (three protons obscured). TLR9 IC₅₀ (nM) = 2100

420	Analytical LC/MS (Method 1): Purity: 91.6 %; Observed Mass: 567.30; Retention Time: 1.09 min. (Method 2): Purity: 97.1 %; Observed Mass: 567.30; Retention Time: 1.49 min. Prep Method 1: 56 mg, 72 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.08-7.96 (m, 2H), 7.96-7.84 (m, 2H), 7.38-7.22 (m, 1H), 7.07-6.90 (m, 1H), 4.15-4.02 (m, 4H), 3.87 (s, 3H), 3.07-2.98 (m, 1H), 2.96-2.88 (m, 1H), 2.86-2.69 (m, 1H), 2.53 (br d, <i>J</i> =19.3 Hz, 8H), 2.31 (br s, 4H), 1.86-1.62 (m, 5H), 1.55-1.35 (m, 2H), 1.28 (t, <i>J</i> =7.0 Hz, 5H), 1.00 (br d, <i>J</i> =6.4 Hz, 6H) (one proton obscured). TLR9 IC ₅₀ (nM) = 140
421	Analytical LC/MS (Method 1): Purity: 93.4 %; Observed Mass: 581.20; Retention Time: 1.13 min. (Method 2): Purity: 96.7 %; Observed Mass: 581.40; Retention Time: 1.69 min. Prep Method 1: 41 mg, 53 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.01 (br dd, <i>J</i> =7.8, 3.5 Hz, 2H), 7.89 (dd, <i>J</i> =12.7, 8.1 Hz, 2H), 7.31 (s, 1H), 6.98 (s, 1H), 4.17-4.01 (m, 4H), 3.88 (s, 3H), 3.06-2.99 (m, 1H), 2.94-2.80 (m, 2H), 2.66-2.58 (m, 1H), 2.55 (s, 5H), 2.39-2.21 (m, 3H), 2.02 (br s, 2H), 1.89-1.61 (m, 8H), 1.53-1.43 (m, 2H), 1.28 (t, <i>J</i> =7.0 Hz, 6H), 0.86 (d, <i>J</i> =6.4 Hz, 6H). TLR9 IC ₅₀ (nM) = 140
422	Analytical LC/MS (Method 1): Purity: 100 %; Observed Mass: 565.30; Retention Time: 0.93 min. (Method 2): Purity: 100 %; Observed Mass: 565.40; Retention Time: 1.48 min. Prep Method 2: 36 mg, 51 % yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.09-8.00 (m, 2H), 7.98-7.89 (m, 2H), 7.46-7.28 (m, 1H), 7.11-6.95 (m, 1H), 4.18-4.00 (m, 4H), 3.91 (s, 3H), 3.73-3.52 (m, 1H), 3.29-2.95 (m, 2H), 2.62-2.47 (m, 9H), 2.40-2.24 (m, 2H), 2.11 (br s, 6H), 1.28 (t, <i>J</i> =7.0 Hz, 6H), 1.04-0.87 (m, 2H), 0.86-0.71 (m, 2H) (two protons obscured). TLR9 IC ₅₀ (nM) = 180

The following Examples were prepared according to the general methods described elsewhere herein using appropriate starting materials, reagents and conditions.

Ex. No.	Structure
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423	
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427	

Ex. No.	Analytical LC/MS, Preparative HPLC method, yield, and ¹ H NMR
425	Analytical LC/MS (Method 2): Purity: 93.4%; Observed Mass: 417.3; Retention Time: 1.5 min.; Prep method 1: 2.7 mg, 8% yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 7.75 (s, 1H), 7.67 (br d, <i>J</i> = 7.9 Hz, 2H), 7.59 (br d, <i>J</i> = 7.9 Hz, 1H), 7.44 (br d, <i>J</i> = 8.5 Hz, 1H), 7.36 (br d, <i>J</i> = 7.9 Hz, 2H), 3.81 (s, 3H), 2.87 (br d, <i>J</i> = 11.6 Hz, 2H), 2.27 (br s, 6H), 2.14 - 2.04 (m, 3H), 2.01 - 1.87 (m, 5H), 1.83 - 1.64 (m, 7H), 1.48 - 1.35 (m, 3H); TLR9 IC ₅₀ (nM) = 61

426	Analytical LC/MS (Method 1): Purity: 100%; Observed Mass: 493.2; Retention Time: 1.18 min; Analytical LC/MS (Method 2): Purity: 97.8%; Observed Mass: 493.2; Retention Time: 1.71 min. Prep method 1: 1.3 mg, 3% yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.14 (br d, <i>J</i> = 7.6 Hz, 2H), 8.03 (s, 1H), 7.96 (br d, <i>J</i> = 8.2 Hz, 2H), 7.91 (br d, <i>J</i> = 7.9 Hz, 2H), 7.81 (d, <i>J</i> = 8.5 Hz, 1H), 7.70 - 7.60 (m, 3H), 4.45 - 4.24 (m, 2H), 4.00 (s, 3H), 3.10 - 2.84 (m, 2H), 2.76 (br s, 6H), 2.26 - 2.18 (m, 2H), 2.02 - 1.84 (m, 3H) (two protons obscured); TLR9 IC ₅₀ (nM) = nd
427	Analytical LC/MS (Method 1): Purity: 100%; Observed Mass: 349.1; Retention Time: 0.67 min; Analytical LC/MS (Method 2): Purity: 90.5%; Observed Mass: 349.1; Retention Time: 0.67 min. Prep method 1: 1.6 mg, 7% yield; ¹ H NMR (500 MHz, DMSO-d ₆) δ 8.20 (s, 1H), 7.84 (s, 1H), 7.73 - 7.68 (m, 3H), 7.52 (br d, <i>J</i> = 7.9 Hz, 1H), 7.39 (br d, <i>J</i> = 7.9 Hz, 2H), 3.89 (s, 3H), 3.53 (s, 1H), 2.93 (br d, <i>J</i> = 10.4 Hz, 2H), 2.59 - 2.50 (m, 6H), 1.99 (br t, <i>J</i> = 11.7 Hz, 2H), 1.85 (br d, <i>J</i> = 11.0 Hz, 2H), 1.60 - 1.47 (m, 2H); TLR9 IC ₅₀ (nM) = nd

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 μ M), TLR8 ligand (R848 at a final concentration of 15.9 μ M) or TLR9 ligand (ODN2006 at a final concentration of 5 nM) to activate NF- κ B 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

- 5 (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.

10

TABLE 1

Ex. No.	TLR 9 IC ₅₀ (μ M)	TLR 7 IC ₅₀ (μ M)	TLR 8 IC ₅₀ (μ M)
1	0.056	5.9	1.1
2	0.123	16	>50
3	0.169	0.28	>50
4	0.253	4.7	>50
5	0.250	6.8	0.84
6	0.191	2.9	29
7	0.283	5.7	>50
8	0.210	2.5	>50
9	0.249	2.7	1.3
10	0.244	>50	>50
11	0.033	5.0	>50
12	0.060	22	>50
13	0.617	>50	>50
14	0.509	>50	>50
15	0.019	7.1	>50
16	0.0104	10	>50
17	0.025	6.5	>50
18	0.029	7.7	>50
19	0.028	2.5	>50
20	0.069	4.1	>50

21	0.024	2.6	>50
22	0.0076	24	>50
23	0.159	8.8	>50
24	0.048	3.0	>50
25	0.164	3.0	>50
26	0.132	32	>50
27	0.106	2.4	>50
28	0.019	2.7	>50
29	0.0112	6.6	>50
30	0.254	9.8	>50
31	0.749	>50	>50
32	0.212	5.7	>50
33	0.681	8.1	35.0
34	0.173	16	>50
35	0.852	25	>50
36	0.357	6.6	4.6
37	0.388	7.5	>50
38	0.208	3.4	>50
39	0.590	6.4	30
40	0.149	2.3	46
41	0.404	3.7	1.6
42	0.255	32	>50
43	0.0098	0.65	31.0
44	0.052	9.1	5.5
45	0.020	11	>50
46	0.610	18	>50
47	0.013	7.2	>50
48	0.019	>50	>50
49	0.065	5.8	>50
50	0.023	2.9	>50

51	0.130	20	>50
52	0.129	4.8	>50
53	0.421	24	>50
54	0.131	7.7	>50
55	0.140	9.3	>50
56	0.050	3.2	>50
57	0.171	16	>50
58	0.047	3.1	>50
59	0.100	3.8	>50
60	0.045	1.5	>50
61	0.049	n.d.	n.d.
62	0.345	0.74	>50
63	0.196	n.d.	n.d.
64	0.091	n.d.	n.d.
65	0.297	n.d.	n.d.
66	0.069	n.d.	n.d.
67	0.044	n.d.	n.d.
68	0.085	n.d.	n.d.
69	0.241	n.d.	n.d.
70	0.208	n.d.	n.d.
71	1.77	n.d.	n.d.
72	0.088	n.d.	n.d.
73	0.270	n.d.	n.d.
74	0.037	n.d.	n.d.
75	0.063	n.d.	n.d.
76	0.257	n.d.	n.d.
77	0.031	n.d.	n.d.
78	0.267	n.d.	n.d.
79	0.111	n.d.	n.d.
80	0.358	n.d.	n.d.

81	0.049	n.d.	n.d.
82	0.032	n.d.	n.d.
83	0.210	n.d.	n.d.
84	0.072	18.6	>25
85	0.106	5.7	>25
86	0.300	5.2	>50
87	0.950	>50	>50
88	0.363	>50	>50
89	0.162	>50	>50
90	0.231	>50	>50
91	0.104	19.4	>50
92	0.105	>50	>50
93	0.650	>50	>50
94	0.073	>50	>50
95	0.029	>50	>50
96	0.073	7.3	>50
97	0.079	47.0	>50
98	0.010	23.8	>50
99	0.358	38.3	>50
100	0.062	39.9	>50
101	0.075	19.5	>50
102	0.030	9.8	>50
103	0.054	25.9	>50
104	0.140	39.2	>50
105	0.095	25.5	>50
106	0.387	35.1	>50
107	0.269	5.8	>50
108	0.0258	24.0	>50
109	0.090	17.2	>50
110	0.083	1.2	>50

111	0.024	1.5	>50
112	0.127	>50	>50
113	0.032	>50	>50
114	0.013	>50	16.7
115	0.024	1.9	n.d.
116	0.051	3.5	>50
117	0.071	2.2	>50
118	0.116	19.2	>25
119	1.09	n.d.	n.d.
120	0.178	n.d.	n.d.
121	0.019	14.5	>25
122	0.139	8.9	>25
123	0.889	n.d.	n.d.
124	0.577	3.1	>50
125	0.028	0.6	2.1
126	0.588	n.d.	4.5
127	0.031	n.d.	n.d.
128	0.268	n.d.	n.d.
129	0.185	n.d.	n.d.
130	0.022	n.d.	n.d.
131	0.059	n.d.	n.d.
132	0.202	n.d.	n.d.
133	2.20	n.d.	n.d.
134	0.020	n.d.	n.d.
135	0.023	n.d.	n.d.
136	0.136	n.d.	n.d.
137	0.019	n.d.	n.d.
138	0.062	n.d.	n.d.
139	0.211	n.d.	n.d.
140	0.290	n.d.	n.d.

