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(54) **BENZO[5,6][1,4]DIOXINO[2,3-B]PYRIDINE
COMPOUNDS USEFUL AS IRAK4
INHIBITORS**

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3, 2020.

(51) **Int. Cl.**

C07D 491/056 (2006.01)

A61K 31/436 (2006.01)

A61P 29/00 (2006.01)

A61P 35/00 (2006.01)

A61P 37/00 (2006.01)

(52) **U.S. Cl.**

CPC **C07D 491/056** (2013.01)

(58) **Field of Classification Search**

CPC ... C07D 491/056; A61K 31/436; A61P 29/00;
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See application file for complete search history.

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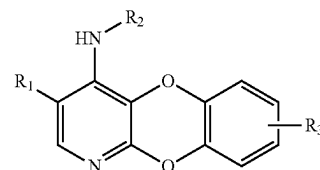
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ABSTRACT

Disclosed are compounds of Formula (I) or a salt or prodrug
thereof, wherein R₁, R₂, and R₃ are defined herein. Also
disclosed are methods of using such compounds as modu-
lators of IRAK4, and pharmaceutical compositions compris-
ing such compounds. These compounds are useful in treat-
ing, preventing, or slowing inflammatory and autoimmune
diseases, or in the treatment of cancer.



(I)

8 Claims, No Drawings

Specification includes a Sequence Listing.

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**BENZO[5,6][1,4]DIOXINO[2,3-B]PYRIDINE
COMPOUNDS USEFUL AS IRAK4
INHIBITORS**

CROSS REFERENCE

This application is a 371 application of International Application No. PCT/US2021/016123, filed Feb. 2, 2021, which claims the benefit of U.S. Provisional Application Ser. No. 62/969,427, filed Feb. 3, 2020, the content of each is hereby fully incorporated herein in its entirety.

DESCRIPTION

The present invention generally relates to benzo[5,6][1,4]dioxino[2,3-b]pyridine compounds useful as kinase inhibitors, including the modulation of IRAK-4. Provided herein are benzo[5,6][1,4]dioxino[2,3-b]pyridine compounds, compositions comprising such compounds, and methods of their use. The invention further pertains to pharmaceutical compositions containing at least one compound according to the invention that are useful for the treatment of conditions related to kinase modulation and methods of inhibiting the activity of kinases, including IRAK-4 in a mammal.

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

Members of the IRAK family of serine/threonine kinases are recruited to the receptor via interactions with MyD88. The family consists of four members. Several lines of evidence indicate that IRAK4 plays a critical and non-redundant role in initiating signaling via MyD88 dependent TLRs and IL-1R family members. Structural data confirms that IRAK4 directly interacts with MyD88 and subsequently recruits either IRAK1 or IRAK2 to the receptor complex to facilitate downstream signaling (Lin, S. et al., *Nature*, 465: 885-890 (2010)). IRAK4 directly phosphorylates IRAK1 to facilitate downstream signaling to the E3 ubiquitin ligase TRAF6, resulting in activation of the serine/threonine kinase TAK1 with subsequent activation of the NF κ B pathway and MAPK cascade (Flannery, S. et al., *Biochem. Pharmacol.*, 80:1981-1991 (2010)). A subset of human patients was identified who lack IRAK4 expression (Picard, C. et al., *Science*, 299:2076-2079 (2003)). Cells from these patients fail to respond to all TLR agonists with the exception of TLR3 as well as to members of the IL-1 family including IL-1 β and IL-18 (Ku, C. et al., *J. Exp. Med.*, 204:2407-2422 (2007)). Deletion of IRAK4 in mice results in a severe block in IL-1, IL-18 and all TLR dependent responses with the exception of TLR3 (Suzuki, N. et al., *Nature*, 416:750-754 (2002)). In contrast, deletion of either IRAK1 (Thomas, J. A. et al., *J. Immunol.*, 163:978-984 (1999); Swantek, J. L. et al., *J. Immunol.*, 164:4301-4306 (2000) or IRAK2 (Wan, Y. et al., *J. Biol. Chem.*, 284:10367-10375 (2009)) results in partial loss of signaling. Furthermore, IRAK4 is the only member of the IRAK family whose kinase activity has been

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shown to be required for initiation of signaling. Replacement of wild type IRAK4 in the mouse genome with a kinase inactive mutant (KDKI) impairs signaling via all MyD88 dependent receptors including IL-1, IL-18 and all TLRs with the exception of TLR3 (Koziczak-Holbro, M. et al., *J. Biol. Chem.*, 282:13552-13560 (2007); Kawagoe, T. et al., *J. Exp. Med.*, 204:1013-1024 (2007); and Fraczek, J. et al., *J. Biol. Chem.*, 283:31697-31705 (2008)).

As compared to wild type animals, IRAK4 KDKI mice show greatly reduced disease severity in mouse models of multiple sclerosis (Staschke, K. A. et al., *J. Immunol.*, 183:568-577 (2009)), rheumatoid arthritis (Koziczak-Holbro, M. et al., *Arthritis Rheum.*, 60:1661-1671 (2009)), atherosclerosis (Kim, T. W. et al., *J. Immunol.*, 186:2871-2880 (2011) and Rekhater, M. et al., *Biochem. Biophys. Res. Comm.*, 367:642-648 (2008)), and myocardial infarction (Maekawa, Y. et al., *Circulation*, 120:1401-1414 (2009)). As described, IRAK4 inhibitors will block all MyD88 dependent signaling. MyD88 dependent TLRs have been shown to contribute to the pathogenesis of multiple sclerosis, rheumatoid arthritis, cardiovascular disease, metabolic syndrome, sepsis, systemic lupus erythematosus, inflammatory bowel diseases including Crohn's disease and ulcerative colitis, autoimmune uveitis, asthma, allergy, type I diabetes, and allograft rejection (Keogh, B. et al., *Trends Pharmacol. Sci.*, 32:435-442 (2011); Mann, D. L., *Circ. Res.*, 108:1133-1145 (2011); Horton, C. G. et al., *Mediators Inflamm.*, Article ID 498980 (2010), doi:10.1155/2010/498980; Goldstein, D. R. et al., *J. Heart Lung Transplant.*, 24:1721-1729 (2005); and Cario, E., *Inflamm. Bowel Dis.*, 16:1583-1597 (2010)). Oncogenically active MyD88 mutations in diffuse large B cell lymphomas have been identified that are sensitive to IRAK4 inhibition (Ngo, V. N. et al., *Nature*, 470:115-121 (2011)). Whole genome sequencing also identified mutations in MyD88 associated with chronic lymphatic leukemia suggesting that IRAK4 inhibitors may also have utility in treating leukemias (Puentes, X. S. et al., *Nature*, 475:101-105 (2011)).

In addition to blocking TLR signaling, IRAK4 inhibitors will also block signaling by members of the IL-1 family. Neutralization of IL-1 has been shown to be efficacious in multiple diseases including gout; gouty arthritis; type 2 diabetes; auto-inflammatory diseases including Cryopyrin-Associated Periodic Syndromes (CAPS), TNF Receptor Associated Periodic Syndrome (TRAPS), Familial Mediterranean Fever (FMF), adult onset stills; systemic onset juvenile idiopathic arthritis; stroke; Graft-versus-Host Disease (GVHD); smoldering multiple myeloma; recurrent pericarditis; osteoarthritis; emphysema (Dinarello, C. A., *Eur. J. Immunol.*, 41:1203-1217 (2011) and Couillin, I. et al., *J. Immunol.*, 183:8195-8202 (2009)). In a mouse model of Alzheimer's disease, blockade of IL-1 receptor improved cognitive defects, attenuated tau pathology and reduced oligomeric forms of amyloid- β (Kitazawa, M. et al., *J. Immunol.*, 187:6539-6549 (2011)). IL-1 has also been shown to be a critical link to adaptive immunity, driving differentiation of the TH17 effector T cell subset (Chung, Y. et al., *Immunity*, 30:576-587 (2009)). Therefore, IRAK4 inhibitors are predicted to have efficacy in TH17 associated diseases including multiple sclerosis, psoriasis, inflammatory bowel diseases, autoimmune uveitis, and rheumatoid arthritis (Wilke, C. M. et al., *Trends Immunol.*, 32:603-661 (2011)).

