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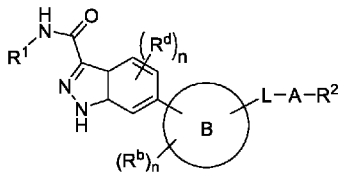

(I)

(57) Abstract: Compounds having formula (I), and enantiomers, and diastereomers, stereoisomers, pharmaceutically-acceptable salts thereof, are useful as kinase modulators, including RIPK1 modulation. All the variables are as defined herein.

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INDAZOLE CARBOXAMIDES AS KINASE INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is entitled to priority pursuant to 35 U.S.C. §119(e) to U.S. provisional patent application No. 62/730,611, filed September 13, 2018, which is incorporated herein in its entirety.

FIELD OF THE INVENTION

The present invention relates to novel compounds that inhibit receptor interacting protein kinases and methods of making and using the same. Specifically, the present invention relates to indazolecarboxamides as receptor interacting protein kinase 1 (RIPK1) inhibitors.

BACKGROUND OF THE INVENTION

Apoptosis and necrosis represent two different mechanisms of cell death. Apoptosis is a highly regulated process involving the caspase family of cysteine proteases, and characterized by cellular shrinkage, chromatin condensation, and DNA degradation. In contrast, necrosis is associated with cellular and organelle swelling and plasma membrane rupture with ensuing release of intracellular contents and secondary inflammation (Kroemer et al., (2009) Cell Death Differ 16:3-11). Necrosis has been considered a passive, unregulated form of cell death; however, recent evidence indicates that some necrosis can be induced by regulated signal transduction pathways such as those mediated by receptor interacting protein kinases (RIPKs) especially in conditions where caspases are inhibited or cannot be activated efficiently (Golstein P & Kroemer G (2007) Trends Biochem. Sci. 32:37-43; Festjens et al. (2006) Biochim. Biophys. Acta 1757:1371-1387). Stimulation of the Fas and TNFR family of death domain receptors (DRs) is known to mediate apoptosis in most cell types through the activation of the extrinsic caspase pathway. In addition, in certain cells deficient for caspase-8 or treated with pan-caspase inhibitor Z-VAD, stimulation of death domain receptors (DR) causes a receptor interacting protein kinase 1 (RIPK1) dependent programmed necrotic cell death instead of apoptosis (Holler et al. (2000) Nat. Immunol. 1:489-495; Degterev et al. (2008) Nat. Chem. Biol. 4:313-321). This novel mechanism of cell death is termed

"programmed necrosis" or "necroptosis" (Degterev et al., (2005) Nat Chem Biol 1:112-119).

Necroptosis can be triggered by a number of mechanisms including of TNF receptor activation, Toll-like receptor engagement, genotoxic stress and viral infection. Downstream of the various stimuli, the signaling pathway that results in necroptosis is dependent on RIPK1 and RIPK3 kinase activity. (He et al., (2009) Cell 137:1100-1111; Cho et. al., (2009) Cell 137:1112-1123; Zhang et al., (2009) Science 325:332-336).

Dysregulation of the necroptosis signaling pathway has been linked to inflammatory diseases such as macrophage necrosis in atheroscelerosis development, virus-induced inflammation, systemic inflammatory response syndrome and ethanol-induced liver injury, neurodegeneration such as detachment of the retina, ischemia, amyotrophic lateral sclerosis (ALS), and Gaucher's disease (Trichonas et al., (2010) Proc. Natl. Acad. Sci. 107, 21695-21700; Lin et al., (2013) Cell Rep. 3, 200-210; Cho et al., (2009) Cell, 137, 1112-1123; Duprez et al., (2011) Immunity 35, 908-918; Roychowdhury et al., Hepatology 57, 1773-1783; Vandenabeele et al., (2010) Nature 10, 700-714; Vandenabeele et al., (2010) Sci. Signalling 3, 1-8; Zhang et al., (2010) Cellular & Mol. Immunology 7, 243-249; Moriwaki et al., (2013) Genes Dev. 27, 1640-1649; Ito et al., (2016) Science 353, 603-608; Vitner et al., (2014) Nature Med. 20, 204-208).

A potent, selective, small molecule inhibitor of RIPK1 activity would block RIPK1-dependent pro-inflammatory signaling and thereby provide a therapeutic benefit in inflammatory diseases characterized by increased and/or dysregulated RIPK1 kinase activity.

SUMMARY OF THE INVENTION

The present invention provides novel indazolecarboxamides including stereoisomers, tautomers, isotopes, prodrugs, pharmaceutically acceptable salts, salts, or solvates thereof, which are useful as inhibitors of RIPK1.

The present invention also provides processes and intermediates for making the compounds of the present invention.

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, isotopes, prodrugs, pharmaceutically acceptable salts, salts, or solvates thereof.

The compounds of the invention may be used in the treatment and/or prophylaxis of conditions associated with aberrant RIPK1 activity.

The compounds of the present invention may be used in therapy.

The compounds of the present invention may be used for the manufacture of a medicament for the treatment and/or prophylaxis of a condition associated with aberrant RIPK1 activity.

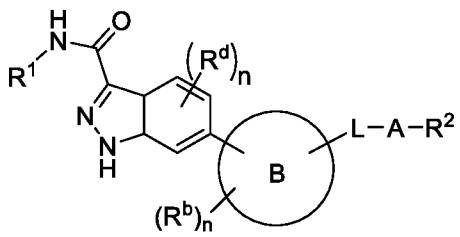
In another aspect, the present invention is directed to a method of treating diseases mediated at least partially by RIPK1 including inflammatory diseases, ischemia, neurodegeneration, and Gaucher's disease, which method comprises administering to a patient in need of such treatment a compound of the present invention as described above.

The compounds of the invention can be used alone, in combination with other compounds of the present invention, or in combination with one or more, preferably one to two other agent(s).

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

DETAILED DESCRIPTION OF EMBODIMENTS OF THE INVENTION

In one aspect, the present invention provides, *inter alia*, compounds of Formula (I) or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein



(I)

Ring B is piperidinyl, piperazinyl, or morpholinyl;

R^1 is H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} deuteroalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{1-3} alkoxy, C_{1-3} haloalkoxy, or C_{1-3} deuteroalkoxy;

R^b is H, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, C_{1-3} deuteroalkyl, C_{1-3} deuteroalkoxy, halo, NH_2, or CN;

R^d is independently H, halo, or C_{1-3} alkyl;

L is $C(O)NR^a$;

R^a is independently H, C_{1-4} alkyl, or C_{1-4} deuteroalkyl;

A is A' or A'-L',

A' is C_{1-4} alkyl substituted with 0-1 OH, C_{1-4} deuteroalkyl substituted with 0-1 OH, C_{3-6} cycloalkyl-C_{0-3}-alkyl-, C_{0-3}-alkyl-C_{3-6} cycloalkyl-, pyrrolyl-C_{1-3}-alkyl-, C_{1-3}-alkyl-pyrrolyl-, pyrazolyl-C_{1-3}-alkyl-, or C_{1-3}-alkyl-pyrazolyl-;

L' is –O-;

R^2 is phenyl, or a 5 to 6 membered heterocycle having 1-4 heteroatoms selected from N and O, wherein any of the phenyl or heterocycle groups are substituted with 0-3 R^{2a};

R^{2a} is halo, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy-C_{1-6} alkoxy, C_{1-6} deuteroalkyl, C_{1-6} deuteroalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, C_{3-6} halocycloalkyl, C_{3-6} cycloalkoxy, C_{3-6} cycloalkyl-C_{1-3} alkoxy-, C_{3-6} cycloalkyl-C_{1-3} deuteroalkoxy-, C_{3-6} cycloalkyl-C_{1-3} haloalkoxy-, C_{1-6} alkoxy-C_{1-3} alkyl-, C_{3-6} cycloalkoxy-C_{1-3} alkyl-, C_{1-4} alkyl-SO_2-, C_{3-6} cycloalkyl-SO_2-, C_{6-10} aryl-S-, $NR^{2c}R^{2d}CO$-, heterocycle-, heterocycle-O-, heterocycle-CH_2-, wherein each heterocycle is independently a 4-6 membered ring having 1-2 heteroatoms selected from N and O, and wherein each alkyl, cycloalkyl, or heterocycle is substituted with 0-2 R^{2b};

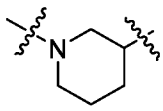
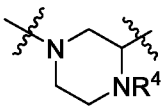
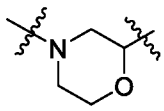
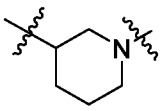
R^{2b}, at each occurrence, is independently C_{1-3} alkyl, halo, C=O, or C_{1-3} haloalkyl;

R^{2c} and R^{2d} are independently selected from H, C_{1-3} alkyl, C_{1-3} deuteroalkyl, C_{3-6} cycloalkyl, or taken together with N to which they are attached to form a 4-6 member heterocyclic ring, having 0-1 additional heteroatoms selected from N, O and S, and being substituted with 0-4 substituents chosen from deuterium or halo; and

n is 0, 1 or 2.

Another embodiment provides a compound of Formula (I), or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

Ring B is




, or  , any of which are substituted with 0-1 R^b ; and

R^4 is H, or C_{1-3} alkyl.

Another embodiment provides a compound of Formula (I), or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R^2 is phenyl, or pyridinyl, or pyrrolyl, any of which are substituted with 0-3 R^{2a}.

Another embodiment provides a compound of Formula (I), or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

A' is C_{1-4} alkyl substituted with 0-1 OH, or C_{1-4} deuteroalkyl substituted with 0-1 OH.

Another embodiment provides a compound of Formula (I), or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R^{2a} is halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy or C_{3-6} cycloalkyl-C_{1-3} alkoxy-.

Another embodiment provides a compound of Formula (I), or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R^b is H, Cl, F, C_{1-3} alkyl, or C_{1-3} alkoxy;

Another embodiment provides a compound of Formula (I), or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

A is $-CH_2-$, CD_2-, $-CH_2CH_2-$, $-CH(CH_3)-$, $-CH(CD_3)-$, $-CH_2CH_2CH(CH_3)-$, $-CH_2CH_2CH(OH)-$, or $-CH_2$-cyclopropyl-.

Another embodiment provides a compound of Formula (I), or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

A is $–CH_2$-, $-CH_2CH_2$-, $-CH_2CH_2CH(CH_3)$-, $-CH_2CH_2CH(OH)$-, $-CH_2CH(OH)CH_2$-O-, $-CH_2CH_2CH_2O$-, -cyclohexyl-, - pyrrolidinyl-CH_2-, or $-CH_2$-cyclopropyl-.

Another embodiment provides a compound of Formula (I), or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

L is C(O)NH; and

R^2 is phenyl substituted with 0-3 R^{2a}.

Another embodiment provides a compound of Formula (I), or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein the compound is selected from the examples.

The present invention is also directed to pharmaceutical compositions useful in treating diseases associated with kinase modulation, including the modulation of receptor interacting protein kinases such as RIPK1, comprising compounds of formula (I), or pharmaceutically-acceptable salts thereof, and pharmaceutically-acceptable carriers or diluents.

The invention further relates to methods of treating diseases associated with kinase modulation, including the modulation of receptor interacting protein kinases such as RIPK1, comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound according to formula (I).

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.

The present invention also provides a method for treating proliferative diseases, allergic diseases, autoimmune diseases and inflammatory diseases and fibrotic diseases, comprising administering to a host in need of such treatment a therapeutically effective

amount of at least one of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof.

The present invention also provides a method for treating a disease, comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of formula (I), wherein the disease is inflammatory bowel disease, Crohn's disease or ulcerative colitis, poriasis, systemic lupus erythematosus (SLE), rheumatoid arthritis, multiple sclerosis (MS), transplant rejection, nonalcoholic steatohepatitis (NASH), or ischemia reperfusion.

The present invention also provides a method of treating a condition comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of formula (I), wherein the condition is selected from systemic lupus erythematosus (SLE), multiple sclerosis (MS), transplant rejection, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, solid tumors, ocular neovasculization, and infantile haemangiomas, B cell lymphoma, systemic lupus erythematosus (SLE), psoriatic arthritis, multiple vasculitides, idiopathic thrombocytopenic purpura (ITP), myasthenia gravis, allergic rhinitis, multiple sclerosis (MS), transplant rejection, Type I diabetes, membranous nephritis, autoimmune hemolytic anemia, autoimmune thyroiditis, cold and warm agglutinin diseases, Evan's syndrome, hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP), sarcoidosis, Sjogren's syndrome, peripheral neuropathies, pemphigus vulgaris and asthma, nonalcoholic steatohepatitis (NASH), or ischemia reperfusion.

The present invention also provides a method of treating a condition comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of formula (I), wherein the condition is selected from macrophage necrosis in atherosclerosis development, virus-induced inflammation, systemic inflammatory response syndrome and ethanol-induced liver injury, neurodegeneration such as detachment of the retina, retinal degeneration, wet and dry age-related macular degeneration (AMD), ischemia, amyotrophic lateral sclerosis (ALS), and Gaucher's disease.