141	0.248	n.d.	n.d.
142	0.068	n.d.	n.d.
143	0.085	n.d.	n.d.
144	0.062	n.d.	n.d.
145	0.024	n.d.	n.d.
146	0.070	n.d.	n.d.
147	0.199	n.d.	n.d.
148	0.034	n.d.	n.d.
149	0.047	n.d.	n.d.
150	0.032	n.d.	n.d.
151	0.172	n.d.	n.d.
152	0.084	14.7	>25
153	0.0123	14.3	>25
154	0.030	9.0	>25
155	0.163	n.d.	n.d.
156	0.031	8.9	>25
157	0.339	n.d.	n.d.
158	1.61	>25	>25
159	0.934	>25	>25
160	0.052	23.5	>25
161	0.211	>25	>25
162	0.061	19.9	>25
163	0.599	6.2	>25
164	0.109	>25	>25
165	1.30	>25	>25
166	0.040	4.7	>25
167	0.788	>25	>25
168	0.051	14.0	>25
169	0.204	10.5	23.7
170	4.44	n.d.	n.d.

171	0.653	n.d.	n.d.
172	1.78	n.d.	n.d.
173	1.11	n.d.	n.d.
174	0.480	>50	>50
175	0.527	n.d.	n.d.
176	0.680	n.d.	n.d.
177	0.120	>50	>50
178	0.238	>50	>50
179	0.184	>50	>50
180		>50	>50
181	0.641	>50	>50
182	0.316	>50	>50
183	0.110	>50	>50
184	0.850	>50	>50
185	0.697	>50	>50
186	7.30	>50	>50
187	0.523	>50	>50
188	0.441	>50	>50
189	0.154	>50	>50
190	2.63	>50	>50
191	0.096	3.8	>50
192	0.186	>50	>50
193	0.082	>50	>50
194	0.631	45.6	>50
195	0.490	>50	>50
196	0.578	>50	>50
197	0.155	>50	>50
198	0.057	>50	>50
199	0.075	25.6	>50
200	0.380	47.8	>50

201	0.097	14.4	>50
202	0.502	>50	>50
203	0.108	15.4	>50
204	0.781	>50	>50
205	0.114	21.3	>50
206	0.840	>50	>50
207	0.110	18.3	>50
208	0.937	>50	>50
209	0.081	16.7	16.7
210		>50	>50
211	0.165	>50	>50
212	0.456	>50	>50
213	0.335	>50	>50
214	4.66	>50	>50
215	0.070	17.0	>50
216	0.269	23.2	>50
217	0.125	12.9	>50
218	0.140	5.6	48.7
219	0.065	18.5	>50
220	0.683	41.9	>50
221	0.354	7.8	>50
222	0.133	35.6	>50
223	0.290	>50	>50
224	0.192	25.7	>50
225	5.35	>50	>50
226	0.898	>50	>50
227	0.407	27.4	>50
228	0.069	1.4	16.7
229	0.095	43.2	>50
230	0.036	32.4	>50

231	0.058	>50	>50
232	0.045	22.4	>50
233	0.058	29.0	>50
234	0.152	>50	>50
235	1.73	>50	>50
236	0.099	>50	>50
237	0.087	>50	>50
238	0.058	34.6	>50
239	0.290	51.2	>50
240	0.121	6.6	>50
241	1.71	>50	>50
242	0.158	14.2	>50
243	0.943	>50	>50
244	3.57	>50	>50
245	1.06	>50	>50
246	0.398	26.2	>50
247	0.030	21.1	>50
248	0.078	>50	>50
249	0.032	21.5	>50
250	0.110	36.7	>50
251	0.071	19.5	>50
252	0.059	14.8	>50
253	0.278	>50	>50
254	5.31	>50	>50
255	0.072	>50	>50
256	0.315	17.6	>50
257	0.049	30.7	>50
258	0.100	18.8	>50
259	0.500	>50	>50
260	0.660	21.5	>50

261	0.154	7.9	>50
262	0.171	14.1	>50
263	1.77	11.9	n.d.
264	0.281	2.3	20.7
265	1.04	7.6	>50
266	0.097	18.6	>50
267	0.347	>50	>50
268	0.060	27.6	>50
269	0.176	12.0	21.5
270	0.065	17.7	>50
271	0.407	31.6	>50
272	0.600	0.0	>50
273	0.303	7.5	>50
274	0.051	26.1	>50
275	0.089	>50	>50
276	0.167	1.5	>50
277	0.269	1.0	16.3
278	0.058	9.0	>50
279	1.22	19.5	>50
280	0.073	0.7	>50
281	0.124	7.0	>50
282	0.108	7.1	>50
283	0.016	4.7	>50
284	0.118	5.3	>50
285	0.248	4.8	>50
286	0.041	29.0	>50
287	0.104	0.0	>50
288	0.105	31.7	>50
289	0.029	3.2	>50
290	0.144	22.2	>50

291	0.057	1.8	34.8
292	0.147	21.7	>50
293	0.011	8.2	44.2
294	0.055	2.3	>50
295	0.024	0.7	>50
296	0.022	14.1	>50
297	0.023	12.5	>50
298	0.058	3.0	>50
299	0.0033	2.1	>50
300	0.020	2.9	>50
301	0.048	3.1	>50
302	0.048	1.9	>50
303	0.014	4.2	>50
304	0.180	12.3	>50
305	0.090	8.6	>50
306	0.017	9.5	>50
307	0.0035	20.5	>50
308	0.0067	2.6	>50
309	0.034	1.9	>50
310	0.046	>50	>50
311	0.072	>50	>50
312	0.064	>50	>50
313	0.069	>50	>50
314	0.192	6.1	>50
315	0.147	6.2	>50
316	0.014	>50	16.7
317	0.018	>50	16.7
318	0.269	10.2	>50
319	0.094	1.4	>50
320	0.077	n.d.	n.d.

321	0.036	1.9	>50
322	0.012	1.4	>50
323	0.060	2.1	>50
324	0.042	1.5	>50
325	0.015	8.2	>50
326	0.023	1.3	>50
327	0.111	2.0	18.4
328	0.012	2.3	>50
329	0.028	1.2	>50
330	1.39	n.d.	n.d.
331	0.143	n.d.	n.d.
332	0.172	>50	>50
333	0.329	>50	>50
334	0.296	>50	>50
335	0.130	>50	>50
336	0.077	25.4	>50
337	0.053	1.2	>50
338	0.258	3.8	>50
339	0.343	12.7	>25
340	0.084	n.d.	n.d.
341	0.037	2.2	16.7
342	0.123	12.7	>25
343	0.156	12.6	>25
344	0.0124	10.8	>50
345	0.132	n.d.	n.d.
346	0.056	7.6	>25
347	0.044	n.d.	n.d.
348	0.180	n.d.	n.d.
349	0.024	n.d.	n.d.
350	0.055	n.d.	n.d.

351	0.048	n.d.	n.d.
352	0.026	n.d.	n.d.
353	0.016	0.1	8.2
354	0.085	7.5	0.7
355	0.011	0.2	3.1
356	0.041	n.d.	n.d.
357	0.032	0.3	7.9
358	0.0081	0.1	2.8
359	0.076	2.9	14.9
360	0.0097	0.7	26.3
361	0.020	n.d.	n.d.
362	0.152	n.d.	n.d.
363	0.100	4.3	n.d.
364	0.310	>50	>50
365	0.300	2.1	14.2
366	0.446	n.d.	n.d.
367	0.508	2.3	1.9
368	0.414	1.4	1.7
369	0.121	0.9	n.d.
370	0.056	1.8	4.5
371	0.055	1.8	6.8
372	0.054	1.4	5.1
374	0.279	0.8	>50
375	0.203	1.3	0.4
376	0.206	0.8	1.4
377	0.346	1.3	19.6
378	0.349	2.2	17.1
379	0.098	1.0	18.8
380	0.174	1.3	0.3
381	0.140	n.d.	n.d.

382	3.24	n.d.	n.d.
383	0.068	2.2	2.3
384	41.0	n.d.	n.d.
385	0.179	1.2	5.6
386	0.267	1.7	4.4
387	0.056	0.0	7.3
388	0.227	0.4	3.2
389	0.327	0.3	1.8
390	0.091	4.2	10.2
391	0.178	2.1	11.7
392	0.466	10.2	6.4
393	0.334	>50	9.5
394	0.563	>50	5.7
395	1.36	11.2	n.d.
396	0.203	6.7	n.d.
397	0.086	2.6	n.d.
398	0.128	1.7	n.d.
399	0.097	1.0	2.7
400	0.076	1.5	1.3
401	0.104	2.7	1.2
402	0.0039	0.6	5.8
403	0.094	0.3	15.8
404	0.069	0.1	7.2
405	0.021	0.3	0.9
406	0.133	0.6	2.0
407	0.046	0.8	5.0
408	0.136	1.6	0.9
409	0.0053	1.5	1.0
410	0.044	n.d.	n.d.
411	0.0009	n.d.	n.d.