In view of the conditions that may benefit by treatment involving modulation of protein kinases, it is immediately apparent that new compounds capable of modulating protein

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kinases such as IRAK-4 and methods of using these compounds could provide substantial therapeutic benefits to a wide variety of patients.

SUMMARY OF THE INVENTION

The present invention relates to a new class of benzo[5,6][1,4]dioxino[2,3-b]pyridine compounds found to be effective inhibitors of protein kinases including IRAK-4. These compounds are provided to be useful as pharmaceuticals with desirable stability, bioavailability, therapeutic index, and toxicity values that are important to their druggability.

The present invention provides compounds of Formula (I) that are useful as inhibitors of IRAK-4, and are useful for the treatment of proliferative diseases, allergic diseases, autoimmune diseases and inflammatory diseases, or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates or prodrugs thereof.

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

The present invention also provides a method for inhibition of IRAK-4 comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof.

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

One embodiment provides a method for treating inflammatory and autoimmune diseases. Particular, inflammatory and autoimmune diseases include, but are not limited to, Crohn's disease, ulcerative colitis, asthma, graft versus host disease, allograft rejection, chronic obstructive pulmonary disease, Graves' disease, rheumatoid arthritis, systemic lupus erythematosus, lupus nephritis, cutaneous lupus, psoriasis, cryopyrin-associated periodic syndromes (CAPS), TNF receptor associated periodic syndrome (TRAPS), familial Mediterranean fever (FMF), adult onset stills, systemic onset juvenile idiopathic arthritis, multiple sclerosis, neuropathic pain, gout, and gouty arthritis.

One embodiment provides a method for treating gout and gouty arthritis.

An alternate embodiment is a method for treating metabolic diseases, including type 2 diabetes and atherosclerosis.

One embodiment provides a method for treating cancer 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 the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, for use in therapy.

The present invention also provides the use of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, for the manufacture of a medicament for the treatment of cancer.

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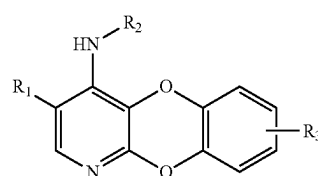
The present invention also provides a compound of Formula (I) or a pharmaceutical composition in a kit with instructions for using the compound or composition.

The present invention also provides processes and intermediates for making the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof.

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

DETAILED DESCRIPTION

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



(I)

or a salt thereof, wherein:

R_1 is:

- (i) $-\text{C}(\text{O})\text{NR}_x\text{R}_{1a}$; or
- (ii) pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, oxadiazolyl, triazolyl, or thiadiazolyl, each substituted with zero to 2 R_{1b} ;

R_{1a} is:

- (i) C_{1-6} alkyl substituted with zero to 6 R_w ; or
- (ii) $-(\text{CR}_x\text{R}_x)_{0-3}\text{R}_{1c}$;

each R_w is independently F, Cl, $-\text{CN}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{NR}_x\text{R}_x$, $-\text{NR}_x\text{C}(\text{O})(\text{C}_{1-3} \text{ alkyl})$, $-\text{NR}_x\text{C}(\text{O})(\text{C}_{3-6} \text{ cycloalkyl})$, or a cyclic group selected from C_{3-6} cycloalkyl, oxetanyl, piperidinyl, tetrahydropyranyl, oxazolyl, isoxazolyl, thiazolyl, and triazolyl, each cyclic group substituted with zero to 1 substituent selected from $-\text{OH}$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, $-\text{OCH}_2\text{CH}_3$, and $-\text{NR}_x\text{R}_x$;

each R_{1b} is independently $-\text{CR}_x\text{R}_x(\text{C}_{3-6} \text{ cycloalkyl})$, tetrahydrofuranyl, pyrrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, or C_{1-6} alkyl substituted with zero to 6 R_w ;

R_{1c} is C_{3-6} cycloalkyl, oxetanyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, dioxido-tetrahydrothiophenyl, dioxidothiomorpholinyl, isoxazolyl, oxazolyl, thiazolyl, oxadiazolyl, triazolyl, or tetrazolyl, each substituted with zero to 3 substituents independently selected from F, Cl, $-\text{CN}$, $-\text{OH}$, $-\text{NR}_x\text{R}_x$, C_{1-3} alkyl, C_{1-3} fluoroalkyl, C_{1-3} hydroxyalkyl, $-\text{NR}_x\text{C}(\text{O})(\text{C}_{1-3} \text{ alkyl})$, $-\text{NR}_x\text{C}(\text{O})\text{O}(\text{C}_{1-3} \text{ alkyl})$, and $-\text{S}(\text{O})_2(\text{C}_{1-2} \text{ alkyl})$;

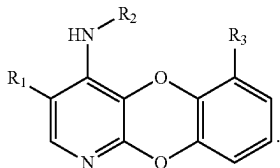
R_2 is:

- (i) hydrogen;
- (ii) C_{1-6} alkyl substituted with zero to 4 substituents independently selected from F, Cl, $-\text{OH}$, $-\text{CN}$, C_{3-6} cycloalkyl, and dimethoxyphenyl; or
- (iii) a cyclic group selected from C_{3-6} cycloalkyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, pyrazolyl, and thiazolyl, wherein said cyclic group is substituted with zero to 3 substituents independently selected from F, Cl, $-\text{OH}$, $-\text{CN}$, C_{1-2} alkyl, C_{1-2} fluoroalkyl, C_{1-2} hydroxyalkyl, and $-\text{S}(\text{O})_2(\text{C}_{1-2} \text{ alkyl})$;

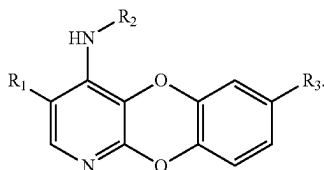
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R_3 is $-\text{CN}$, $-\text{C}(\text{O})\text{NR}_x\text{R}_x$, or a cyclic group selected from phenyl, pyrazolyl, imidazolyl, triazolyl, pyridinyl, pyridinonyl, and pyrimidinyl, each cyclic group substituted with zero to 3 substituents selected from F, Cl, $-\text{OH}$, $-\text{CN}$, C_{1-2} alkyl, $-\text{CF}_3$, and $-\text{CH}_2\text{OH}$; and each R_x is hydrogen or $-\text{CH}_3$.

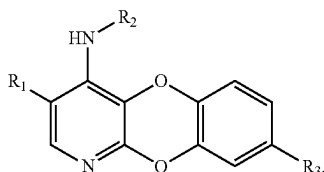
In one embodiment, a compound of Formula (I) or a salt thereof is provided having the structure:



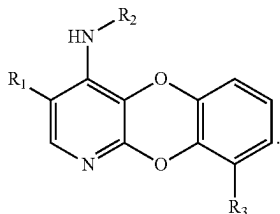
In one embodiment, a compound of Formula (I) or a salt thereof is provided having the structure:



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



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



In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R_1 is $-\text{C}(\text{O})\text{NR}_x\text{R}_{1a}$. Included in this embodiment are compounds in which R_1 is $-\text{C}(\text{O})\text{NHR}_{1a}$.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R_1 is pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, oxadiazolyl, triazolyl, or thiadiazolyl, each substituted with zero to 2 R_{1b} . Included in this embodiment are compounds in which R_1 is pyrazolyl, isoxazolyl, oxazolyl, or thiazolyl, each substituted with zero to 2 R_{1b} .