The present invention also provides a method of treating a condition comprising administering to a patient in need of such treatment a therapeutically-effective amount of

a compound of formula (I), wherein the condition is selected from inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis, rheumatoid arthritis (RA), heart failure, and nonalcoholic steatohepatitis (NASH).

The present invention also provides a method of treating a condition comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of formula (I), wherein the condition is selected from inflammatory bowel disease, Crohn's disease, ulcerative colitis, and psoriasis.

The present invention also provides a method of treating a condition comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of formula (I), wherein the condition is selected from nonalcoholic steatohepatitis (NASH), and ischemia reperfusion.

The present invention also provides a method for treating rheumatoid arthritis, comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of formula (I),

The present invention also provides a method of treating diseases, comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of formula (I), or pharmaceutically acceptable salt thereof, in combination with other therapeutic agents.

The present invention also provides the compounds of the present invention or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, for use in therapy.

In another embodiment, compounds of formula (I), are selected from exemplified examples or combinations of exemplified examples or other embodiments herein.

The present invention also provides the use of the compounds of the present invention or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, for the manufacture of a medicament for the treatment of cancers, an allergic disease, an autoimmune disease or an inflammatory disease.

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

embodiments. It is also to be understood that each individual element of the embodiments is its own independent embodiment. Furthermore, any element of an embodiment is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment.

The following are definitions of terms used in this specification and appended claims. The initial definition provided for a group or term herein applies to that group or term throughout the specification and claims, individually or as part of another group, unless otherwise indicated.

When any variable (e.g., R^3) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^3, then said group may optionally be substituted with up to two R^3 groups and R^3 at each occurrence is selected independently from the definition of R^3. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

In cases wherein there are nitrogen atoms (e.g., amines) on compounds of the present invention, these can be converted to N-oxides by treatment with an oxidizing agent (e.g., MCPBA and/or hydrogen peroxides) to afford other compounds of this invention. Thus, all shown and claimed nitrogen atoms are considered to cover both the shown nitrogen and its N-oxide (N→O) derivative.

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.

A dash "-" that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, $-CONH_2$ is attached through the carbon atom.

The term "optionally substituted" in reference to a particular moiety of the compound of Formula (I), (*e.g.*, an optionally substituted heteroaryl group) refers to a moiety having 0, 1, 2, or more substituents. For example, "optionally substituted alkyl" encompasses both "alkyl" and "substituted alkyl" as defined below. It will be understood by those skilled in the art, with respect to any group containing one or more substituents, that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical, synthetically non-feasible and/or inherently unstable.

As used herein, the term "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, "C_{1-10} alkyl" (or alkylene), is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkyl groups. Additionally, for example, "C_1-C_6 alkyl" denotes alkyl having 1 to 6 carbon atoms. Alkyl groups can be unsubstituted or substituted so that one or more of its hydrogens are replaced by another chemical group. Example alkyl groups include, but are not limited to, methyl (Me), ethyl (Et), propyl (*e.g.*, n-propyl and isopropyl), butyl (*e.g.*, n-butyl, isobutyl, t-butyl), pentyl (*e.g.*, n-pentyl, isopentyl, neopentyl), and the like.

When the term "alkyl" is used together with another group, such as in "arylalkyl", this conjunction defines with more specificity at least one of the substituents that the substituted alkyl will contain. For example, "arylalkyl" refers to a substituted alkyl group as defined above where at least one of the substituents is an aryl, such as benzyl. Thus, the term aryl(C_{0-4})alkyl includes a substituted lower alkyl having at least one aryl substituent and also includes an aryl directly bonded to another group, *i.e.*, aryl(C_0)alkyl. The term "heteroarylalkyl" refers to a substituted alkyl group as defined above where at least one of the substituents is a heteroaryl.

"Alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either straight or branched configuration and having one or more double carbon-carbon bonds that may occur in any stable point along the chain. For example, "C_{2-6} alkenyl" (or alkenylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkenyl groups. Examples of alkenyl include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3, pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-methyl-2-propenyl, 4-methyl-3-pentenyl, and the like.

"Alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either straight or branched configuration and having one or more triple carbon-carbon bonds that may occur in any stable point along the chain. For example, "C_{2-6} alkynyl" (or alkynylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkynyl groups; such as ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like.

When reference is made to a substituted alkenyl, alkynyl, alkylene, alkenylene, or alkynylene group, these groups are substituted with one to three substituents as defined above for substituted alkyl groups.

The term "alkoxy" refers to an oxygen atom substituted by alkyl or substituted alkyl, as defined herein. For example, the term "alkoxy" includes the group -O-C_{1-6}alkyl such as methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyloxy, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, 3-methylpentoxy, and the like. "Lower alkoxy" refers to alkoxy groups having one to four carbons.

It should be understood that the selections for all groups, including for example, alkoxy, thioalkyl, and aminoalkyl, will be made by one skilled in the field to provide stable compounds.

The term "substituted", as used herein, means that any one or more hydrogens on the designated atom or group is replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded. When a substituent is oxo, or keto, (*i.e.*, =O) then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties. Unless otherwise specified, substituents are named into the core structure. For example, it is to be understood that when (cycloalkyl)alkyl is listed as a possible substituent, the point of attachment of this substituent to the core structure is in the alkyl portion. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (e.g., C=C, C=N, or N=N).

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds or useful synthetic intermediates. A stable compound or stable structure is meant to imply a compound that is sufficiently robust to survive isolation from a reaction mixture to a useful degree of purity, and subsequent formulation into an efficacious therapeutic agent. It is preferred that the presently recited compounds do not contain a N-halo, $S(O)_2H$, or S(O)H group.

The term "carbocyclyl" or "carbocyclic" refers to a saturated or unsaturated, or partially unsaturated, monocyclic or bicyclic ring in which all atoms of all rings are carbon. Thus, the term includes cycloalkyl and aryl rings. Monocyclic carbocycles have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles have 7 to 12 ring atoms, e.g., arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, anthracenyl, and tetrahydronaphthyl (tetralin). As shown above, bridged rings are also included in the definition of carbocycle (*e.g.*, [2.2.2]bicyclooctane). Carbocycles, can include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and phenyl. When the term "carbocycle" is used, it is intended to include "aryl". A bridged ring occurs when one or more carbon atoms link two non-adjacent carbon atoms. Preferred bridges are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a bicyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

The term "aryl" refers to monocyclic or bicyclic aromatic hydrocarbon groups having 6 to 12 carbon atoms in the ring portion, such as phenyl, and naphthyl groups, each of which may be substituted. A preferred aryl group is optionally-substituted phenyl.

The term "cycloalkyl" refers to cyclized alkyl groups, including mono-, bi- or poly-cyclic ring systems. C_{3-7} cycloalkyl is intended to include C_3, C_4, C_5, C_6, and C_7 cycloalkyl groups. Example cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, and the like, which optionally may be substituted at any available atoms of the ring(s).

The terms "heterocycloalkyl", "heterocyclo", "heterocycle", "heterocyclic", or "heterocyclyl" may be used interchangeably and refer to substituted and unsubstituted aromatic or non-aromatic 3-to 7-membered monocyclic groups, 7-to 11-membered bicyclic groups, and 10-to 15-membered tricyclic groups, in which at least one of the rings has at least one heteroatom (O, S or N), said heteroatom containing ring preferably

having 1, 2, or 3 heteroatoms selected from O, S, and N. Each ring of such a group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less, and further provided that the ring contains at least one carbon atom. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The heterocyclo group may be attached at any available nitrogen or carbon atom. The term "heterocycle" includes "heteroaryl" groups. As valence allows, if said further ring is cycloalkyl or heterocyclo it is additionally optionally substituted with =O (oxo).

Exemplary monocyclic heterocyclyl groups include azetidinyl, pyrrolidinyl, oxetanyl, imidazolinyl, oxazolidinyl, isoxazolinyl, thiazolidinyl, isothiazolidinyl, tetrahydrofuranyl, piperidyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, 1-pyridonyl, 4-piperidonyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl and the like, including the exemplary groups listed under "heteroaryl". Exemplary bicyclic heterocyclo groups include quinuclidinyl.

The term "heteroaryl" refers to substituted and unsubstituted aromatic 5- or 6-membered monocyclic groups, 9- or 10-membered bicyclic groups, and 11- to 14-membered tricyclic groups which have at least one heteroatom (O, S or N) in at least one of the rings, said heteroatom-containing ring preferably having 1, 2, or 3 heteroatoms selected from O, S, and N. Each ring of the heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less and each ring has at least one carbon atom. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. Heteroaryl groups which are bicyclic or tricyclic must include at least one fully aromatic ring but the other fused ring or rings may be aromatic or non-aromatic. The heteroaryl group may be attached at any available nitrogen or carbon

atom of any ring. As valence allows, if said further ring is cycloalkyl or heterocyclo it is additionally optionally substituted with =O (oxo).

Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl, pyrazolinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furanyl, thienyl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and the like.

Exemplary bicyclic heteroaryl groups include indolyl, benzothiazolyl, benzodioxolyl, benzoxazolyl, benzothienyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuranyl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridyl, dihydroisoindolyl, tetrahydroquinolinyl, and the like.

Exemplary tricyclic heteroaryl groups include carbazolyl, benzindolyl, phenanthrollinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

Unless otherwise indicated, when reference is made to a specifically-named aryl (*e.g.*, phenyl), cycloalkyl (*e.g.*, cyclohexyl), heterocyclo (*e.g.*, pyrrolidinyl, piperidinyl, and morpholinyl) or heteroaryl (*e.g.*, tetrazolyl, imidazolyl, pyrazolyl, triazolyl, thiazolyl, and furyl) the reference is intended to include rings having 0 to 3, preferably 0-2, substituents, as appropriate.

The term "halo" or "halogen" refers to chloro, bromo, fluoro and iodo.

The term "haloalkyl" means a substituted alkyl having one or more halo substituents. For example, "haloalkyl" includes mono, bi, and trifluoromethyl.

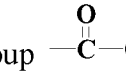
The term "haloalkyl" means a substituted alkyl having one or more halo substituents. For example, "haloalkyl" includes mono, bi, and trifluoromethyl.

The term "haloalkoxy" means an alkoxy group having one or more halo substituents. For example, "haloalkoxy" includes OCF_3.

The term "deuteroalkyl" means a substituted alkyl having one or more deuterium atom. For example, the term "deuteroalkyl" includes mono, bi, and trideuteromethyl.

The term "heteroatoms" shall include oxygen, sulfur and nitrogen.

When the term "unsaturated" is used herein to refer to a ring or group, the ring or group may be fully unsaturated or partially unsaturated.

One skilled in the field will understand that, when the designation "CO_2" is used herein, this is intended to refer to the group  .

Throughout the specification, groups and substituents thereof may be chosen by one skilled in the field to provide stable moieties and compounds and compounds useful as pharmaceutically-acceptable compounds and/or intermediate compounds useful in making pharmaceutically-acceptable compounds.

The compounds of formula (I) may exist in a free form (with no ionization) or can form salts which are also within the scope of this invention. Unless otherwise indicated, reference to an inventive compound is understood to include reference to the free form and to salts thereof. The term "salt(s)" denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. In addition, the term "salt(s) may include zwitterions (inner salts), *e.g.*, when a compound of formula (I), contains both a basic moiety, such as an amine or a pyridine or imidazole ring, and an acidic moiety, such as a carboxylic acid. Pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable) salts are preferred, such as, for example, acceptable metal and amine salts in which the cation does not contribute significantly to the toxicity or biological activity of the salt. However, other salts may be useful, *e.g.*, in isolation or purification steps which may be employed during preparation, and thus, are contemplated within the scope of the invention. Salts of the compounds of the formula (I) may be formed, for example, by reacting a compound of the formula (I) with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides (formed with hydrochloric acid), hydrobromides (formed with hydrogen bromide), hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates (formed with maleic acid), methanesulfonates (formed with methanesulfonic acid), 2-naphthalenesulfonates, nicotinates, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed

with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates such as tosylates, undecanoates, and the like.

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

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.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic groups such as amines; and alkali or organic salts of acidic groups such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic,

benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Company, Easton, PA, **1990**, the disclosure of which is hereby incorporated by reference.

All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. Stereoisomers may include compounds which are optical isomers through possession of one or more chiral atoms, as well as compounds which are optical isomers by virtue of limited rotation about one or more bonds (atropisomers). The definition of compounds according to the invention embraces all the possible stereoisomers and their mixtures. It very particularly embraces the racemic forms and the isolated optical isomers having the specified activity. The racemic forms can be resolved by physical methods, such as, for example, fractional crystallization, separation or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates from the conventional methods, such as, for example, salt formation with an optically active acid followed by crystallization.