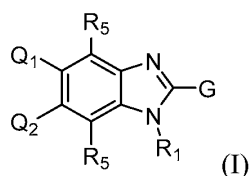
412	0.077	n.d.	n.d.
413	1.88	>50	5.4
414	177	n.d.	n.d.
415	0.065	n.d.	n.d.
416	1.19	n.d.	n.d.
417	0.800	n.d.	n.d.
418	2.51	n.d.	n.d.
419	2.14	2.3	8.4
420	0.136	>50	42.2
421	0.139	0.7	>50
422	0.180	4.0	27.3

n.d.: not determined

CLAIMS

What is claimed is:

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

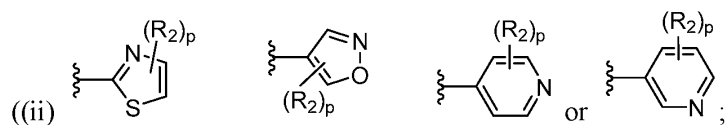


or stereoisomers, tautomer, solvates or salts thereof, wherein:

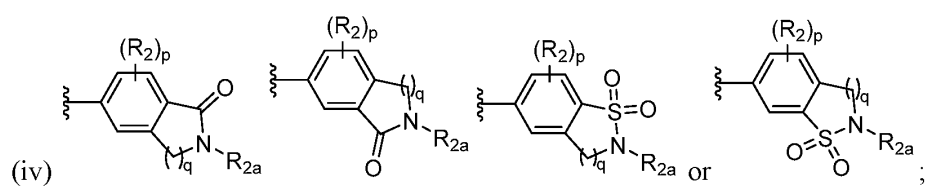
one of Q₁ and Q₂ is A and the other of Q₁ and Q₂ is R₅;

G is:

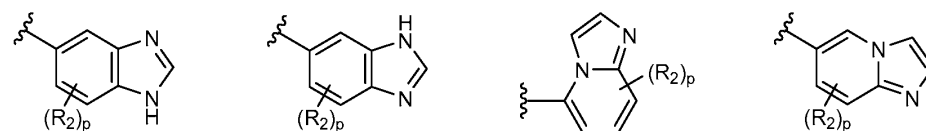
- 10 (i) phenyl substituted with 1 to 2 substituents independently selected from F, Cl, Br, -CN, C₁₋₃ alkyl, C₁₋₂ fluoroalkyl, C₁₋₃ alkoxy, C₁₋₂ fluoroalkoxy, C₃₋₆ cycloalkyl, -NR_xR_x, -C(O)NR_yR_y, -S(O)₂(C₁₋₃ alkyl), -S(O)₂(phenyl), -S(O)₂NR_xR_x, -NR_xS(O)₂(C₁₋₃ alkyl), -S(O)(NH)NR_xR_x, and -P(O)(OCH₂CH₃)₂;

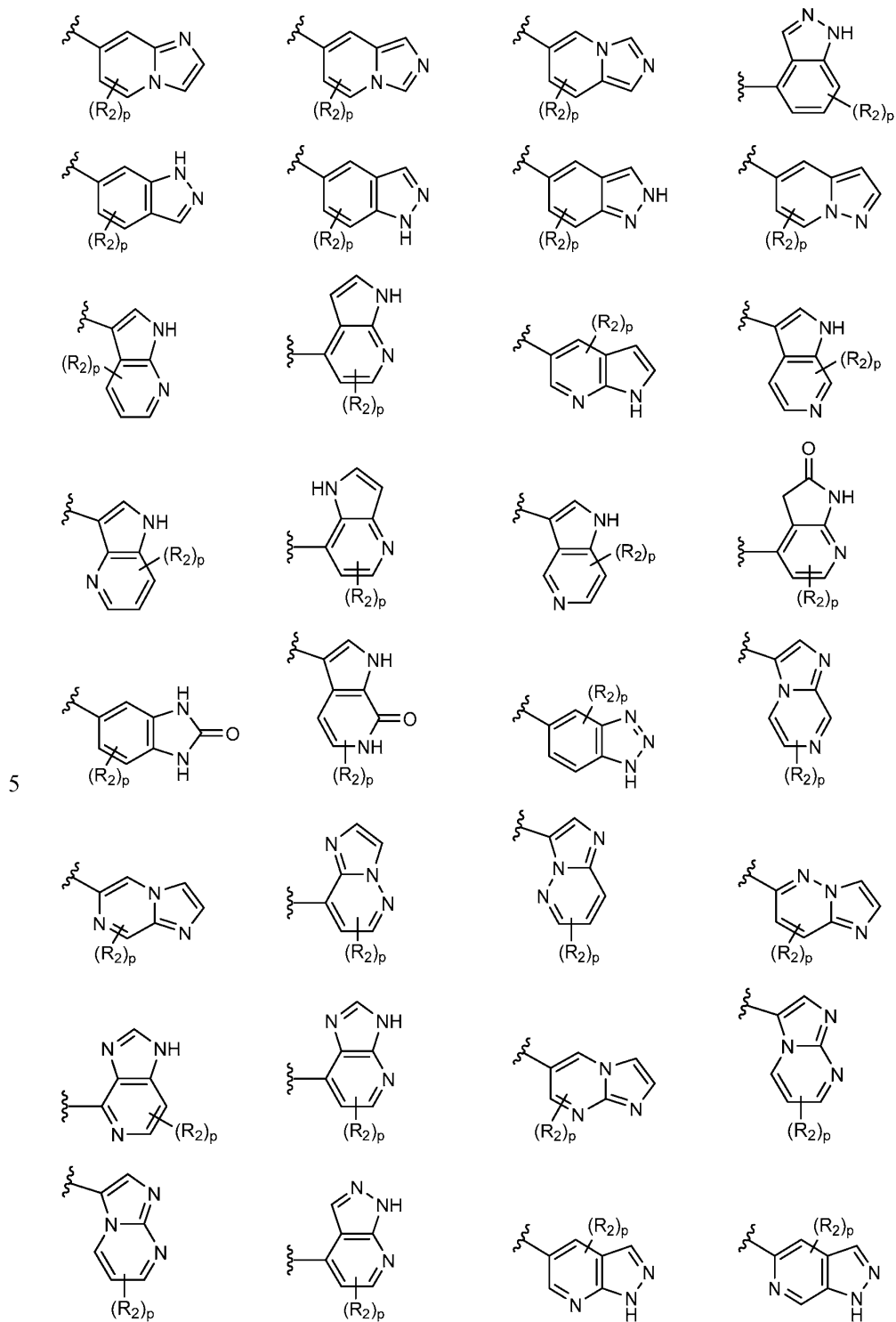


- 15 (iii)
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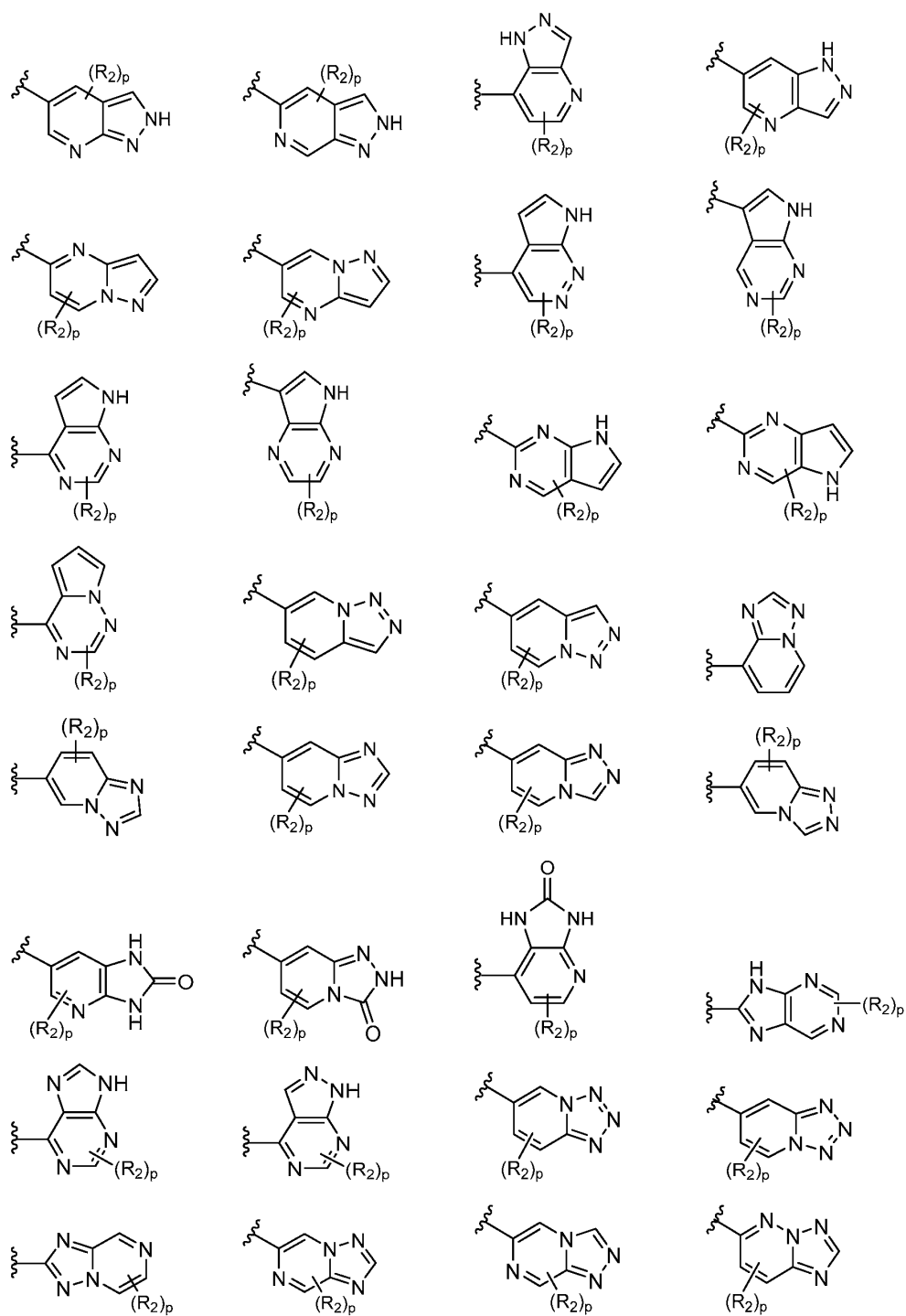