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R_{1a} is C_{1-6} alkyl substituted with

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zero to 6 R_w . Included in this embodiment are compounds in which R_{1a} is C_{1-5} alkyl substituted with zero to 4 R_w . Also included in this embodiment are compounds in which R_{1a} is $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)\text{OH}$, $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2\text{OH}$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CHFC}(\text{CH}_3)_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$, or $-\text{CH}(\text{cyclopropyl})\text{CH}_2\text{CH}_2\text{OH}$.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R_{1a} is $-(\text{CR}_x\text{R}_x)_{0-3}\text{R}_{1c}$. Included in this embodiment are compounds in which R_{1a} is $-(\text{CR}_x\text{R}_x)_{0-2}\text{R}_{1c}$. Also included in this embodiment are compounds in which R_{1a} is $-\text{CH}_2(\text{hydroxymethylcyclopropyl})$, $-\text{CH}_2(\text{hydroxymethylloxetanyl})$, $-\text{CH}_2(\text{oxazolyl})$, $-\text{CH}_2(\text{methylisoxazolyl})$, $-\text{CH}_2(\text{thiazolyl})$, $-\text{CH}_2(\text{triazolyl})$, hydroxycyclohexyl, aminocyclohexyl, piperidinyl, or tetrahydropyranyl.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein each R_w is independently F, $-\text{CN}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{NHR}_x$, $-\text{NHC}(\text{O})$ (C_{1-3} alkyl), $-\text{NHC}(\text{O})(\text{C}_{3-6}$ cycloalkyl), or a cyclic group selected from C_{3-6} cycloalkyl, oxetanyl, piperidinyl, tetrahydropyranyl, oxazolyl, isoxazolyl, thiazolyl, and triazolyl, each cyclic group substituted with zero to 1 substituent selected from $-\text{OH}$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, $-\text{OCH}_2\text{CH}_3$, and $-\text{NR}_x\text{R}_x$.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R_2 is hydrogen.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R_2 is C_{1-4} alkyl substituted with zero to 4 substituents independently selected from F, Cl, $-\text{OH}$, $-\text{CN}$, C_{3-6} cycloalkyl, and dimethoxyphenyl. Included in this embodiment are compounds in which R_2 is C_{1-4} alkyl substituted with zero to 4 substituents independently selected from F, Cl, $-\text{OH}$, and $-\text{CN}$. Also included in this embodiment are compounds in which R_2 is C_{1-4} alkyl substituted with zero to 4 substituents independently selected from F, $-\text{OH}$, and $-\text{CN}$. Additionally, included in this embodiment are compounds in which R_2 is $-\text{CH}(\text{CH}_3)_2$.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R_2 is a cyclic group selected from C_{3-6} cycloalkyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, and piperidinyl, wherein said cyclic group is substituted with zero to 3 substituents independently selected from F, $-\text{OH}$, $-\text{CN}$, C_{1-2} alkyl, C_{1-2} fluoroalkyl, C_{1-2} hydroxyalkyl, and $-\text{S}(\text{O})_2(\text{C}_{1-2}$ alkyl).

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R_3 is $-\text{CN}$ or $-\text{C}(\text{O})\text{NR}_x\text{R}_x$. Included in this embodiment are compounds in which R_3 is $-\text{CN}$, $-\text{C}(\text{O})\text{NH}_2$, or $-\text{C}(\text{O})\text{NH}(\text{CH}_3)$. Also included in this embodiment are compounds in which R_3 is $-\text{CN}$ or $-\text{C}(\text{O})\text{NH}_2$. Additionally, included in this embodiment are compounds in which R_3 is $-\text{CN}$.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R_3 is a cyclic group selected from phenyl, pyrazolyl, imidazolyl, triazolyl, pyridinyl, pyridinonyl, and pyrimidinyl, each cyclic group substituted with zero to 3 substituents selected from F, Cl, $-\text{OH}$, $-\text{CN}$, C_{1-2} alkyl, $-\text{CF}_3$, and $-\text{CH}_2\text{OH}$.

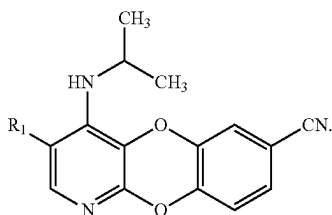
In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R_{1a} is: (i) C_{1-6} alkyl substituted with zero to 6 R_w ; or (ii) $-(\text{CR}_x\text{R}_x)_{0-2}\text{R}_{1c}$; R_2 is: (i) hydrogen; (ii) C_{1-4} alkyl substituted with zero to 4 substituents independently selected from F, Cl, $-\text{OH}$, $-\text{CN}$, C_{3-6} cycloalkyl, and dimethoxyphenyl; or (ii) a cyclic group selected from C_{3-6} cycloalkyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, and piperidinyl, wherein said cyclic

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group is substituted with zero to 3 substituents independently selected from F, —OH, —CN, C₁₋₂ alkyl, C₁₋₂ fluoroalkyl, C₁₋₂ hydroxyalkyl, and —S(O)₂(C₁₋₂ alkyl); and R₃ is —CN or —C(O)NR_xR_x.

In one embodiment, a compound of Formula (I) or a salt thereof is provided wherein R₂ is —CH(CH₃)₂; and R₃ is —CN.

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



Included in this embodiment are compounds in which R₁ is —C(O)NR_xR_{1a}. Included in this embodiment are compounds in which R₁ is —C(O)NHR_{1a}.

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

(R)-7-cyano-N-(2-fluoro-3-hydroxy-3-methylbutyl)-4-(isopropylamino) benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (1);

(R)-8-cyano-N-(2-fluoro-3-hydroxy-3-methylbutyl)-4-(isopropylamino)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (2);

7-cyano-4-(isopropylamino)-N-(tetrahydro-2H-pyran-4-yl) benzo[5,6][1,4]dioxino [2,3-b]pyridine-3-carboxamide (3);

7-cyano-N-(2-ethoxyethyl)-4-(isopropylamino)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (4);

7-cyano-4-(isopropylamino)-N-(2-methoxyethyl)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (5);

7-cyano-N-((1R,4R)-4-hydroxycyclohexyl)-4-(isopropylamino)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (6);

7-cyano-N-(3-hydroxy-2,2-dimethylpropyl)-4-(isopropylamino)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (7);

7-cyano-N-(1-cyclopropyl-3-hydroxypropyl)-4-(isopropylamino)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (8);

7-cyano-4-(isopropylamino)-N-(tetrahydro-2H-pyran-3-yl) benzo[5,6][1,4]dioxino [2,3-b]pyridine-3-carboxamide (9);

(R)-7-cyano-N-(4-hydroxybutan-2-yl)-4-(isopropylamino) benzo[5,6][1,4]dioxino [2,3-b]pyridine-3-carboxamide (10);

7-cyano-N-((1-(hydroxymethyl)cyclopropyl)methyl)-4-(isopropylamino)benzo [5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (11);

N-((4H-1,2,4-triazol-3-yl)methyl)-7-cyano-4-(isopropylamino)benzo[5,6][1,4]dioxino [2,3-b]pyridine-3-carboxamide (12);

7-cyano-4-(isopropylamino)-N-(oxazol-5-ylmethyl)benzo [5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (13);

7-cyano-4-(isopropylamino)-N-((3-methylisoxazol-5-yl)methyl)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (14);

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7-cyano-N-(3-hydroxy-3-methylbutyl)-4-(isopropylamino) benzo[5,6][1,4]dioxino [2,3-b]pyridine-3-carboxamide (15);

7-cyano-N-isopentyl-4-(isopropylamino)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (16);

N-((1R,4R)-4-aminocyclohexyl)-7-cyano-4-(isopropylamino)benzo[5,6][1,4]dioxino [2,3-b]pyridine-3-carboxamide (17);

7-cyano-N-((3-(hydroxymethyl)oxetan-3-yl)methyl)-4-(isopropylamino)benzo [5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (18);

7-cyano-4-(isopropylamino)-N-(thiazol-2-ylmethyl)benzo [5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (19);

and
7-cyano-4-(isopropylamino)-N-(piperidin-4-yl)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (20).

One embodiment provides compounds of the Formula (I) having IRAK4 IC₅₀ values of ≤0.6 μM.

One embodiment provides compounds of the Formula (I) having IRAK4 IC₅₀ values of ≤0.1 μM.