The present invention is 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 and tritium. As an example, an alkyl substituent is intended to cover alkyl groups have either hydrogen, deuterium, and/or some combination thereof. Isotopes of carbon include ^{13}C and ^{14}C. Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

Prodrugs and solvates of the inventive compounds are also contemplated. The term "prodrug" denotes a compound which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the formula (I), and/or a salt and/or solvate thereof. Any compound that will be converted *in vivo* to provide the bioactive agent (*i.e.*, the compound for formula (I)) is a prodrug within the scope and spirit of the invention. For example, compounds containing a carboxy group can form physiologically hydrolyzable esters which serve as prodrugs by being hydrolyzed in the body to yield formula (I) compounds *per se*. Such prodrugs are preferably administered orally since hydrolysis in many instances occurs principally under the influence of the digestive enzymes. Parenteral administration may be used where the ester *per se* is active, or in those instances where hydrolysis occurs in the blood. Examples of physiologically hydrolyzable esters of compounds of formula (I) include C_{1-6}alkylbenzyl, 4-methoxybenzyl, indanyl, phthalyl, methoxymethyl, C_{1-6}alkanoyloxy-C_{1-6}alkyl, *e.g.* acetoxymethyl, pivaloyloxymethyl or propionyloxymethyl, C_{1-6}alkoxycarbonyloxy-C_{1-6}alkyl, *e.g.* methoxycarbonyl-oxymethyl or ethoxycarbonyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)-methyl and other well known physiologically hydrolyzable esters used, for example, in the penicillin and cephalosporin arts. Such esters may be prepared by conventional techniques known in the art.

Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

a) *Design of Prodrugs*, edited by H. Bundgaard, (Elsevier, 1985) and *Methods in Enzymology*, Vol. 112, pp. 309-396, edited by K. Widder, et al. (Academic Press, 1985);

b) *A Textbook of Drug Design and Development*, edited by Krosgaard-Larsen and H. Bundgaard, Chapter 5, "Design and Application of Prodrugs," by H. Bundgaard, pp. 113-191 (1991); and

c) H. Bundgaard, *Advanced Drug Delivery Reviews*, Vol. 8, pp. 1-38 (1992), each of which is incorporated herein by reference.

Compounds of the formula (I) and salts thereof may exist in their tautomeric form, in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. It should be

understood that the all tautomeric forms, insofar as they may exist, are included within the invention.

Compounds of this invention may have one or more asymmetric centers. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms of compounds of the present invention are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. The present compounds can be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. All chiral, (enantiomeric and diastereomeric) and racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated. All geometric isomers, tautomers, atropisomers, hydrates, solvates, polymorphs, and isotopically labeled forms of the compounds referred to herein, and mixtures thereof, are considered within the scope of the present invention. Methods of solvation are generally known in the art.

UTILITY

The compounds of the invention modulate kinase activity, including the modulation of RIPK1. Accordingly, compounds of formula (I) have utility in treating conditions associated with the modulation of kinase activity, and particularly the selective inhibition of RIPK1 activity. In another embodiment, compounds of formula (I) have advantageous selectivity for RIPK1 activity preferably from at least 20 fold to over 1,000 fold more selective over other kinases.

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 of RIPK1, compounds of Formula (I) are useful in treating RIPK1-associated conditions including, but not limited to, inflammatory diseases such as Crohn's disease and ulcerative colitis, inflammatory bowel disease, asthma, graft versus host disease, chronic obstructive pulmonary disease; autoimmune diseases such as Graves' disease, rheumatoid arthritis, systemic lupus erythematosis, psoriasis; 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 neovasculization, and infantile haemangiomas; infectious diseases such as sepsis, septic shock, and Shigellosis; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, ALS, 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; fibrotic conditions such as, nonalcoholic steatohepatitis (NASH); and cardiac conditions such as, ischemia reperfusion; 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 erythematosis, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, ALS, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis, graft vs. host disease, inflammatory reaction induced by endotoxin, tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, gout, traumatic arthritis, rubella arthritis, acute synovitis, pancreatic β-cell disease; diseases characterized by massive neutrophil infiltration; rheumatoid spondylitis, gouty arthritis and other arthritic conditions, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis, bone resorption disease, allograft rejections, fever and myalgias due to infection, cachexia secondary to infection, meloid 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 neovasculization, 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 hyposia, vascular hyperplasia, cardiac and renal reperfusion injury, thrombosis, cardiac hypertrophy, thrombin-induced platelet aggregation, endotoxemia and/or toxic shock syndrome, conditions associated with prostaglandin endoperoxidase syndase-2, and pemphigus vulgaris. Preferred methods of treatment are those wherein the condition is selected from inflammatory bowel disease, Crohn's disease and ulcerative colitis, allograft rejection, rheumatoid arthritis, psoriasis, ankylosing spondylitis, psoriatic arthritis, and pemphigus vulgaris, and nonalcoholic steatohepatitis (NASH), and ischemia reperfusion.. Alternatively preferred methods of treatment are those wherein the condition is selected from ischemia reperfusion injury, including cerebral ischemia reperfusions injury arising from stroke and cardiac ischemia reperfusion injury arising from myocardial infarction.

When the terms "RIPK1-associated condition" or "RIPK1 -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 RIPK1 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 RIPK1.

The methods of treating RIPK1 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 RIPK1 and/or treat diseases associated with RIPK1.

Exemplary of such other therapeutic agents include corticosteroids, rolipram, calphostin, cytokine-suppressive anti-inflammatory drugs (CSAIDs), Interleukin-10, glucocorticoids, salicylates, nitric oxide, and other immunosuppressants; nuclear translocation inhibitors, such as deoxyspergualin (DSG); non-steroidal antiinflammatory drugs (NSAIDs) such as ibuprofen, celecoxib and rofecoxib; steroids such as prednisone or dexamethasone; anti-inflammatory anti-bodies such as vedolizumab and ustekinumab, anti-infammatory kinase inhibitors such as TYK2 inhibitors, antiviral agents such as abacavir; antiproliferative agents such as methotrexate, leflunomide, FK506 (tacrolimus, Prograf); cytotoxic drugs such as azathiprine and cyclophosphamide; TNF-α inhibitors such as tenidap, anti-TNF antibodies or soluble TNF receptor, rapamycin (sirolimus or Rapamune) or derivatives thereof, and agonists of FGF21.

The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art. In the methods of the present invention, such other therapeutic agent(s) may be administered prior to, simultaneously with, or following the administration of the inventive compounds. The present invention also provides pharmaceutical compositions capable of treating RIPK1 kinase-associated conditions, including IL-1, IL-6, IL-8, IFNγ and TNF-α-mediated conditions, 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 ed., **1985**, which is incorporated herein by reference in its entirety.

The compounds of Formula (I) may be administered by any means suitable for the condition to be treated, which may depend on the need for site-specific treatment or quantity of drug to be delivered. Topical administration is generally preferred for skin-related diseases, and systematic treatment preferred for cancerous or pre-cancerous conditions, although other modes of delivery are contemplated. For example, the compounds may be delivered orally, such as in the form of tablets, capsules, granules, powders, or liquid formulations including syrups; topically, such as in the form of solutions, suspensions, gels or ointments; sublingually; bucally; parenterally, such as by subcutaneous, intravenous, intramuscular or intrasternal injection or infusion techniques (*e.g.*, as sterile injectable aq. or non-aq. solutions or suspensions); nasally such as by inhalation spray; topically, such as in the form of a cream or ointment; rectally such as in the form of suppositories; or liposomally. Dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents may be administered. The compounds may be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved with suitable pharmaceutical compositions or, particularly in the case of extended release, with devices such as subcutaneous implants or osmotic pumps.

Exemplary compositions for topical administration include a topical carrier such as PLASTIBASE® (mineral oil gelled with polyethylene).

Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium

alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The inventive compounds may also be orally delivered by sublingual and/or buccal administration, *e.g.*, with molded, compressed, or freeze-dried tablets. Exemplary compositions may include fast-dissolving diluents such as mannitol, lactose, sucrose, and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (AVICEL®) or polyethylene glycols (PEG); an excipient to aid mucosal adhesion such as hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), sodium carboxymethyl cellulose (SCMC), and/or maleic anhydride copolymer (*e.g.*, GANTREZ®); and agents to control release such as polyacrylic copolymer (*e.g.*, CARBOPOL 934®). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

Exemplary compositions for nasal aerosol or inhalation administration include solutions which may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance absorption and/or bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

Exemplary compositions for rectal administration include suppositories which may contain, for example, suitable non-irritating excipients, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures but liquefy and/or dissolve in the rectal cavity to release the drug.

The therapeutically-effective amount of a compound of the present invention may be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for a mammal of from about 0.05 to 1000 mg/kg; 1-1000 mg/kg; 1-50 mg/kg; 5-250

mg/kg; 250-1000 mg/kg of body weight of active compound per day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. It will be understood that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors, including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. Preferred subjects for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats, horses, and the like. Thus, when the term "patient" is used herein, this term is intended to include all subjects, most preferably mammalian species, that are affected by mediation of RIPK1 enzyme levels.

MLKL Phosphorylation High-Content Assay

HT29-L23 human colorectal adenocarcinoma cells were maintained in RPMI 1640 medium containing 10% heat-inactivated FBS, 1% Penicillin-Streptomycin and 10 mM HEPES. Cells were seeded at 2,000 cells/well in 384 well tissue culture-treated microplates (Greiner # 781090-3B) and incubated at 37 °C (5% CO_2/95% O_2) for 2 d. On the day of the assay, the cells were treated with test compounds at final concentrations of 6.25 to 0.106 μM for 30 min at 37 °C (5% CO_2/95% O_2). Necroptopsis was induced using a mixture of human TNFα (35 ng/mL) (Peprotech #300-01A), SMAC mimetic (from US 2015/0322111 A1) (700 nM) and Z-VAD (140 nM) (BD pharmingen #51-6936). Following 6 h incubation at 37 °C (5% CO_2/95% O_2), the cells were fixed with 4% formaldehyde (ACROS 11969-0010) for 15 min at rt, then permeabilized with phosphate buffered saline (PBS) containing 0.2% Triton-X-100 for 10 min. MLKL phosphorylation was detected using anti-MLKL (phospho S358) antibody (Abcam #ab187091) (1:1000 dilution in Blocking Buffer [PBS supplemented with 0.1% BSA]) with ON incubation at 4 °C. After washing three times in PBS, goat anti-rabbit Alexa-488 (1:1000 dilution) (Life Technologies, A11008) and Hoechst 33342 (Life Technologies, H3570) (1:2000 dilution) in Blocking Buffer were added for 1 h at rt. Following another three cycles of washes in PBS, the microplates were sealed, and cellular images were acquired in the Cellomics ArrayScan VTI high-content imager

equipped with an X1 camera. Fluorescent images were taken using a 10x objective and the 386-23 BGRFRN_BGRFRN and 485-20 BGRFRN_BGRFRN filter sets, for nuclei and MLKL phosphorylation, respectively. The image sets were analyzed using the Compartmental Analysis Bioapplication software (Cellomics). The level of MLKL phosphorylation was quantified as MEAN_CircRingAvgIntenRatio. The maximal inhibitory response was defined by the activity induced by Nec1s (CAS #: 852391-15-2, 6.25 μM). The IC50 value was defined as the concentration of compound that produces 50% of the maximal inhibition. The data were fitted using the 4-parameter logistic equation to calculate the IC50 and Ymax values.

RIPK1 HTRF Binding Assay

A solution was prepared containing 0.2 nM Anti GST-Tb (Cisbio, 61GSTTLB), 90.6 nM probe and 1 nM His-GST-TVMV-hRIPK1(1-324) in FRET Buffer (20 mM HEPES, 10 mM MgCl2, 0.015% Brij-35, 4mM DTT, 0.05 mg/mL BSA). Using Formulatrix Tempest, the detection antibody/enzyme/probe solution (2 mL) was dispensed into wells of a 1536 plate (Black Low Binding Polystyrene 1536 Plate (Corning, 3724)) containing 10 nL of compounds of interest at appropriate concentration in DMSO. The plate was incubated at rt for 1 h. FRET was measured using the EnVision plate reader (Excitation: 340 nM, Emission: 520 nM/495 nM). Total signal (0% inhibition) was calculated from wells containing 10 nL DMSO only. Blank signal (100% inhibition) calculated from wells containing 10 nL of 15 nM staurosporine and internal controls.

Cloning and Baculovirus Expression of RIPK1 Construct

The coding region of human RIPK1(1-324) flanked by NdeI site at 5' end and stop codon TGA and XhoI site at 3' end was codon optimized and gene synthesized at GenScript USA Inc. (Piscataway, NJ) and subcloned into a modified pFastBac1 vector (Invitrogen, Carlsbad, CA) with N-terminal His-GST-TVMV tag, to generate His-GST-TVMV-hRIPK1(1-324)-pFB. The fidelity of the synthetic fragment was confirmed by sequencing.

Baculovirus was generated for the construct using the Bac-to-Bac baculovirus expression system (Invitrogen) according to the manufacturer's protocol. Briefly, recombinant bacmid was isolated from transformed DH10Bac E.coli competent cells (Invitrogen) and used to transfect Spodoptera frugiperda (Sf9) insect cells (Invitrogen).