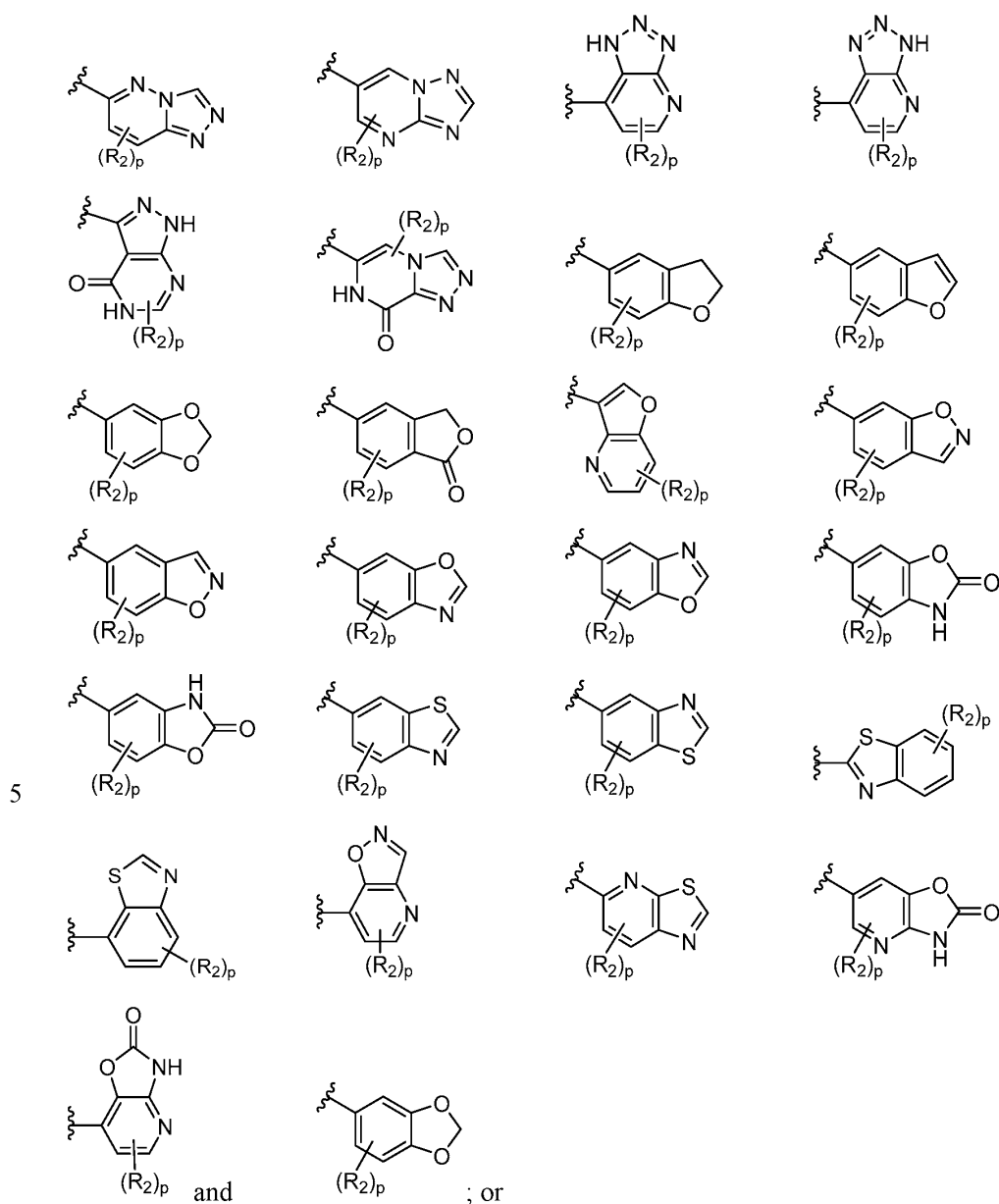
(v) a 9-membered heterocyclic ring selected from:



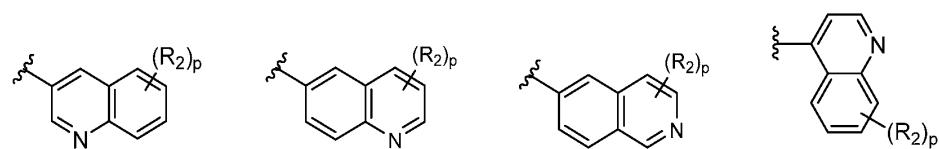


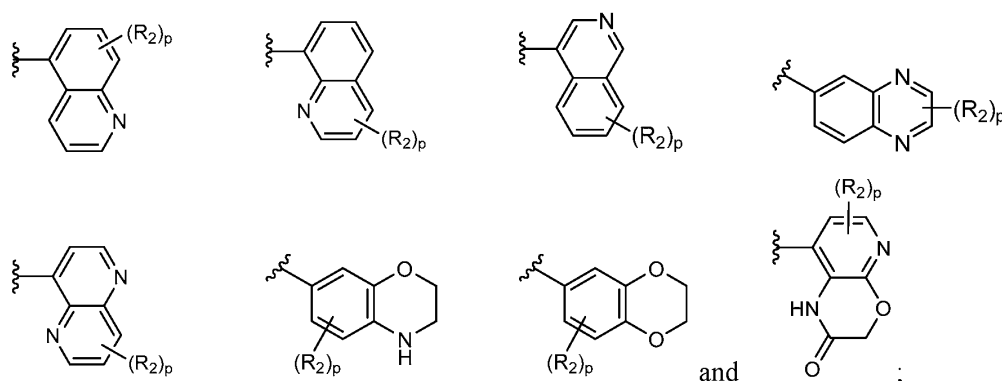
5





(vi) 10-membered heterocyclic ring selected from:





A is piperidinyl, phenyl, pyridinyl, pyrimidinyl, 6-azabicyclo[3.2.1]octanyl, or azabicyclo[3.2.1]octanyl, each substituted with $-L-R_4$ and zero to 3 R_{4b} ;

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

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

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

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

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

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

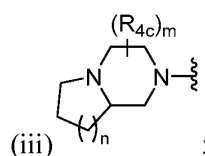
R_{2c} is R_{2a} or R_{2b} ;

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

5 R_4 is:

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

(ii) pyrrolidinyl, piperidinyl, piperazinyl, or pyridinyl, each substituted with zero to 2 R_{4a} ; or



10 each R_{4a} is independently C_{1-6} alkyl, C_{1-3} fluoroalkyl, $-(\text{CH}_2)_{1-2}\text{O}(\text{C}_{1-2} \text{ alkyl})$, C_{3-6} cycloalkyl, $-\text{CH}_2(\text{C}_{3-6} \text{ cycloalkyl})$, $-\text{CH}_2(\text{oxetanyl})$, $-\text{C}(\text{O})(\text{C}_{1-4} \text{ alkyl})$, $-\text{C}(\text{O})(\text{C}_{3-6} \text{ cycloalkyl})$, $-\text{C}(\text{O})(\text{phenyl})$, $-\text{C}(\text{O})\text{CH}_2(\text{C}_{3-6} \text{ cycloalkyl})$, $-\text{C}(\text{O})\text{CH}_2(\text{phenyl})$, $-\text{C}(\text{O})\text{O}(\text{C}_{1-4} \text{ alkyl})$, $-\text{NR}_x(\text{C}_{1-3} \text{ alkyl})$, $-\text{NR}_x(\text{C}_{3-6} \text{ cycloalkyl})$, azetidiny, oxetanyl, tetrahydropyranyl, pyrrolidinyl, phenyl, or piperidinyl substituted with zero to 2

15 substituents selected from $-\text{OH}$ or $-\text{CH}_3$;

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

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

each R_5 is independently hydrogen, F, Cl, C_{1-2} alkyl, C_{1-2} fluoroalkyl, or cyclopropyl;

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

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

m is zero, 1, or 2;

n is zero, 1, or 2;

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

25 q is 1 or 2.

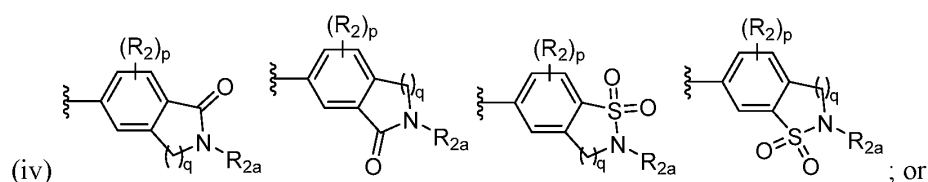
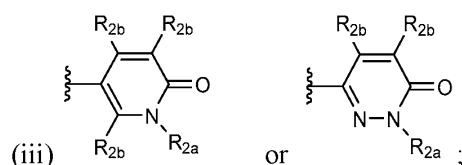
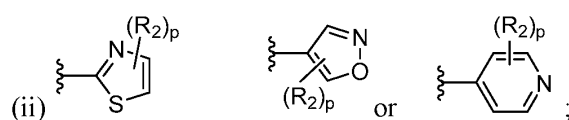
2. The compound according to claim 1 or stereoisomers, tautomer, solvates or salts thereof, wherein Q_1 is R_5 and Q_2 is A.

3. The compound according to claim 1 or stereoisomers, tautomer, solvates or salts thereof, wherein Q₁ is A and Q₂ is R₅.

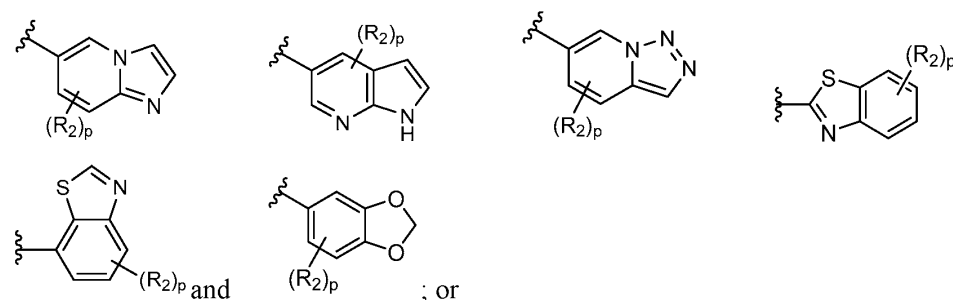
5 4. The compound according to claim 1 or stereoisomers, tautomer, solvates or salts thereof, wherein:

G is:

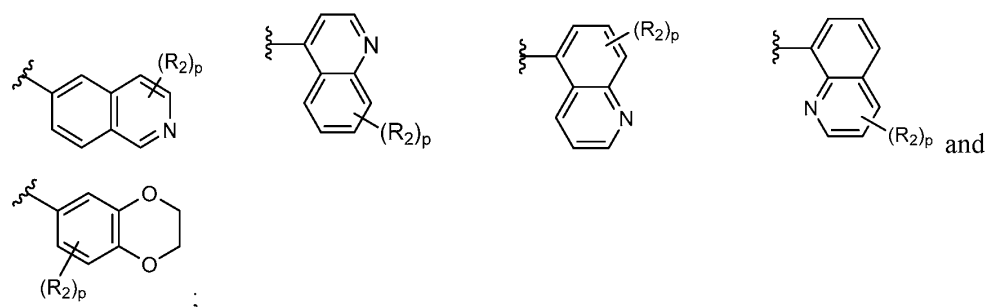
(i) phenyl substituted with 1 to 2 substituents independently selected from F, Cl, Br, -CN, -CH₃, -OCH₃, -OCHF₂, -OCF₃, cyclopropyl, -C(O)NR_yR_y, -N(CH₃)₂, -S(O)₂CH₃,
 10 -S(O)₂(phenyl), -S(O)₂NR_xR_x, -NHS(O)₂CH₃, -S(O)(NH)NR_xR_x, and
 -P(O)(OCH₂CH₃)₂;