One embodiment provides compounds of the Formula (I) having IRAK4 IC₅₀ values of ≤0.05 μM.

One embodiment provides compounds of the Formula (I) having IRAK4 IC₅₀ values of ≤0.025 μM.

One embodiment provides compounds of the Formula (I) having IRAK4 IC₅₀ values of ≤0.015 μM.

One embodiment provides compounds of the Formula (I) having IRAK4 IC₅₀ values of ≤0.01 μM.

Definitions

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

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

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

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

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

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

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

In accordance with a convention used in the art,



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

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

The term “cyano” refers to the group —CN.

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

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

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

It should further be understood that solvates (e.g., hydrates) of the compounds of Formula (I) are also within the scope of the present invention. The term “solvate” means a physical association of a compound of Formula (I) with one or more solvent molecules, whether organic or inorganic. This physical association includes hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. “Solvate” encompasses both solution-phase and isolable solvates. Exemplary solvates include hydrates, ethanolates, methanolates, isopropanolates, acetonitrile solvates, and ethyl acetate solvates. Methods of solvation are known in the art.

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

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

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

“Therapeutically effective amount” is intended to include an amount of a compound of the present invention alone or an amount of the combination of compounds claimed or an amount of a compound of the present invention in combination with other active ingredients effective to act as an inhibitor to IRAK4; or effective to treat or prevent autoimmune and/or inflammatory disease states, such as multiple sclerosis and rheumatoid arthritis; or effective to treat cancer.

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

The compounds of the present invention are intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium (D) and tritium (T). Isotopes of carbon include ¹³C and ¹⁴C. Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed. For example, methyl (—CH₃) also includes deuterated methyl groups such as —CD₃.

Utility

The compounds of the invention modulate kinase activity, including the modulation of IRAK-4. Other types of kinase activity that may be modulated by the compounds of the instant invention include, but are not limited to, the Pelle/IRAK family and mutants thereof.

Accordingly, compounds of Formula (I) have utility in treating conditions associated with the modulation of kinase activity, and particularly the selective inhibition of IRAK-4 activity or the inhibition of IRAK and other Pelle family kinases. Such conditions include TLR/IL-1 family receptor associated diseases in which cytokine levels are modulated as a consequence of intracellular signaling. Moreover, the compounds of Formula (I) have advantageous selectivity for IRAK-4 activity, preferably from at least 20 fold to over 1,000 fold more selective.

As used herein, the terms “treating” or “treatment” encompass the treatment of a disease state in a mammal, particularly in a human, and include: (a) preventing or delaying the occurrence of the disease state in a mammal, in

particular, when such mammal is predisposed to the disease state but has not yet been diagnosed as having it; (b) inhibiting the disease state, i.e., arresting its development; and/or (c) achieving a full or partial reduction of the symptoms or disease state, and/or alleviating, ameliorating, lessening, or curing the disease or disorder and/or its symptoms.

In view of their activity as selective inhibitors IRAK-4, compounds of Formula (I) are useful in treating TLR/IL-1 family receptor associated diseases, but not limited to, inflammatory diseases such as Crohn's disease, ulcerative colitis, asthma, graft versus host disease, allograft rejection, chronic obstructive pulmonary disease; autoimmune diseases such as Graves' disease, rheumatoid arthritis, systemic lupus erythematosus, psoriasis; auto-inflammatory diseases including CAPS, TRAPS, FMF, adult onset stills, systemic onset juvenile idiopathic arthritis, gout, gouty arthritis; metabolic diseases including type 2 diabetes, atherosclerosis, myocardial infarction; destructive bone disorders such as bone resorption disease, osteoarthritis, osteoporosis, multiple myeloma-related bone disorder; proliferative disorders such as acute myelogenous leukemia, chronic myelogenous leukemia; angiogenic disorders such as angiogenic disorders including solid tumors, ocular neovascularization, and infantile haemangiomas; infectious diseases such as sepsis, septic shock, and Shigellosis; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, cerebral ischemias or neurodegenerative disease caused by traumatic injury, oncologic and viral diseases such as metastatic melanoma, Kaposi's sarcoma, multiple myeloma, and HIV infection and CMV retinitis, AIDS, respectively.

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

drome, conditions associated with prostaglandin endoperoxidase synthase-2, and pemphigus vulgaris. Preferred methods of treatment are those wherein the condition is selected from Crohn's disease, ulcerative colitis, allograft rejection, rheumatoid arthritis, psoriasis, ankylosing spondylitis, psoriatic arthritis, and pemphigus vulgaris. Alternatively preferred methods of treatment are those wherein the condition is selected from ischemia reperfusion injury, including cerebral ischemia reperfusion injury arising from stroke and cardiac ischemia reperfusion injury arising from myocardial infarction. Another preferred method of treatment is one in which the condition is multiple myeloma.

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

In addition, the kinase inhibitors of the present invention inhibit the expression of inducible pro-inflammatory proteins such as prostaglandin endoperoxide synthase-2 (PGHS-2), also referred to as cyclooxygenase-2 (COX-2), IL-1, IL-6, IL-18, chemokines. Accordingly, additional IRAK-4-associated conditions include edema, analgesia, fever and pain, such as neuromuscular pain, headache, pain caused by cancer, dental pain and arthritis pain. The inventive compounds also may be used to treat veterinary viral infections, such as lentivirus infections, including, but not limited to equine infectious anemia virus; or retrovirus infections, including feline immunodeficiency virus, bovine immunodeficiency virus, and canine immunodeficiency virus.

When the terms "IRAK-4-associated condition" or "IRAK-4-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 IRAK-4 kinase activity.

The present invention thus provides methods for treating such conditions, comprising administering to a subject in need thereof a therapeutically-effective amount of at least one compound of Formula (I) or a salt thereof "Therapeutically effective amount" is intended to include an amount of a compound of the present invention that is effective when administered alone or in combination to inhibit IRAK-4 and/or treat diseases.

The methods of treating IRAK-4 kinase-associated conditions may comprise administering compounds of Formula (I) alone or in combination with each other and/or other suitable therapeutic agents useful in treating such conditions. Accordingly, "therapeutically effective amount" is also intended to include an amount of the combination of compounds claimed that is effective to inhibit IRAK-4 and/or treat diseases associated with IRAK-4.

Exemplary of such other therapeutic agents include corticosteroids, rolapram, calphostin, cytokine-suppressive anti-inflammatory drugs (CSAIDs), Interleukin-10, glucocorticoids, salicylates, nitric oxide, and other immunosuppressants; nuclear translocation inhibitors, such as deoxyspergualin (DSG); non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, celecoxib and rofecoxib; steroids such as prednisone or dexamethasone; antiviral agents such as abacavir; antiproliferative agents such as methotrexate, leflunomide, FK506 (tacrolimus, PROGRAF®); anti-malarials such as hydroxychloroquine; cytotoxic drugs such as azathioprine and cyclophosphamide; TNF- α inhibitors such as tenidap, anti-TNF antibodies or

soluble TNF receptor, and rapamycin (sirolimus or RAPA-MUNE®) or derivatives thereof.

The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts indicated in the Physicians' DeskReference (PDR) or as otherwise determined by one of ordinary skill in the art. In the methods of the present invention, such other therapeutic agent(s) may be administered prior to, simultaneously with, or following the administration of the inventive compounds. The present invention also provides pharmaceutical compositions capable of treating IRAK-4 kinase-associated conditions, including TLR and IL-1 family receptor mediated diseases as described above.