Baculovirus was harvested 72 hours post transfection and a virus stock was prepared by infecting fresh Sf9 cells at a 1/1000 (v/v) ratio for 66 hours.

For large scale protein production, Sf9 cells (Expression System, Davis, CA) grown in ESF921 insect medium (Expression System) at 2 × 106 cells/ml were infected with virus stock at a 1/100 (v/v) ratio for 66 hours. The production was carried out either at a 10 L scale in a 22 L cellbag (GE Healthcare Bioscience, Pittsburgh, PA) or at a 20 L scale in a 50 L cellbag using WAVE-Bioreactor System 20/50 (GE Healthcare Bioscience). The infected cells were harvested by centrifugation at 2000 rpm for 20 min at 4 °C in a SORVALL® RC12BP centrifuge. The cell pellets was stored at -70 °C before protein was purified.

Purification of His-GST-TVMV-hRIPK1(1-324)

RIPK1 containing cell paste was resuspended in 50 mM Tris pH 7.5, 150 mM NaCl, 10 mM imidazole, 5% glycerol, 5 mM $MgSO_4$, 1 mM TCEP, 25 U/ml Benzonase, and Complete Protease Inhibitor tablets (1/50 ml, Roche Diagnostics, Indianapolis, IN). The cells were lysed by nitrogen cavitation using an unstirred pressure vessel @ 525 PSI (Parr Instrument Company, Moline, IL). The suspension was clarified by centrifugation at 136,000 x g for 40 min, at 4 °C. The lysate was decanted from the pellet and passed through a 5 ml NiNTA Superflow cartridge (Qiagen,Valencia, CA) using an AKTA Pure (GE Healthcare). Column was eluted with 10 CV linear gradient into 50 mM Tris 7.5, 150 mM NaCl, 500 mM imidazole, 5% glycerol, 1 mM TCEP. Peak fractions were pooled and loaded directly onto 5 ml GSTrap 4B column (GE Healthcare). Column was washed with 50 mM Tris 7.0, 150 mM NaCl, 5% glycerol, 1 mM DTT and eluted in 10 CV linear gradient into 50 mM Tris 8.0, 150 mM NaCl, 20 mM reduced glutathione, 5% glycerol, 1 mM DTT. Fractions identified by SDS-PAGE as containing RIPK1 were pooled and concentrated using 30 kDa MWCO spin concentrators (Amicon Ultra-15, Millipore, Billerica, MA) and loaded onto a HiLoad 26/600 Superdex 200 column (GE Healthcare) equilibrated in 25 mM Tris 7.5, 150 mM NaCl, 2 mM TCEP, 5% glycerol. The RIPK1 protein eluted as a dimer off the SEC column.

The yield was ~8 mg/L with a purity >95% as determined by Coomassie stain SDS-PAGE gel analysis. LCMS analysis of the protein showed that the protein had lost the N-terminal methionine, had one phosphorylated site, and was partially acetylated. Protein was aliquoted and stored at -80 °C.

Using these assays, the IC_{50} values of the following compounds were determined. See **Table A**.

Table A

Ex	RIPK1 HTRF (IC50, nM)	pMLKL (IC50, μM)
1	290	0.66
2	>15,000	>6.2
3	1100	4.3
4	1100	3.2
5	25	0.19
6	52	4.3
7	170	2.2
8	515	0.11
9	1000	3.5
10	410	3.6
11	540	2.5
12	110	0.29
13	1300	3.2
14	310	2.4
15	440	1.9
16	1600	3.1
17	22	0.20
18	>15,000	2.4
19	790	0.69
20	2200	2.3
21	310	1.2
22	100	0.44
23	280	1.6
24	51	0.11
25	1600	4.5
26	290	2.5

Methods of Preparation

Compounds of Formula (I), and intermediates used in the preparation of compounds of Formula (I), can be prepared using procedures shown in the following examples and related procedures. The methods and conditions used in these examples, and the actual compounds prepared in these examples, are not meant to be limiting, but are meant to demonstrate how the compounds of Formula (I) can be prepared. Starting materials and reagents used in these examples, when not prepared by a procedure

described herein, are generally either commercially available, or are reported in the chemical literature, or may be prepared by using procedures described in the chemical literature.

Abbreviations as used herein, are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, “aq” or “aq.” for aqueous, "ºC" for degrees Celsius, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "L" for liter or liters, "mL" for milliliter or milliliters, "μL" for microliter or microliters, "N" for normal, "M" for molar, "mmol" for millimole or millimoles, "min" for minute or minutes, "h" for hour or hours, "rt" for room temperature, "ON" for overnight, "RT" for retention time, "atm" for atmosphere, "psi" for pounds per square inch, "conc." for concentrate, "sat" or "saturated " for saturated, "CVs" for column volumes, "MW" for molecular weight, "mp" for melting point, "ee" for enantiomeric excess, "MS" or "Mass Spec" for mass spectrometry, "ESI" for electrospray ionization mass spectroscopy, "HR" for high resolution, "HRMS" for high resolution mass spectrometry, "LCMS" or “LC/MS” for liquid chromatography mass spectrometry, "HPLC" for high pressure liquid chromatography, "RP HPLC" for reverse phase HPLC, "TLC" or "tlc" for thin layer chromatography, “SFC” for supercritical fluid chromatography, "NMR" for nuclear magnetic resonance spectroscopy, "nOe" for nuclear Overhauser effect spectroscopy, "^{1}H" for proton, "δ" for delta, "s" for singlet, "d" for doublet, "t" for triplet, "q" for quartet, "m" for multiplet, "br" for broad, "MHz" for megahertz, and "α", "β", "R", "S", "E", and "Z" are stereochemical designations familiar to one skilled in the art.

Me	methyl
Et	ethyl
Pr	propyl
i-Pr	isopropyl
Bu	butyl
i-Bu	isobutyl
t-Bu	*tert*-butyl
Ph	phenyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl

AcOH or HOAc	acetic acid
Ac_2O	acetic anhydride
Boc	(tert-butoxy)carbonyl
BOP	benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
CBz	carbobenzyloxy
CH_2Cl_2	dichloromethane
CH_3CN or ACN	acetonitrile
$CDCl_3$	deutero-chloroform
$CHCl_3$	chloroform
Cs_2CO_3	cesium carbonate
DCE	1,2 dichloroethane
DCM	dichloromethane
DIEA/DIPEA/Hünig's Base	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
Et_3N or TEA	triethylamine
EtOAc	ethyl acetate
Et_2O	diethyl ether
EtOH	ethanol
HCl	hydrochloric acid
Hex	hexane
K_2CO_3	potassium carbonate
KOAc	potassium acetate
K_3PO_4	potassium phosphate
LiOH	lithium hydroxide
MeOH	methanol
MeI	iodomethane
$MgSO_4$	magnesium sulfate

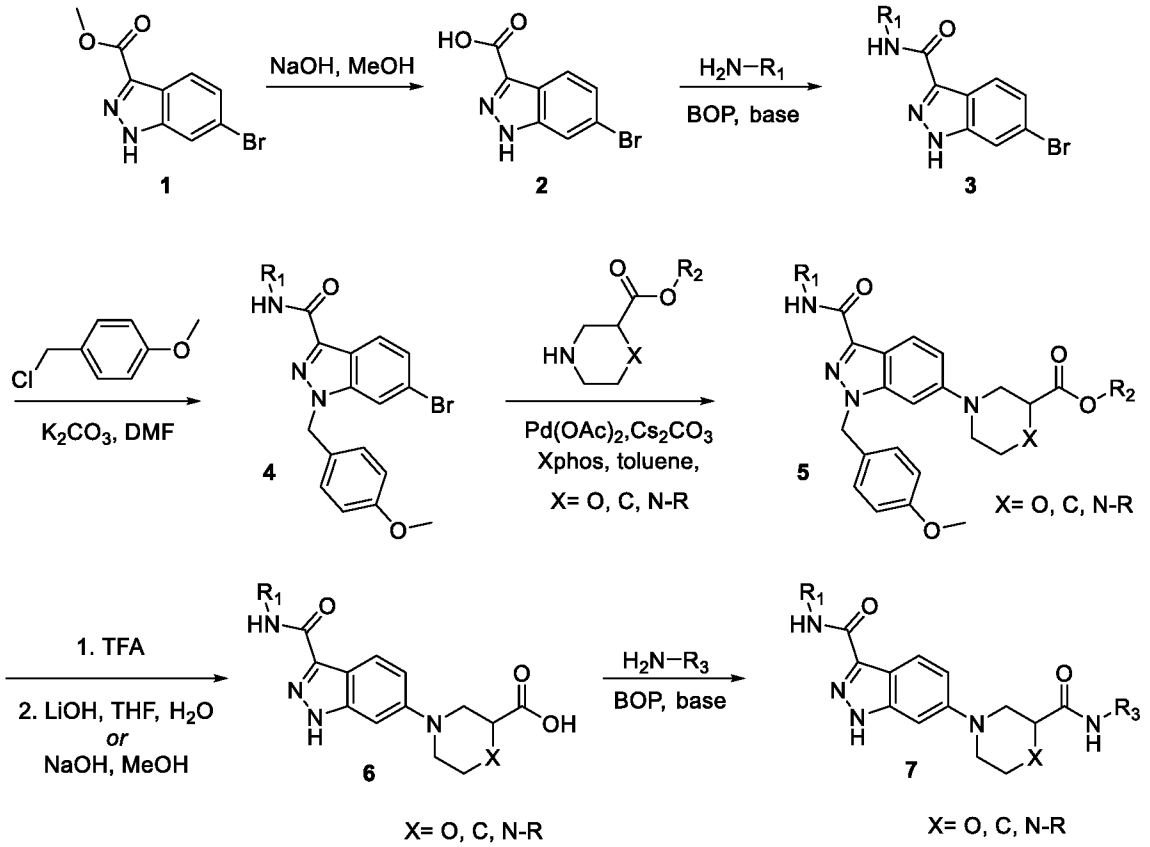
NaCl	sodium chloride
NaH	sodium hydride
$NaHCO_3$	sodium bicarbonate
Na_2CO_3	sodium carbonate
NaOH	sodium hydroxide
Na_2SO_3	sodium sulfite
Na_2SO_4	sodium sulfate
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NH_3	ammonia
NH_4Cl	ammonium chloride
NH_4OH	ammonium hydroxide
Pd/C	palladium on carbon
$PdCl_2$(dppf)	[1,1´-bis(diphenylphosphino)-ferrocene]dichloropalladium(II)
PG	protecting group
i-PrOH or IPA	isopropanol
SiO_2	silica oxide
TBAI	tetra-*n*-butylammonium iodide
TFA	trifluoroacetic acid
THF	tetrahydrofuran

The compounds of the present invention may be synthesized by many methods available to those skilled in the art of organic chemistry (Maffrand, J. P. et al., Heterocycles, 16(1):35-7 (1981)). General synthetic schemes for preparing compounds of the present invention are described below. These schemes are illustrative and are not meant to limit the possible techniques one skilled in the art may use to prepare the compounds disclosed herein. Different methods to prepare the compounds of the present invention will be evident to those skilled in the art. Additionally, the various steps in the synthesis may be performed in an alternate sequence in order to give the desired compound or compounds.

Examples of compounds of the present invention prepared by methods described in the general schemes are given in the intermediates and examples section set out hereinafter. Example compounds are typically prepared as racemic mixtures. Preparation of homochiral examples may be carried out by techniques known to one skilled in the art. For example, homochiral compounds may be prepared by separation of racemic products by chiral phase preparative HPLC. Alternatively, the example compounds may be prepared by methods known to give enantiomerically enriched products. These include, but are not limited to, the incorporation of chiral auxiliary functionalities into racemic intermediates which serve to control the diastereoselectivity of transformations, providing enantio-enriched products upon cleavage of the chiral auxiliary.