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



(vi) 10-membered heterocyclic ring selected from:



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

5 L is a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{O}-$, or $-\text{C}(\text{O})(\text{CH}_2)_{0-2}-$;

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

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, $-(\text{CH}_2)_{0-2}\text{O}(\text{C}_{1-3} \text{ alkyl})$, C_{3-6} cycloalkyl,

$-\text{NR}_x\text{R}_x$, $-(\text{CH}_2)_{0-2}\text{C}(\text{O})\text{NR}_x\text{R}_x$, $-\text{CH}_2(\text{C}_{3-6} \text{ cycloalkyl})$, $-\text{CH}_2(\text{phenyl})$, or phenyl;

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

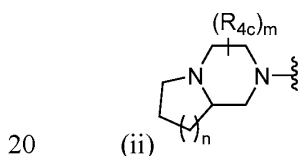
each R_{2b} is independently hydrogen, F, Cl, $-\text{CN}$, $-\text{NR}_x\text{R}_x$, C_{1-6} alkyl, C_{1-2} fluoroalkyl,

C_{1-3} hydroxyalkyl, $-(\text{CH}_2)_{0-2}\text{O}(\text{C}_{1-2} \text{ alkyl})$, $-(\text{CH}_2)_{0-2}\text{C}(\text{O})\text{NR}_x\text{R}_x$,

15 $-(\text{CH}_2)_{1-3}(\text{cyclopropyl})$, $-\text{C}(\text{O})\text{O}(\text{C}_{1-2} \text{ alkyl})$, $-\text{C}(\text{O})\text{NR}_x(\text{C}_{1-3} \text{ alkyl})$, $-\text{CR}_x=\text{CH}_2$, or $-\text{CH}=\text{CH}(\text{C}_{3-6} \text{ cycloalkyl})$;

R_4 is:

(i) pyrrolidinyl, piperidinyl, piperazinyl, pyridinyl, azaspiro[3.3]heptanyl, or azabicyclo[3.2.1]octanyl, each substituted with zero to 2 R_{4a} ; or



each R_{4a} is independently C_{1-6} alkyl, C_{1-3} fluoroalkyl, $-(\text{CH}_2)_{1-2}\text{OCH}_3$, C_{3-6} cycloalkyl,

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

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

—NR_x(C₁₋₃ alkyl), —NR_x(cyclopropyl), azetidiny, oxetanyl, tetrahydropyranyl, pyrrolidinyl, phenyl, or piperidinyl substituted with zero to 2 substituents selected from —OH or —CH₃;

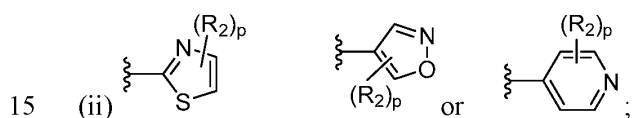
R_{4b} is F or —CH₃;

- 5 each R_{4c} is independently C₁₋₆ alkyl, C₁₋₃ fluoroalkyl, —CH₂(C₃₋₆ cycloalkyl), —C(O)(C₁₋₄ alkyl), —C(O)(phenyl), —C(O)CH₂(phenyl), —C(O)OCH₂CH₃, or C₃₋₆ cycloalkyl; and each R₅ is independently hydrogen, F, Cl, C₁₋₂ alkyl, C₁₋₂ fluoroalkyl, or cyclopropyl.

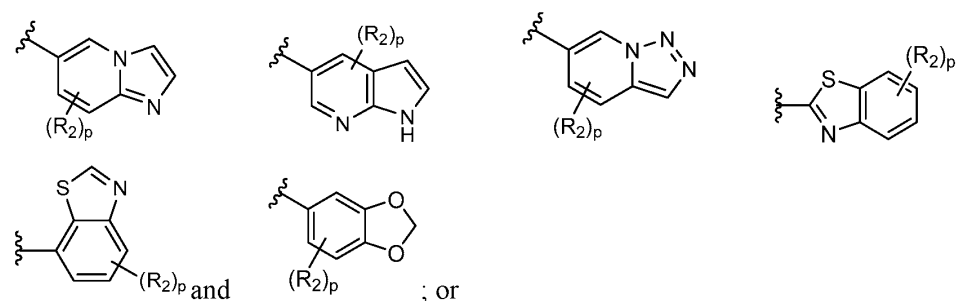
5. The compound according to claim 1 or stereoisomers, tautomer, solvates or salts thereof, wherein:

G is:

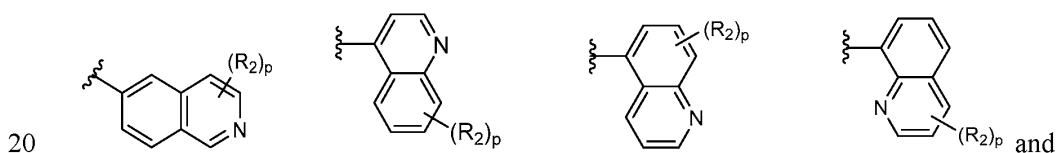
- (i) phenyl substituted with zero to 2 substituents independently selected from F, Cl, Br, —CN, —CH₃, —OCH₃, —OCHF₂, —OCF₃, cyclopropyl, —N(CH₃)₂, —S(O)₂CH₃, —S(O)₂(phenyl), —NHS(O)₂CH₃, and —P(O)(OCH₂CH₃)₂;

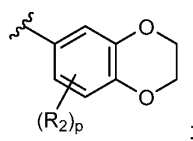


- (iii) a 9-membered heterocyclic ring selected from:



- (iv) 10-membered heterocyclic ring selected from:





- A is piperidinyl, phenyl, pyridinyl, or azabicyclo[3.2.1]octanyl, each substituted with $-L-R_4$ and zero to 2 R_{4b} ;
- L is a bond, $-CH_2-$, $-CH_2CH_2-$, or $-O-$;
- 5 R_1 is hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CHF_2$, or cyclopropyl;
each R_2 is independently F, $-CH_3$, or $-OCH_3$;
- R_4 is pyrrolidinyl, piperidinyl, piperazinyl, azepanyl, diazepanyl, pyridinyl, azaspiro[3.3]heptanyl, azabicyclo[3.2.1]octanyl, diazaspiro[3.3]heptanyl, or hexahydropyrrolo[3,4-c]pyrrolyl, each substituted with zero to 2 R_{4a} ;
- 10 R_{4a} is independently $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH_2CH_2OCH_3$, $-C(O)CH(CH_3)_2$, cyclopropyl, cyclobutyl, $-CH_2(cyclopropyl)$, $-CH_2(cyclobutyl)$, $-CH_2(oxetanyl)$, $-N(CH_3)_2$, $-N(CH_3)(CH_2CH_3)$, $-N(CH_3)(cyclopropyl)$, azetidiny, oxetanyl, tetrahydropyranyl, pyrrolidinyl, phenyl, or piperidinyl substituted with zero to 2 substituents selected from $-OH$ or $-CH_3$; and
- 15 each R_5 is independently hydrogen, $-CH_3$, or $-CF_3$.
6. The compound according to claim 5 or stereoisomers, tautomer, solvates or salts thereof, wherein:
- Q_1 is R_5 ;
- 20 Q_2 is A.
7. The compound according to claim 1 or stereoisomers, tautomer, solvates or salts thereof, wherein:
- Q_1 is A;
- 25 Q_2 is R_5 ;
- G is dimethoxyphenyl;
- A is piperidinyl substituted with $-L-R_4$;
- L is a bond;
- R_1 is hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, or $-CH_2CHF_2$;

each R₂ is independently F, -CH₃, or -OCH₃;

R₄ is piperidinyl substituted with R_{4a};

R_{4a} is independently -CH(CH₃)₂, -CH₂CH(CH₃)₂, or cyclopropyl; and

each R₅ is independently hydrogen or -CF₃.

5

8. The compound according to claim 1 or stereoisomers, tautomer, solvates or salts thereof, wherein said compound is:

2-(3,4-dimethoxyphenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1-methyl-1H-benzo[d]imidazole (26);

10 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3,4-dimethoxyphenyl)-1-methyl-1H-benzo[d]imidazole (27);

2-(3,4-dimethoxyphenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (28);

15 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3,4-dimethoxyphenyl)-1H-benzo[d]imidazole (29);

2-(3,4-dimethoxyphenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1-isopropyl-1H-benzo[d]imidazole (30);

6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3,4-dimethoxyphenyl)-1-isopropyl-1H-benzo[d]imidazole (31);

20 1-(2,2-difluoroethyl)-2-(3,4-dimethoxyphenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (32);

6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-1-(2,2-difluoroethyl)-2-(3,4-dimethoxyphenyl)-1H-benzo[d]imidazole (33);

25 2-(3,4-dimethoxyphenyl)-5-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1-methyl-1H-benzo[d]imidazole (34);

5-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3,4-dimethoxyphenyl)-1-methyl-1H-benzo[d]imidazole (35);

2-(3,4-dimethoxyphenyl)-5-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1-isopropyl-1H-benzo[d]imidazole (36);

30 5-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3,4-dimethoxyphenyl)-1-isopropyl-1H-benzo[d]imidazole (37);