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

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

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

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

Also embraced within this invention is a class of pharmaceutical compositions comprising a compound of Formula (I) and one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The compounds of Formula (I) may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and compositions of the present invention may, for example, be administered orally, mucosally, or parentally including intravascularly, intravenously, intraperitoneally, subcutaneously, intramuscularly, and intrasternally in dosage unit formulations containing

conventional pharmaceutically acceptable carriers, adjuvants, and vehicles. For example, the pharmaceutical carrier may contain a mixture of mannitol or lactose and microcrystalline cellulose. The mixture may contain additional components such as a lubricating agent, e.g. magnesium stearate and a disintegrating agent such as croscopolidone. 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, hydroxypropylmethyl-cellulose, sodium alginate, alginic acid, polyvinyl-pyrrolidone, gum tragacanth, and gum acacia; dispersing or wetting agents, such as, for example, a naturally-occurring phosphatide, e.g., lecithin; condensation products of alkylene oxide with fatty acids, such as, for example, polyoxyethylene stearate; condensation products of ethylene oxide with long chain aliphatic alcohols, such as, for example heptadecaethylene-oxyctanol; 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 antioxidant, such as, for example, butylated hydroxyanisole, 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 cyclo-dextrin (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

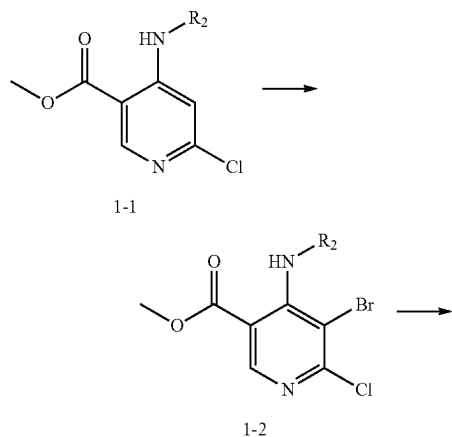
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organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in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

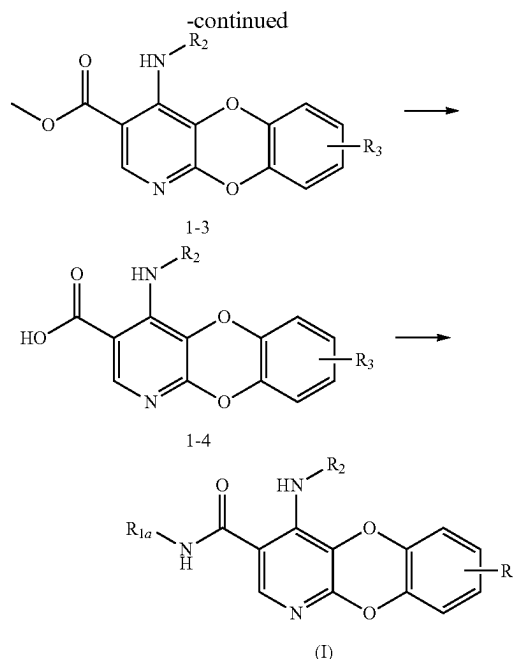
The reactions and techniques described in this section are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction 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)).

Compounds of the general formula I may be prepared according to the following schemes. For example, as outlined in Scheme 1, treatment of an appropriately substituted chloropyridine ester 1-1 with a brominating reagent, such as NBS may provide intermediate 1-2. Further treatment of 1-2, with a substituted aromatic diol may provide compounds of the general formula 1-3. Hydrolysis of the ester moiety may provide 1-4 which can be further reacted with a variety of amines under standard amide bond forming conditions to provide compounds of the general formula I.

SCHEME 1



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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

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 increas-

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

aq. aqueous

brine saturated aqueous sodium chloride

DMF N,N-dimethylformamide

DMSO dimethyl sulfoxide

EtOH ethanol

g gram(s)

h hour(s)

HPLC High Performance Liquid Chromatography

LCMS Liquid Chromatography-Mass Spectroscopy

MeOH methanol

NBS N-bromosuccinimide

NMP N-methylpyrrolidinone

NH₄OAc ammonium acetate

pet ether petroleum ether

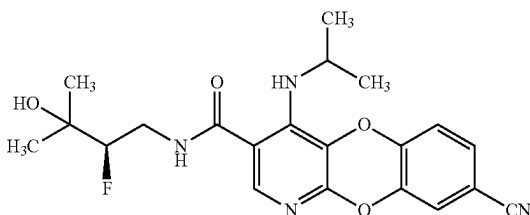
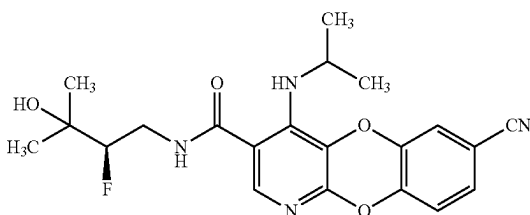
t-BuOH tert-butanol

TEA triethylamine

TFA trifluoroacetic acid

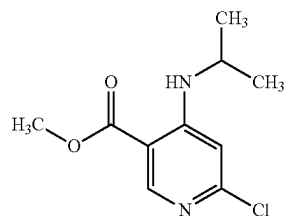
Examples 1 and 2

(R)-7-cyano-N-(2-fluoro-3-hydroxy-3-methylbutyl)-4-(isopropylamino) benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (1) and (R)-8-cyano-N-(2-fluoro-3-hydroxy-3-methylbutyl)-4-(isopropylamino)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (2)



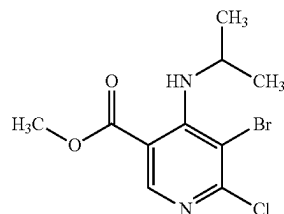
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Intermediate 1A: Methyl
6-chloro-4-(isopropylamino)nicotinate



A mixture of methyl 4,6-dichloronicotinate (20.6 g, 100 mmol), isopropylamine (11.1 mL, 130 mmol) and TEA (28 mL, 200 mmol) was stirred at 70° C. for 3 h and refluxed for an additional 1 h. The reaction mixture was cooled and concentrated. The reaction mixture was diluted with methylene chloride and washed with water. The organic phase was dried (MgSO₄) and concentrated to afford the crude product which solidified under vacuum. Methyl 6-chloro-4-(isopropylamino) nicotinate (22.6 g, 99% yield). ¹H NMR (400 MHz, CHLOROFORM-d) δ 8.66 (s, 1H), 8.09 (br s, 1H), 6.55 (s, 1H), 3.88 (s, 3H), 3.69 (qd, J=6.5, 13.3 Hz, 1H), 1.29 (d, J=6.4 Hz, 6H). LCMS m/z 229.2 (M+1).

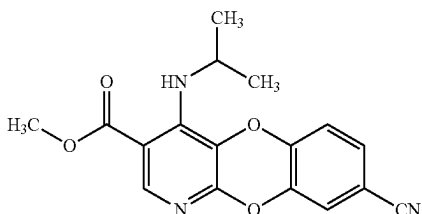
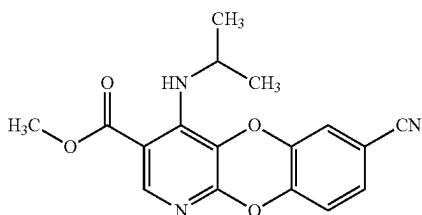
Intermediate 1B: Methyl
5-bromo-6-chloro-4-(isopropylamino)nicotinate



NBS (4.28 g, 24.1 mmol) was added to a stirred solution of methyl 6-chloro-4-(isopropylamino)nicotinate (5 g, 21.9 mmol) in DMF (35 mL) at room temperature. The reaction mixture was stirred for 3 h. Water and ice (ca. 70 mL) was added and the mixture was stirred for 5 min. The reaction mixture was filtered to isolate the methyl 5-bromo-6-chloro-4-(isopropylamino) nicotinate (6.3 g, 94% yield) as a white solid. ¹H NMR (400 MHz, CHLOROFORM-d) δ 8.61 (s, 1H), 8.03 (d, J=5.4 Hz, 1H), 4.59-4.77 (m, 1H), 3.92 (s, 3H), 1.27 (d, J=6.4 Hz, 6H).