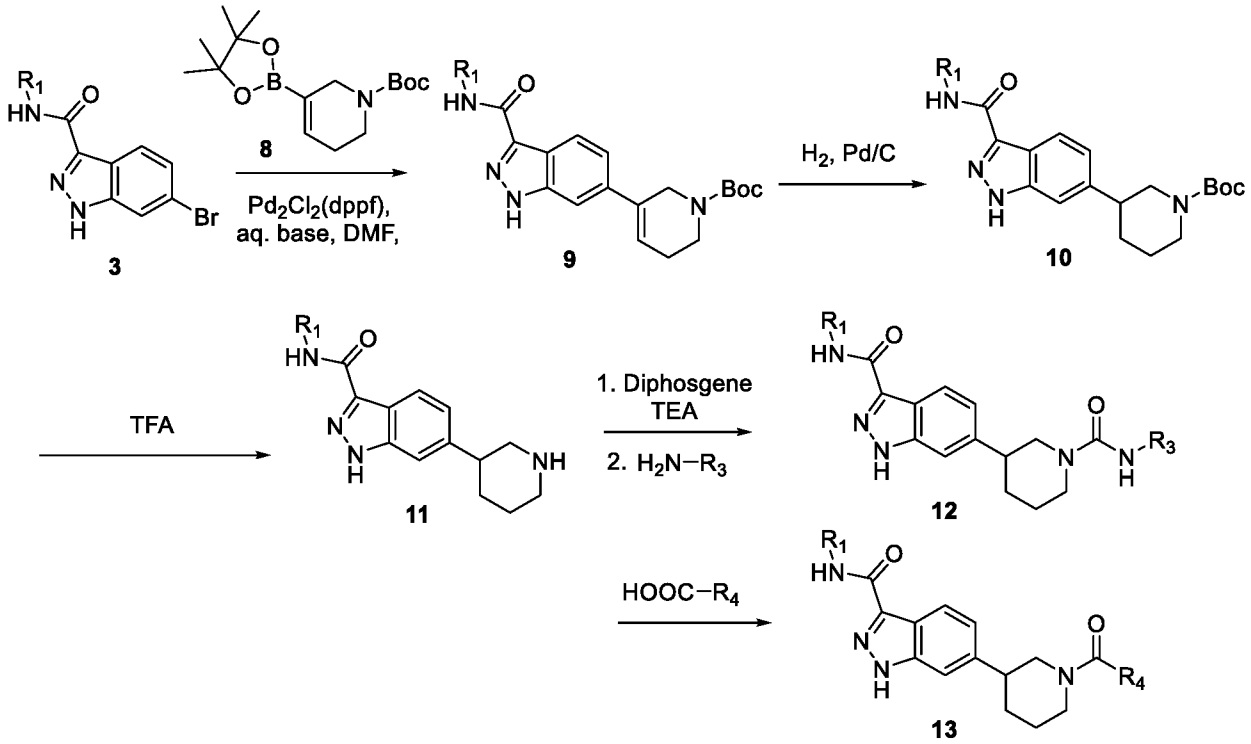
Scheme 1 describes a synthetic route for compound **7**. Hydrolysis and amide coupling can yield **3**. Protection of the 1H-indazole group in **3** with a para-methoxybenzyl group preceded a Buchwald reaction to yield compound **5**. Deprotection under acidic conditions at elevated temperatures and hydrolysis provided compounds similar to **6**. Compounds exemplified by **7** can be formed by an amide coupling mediated by BOP reagent as shown in the scheme or an alternative amide coupling reagent. Use of an anhydride or carboxylic acid chloride may also effect this transformation.

Scheme 1



Scheme 2 illustrates access to compounds containing a 3-piperidine linker (**12**, **13**). Compound **3** can undergo Suzuki coupling reaction with **8** to yield compounds like **9**. Reduction and deprotection of **9** can yield piperidines similar to **11**. The analogs exemplified by compound **12** can be accessed via a single pot coupling reaction with diphosgene, followed by the addition of amines. Compounds exemplified by **13** can be formed by an amide coupling mediated by BOP reagent as shown in the scheme or an alternative amide coupling reagent. Use of an anhydride or carboxylic acid chloride may also effect this transformation.

Scheme 2



Purification of intermediates and final products was carried out via either normal or reverse phase chromatography. Normal phase chromatography on an ISCO system was carried out using prepacked SiO2 cartridges eluting with either gradients of hexanes and ethyl acetate or dichloromethane and methanol unless otherwise indicated. Reverse phase preparative HPLC or LCMS was carried out using C18 columns eluting with gradients of Solvent A (90% water, 10% methanol, 0.1% TFA) and Solvent B (10% water, 90% methanol, 0.1% TFA, UV 220 nm), or with gradients of Solvent A (95% water, 5% acetonitrile, 0.1% TFA) and Solvent B (5% water, 95% acetonitrile, 0.1% TFA, UV 220 nm), or with gradients of Solvent A (98% water, 2% acetonitrile, 0.05% TFA) and Solvent B (98% acetonitrile, 2% water, 0.05% TFA, UV 254 nm), or with gradients of Solvent A (95% water, 5% acetonitrile with 10 mM ammonium acetate) and Solvent B (95% acetonitrile, 5% water with 10 mM ammonium acetate).

In the majority of examples, two analytical LCMS injections were used to determine final purity.

Method A: Column: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7 μM particles; Mobile phase A: 5:95 acetonitrile:water with 10 mM ammonium acetate; Mobile phase B: 95:5 acetonitrile:water with 10 mM ammonium acetate; Temperature: 50

°C; Gradient: 0-100% B over 3 minutes, then a 0.75 minute hold at 100% B; Flow: 1.11 mL/min; Detection: UV at 220 nm.

Method B: Column: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7 μm particles; Mobile phase A: 5:95 acetonitrile:water with 0.1% TFA; Mobile phase B: 95:5 acetonitrile:water with 0.1% TFA; Temperature: 50 °C; Gradient: 0-100% B over 3 min, then a 0.75 min hold at 100% B; Flow: 1.11 mL/min; Detection: UV at 220nm.

In a minority of examples analytical HPLC injections were used to determine final purity.

Method A: Column: Sunfire C18, 3.0 x 150 mm, 3.5 μM particles; Mobile phase A: 5:95 acetonitrile:water with 0.1% TFA; Mobile phase B: 95:5 acetonitrile:water with 0.1% TFA; Gradient: 0-100% B over 10 minutes; Flow: 1 mL/min; Detection: UV at 220 and 254 nm

Method B: Column: Xbridge Phenyl, 3.0 x 150 mm, 3.5 μM particles; Mobile phase A: 5:95 acetonitrile:water with 0.1% TFA; Mobile phase B: 95:5 acetonitrile:water with 0.1% TFA; Gradient: 0-100% B over 10 minutes; Flow: 1 mL/min; Detection: UV at 220 and 254 nm

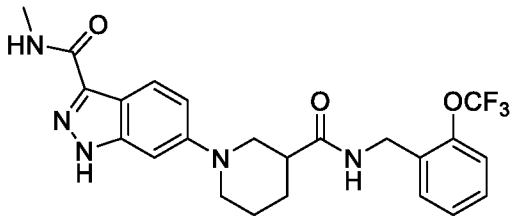
Method C: Column: XBridge C18, 3.0 x 150 mm, 3.5 μM particles; Mobile phase A: 5:95 methanol:water with 10 mM ammonium bicarbonate; Mobile phase B: 95:5 methanol:water with 10 mM ammonium bicarbonate; Gradient: 0-100% B over 15 minutes; Flow: 1 mL/min; Detection: UV at 220 and 254 nm.

Method D: Column: XBridge Phenyl, 3.0 x 150 mm, 3.5 μM particles; Mobile phase A: 5:95 methanol:water with 10 mM ammonium bicarbonate; Mobile phase B: 95:5 methanol:water with 10 mM ammonium bicarbonate; Gradient: 0-100% B over 15 minutes; Flow: 1 mL/min; Detection: UV at 220 and 254 nm.

A majority of mass spectra runs were: LCMS (ESI) m/z: $[M+H]^+$ BEH C18, 2.11 x 50mm, 1.7 μm; Mobile phase A: 2:98 water:acetonitrile with 0.1% TFA; Mobile phase B: 98:2 acetonitrile:water with 0.1% TFA; Gradient: 0-100% B over 2 minutes; Flow: 0.8 mL/min; Detection: UV at 220 nm.

NMR spectra were run with water suppression, unless otherwise noted. When water suppression affected characterization of the compounds by NMR, it is noted in the text.

Example 1 N-methyl-6-[3-({[2-(trifluoromethoxy)phenyl]methyl}carbamoyl)piperidin-1-yl]-1H-indazole-3-carboxamide



1A: 6-bromo-1H-indazole-3-carboxylic acid: A solution of methyl 6-bromo-1H-indazole-3-carboxylate (5 g, 19.60 mmol) and 1 N NaOH (49.0 mL, 49.0 mmol) in MeOH (70 mL) was heated to 80 °C for 2 h. The reaction mixture was concentrated to yield a crude product which was dissolved in water (100 mL). The aqueous solution was acidified at 0 °C with 1 N HCl solution until the pH reached about 4-5. The solid was collected as 6-bromo-1H-indazole-3-carboxylic acid (4.60 g, 19.08 mmol, 97 %).

MS ESI m/z 241.1 (M+H)

^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (dd, *J*=8.7, 0.6 Hz, 1H), 7.87 - 7.77 (m, 1H), 7.41 (dd, *J*=8.7, 1.6 Hz, 1H).

1B: 6-bromo-N-methyl-1H-indazole-3-carboxamide: To a solution of 6-bromo-1H-indazole-3-carboxylic acid (1.7 g, 7.05 mmol), methanamine, HCl (0.595 g, 8.82 mmol) and DIPEA (3.08 mL, 17.63 mmol) in DMF (25 mL) was added BOP (3.90 g, 8.82 mmol). The reaction mixture was stirred at 23 °C for 16 h. The reaction mixture was concentrated. Water (100 mL) was added to the crude material and the mixture was sonicated for 10 min. The solid was collected as 6-bromo-N-methyl-1H-indazole-3-carboxamide (1.95 g, 7.55 mmol, 107 %).

MS ESI m/z 254.0 (M+H).

1C: 6-bromo-1-(4-methoxybenzyl)-N-methyl-1H-indazole-3-carboxamide: To a solution of 6-bromo-N-methyl-1H-indazole-3-carboxamide (1.95 g, 7.67 mmol) and K_2CO_3 (2.65 g, 19.19 mmol) in DMF (25 mL) was added 4-methoxybenzyl chloride (1.359 mL, 9.98 mmol). The reaction mixture was heated to 70 °C for 1 h. After cooling to rt, the reaction mixture was concentrated and purified on a silica gel column with CH_2Cl_2/EtOAc (10/1) to yield 6-bromo-1-(4-methoxybenzyl)-N-methyl-1H-indazole-3-carboxamide (2.609 g, 6.72 mmol, 88 %).

MS ESI m/z 374.0 (M+H).

1D: methyl 1-(1-(4-methoxybenzyl)-3-(methylcarbamoyl)-1H-indazol-6-yl)piperidine-3-carboxylate: A degassed solution of 6-bromo-1-(4-methoxybenzyl)-N-methyl-1H-indazole-3-carboxamide (700 mg, 1.870 mmol), methyl piperidine-3-

carboxylate, HCl (504 mg, 2.81 mmol), $Pd(OAc)_2$ (25.2 mg, 0.112 mmol), Cs_2CO_3 (1524 mg, 4.68 mmol) and 2-(dicyclohexylphosphino)-2',4',6'-triisopropylbiphenyl, XPhos (89 mg, 0.187 mmol) in DMF (8 mL) was heated to 100 °C for 16 h. The reaction mixture was diluted with EtOAc (150 mL). The solution was washed with 10% LiCl solution (30 mL x 2) and brine (30 mL) and dried over Na_2SO_4. Filtration and concentration yielded a crude product which was purified on a silica gel column with CH_2Cl_2/EtOAc (1/0 - 5/1) to yield methyl 1-(1-(4-methoxybenzyl)-3-(methylcarbamoyl)-1H-indazol-6-yl)piperidine-3-carboxylate (235 mg, 0.535 mmol, 29 %).

MS ESI m/z 437.2 (M+H)

^{1}H NMR (400 MHz, CD_3OD) δ 8.00 (d, *J*=9.0 Hz, 1H), 7.19 (d, *J*=8.8 Hz, 2H), 7.05 (dd, *J*=9.0, 2.1 Hz, 1H), 6.89 - 6.83 (m, 2H), 6.80 (d, *J*=1.8 Hz, 1H), 5.52 (s, 2H), 3.74 (s, 3H), 3.72 - 3.62 (m, 4H), 3.53 - 3.43 (m, 1H), 3.12 (dd, *J*=12.5, 9.3 Hz, 1H), 2.94 (s, 3H), 2.93 - 2.84 (m, 1H), 2.75 - 2.64 (m, 1H), 2.01 - 1.94 (m, 1H), 1.86 - 1.63 (m, 3H).

1E: methyl 1-(3-(methylcarbamoyl)-1H-indazol-6-yl)piperidine-3-carboxylate, TFA: A solution of methyl 1-(1-(4-methoxybenzyl)-3-(methylcarbamoyl)-1H-indazol-6-yl)piperidine-3-carboxylate (242 mg, 0.554 mmol) in TFA (0.043 mL, 0.554 mmol) was heated to 130 °C for 45 min under microwave. The reaction mixture was concentrated to yield methyl 1-(3-(methylcarbamoyl)-1H-indazol-6-yl)piperidine-3-carboxylate, TFA which was immediately used in subsequent chemistry.

MS ESI m/z 317.2 (M+H).