- 1-(2,2-difluoroethyl)-2-(3,4-dimethoxyphenyl)-5-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (38);
- 5-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-1-(2,2-difluoroethyl)-2-(3,4-dimethoxyphenyl)-1H-benzo[d]imidazole (39);
- 5 2-(3,4-dimethoxyphenyl)-1-ethyl-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (40);
- 2-(3,4-dimethoxyphenyl)-1-ethyl-5-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (41);
- 2-(3,4-dimethoxyphenyl)-5-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-6-(trifluoromethyl)-10 1H-benzo[d]imidazole (42);
- 2-(3,4-dimethoxyphenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole tris(2,2,2-trifluoroacetate) (43);
- 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3,4-dimethoxyphenyl)-4-methyl-1H-benzo[d]imidazole (44);
- 15 2-(3,4-dimethoxyphenyl)-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-1H-benzo[d]imidazole (45);
- 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3,4-dimethoxyphenyl)-1,4-dimethyl-1H-benzo[d]imidazole tris(2,2,2-trifluoroacetate) (46);
- 2-(3,4-dimethoxyphenyl)-6-(1-(2-isobutyl-2-azaspiro[3.3]heptan-6-yl)piperidin-4-yl)-1,4-dimethyl-1H-benzo[d]imidazole tris(2,2,2-trifluoroacetate) (47);
- 20 1,4-dimethyl-1H-benzo[d]imidazole tris(2,2,2-trifluoroacetate) (47);
- 6-(1-(2-(cyclopropylmethyl)-2-azaspiro[3.3]heptan-6-yl)piperidin-4-yl)-2-(3,4-dimethoxyphenyl)-1,4-dimethyl-1H-benzo[d]imidazole (48);
- 6-(1-(2-cyclobutyl-2-azaspiro[3.3]heptan-6-yl)piperidin-4-yl)-2-(3,4-dimethoxyphenyl)-1,4-dimethyl-1H-benzo[d]imidazole (49);
- 25 2-(3,4-dimethoxyphenyl)-6-(8-(1-isobutylpiperidin-4-yl)-8-azabicyclo[3.2.1]octan-3-yl)-1,4-dimethyl-1H-benzo[d]imidazole (50);
- 6-(8-(1-cyclopropylpiperidin-4-yl)-8-azabicyclo[3.2.1]octan-3-yl)-2-(3,4-dimethoxyphenyl)-1,4-dimethyl-1H-benzo[d]imidazole (51);
- 6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (52);
- 30 1H-benzo[d]imidazole (52);
- 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (53);

- 2-(3-fluoro-4-methoxyphenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-1H-benzo[d]imidazole (54);
- 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3-fluoro-4-methoxyphenyl)-1,4-dimethyl-1H-benzo[d]imidazole (55);
- 5 2-(3-fluoro-4-methoxyphenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole (56);
- 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3-fluoro-4-methoxyphenyl)-4-methyl-1H-benzo[d]imidazole (57);
- 6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole tris(2,2,2-trifluoroacetate) (58);
- 10 4-(6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazol-2-yl)quinoline (59);
- 2-(2,6-dimethylpyridin-4-yl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole (60);
- 15 6-(6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazol-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine tris(2,2,2-trifluoroacetate) (61);
- 2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole (62);
- 6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-2-(4-(trifluoromethoxy)phenyl)-1H-benzo[d]imidazole (63);
- 20 2-(3-chloro-4-methoxyphenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole (64);
- 2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole tris(2,2,2-trifluoroacetate) (65);
- 25 2-(3-fluoro-4-(methylsulfonyl)phenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole (66);
- 2-(3-bromo-4-(methylsulfonyl)phenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole (67);
- 2-(4-cyclopropylphenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole (68);
- 30 2-(4-(difluoromethoxy)-3-fluorophenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole tris(2,2,2-trifluoroacetate) (69);

- 2-(6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazol-2-yl)benzo[d]thiazole tris(2,2,2-trifluoroacetate) (70);
- 4-(6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazol-2-yl)-3,5-dimethylisoxazole (71);
- 5 5-(6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazol-2-yl)quinoline tris(2,2,2-trifluoroacetate) (72);
- 2-(3-chloro-4-(trifluoromethoxy)phenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole tris(2,2,2-trifluoroacetate) (73);
- 6-(6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazol-2-yl)isoquinoline (74);
- 6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-2-(4-(phenylsulfonyl)phenyl)-1H-benzo[d]imidazole tris(2,2,2-trifluoroacetate) (75);
- 2-(3-(difluoromethoxy)phenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole (76);
- 15 7-(6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazol-2-yl)benzo[d]thiazole (77);
- 2-(4-(difluoromethoxy)phenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazole (78);
- 2-(6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazol-2-yl)thiazole
- 20 (79);
- 6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-2-(2-(trifluoromethoxy)phenyl)-1H-benzo[d]imidazole tris(2,2,2-trifluoroacetate) (80);
- 6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-2-(1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-benzo[d]imidazole (81);
- 25 8-(6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-4-methyl-1H-benzo[d]imidazol-2-yl)quinoline (82);
- 2-(3,4-dimethoxyphenyl)-4-fluoro-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (83);
- 6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (84-85);
- 30 6-(4-(4-isopropylpiperazin-1-yl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (86);

- 7-fluoro-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (87);
- 4-fluoro-5-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (88);
- 5 4-fluoro-5-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (89-90);
- 7-fluoro-5-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (91);
- 7-fluoro-5-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-methyl-2-
- 10 (4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (92-93);
- 7-fluoro-6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (94-95);
- 5-fluoro-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (96);
- 15 5-fluoro-6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (97-98);
- 6-fluoro-5-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (99);
- 6-fluoro-5-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-methyl-2-
- 20 (4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (100-101);
- 7-fluoro-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (102);
- 7-fluoro-6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-methyl-2-
- (4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (103-104);
- 25 4-fluoro-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (105);
- 4-fluoro-6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-methyl-2-
- (4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (106-107);
- 4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(1-(oxetan-3-yl)azepan-4-yl)
- 30 piperidin-4-yl)-1H-benzo[d]imidazole (108-109);
- 6-(1-(1-cyclobutylazepan-4-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (110-111);

- 4-(6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-1H-benzo[d]imidazol-2-yl) benzenesulfonamide (112);
- 7-fluoro-6-(1-(1-isopropylazepan-4-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (113-114);
- 5 1-cyclopropyl-4-fluoro-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (115);
- 1-cyclopropyl-4-fluoro-6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (116-117);
- 6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (118);
- 10 6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (119);
- 6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1,5-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (120);
- 15 6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (121);
- 2-(3-fluoro-4-(methylsulfonyl)phenyl)-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-1H-benzo[d]imidazole (122);
- 6-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(3-fluoro-4-(methylsulfonyl)phenyl)-1,4-dimethyl-1H-benzo[d]imidazole (123-124);
- 20 6-(6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-1H-benzo[d]imidazol-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (125);
- 6-(6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-1H-benzo[d]imidazol-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (126);
- 25 2-(3,4-dimethoxyphenyl)-4-fluoro-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (127);
- 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3,4-dimethoxyphenyl)-4-fluoro-1H-benzo[d]imidazole (128);
- 2-(3,4-dimethoxyphenyl)-5-fluoro-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (129);
- 30 2-(3,4-dimethoxyphenyl)-5-fluoro-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (130);

- 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3,4-dimethoxyphenyl)-5-fluoro-1H-benzo[d]imidazole (131);
- 2-(3,4-dimethoxyphenyl)-7-fluoro-6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (132);
- 5 2-(3,4-dimethoxyphenyl)-7-fluoro-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (133);
- 6-(1-(1-isopropylazepan-4-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (134);
- 6-(1-(1-cyclobutylazepan-4-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-
- 10 (methylsulfonyl)phenyl)-1H-benzo[d]imidazole (135);
- 6-(1-(1-isobutylazepan-4-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (136);
- 6-(1-(1-(cyclopropylmethyl)azepan-4-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (137);
- 15 6-(1-(1-(cyclobutylmethyl)azepan-4-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (138);
- 6-(1-(2-isopropyl-2-azaspiro[3.3]heptan-6-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (139);
- 6-(1-(2-cyclobutyl-2-azaspiro[3.3]heptan-6-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-
- 20 (methylsulfonyl)phenyl)-1H-benzo[d]imidazole (140);
- 6-(1-(2-isobutyl-2-azaspiro[3.3]heptan-6-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (141);
- 6-(1-(2-(cyclopropylmethyl)-2-azaspiro[3.3]heptan-6-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (142);
- 25 6-(1-(2-(cyclobutylmethyl)-2-azaspiro[3.3]heptan-6-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (143);
- 2-(3,4-dimethoxyphenyl)-6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-1H-benzo[d]imidazole (144-145);
- 6-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(3,4-
- 30 dimethoxyphenyl)-1,4-dimethyl-1H-benzo[d]imidazole (146-147);
- 6-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(3,4-dimethoxyphenyl)-1,4-dimethyl-1H-benzo[d]imidazole (148-149);

- 6-(1-(8-(cyclobutylmethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(3,4-dimethoxyphenyl)-1,4-dimethyl-1H-benzo[d]imidazole (150-151);
- 6-(1-(8-(cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (152-153);
- 5 6-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (154-155);
- 6-(1-(8-(cyclobutylmethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (156-157);
- 1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(8-(oxetan-3-yl)-8-
- 10 azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1H-benzo[d]imidazole (158-159);
- 1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(8-(tetrahydro-2H-pyran-4-yl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1H-benzo[d]imidazole (160-161);
- 6-(1-(8-(2-methoxyethyl)-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (162-163);
- 15 2-(3,4-dimethoxyphenyl)-1,4-dimethyl-6-(1-(8-(oxetan-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1H-benzo[d]imidazole (164-165);
- 2-(3,4-dimethoxyphenyl)-1,4-dimethyl-6-(1-(8-(tetrahydro-2H-pyran-4-yl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1H-benzo[d]imidazole (166-167);
- 2-(3,4-dimethoxyphenyl)-6-(1-(8-(2-methoxyethyl)-8-azabicyclo[3.2.1]octan-3-
- 20 yl)piperidin-4-yl)-1,4-dimethyl-1H-benzo[d]imidazole (168-169);
- 6-(4-(4-isobutylpiperazin-1-yl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (170);
- 6-(4-(4-(cyclopropylmethyl)piperazin-1-yl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (171);
- 25 6-(4-(4-(cyclobutylmethyl)piperazin-1-yl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (172);
- 6-(4-(4-(2-methoxyethyl)piperazin-1-yl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (173);
- 6-(4-(4-cyclobutylpiperazin-1-yl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-
- 30 1H-benzo[d]imidazole (174);
- 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3,4-dimethoxyphenyl)-7-fluoro-1H-benzo[d]imidazole (175);