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Intermediates 1C and 1D: Methyl 7-cyano-4-(isopropylamino)benzo[5,6][1,4]dioxino [2,3-b]pyridine-3-carboxylate (1C) and methyl 8-cyano-4-(isopropylamino)benzo [5,6][1,4]dioxino[2,3-b]pyridine-3-carboxylate (1D)



A mixture of methyl 5-bromo-6-chloro-4-(isopropylamino)nicotinate (6.7 g, 21.8 mmol), 3,4-dihydroxybenzonitrile (2.94 g, 21.8 mmol) and potassium carbonate (3.01 g, 21.8 mmol) in NMP (4 mL) was heated in a sealed vial at 130-150° C. for 1 h. After cooling, the reaction mixture was diluted with methylene chloride and washed with water. The organic phase was dried (MgSO₄) and concentrated to a volume of ca. 4 mL. Water (ca. 20 mL) was added slowly to the solution from above while stirring. The precipitated white solid was isolated by filtration and the residue was washed with water. The crude product was triturated with ether to afford the product (2.0 g, 28% yield) as a mixture of regio isomers. A portion was separated by SFC (ChiralCel OJ-H 25x5 cm, 5 m at 40° C.; Flow rate 340 mL/min; Mobile phase 70:30 CO₂/MeOH; Detection at 220 nM) to afford the first eluting peak: methyl 7-cyano-4-(isopropylamino) benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxy-

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late (Isomer A). ¹H NMR (400 MHz, CHLOROFORM-d) δ 8.37 (s, 1H), 8.22 (d, J=7.5 Hz, 1H), 7.28 (d, J=2.0 Hz, 1H), 7.26-7.26 (m, 1H), 7.22 (d, J=2.0 Hz, 1H), 6.90 (d, J=8.4 Hz, 1H), 4.33-4.46 (m, 1H), 3.87 (s, 3H), 1.31 (d, J=6.4 Hz, 6H). Second eluting peak: methyl 8-cyano-4-(isopropylamino) benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxylate (Isomer B). ¹H NMR (400 MHz, CHLOROFORM-d) δ 8.37 (s, 1H), 8.22 (d, J=7.5 Hz, 1H), 7.28 (d, J=2.0 Hz, 1H), 7.26-7.26 (m, 1H), 7.22 (d, J=2.0 Hz, 1H), 4.34-4.44 (m, 1H), 3.87 (s, 3H), 1.31 (d, J=6.4 Hz, 6H). LCMS m/z 326.1 (M+1).

Examples 1 and 2

A mixture of Intermediate 1C (353 mg, 1.09 mmol) and 1 N NaOH (1085 μL, 1.09 mmol) in dioxane (8 mL) was stirred at 50° C. for 5 h. Next, 1 N HCl (1.09 mL) was added to the reaction mixture. The mixture was concentrated and the resulting acid isomer A contaminated with 1 equivalent sodium chloride was used in the next step described below. LCMS m/z 312.0 (M+1).

TEA (8.95 μL, 0.064 mmol) was added to a stirred mixture of (R)-4-amino-3-fluoro-2-methylbutan-2-ol (7.78 mg, 0.064 mmol), acid isomer A (20 mg, 0.064 mmol) and BOP (28.4 mg, 0.064 mmol) in DMF (0.5 mL) at room temperature. The mixture was stirred at room temperature for 1 h. The mixture was concentrated and subjected to preparative HPLC (ODS column/water-MeOH-TFA 90:10:0.1 to 10:90:0.1 gradient) to afford (R)-7-cyano-N-(2-fluoro-3-hydroxy-3-methylbutyl)-4-(isopropylamino) benzo [5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (Example 1). ¹H NMR (400 MHz, DMSO-d₆) δ 8.71 (t, J=5.4 Hz, 1H), 8.22 (d, J=8.3 Hz, 1H), 8.00 (s, 1H), 7.65 (d, J=1.8 Hz, 1H), 7.52 (dd, J=2.0, 8.3 Hz, 1H), 7.23 (d, J=8.4 Hz, 1H), 4.19-4.41 (m, 2H), 3.53-3.78 (m, 1H), 3.33-3.45 (m, 1H), 1.19 (dd, J=1.2, 6.3 Hz, 6H), 1.15 (dd, J=1.2, 5.5 Hz, 6H). MS m/z 415 (M+H).

Intermediate 1D was similarly converted to (R)-8-cyano-N-(2-fluoro-3-hydroxy-3-methylbutyl)-4-(isopropylamino) benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (Example 2). ¹H NMR (400 MHz, DMSO-d₆) δ 8.71 (t, J=5.4 Hz, 1H), 8.22 (d, J=7.2 Hz, 1H), 8.00 (s, 1H), 7.62 (d, J=1.8 Hz, 1H), 7.52 (dd, J=2.0, 8.4 Hz, 1H), 7.22 (d, J=8.4 Hz, 1H), 4.22-4.41 (m, 2H), 3.43-3.74 (m, 2H), 1.19 (dd, J=1.2, 6.3 Hz, 6H), 1.15 (dd, J=1.3, 5.6 Hz, 6H). MS m/z 415 (M+H).

TABLE 1

Ex. No.	Structure	HPLC RT (min)	HPLC cond.	LCMS
3		1.68	A	395.1

TABLE 1-continued

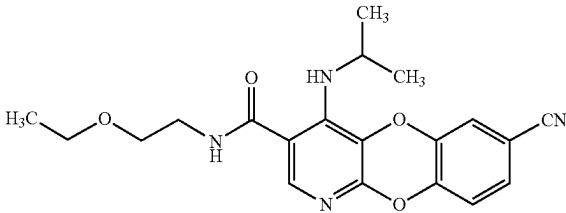
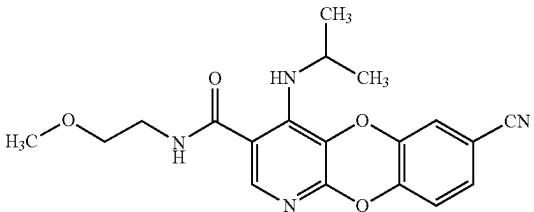
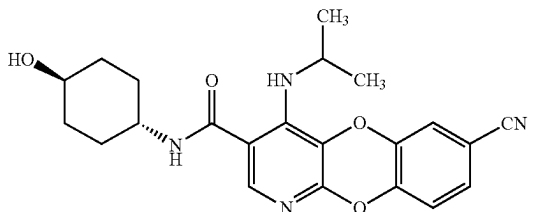
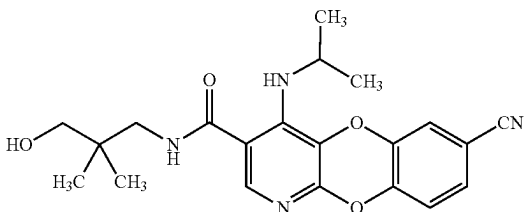
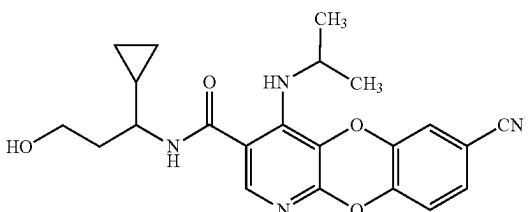
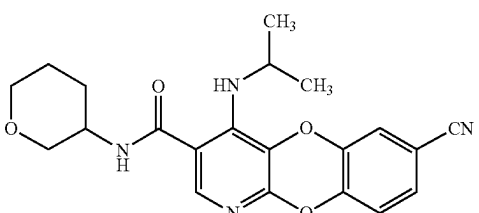
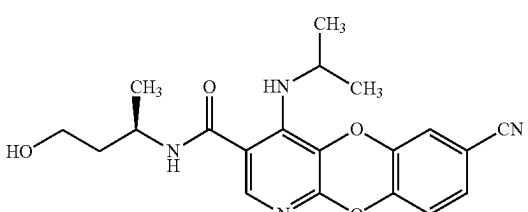
Ex. No.	Structure	HPLC RT (min)	HPLC cond.	LCMS
4		1.87	A	382.9
5		1.64	A	369.1
6		1.56	B	409.2
7		1.83	A	396.9
8		1.67	A	409.2
9		1.83	A	395.2
10		1.74	A	383.0