1F: 1-(3-(methylcarbamoyl)-1H-indazol-6-yl)piperidine-3-carboxylic acid: A solution of methyl 1-(3-(methylcarbamoyl)-1H-indazol-6-yl)piperidine-3-carboxylate (175 mg, 0.554 mmol) and 1 N NaOH (1.385 mL, 1.385 mmol) in MeOH (10 mL) was heated to 100 °C for 30 min under microwave. The reaction mixture was concentrated to yield a crude product. Water (10 mL) was added to the crude product and the solution acidified with 1N HCl until the pH was about 4 to 5. The solid was collected as (205.4 mg, 0.586 mmol, 106 %).

MS ESI m/z 303.2 (M+H).

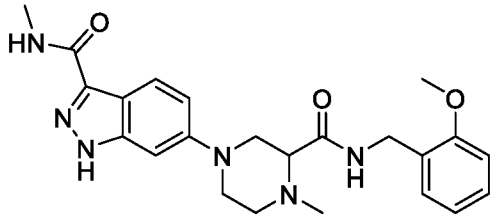
1: Reagents were received in stubby tubes and placed in a Bohdan Miniblock XT. A solution was prepared by dissolving 1-(3-(methylcarbamoyl)-1H-indazol-6-yl)piperidine-3-carboxylic acid (150 mg) in DMF (3.0 mL). Another solution was prepared by dissolving BOP (439 mg)) in DMF (3.0 mL). To a vial containing (2-

(trifluoromethoxy)phenyl)methanamine (12.7 mg, 0.066 mmol) was added 1-(3-(methylcarbamoyl)-1H-indazol-6-yl)piperidine-3-carboxylic acid (10 mg, 0.033 mmol, 200 μL of the solution) followed by BOP (29.3 mg, 0.066 mmol, 200 μL of the solution) and DIEA (0.029 mL, 0.165 mmol). The reaction mixture was stirred at rt ON. The crude material was purified via preparative LC/MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 15-60% B over 20 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation. N-methyl-6-[3-({[2-(trifluoromethoxy)phenyl]methyl}carbamoyl)piperidin-1-yl]-1H-indazole-3-carboxamide (10.3 mg, 21.7 μmol, 65.6 %) was isolated.

MS ESI m/z 476.3 (M+H)

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.46 (br t, *J*=5.6 Hz, 1H), 8.18 (br d, *J*=4.6 Hz, 1H), 7.93 (d, *J*=8.9 Hz, 1H), 7.44 - 7.30 (m, 4H), 7.04 (br d, *J*=8.9 Hz, 1H), 6.80 (s, 1H), 4.44 - 4.27 (m, 2H), 3.82 - 3.64 (m, 2H), 2.86 (br t, *J*=11.6 Hz, 1H), 2.79 (d, *J*=4.6 Hz, 3H), 2.76 - 2.68 (m, 1H), 2.59 (br s, 1H), 1.91 (br d, *J*=3.4 Hz, 1H), 1.77 (br s, 1H), 1.66 - 1.54 (m, 2H), NH lost in water suppression.

Example 2 6-(3-{[(2-methoxyphenyl)methyl]carbamoyl}-4-methylpiperazin-1-yl)-N-methyl-1H-indazole-3-carboxamide



2A: 1-tert-butyl 2-methyl 4-(1-(4-methoxybenzyl)-3-(methylcarbamoyl)-1H-indazol-6-yl)piperazine-1,2-dicarboxylate: A degassed solution of 6-bromo-1-(4-methoxybenzyl)-N-methyl-1H-indazole-3-carboxamide (148 mg, 0.395 mmol), 1-N-Boc-piperazine-2-carboxylic acid methyl ester (145 mg, 0.593 mmol), $Pd(OAc)_2$ (5.33 mg, 0.024 mmol), Cs_2CO_3 (193 mg, 0.593 mmol) and 2-(dicyclohexylphosphino)-2',4',6'-triisopropylbiphenyl, XPhos (18.85 mg, 0.040 mmol) in toluene (1 mL) was heated to 100 °C for 2 d. The reaction mixture was concentrated. Water was added and the slurry

was sonicated for 10 min. The solid was collected as 1-tert-butyl 2-methyl 4-(1-(4-methoxybenzyl)-3-(methylcarbamoyl)-1H-indazol-6-yl)piperazine-1,2-dicarboxylate.

MS ESI m/z 538.4 (M+H).

2B: 1-(tert-butoxycarbonyl)-4-(1-(4-methoxybenzyl)-3-(methylcarbamoyl)-1H-indazol-6-yl)piperazine-2-carboxylic acid: A solution of 1-tert-butyl 2-methyl 4-(1-(4-methoxybenzyl)-3-(methylcarbamoyl)-1H-indazol-6-yl)piperazine-1,2-dicarboxylate (225 mg, 0.419 mmol) and 1 N NaOH solution (0.628 mL, 0.628 mmol) in MeOH (2 mL) was heated to 100 °C for 40 min under microwave. The reaction mixture was concentrated. Water (10 mL) was added to the crude residue which was acidified until the pH was about 4. The solid was collected as (186 mg, 0.334 mmol, 80 %).

MS ESI m/z 524.4 (M+H)

^{1}H NMR (400 MHz, CD_3OD) δ 8.03 (d, *J*=9.0 Hz, 1H), 7.21 (d, *J*=8.8 Hz, 2H), 6.90 - 6.84 (m, 4H), 5.54 (s, 2H), 4.78 - 4.65 (m, 1H), 4.32 - 4.20 (m, 1H), 4.00 - 3.91 (m, 1H), 3.77 - 3.74 (m, 4H), 3.59 (br dd, *J*=7.2, 4.5 Hz, 1H), 2.98 - 2.92 (m, 4H), 2.84 - 2.70 (m, 1H), 1.49 (br d, *J*=11.9 Hz, 9H).

2C: 4-(1-(4-methoxybenzyl)-3-(methylcarbamoyl)-1H-indazol-6-yl)piperazine-2-carboxylic acid, TFA: A solution of 1-(tert-butoxycarbonyl)-4-(1-(4-methoxybenzyl)-3-(methylcarbamoyl)-1H-indazol-6-yl)piperazine-2-carboxylic acid (144.2 mg, 0.275 mmol) and TFA (0.424 mL, 5.51 mmol) in CH_2Cl_2 (2 mL) was stirred at 23 °C for 1 h. The reaction mixture was concentrated to yield 4-(1-(4-methoxybenzyl)-3-(methylcarbamoyl)-1H-indazol-6-yl)piperazine-2-carboxylic acid, TFA (163 mg, 0.274 mmol, 100 %).

MS ESI m/z 424.2 (M+H).

2D: 4-(1-(4-methoxybenzyl)-3-(methylcarbamoyl)-1H-indazol-6-yl)-1-methylpiperazine-2-carboxylic acid: A solution of 4-(1-(4-methoxybenzyl)-3-(methylcarbamoyl)-1H-indazol-6-yl)piperazine-2-carboxylic acid, TFA (163 mg, 0.303 mmol) and formaldehyde (0.113 mL, 1.516 mmol) in CH_2Cl_2 (2 mL) and acetic acid (0.050 mL) was stirred at 23 °C for 1 h. Sodium triacetoxyborohydride (64.3 mg, 0.303 mmol) was added and the mixture was stirred for 16 h. The reaction mixture was concentrated and purified on prep HPLC to yield (88 mg, 0.201 mmol, 66 %).

MS ESI m/z 438.1 (M+H)

^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (d, *J*=8.9 Hz, 1H), 7.20 (d, *J*=8.7 Hz, 2H), 7.14 - 7.08 (m, 1H), 7.00 - 6.96 (m, 1H), 6.89 - 6.82 (m, 2H), 5.57 (s, 2H), 4.14 - 4.00 (m, 1H), 3.87 - 3.77 (m, 1H), 3.75 (s, 3H), 3.70 - 3.61 (m, 1H), 3.44 - 3.33 (m, 2H), 3.27 - 3.16 (m, 2H), 3.05 (s, 2H), 2.95 (s, 3H).

2E: 1-methyl-4-(3-(methylcarbamoyl)-1H-indazol-6-yl)piperazine-2-carboxylic acid, TFA: A solution of 4-(1-(4-methoxybenzyl)-3-(methylcarbamoyl)-1H-indazol-6-yl)-1-methylpiperazine-2-carboxylic acid (88 mg, 0.201 mmol) in TFA (0.015 mL, 0.201 mmol) and water (0.030 mL) was heated to 120 °C for 25 min under microwave. The reaction mixture was concentrated to yield 1-methyl-4-(3-(methylcarbamoyl)-1H-indazol-6-yl)piperazine-2-carboxylic acid, TFA (113.6 mg) which was used as is in subsequent chemistry.

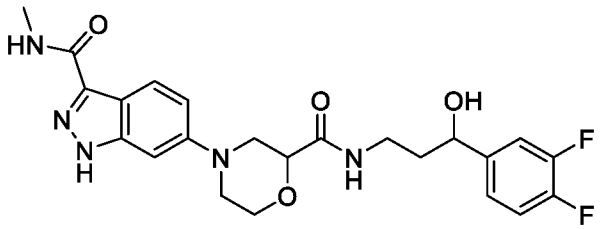
MS ESI m/z 318.1 (M+H).

2: To a solution of 1-methyl-4-(3-(methylcarbamoyl)-1H-indazol-6-yl)piperazine-2-carboxylic acid (15 mg, 0.047 mmol), (2-methoxyphenyl)methanamine (6.11 µl, 0.047 mmol) and DIPEA (0.041 mL, 0.236 mmol) in DMF (1 mL) was added BOP (31.4 mg, 0.071 mmol). The reaction mixture was stirred at 23 °C for 2 d. The crude material was purified via preparative LC/MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 10-50% B over 23 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation. 6-(3-{[(2-methoxyphenyl)methyl]carbamoyl}-4-methylpiperazin-1-yl)-N-methyl-1H-indazole-3-carboxamide (3 mg, 6.9 µmol, 14.6 %) was isolated.

MS ESI m/z 437.2 (M+H)

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.30 - 8.20 (m, 2H), 7.94 (d, *J*=8.9 Hz, 1H), 7.23 (br t, *J*=7.5 Hz, 1H), 7.16 (br d, *J*=7.3 Hz, 1H), 7.03 (br d, *J*=8.8 Hz, 1H), 6.97 (br d, *J*=8.2 Hz, 1H), 6.89 (br t, *J*=7.4 Hz, 1H), 6.81 (s, 1H), 4.28 (br d, *J*=5.7 Hz, 2H), 3.78 (s, 3H), 3.68 - 3.57 (m, 1H), 3.03 - 2.73 (m, 8H), 2.35 - 2.26 (m, 1H), 2.19 (s, 3H).

Example 3 6-(2-{[3-(3,4-difluorophenyl)-3-hydroxypropyl]carbamoyl}morpholin-4-yl)-N-methyl-1H-indazole-3-carboxamide



3A: ethyl 4-(1-(4-methoxybenzyl)-3-(methylcarbamoyl)-1H-indazol-6-yl)morpholine-2-carboxylate: A degassed solution of 6-bromo-1-(4-methoxybenzyl)-N-methyl-1H-indazole-3-carboxamide (195.6 mg, 0.523 mmol), ethyl morpholine-2-carboxylate (125 mg, 0.784 mmol), $Pd(OAc)_2$ (7.04 mg, 0.031 mmol), Cs_2CO_3 (255 mg, 0.784 mmol) and 2-(dicyclohexylphosphino)-2',4',6'-triisopropylbiphenyl, XPhos (24.92 mg, 0.052 mmol) in toluene (3 mL) was heated to 100 °C for 16 h. The reaction mixture was filtered and concentrated to yield a crude product which was purified on a silica gel column with CH_2Cl_2/EtOAc (2/1) to yield ethyl 4-(1-(4-methoxybenzyl)-3-(methylcarbamoyl)-1H-indazol-6-yl)morpholine-2-carboxylate (99 mg, 0.208 mmol, 40 %).

MS ESI m.z 453.1 (M+H)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J*=8.9 Hz, 1H), 7.16 - 7.10 (m, 2H), 7.03 (dd, *J*=9.0, 2.0 Hz, 1H), 6.89 - 6.83 (m, 2H), 6.61 (d, *J*=1.7 Hz, 1H), 5.46 (s, 2H), 4.36 (dd, *J*=9.0, 3.1 Hz, 1H), 4.31 (q, *J*=7.1 Hz, 2H), 4.18 (dt, *J*=11.5, 3.4 Hz, 1H), 3.90 - 3.81 (m, 1H), 3.78 (s, 3H), 3.70 (dd, *J*=12.5, 2.1 Hz, 1H), 3.38 - 3.31 (m, 1H), 3.12 (dd, *J*=12.1, 8.9 Hz, 1H), 3.07 - 2.99 (m, 4H), 1.35 (t, *J*=7.2 Hz, 3H).

3B: ethyl 4-(3-(methylcarbamoyl)-1H-indazol-6-yl)morpholine-2-carboxylate, TFA: A solution of ethyl 4-(1-(4-methoxybenzyl)-3-(methylcarbamoyl)-1H-indazol-6-yl)morpholine-2-carboxylate (100 mg, 0.221 mmol) in TFA (1 mL) was heated to 130 °C for 45 min under microwave. The reaction mixture was concentrtated to yield ethyl 4-(3-(methylcarbamoyl)-1H-indazol-6-yl)morpholine-2-carboxylate, TFA which was used as is in subsequent chemistry.