- 1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(4-(4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl)phenyl)-1H-benzo[d]imidazole (176);
- 7-fluoro-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (177);
- 5 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-7-fluoro-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (178);
- 6-(1'-(cyclopropylmethyl)-[1,4'-bipiperidin]-4-yl)-7-fluoro-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (179);
- 6-(1'-cyclobutyl-[1,4'-bipiperidin]-4-yl)-7-fluoro-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (180);
- 10 7-fluoro-2-(4-(methylsulfonyl)phenyl)-6-(1'-(oxetan-3-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (181);
- 7-fluoro-2-(4-(methylsulfonyl)phenyl)-6-(1'-(tetrahydro-2H-pyran-4-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (182);
- 15 7-fluoro-2-(4-(methylsulfonyl)phenyl)-6-(1'-(oxetan-3-ylmethyl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (183);
- 4-fluoro-5-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (184);
- 5-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (185);
- 20 4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1'-(oxetan-3-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (186);
- 4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1'-(tetrahydro-2H-pyran-4-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (187);
- 25 4-fluoro-5-(1'-(2-methoxyethyl)-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (188);
- 4-fluoro-5-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (189-190);
- 5-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (191-192);
- 30 4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1-(8-(oxetan-3-ylmethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1H-benzo[d]imidazole (193-194);

- 4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1-(8-(oxetan-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1H-benzo[d]imidazole (195-196);
- 4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1-(8-(tetrahydro-2H-pyran-4-yl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1H-benzo[d]imidazole (197-198);
- 5 4-fluoro-5-(1-(8-(2-methoxyethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (199-200);
- 7-fluoro-5-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (201);
- 5-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (202);
- 10 5-(1'-(cyclopropylmethyl)-[1,4'-bipiperidin]-4-yl)-7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (203);
- 7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1'-(oxetan-3-ylmethyl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (204);
- 15 5-(1'-cyclobutyl-[1,4'-bipiperidin]-4-yl)-7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (205);
- 7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1'-(oxetan-3-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (206);
- 7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1'-(tetrahydro-2H-pyran-4-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (207);
- 20 7-fluoro-5-(1'-(2-methoxyethyl)-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (208);
- 7-fluoro-5-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (209-210);
- 25 7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1-(8-(tetrahydro-2H-pyran-4-yl)-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-1H-benzo[d]imidazole (211-212);
- 7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1-(8-(oxetan-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1H-benzo[d]imidazole (213-214);
- 5-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (215-216);
- 30 5-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (217-218);

- 7-fluoro-6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (219-220);
- 5-fluoro-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (221);
- 5 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-5-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (222);
- 6-(1'-cyclobutyl-[1,4'-bipiperidin]-4-yl)-5-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (223);
- 6-(1'-(cyclopropylmethyl)-[1,4'-bipiperidin]-4-yl)-5-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (224);
- 10 5-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1'-(oxetan-3-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (225);
- 5-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1'-(tetrahydro-2H-pyran-4-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (226);
- 15 5-fluoro-6-(1'-(2-methoxyethyl)-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (227);
- 5-fluoro-6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (228-229);
- 6-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-5-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (230-231);
- 20 6-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-5-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (232-233);
- 5-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(8-(oxetan-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1H-benzo[d]imidazole (234-235);
- 25 5-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(8-(tetrahydro-2H-pyran-4-yl)-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-1H-benzo[d]imidazole (236-237);
- 5-fluoro-6-(1-(8-(2-methoxyethyl)-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (238-239);
- 6-fluoro-5-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (240);
- 30 5-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-6-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (241);

- 5-(1'-(cyclopropylmethyl)-[1,4'-bipiperidin]-4-yl)-6-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (242);
- 5-(1'-cyclobutyl-[1,4'-bipiperidin]-4-yl)-6-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (243);
- 5 6-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1'-(oxetan-3-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (244);
- 6-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1'-(tetrahydro-2H-pyran-4-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (245);
- 6-fluoro-5-(1'-(2-methoxyethyl)-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (246);
- 10 6-fluoro-5-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (247-248);
- 5-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-6-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (249-250);
- 15 5-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-6-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (251-252);
- 6-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1-(8-(oxetan-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1H-benzo[d]imidazole (253-254);
- 6-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-5-(1-(8-(tetrahydro-2H-pyran-4-yl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1H-benzo[d]imidazole (255-256);
- 20 6-fluoro-5-(1-(8-(2-methoxyethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (257-258);
- 7-fluoro-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (259);
- 25 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (260);
- 6-(1'-(cyclopropylmethyl)-[1,4'-bipiperidin]-4-yl)-7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (261);
- 6-(1'-cyclobutyl-[1,4'-bipiperidin]-4-yl)-7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (262);
- 30 7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1'-(oxetan-3-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (263);

- 7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1'-(tetrahydro-2H-pyran-4-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (264);
- 7-fluoro-6-(1'-(2-methoxyethyl)-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (265);
- 5 7-fluoro-6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (266-267);
- 6-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (268-269);
- 6-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-7-fluoro-1-methyl-2-
- 10 (4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (270-271);
- 7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(8-(oxetan-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1H-benzo[d]imidazole (272-273);
- 7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(8-(tetrahydro-2H-pyran-4-yl)-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-1H-benzo[d]imidazole (274-275);
- 15 7-fluoro-6-(1-(8-(2-methoxyethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (276-277);
- 4-fluoro-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (278);
- 4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1'-(oxetan-3-yl)-[1,4'-bipiperidin]-
- 20 4-yl)-1H-benzo[d]imidazole (279);
- 4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1'-(tetrahydro-2H-pyran-4-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (280);
- 4-fluoro-6-(1'-(2-methoxyethyl)-[1,4'-bipiperidin]-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (281);
- 25 6-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (282-283);
- 4-fluoro-6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (284-285);
- 4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(8-(oxetan-3-yl)-8-
- 30 azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1H-benzo[d]imidazole (286-287);
- 4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(8-(tetrahydro-2H-pyran-4-yl)-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-1H-benzo[d]imidazole (288-289);

- 4-fluoro-6-(1-(8-(2-methoxyethyl)-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (290-291);
- 6-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (292-293);
- 5 4-fluoro-6-(1-(1-isopropylazepan-4-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (294-295);
- 4-fluoro-6-(1-(1-isobutylazepan-4-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (296-297);
- 6-(1-(1-(cyclopropylmethyl)azepan-4-yl)piperidin-4-yl)-4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (298-299);
- 10 4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(1-(tetrahydro-2H-pyran-4-yl)azepan-4-yl)piperidin-4-yl)-1H-benzo[d]imidazole (300-301);
- 4-fluoro-6-(1-(1-(2-methoxyethyl)azepan-4-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (302-303);
- 15 1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(1-(oxetan-3-yl) azepan-4-yl) piperidin-4-yl)-1H-benzo[d]imidazole (304-305);
- 1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(1-(tetrahydro-2H-pyran-4-yl)azepan-4-yl)piperidin-4-yl)-1H-benzo[d]imidazole (306-307);
- 6-(1-(1-(2-methoxyethyl)azepan-4-yl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (308-309);
- 20 7-fluoro-6-(1-(1-isobutylazepan-4-yl)piperidin-4-yl)-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (310-311);
- 6-(1-(1-cyclobutylazepan-4-yl)piperidin-4-yl)-7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (312-313);
- 25 7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(1-(oxetan-3-yl)azepan-4-yl)piperidin-4-yl)-1H-benzo[d]imidazole (314-315);
- 7-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(1-(1-(tetrahydro-2H-pyran-4-yl)azepan-4-yl)piperidin-4-yl)-1H-benzo[d]imidazole (316-317);
- 1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(1'-phenyl-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (318);
- 30 1-cyclopropyl-4-fluoro-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (319);

- 1-cyclopropyl-6-(1'-(cyclopropylmethyl)-[1,4'-bipiperidin]-4-yl)-4-fluoro-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (320);
- 1-cyclopropyl-4-fluoro-2-(4-(methylsulfonyl)phenyl)-6-(1'-(tetrahydro-2H-pyran-4-yl)-[1,4'-bipiperidin]-4-yl)-1H-benzo[d]imidazole (321);
- 5 1-cyclopropyl-4-fluoro-6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (322-323);
- 1-cyclopropyl-6-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-fluoro-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (324-325);
- 6-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1-cyclopropyl-4-
10 fluoro-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (326-327);
- 1-cyclopropyl-4-fluoro-2-(4-(methylsulfonyl)phenyl)-6-(1-(8-(tetrahydro-2H-pyran-4-yl)-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-1H-benzo[d]imidazole (328-329);
- 6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1,7-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (330);
- 15 6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1,5-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (331);
- 6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (332-333);
- 6-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-methyl-2-(4-
20 (methylsulfonyl)phenyl)-1H-benzo[d]imidazole (334);
- 6-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl) piperidin-4-yl)-4-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (335-336);
- 6-(1'-cyclobutyl-[1,4'-bipiperidin]-4-yl)-2-(3-fluoro-4-(methylsulfonyl)phenyl)-1,4-dimethyl-1H-benzo[d]imidazole (337);
- 25 6-(1'-(cyclopropylmethyl)-[1,4'-bipiperidin]-4-yl)-2-(3-fluoro-4-(methylsulfonyl)phenyl)-1,4-dimethyl-1H-benzo[d]imidazole (338);
- 6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-2-(3-fluoro-4-(methylsulfonyl)phenyl)-1,4-dimethyl-1H-benzo[d]imidazole (339);
- 6-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(3-
30 fluoro-4-(methylsulfonyl)phenyl)-1,4-dimethyl-1H-benzo[d]imidazole (340-341);
- 2-(3-fluoro-4-(methylsulfonyl)phenyl)-6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-1H-benzo[d]imidazole (342);