TABLE 1-continued

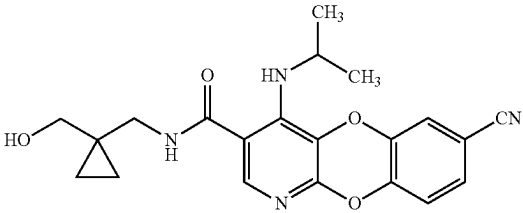
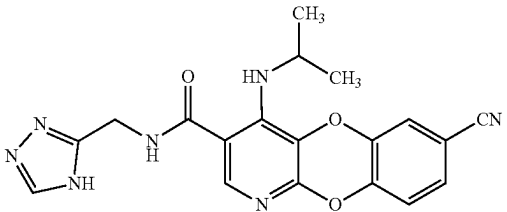
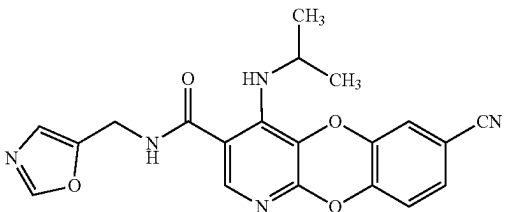
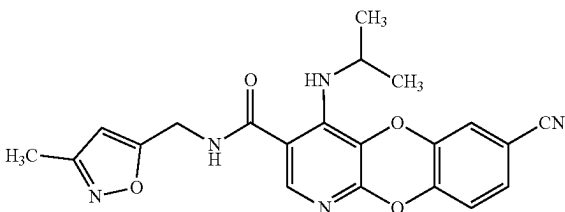
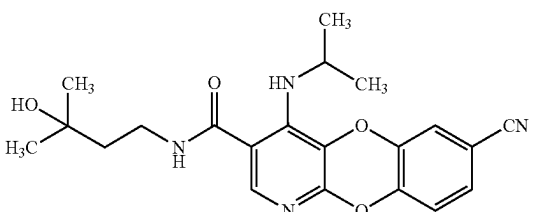
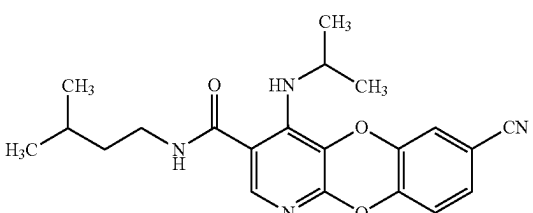
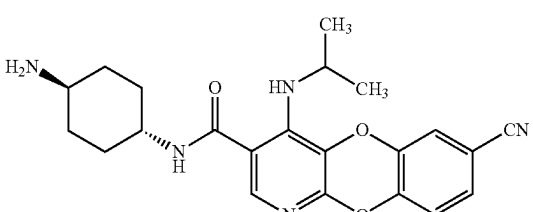
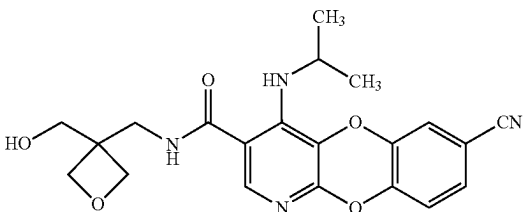
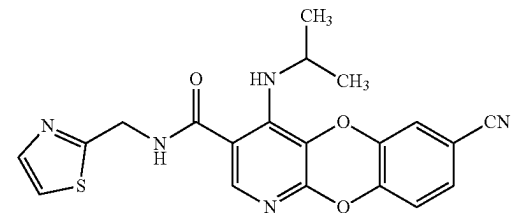
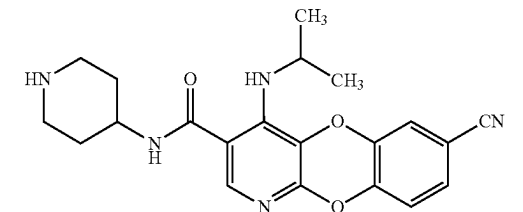
Ex. No.	Structure	HPLC RT (min)	HPLC cond.	LCMS
11		1.64	B	395.2
12		1.35	B	392.1
13		1.63	B	392.1
14		1.79	B	406.2
15		1.63	A	397.0
16		2.25	A	380.9
17		1.46	A	408.0

TABLE 1-continued

Ex. No.	Structure	HPLC RT (min)	HPLC cond.	LCMS
18		1.42	A	411.2
19		1.71	A	408.1
20		1.36	A	394.1

HPLC Conditions:

Method A: Waters Acquity UPLC BEH C18, 2.1×50 mm, 1.7 m 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: 0-100% B over 3 minutes, then a 0.75-minute hold at 100% B; Flow: 1.0 mL/min; Detection: UV at 220 nm.

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

Method C: Waters Acquity UPLC BEH C18 2.1×50 mm, 1.7 m; Mobile Phase A: 2:98 acetonitrile:water with 0.05% trifluoroacetic acid; Mobile Phase B: 98:2 acetonitrile:water with 0.05% trifluoroacetic acid; Temperature: 50° C.; Gradient: 0-100% B over 1 minutes, then a 0.50-minute hold at 100% B; Flow: 1.0 mL/min; Detection: UV at 220 nm.

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.

IRAK4 Inhibition Assay

The assays were performed in U-bottom 384-well plates. The final assay volume was 30 μL prepared from 15 μL additions of enzyme and substrates (fluoresceinated peptide and ATP) and test compounds in assay buffer (20 mM HEPES pH 7.2, 10 mM MgCl₂, 0.015% Brij 35 and 4 mM DTT). The reaction was initiated by the combination of IRAK4 with substrates and test compounds. The reaction mixture was incubated at room temperature for 60 min. and

terminated by adding 45 μL of 35 mM EDTA to each sample. The reaction mixture was analyzed on the Caliper LABCHIP® 3000 (Caliper, Hopkinton, MA) by electrophoretic separation of the fluorescent substrate and phosphorylated product. Inhibition data were calculated by comparison to no enzyme control reactions for 100% inhibition and vehicle-only reactions for 0% inhibition. The final concentrations of reagents in the assays are ATP, 500 μM; FL-IPTSPITTTYFFFKKK peptide 1.5 μM; IRAK4, 0.6 nM; and DMSO, 1.6%.

IRAK4 Whole Blood Assay

Human whole blood containing the anti-coagulant ACD-A was plated in 384-well plate (25 μL/well) and incubated with compounds for 60 minutes at 37° C. in a 5% CO₂ incubator. The blood was stimulated with a TLR2 agonist, 10 μg/mL final concentration of lipoteichoic acid (Invivogen, San Diego, CA) in 25 μL RPMI (Gibco) for 5 hours in a 5% CO₂ incubator. At the end of the incubation, plates were centrifuged at 2300 rpm for 5 minutes. Supernatants were harvested and analyzed for IL-6 levels by Flow Cytometry beads assay (BD Biosciences, San Jose, CA).