MS ESI m/z 333.1 (M+H).

3C: 4-(3-(methylcarbamoyl)-1H-indazol-6-yl)morpholine-2-carboxylic acid: A solution of ethyl 4-(3-(methylcarbamoyl)-1H-indazol-6-yl)morpholine-2-carboxylate (73.5 mg, 0.221 mmol) and 1 N NaOH solution (0.553 mL, 0.553 mmol) in ethanol (2 mL) was stirred at 23 °C for 2 h. The reaction mixture was concentrated to yield a crude product. Water (5 mL) was added and the solution acidified with 1 N HCl solution until

the pH was about 4. The solid was collected as 4-(3-(methylcarbamoyl)-1H-indazol-6-yl)morpholine-2-carboxylic acid (63.5 mg, 0.199 mmol, 90 %).

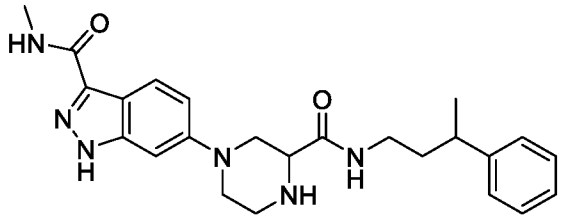
MS ESI m/z 305.1 (M+H).

3: To a solution of 4-(3-(methylcarbamoyl)-1H-indazol-6-yl)morpholine-2-carboxylic acid (9 mg, 0.030 mmol), 3-amino-1-(3,4-difluorophenyl)propan-1-ol (5.54 mg, 0.030 mmol) and DIPEA (0.013 mL, 0.074 mmol) in DMF (1 mL) was added BOP (15.70 mg, 0.035 mmol). The reaction mixture was stirred at 23 °C for 1 h. The crude material was purified via preparative LC/MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 10-60% B over 18 minutes, then a 3-minute hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation. 6-(2-{[3-(3,4-difluorophenyl)-3-hydroxypropyl]carbamoyl}morpholin-4-yl)-N-methyl-1H-indazole-3-carboxamide (8.6 mg, 18.2 µmol, 60.5 %) was isolated.

MS ESI m/z 473.9 (M+H)

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.24 (br d, *J*=4.5 Hz, 1H), 7.99 - 7.89 (m, 2H), 7.38 - 7.28 (m, 2H), 7.15 (br s, 1H), 7.05 (br d, *J*=8.8 Hz, 1H), 6.84 (s, 1H), 4.58 (br s, 1H), 4.13 - 3.96 (m, 2H), 3.52 (br d, *J*=11.7 Hz, 1H), 3.24 - 3.10 (m, 2H), 2.86 - 2.74 (m, 4H), 2.67 (br t, *J*=11.3 Hz, 1H), 1.84 - 1.67 (m, 2H). 2 CHs buried by water suppression.

Example 4 N-methyl-6-{3-[(3-phenylbutyl)carbamoyl]piperazin-1-yl}-1H-indazole-3-carboxamide



4A: tert-butyl 4-(1-(4-methoxybenzyl)-3-(methylcarbamoyl)-1H-indazol-6-yl)-2-((3-phenylbutyl)carbamoyl)piperazine-1-carboxylate: To a solution of 1-(tert-butoxycarbonyl)-4-(1-(4-methoxybenzyl)-3-(methylcarbamoyl)-1H-indazol-6-yl)piperazine-2-carboxylic acid (25 mg, 0.048 mmol), 3-phenylbutan-1-amine, HCl (8.87 mg, 0.048 mmol) and DIPEA (0.021 mL, 0.119 mmol) in DMF (1 mL) was added BOP

(25.3 mg, 0.057 mmol). The reaction mixture was stirred at 23 °C for 1 h. The reaction mixture was concentrated, water (2 mL) was added and the slurry sonicated for 5 min. The solid was collected as tert-butyl 4-(1-(4-methoxybenzyl)-3-(methylcarbamoyl)-1H-indazol-6-yl)-2-((3-phenylbutyl)carbamoyl)piperazine-1-carboxylate (58.2 mg) which was used as is in subsequent chemistry.

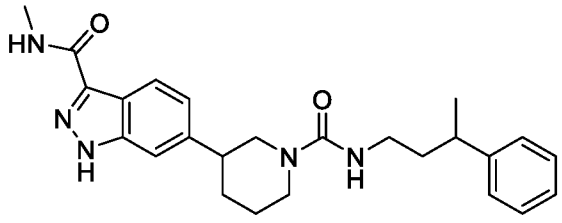
MS ESI m/z 655.4 (M+H)

4: A solution of tert-butyl 4-(1-(4-methoxybenzyl)-3-(methylcarbamoyl)-1H-indazol-6-yl)-2-((3-phenylbutyl)carbamoyl)piperazine-1-carboxylate (58.2 mg, 0.089 mmol) in TFA (1 mL) was stirred at 23 °C for 30 min. Water (0.030 mL) was added and the reaction mixture was heated to 100 °C in an oil bath for 4 h and under microwave at 120 °C for 30 min. The reaction mixture was concentrated and dissolved in MeOH (1 mL). The crude material was purified via preparative LC/MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 15-55% B over 19 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation. N-methyl-6-{3-[(3-phenylbutyl)carbamoyl]piperazin-1-yl}-1H-indazole-3-carboxamide (15.6 mg, 35.9 μmol, 40.3 %) was isolated.

MS ESI m/z 435 (M+H)

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.21 (br d, *J*=4.7 Hz, 1H), 7.93 (br d, *J*=9.1 Hz, 1H), 7.84 (br s, 1H), 7.28 (br d, *J*=4.2 Hz, 2H), 7.21 (br d, *J*=7.2 Hz, 2H), 7.19 - 7.13 (m, 1H), 7.03 (br d, *J*=8.6 Hz, 1H), 6.77 (s, 1H), 3.51 (br d, *J*=9.2 Hz, 1H), 3.11 - 2.67 (m, 11H), 1.78 - 1.64 (m, 2H), 1.19 (br d, *J*=6.8 Hz, 3H). Note: One CH obscured by NMR solvent.

Example 5 N-methyl-6-{1-[(3-phenylbutyl)carbamoyl]piperidin-3-yl}-1H-indazole-3-carboxamide



5A: tert-butyl 3-(3-(methylcarbamoyl)-1H-indazol-6-yl)-5,6-dihydropyridine-1(2H)-carboxylate: A degassed solution of 6-bromo-N-methyl-1H-indazole-3-carboxamide (100 mg, 0.394 mmol), tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2h)-carboxylate (122 mg, 0.394 mmol), $PdCl_2(dppf)$-CH_2Cl_2 adduct (19.28 mg, 0.024 mmol) and potassium phosphate tribasic 2 M solution (0.590 mL, 1.181 mmol) in DMF (2.0 mL) was stirred at 100 °C for 4 h. The reaction mixture was diluted with EtOAc (50 mL) which was washed with 10 % LiCl (20 mL x 2), brine (20 mL) and dried over Na_2SO_4. Filtration and concentration yielded a crude product which was triturated in MeOH (2 mL). The solid was collected as tert-butyl 3-(3-(methylcarbamoyl)-1H-indazol-6-yl)-5,6-dihydropyridine-1(2H)-carboxylate (96.5 mg, 0.267 mmol, 68 %).

MS ESI m/z 357.3 (M+H).

5B: tert-butyl 3-(3-(methylcarbamoyl)-1H-indazol-6-yl)piperidine-1-carboxylate: A suspension solution of tert-butyl 3-(3-(methylcarbamoyl)-1H-indazol-6-yl)-5,6-dihydropyridine-1(2H)-carboxylate (86.5 mg, 0.243 mmol) and Pd/C (15.50 mg, 0.015 mmol) in MeOH (5 mL) was stirred under a H_2 balloon (0.489 mg, 0.243 mmol) for 24 h. The reaction mixture was filtered and concentrated to yield (64 mg, 0.179 mmol, 74 %).

MS ESI m/z 357.4 (M-H).

5C: N-methyl-6-(piperidin-3-yl)-1H-indazole-3-carboxamide, HCl: A solution of tert-butyl 3-(3-(methylcarbamoyl)-1H-indazol-6-yl)piperidine-1-carboxylate (64 mg, 0.179 mmol) and TFA (0.014 mL, 0.179 mmol) in CH_2Cl_2 (1 mL) was stirred at 23 °C for 1 h. The reaction mixture was concentrated to yield a crude material. The crude product was purified using a reverse phase Isco chromatography (Combiflash RF200, 30 g C18 Redisep Rf high performance gold column, solvent A: 0.1 % TFA in water/MeOH (90/10), solvent B: 0.1 % TFA in water/MeOH (10/90), flow rate: 35 mL/min, 10 – 70% B) to yield the product. The product was treated with 2.5 M HCl in EtOH (0.5 mL) and concentrated to provide N-methyl-6-(piperidin-3-yl)-1H-indazole-3-carboxamide, HCl (37 mg, 0.126 mmol, 70 %).

MS ESI m/z 259.1 (M+H).

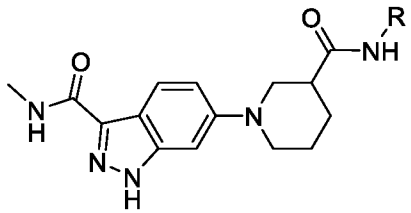
5: To a solution of N-methyl-6-(piperidin-3-yl)-1H-indazole-3-carboxamide, 6 TFA (14.6 mg, 0.015 mmol) and Et_3N (10.80 µl, 0.077 mmol) in CH_2Cl_2 (1 mL) at 23 °C was added diphosgene (2.80 µl, 0.023 mmol). The reaction mixture was stirred for 30

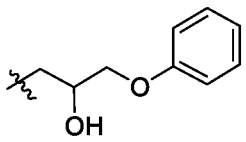
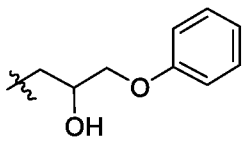
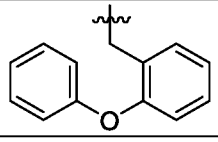
min. To the reaction mixture was added 3-phenylbutan-1-amine (11.56 mg, 0.077 mmol) and stirring was continued for 48 h. The crude material was purified via preparative LC/MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 20-60% B over 22 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation. N-methyl-6-{1-[(3-phenylbutyl)carbamoyl]piperidin-3-yl}-1H-indazole-3-carboxamide (4.8 mg, 11.1 µmol, 73.8 %) was isolated.

MS ESI m/z 434.1 (M+H)

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.31 (br d, *J*=4.6 Hz, 1H), 8.07 (d, *J*=8.3 Hz, 1H), 7.41 (s, 1H), 7.31 - 7.25 (m, 2H), 7.24 - 7.13 (m, 4H), 6.44 (br s, 1H), 4.08 - 3.94 (m, 2H), 3.02 - 2.92 (m, 1H), 2.91 - 2.84 (m, 1H), 2.80 (d, *J*=4.7 Hz, 3H), 2.77 - 2.62 (m, 4H), 1.93 (br d, *J*=9.7 Hz, 1H), 1.75 - 1.64 (m, 4H), 1.50 - 1.40 (m, 1H), 1.18 (d, *J*=6.9 Hz, 3H).

Table 1. The compounds in Table 1 were prepared by methods similar to those described in Example 1. All compounds are racemic unless otherwise noted.