- 2-(3-fluoro-4-(methylsulfonyl)phenyl)-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-1H-benzo[d]imidazole (343);
- 2-(3-fluoro-4-(methylsulfonyl)phenyl)-6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-1H-benzo[d]imidazole (344);
- 5 6-(1-(8-cyclopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(3-fluoro-4-(methylsulfonyl)phenyl)-1,4-dimethyl-1H-benzo[d]imidazole (345);
- 2-(3-fluoro-4-(methylsulfonyl)phenyl)-6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-methyl-1H-benzo[d]imidazole (346);
- 6-(1-(8-cyclopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(3-fluoro-4-(methylsulfonyl)phenyl)-4-methyl-1H-benzo[d]imidazole (347);
- 10 2-(3-fluoro-4-(methylsulfonyl)phenyl)-6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-methyl-1H-benzo[d]imidazole (348);
- 6-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(3-fluoro-4-(methylsulfonyl)phenyl)-4-methyl-1H-benzo[d]imidazole (349-350);
- 15 6-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-2-(3-fluoro-4-(methylsulfonyl)phenyl)-4-methyl-1H-benzo[d]imidazole (351-352);
- 6-(6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-1H-benzo[d]imidazol-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (353);
- 6-(6-(1-(8-cyclopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-1H-benzo[d]imidazol-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (354);
- 20 6-(6-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-1H-benzo[d]imidazol-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (355-356);
- 6-(6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-1H-benzo[d]imidazol-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (357);
- 25 6-(6-(1-(8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-1,4-dimethyl-1H-benzo[d]imidazol-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (358);
- 6-(6-(1-(8-isobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-methyl-1H-benzo[d]imidazol-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (359);
- 6-(6-(1-(8-cyclopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-methyl-1H-benzo[d]imidazol-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (360);
- 30 6-(6-(1-(8-cyclobutyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-methyl-1H-benzo[d]imidazol-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (361);

- 6-(6-(1-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)piperidin-4-yl)-4-methyl-1H-benzo[d]imidazol-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (362);
- 1,4-dimethyl-6-(4-(1-methylpiperidin-4-yl)phenyl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (363);
- 5 1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(4-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl)phenyl)-1H-benzo[d]imidazole (364);
- 6-(6-(1-isopropylpiperidin-4-yl)pyridin-3-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (365);
- 1-(4-(1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)phenethyl)-4-methylpiperidin-4-ol (366);
- 10 1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(4-(4-(pyrrolidin-1-yl)piperidin-1-yl)phenyl)-1H-benzo[d]imidazole (367);
- 1-(4-(1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)phenyl)-N,N-dimethylpiperidin-4-amine (368);
- 15 1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(4-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)phenyl)-1H-benzo[d]imidazole (369);
- 1,4-dimethyl-6-(4-((6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (370);
- 6-(4-((6-isobutyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (371);
- 20 1-cyclopropyl-4-methyl-2-(4-(methylsulfonyl)phenyl)-6-(4-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)phenyl)-1H-benzo[d]imidazole (372);
- N,N-dimethyl-1-(4-(1-methyl-2-phenyl-1H-benzo[d]imidazol-6-yl)benzyl)piperidin-4-amine (374);
- 25 N,N-dimethyl-1-(4-(1-methyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)benzyl)piperidin-4-amine (375);
- 1-(4-(2-(4-methoxyphenyl)-1-methyl-1H-benzo[d]imidazol-6-yl)benzyl)-N,N-dimethylpiperidin-4-amine (376);
- 1-(4-(2-(3-fluorophenyl)-1-methyl-1H-benzo[d]imidazol-6-yl)benzyl)-N,N-dimethylpiperidin-4-amine (377);
- 30 1-(4-(2-(4-fluorophenyl)-1-methyl-1H-benzo[d]imidazol-6-yl)benzyl)-N,N-dimethylpiperidin-4-amine (378);

- N,N-dimethyl-1-(4-(1-methyl-2-(2-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)benzyl)piperidin-4-amine (379);
- 1-(4-(2-(2-fluoro-4-(methylsulfonyl)phenyl)-1-methyl-1H-benzo[d]imidazol-6-yl)benzyl)-N,N-dimethylpiperidin-4-amine (380);
- 5 1-(4-(2-(3,5-difluorophenyl)-1-methyl-1H-benzo[d]imidazol-6-yl)benzyl)-N,N-dimethylpiperidin-4-amine (381);
- 1-(4-(2-(3,4-difluorophenyl)-1-methyl-1H-benzo[d]imidazol-6-yl)benzyl)-N,N-dimethylpiperidin-4-amine (382);
- 4-(6-(4-((4-(dimethylamino)piperidin-1-yl)methyl)phenyl)-1-methyl-1H-benzo[d]imidazol-2-yl)benzonitrile (383);
- 10 N,N-dimethyl-1-(4-(1-methyl-2-(3-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)benzyl)piperidin-4-amine (384);
- 1-(4-(1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)benzyl)-N,N-dimethylpiperidin-4-amine (385);
- 15 1-(4-(1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)phenyl)-N-ethyl-N-methylpiperidin-4-amine (386);
- 6-(3-fluoro-4-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (387);
- 6-(3-fluoro-4-((cis-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methyl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (388);
- 20 6-(4-((4-ethyl-1,4-diazepan-1-yl)methyl)-3-fluorophenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (389);
- 1-(4-(1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)-2-fluorobenzyl)-N,N-dimethylpiperidin-4-amine (390);
- 25 6-(3,5-difluoro-4-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (391);
- 1-(4-(1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)-2,6-difluorobenzyl)-N,N-dimethylpiperidin-4-amine (392);
- N-cyclopropyl-1-(4-(1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)benzyl)-N-methylpiperidin-4-amine (393);
- 30 N-cyclopropyl-1-(4-(1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-6-yl)-2-fluorobenzyl)-N-methylpiperidin-4-amine (394);

- 1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-6-(4-(pyrrolidin-1-ylmethyl)phenyl)-1H-benzo[d]imidazole (395);
- 6-(4-((cis-5-isobutylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methyl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (396);
- 5 6-(4-((cis-5-isopropylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methyl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (397);
- 1,4-dimethyl-6-(4-((cis-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methyl)phenyl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (398);
- 6-(4-((6-isopropyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (399);
- 10 1,4-dimethyl-6-(4-(1'-methyl-[1,4'-bipiperidin]-4-yl)phenyl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (400);
- 6-(4-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (401);
- 15 6-(4-((4-(azetidin-1-yl)piperidin-1-yl)methyl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (402);
- 6-(4-((4-(azetidin-1-yl)piperidin-1-yl)methyl)-3-fluorophenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (403);
- 6-(3-fluoro-4-((6-isopropyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (404);
- 20 6-(3-fluoro-5-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (405);
- 6-(3-((4-(azetidin-1-yl)piperidin-1-yl)methyl)-5-fluorophenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (405);
- 25 1-cyclopropyl-4-methyl-2-(4-(methylsulfonyl)phenyl)-6-(3-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)phenyl)-1H-benzo[d]imidazole (407);
- 1-cyclopropyl-4-fluoro-2-(4-(methylsulfonyl)phenyl)-6-(4-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)phenyl)-1H-benzo[d]imidazole (408);
- 4-fluoro-1-methyl-2-(4-(methylsulfonyl)phenyl)-6-(4-((4-(pyrrolidin-1-yl)piperidin-1-yl)methyl)phenyl)-1H-benzo[d]imidazole (409);
- 30 1-cyclopropyl-4-fluoro-6-(4-((6-isopropyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (410);

- 1-cyclopropyl-4-fluoro-6-(4-((6-isobutyl-2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (411);
- 1-cyclopropyl-4-fluoro-2-(4-(methylsulfonyl)phenyl)-6-(4-((6-(tetrahydro-2H-pyran-4-yl)-2,6-diazaspiro[3.3]heptan-2-yl)methyl)phenyl)-1H-benzo[d]imidazole (412);
- 5 6-(4-((4-isopropylpiperazin-1-yl)methyl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (413);
- 6-(4-((4-isobutylpiperazin-1-yl)methyl)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (414);
- 1-cyclopropyl-7-fluoro-6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (415);
- 10 6-(4-((1-isopropylpiperidin-4-yl)oxy)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (416);
- 6-(4-((1-isobutylpiperidin-4-yl)oxy)phenyl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (417);
- 15 6-(1-((2,6-dimethylpyridin-4-yl)methyl)piperidin-4-yl)-1,4-dimethyl-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (418);
- 1,4-dimethyl-6-(1-((6-methylpyridin-3-yl)methyl)piperidin-4-yl)-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazole (419);
- diethyl (4-(6-(1'-isopropyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-1H-benzo[d]imidazol-2-yl)phenyl)phosphonate (420);
- 20 diethyl (4-(6-(1'-isobutyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-1H-benzo[d]imidazol-2-yl)phenyl)phosphonate (421);
- diethyl (4-(6-(1'-cyclopropyl-[1,4'-bipiperidin]-4-yl)-1,4-dimethyl-1H-benzo[d]imidazol-2-yl)phenyl)phosphonate (422);
- 25 1-((4-(1-(115-ethyl)-2-(p-tolyl)-1H-benzo[d]imidazol-6-yl)phenyl)methyl)-N,N-dimethylpiperidin-4-amine (423);
- N-(4-(6-(4-((4-(dimethylamino)piperidin-1-yl)methyl)phenyl)-1-methyl-1H-benzo[d]imidazol-2-yl)phenyl)methanesulfonamide (424);
- 1-(4-(2-(4-(dimethylamino)phenyl)-1-methyl-1H-benzo[d]imidazol-6-yl)benzyl)-N,N-dimethylpiperidin-4-amine (425);
- 30 1-(4-(2-(4-(1H-imidazol-1-yl)phenyl)-1-methyl-1H-benzo[d]imidazol-6-yl)benzyl)-N,N-dimethylpiperidin-4-amine (426); or

N-(3-(6-(4-((4-(dimethylamino)piperidin-1-yl)methyl)phenyl)-1-methyl-1H-benzo[d]imidazol-2-yl)phenyl)methanesulfonamide (427).

9. A pharmaceutical composition comprising one or more compounds according to any
5 one of claims 1 to 8 or stereoisomers, tautomer, solvates or pharmaceutically-acceptable salts thereof; and a pharmaceutically acceptable carrier.
10. A compound according to any one of claims 1 to 8 or stereoisomers, tautomers,
10 solvates or pharmaceutically-acceptable salts thereof, for use in treating pathological fibrosis.
11. The compound or stereoisomers, tautomers, solvates or a pharmaceutically-
acceptable salt thereof, or pharmaceutically-acceptable salts thereof, for use according to
claim 10 wherein said pathological fibrosis is liver fibrosis, renal fibrosis, biliary fibrosis,
15 or pancreatic fibrosis.
12. A compound according to any one of claims 1 to 8 or stereoisomers, tautomers,
solvates or pharmaceutically-acceptable salts thereof, for use in treating nonalcoholic
steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), chronic kidney
20 disease, diabetic kidney disease, primary sclerosing cholangitis (PSC), or primary biliary cirrhosis (PBC).
13. A compound according to any one of claims 1 to 8 or stereoisomers, tautomers,
solvates or pharmaceutically-acceptable salts thereof, for use in treating idiopathic
25 pulmonary fibrosis (IPF).