TABLE A

IRAK4 Inhibition Data		
Example No.	IRAK4 IC ₅₀ (μM)	Whole Blood EC ₅₀ (μM)
1	1.18	—
2	0.0085	1.70
3	0.060	—
4	0.082	—
5	0.15	—
6	0.031	—
7	0.27	—

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TABLE A-continued

IRAK4 Inhibition Data		
Example No.	IRAK4 IC ₅₀ (μM)	Whole Blood EC ₅₀ (μM)
8	0.22	—
9	0.092	—
10	0.16	—
11	0.44	—
12	0.14	—
13	0.18	—
14	0.53	—
15	0.022	—
16	0.023	—
17	0.034	—
18	0.24	—
19	0.17	—
20	0.085	—

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 1

<210> SEQ ID NO 1

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<221> NAME/KEY: misc_feature

<223> OTHER INFORMATION: Flourescent tag attached to amino acid 1

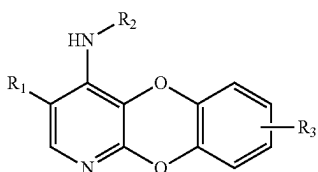
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Ile Pro Thr Ser Pro Ile Thr Thr Thr Tyr Phe Phe Phe Lys Lys Lys

1 5 10 15

What is claimed is:

1. A compound of Formula (I)



or a pharmaceutically acceptable salt thereof, wherein:

R₁ is:

- (i) —C(O)NR_xR_{1a}; or
- (ii) pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, oxadiazolyl, triazolyl, or thiadiazolyl, each substituted with zero to 2 R_{1b};

R_{1a} is:

- (i) C₁₋₆ alkyl substituted with zero to 6 R_w; or
- (ii) —(CR_xR_x)₀₋₃R_{1c};

each R_w is independently F, Cl, —CN, —OH, —OCH₃, —OCH₂CH₃, —NR_xR_x, —NR_xC(O)(C₁₋₃ alkyl), —NR_xC(O)(C₃₋₆ cycloalkyl), or a cyclic group selected from C₃₋₆ cycloalkyl, oxetanyl, piperidinyl, tetrahydropyranyl, oxazolyl, isoxazolyl, thiazolyl, and triazolyl, each cyclic group substituted with zero to 1 substituent selected from —OH, —CH₃, —CH₂OH, —OCH₂CH₃, and —NR_xR_x;

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each R_{1b} is independently —CR_xR_x(C₃₋₆ cycloalkyl), tetrahydrofuranlyl, pyrrolidinyl, tetrahydropyranlyl, piperidinyl, piperazinyl, morpholinyl, or C₁₋₆ alkyl substituted with zero to 6 R_w;

5 R_{1c} is C₃₋₆ cycloalkyl, oxetanyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyranlyl, dioxido-tetrahydrothiophenyl, dioxidothiomorpholinyl, isoxazolyl, oxazolyl, thiazolyl, oxadiazolyl, triazolyl, or tetrazolyl, each substituted with zero to 3 substituents independently selected from F, Cl, —CN, —OH, —NR_xR_x, C₁₋₃ alkyl, C₁₋₃ fluoroalkyl, C₁₋₃ hydroxyalkyl, —NR_xC(O)(C₁₋₃ alkyl), —NR_xC(O)O(C₁₋₃ alkyl), and —S(O)₂(C₁₋₂ alkyl);

R₂ is:

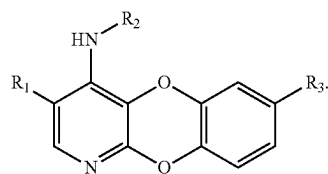
- 15 (i) hydrogen;
- (ii) C₁₋₆ alkyl substituted with zero to 4 substituents independently selected from F, Cl, —OH, —CN, C₃₋₆ cycloalkyl, and dimethoxyphenyl; or

(ii) a cyclic group selected from C₃₋₆ cycloalkyl, oxetanyl, tetrahydrofuranlyl, tetrahydropyranlyl, piperidinyl, pyrazolyl, and thiazolyl, wherein said cyclic group is substituted with zero to 3 substituents independently selected from F, Cl, —OH, —CN, C₁₋₂ alkyl, C₁₋₂ fluoroalkyl, C₁₋₂ hydroxyalkyl, and —S(O)₂(C₁₋₂ alkyl);

R₃ is —CN, —C(O)NR_xR_x, or a cyclic group selected from phenyl, pyrazolyl, imidazolyl, triazolyl, pyridinyl, pyridinonyl, and pyrimidinyl, each cyclic group substituted with zero to 3 substituents selected from F, Cl, —OH, —CN, C₁₋₂ alkyl, —CF₃, and —CH₂OH;

and each R_x is hydrogen or —CH₃.

2. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, having the structure:



3. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein:

R_{1a} is:

- (i) C₁₋₆ alkyl substituted with zero to 6 R_w; or
- (ii) —(CR_xR_x)₀₋₂R_{1c};

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R₂ is:

- (i) hydrogen;
- (ii) C₁₋₄ alkyl substituted with zero to 4 substituents independently selected from F, Cl, —OH, —CN, C₃₋₆ cycloalkyl, and dimethoxyphenyl; or
- (ii) a cyclic group selected from C₃₋₆ cycloalkyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, and piperidinyl, wherein said cyclic group is substituted with zero to 3 substituents independently selected from F, —OH, —CN, C₁₋₂ alkyl, C₁₋₂ fluoroalkyl, C₁₋₂ hydroxyalkyl, and —S(O)₂(C₁₋₂ alkyl); and

R₃ is —CN or —C(O)NR_xR_x.

4. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein:

R₁ is —C(O)NHR_{1a};

R_{1a} is —CH₂CH₂CH(CH₃)₂, —CH₂CH₂C(CH₃)OH, —CH₂C(CH₃)₂CH₂OH, —CH(CH₃)CH₂CH₂OH, —CH₂CHFC(CH₃)₂OH, —CH₂CH₂OCH₃, —CH₂CH₂OCH₂CH₃, —CH(cyclopropyl)CH₂CH₂OH, —CH₂(hydroxymethylcyclopropyl), —CH₂(hydroxymethyloxetanyl), —CH₂(oxazolyl), —CH₂(methylisoxazolyl), —CH₂(thiazolyl), —CH₂(triazolyl), hydroxycyclohexyl, aminocyclohexyl, piperidinyl, or tetrahydropyranyl;

R₂ is —CH(CH₃)₂; andR₃ is —CN.

5. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein R_{1a} is C₁₋₆ alkyl substituted with zero to 6 R_w.

6. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein R_{1a} is —(CR_xR_x)₀₋₂ R_{1c}.

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

(R)-7-cyano-N-(2-fluoro-3-hydroxy-3-methylbutyl)-4-(isopropylamino) benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (1);

(R)-8-cyano-N-(2-fluoro-3-hydroxy-3-methylbutyl)-4-(isopropylamino)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (2);

7-cyano-4-(isopropylamino)-N-(tetrahydro-2H-pyran-4-yl)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (3);

7-cyano-N-(2-ethoxyethyl)-4-(isopropylamino)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (4);

7-cyano-4-(isopropylamino)-N-(2-methoxyethyl)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (5);

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7-cyano-N-((1r,4r)-4-hydroxycyclohexyl)-4-(isopropylamino)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (6);

7-cyano-N-(3-hydroxy-2,2-dimethylpropyl)-4-(isopropylamino)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (7);

7-cyano-N-(1-cyclopropyl-3-hydroxypropyl)-4-(isopropylamino)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (8);

7-cyano-4-(isopropylamino)-N-(tetrahydro-2H-pyran-3-yl)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (9);

(R)-7-cyano-N-(4-hydroxybutan-2-yl)-4-(isopropylamino)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (10);

7-cyano-N-((1-(hydroxymethyl)cyclopropyl)methyl)-4-(isopropylamino)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (11);

N-((4H-1,2,4-triazol-3-yl)methyl)-7-cyano-4-(isopropylamino)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (12);

7-cyano-4-(isopropylamino)-N-(oxazol-5-ylmethyl)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (13);

7-cyano-4-(isopropylamino)-N-(3-methylisoxazol-5-ylmethyl)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (14);

7-cyano-N-(3-hydroxy-3-methylbutyl)-4-(isopropylamino)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (15);

7-cyano-N-isopentyl-4-(isopropylamino)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (16);

N-((1R,4R)-4-aminocyclohexyl)-7-cyano-4-(isopropylamino)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (17);

7-cyano-N-((3-(hydroxymethyl)oxetan-3-yl)methyl)-4-(isopropylamino)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (18);

7-cyano-4-(isopropylamino)-N-(thiazol-2-ylmethyl)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (19); or

7-cyano-4-(isopropylamino)-N-(piperidin-4-yl)benzo[5,6][1,4]dioxino[2,3-b]pyridine-3-carboxamide (20).

8. A pharmaceutical composition comprising an effective amount of one or more compounds of Formula (1) according to claim 1 or a pharmaceutically-acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

* * * * *