Ex	Name	R	Obs Ion (M+H)
6	6-{3-[(2-hydroxy-3-phenoxypropyl)carbamoyl]piperidin-1-yl}-N-methyl-1H-indazole-3-carboxamide, homochiral, unknown isomer		452.2
7	6-{3-[(2-hydroxy-3-phenoxypropyl)carbamoyl]piperidin-1-yl}-N-methyl-1H-indazole-3-carboxamide, homochiral, unknown isomer		452.3
8	N-methyl-6-(3-{[(2-phenoxyphenyl)methyl]carbamoyl}piperidin-1-yl)-1H-indazole-3-carboxamide		484.0

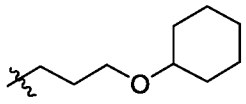
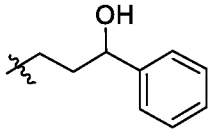
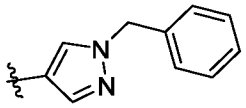
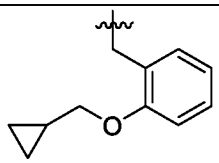
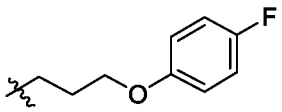
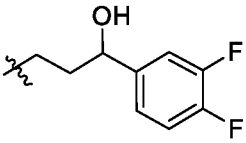
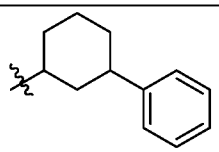
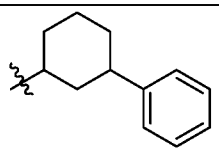
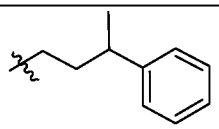
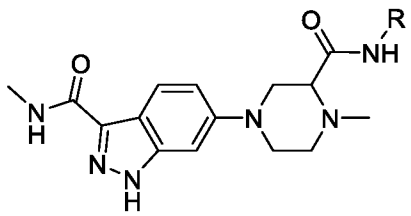
9	6-(3-{[3-(cyclohexyloxy)propyl]carbamoyl}piperidin-1-yl)-N-methyl-1H-indazole-3-carboxamide		442.2
10	6-{3-[(3-hydroxy-3-phenylpropyl)carbamoyl]piperidin-1-yl}-N-methyl-1H-indazole-3-carboxamide, diastereomeric mixture		436.3
11	6-{3-[(1-benzyl-1H-pyrazol-4-yl)carbamoyl]piperidin-1-yl}-N-methyl-1H-indazole-3-carboxamide		457.9
12	6-[3-({[2-(cyclopropylmethoxy)phenyl]methyl}carbamoyl)piperidin-1-yl]-N-methyl-1H-indazole-3-carboxamide		462.3
13	6-(3-{[3-(4-fluorophenoxy)propyl]carbamoyl}piperidin-1-yl)-N-methyl-1H-indazole-3-carboxamide		453.9
14	6-(3-{[3-(3,4-difluorophenyl)-3-hydroxypropyl]carbamoyl}piperidin-1-yl)-N-methyl-1H-indazole-3-carboxamide, diastereomeric mixture		472.0
15	N-methyl-6-{3-[(3-phenylcyclohexyl)carbamoyl]piperidin-1-yl}-1H-indazole-3-carboxamide, diastereomeric mixture, unknown cis or trans		460.4
16	N-methyl-6-{3-[(3-phenylcyclohexyl)carbamoyl]piperidin-1-yl}-1H-indazole-3-carboxamide diastereomeric mixture, unknown cis or trans		460.4
17	N-methyl-6-{3-[(3-phenylbutyl)carbamoyl]piperidin-1-yl}-1H-indazole-3-carboxamide, diastereomeric mixture		434.4

Table 2. The compounds in Table 1 were prepared by methods similar to those described in Example 2. All compounds are diastereomeric mixtures.



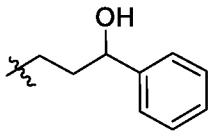
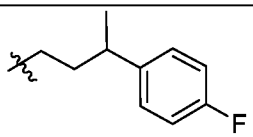
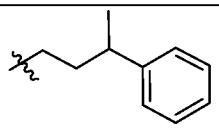
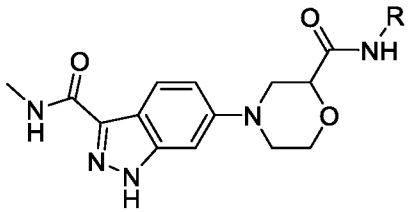
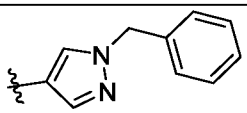
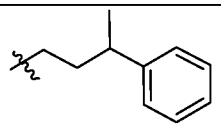
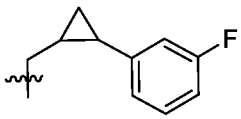
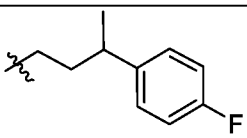
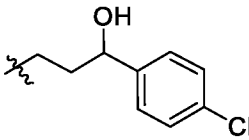
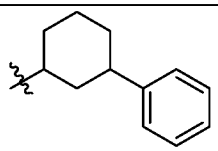
Ex	Name	R	Obs Ion (M+H)
18	6 6-{3-[(3-hydroxy-3-phenylpropyl)carbamoyl]-4-methylpiperazin-1-yl}-N-methyl-1H-indazole-3-carboxamide		451.3
19	6-(3-{[3-(4-fluorophenyl)butyl]carbamoyl}-4-methylpiperazin-1-yl)-N-methyl-1H-indazole-3-carboxamide		467.1
20	N-methyl-6-{4-methyl-3-[(3-phenylbutyl)carbamoyl]piperazin-1-yl}-1H-indazole-3-carboxamide		449.3

Table 3. The compounds in Table 1 were prepared by methods similar to those described in Example 3. All compounds are racemic unless otherwise noted.

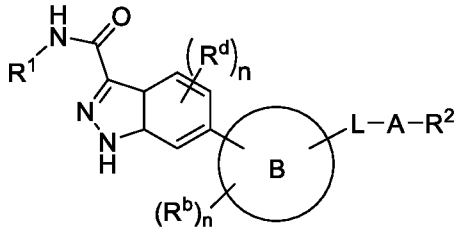


Ex	Name	R	Obs Ion (M+H)
21	6-{2-[(1-benzyl-1H-pyrazol-4-yl)carbamoyl]morpholin-4-yl}-N-methyl-1H-indazole-3-carboxamide		460.2
22	N-methyl-6-{2-[(3-phenylbutyl)carbamoyl]morpholin-4-yl}-1H-indazole-3-carboxamide, diastereomeric mixture		436.2
23	6-[2-({[2-(3-fluorophenyl)cyclopropyl]methyl}carbamoyl)morpholin-4-yl]-N-methyl-1H-indazole-3-carboxamide, TFA, diastereomeric mixture		452.1
24	6-(2-{[3-(4-fluorophenyl)butyl]carbamoyl}morpholin-4-yl)-N-methyl-1H-indazole-3-carboxamide, diastereomeric mixture		454.2
25	6-(2-{[3-(4-chlorophenyl)-3-hydroxypropyl]carbamoyl}morpholin-4-yl)-N-methyl-1H-indazole-3-carboxamide, diastereomeric mixture		472.0

26	N-methyl-6-{2-[(3-phenylcyclohexyl)carbamoyl]morpholin-4-yl}-1H-indazole-3-carboxamide, diastereomeric mixture		462.1

WHAT IS CLAIMED IS:

1. Compounds having formula (I), or salt thereof, wherein



(I)

Ring B is piperidinyl, piperazinyl, or morpholinyl;

R^1 is H, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} deuteroalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{1-3} alkoxy, C_{1-3} haloalkoxy, or C_{1-3} deuteroalkoxy;

R^b is H, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, C_{1-3} deuteroalkyl, C_{1-3} deuteroalkoxy, halo, NH_2, or CN;

R^d is independently H, halo, or C_{1-3} alkyl;

L is $C(O)NR^a$;

R^a is independently H, C_{1-4} alkyl, or C_{1-4} deuteroalkyl;

A is A' or A'-L',

A' is C_{1-4} alkyl substituted with 0-1 OH, C_{1-4} deuteroalkyl substituted with 0-1 OH, C_{3-6} cycloalkyl-C_{0-3}-alkyl-, C_{0-3}-alkyl-C_{3-6} cycloalkyl-, pyrrolyl-C_{1-3}-alkyl-, C_{1-3}-alkyl-pyrrolyl-, pyrazolyl-C_{1-3}-alkyl-, or C_{1-3}-alkyl-pyrazolyl-;

L' is –O-;

R^2 is phenyl, or a 5 to 6 membered heterocycle having 1-4 heteroatoms selected from N and O, wherein any of the phenyl or heterocycle groups are substituted with 0-3 R^{2a};

R^{2a} is halo, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy-C_{1-6} alkoxy, C_{1-6} deuteroalkyl, C_{1-6} deuteroalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, C_{3-6} halocycloalkyl, C_{3-6} cycloalkoxy, C_{3-6} cycloalkyl-C_{1-3} alkoxy-, C_{3-6} cycloalkyl-C_{1-3} deuteroalkoxy-, C_{3-6} cycloalkyl-C_{1-3} haloalkoxy-, C_{1-6} alkoxy-C_{1-3} alkyl-, C_{3-6} cycloalkoxy-C_{1-3} alkyl-, C_{1-4} alkyl-SO_2-, C_{3-6} cycloalkyl-SO_2-, C_{6-10} aryl-S-, $NR^{2c}R^{2d}CO$-, heterocycle-, heterocycle-O-, heterocycle-CH_2-, wherein each heterocycle is independently a 4-6 membered ring having 1-2 heteroatoms

selected from N and O, and wherein each alkyl, cycloalkyl, or heterocycle is substituted with 0-2 R^{2b};

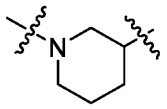
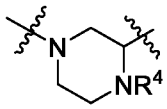
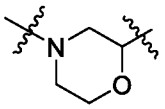
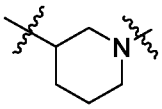
R^{2b}, at each occurrence, is independently C_{1-3} alkyl, halo, C=O, or C_{1-3} haloalkyl;

R^{2c} and R^{2d} are independently selected from H, C_{1-3} alkyl, C_{1-3} deuteroalkyl, C_{3-6} cycloalkyl, or taken together with N to which they are attached to form a 4-6 member heterocyclic ring, having 0-1 additional heteroatoms selected from N, O and S, and being substituted with 0-4 substituents chosen from deuterium or halo; and

n is 0, 1 or 2.

2. A compound of claim 1, or salt thereof, wherein

Ring B is


, 
, 
, or 
, any of which are substituted with 0-1 R^b ; and

R^4 is H, or C_{1-3} alkyl.

3. A compound of claims 1-2, or salt thereof, wherein

R^2 is phenyl, pyridinyl, or pyrrolyl, any of which are substituted with 0-3 R^{2a}.

4. A compound of claims 1-3, or salt thereof, wherein

A' is C_{1-4} alkyl substituted with 0-1 OH, or C_{1-4} deuteroalkyl substituted with 0-1 OH.

5. A compound of claims 1-4, or salt thereof, wherein

R^{2a} is halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy or C_{3-6} cycloalkyl-C_{1-3} alkoxy-.

6. A compound of claims 1-5, or salt thereof, wherein

R^b is H, Cl, F, C_{1-3} alkyl, or C_{1-3} alkoxy;

7. A compound of claims 1-6, or salt thereof, wherein

A is $-CH_2-$, CD_2-, $-CH_2CH_2-$, $-CH(CH_3)-$, $-CH(CD_3)-$, $-CH_2CH_2CH(CH_3)-$, $-CH_2CH_2CH(OH)-$, or $-CH_2$-cyclopropyl-.

8. A compound of claims 1-6, or salt thereof, wherein

A is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH(CH_3)-$, $-CH_2CH_2CH(OH)-$, $-CH_2CH(OH)CH_2-O-$, $-CH_2CH_2CH_2O-$, -cyclohexyl-, - pyrrolidinyl-CH_2-, or $-CH_2$-cyclopropyl-.

9. A compound of claim 7, or salt thereof, wherein

L is C(O)NH; and

R^2 is phenyl substituted with 0-3 R^{2a}.

10. A compound of claims 1-9, or salt thereof, wherein the compound is selected from the examples.

11. A pharmaceutical composition comprising one or more compounds of claims 1-10, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

12. A method of inhibiting casein kinase RIPK1 activity in a patient, comprising administering to the patient in need thereof, a therapeutically effective amount of one or more compounds according to claims 1-10.

13. A method for treating a disease comprising the administration to a subject in need thereof a therapeutically effective amount of at least one of claims 12, wherein the disease is selected from inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis, rheumatoid arthritis (RA), and heart failure.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/050721

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04 C07D401/14 C07D413/14 A61K31/416 A61P29/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2018/067432 A1 (SQUIBB BRISTOL MYERS CO [US]) 12 April 2018 (2018-04-12) page 1, lines 10-16; pages 106-113, "Biological Assays"; claims	1-13
A	JULIO CABALLERO ET AL: "Binding Studies and Quantitative Structure-Activity Relationship of 3-Amino-1H-Indazoles as Inhibitors of GSK3beta", CHEMICAL BIOLOGICAL & DRUG DESIGN,, vol. 78, 2011, pages 631-641, XP002795447, DOI: 10.1111/J.1747-0285.2011.01186.X page 631, left-hand column, line 4 from the bottom to right-hand column, third paragraph; page 633, Table 1, compounds 11, 29	1-13

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 November 2019	27/11/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sen, Alina

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/050721

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2009/203690 A1 (AKRITOPOULOU-ZANZE IRINI [US] ET AL) 13 August 2009 (2009-08-13) [0002]; [0024]-[0048]; [1161]-[1163]; claims -----	1-13

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2019/050721

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2018067432 A1	12-04-2018	CN 110036015 A	19-07-2019
		EP 3523305 A1	14-08-2019
		JP 2019530699 A	24-10-2019
		KR 20190057132 A	27-05-2019
		US 2019225620 A1	25-07-2019
		WO 2018067432 A1	12-04-2018
US 2009203690 A1	13-08-2009	US 2009203690 A1	13-08-2009
		US 2014343066 A1	20-11-2014